Recent Progresses on the High Molecular Polymer of Lactobacillus Extracellular Polysaccharides

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Abstract. Lactobacillus-extracellular polysaccharides (LAB-EPS) is a natural high molecular polymer with various functional properties, such as improving fermented milk texture and improving human health. Many scholars have carried out extensive and in-depth research on the structure, functional properties and structure-activity relationship of lactic acid bacteria extracellular polysaccharides, yet lacking systematic summary on the relationship among LAB-EPS types, chemical composition, structure and nutritional functions. This paper sorts out the research progress in this field and provides reference for further research and development.

1. Introduction
Lactic acid bacteria (LAB) are bacteria that use carbohydrates to produce lactic acid during long-term metabolism.

Among them, some strains are widely used in the food industry, including Streptococcus, Lactobacillus, Bifidobacterium research, lactic acid bacteria as one of the main types of probiotics, in the dispatcher Channel micro-ecological balance, dispatcher immune system and disease prevention play a vital role.

Therefore, in this review, we outline the progress that has been made in the several aspects in recent years, and also discuss existing issues that need to be addressed.

2. Nutritional Functions

2.1. Classification of LAB and LAB-EPS
It has been found that LAB such as Lactobacillus acidophilus, Lactobacillus subtilis, Lactobacillus plantarum, Lactobacillus rhamnose, Lactobacillus casei, Lactobacillus bulgaricus produce EPS(Exopolysaccharides) during the process of growth and metabolism, their yields also showed in the Table 1.
Table 1. Main LAB strains in the fermented sourdough

| Strain                   | Temperature/℃ | Time/h | pH | EPS-Yield | Reference |
|-------------------------|---------------|--------|----|----------|-----------|
| L.rhamnosus 9595M        | 32-37         | 72     | 6  | ~1000    | 1,2       |
| L.delb. bulgaricus RR    | 38            | 24-28  | 5  | 95-110   | 3         |
| L.rhamnosus R            | 37            | 72     | 6  | 500      | 4         |
| L.rhamnosus R            | 42            | 24     | /  | 110      | 5         |
| L.delbrueckii bulgaricus | 40            | 18     | /  | 263      | 6         |
| L.rhamnosus GG           | 37            | 20     | /  | 80       | 7         |
| L.delb. Bulgaricus 291   | 37            | 22     | /  | 80       | 8         |
| L.casei CG11             | 25            | 48     | /  | 130      | 9         |
| L.helveticus             | 37            | 60     | 5  | 730      | 10        |
| L.delb. bulgaricus       | 37            | 18     | 6  | 800      | 3         |
| L.rhamnosus 9595         | 37            | 24     | 6  | 2775     | 11        |
| L.paracasei              | 32-37         | 72     | 6  | ~80      | 12        |

At the beginning, researchers thought that EPS was composed of glycoprotein or carbohydrate-protein, but later on a large number of researches, analysis and comparisons, revealed that EPS was composed of repeating unit with some branches, which including EPS-HOPS (homopolysaccharide) and EPS-HEPS (heteropolysaccharide).

Molecular weight of the EPS-HOPS was found to be between $4.0 \times 10^4$-$6.0 \times 10^6$, which can be categorized into four types:

1. α-D-glucose, bond with α-1, 6 glucoside bond, with a branching structure at α-1,3 glucoside bond or α-1,2 glucoside bond and α-1, 4 glucoside bond, e.g. of this type of EPS are those that are metabolized by *L. Parabuchneri* 33, *S. sobrinus*, *L. reuteri* 180 and *L. reuteri* 35-5.
2. β-D-glucose, fructan residue bond with β-1,3 glucoside bond, with a branching structure at β-1,2 glucoside bond, e.g. of this type are EPS metabolized by *Pediococcus damnosus* 2.6 and *L. brevis* G-77.
3. β-D-fructan, fructan residue bond with β-2,6 glucoside bond, with branching structure at β-2,1 glucoside bond, e.g. of this EPS-type are those that are metabolizable by *L. frumenti* and *S. mutans* Ingbritt A.
4. Other EPS-HOPS, e.g. polygalactose.

