An important polysaccharide from fermentum

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ABSTRACT

Fermentum is a common unicellular fungus with many biological activities attributed to β-polysaccharides. Different in vivo and in vivo experimental studies have long proven that fermentum β-polysaccharides have antioxidant, anti-tumor, and fungal toxin adsorption properties. However, there are many uncertainties regarding the relationship between the structure and biological activity of fermentum β-polysaccharides, and a systematic summary of fermentum β-polysaccharides is still lacking. Herein, we reviewed the research progress about the extraction, structure and modification, structure–activity relationship, activity and application of fermentum β-polysaccharides, compared the extraction methods of fermentum β-polysaccharide, and paid special attention to the structure–activity relationship and application of fermentum β-polysaccharide, which provided a strong basis for the development and application of fermentum β-polysaccharide.

Introduction

Fermentum is a single-celled fungal organism, as early as 3000 BCE, humans began to use Fermentum to make fermented food, Fermentum and its fermentation products greatly improved and enriched the life of mankind, it can be said that Fermentum is the history of human civilization was applied to the earliest microorganisms (Zimmermann et al., 2018). In ancient China, the agronomic work "Qi Min Yao Shu", written during the Northern Wei Dynasty, describes how the ancient Chinese people used Fermentum to make wine. Dietary habits vary from place to place and the use and consumption of Fermentum in Europe and America are even more enormous. The world is rich in Fermentum resources, and most of the waste Fermentum is used as animal feed in daily food processing production, which is not well recycled and reused. If Fermentum can be exploited in an integrated manner, it is likely to bring considerable economic benefits. The cell wall accounts for about 20%-30% of the entire cell dry weight in the Fermentum cell and maintains cell morphology and intercellular recognition. Under electron microscopy, Fermentum cell walls can be observed to have a "sandwich" structure, consisting of two higher electron-density layers inside and outside sandwiched by a lower electron-density layer. The outer layer of the Fermentum cell wall is composed of mannans, the middle layer is mainly composed of proteins, and the inner layer is polysaccharide, which is one of the most important components of the Fermentum cell wall and has a variety of biological activities (Okada & Ohya, 2016), as shown in Fig. 1. Numerous experimental studies have shown that polysaccharide has various physiological functions such as immune enhancement (Yuan et al., 2019), prevention or treatment of diseases (Su et al., 2021), growth promotion, and inhibition of systemic inflammation (No et al., 2021), adsorption of mycotoxins and nutritional supplementation (Cao et al., 2017; Hamza et al., 2019). As the biological activities of polysaccharides have been discovered, the structure of polysaccharides has also been studied more clearly, with most polysaccharides being polymers composed of D-polysaccharides bound by β-D- (1, 3) bonds and a small number of polysaccharides bound by highly branched β-D- (1, 6) bonds. The neutral polysaccharide accounts for about 34% of the cell wall (Grün et al., 2005; Han et al., 2020). To further exploit the usefulness of Fermentum β-polysaccharide, many researchers have modified Fermentum β-polysaccharide in different ways. For example, by introducing different reactive groups using chemical reagents or by changing the chain length of Fermentum β-polysaccharide (see Table 1).

In recent years, the research on β-polysaccharides activity and application has been increasing year by year, and the research involves many different fields such as medicine, health food and cosmetics. However, all these researches and applications are in the basic stage. Ultimately, despite the abundance of Fermentum resources, Fermentum β-polysaccharides have not yet been produced on a large scale, the optimal extraction and production method of Fermentum β-polysaccharides have not yet been determined, and in-depth studies on the

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relationship between the advanced structure and activity of Fermentum β-polysaccharides are still relatively few. This paper summarizes the extraction, modification, structural characterization, conformational relationships, biological activities and their applications of Fermentum β-polysaccharides, aiming to provide a reference for the efficient development and comprehensive application of Fermentum β-polysaccharides.

Extraction of β-polysaccharides

Since β-polysaccharide is in the inner layer of the Fermentum cell wall, the key step of β-polysaccharide extraction is to remove the protein and mannose. And the extraction rate, molecular mass, dispersion coefficient and average molecular radius of β-polysaccharide extracted by different methods are significantly different. polysaccharides from the modified acid-base extraction method were found to be more biologically active than the aqueous extraction method (Mahmoud Amer et al., 2021). It is clear that the extraction method of Fermentum β-polysaccharide occupies an important position and it is necessary to study the extraction method of Fermentum β-polysaccharides to gain insight into the differences in physicochemical properties and biological activity of Fermentum β-polysaccharides.

Chemical extraction methods

Acid extraction methods, alkaline extraction methods and acid-base extraction methods are the most commonly used chemical methods for extracting β-polysaccharide from Fermentum cell walls. The extraction of β-polysaccharide from Fermentum cell walls by an acid method generally uses milder acids, such as phosphoric acid, formic acid and acetic acid, which can lead to a higher yield of β-polysaccharide. However, the β-polysaccharide extracted by the acid method is not high in purity due to the mixture of glycogen, mannose and protein. Such β-polysaccharide cannot be used in industrial production that requires high purity of β-polysaccharide (Utama et al., 2021). The general procedure for alkaline extraction is to suspend the Fermentum cells in a 4% NaOH solution, stir in a boiling water bath for 2 h, adjust to neutral and then centrifuge to remove the precipitate, which is then dehydrated in anhydrous ethanol and dried to obtain the finished product. The yield of β-polysaccharide extracted by Li et al. using the alkali method was 86.1%. Pigs fed diets supplemented with β-polysaccharide showed a significant increase in the antibody response to ovalbumin in their bodies after day 21, and the immunomodulatory ability of piglets was significantly enhanced (Li et al., 2006). In another study, Bastos et al. extracted β-polysaccharide from Fermentum cell walls by hot water extraction and alkali method, respectively. In contrast, the β-polysaccharide extracted by the alkali method was purer (92%) (Bastos et al., 2015). Despite the higher purity of β-polysaccharides extracted by the alkali method, the structure of β-polysaccharides is likely to be damaged at too high a concentration of alkali solution, which affects its biological activity.

There are obvious deficiencies in the simple extraction of β-polysaccharide by alkaline or acid methods, such as the inability to completely separate mannose and polysaccharide, or the destruction of the structure of β-polysaccharide. Therefore, many scholars have adopted the combined acid-base method to extract β-polysaccharide. Huang extracted β-polysaccharide from the Fermentum cell wall with 6% NaOH at 60 °C, extracted it twice with 4% phosphoric acid at room temperature, and recovered the β-polysaccharide product by spray drying after centrifugation in a yield of 13.5% (Huang, 2008). Compared with the alkali method or the acid method, the organic solvent used is reduced. Luan et al. extracted β-polysaccharides from the Fermentum with 3% sodium hydroxide at 90 °C and then washed the residue with hydrochloric acid, ether, ethanol and deionized water in turn. The final sample was analysed and found to contain 92% β-polysaccharides (Luan le & Uyen, 2014). This method uses lower concentrations of acid and alkali, is more environmentally friendly than the previous two methods, and increases the purity of the product. It is clear from the above that the acid and alkaline extraction methods, although yielding high amounts of mannose and protein, also lead to degradation of the polysaccharides and that a higher purity of β-polysaccharide is still required for better use in daily production applications. Although the purity and yield of the polysaccharides extracted by the acid-base method are improved, the reaction conditions are harsh, and corrosive and still do not avoid contamination and may even cause degradation of the polysaccharides (Varelas et al., 2016).

These extraction methods are not ideal if you want to extract a large amount of Fermentum β-polysaccharide with high purity for industrial production. In the industrial production of Fermentum β-polysaccharide, the extraction conditions should be optimized at each step. For example, the crude extracted Fermentum β-polysaccharide is wet, so many researchers will dry the wet Fermentum β-polysaccharide, and different drying methods will affect the taste, activity and size of Fermentum β-polysaccharide, so the extraction process should also take into account the application of the extracted Fermentum β-polysaccharide.

Physical extraction method

High-pressure homogenisation is generally applied for cell fragmentation, extraction and homogenisation of extracellular and intracellular substances for bioengineered products. To obtain specific
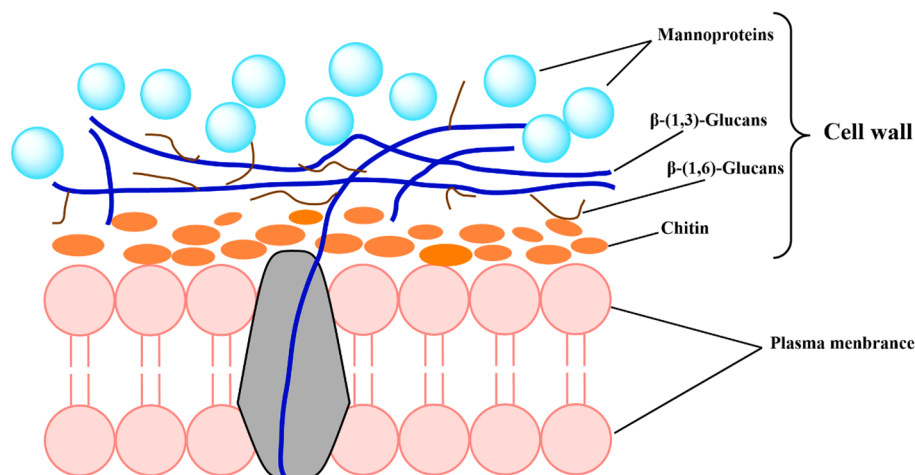

Fig. 1. The cell wall of Fermentum.

Table 1
Structure-Activity Relationship of Fermentum β-polysaccharide.

Compound name	Molecular weight	Structure/Construction	Purity	biological activity	Experimental model	Mechanism	References
BYGlc	25 kDa	Linear β-(1 → 3)-polysaccharide	99%	Hypoglycemic	Diabetic mice	Inhibits the expression of SGLT-1 in the intestinal mucosa and significantly reduces blood sugar, promotes glycogen synthesis, inhibits hepatic fat accumulation, inhibits macrophage infiltration and the production of pro-inflammatory cytokines	(Cao et al., 2016)
YG2-21	2496 kDa	β-D-polysaccharide		Regulate immunity	Macrophages	Induced expression in RAW264.7 cells	(Zheng, Huang, & Ling, 2019)
sGSC1	12.9 kDa	β-D-polysaccharide		Antioxidants regulate immunity	Mouse	Decreases malondialdehyde (MDA) levels; promotes the secretion of IL-2 and IFN-γ, and increases the CD4+/CD8 + ratio of lymphocytes	(Lei et al., 2015)
β-polysaccharide	27.9 kDa	Linearly linked β-d-glucopyranosyl units with (1 → 3) and (1 → 6) linkages	91%	Anti-oxidation	In vitro test		(Khan et al., 2016)
BCS004	689.351 kDa	Linear configuration containing (1–6)-branched (1–3)-β-D-polysaccharide	90%	Anti-oxidation	In vitro test		(Reyes-Becerril et al., 2020)
sGSC3	19.2 kDa	β-D-polysaccharide		Antioxidants regulate immunity	Mouse	Decreases malondialdehyde (MDA) levels; promotes the secretion of IL-2 and IFN-γ, and increases the CD4+/CD8 + ratio of lymphocytes	(Lei et al., 2015)
BYG		Rod-like structures of native triplex and nanoparticle-like substructures	85.3%	Anti-inflammatory	Colitis mice	Inhibition of oxidative stress (NO, MDA, and MPO) ameliorates inflammation in a DSS-induced colitis mouse model	(Qiao et al., 2022)
YG2-32	1335 kDa	β-D-polysaccharide		Regulate immunity	Macrophages	Induced expression in RAW264.7 cells	(Zheng, Huang, & Ling, 2019)
sGSC2	16.5 kDa	β-D-polysaccharide		Antioxidants regulate immunity	Mouse	Decreases malondialdehyde (MDA) levels; promotes the secretion of IL-2 and IFN-γ, and increases the CD4+/CD8 + ratio of lymphocytes	(Lei et al., 2015)
β-polysaccharide		With β-glycosidic bonds, (1–3)-β-polysaccharide chains form a triple helix three-dimensional structure		Antibacterial, anticancer	A549 human lung cancer cells, MDA-MB-231 human breast cancer cells, HePG-2 human liver cancer cells	Induces apoptosis of cancer cells, and highly induces TNFα, IL-6, IFN-γ and IL-2 to play an immunoregulatory role	(Mahmoud Amer et al., 2021)
BBG1		Highly branched beta-(1,6) polysaccharide		Anti-inflammatory	Mouse colon	Reduces pro-inflammatory mediators of IL-6, iNOS and IL-1β at protein and mRNA levels	(Sun, Shi, Zheng, Nie, & Xu, 2019)
BBG2		Linear β-(1,3)-polysaccharide		Anti-inflammatory	Mouse colon	Reduces pro-inflammatory mediators of IL-6, iNOS and IL-1β at protein and mRNA levels	(Sun, Shi, Zheng, Nie, & Xu, 2019)
BBG3		A mixture of β-(1,6) branched β-(1,3)-polysaccharides and linear β-(1,3)-polysaccharides		Anti-inflammatory	Mouse colon	Reduces pro-inflammatory mediators of IL-6, iNOS and IL-1β at protein and mRNA levels	(Sun, Shi, Zheng, Nie, & Xu, 2019)
BBG4		A mixture of β-(1,6) branched β-(1,3)-polysaccharides and linear β-(1,3)-polysaccharides		Anti-inflammatory	Mouse colon	Reduces pro-inflammatory mediators of IL-6, iNOS and IL-1β at protein and mRNA levels	(Sun, Shi, Zheng, Nie, & Xu, 2019)
P-PJ		(1 → 3)-D-polysaccharide		Anti-oxidation	In vitro test		(Tang, Huang, Zhao, Zhou, Huang, & Li, 2017)
CM-PJ		(1 → 3)-D-polysaccharide		Anti-oxidation	In vitro test		(Tang, Huang, Zhao, Zhou, Huang, & Li, 2017)
CS-PJ		(1 → 3)-D-polysaccharide		Anti-oxidation	In vitro test		(Tang, Huang, Zhao, Zhou, Huang, & Li, 2017)
WYG-1	3700 kDa	Confirmation is spherical, highly branched					(Zheng et al., 2021)
WYG-2	2830 kDa						

components of the Fermentum cell wall, researchers have used this physical method to extract β-polysaccharide. The sample (emulsion or suspension) is passed through the homogenisation valve under high pressure to produce shear, impact and cavitation. When a sample is passed through a homogenising valve at high pressure, the sample accelerates and under pressure potential energy is converted, producing shear, impaction and cavitation effects. The extraction of Fermentum cell wall polysaccharides by high-pressure homogenisation reduces the product's protein content and provides certain conditions for the subsequent purification of β-polysaccharide (Dimopoulos et al., 2020). Zhang et al. used the ultrasonic method to extract β-polysaccharide from Fermentum cells and also tried to improve the release selectivity by controlling the process parameters. Among them, a 20 kHz angular ultrasonic instrument is used. The main reason for controlling the ultrasound frequency at 20 kHz was to reduce the cost of the subsequent purification work, and the fact that too high a frequency of ultrasound could also lead to deactivation of the whole organism and not obtain the desired β-polysaccharide. They found that extraction of Fermentum β-polysaccharide by ultrasound method, controlling the temperature and frequency of ultrasound can achieve selective release of polysaccharides and proteins. Ultrasonic treatment at high temperature is more favourable for the release of polysaccharides, because the protein has been deformed under high-temperature conditions and cannot be released, while ultrasonic treatment can destroy the cell wall of Fermentum cells, making the release of polysaccharides from the Fermentum cell wall (Zhang et al., 2014). The physical extraction method has great potential for development as it saves time and effort and is compatible with contemporary requirements for environmental protection. Furthermore, physical extraction methods can reduce the release of impurities, such as proteins, during the extraction process. This is an excellent aid to the subsequent purification process and also improves the purity of Fermentum β-polysaccharide.

Combined extraction methods

Nowadays, many clinical studies require Fermentum β-polysaccharide of high purity and quality, but traditional extraction methods are unable to satisfy this demand, so many researchers are now combining different extraction methods to make the extracted β-polysaccharide more suitable for practical applications and production. Borchani et al. extracted the Fermentum cell wall precipitated by hot water extraction and washed it with distilled water to remove mannoproteins and some of the soluble polysaccharides; peptides and lipids were then removed by centrifugation with protease and lipase, which not only reduced the use of organic solvents but also kept the active structure of β-polysaccharide intact to the greatest extent possible, and the yield of β-polysaccharide after extraction was very significant

(Borchani et al., 2014). Zheng et al. obtained β-polysaccharide by extraction with ethyl acetate and acetone for 6 h and then extracted it by ultrasound-assisted alkali method, with the increase of ultrasound time, more and more large size aggregates were degraded to small size molecules, and the yield of β-polysaccharide extracted by this method was increased to $36.2 \pm 0.3\%$ compared to the common extraction method. Furthermore, the combination of ultrasound and alkali treatment of Fermentum β-polysaccharide loosens the aggregation structure and increases the specific surface area, thus increasing solubility (Zheng, Huang, Luo et al., 2019). Liu et al. induced autolysis of Fermentum cells by dissolving them in NaCl solution and then homogenized the Fermentum cells for three cycles using a dynamic high-pressure microfluidizer. The concentration of β-polysaccharide was determined to be 81.07%. This series of extraction processes significantly increased the concentration of β-polysaccharide, removed most of the protein and reduced the complexity of the subsequent purification process (Liu et al., 2016). Pinto et al. first extracted Fermentum β-polysaccharide with hot water and then with alkali under a nitrogen atmosphere, and the final extracted product was enriched with 52 mol% polysaccharides because the product obtained after hot water extraction did not contain cellulose and β-polysaccharide had better solubilization under high strength alkali, so the subsequent extraction with alkali resulted in an increased yield of Fermentum β-polysaccharide (Pinto et al., 2015). It can be seen that with the emergence of new extraction techniques, researchers no longer stick to a single extraction technique, but use a combination of techniques to make the extracted β polysaccharide purer and more effective in its biological activity.

Modification of Fermentum β-polysaccharide

Fermentum β-polysaccharide is electrically neutral and does not carry an electrical charge. Because of the many hydroxyl groups within the β-1,3-polysaccharide molecule, the hydroxyl groups interact with each other to form a tight and stable triple helix structure, so Fermentum β-polysaccharide is insoluble in water and most organic solvents, and slightly soluble in dichlorosulfoxide. This property limits the industrial use of Fermentum β-polysaccharide, but its solubility can be improved if it can be modified. The most common modification method used in current research is chemical modification, which generally involves the introduction of certain reactive groups into the molecular chain of β-polysaccharide, resulting in a change in its molecular structure and thus greater biological activity. The chemical modification method is very effective, however, due to the use of many chemical reagents, the molecular chain of β-polysaccharide may be broken during the actual operation, which may have a significant impact on its structure. The physical modification method does not destroy the basic structure and functional groups of β-polysaccharide, and generally uses physical

Table 1 (*continued*)

Compound name	Molecular weight	Structure/Construction	Purity	biological activity	Experimental model	Mechanism	References
		Confirmation is spherical, highly branched					(Zheng, Huang, Kang, Liu, & Luo, 2021)
WYG-3	1320 kDa	Confirmation is spherical, highly branched					(Zheng, Huang, Kang, Liu, & Luo, 2021)
WYG-4	172.5 kDa	Has a triple helix structure and rigid chain					(Zheng, Huang, Kang, Liu, & Luo, 2021)
WYG-5	54.5 kDa	Has a triple helix structure and rigid chain					(Zheng, Huang, Kang, Liu, & Luo, 2021)
SBG		1,6-linked branched chain with regular comb-like branches, triple helix structure					(Qin, Sletmoen, Stokke, & Christensen, 2013)

methods to break the main chain of the polysaccharide to form soluble β-polysaccharide of small molecular weight and increase its solubility. The biomodification method is not used much yet, but it has a good application prospect because it is environmentally friendly and can better exploit the activity of β-polysaccharide.

Physical modification methods

Researchers are looking for an inexpensive, convenient and fast method to prepare low molecular weight Fermentum β-polysaccharide. New physical modification methods have been increasingly accepted by the public because of their low input, non-pollution and fast speed. For example, microencapsulation of traditional Chinese medicine polysaccharides can effectively reduce its hygroscopic rate. The microcapsule method can form a polymer film on the surface of the extract to hinder the entry of external water, which plays the role of moisture-proof to a certain extent. Irradiation and ultrasound modification are the more common methods of physical modification. Luan et al. degraded the extracted Fermentum β-polysaccharide by irradiation with a Co-60 irradiator at a dose rate of 3 kGy/h. The results showed that the water solubility of β-polysaccharide increased and the molecular weight decreased with increasing irradiation dose, and carbonyl groups were formed by breaking the sugar chains as the polysaccharide molecules were irradiated (Luan le & Uyen, 2014). Besides the modification of β-polysaccharide by radiation, it was also shown that the particle size of Fermentum β-polysaccharide extracted from brewer's Fermentum by sonication at a solid–liquid ratio of 1:1000 g/mL and a volume of 300 mL decreased with increasing sonication time from 8.80 μm to 1.77 μm. The large size aggregates were broken into smaller particles and the polysaccharide molecular chains were also broken into smaller molecular chains (Zheng, Huang, Luo, Xiao, Cai, & Ma, 2019). The change in the structural properties of polysaccharides is the fundamental reason for the changes in other properties, so it is of great significance to study the effect of ultrasonic modification on the structural properties of Fermentum β-polysaccharides. The application of high-pressure microfluidics provides a new idea to improve the water solubility of Fermentum β-polysaccharides. According to the study by Liu et al., the modification of Fermentum β-polysaccharide under the condition of pressure from 12,000 psi to 28,000 psi, the solubility of Fermentum β-polysaccharide (YG) was significantly improved, and the relative molecular weight decreased from 3.833×10^6 to 2.417×10^6. Analysis by X-ray diffractometer technology shows that the crystallinity of modified YG is significantly reduced. It is worth noting that the original triple helix structure of YG was gradually broken after modification and became a random chain (Liu et al., 2020) The reason why the water solubility of YG can be significantly improved is that the intramolecular and intermolecular hydrogen bonds are broken, resulting in a decrease in crystallinity, and the higher structure of YG is also changed, thereby improving the water solubility. In general, the mechanism of physical modification is to degrade the polysaccharide chain by physical means under the condition that the basic structure of the polysaccharide remains unchanged, causing the spatial structure and conformation of the polysaccharide to change to improve its water solubility and biological activity.

Chemical modification

It has been found that the activity of chemically modified β-polysaccharide is significantly increased, so the chemical modification of β-polysaccharide has become a hot research topic. The principle of chemical modification is to introduce different groups on the long chain of β-polysaccharide or change the length of its molecular chain. Among them, sulphation modification is an effective and simple chemical modification method, which can improve water solubility and change the chain conformation, thus altering its biological activity. Zhang et al. modified Fermentum β-polysaccharide by the chlorosulfonic acid-pyridine method. The experimental results showed that the solubility of sulfated β-polysaccharide increased by 28 times. When mice damaged by radiation exposure were fed with sulphated β-polysaccharide, it was observed by transmission electron microscopy that the mitochondria in the cells were normal and the organelle membranes and spleen were still intact (Zhang et al., 2017). This indicates that sulfated β-polysaccharide can effectively treat radiation damage of splenocytes caused by oxidative stress, which may provide different ideas for preventing and treating radiation damage in clinical medicine in the future. Of course, modification of β-polysaccharide by phosphorylation can also achieve the effect of improving its water solubility. Shi et al. prepared Fermentum β-polysaccharide by mechanical grinding. After grinding, the tight helical structure of β-polysaccharide was disrupted and opened, which then reacted well with phosphorylation reagents to produce phosphorylated derivatives. After testing, it was found that the phosphorylated β-polysaccharide prepared under controlled conditions has low molecular weight and high water solubility. And most importantly, it is more environmentally friendly and convenient, which is an advantage that the traditional phosphorylation process does not have (Shi et al., 2014). β-polysaccharide contains several sites that can be replaced by phosphate groups, such as the C-2,4,6 sites (Mei et al., 2020). The phosphorylation modification of Fermentum β-polysaccharide can affect its solubility mainly because of the hydrophilic nature of the substituents, the distribution of the hydrophilic groups greatly affects the properties and stability of the modified product. Phosphorylation modifications can introduce phosphate groups at multiple sites of β-polysaccharide, resulting in phosphorylated derivatives with high water solubility. Sulphonation modification means that the hydroxyl group in the monomeric sugar unit is replaced by a sulphonyl hydroxyl group, and the polysaccharide modified by sulfonylation can exhibit more biological activities. Calegari et al. prepared sulphonation reagents with chlorosulfonic acid and pyridine. They found that with a higher volume fraction of sulfonylation reagents, the degree of substitution of β-polysaccharide also increased. The experimental results showed that the solubility of sulfonylated β-polysaccharide was higher than that of unmodified β-polysaccharide, and the sulfonylated β-polysaccharide exhibited good antioxidant activity and enhanced thermal stability (Calegari et al., 2019). Ding et al. ball-milled Fermentum β-polysaccharide before carboxymethylation and then synthesized carboxymethylated Fermentum β-polysaccharide by two-step alkalinization and etherification based on the Williamson synthesis method. The solubility of the carboxymethylated Fermentum β-polysaccharide was increased by 22% compared to the unmodified β-polysaccharide. In previous work, they found that ball milling also increased the solubility of β-polysaccharide, but less than that of carboxymethylated modified β-polysaccharide (Ding et al., 2013). According to the majority of the research, most of the different chemical modification methods improve the solubility of β-polysaccharide, and the amount of modifier has a strong influence on the substitution of -polysaccharide. Some pretreatment before chemical modification is more favourable, such as mechanical ball milling. However, the optimal degree of substitution of Fermentum β-polysaccharide is still inconsistent, and further investigation is needed to determine which modification method is the best to improve the solubility of Fermentum β-polysaccharide.

Structure of Fermentum β-polysaccharides

The active structure of Fermentum cell wall β-polysaccharide is composed of glucose units, which share a common structure: the main chain consists of glucose groups linked by β-(1,3)-glycosidic bonds, and glucose groups linked by β-(1,6)-glycosidic bonds are randomly distributed along the main chain, showing a comb-like structure. It has been reported that the reducing segment of β-(1,6)-polysaccharide is linked to the terminal glucose at the non-reducing end of β-(1,3)-polysaccharide. The 1–3-β-D-polysaccharide backbone forms a mixture with individual 1–6-β-D-glucopyranosyl side branch units, every two residues

being the main unit. 1–3-β-D-polysaccharide backbone with single 1–6-β-D-glucopyranosyl side units every three residues as secondary units (the ratio of primary to secondary units is approximately 7:3) (Boutros et al., 2022; Tada et al., 2008). The structure of Fermentum β-polysaccharide is shown in Fig. 2. In another study, it was demonstrated that Fermentum β-(1,6)-polysaccharide is a highly branched polymer containing 65–70% of C-1 and C-6 co-linked glucose residues, 15% of non-reducing terminal glucopyranose residues, 5% of C-1 and C-3 co-linked glucose and 10–15% of triple-linked residues at C-1, C-3 and C-6 (Schiavone et al., 2014). Khan et al. found that the average molecular weight of Fermentum β-D-polysaccharide was 175 kDa (Khan et al., 2016). Analysis of the morphology and conformation of Fermentum β-polysaccharide can help to understand the conformational relationships and develop its applications in different fields, usually by X-ray diffraction, atomic force microscopy, etc. X-ray diffraction (XRD) can be used to study the helical structure and calculate the helical spacing. It has been reported that the surface of Fermentum β-polysaccharide particles can be observed as inhomogeneous by scanning electron microscopy. The β-polysaccharide particles are usually ellipsoidal, and many of them have one or more ring-like structures. After analysis, it is clear that β-polysaccharide is very abundant in the Fermentum cell wall and that β-polysaccharide can form a mesh skeletal structure with a grid size of about 50 nm. However, when the Fermentum β-polysaccharide is dried in air and then observed, it can be found that the β-polysaccharide particles become flat and disc-shaped, with a height of only 200–300 nm (Li et al., 2020). This three-dimensional mesh is formed by hydrogen bonding, and under normal osmotic pressure, the mesh extends extensively, whereas when Fermentum cells are under high osmotic pressure the three-dimensional mesh shrinks rapidly. Raikos et al. also observed by scanning electron microscopy that Fermentum β-polysaccharide was ridged, with a smooth surface and undulating edges, and that the granular polysaccharide was oval (Raikos et al., 2018). At present, there is no lack of studies showing that Fermentum β-polysaccharide has a triple-helix structure. It has been reported that Congo red reagent binds to the triple-helical structure of Fermentum β-polysaccharide with characteristic red shift, and there is an absorption value at 523 nm after redshift, and there is a linear relationship between the mass concentration of Congo red reagent and the triple-helical structure of β-polysaccharide under certain conditions. Qin et al. demonstrated under dynamic light scattering (DLS) and tapping mode atomic force microscopy (AFM) based measurements that Fermentum β-polysaccharide solution contains single-stranded and triple-stranded species as well as larger structures (Qin et al., 2013).