Molecular weight of the EPS-HEPS was found to be between $10^4$-$6.0 \times 10^6$, the structure is more complex than HOPS. EPS-HEPS consist of duplicate units with or without branches.
Table 2. Monosaccharide Composition of Some HEPS Produced By LAB

| Strain                                      | Monosaccharide composition | Proportion | Reference |
|---------------------------------------------|----------------------------|------------|-----------|
| *Lactobacillus Fermentum* TDS030603         | Glucose: galactose         | 3:1        | 14        |
| *Lactobacillus kefiranofaciens*             | Glucose: galactose         | 2:4        | 15        |
| *Lactobacillus rhamnosus* KL37B             | Glucose: galactose         | 3:6        | 16        |
| *Lactis* IPLA-R1                            | Glucose: galactose: rhamnose | 1:2:3     | 17        |
| *Lactobacillus johnsonii* 142               | Glucose: galactose         | 1:4        | 18        |
| *Lactobacillus helveticus* Lb161            | Glucose: galactose         | 5:2        | 19        |
| *Lactobacillus helveticus* K16              | Glucose: galactose         | 4:2        | 20        |
| *Escherichia coli* 180/C3                   | Glucose: galactose         | 1:2:1      | 21        |
| *Lactobacillus rhamnosus* GG                | Glucose: galactose: rhamnose | 1:4:1     | 22        |
| *Streptococcus thermophilus* THS            | Glucose: galactose         | 3:2        | 23        |
| *Lactobacillus delbrueckii* ssp. bulgaricus LBB.B26 | Glucose: galactose         | 2:3        | 24        |
| *Lactobacillus delbrueckii* ssp. bulgaricus LBB.B332 | Glucose: galactose: rhamnose | 1:2:2     | 25        |
| *Lactobacillus acidophilus* 5e2             | Glucose: galactose         | 4:3        | 26        |
| *Lactobacillus pentosus* LPS26              | Glucose: rhamnose          | 3:2        | 27        |

The primary structure of EPS determines its advanced structure, its hierarchical structure is roughly the same as proteins, it is divided into first, second, third and fourth structures\(^24,25\).

The two level structures of EPS refers to the polymer formed by hydrogen bonding between the backbone chains of polysaccharides, that is, the main chain conformation of polysaccharide molecules does not involve the spatial arrangement of the side chains\(^24\). The two level structure is further curled and folded to form the third conformation of a specific conformation. The four level structure of polysaccharides is the synergistic combination of polysaccharide chains, that is, the subunit phenomenon.

2.2. The relationship between composition and anti-cancer functions of LAB-EPS

2.2.1. Immunology. Clas\(^22\) studied the role of EPS in the intestine produced by Lactobacillus rhamnosus strain GG(LGG), suggested that LGG had the ability to adhere to and colonize intestinal mucosa through EPS, LGG produced EPS, but the nonadhesive L. rhamnosus LC-705 did not.

The structures of LAB-EPS not only affects the physical properties of the polysaccharides, but also affects their physiological activities\(^28\).

The physiological activities of EPS are related to the molecular weight of the polysaccharides, the composition of monosaccharides, the type and number of substituted groups, the position of substitution, and the degree of branching (primary structure)\(^29\).

1. Normally, glucan composed of β-glucosidase bond has more antitumor activity than glucan which are composed of α-glucoside bonds\(^30\).

2. Oberlender et al. found that the sulfate substituent group and the substitutional position had significant influence on the physiological activity of the polysaccharide\(^31\).

In addition, the functions of the LAB-EPS also has a relationship with the fineness of the structure and other physical factors (such as solubility, viscosity, etc.)\(^30\).
3. Functional characteristic of LAB-EPS

3.1. Intervention and mechanism of EPS on type 2 diabetes mellitus

More and more evidence shows that the intake of whole grain foods and cereal fiber (fermented with the sourdough) can prevent chronic diseases, such as type 2 diabetes and cardiovascular disease due to retard starch digestibility\textsuperscript{32,33}.

Bajpai \textit{et al.}\textsuperscript{33} found that LAB-EPS extracted from L. Sakei Probio 65 had a consistent antioxidant activity of \(\alpha\)-glucosidase in vitro, thus it has the potential use for hypoglycemia.

LAB-EPS extracted from \textit{L. plantarum} RJF4 has antioxidant, cholesterol-lowering and inhibited \(\alpha\)-amylase activities, it showed that it had the effect of alleviating diabetes in vitro\textsuperscript{30}.