Structure-activity relationships

The branching degree (DB) of β-polysaccharide, molecular weight and charge of the polymer all affect the activity of β-polysaccharide. Lei et al. reported that Fermentum β-polysaccharide with low molecular weight is more effective in its biological activity. they prepared three sulfated Fermentum polysaccharides (sGSCs) with different molecular weights and tested the reactive oxygen species scavenging activity by in vitro experiments. The results showed that all three sulphated Fermentum β-polysaccharide could scavenge 1,1-diphenyl-2-picrylhydrazyl (DPPH), superoxide and hydroxyl radicals. However, the best scavenging activity was achieved by the lowest molecular weight, sGSCs1, with a scavenging activity of 42.16% at a concentration of 5 mg/mL (Lei et al., 2015). In another study, Reyes-Becerril et al. isolated a low molecular weight β-polysaccharide from Fermentum strain BCS004, and this low molecular weight Fermentum β-polysaccharide was able to scavenge DPPH radicals well and showed strong antioxidant activity (Reyes-Becerril et al., 2021). It seems that Fermentum β-polysaccharide with a lower molecular weight has better biological activity, but this is not absolute. By comparing different studies, we know that the different molecular weights may lead to different mechanisms of action of β-polysaccharide, while Fermentum β-polysaccharide with lower molecular weight has stronger antioxidant activity, Fermentum β-polysaccharide with higher molecular weight is more beneficial to promoting the release of cytokines that affect immunity, thus improving its immune activity. Zheng et al. prepared pure β-polysaccharide from brewer's Fermentum by extraction, acid digestion and fractionation, and isolated 14 fractions with different molecular weights. They found that all these fractions could stimulate the proliferation of RAW264.7 macrophages, but the largest molecular weight fraction (Mw = 2496 kDa) was effective in promoting the proliferation of macrophages at a low concentration (1.56 μg/mL), with a cell proliferation rate of 145.8 ± 4.3% (Zheng, Huang, & Ling, 2019). Therefore, if Fermentum β-polysaccharide needs to be used in a certain field, we need to consider the molecular weight size of Fermentum β-polysaccharide. For example, when applied to food additives or cosmetic processing these fields should choose Fermentum β-polysaccharide with low molecular weight and high solubility.

It has been demonstrated that β-polysaccharides are linked by 1, 3-glycosidic bonds, that acetylated and methylated derivatives exhibit low specific rotation in water as well as upward rotation, and that 1, 3-glycosidic bonds dominate the conformational transformation of β-polysaccharide derivatives. Liu et al. also showed that the Fermentum β-polysaccharide extracted by different methods had 1,3-glycosidic bonds, and when the 1,3-glycosidic bonds were not broken, the
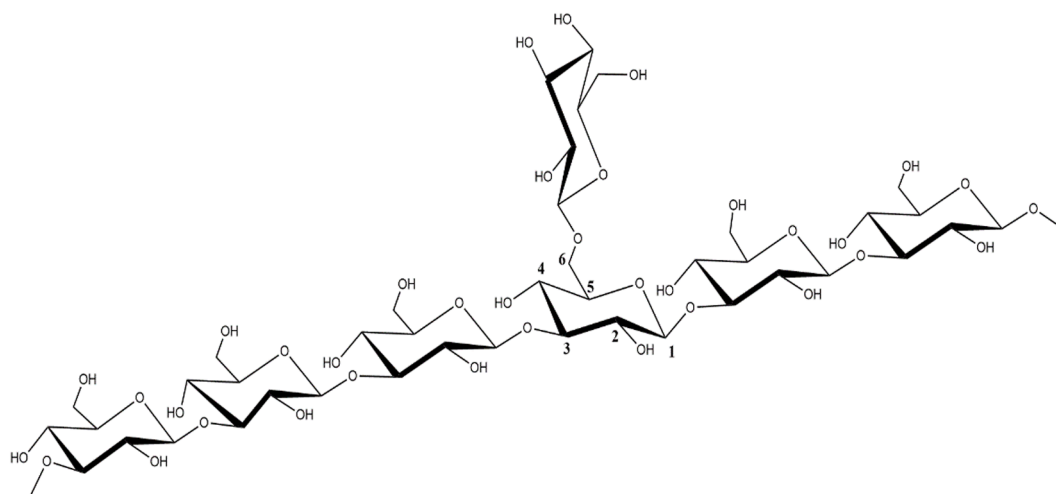

Fig. 2. Structure of Fermentum β-polysaccharide.

β-polysaccharide extracted by different methods had the same biological activity and the intensity of the activity did not differ much (Liu et al., 2016). It indicates that 1,3-glycosidic bonds dominate the biological activity of Fermentum β-polysaccharide. In another study, researchers found that polysaccharides with β-glycosidic bonds could remove about 80% of aflatoxin, and the main interaction between aflatoxin and β-polysaccharide could be obtained from the O—H bond and β-glycosidic bond of β-polysaccharide by infrared analysis (Mahmoud Amer et al., 2021). However, it is interesting to note that when all β-1,6-branched chains of Fermentum β-polysaccharide were chemically removed, Fermentum β-polysaccharide without branched chains showed little anticancer activity compared to Fermentum β-polysaccharide before treatment, suggesting that β-1,6-branched chains influence the anticancer activity of Fermentum β-polysaccharide. It has been reported that β-(1,6)-polysaccharides with high branching exhibit stronger inhibition of pro-inflammatory mediators such as NO/iNOS, IL-6, and IL-1β, effectively treating colonic mucosal damage. In contrast, the inhibitory effect of linear β-(1,3)-polysaccharide was not as strong (Sun et al., 2019).

The biological activity of Fermentum β-polysaccharide is related to its molecular size and chain conformation. However, the complex relationship between the higher structure, chain conformation and biological activity of Fermentum β-polysaccharide has not been well elucidated. Researchers have found that most antitumor polysaccharide main chain structures contain β-ᴅ-polysaccharide, and this is also true for Fermentum β-polysaccharide. The triple helix structure of Fermentum β-polysaccharide has higher antitumor activity than a single chain, and β-polysaccharide with a triple helix structure can significantly inhibit tumour growth without causing harm to the organism and has stronger antitumor activity (Du et al., 2019). Not only that, but Fermentum β-polysaccharide also has good antioxidant activity. The helical structure of Fermentum β-polysaccharide makes the overall β-polysaccharide more stable and less likely to be destroyed, speeding up the scavenging of free radicals. The helical structure is hydrophobic at one end, which helps to burst free radicals, thus improving the antioxidant properties (Iswarya et al., 2019). An experimental study showed that Fermentum β-1,3-polysaccharide (BYG) has a rod-like structure with natural triple chain bodies and nanoparticle-like substructures. Due to this advanced structure, BYG can improve inflammation in mice with colitis by inhibiting oxidative stress, and also balance the production of pro-inflammatory factors, resulting in enhanced immune activity in mice (Qiao et al., 2022). The triple helical structure of Fermentum β-polysaccharide is hydrophobic and hydrophilic, and it has chirality. Therefore, it can be well self-assembled into stable ordered structures. Not only that, the triple helix motif in the Fermentum β-polysaccharide carrier can track the encapsulation and release of drugs using circular dichroism, so it is often used as a drug carrier at present (Jin et al., 2020). Fermentum β-polysaccharide is well known to have immunostimulatory activity, but in fact, its activity is affected by the state of aggregation of Fermentum β-polysaccharide molecules, which can exert strong immunostimulatory activity if Fermentum β-polysaccharide maintains its triple helix structure and chiral state. β-polysaccharide nanoparticles exert immunostimulatory activity by activating macrophages to produce immune-enhancing cytokines (IL-1β, IL-6, TNF-α, IFN-γ). A non-specific physical uptake may occur when chiral Fermentum β-polysaccharide is used as a carrier loaded with other chiral drugs (adriamycin), allowing the drug to be encapsulated onto the carrier with a drug loading capacity of 13.9% to 38.2% (Huang et al., 2020). However, if the hydrophobic group of Fermentum β-polysaccharide is too much, it will affect the drug release and delivery, so structural modification can be considered to adjust the number of hydrophobic and hydrophilic groups on the Fermentum β-polysaccharide chain to enhance the target delivery effect.

From different experiments, we can learn that the introduction of active groups can change the conformation of Fermentum β-polysaccharide and enhance its biological activity, and the modified

Fermentum β-polysaccharide can be aggregated into triple helix conformation in solution, which has good water solubility and immunological activity, and is safe for human and animals in a wide range of doses and does not produce toxic effects, which generally proves the safety of Fermentum β-polysaccharide derivatives (Kagimura et al., 2015; Mei, Tang, Huang, Long, & Huang, 2020; Preece et al., 2021). It was reported that carboxymethylation modification could effectively improve the water solubility of Fermentum β-polysaccharide, which showed a partially helical conformation in an aqueous solution with an average molecular mass of 10^5 orders of magnitude after carboxymethylation modification. The carboxymethylated Fermentum β-polysaccharide has no cytotoxicity and genotoxicity (Ding, Wang, Xiong, Zhao, & Huang, 2013; Taubner et al., 2020; Wang et al., 2017). Therefore, some scholars applied it to the treatment of hypertension in mice, and they found that Fermentum β-polysaccharide modified by carboxymethylation could promote lower blood pressure and thus reduce myocardial hypertrophy. The mechanism of blood pressure-lowering lies in improving pressure reflex sensitivity by modulating sympathetic tone and possibly regulating renal function in mice to achieve a blood pressure-lowering effect (Bezerra et al., 2017; Bezerra et al., 2021). In addition, carboxymethylated Fermentum beta-polysaccharide was able to reduce the degree of oxidative damage in the body by significantly reducing malondialdehyde in men (Araújo et al., 2015). In the in vitro antioxidant test, it can also scavenge various free radicals very well. By comparison, it can be seen that the strength of the biological activity of carboxymethylated Fermentum β-polysaccharide largely depends on the degree of substitution (DS), and the antioxidant activity of carboxymethylated β-polysaccharide with a degree of substitution of 0.45 was 49.8%, while β-polysaccharide with a degree of substitution of 0.43 had only 34.1% antioxidant activity (Machová et al., 2014). Many sulfated polysaccharides have shown promising antitumor activity. The introduction of sulfate makes the modified Fermentum β-polysaccharide have a semi-flexible chain or rigid chain conformation, which has a stiffer chain conformation than before modification because sulfate esterification can promote the formation of intermolecular hydrogen bonds. (Calegari, Queiroz Santos, Barbosa-Dekker, Busso, Dekker, & Alves da Cunha, 2019). In a study, administration of sulfated Fermentum β-polysaccharide (sGSC) to chickens significantly increased IFN-γ and IL-6 concentrations and promoted lymphocyte proliferation; improved intestinal bifidobacteria and lactobacilli in the gastrointestinal tract of chickens, and effectively alleviated cyclophosphamide-induced immunosuppression (Wang et al., 2019). Although the biological activity of Fermentum β-polysaccharide can be improved by the introduction of different groups, the intensity of activity varies with the group. Tang et al. prepared six different Fermentum β-polysaccharide derivatives (sulfated, carboxymethylated, phosphorylated, carboxymethylated, phosphorylated, carboxymethylated sulfated and sulfated phosphorylated polysaccharide), and they determined the effects of these six substances on hydroxyl radicals, superoxide anions, reducing substances and lipid peroxidation. The comparison shows that phosphorylation has a better scavenging effect and exhibits stronger antioxidant properties (Tang et al., 2017).

The systematic study of the conformational relationship of Fermentum β-polysaccharide, which is the basis for the development of drugs and functional foods, has not yet made much progress, and therefore research in this area is of great importance and needs to be strengthened in the future.

Activity

Immunomodulatory activity

The human immune system is a defence network that covers the entire body and its most important task is to protect the body from viruses or bacteria. Immunity can be divided into specific and non-specific immunity. In recent years, many scholars have been studying the

immunomodulatory activity of β-polysaccharide. Currently, the immunomodulatory effect of β-polysaccharide on the body is mainly achieved in the following ways: by binding to receptors; regulating the expression of related genes, and acting through immune cell signalling.

Binding to receptors

It has been reported that the surface of human white blood cells has receptor sites for β-polysaccharide that are particularly well matched to the structural composition of β-polysaccharide. When beta-polysaccharide binds to the receptor, it activates white blood cells in a specific way to defend against invading organisms. Polysaccharides are normally hydrolyzed in the digestive tract to glucose, which provides energy to the organism. However, beta-polysaccharide is acid-resistant and therefore is not hydrolyzed and utilized as it passes through the gut. When beta-polysaccharide crosses the intestine, it is first recognized by specific cells in the gut. The non-specific immune process cannot be achieved without the recognition and phagocytosis of phagocytes. β-polysaccharide acts by binding to polysaccharide receptors on the surface of monocytes, macrophages, neutrophils and NK cells. When β-polysaccharide binds to cellular receptors, it produces prostaglandins or leukotrienes, among other immunomodulatory substances, and the body's non-specific immune function is then activated (Zheng, Huang, Kang, Liu, & Luo, 2021). Dectin-1 and CR3 are currently the most studied receptors and they open up a whole new field for the study of immune responses to β-polysaccharide immune recognition. Fermentum β-polysaccharide pattern recognition receptors and their functions are shown in Fig. 3 (Akkerman et al., 2020). Karumuthil-Melethil et al. investigated the role of the Dectin-1 receptor in the regulation of innate immune responses and found that the Dectin-1 receptor could regulate immunity through induction of innate regulation. When they treated pre-diabetic mice with low doses of β-polysaccharide, they found that the combination of the Dectin-1 receptor and β-polysaccharide resulted in the protection of pancreatic B cells from immune destruction and a significant reduction in IL-2 and TGF-b1 expression levels, protecting the mice from damage caused by type 1 diabetes (Karumuthil-Melethil et al., 2014). Macrophages are specialized white blood cells that consume invading cells to destroy pathogens. They are considered to be the "front-line fighters" of the body's immune system, but invasion by germs or viruses is likely to cause apoptosis of macrophages, resulting in impaired immunity. Fermentum β-polysaccharide can bind to the Dectin-1 receptor and down-regulate the cell death induced by the

invasion of macrophages by actinomycetes, ensuring the proper functioning of the body's immune system (Inoue et al., 2019). It was shown that both water-soluble and granular β-polysaccharides recognize the Dectin-1 receptor, but that granular β-polysaccharides bind to the Dectin-1 receptor to better trigger the production of pro-inflammatory cytokines. In a study, Pedro and colleagues assessed the difference in the response of the Dectin-1 receptor to water-soluble and granular β-polysaccharide and demonstrated that water-soluble β-polysaccharide did not promote the release of pro-inflammatory factors in vitro, regardless of the increase in concentration. In contrast, granular β-polysaccharide not only upregulated the expression of surface co-stimulatory molecules CD80 and CD86 in bovine monocytes but also caused a dose-dependent increase in the mRNA expression of IL-8, TNF, IL1B and IL6 in stimulated cells (Pedro et al., 2021). This further proves that Dectin-1 can combine with β-polysaccharide to induce the production of cytokines to achieve the purpose of regulating immune activity.

Regulation of cytokine expression

Ryan et al. used 49 newborn day-old piglets as experimental subjects and added Fermentum cell β-polysaccharide to a portion of the piglets' diets as a control group. Liver tissue from the control piglets was examined and it was found that cytokine responses in the liver were significant following lipopolysaccharide stimulation, cytokine IL-6 expression was significantly reduced and innate immunity was activated in the piglets' intestinal system. It is thus known that Fermentum β-polysaccharide can exert an immune effect by regulating the expression of cytokines. Unfortunately, it is still unknown whether this immune effect is exerted during or after the absorption of β-polysaccharide in the liver, or whether it is indirectly attributed to the alteration of the intestinal microbiota, which needs to be further investigated (Ryan et al., 2012). Natural killer cells (NK cells) are extremely important immune cells in the body, which are naturally occurring non-specific immune killer cells in the organism and play a crucial role in intracellular immune processes against parasitic infections, tumours and viruses, and have both immunomodulatory and cytotoxic functions. In an in vitro experiment to investigate how Fermentum β-polysaccharide activates porcine NK cells, the addition of β-polysaccharide to porcine NK cells triggered the release of cytokines TNF-α, IL-6 and IL-10 from peripheral blood mononuclear cells (Hermans et al., 2021). Increased NK cytotoxicity can mediate the killing of tumour cells and virus-
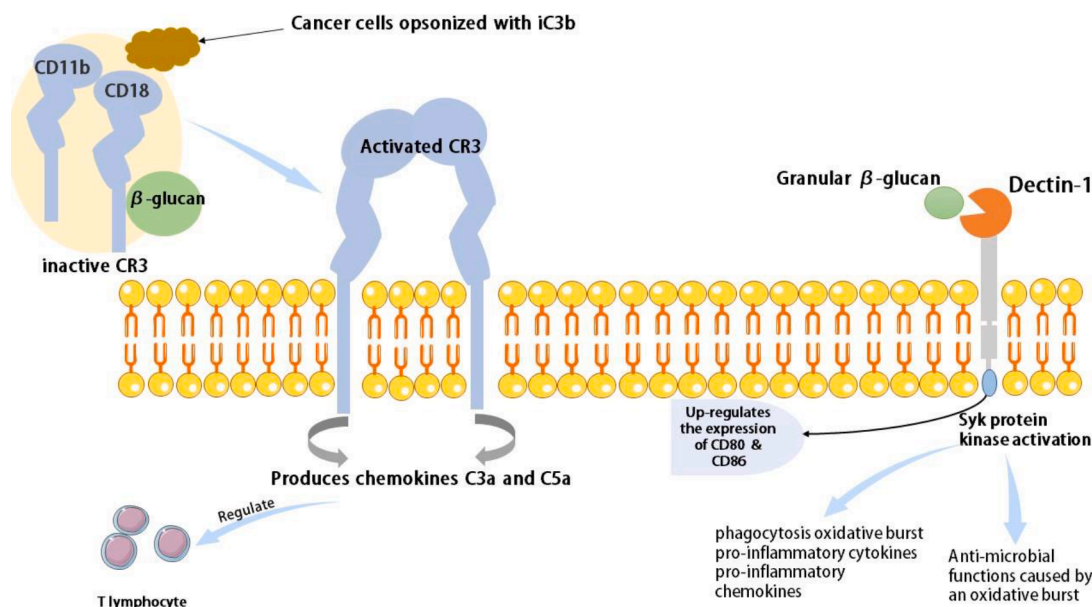

Fig. 3. Fermentum β-polysaccharide pattern recognition receptor and its effects (Brown & Gordon, 2005; De Marco Castro et al., 2021).

infected cells, thus enhancing the non-specific immune function of the body. Chen et al. used mice as a model to study the effect of β-poly-saccharide on cytokine secretion by mouse macrophages and lymphocytes. They extracted mouse macrophages and lymphocytes and treated them with 1,3-beta-polysaccharide and found that 1,3-beta-polysaccharide decreased the secretion of Th1 cytokines and increased the secretion of Th2 cytokines in the medium. In addition, 1,3-beta-polysaccharide increased the secretion of IL-10 and TGF-β in the medium (Chen et al., 2013). Unlike Fermentum β-polysaccharide, which exerts immunomodulatory effects through receptor recognition, granular Fermentum β-polysaccharide binds better to receptors, but water-soluble Fermentum β-polysaccharide better regulates the expression of immune factors and thus exerts immunomodulatory effects. Javmen et al. established in vivo and in vitro BALB/c mouse models to study the secretion of interferon IFN-γ. In the in vivo experiments, mice were orally administered a Fermentum β-polysaccharide preparation. The results showed that oral administration of β-polysaccharide from Fermentum enhanced IFN-γ production in an in vivo model of BALB/c mice. Notably, water-soluble β-polysaccharide enhanced the production of IFN-γ more effectively than granular β-polysaccharide. With increased secretion of IFN-γ, mice showed enhanced immunity and better resistance to viral and bacterial infections (Javmen et al., 2015). The normalization of cytokine production implies that β-polysaccharide can efficiently regulate the immune function of the body. Although many studies have been conducted to demonstrate the ability of β-polysaccharide to modulate cytokine expression and thus the immune function of the body, the underlying mechanisms remain unclear.

Immune cell signalling

Fermentum β-polysaccharide exerts immunomodulatory effects through immune cell signalling, which can be divided into three mitigating processes: receiving recognition signals, signalling processes and effect generation processes. Protein kinases are enzymes that catalyze the process of protein phosphorylation. ERK belongs to extracellular regulatory protein kinases, which include ERK1 and ERK2, and ERK is the key to transducing signals from surface receptors to the nucleus. Many other signalling pathways can be activated by apparent activation of the protein kinase ERK signalling pathway, and other signalling pathways can be activated by apparent activation of ERK. Cohen-Kedar et al. reported that in their previous work it was possible to infer indirectly that Fermentum β-polysaccharide affected cytokine secretion, but it was still unclear how Fermentum β-polysaccharide induced cytokine secretion. Therefore, they mixed ERK-specific inhibitors with human intestinal endothelial cells and then tested whether ERK affected Fermentum β-polysaccharide-induced cytokine secretion. The results showed that the ERK inhibitor caused a significant reduction in the level of cytokine secretion otherwise induced by β-polysaccharide. It can be seen that the ERK signalling pathway plays a role in the induction of cytokines by β-polysaccharide. From the experiments, it can be seen that in addition to ERK, a protein kinase, JNK and p38 were activated. The activation is evidenced by the phosphorylation of ERK, JNK and p38 MAPK when human intestinal endothelial cells are exposed to β-poly-saccharide, which is involved in cytokine secretion and reduces inflammation in the intestine (Cohen-Kedar et al., 2021). Of course, cell signalling is not restricted to protein kinase signalling pathways but can be mediated by activating Syk-dependent or Syk-independent signalling pathways. Immunohistochemical results showed that Syk was mainly distributed in the rumen mucosal epithelium of sheep, while the lamina propria and submucosa were not stained. The intracellular phosphorylation of Syk was significant after 15 min of treatment of sheep with Fermentum β-polysaccharide, and Syk was involved in β-poly-saccharide-induced β-defensin-1 expression in sheep (Zhang et al., 2019) Another study showed that Fermentum β-polysaccharide also activates the Myd88 regulator for signalling, which induces goat leukocytes to produce TNF-α and IL-10, activate phagocytes to engulf E. coli, and produce NO to destroy pathogens (Angulo et al., 2021) As mentioned

earlier, Fermentum β-polysaccharide can bind to specific receptors and exert immunostimulatory activity, but to achieve immunomodulatory effects, the receptor Dectin-1 requires signalling pathways that trigger NF-jB and Syk activation, and on the other hand, activation of the kinase Raf-1. These two signaling pathways converge at the level of NF-jB activation and regulation. β-polysaccharide binding to Dectin-1 triggers a series of intracellular signaling pathways through Syk kinase and Raf-1 signaling pathways, activating cells and inducing a variety of cellular responses, leading to immunomodulatory effects (Ding et al., 2015). Recently, it has been shown that Fermentum β-polysaccharide can affect intracytoplasmic free calcium ion concentration by promoting the inward flow of extracellular calcium ions and intracellular release of calcium ions to influence cell signalling. However, the specific mechanisms and effects of immunomodulation are still unknown and need to be further investigated.

Anti-radiation

The anti-radiation mechanism of Fermentum β-polysaccharide has three main aspects: Firstly, the main biological effect of radiation is the production of free radicals, which are electron-deficient predators that compete for electrons from normal cells everywhere in the body and directly attack the structure of nucleic acids and proteins and the antioxidant system in the body, thus causing damage. Fermentum β-poly-saccharide scavenges free radicals in the body, inhibits oxidative damage and protects macrophages from free radical attack both during and after being irradiated to continue to function normally. Secondly, radiation damages the blood and hematopoietic system, the immune system and so on, impairing the function of bone marrow hematopoietic stem cells and affecting the differentiation and maturation of red blood cells. Fermentum beta-polysaccharide protects the hematopoietic system, enhances the body's hematopoietic function and promotes the production of blood cells, thus improving immunity. Finally, the body is exposed to radiation that causes chromosomal abnormalities and damage. Fermentum β-polysaccharide can prevent and reduce chromosomal abnormalities or damage, inhibit apoptosis, repair damaged cells and help the body recover. Liu et al. examined the radiation protection effect of Fermentum β-polysaccharide in vivo after oral administration using mice as experimental subjects. They irradiated control mice with X-rays after continuous pretreatment with β-polysaccharide and then irradiated blank and control mice with a sublethal dose (6 Gy) of X-rays to observe their survival rate. Forty percent of the blank mice that were not fed β-polysaccharide died after 30 days of irradiation, but the control mice that were fed β-polysaccharide were still alive after 30 days. To study how β-polysaccharide reduces the mortality of mice, they compared the bone marrow hematopoietic cells of the two groups of mice and found that the hematopoietic stem cells of the two groups of mice were damaged after being irradiated by X-rays. Mice pretreated with Fermentum beta-polysaccharide had far fewer damaged hematopoietic cells than mice not pretreated with beta-polysaccharide. This is because β-polysaccharide can promote the proliferation of bone marrow cells and reduce the damage to hematopoietic cells, thus achieving the anti-radiation effect (Liu et al., 2018). This research has led to the development of oral anti-radiation agents.

Antioxidant

Scientific studies have shown that cancer, ageing and other diseases are mostly linked to the production of excess free radicals. Anti-oxidation is one of the most important functional claims in the market, as it can effectively overcome the harmful effects of these radicals (Mu et al., 2021; Zhou, Huang, & Huang, 2022; Tang & Huang, 2022; Lin & Huang, 2022; Tang & Huang, 2022; Li, Fan, Huang & Huang, 2022; Zhou & Huang, 2021). Khan et al. used free radical scavenging capacity and ferric reducing antioxidant capacity as indicators to assess the antioxidant activity of Fermentum β-polysaccharide and found that

Fermentum β-polysaccharide had good antioxidant activity and the lower the molecular weight, the better the antioxidant capacity (Khan et al., 2016). Lei et al. reported that Fermentum β-polysaccharide showed good reactive oxygen species (ROS) scavenging activity in vitro and that both high and low molecular weight Fermentum β-polysaccharide were able to scavenge 1,1-diphenyl-2-picolinic acid hydrazide (DPPH), superoxide and hydroxyl radicals in mice (Lei et al., 2015). Oxidative stress refers to a state of imbalance between oxidation and antioxidant action in the body, a negative effect produced by free radicals in the body, which leads to inflammatory infiltration of neutrophils, increased secretion of proteases and the production of large amounts of oxidative intermediates. Oxidative stress is an important factor in causing ageing and disease in humans (Kudryavtseva et al., 2016). Iswarya et al. reported on their assessment of the antioxidant properties of brewer's Fermentum β-polysaccharide. It was also investigated how the β-polysaccharide recognition protein interacted with the antioxidant molecules of Fermentum cells. They found that Fermentum β-polysaccharide was effective in scavenging DPPH free radicals and hydrogen peroxide activity and found that Fermentum β-polysaccharide could scavenge 73% of free radicals. The percentage of scavenging activity was close to that of ascorbic acid. It was also effective in scavenging peroxyl radicals generated by ABTS, achieving 82% scavenging at a concentration of 100 µg/mL (Iswarya, Anjugam, Shanthini, & Vaseeharan, 2019). Tang et al. tested the reducing ability of Fermentum β-polysaccharide and found that it had a good reducing ability, scavenged hydroxyl radicals up to 67.59% and had a significant anti-lipid peroxidation effect (Tang, Huang, Zhao, Zhou, Huang, & Li, 2017). Yu et al. investigated the molecular mechanism of β-polysaccharide antioxidants and examined the expression levels of three proteins, Dectin-1, Nrf2 and HO-1. They found that Fermentum β-polysaccharide significantly increased the expression levels of proteins inhibited by LPS and that β-polysaccharide down-regulated ROS production through the Dectin-1/Nrf2/HO-1 signalling pathway, thereby achieving antioxidant effects and reducing damage to the body (Yu et al., 2021). These results indicate that Fermentum β-polysaccharide has excellent antioxidant activity and can be prepared as an antioxidant to mitigate the harmful effects of oxidative stress. However, more attention needs to be paid to the practical application and safety of antioxidants, as internal antioxidants are more effective than external ones, and to make Fermentum β-polysaccharide into an antioxidant, it is necessary to consider not only the antioxidant activity but also the safety and non-toxicity. This is an issue that deserves in-depth study.