LAB-EPS extracted from \textit{Streptococcus thermophilus} can inhibit angiotensin converting enzyme (ACE) activity and has \(\alpha\)-glucosidase activity. These results indicate that it has anti-diabetic benefits\textsuperscript{34}.

3.2. Anticancer capacity (in vivo/in vitro)

It is encouraging to understand that our understanding of the mechanism of apoptosis enabled the proposal for a more reasonable approach to cancer treatment.

The anticancer activity of EPS may be played out through the following mechanisms:

(1) Prevention of carcinogenesis;
(2) inducing apoptosis of cancer cells;
(3) Inhibition of cell proliferation.

Zhou \textit{et al.}\textsuperscript{35} found that the cell viability inhibition effect was significantly in mouse cholelrectal carcinoma CT26 cells rather than human cells (the effect was only found in the CT26 test, and was not found in the other types of cancer cells), the expression of Fas, c-Jun and TLR2 was markedly up-regulated in CT26 cell by exposure of EPS116 (\textit{Lactobacillus plantarum} NCU116) rather than the other control group, and the further experiments found that EPS116 regulate CT26 cells via apoptosis, and EPS-induced apoptosis mainly related to the Fas/Fasl pathway (EPS could not penetrate cells, so it influenced TLR2, then TLR2 affecting c-Jun, which transactivated Fas and Fasl to initiate apoptosis) rather than mitochondrial pathway\textsuperscript{34,36}.

The majority of anticancer agents were found to be toxic to cells, but as GRAS (generally regarded as safe) most of the papers found that LAB-EPS had no toxic effect on normal cells (neutral red assay)\textsuperscript{37}.

Other studies found that LAB-EPS affected the P53 gene (tumor suppressor P53 affect tumor cells apoptosis via inhibition of NF-\(\kappa\)B and up-regulating I\(\kappa\)B\(\alpha\) expression) significantly. Meanwhile, LAB-EPS affected TGF gene with down regulatory action on I\(\kappa\)B\(\alpha\), it induced TGF-\(\beta\) to retrieve its own character in normal cells as a potent tumor suppressor, to attenuate the TGF-\(\beta\)-SMAD pathway\textsuperscript{38}.
### Table 3. Anticancer properties of LAB-EPS (in vitro)

| Biochemical property                  | Cancer type          | Cells tested | Functional endpoint                 | Molecules involved                                                                 | Reference |
|--------------------------------------|----------------------|--------------|-------------------------------------|-------------------------------------------------------------------------------------|-----------|
| *Lactobacillus plantarum NCU116*     | colorectal cancer    | CT26         | Induction of apoptosis              | up-regulated the expression of death receptor Fas and its ligand Fasl               | 34, 36    |
| *Lactobacillus acidophilus DSM Z 20079* | colon cancer         | CaCo-2       | Induction of apoptosis at sub-G0/G1 | attenuate the attenuate TGF-β-SMAD pathway.                                         | 37        |
| *Lactobacillus acidophilus*           | colorectal cancer    | CaCo-2       | Inhibition of cell growth           | up-regulated the expression of PPARγ and EPO                                         | 39        |
| *Lactobacillus plantarum NRRL B-4496* | intestinal carcinoma| CaCo-2       | Inhibition of cell proliferation    | -                                                                                   | 40        |
| *Lactobacillus delbrueckii ssp. bulgaricus,* | colon carcinoma      | HCT116       | Inhibition of cell proliferation    | -                                                                                   | 40        |
| *Lactobacillus delbrueckii ssp. bulgaricus,* | tumor leukemia       | K-562        | Inhibition of cell proliferation    | -                                                                                   | 38        |
| *Bifidobacterium Infantis*            | tumor human cervix   | Hela cell    | Inhibition of cell proliferation    | -                                                                                   | 38        |

Gu et al.\textsuperscript{41} found that LAB-EPS affected the anticancer capacity significantly according the model of transplanted S180 sarcoma in mice, most of the results found that LAB-EPS had positive effect on the tumor in vivo.

In most of the studies, the content of antibody in plasma increased (such as IL-2), cell activity increased including other functional substances, such as TNF-α in plasma\textsuperscript{38-41}.