In general, the antioxidant mechanisms of Fermentum β-polysaccharide can be roughly divided into three categories. First, it is more common to eliminate free radicals directly or indirectly. For example, it can directly scavenge hydroxyl radicals, superoxide anion radicals and DPPH, or enhance the activity of SOD, because SOD is an antioxidant metalloenzyme, which can catalyze the disproportionation of superoxide anion radicals to generate oxygen and hydrogen peroxide. Maintain the balance of free radicals in the body and avoid the occurrence of diseases (Çetin, 2019; Kim et al., 2014). Second, alleviating oxidative damage by regulating major signalling pathways, such as regulating the expression of inflammatory factor genes in the body or cells by regulating the inflammatory response signalling (NF-κB) pathway, and regulating the accumulation of NRF1 signalling can inhibit ROS-mediated apoptosis. Activation of the MAPK signalling pathway activates Nrf2 to induce the expression of the HO-1 (heme oxygenase) gene. Finally, in addition to the above-mentioned signalling pathways, there are still other ways to inhibit oxidative stress damage, for example, antioxidation can be achieved by regulating the expression of some related proteins.

Anti-tumour

From the International Agency for Research on Cancer (IARC) Global Cancer Statistics 2020 report released in January 2021, we know that cancer remains a major public health problem worldwide and that cancer incidence and mortality rates continue to rise (Sung et al., 2021). Wang et al. found that water-soluble Fermentum β-D-polysaccharide (WSG) is a novel inhibitor of autophagy and significantly inhibited the proliferation, metabolism and tumour growth of hepatocellular carcinoma cells when WSG was ingested by humans. the inhibitory effect of WSG on hepatocellular carcinoma cells increased with increasing dose. Through further studies, they found that WSG inhibited autophagic degradation by increasing lysosomal pH and inhibiting histone protease (Cathepsin B and D) activity in the lysosome. More importantly, WSG as a single drug showed significant antitumor effects in both a xenograft mouse subcutaneous tumorigenesis model and a diethylnitrosamine/CTC-induced primary liver cancer model with subcutaneous tumorigenesis, with no significant toxic side effects (Wang et al., 2020). This study provides a theoretical basis for the safe and successful clinical use of autophagy inhibitors, which may become a new idea for tumour treatment in the future when adjuvant autophagy-inhibiting drugs are used in conjunction with chemotherapy and low-dose radiation therapy. In addition to targeting autophagy and lysosomes for cancer treatment, Mo et al. found that S180 tumour cells in mice treated with $(1 \rightarrow 3)$-β-polysaccharide showed significant apoptotic features, and there were no abnormalities in the physical function of the mice when they were fed with $(1 \rightarrow 3)$-β-polysaccharide for 16 days. This indicates that $(1 \rightarrow 3)$-β-polysaccharide is not toxic. Treatment of tumour-bearing mice with different doses of $(1 \rightarrow 3)$-β-polysaccharide showed that the anti-tumour activity of the high dose of $(1 \rightarrow 3)$-β-polysaccharide was higher than that of the low dose, with a tumour inhibition rate of 27.9%. Comparing the proportion of apoptotic cells in the experimental group with that in the control group, it was found that $(1 \rightarrow 3)$-β-polysaccharide had a significant apoptosis-inducing effect on S180 tumour-bearing cells (Mo et al., 2017). In analyzing the anti-tumour mechanism of Fermentum β-polysaccharide, we found that it can exert anti-tumour effects by enhancing the immune function of the body. Tumour-associated macrophages (TAMs) are involved in regulating the tumour microenvironment and can polarize into M1 and M2 types after microenvironmental changes or TAM stimulation by specific signals. After stimulation with Fermentum β-polysaccharide, the secretion of cytokines such as IL-6, TNF-α and IL-10 is significantly increased, inhibiting melanoma growth (de Graaff et al., 2021). Appropriate activation of the immune response is beneficial in suppressing tumour growth, but excessive activation of the immune system is likely to be counterproductive, triggering a corresponding inflammatory response and allowing cancer recurrence. Interestingly, however, Fermentum β-polysaccharide has a bidirectional modulatory effect on the immune response. While enhancing phagocytosis, lipopolysaccharide can be used to activate phagocytes, resulting in less secretion of pro-inflammatory factors by phagocytes and avoiding infection due to immune over-activation during cancer treatment. The immune organs are organs dominated by lymphoid tissue, among which the central immune organs are the sites of differentiation and maturation of immune cells and the peripheral immune organs are the sites of settlement of mature T and B cells, the expression of whose relevant indices play an important role in the anti-tumour process. Therefore, enhancing the immune function of the body is very important for anti-tumour. More than 20 years ago, bone marrow-derived suppressor cells (MDSCs) were identified in cancer patients, and extensive evidence demonstrated their function in negatively regulating the immune response in cancer and other diseases. MDSCs exert immunosuppressive functions through various pathways and mechanisms and can suppress lymphocytes by expressing Arg-1 and iNOS and producing ROS, etc. They can also induce Treg production to indirectly suppress the body's immune response (Albeituni et al., 2016). Clinical trials are a key engine for the discovery and development of new therapies, and they are the cornerstone for providing objective and evidence-based answers to the most important questions. Also, clinical trials can determine the safety of new drugs. To determine the safety of Fermentum-derived β-polysaccharide for the treatment of patients with

relapsed or refractory high-risk neuroblastoma, Cardenas et al. made Fermentum β-polysaccharide into an oral drug, and 44 patients had varying degrees of relief from tumour symptoms after 141 cycles of the drug (Cardenas et al., 2021). This is certainly good news for the widespread use of Fermentum β-polysaccharide-related drugs in the future. Targeted drugs are the product of the development of the integration of biotechnology and information technology. Because of their high specificity, less toxic side effects and remarkable efficacy against a variety of malignant tumours, they have become the mainstream new antitumours in the last decade. Although Fermentum β-polysaccharide is known to have good antitumour activity, it remains to be studied whether Fermentum β-polysaccharide can be used as a targeted drug to effectively treat malignant tumours.

Lowering blood sugar and blood lipids

With the worsening global obesity and diabetes situation, and the side effects of long-term chemical drugs, how to balance blood glucose and lipid-lowering and reduce the side effects of drugs has become an issue of concern. Fermentum β-polysaccharide, as a polysaccharide with multiple biological activities and is easy to obtain, is expected by many researchers to be applied to hypoglycemia and hypolipidemia treatment. Ikewaki et al. found that the mortality rate of patients with diabetes mellitus increased significantly after infection with the novel coronavirus. However, β-polysaccharide extracted from black Fermentum could control blood glucose levels in human subjects. In addition, β-polysaccharide can enhance the immunity of the subjects and downregulate the inflammatory factors that cause cytokine storm, thus reducing morbidity and mortality (Ikewaki et al., 2020). Ferreira et al. prepared Fermentum β-polysaccharide at a concentration of 0.1% as a dietary supplement to test its effects on insulin, serum triglycerides, cholesterol, inflammatory cytokines and markers of satiety in obese dogs. They found that Fermentum β-polysaccharide at a concentration of 0.1% could reduce these indicators in obese dogs, maintain blood glucose stability, and restore obese dogs to the same level as ordinary lean dogs (Ferreira et al., 2022). Blood glucose levels rise after a meal because the food consumed is converted into glucose, which can cause a decrease in insulin sensitivity in diabetics, leading to serious complications and aggravation of the disease. Enzymes in the human intestine, such as α-glucosidase, play an important role in digestion and absorption. α-glucosidase is considered to be a clinical therapeutic target for regulating postprandial hyperglycemia. Therefore, relevant drugs can lower postprandial blood glucose levels by inhibiting α-glucosidase activity, thus preventing and treating diabetes and its complications, which is the more common mechanism for lowering blood glucose. However, in one study, researchers found that obese mice had significantly lower blood glucose levels after being injected with Fermentum β-polysaccharide. To further investigate the hypoglycemic mechanism of Fermentum beta-polysaccharide, they studied the liver tissue of mice. They found that Fermentum β-polysaccharide promoted hepatic glycogen formation and inhibited lipid accumulation in the liver. Unlike common hypoglycemic mechanisms, Fermentum β-polysaccharide does not act as an appetite suppressant or an α-glucosidase inhibitor in the hypoglycemic process, but by reducing the expression of glucose transport proteins in the intestinal mucosa of diseased mice, which reduces the absorption of glucose into the intestinal tract, thus achieving hypoglycemia (Cao et al., 2016). It has been reported that Fermentum β-polysaccharide forms a gel-like barrier in the intestinal lumen after entering the intestine of rats, which hinders intestinal absorption and reduces intestinal lipid absorption in favour of promoting the formation of bile salts in the liver from excess cholesterol, which in turn leads to a reduction in total cholesterol and low-density lipoprotein (LDL-C) concentrations in the blood, effectively improving metabolic parameters in type II diabetic rats (Andrade et al., 2016). In a study, it was also reported that Fermentum β-polysaccharide induced changes in viscosity in the intestinal environment, resulting in reduced lipid absorption and

decreased cholesterol capture in the intestine. However, even though total cholesterol levels were reduced, consumption of Fermentum β-polysaccharide did not change LDL-C, very low-density lipoprotein (VLDL-C) and high-density lipoprotein (HDL-C) levels (de Araújo et al., 2017). Interestingly, in another study, researchers found that Fermentum β-polysaccharide ingested by rats adsorbed bile salts and that cholesterol and LDL-C in the rats' livers were reduced as a result. These reductions occurred at a minimum dose of 10 mg/kg. The reason for the reduction in LDL-C in this study is that the reduction in cholesterol in rats was able to regulate the synthesis of LDL-C receptors and the subsequently increased uptake of LDL-C by the liver. Subsequently, the gut negatively regulates 3′-hydroxy 3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the enzyme responsible for cholesterol synthesis, through fermentation and production of SCFA (de Sales Guilarducci et al., 2020). It is notable that the irradiated degraded β-polysaccharide, whose molecular weight became 11 to 48 kDa, had a stronger effect in reducing blood lipids and blood glucose in mice, with a significant decrease in all indicators. Among them, irradiated β-polysaccharide with a molecular weight of about 25 kDa showed the strongest reduction in all tested indicators (47.2% in total cholesterol, 45.7% in LDL cholesterol and 45.5% in triglycerides) (Long et al., 2019). Therefore, the use of Fermentum β-polysaccharide with a lower molecular weight should be considered among relevant treatments. Fermentum β-polysaccharide with a lower molecular weight might be more easily ingested and then inhibit cholesterol in the liver. Unfortunately, among these studies, there are very few detailed reports on the modulation of HDL-C and non-HDL-C by Fermentum β-polysaccharide, which plays an important role in the prevention and control of atheromatous plaque formation and the transport of cholesterol out of the plaque (cholesterol reversal transport). In lipid-lowering therapy, LDL-C is used as a primary indicator and non-HDL-C as a secondary indicator. However, in patients with combined diabetes, metabolic syndrome, obesity and high TG, non-HDL-C is the primary target (Ganesh et al., 2014; Kusmiati & Dhewantara, 2016). Hence, an in-depth study of the hypoglycemic and hypolipidemic mechanisms associated with Fermentum β-polysaccharide is necessary.

Anti-inflammatory

Cytokines are mediators of cellular interactions and play an important role in developing and maintaining inflammation. Th1 immune response is an immune response generated by Th1 cells against intracellular microorganisms such as bacteria and viruses, which is proinflammatory and can lead to cell-mediated immunity. The polarizing cytokine IL-12 is responsible for triggering the Th1 immune response by activating Th1 cells. In addition, activated Th1 cells secrete cytokines such as interferon-gamma (IFN-γ) and interleukin-2 (IL-2). Th2 immune response is an immune response produced by Th2 cells against extracellular microorganisms. The polarizing cytokines IL-4 and IL-2 trigger the Th2 immune response by activating Th2 cells. Fermentum β-1,3-polysaccharide effectively stimulates Th1 cells to reduce the secretion of cytokines IFN-γ and IL-2, but promotes increased expression of Th2 cytokines IL-4, IL-5, IL-9, and consequently increased secretion of anti-inflammatory factors IL-10 and TGF-β (Cao et al., 2018; Chen et al., 2013). To test the actual anti-inflammatory activity of Fermentum beta-polysaccharide, Mosikanon et al. conducted a clinical trial in humans in which 44 obese participants were given either oral Fermentum β-polysaccharide capsules or a placebo for six weeks, and their blood pressure and waist circumference decreased after six weeks (Mosikanon et al., 2017). The anti-inflammatory activity of Fermentum β-1,3-polysaccharide has been further demonstrated in one study. It was reported that the effect of treating inflammation in mice with purified Fermentum polysaccharide with β-1,3-polysaccharide removed was greatly reduced, and only by treating mice with β-1,3-polysaccharide was the expression of Th1 cells in mice inhibited and the anti-inflammatory response promoted, and murine colitis and experimental autoimmune

encephalomyelitis were effectively treated (Lee et al., 2021). Of course, Fermentum β-1,3-polysaccharide interferes with the damage caused by inflammation to the body by regulating the expression of anti-inflammatory/pro-inflammatory cytokines is only one way to interfere with inflammation, but also by modulating signaling pathways. It has been reported that β-polysaccharide can attenuate LPS-activated inflammatory responses by inhibiting the phosphorylation of mitogen-activated protein kinase (MAPK). On the other hand, β-polysaccharide increased NF-κB activity in RAW264.7 cells, and β-polysaccharide was also able to compete with LPS for binding sites on the TLR-4 receptor, thereby attenuating its effect (Xu et al., 2012). The anti-inflammatory mechanism of Fermentum β-polysaccharide is more complex, and over the past decade, numerous clinical studies have shown that inflammation alters intestinal microbes and their metabolites. In turn, the affected gut, as well as gut microbes, stimulate immune response and metabolic activity, which leads to chronic inflammation and eventually evolves into a chronic disease, so regulating gut flora is one of the ways to suppress inflammation (Chen et al., 2021). Rehman et al. found that feeding zebrafish with Fermentum β-polysaccharide altered the diversity and composition of the zebrafish gut microbiota significantly reduced the width of the intrinsic layer of the zebrafish gut, and led to a reduction in inflammation in zebrafish (Rehman et al., 2021). Relevant studies have proved that long-term oral administration of Fermentum β-polysaccharide is beneficial to increasing beneficial flora, reducing harmful flora (such as enterohemorrhagic Escherichia coli), increasing the production of short-chain fatty acids (SCFA), and preventing colitis (Gudi et al., 2020). Furthermore, Fermentum β-polysaccharide can improve intestinal permeability and structural integrity of tight junctions, enhance the mucous membrane of intestinal epithelial cells against foreign pathogenic factors, build a barrier function, and have a significant reduction effect on inflammatory reactions caused by intestinal wall destruction (Carballo et al., 2019). However, the anti-inflammatory effect of regulating the gastrointestinal flora is a comprehensive effect of multiple targets and multiple pathways, so the anti-inflammatory activity of Fermentum β-polysaccharide remains to be further explored. It is worth noting that if the patient is receiving antibiotics and taking Fermentum beta-polysaccharide at the same time, it is likely to exacerbate the condition of colitis rather than improve it. Therefore, further research is needed to reveal the potential mechanism of Fermentum β-polysaccharide in the treatment of colitis and the regulation of intestinal flora.

Regulate intestinal flora and improve intestinal health

The human gut hosts 10 trillion bacteria that can affect human weight and digestion, defend against infection and the risk of autoimmune disease, and control the body's response to cancer treatment drugs (Hills et al., 2019). Polysaccharides may suppress inflammation or reduce the risk of disease by modulating intestinal flora, protecting the intestinal mucosa, and increasing the content of short-chain fatty acids. The regulation of Fermentum β-polysaccharide in the gut is shown in Fig. 4. So et al. demonstrated that 2% of granulated Fermentum β-polysaccharide induced changes in the intestinal microbial community. Among them, gallbladder bacteria are closely related to the formation of obesity, and Fermentum β-polysaccharide could significantly reduce the abundance of gallbladder bacteria. In addition to reducing obesity-related gallbladder bacteria, Fermentum β-polysaccharide also increased the abundance of liver Cyp7a1 mRNA and bile acid synthesis, effectively alleviating obesity-related diseases in obese mice (So et al., 2021). According to another study, Fermentum β-polysaccharide significantly inhibited the high expression of SGLT-1, a major glucose transporter protein in the small intestinal mucosa. A high-fat diet (HFD) causes more thick-walled bacteria to be produced in the mouse intestine and reduces the production of anthropoid bacteria, and the same situation exists in the human intestine. However, oral administration of Fermentum β-polysaccharide to mice significantly reduced the relative abundance of thick-walled bacteria, increasing the beneficial intestinal flora of mice, which exhibited good hypoglycemic activity (Cao et al., 2016). Chen et al. also reported that Fermentum β-polysaccharide treatment significantly ameliorated HFD-induced metabolic syndrome in mice. The mechanism of action is that Fermentum β-polysaccharide modulates the diversity and composition of the HFD-induced intestinal microbiota, decreases the relative abundance of Lactobacillus and Lactococcus, which are significantly positively associated with metabolic changes, and subsequently reduces plasma pro-inflammatory cytokines (including IL-6 and IL-1β), alleviating the metabolic syndrome in mice (Chen et al., 2021) (see Fig. 5).

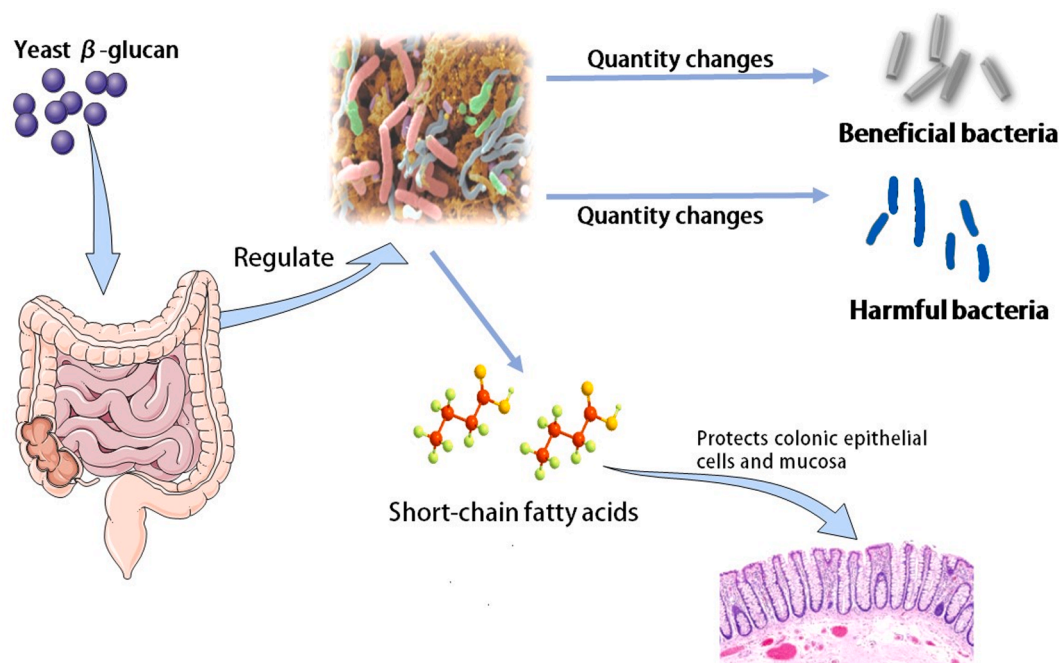However, different polysaccharides can promote the growth of

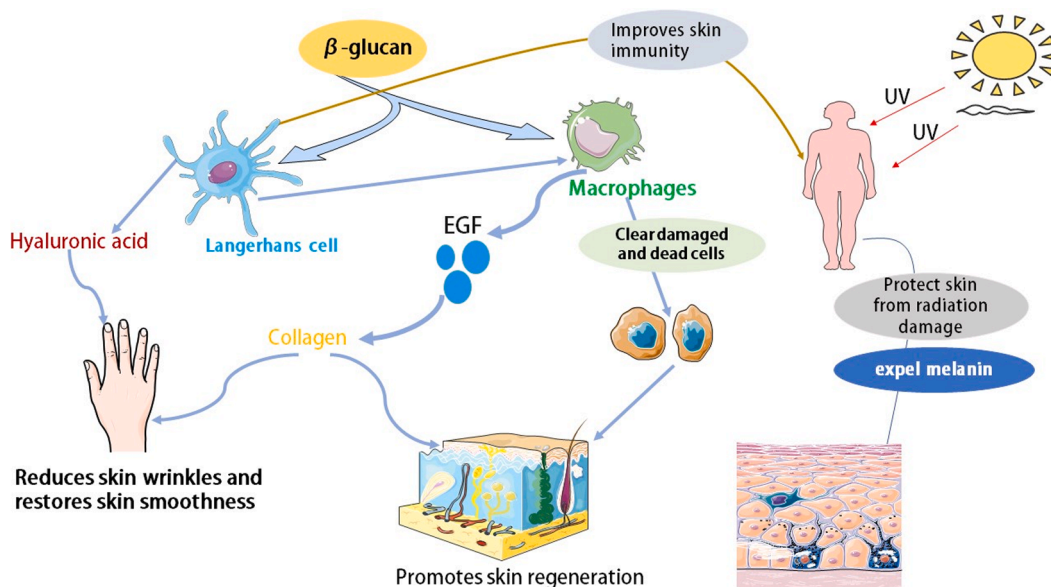**Fig. 4.** Intestinal regulation of Fermentum β-polysaccharide.

Fig. 5. The protective mechanism of Fermentum β-polysaccharide on skin.

different intestinal flora, which is related to the structure of poly-saccharides themselves (Cui et al., 2021). In a study by Reyes-Becerril et al. they extracted a (1–3)-β-ᴅ-polysaccharide containing (1–6)-branched chains from Fermentum. When this low molecular weight β-configuration polysaccharide (689.351 kDa) acts on the fish intestine, it causes the production of a large number of cupped cell vacuoles in the fish intestine, which in turn improves the intestinal barrier function, stimulates the production of intestinal immune cells, reduces the toxicity caused by harmful bacteria (H. pylori) and promotes the production of beneficial flora (Reyes-Becerril, Angulo, Sanchez, Guluarte, & Angulo, 2020). The structure of polysaccharides affects their function in regulating various intestinal microflora, and it is known from the present study that most of the Fermentum polysaccharides that can regulate intestinal flora are linked by (1 → 3) glycosidic bonds. However, the relationship between the structure of β-polysaccharide and the regulation of intestinal flora needs to be further investigated.

Fermentum β-polysaccharide can regulate the balance of intestinal flora, but Fermentum β,-polysaccharide is difficult to be digested, and this is when intestinal flora plays an important role. The intestinal flora can promote Fermentum β-polysaccharide metabolism, and Fermentum β-polysaccharide will be broken down into some short-chain fatty acids by the intestinal flora. Short-chain fatty acids are not only an important source of energy for the body, but they also protect the intestinal epithelium, regulate the body's immune response, and have a therapeutic effect on inflammatory reactions. In a study in which researchers used mice and suckling pigs as test models, the addition of Fermentum β-polysaccharide increased Lactobacillus counts and butyric acid (the major short-chain fatty acid) as observed in a split-white fermentation test (P < 0.05). In the pure culture growth assay, Lactobacillus plantarPlantarumbacillus roxellanae and L. thermophiles were increased and Salmonella typhimurium was decreased. The generated butyrate, a histone deacetylase inhibitor, interfered with the expression of pro-inflammatory cytokines in mice and suckling pigs, reducing inflammation in suckling pigs and promoting the maintenance of a healthy gut (Venardou et al., 2021). Xu et al. found that injection of Fermentum β-polysaccharide improved neuroinflammation and brain insulin resistance. The underlying reason is that Fermentum β-polysaccharide restores intestinal flora balance in mice, enriches beneficial bacteria and reduces pathogenic bacteria associated with neuroinflammation, and increases short-chain fatty acids (propionate) in the intestine of mice. Short-chain fatty acids are associated with brain function and can affect the gut-brain axis, which in turn affects cognitive performance. Propionate avoids Alzheimer's disease by interfering with beta-amyloid production of protein interactions and disrupting its assembly into neurotoxic oligomers (Xu et al., 2020). In addition, Fermentum β-polysaccharide can alter the expression of tight junction proteins by activating AMP-activated protein kinase (AMPK) after increasing the abundance of short-chain fatty acids, thus enhancing intestinal barrier function and reducing intestinal inflammation, thereby maintaining the integrity of the intestine (Dalile et al., 2019). Current studies related to the effects of Fermentum β-polysaccharide broken down into short-chain fatty acids on the brain-gut axis are mainly based on animal studies and lack evidence from human trials, so more human trials are needed to prove its usefulness. Many reports suggest that Fermentum β-polysaccharide may be a novel dietary supplement to modulate gut microbiota and improve memory dysfunction due to infection and cognitive deficits due to diabetes, but these are not more direct evidence and may be further validated by studying faecal mfaecaliota transplantation and insulin signaling pathway inhibitors.

Other activities

Studying the relevant activities of Fermentum β-polysaccharide can provide a reference for the industrial exploitation of Fermentum β-polysaccharide resources. In addition to the relevant activities mentioned above, Fermentum β-polysaccharide also has additional activities. Valasques et al. evaluated the analgesic effect of Fermentum β-polysaccharide using the acetic acid twist test, formalin test, and tail immersion test. They found that β-polysaccharide extracted from red Fermentum does not block painful neurotransmission like morphine and that the mechanism of analgesia is to elicit a peripheral anti-inoculation response (Valasques Junior et al., 2014). Haider et al. reported that β-polysaccharide can interact with the central cholinergic system. They treated male rats with β-polysaccharide and found that Fermentum β-polysaccharide had a very high affinity for the active site of acetylcholinesterase and that the hippocampus of the rats showed a dose-dependent inhibition of the AChE enzyme during the treatment. Therefore, it can be concluded that β-polysaccharide can enhance central cholinergic tone by inhibiting the AChE enzyme (Haider et al., 2016).

Applications

Vaccine engineering

With the development of molecular genetics and molecular biotechnology, the genome sequence of Fermentum has been completely determined and many expression vectors related to Fermentum have been developed. Currently, there are not many technical barriers to the systematic application of Fermentum in the development of viral vaccines. Moreover, Fermentum has great advantages over bacteria as a delivery vehicle for oral vaccines. First, Fermentum does not produce endotoxin, does not contain specific viruses, and is not invasive to the intestinal tract. Secondly, Fermentum can interact with intestinal epithelial cells and induce a mucosal immune response in the body. Finally, the Fermentum itself is a high-quality source of nutrition. Vaccines produced with Fermentum cells are called recombinant Fermentum vaccines, and recombinant Fermentum vaccines have been used for a long time to prevent hepatitis B virus (HBV) and human papillomavirus (HPV) (Khan & Noordin, 2019). Liu et al. designed an antigen delivery system formed by combining aluminium salts and Fermentum β-polysaccharide particles, and the hepatitis B vaccine prepared from these aluminium salts and Fermentum β-polysaccharide particles was able to promote antigen cross-presentation after subcutaneous injection, with excellent targeting ability. In addition, the vaccine strongly induces dendritic cell (DC) maturation and cytokine secretion, resulting in a strong humoral and cellular immune response to hepatitis B antigens (Liu, H. et al., 2021). Eukaryotic Fermentum cells are low-level biological cells. Therefore, the advantages of recombinant Fermentum vaccines are that the production system is simple to operate, has high expression and strong targeting, and can be used for large-scale industrial production, especially for the production of veterinary oral vaccines (Tipper & Szomolanyi-Tsuda, 2016). The "whole Fermentum vaccine" approach does not require complex and expensive downstream protein purification steps and is certainly a powerful aid in the treatment of several chronic infections and cancers.

Rodríguez et al. tested whether β-polysaccharide enhances the adaptive immune response to vaccines in salmon by adding Fermentum β-polysaccharide vaccine to their diet. They found that diets supplemented with β-polysaccharide vaccine increased the transcript levels of key genes associated with the innate and adaptive immune response in salmon, leading to an enhanced response to the model vaccine (Rodríguez et al., 2016). Berner et al. reported that a vaccine conjugate made from Fermentum β-polysaccharide and ovalbumin was able to activate CD4 + and CD8 + antigen-specific T cells in vitro, increasing the number of these T cells. The vaccine conjugate also resulted in increased cross-presentation of CD8 + cytotoxic T cells by bone marrow-derived dendritic cells, demonstrating the potential of β-polysaccharide as a vaccine adjuvant (Berner et al., 2015). Jha et al. used a Fermentum system to express VP19 and VP28 proteins of shrimp white spot syndrome virus (WSSV) and fed the whole recombinant Fermentum vaccine with feed to crayfish for 25 days. The results showed that the survival rate of the crayfish fed the whole recombinant Fermentum vaccine was significantly higher than that of the control group, indicating the feasibility of developing an oral vaccine using the recombinant proteins reVP19Y and reVP28Y expressed in Fermentum (Jha et al., 2007). Aouadi designed β-polysaccharide encapsulated siRNA particles (GeRPs), which are simply purified RNA placed in porous hollow β-polysaccharide shells, to be used as effective oral vaccine delivery vehicles. GeRPs have been tested by feeding mice with GeRPs and be effective in silencing genes in mouse macrophages both in vitro and in vivo, protecting mice from lipopolysaccharide-induced injury (Aouadi et al., 2009), this is undoubtedly a discovery for the protection of humans from inflammation. Of course, the current theory about the mechanism of immunomodulation stimulated by oral Fermentum β-polysaccharide vaccine is still incomplete, and Fermentum β-polysaccharide still lacks a large number of human clinical experiments to prove, researchers still need to conduct

is in-depth exploration, and the differences of vaccines for different individuals also need further experiments and thinking, but the powerful utility of Fermentum cell wall β-polysaccharide as a vaccine adjuvant predicts that full recombinant Fermentum vaccines and Fermentum surface display vaccines for direct oral immunization will gradually be widely used. Fermentum β-polysaccharide as a novel vaccine antigen adjuvant delivery system has a high potential to improve vaccine efficacy and reduce antigenic agents. Its utility in the subcutaneous delivery of purified antigens is well established. However, parenteral vaccination often fails to generate the effective mucosal immune responses required to fight common intestinal (and other mucosal) infections, and the development of effective oral vaccination routes would be a major advance, especially in developing countries.