### Table 4. Anticancer Properties of LAB-EPS (in vivo)

| Biochemical property                  | Animal model                  | Animal type   | Functional endpoint       | Molecules involved       | Reference |
|--------------------------------------|-------------------------------|---------------|---------------------------|--------------------------|-----------|
| *Lactobacillus delbrueckii bulgaricus ssp EPS* | Sarcoma 180 by oral          | BALB/c mice   | Inhibition of sarcoma growth | TNF-α↑ IL-2↑ | 41        |
| *Lactobacillus plantarum NRRL B-4496* | Ehrlich ascites carcinoma solid tumor bearing | female mice | reduced the tumor volume | MST↑ ILS↑ | 42-43     |
| *L. acidophilus*                      |                                | Mice          | reduction the tumor volume | -                       | 44        |
| *Lactobacillus acidophilus LAI*       | Albinism                      | Adult male Swiss mice | Tumor growth inhibition | ALT ↓ AST ↓ | 45        |
| *Bifidobacterium Infantis*            | Lewis lung cancer (LLC)       | Mice          |                           | sFlt-1↑                  | 46-47     |
In general, all LAB-EPS have anticancer abilities both in vitro and in vivo, but the pathways and their efficiencies vary with different LAB-EPS\textsuperscript{42}. While, most of the LAB-EPS had no toxic effect on the normal cells or animals, the distinction(s) among them have not been fully studied.

So the two aspects worthy of further investigations, especially in the sourdough are:

① LAB-EPS affected the P53 gene (tumor suppressor P53 affect tumor cells apoptosis via inhibition of NF-κB and up-regulating IκBα expression) significantly\textsuperscript{42}.

② LAB-EPS affected TGF gene with down regulatory action on IκBα, it induced TGF-β to retrieve its own character in normal cells as a potent tumor suppressor, to attenuate the TGF-β-SMAD pathway\textsuperscript{38}.

3.3. Antioxidant capacity (in vivo/in vitro)

LAB-EPS has strong antioxidant capacity and no cyto-toxicity has been widely reported\textsuperscript{48-49}. The antioxidant mechanism of the polysaccharides are still at the conjecture stage. There are several possible explanations:

① LAB-EPS affects free radicals, by providing hydrogen atoms which reacts with OH- rapidly to form water; as well as, oxidizes O$_2^-$ \textsuperscript{50}.

② LAB-EPS chelates with the metal ion catalyzed by ROS, which repressed the production of ROS finally \textsuperscript{51}.

③ LAB-EPS improves the activity of antioxidant enzymes in the body. Lactic acid bacteria (LAB) are Gram-positive bacteria, widely distributed in nature, and industrially important as they are used in a variety of industrial food fermentations. Lately, some LAB strains have been found with important biological functions, such as antioxidant activities\textsuperscript{50-51}.

However, the study on structure-activity relationship of antioxidant activity of polysaccharides is not as intense as the structure-activity relationship of cancer research or strains’ functions. The study of structure-activity relationship is a systematic and huge project, and the research is just beginning.

The hemiacetal group in the LAB-EPS, hydroxyl etc. have a significant relationship with the free radicals\textsuperscript{52}. According to reports, the more the number of hydroxyl groups, the stronger the antioxidant capacity, however, their ability is not only dependent on the number of hydroxyl groups, but also on its active state\textsuperscript{53}.

The yield and antioxidant properties of LAB-EPS have significant difference between different strains (Table 6), meanwhile, the character of the total activities, anion and hydroxyl radical scavenging activities maintain the arrangement direction uniformity basically, but it is still a little different among different strain\textsuperscript{30}.