Skincare

Many skincare products are now added with the Fermentum β-polysaccharide. Fermentum β-polysaccharide is favoured by many cosmetic manufacturers for its ability to help reduce skin irritation, effectively reduce wrinkles, improve skin hydration and smoothness, promote scar healing and regeneration, etc. Fermentum β-polysaccharide has a spiral structure that is extremely insoluble in water, so the Fermentum β-polysaccharide that was first used in cosmetics was a water-insoluble solid particle, a structure suitable for use in wound healing (Cao et al., 2021). In the human skin, there are dendritic cells called Langerhans cells, which are mainly located in the upper-middle layer of the epidermis. These cells play an important role in skin immunity by interacting with Fermentum β-polysaccharide to activate the immune response (Liu, X. et al., 2021). When Fermentum β-polysaccharide enters the body, it interacts with Langerhans cells and activates macrophages to produce epidermal cell growth factor. As the epidermal cell growth factor increases, the skin gradually produces collagen, which is important for maintaining the integrity of the skin, and the increase in collagen means that fine wrinkles on the skin can disappear as well.

Fermentum β-polysaccharide is beneficial in the treatment and prevention of atopic dermatitis, in addition to addressing people's normal maintenance needs. Kim et al. used mice that had exhibited signs of dermatitis as subjects and fed them a dose of Fermentum β-polysaccharide. After one cycle, vasodilation in the skin of the mice was significantly reduced, and dermatitis symptoms such as pruritus and oedema that had previously been present in the skin of the mice were also alleviated (Kim et al., 2019). Melanoma is a neoplastic disease that occurs mostly in the skin, but can also be seen in the mucous membranes and internal organs. However, the cause of melanoma is not fully understood and is thought to be multifactorial, such as race and genetics, trauma and irritation, sunlight, immunity, etc. Eom et al. used an ultrasound-assisted alkaline method to extract β-polysaccharide from Fermentum for the treatment of mice with melanoma. The proliferation of melanoma cells in the mice treated with Fermentum β-polysaccharide was reduced compared to the untreated group, and the tendency to increase tumour volume was significantly reduced in the treated mice. The reduction in tumour size started to occur 2 days after treatment, with a very significant effect on day 6 of treatment (Eom et al., 2021). In recent years, the incidence and mortality rate of malignant melanoma has increased each year, with a lower age of death compared to other solid tumours. There is still a lack of specific treatment for malignant melanoma other than early surgical excision as a method. Therefore, early diagnosis and treatment are very important. Research has shown that Fermentum β-polysaccharide is a promising option for the prevention and treatment of melanoma. Because of its immunomodulatory activity, Fermentum beta-polysaccharide can improve the body's immune system and prevent the development of melanoma due to external stimuli and can also be used to treat melanoma when it occurs.

Wound repair is a dynamic process, and if treated with a dressing, the dressing has to provide a good environment for wound repair. During

the repair process, it is mainly cytokines that regulate the proliferation and differentiation of relevant cells. Among them, macrophages play an important role in the repair process. Macrophages not only have the function of phagocytosis and removal of foreign bodies and necrotic tissues but also can produce a series of immune responses at the site of injury by secreting cytokines such as inflammatory factors and chemokines to clean up the environment around the damaged site, which can mediate the secretion of growth factors by the repair tissue cells themselves and play an active role in repairing the tissue regeneration at the damaged site (Nissola et al., 2021). Dos Santos Voloski et al. investigated the effect of Fermentum β-polysaccharide on wound trauma. They removed small portions of fish skin and muscle and soaked the fish with β-polysaccharide (0.1% and 0.5%) daily until the wounds healed completely over 28 days. During this period, they observed a significant reduction in wound size and wound inflammation after the fish were soaked with 0.5% β-polysaccharide from day 7 onwards. The deposition of collagen fibres and fibroblasts in the fish skin tissue was improved, and muscle and dermal regeneration were effective (Dos Santos Voloski et al., 2019). Michalska-Sionkowska et al. used fish skin collagen as raw material and prepared a polymer sheet by modifying β-polysaccharide. This wound dressing allows to simplify the steps of wound care and significantly reduces the pain after an injury. Moreover, it can fully promote skin cell growth during application (Michalska-Sionkowska et al., 2021).

Fermentum β-polysaccharide is often used in wound care and repair products because of its significant anti-inflammatory and anti-allergic activity, as well as its ability to enhance the recovery function of damaged skin and accelerate skin wound healing (Bacha et al., 2017; Hsiao et al., 2016). Despite its large molecular weight, Fermentum beta-polysaccharide can enter the epidermis and dermis through the intercellular space, a feature that provides a new option for non-injectable natural treatment of skin wrinkles. Although Fermentum β-polysaccharide has good restorative effects, there are difficulties in the formulation application. The biggest problem lies in the poor water solubility of most Fermentum β-1,3-polysaccharides and the difficulty in formulating solutions that cannot effectively penetrate the skin to exert physiological activity, resulting in a significant reduction in the actual effect. Under these limitations, researchers have been able to improve the water solubility of Fermentum β-1,3-polysaccharide by introducing groups for structural modification, thus enhancing the bioactivity and making Fermentum β-polysaccharide more useful in cosmetics or wound dressing production. In addition, some scholars have combined nanofibers and Fermentum β-polysaccharide, which have been increasingly recognized in recent years, into wound dressings to optimize the conditions for drug release and accelerate skin regeneration and wound healing (Grip et al., 2018; Yasuda et al., 2018). Alternatively, Fermentum β-polysaccharide is made into a high water-retaining hydrogel as a wet wound dressing, which shortens the wound healing time and promotes the development of skin appendages in the regenerated skin tissue (Muthuramalingam et al., 2019). It can be said that all these research directions have good potential. In the future, the application of Fermentum β-polysaccharide in skincare can be developed in these directions to create more beneficial products.

Food industry

In terms of food industry consumption trends, people are increasingly concerned about the health benefits of food, in addition to food safety. β-polysaccharide is a natural dietary fibre with a variety of biological activities, so adding Fermentum cell wall β-polysaccharide to food processing is beneficial to human health. Fermentum β-polysaccharide is a class of biologically active natural molecules that is gaining increasing attention as an important food additive. Fermentum β-polysaccharide has a high viscosity, water holding capacity, and emulsion stability and is often used in the food industry as a thickening agent, water-holding agent, and emulsifier in seasonings, desserts, and other food products. Replacing fat with Fermentum polysaccharides in meat products can provide low-fat meat products with a smooth, rich texture and also improve the crispness and hardness of meat products (Ahmad et al., 2012).

Because of the growing demand for better taste and longer shelf life, Suwannarong et al. used the response surface methodology to explore the effect of Fermentum β-polysaccharide addition on the characteristics of cold bread. They found that the addition of Fermentum β-polysaccharide could control the overall quality of bread during storage and could delay the deterioration of bread during refrigeration. By constantly adjusting the ratio of β-polysaccharide to water, they found that cold bread with 0.28% Fermentum β-polysaccharide and 11.69% water, stored frozen for 4 days, tasted better and had a longer shelf life than bread that had been on the shelf for one day, and that Fermentum β-polysaccharide resulted in better rheological properties and better quality of the dough made from wheat flour. It can be said that Fermentum beta-polysaccharide has opened the way for the development of more bakery products (Mukhopadhya et al., 2019; Suwannarong et al., 2019). Although bread is delicious, baking often requires more fat to add colour, flavour, and taste to the bread, which can be detrimental to some dieters or people with high blood fats. Researchers have found that Fermentum beta-polysaccharide can be used as a fat substitute to reduce the fats in cakes and bread. They used β-polysaccharide as a fat substitute to replace some of the fat in heavy fat cake recipes and showed that the addition of β-polysaccharide made the heavy fat cake puffier and fluffier, with similar organoleptic properties to the heavy fat cake. The addition of β-polysaccharide to cakes as a fat substitute will be appreciated by food manufacturers and consumers alike, as it will not only reduce fat intake but also taste (Marukhnenko et al., 2020). The quest to reduce fat intake is not just about bread. Worrasinchai and colleagues investigated the use of beta-polysaccharide prepared from Fermentum as a fat substitute in mayonnaise and found that although all the beta-polysaccharide substituted mayonnaise was lower in energy than full-fat mayonnaise, it was significantly higher in moisture than full-fat mayonnaise. And most importantly, the mayonnaise made with beta-polysaccharide as a fat substitute was more resistant to storage and did not compromise on appearance or taste (Worrasinchai et al., 2006). Raiko's et al. extracted powdered β-polysaccharide from brewer's Fermentum and added it to yoghurt as a thickening agent to assess its performance. After about two hours of adding Fermentum β-polysaccharide to yoghurt, the yoghurt started to solidify, a solidification point appeared and the turbidity scan stability index increased sharply, with the yoghurt with Fermentum β-polysaccharide forming faster than the normal yoghurt formation time. To further understand the quality of the yoghurt, they used confocal scanning laser microscopy to observe the microstructure of the proteins in the Fermentum β-polysaccharide-added yoghurt and found that the protein network formed by the aggregation of casein was not affected by the β-polysaccharide, probably because of the low solubility of the Fermentum β-polysaccharide particles (Raikos, Grant, Hayes, & Ranawana, 2018). Fermentum β-polysaccharide is increasingly important in improving the taste and health safety of food products. For example, it reduces the time consumed in food processing, enhances the flavour of food, and gives consumers a better sensory experience. This has opened up new avenues for the development of different products using Fermentum β-polysaccharide as a functional additive.

Animal husbandry

There is a global push to reduce the use of antibiotics in the livestock sector. Why should the use of antibiotics be reduced or even banned? Because many surveys have shown that antibiotic resistance is a problem in all regions. The presence of drug residues in livestock products is potentially harmful to humans. Antibiotic residues in meat products, eggs and milk, livestock, and aquatic products are constantly invading the human organism from all food chains. A large number of antibiotics

enter the animal body and are excreted into the external environment as metabolites, which, if they exceed the self-cleaning capacity of the environment, will cause environmental pollution and, ultimately, a threat to humans and other biosecurity. It is therefore crucial and urgent to reduce the use of antibiotics in animal husbandry. Long after researchers discovered that feeding Fermentum beta-polysaccharide could improve the immunity of poultry without affecting their intestinal function, many researchers began to investigate the mechanism of action of Fermentum beta-polysaccharide to create more relevant drugs that could be used in place of antibiotics. Zhen et al. investigated the effects of adding Fermentum β-polysaccharide to the feed of breeding hens on their reproductive function, egg production, and immune function. They found that 200 mg/kg of Fermentum β-polysaccharide effectively improved eggshell colour, significantly enhanced the proliferative response of peripheral blood *T*-lymphocyte populations to lipopolysaccharide (LPS), increased immunity of hens to viral infections, reduced mortality to 3.9%, and significantly increased hatchability of fertile eggs (Zhen et al., 2020). To regulate rumen fermentation and increase milk production in sheep, Jin et al. extracted Fermentum β-polysaccharide from brewer's Fermentum cells and added it to the feed. They found that feeding sheep with the Fermentum β-polysaccharide supplemented feed promoted β-defensin-1 expression in sheep rumen epithelial cells (ORECs), regulated the number and species of beneficial bacteria in the sheep's gastrointestinal tract, maintained the balance of the gastrointestinal microecological environment, and improved the immunity of sheep (Jin et al., 2019). Of course, besides production performance, there is also a need to focus on disease control and immunity of livestock in the process of raising livestock. A study has reported that a nanoparticle consisting of laminated hydroxyzine chloride and Fermentum β-polysaccharide, synthesized by ion exchange, stimulated splenic leukocytes of the Lutjanus Peru with a survival rate of more than 80% and that the nanoparticle stimulated the production of pro-inflammatory cytokines better than other drugs, resulting in better immune activity (Velazquez-Carriles et al., 2018). Another study showed that Fermentum β-polysaccharide as a drug could increase specific beneficial colonic microbial communities and improve the intestinal health of weaned piglets, thereby enhancing their immunity (Leonard et al., 2012; Venardou et al., 2021). Newborn piglets have no innate immunity and must acquire immunity by suckling colostrum. Since newborn piglets can no longer obtain immunity from the sow's milk after weaning, they are subject to various negative effects, such as attack by lipopolysaccharides, which affect growth and health. Fermentum β-polysaccharide reduced the secretion of plasma interleukin 6 and tumour necrosis factor-α in piglets and increased plasma IL-10 3 to 7.5 h after LPS attack. The β-polysaccharide treatment did not have any effect on growth hormones in piglets. Fermentum β-polysaccharide selectively improved growth performance and partially improved humoral and cellular immunity in LPS-attacked weaned piglets (Li et al., 2005). Piglets are likely to suffer from diarrhoea due to gastrointestinal discomfort as a result of "sudden" weaning, so piglets are fed some zinc oxide as a dietary supplement, but it is gradually being discontinued due to contamination and side effects, so many researchers have tried to replace zinc oxide with Fermentum β-polysaccharide as a dietary supplement. One study reported that the addition of Fermentum β-polysaccharide and bovine casein hydrolysate as dietary supplements had no negative effect on the intestinal microbiota, while zinc oxide hurt the abundance of bifidobacteria (P < 0.05). Fermentum β-polysaccharide and bovine casein hydrolysate may alleviate diarrheal symptoms and improve intestinal health in piglets by inhibiting the inflammatory NFκB pathway (Mukhopadhya, O'Doherty, & Sweeney, 2019). The ability of Fermentum β-polysaccharide to alleviate diarrhoea in piglets has also been reported in a non-blinded randomized clinical trial during breeding. Swine fever is a major problem in farming, and weaned piglets are more susceptible due to their low immunity. The control of swine fever is generally based on extensive and systematic vaccination with swine fever vaccine, combined with comprehensive veterinary health

measures to control the widespread epidemic of swine fever. One study showed that the proliferative activity of peripheral blood lymphocytes in weaned piglets was significantly increased (P < 0.01) by adding high-purity Fermentum β-polysaccharide to their diets for 14 consecutive days after live attenuated cell vaccination at 26 days of age (Wang et al., 2008). Notably, continuous β-polysaccharide supplementation can increase the rate of swine fever antibody blockade. However, pigs that are given Fermentum β-polysaccharide continuously over a long period are likely to have no significant effect on lymphocyte proliferation. The underlying cause may be the depletion of immune cells in the piglets or a reduction in the Fermentum β-polysaccharide receptors that do not respond to prolonged stimulation with Fermentum β-polysaccharide. Therefore, to achieve a better immune enhancement effect, it is better to supplement the weaned piglets with Fermentum β-polysaccharide for 2 weeks, during which time the piglets have the highest rate of lymphocyte proliferation and antibody blockade against swine fever. Another study showed that the addition of 7.5% Fermentum β-polysaccharide to the diet of piglets may enhance the antibody response to swine fever virus 30 days after vaccination (Pornanek & Phoemchalard, 2020). Comparing the two studies, it can be seen that the purity and concentration of Fermentum β-polysaccharide added to the diet affects the degree of antibody response of piglets to swine fever, and only the addition of Fermentum β-polysaccharide with higher purity and concentration can increase the platelets and antibody response to swine fever virus in piglets. If the purity or concentration is low, it may only enhance the immunity and not the antibodies against the swine fever virus. It is noteworthy that oral administration of beta-polysaccharide as an adjunctive treatment can facilitate the healing of sick piglets even if they are not vaccinated against the virus. IFNγ and NOx concentrations in the affected piglets increased significantly by the third day of feeding Fermentum β-polysaccharide, which cleared the virus and inflammation from the piglets (Chethan et al., 2017).