Recently, LAB-EPS are rarely analyzed in vivo, especially, CAT, SOD and MDA are mostly analyzed in vitro\textsuperscript{53}. Although EPS-I’s antioxidant mechanism is unclear, it is possible that the effects of EPS-I on SOD and CAT are associated with triggering SOD and CAT gene expressions \textsuperscript{54}. 
### Table 5. Antioxidant properties of LAB-EPS (in vitro)

| Strains                   | LAB-EPS yield (g/L) | Total activities | Anion scavenging activity | Hydroxyl radical scavenging activity | Results | References |
|---------------------------|---------------------|------------------|---------------------------|--------------------------------------|---------|------------|
| *L. lactis* subsp. *lactis* 12 | 0.95                | Ascorbic acid was used as a standard | Total activity(p<0.05)† | Ascorbic acid was used as a standard | Vitamin C showed a slightly stronger effect on hydroxyl radicals than EPS-1 under the same conditions(p<0.05). † | 48       |
| *Streptococcus phocae* P180 | 11.75               | Ascorbic acid was used as a standard | Total activity(p<0.05)† | Ascorbic acid was used as a standard | (p<0.05)† | 48       |
| *Lactobacillus* plantarum LP6 | -                   | Ascorbic acid was used as a standard | DPPH radical 1.38 (p<0.05)† | Ascorbic acid was used as a standard | (p<0.05)† | 53       |
| *Lactobacillus helveticus* MB2-1 | 0.15                | Ascorbic acid was used as a standard | DPPH_1.4 | Ascorbic acid was used as a standard | Crude EPS(p<0.05) EPS2EPS-3EPS-2EPS-1 | 50       |
| *Lactobacillus plantarum* KM041 | 0.599               | Ascorbic acid was used as a standard | DPPH 0.10~0.20 | Ascorbic acid was used as a standard | (p<0.05)† | 51       |
| *Lactobacillus* plantarum N TM05 | 0.956               | Ascorbic acid was used as a standard | DPPH >3 | Ascorbic acid was used as a standard | (p<0.05)† | 52       |
| *Lactobacillus* plantarum N TM20 | 0.872               | Ascorbic acid was used as a standard | DPPH 0.10~0.30 | Ascorbic acid was used as a standard | (p<0.05)† | 52       |
| *Lactobacillus* plantarum LP6 | 1.5                 | Ascorbic acid was used as a standard | DPPH 1.38 | Ascorbic acid was used as a standard | Crude EPS(p<0.05) EPS2EPS-3EPS-2EPS-1 | 53       |
| *Lactobacillus* plantarum RJ F4 | 0.325               | Ascorbic acid was used as a standard | DPPH >2 | Ascorbic acid was used as a standard | (p<0.05)† | 54       |
| *Lactobacillus* plantarum B C-25 | 0.429               | Ascorbic acid was used as a standard | DPPH >2.5 | Ascorbic acid was used as a standard | (p<0.05)† | 28       |
| *Lactobacillus* plantarum Z DY2015 | 0.133               | Ascorbic acid was used as a standard | DPPH >5 | Ascorbic acid was used as a standard | (p<0.05)† | 56       |
| *Lactobacillus* plantarum N W11 | -                   | Ascorbic acid was used as a standard | DPPH >5 | Ascorbic acid was used as a standard | (p<0.05)† | 29       |
| *Lactobacillus* plantarum S KT09 | 0.059               | Ascorbic acid was used as a standard | DPPH >40 | Ascorbic acid was used as a standard | (p<0.05)† | 57       |
| *Lactobacillus* plantarum Y ML009 | 0.26                | Ascorbic acid was used as a standard | DPPH >40 | Ascorbic acid was used as a standard | (p<0.05)† | 57-58    |
| *Lactobacillus* plantarum C 88 | 0.069               | Ascorbic acid was used as a standard | DPPH >4 | Ascorbic acid was used as a standard | (p<0.05)† | 58       |
4. Conclusion
On the basis of the findings from several investigations, there are numerous LAB-EPS strains in the sourdough. Although several effective strains have been successfully utilized and designed for highly efficiency, significant improvements in their performance are still required in order to satisfy the future demands in variety of fields, especially in the high production of LAB-EPS (including the isolation of the effective strains and the selection of fermentation process) based on this current review.

On the other hand, it is expected that the selected strains may be very promising candidates for effective LAB-EPS production, we need to further study the structure and the constitution of LAB-EPS in the higher yield LAB strains, based on the conclusion in difference in LAB-EPS efficiency (in the anticancer, antioxidant, antidiabetic etc.).

In addition, the development of sourdough product with novel functionality or multi-functionalities (of LAB-EPS) may become research interest in the nearest future. If one can assemble sourdough products with the functional substance, such as LAB-EPS, a large variety of functions can be incorporated, and this may have great commercial potential for practical applications.

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