Whether Fermentum β-polysaccharide is used as a feed additive or made into pharmaceuticals to treat livestock diseases, Fermentum β-polysaccharide has been used with great success in animal husbandry. However, there are still issues that need to be researched and solved, such as the appropriate proportion of Fermentum β-polysaccharide to be added to different animals to ensure optimal feeding results for different animals. β-polysaccharide is of great importance for the development of an antibiotic-free era.

Adsorption of mycotoxins

Mycotoxins are secondary toxic metabolites produced by certain fungi in the process of growth and reproduction, and there are more than 300 known mycotoxins. Representative ones include aflatoxin, penicillin, ochratoxin, and zearalenone, among others. These toxins can widely contaminate food, crops, and their products. When humans or animals ingest agricultural and livestock products contaminated with mycotoxins, or when they come into contact with mycotoxins through the skin, a variety of symptoms of toxicity can occur. These include hallucinations, vomiting, haemorrhage, central nervous system damage, and in severe cases, death (Pleadin et al., 2019). This range of problems has attracted the attention of a wide range of researchers who are keen to identify suitable drugs or methods to eliminate the toxins. Aflatoxin (AF) is one of the most toxic fungal toxins ever found in agricultural contamination and is highly mutagenic, carcinogenic, and teratogenic to humans and animals. The removal and degradation of mycotoxins are currently carried out by physical, chemical, and biological methods. The physical method is simple but inefficient and time-consuming; the chemical method uses chemical reagents that can severely damage nutrients and cause environmental pollution; the biological method is widely accepted because it mainly uses microorganisms or fungi for detoxification, and is more widely accepted by researchers because it is more efficient and almost pollution-free.

It has been previously reported that Fermentum can adsorb

Mycotoxins, but there is still disagreement as to which part of the Fermentum cell is the main player, which is why researchers have conducted a study. García-Béjar et al. investigated the role of the Fermentum cell wall in the adsorption of aflatoxin, choosing aflatoxin AFB1 as a representative to explore its proteomic response in the presence of brewer's Fermentum (EB83) to determine the proteomic response of Fermentum to AFB1. From this experiment, it can be tentatively assumed that the main part that plays a role in the adsorption of toxins in the cell wall of Fermentum cells since AFB1 does not induce proteins to remodel. To further understand the adsorption of AFB1 by the Fermentum cell wall, they disrupted the structure of the Fermentum cell wall using an antifungal drug (caspofungin) and found that the amount of β-polysaccharide was higher than the amount of mannose. By observing the growth of Fermentum with damaged cell walls exposed to AFB1, they found that Fermentum with intact cell walls had a stronger ability to adsorb toxins than Fermentum with damaged cell walls (García-Béjar et al., 2021). Perhaps it is because the β-polysaccharide in the intact Fermentum cell wall adsorbs AFB1 in synergy with other proteins. Hamza et al. prepared a non-nutritive mycotoxin binding agent using β-polysaccharide from Fermentum cell walls and tested its detoxification of AFB1 using an in vitro gastrointestinal model. This binder could isolate toxin molecules by forming a complex in the gastrointestinal tract. They found that the binding agent had the highest rate of toxin adsorption in simulated gastric fluid (SGF) after 10 min and in simulated intestinal fluid (SIF) after 1 h. Moreover, the controlled ratio between particles and cells can make this binding agent highly safe and does not damage normal cells (Hamza et al., 2019). This simulated gastrointestinal digestive model system tested that this binding agent has good stability and adsorption properties, which provides an important reference for in vivo experiments and lays the foundation for subsequent clinical applications. Deoxynivalenol (DON), often referred to as vomitoxin, is a highly toxic metabolite. Guo et al. investigated the mitigating effect of Fermentum cell wall components on DON-induced injury and found that β-polysaccharide was a key component in mitigating DON injury, and the release of pro-inflammatory cytokines increased significantly after treatment with β-polysaccharide, and cell viability improved significantly. Although the adsorption amount of Fermentum β-polysaccharide on DON was only 2.31% when measured by HPLC, it is undeniable that Fermentum β-polysaccharide has strong strength in eliminating DON (Guo et al., 2019). In future studies, if it is desired to improve the adsorption of Fermentum β-polysaccharide on DON, it may be possible to improve its water solubility or increase the surface area size of the particles.

Drug carriers

Fermentum β-polysaccharide has a simple structure, good water solubility, high biocompatibility, and is non-toxic and harmless to the organism. Therefore, the application in the field of drug carriers has become one of the research hotspots of interest to many researchers. Fermentum β-polysaccharide has a triple helix structure, and the *C*2-OH side of the backbone is relatively hydrophobic, while the C6-OH side is relatively hydrophilic, so its triple helix structure shows an overall amphiphilic nature, which makes it easy to form a polymer. If dimethyl sulfoxide solution is added, the triple helix structure can be broken into single chains, and the interesting point is that if the state of the solution is changed, the single chains can assemble again to form the triple helix structure. Based on this feature of Fermentum β-polysaccharide, it can be self-assembled into nanotubes or nanoparticles, and the drug is grafted onto the glycan chains of Fermentum β-polysaccharide and then chemically cross-linked to obtain cross-linked copolymers with amphipathic properties. The drug-loaded nanoparticles are highly targeted and can be rapidly internalized and translocated to the relevant lymphoid tissues to achieve therapeutic effects on inflammation (Chen et al., 2022). Fermentum β-polysaccharide particles also have a hollow and hollow spherical structure, which makes them play a crucial role in

drug and antigen delivery systems. Fermentum β-polysaccharide is prepared into capsules with an opposite charge between the capsule and the drug, and a drug-carrying Fermentum β-polysaccharide capsule is synthesized using the mutual electrostatic interaction between the two. Generally, when administered orally, drug delivery in Fermentum β-polysaccharide carriers is significantly improved because β-polysaccharide-associated receptor-mediated endocytosis enhances cellular uptake (Sabu et al., 2019; Zhu et al., 2021). east β-D-polysaccharide particles were used as porous hollow nanocarriers, and carbazole was packaged inside Fermentum β-D-polysaccharide particles by electrostatic interactions to construct a kind of nanomicrocapsules. This capsule has good drug release and stability after entering the gut. Carbazole was rapidly and efficiently taken up by macrophages under endocytosis mediated by the receptor dectin-1, and its bioavailability was increased to 32.1% (Ren et al., 2018). Many previous studies have focused on drugs with good water solubility, although more recent studies have focused more on drugs with average water solubility, such as curcumin. Fermentum beta-polysaccharide is not digestible in the human gastrointestinal tract, and curcumin is loaded in Fermentum beta-polysaccharide and protected as it passes through the gastrointestinal tract. How curcumin is released and works is not a concern because macrophages can take up Fermentum beta-polysaccharide, causing the carrier to break down and release the drug (Treml et al., 2021). Releasing a drug at the ideal location to treat a disease can be considered one of the goals pursued by researchers.

Spray drying or slurry evaporation can be used for drug encapsulation, as the active pharmaceutical ingredient can be better dispersed into the polymer matrix uniformly (Ruphuy et al., 2020). In a study by Plavcová et al, curcumin was encapsulated in Fermentum β-polysaccharide to increase its bioavailability, and this complex, when administered orally into the body, resulted in a decrease in the production of two pro-inflammatory cytokines, TNF-α and IL-1, which was more pronounced at higher concentrations. Although Fermentum β-polysaccharide itself has this effect, the results of the study showed that Fermentum β-polysaccharide encapsulated with curcumin was more effective in reducing the production of pro-inflammatory cytokines and that higher concentrations of encapsulated curcumin also significantly reduced the formation of reactive oxygen species, effectively reducing inflammation in the body (Plavcová et al., 2019). In another study, curcumin at a concentration equivalent to 20% w/w was encapsulated into dextran particles by slurry evaporation, and the actual mass fraction of curcumin added to polysaccharide particles after this method was 20.47% ± 0.65%, which implies that the slurry evaporation loading of the drug was quite effective. Composites formed after drug encapsulation were more effective in reducing the expression levels of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 and alleviating the symptoms of colitis caused by sodium dextran sulfate than using Fermentum β-polysaccharide or curcumin alone (Rotrekl et al., 2021). In addition to curcumin, other drugs can also show good effects when encapsulated by spray drying. Šalamúnová et al. compared the anti-inflammatory and antioxidant properties of encapsulated drugs (artemisinin, ellagic acid, mangiferin or trans-resveratrol) using two different methods - slurry evaporation and spray drying. The results showed that the drugs encapsulated by spray drying showed greater activity, they could inhibit the activity of transcription factor NF-κB/AP-1 and the secretion of pro-inflammatory cytokine TNF-α, which led to the better anti-inflammatory activity of these drugs (Šalamúnová et al., 2021). Whether applied to reduce inflammation or to combat leishmaniasis, encapsulation of a specific drug into Fermentum β-polysaccharide was able to better mitigate the toxicity of the specific drug to cells than treatment with the drug alone, even at the highest concentration of the encapsulated drug, without toxicity to RAW 264.7 macrophages (Volpato et al., 2018). Why do researchers prefer to encapsulate pharmaceuticals with Fermentum -polysaccharide? This is because the loaded drug's effectiveness can be greatly enhanced by the receptor-mediated uptake of Fermentum -polysaccharide by its receptor phagocytes. This

can also occur when immunosuppressive phagocytes are activated by the drug (Upadhyay et al., 2019). This strategy of adjuvant medication encapsulation improves immune response establishment and can even be employed at a lower dose than when treated with a specific drug alone. In the future, researchers will be more interested in extending the duration that pharmaceuticals stay in the body, creating enough possibilities for transport and absorption, lowering the toxicity of drugs to cells, and boosting the likelihood that drugs will be taken up by cells. Creating a more efficient and highly targeted delivery method will necessitate the screening and optimization of Fermentum -polysaccharide carriers.

Other applications

Although we know that Fermentum β-polysaccharide has numerous benefits, such as high safety factors, comprehensive efficacy, etc. However, there are great differences in the active ingredient content and water solubility of different sources of β-polysaccharide, and thus their applications in different aspects may vary. In addition to the applications mentioned above, Luan et al. found that Fermentum β-polysaccharide with different molecular weights stimulated plant height, root length, fresh biomass, and dry matter content of mustard green. Fermentum β-polysaccharide can be prepared as a plant growth promoter to promote the growth of vegetables, melons, fruits, and other crops, improve crop quality, increase crop yield, and make the crop colourful and thicker leaves (Luan le & Uyen, 2014). Some studies have reported that there is a porous structure in Fermentum β-polysaccharide, so it can absorb the odour (1-octen-3-ol, hexanal and nonanal) in silver carp minced meat, in the order of 1-octen-3-ol > hexanal > nonanal. The adsorption of these three off-flavours by Fermentum β-polysaccharide was heat-absorbing and spontaneous, driven mainly by physical adsorption and hydrophobic interactions (Zhang et al., 2020). Therefore, in daily seafood transportation, Fermentum β-polysaccharide particles can be added as odor adsorbents to reduce the release of odors from seafood products. Notably, Fermentum β-polysaccharide is closely associated with histone deacetylase 5 (HDAC5), which is essential for angiogenesis. β-polysaccharide can stimulate HDAC5 phosphorylation and release it from the nucleus to the cytoplasm. In addition, Fermentum β-polysaccharide can be used as a therapeutic agent to stimulate HDAC5 translocation to mediate transcriptional activation of MEF2 and regulate angiogenesis. In the case of tumours, the formation of new blood vessels is an important part of tumour progression and metastasis. Fermentum β-polysaccharide, as a therapeutic agent, has a modulating effect on angiogenesis. This offers a different possibility for modern tumour therapy (Choi et al., 2022).

Conclusions and prospective

With the development of science and technology, the research on various aspects of Fermentum β-polysaccharide has become more in-depth, and its application value has been increasingly emphasized and explored. At the same time, with the continuous reform and innovation of separation and purification technology, the purity and yield of Fermentum β-polysaccharide will also be gradually improved, which provides great technical support for its processing and production for other products. Nowadays, consumers pay more and more attention to health care and wellness and tend to choose green, natural and healthy products, natural medicine and functional food have gradually become the mainstream. However, the current research on the mechanism of various biological activities of Fermentum β-polysaccharide is not thorough enough, and the research on the relationship between its structure and activity is also insufficient. In the production process related to Fermentum β-polysaccharide, more attention should be paid to the side chain and advanced structure of Fermentum β-polysaccharide, and the connection between Fermentum β-polysaccharide and its biological activity should be explored through different clinical

trials before different modification methods can be used to modify the structure of Fermentum β-polysaccharide and better utilize its biological activity. If future research can solve these problems, then the application potential of Fermentum β-polysaccharide in different industries will be further developed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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