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Mini-Review

Impact of Postbiotics on Inflammation: A Mini Review

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ABSTRACT

Inflammation leads to numerous health implications. Probiotics can synthesis a plethora of compounds, also known as postbiotics. Antioxidants, enzymes, exopolysaccharides and short chain fatty acids can prevent and treat inflammation by means of antioxidant activity, antimicrobial properties and regulation of the immune response. This article reviews in detail the definition, source and bioactivity of lactic acid bacteria supernatant, short-chain fatty acids, exopolysaccharides, and enzymes, summarizing the recent five years of innovative applications of prebiotics in food, including new food additives used in food preservation, pure dietary supplements as well as mixed dietary supplements and new postbiotics beverages.

Keywords: Antioxidants; Enzymes; Exopolysaccharides; Postbiotics; Probiotics

INTRODUCTION

Inflammation is a term that encompasses a series of acute and chronic symptoms, such as diabetes and cardiovascular disease, caused by the exposure to toxicants, pathogens and oxidative stress. Probiotic microorganisms synthesize a range of bioactive compounds that can inhibit such mechanisms, thus preventing inflammation.

Probiotics inhibit the growth of pathogens in the intestine by releasing antibiotics [1]. Some probiotics have specific benefits, such as regulating specific immunity and inhibiting specific intestinal inflammation [2]. The study of Raman [3] showed that extracts of probiotics such as *Lactobacillus* and *Bifidobacterium* showed tumor inhibitory effects. These extracts, or the biological factors of probiotics, are called postbiotics [4]. Postbiotics, mainly through their own biological activity, can provide host health benefits even when probiotics are inactivated [4]. Numerous types of postbiotics exist, which can be classified according to their chemical composition, such as proteins, organic acids, vitamin C and exopolysaccharides [5]. They can also be classified by their physiological function [4].

Postbiotics exert several biological activities [4]. The study of Robles-Vera [6] showed that postbiotics could prevent and reduce intestinal inflammation and restore the isolation function of harmful substances in the intestinal tract. Postbiotics activate the β-oxidation of fatty acids, thereby reducing both triglycerides [7]. In addition, according to different species, postbiotics also have antioxidant, anti-proliferation, immune regulation and other abilities [4].

Postbiotics are deemed safer than probiotics (without consuming large amounts of live bacteria) [8]. Therefore, it has great potential value in the field of food. Sawada's [9] team developed a drink containing *Lactobacillus gaigeri* as a para-probiotics for constipated patients. By observing these constipated patients, they found that the intestinal function of the patients improved after continuous drinking this drink for three weeks. At the same time, postbiotics can also be used as food additives, such as Extracellular Polysaccharides (EPS). It has high stability, can also increase the viscosity of food, and has excellent binding ability with water [10].

The objective of this mini-review is to describe the anti-inflammatory mechanisms of key metabolites produced by probiotics.

LITERATURE REVIEW

Types of postbiotics

Organic acids: It includes lactic acid and short-chain fatty acids.

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Lactic acid: The *Lactobacillus spp.* are widely known and used probiotic microorganisms [11]. They are unstable and easily affected by external factors, such as temperature and pH value, so the shelf life of food containing *lactobacillus* is limited to a certain extent [12]. It was found in earlier studies that the antibacterial activity of lactic acid bacteria is due to the organic acids, bacteriocins and other substances secreted by lactic acid bacteria, which have a very significant inhibitory effect on Gram-positive bacteria, and usually these substances are in the cell-free supernatant of the bacteria [13].

Mehran and their team [14] extracted cell-free supernatants of *Lactobacillus acidophilus LA5*, *Lactobacillus casei 431* and *Lactobacillus salivalis* respectively, and found a large number of organic acids, peptides, fatty acid-containing compounds, alcohols, esters and aldehydes in these supernatants. The cell-free supernatant of *Lactobacillus acidophilus LA5* and *Lactobacillus casei 431* has been proved to effectively remove the biofilm of *Staphylococcus aureus* at a certain concentration, and the cell-free supernatant of *Lactobacillus acidophilus* has a more significant removal effect than *Lactobacillus casei* [15]. Mehran [14] found that the cell-free supernatant of *Lactobacillus salivarius* had the strongest ability in removing bacterial biofilms. By gas chromatography, they found a surfactant named laurostearic acid in the acell-free supernatant of *Lactobacillus salivarius*. Laurostearic acid is not a new organic acid, which has been demonstrated in earlier studies to have the ability to remove pathogen biofilms [16].

Later, Mehran [14] tried to add the cell-free supernatant of *Lactobacillus salivarius* into the meat soup and milk containing *Listeria monocytogenes*, and it was observed that the growth rate of Listeria in both of them was significantly inhibited. Another study found that *Lactobacillus acidophilus* in milk, when mixed with cell-free supernatants of other lactic acid bacteria, exhibited strong antibacterial activity against *Escherichia coli*, *Lactobacillus acidophilus* (EMCC 1324), *Bifidobacterium bifidum* (EMCC 1334), and *Lactobacillus plantophyllum* (EMCC 1845). They concluded that the mixture of supernatants of various lactic acid bacteria could be used in food safety because of its strong antibacterial activity against pathogenic bacteria [17].

Short-chain fatty acids: The Short-Chain Fatty Acids (SCFA) are organic acids produced from glucose *via* the process of glycolysis through different fermentation pathways [18]. These acids are usually composed of 1 to 6 carbon atoms [19]. Short-chain fatty acids with different amounts of carbon atoms have different physiological functions for the human body, such as acetic, propionic and butyric acid [18]. Short-chain fatty acids synthesized in the human body are generally secreted by symbiotic intestinal microorganisms, which release microbial molecules to resist pathogen invasion and simultaneously secrete short-chain fatty acids to enhance the intestinal barrier function [18]. Recent studies have shown that acetic acid, propionic acid and butyric acid can inhibit the proliferation of certain bacteria under certain pH conditions, thus preventing the dysregulation of human intestinal tract caused by excessive bacterial proliferation [20]. It is important to note that the colon cells in the human body usually choose butyrate as the first source of energy, so butyrate can promote the proliferation of healthy colon cells to enhance the intestinal barrier function to a certain extent, but butyrate can also induce the apoptosis of transformed cells [21].

On the other hand, short-chain fatty acids can be an important immune factor involved in the human response [19]. Previous studies have shown that propionic acid and butyric acid have the potential to inhibit the production and function of regulatory T-cells by inhibiting Histone Deacetylases (HDAC) induction [22]. This also suggests that SCFA is an important factor in building the link between the microbiome and the immune system [22]. However, whether SCFA indirectly induces tolerance to the host-associated microbiome through signaling or directly serves as a signal to reduce inflammatory response has not been studied in detail.

Exopolysaccharides: Exopolysaccharides are polymers with a variety of chemical properties produced by microorganisms that can be released outside the cell wall of the bacteria, hence the name Exopolysaccharides (EPS) [23]. At present, the biological function of EPS has not been fully explored. Based on its biological activity, it has been used in functional foods and drugs.

EPS can be detected by dendritic cells and macrophages under intestinal epithelial cells, thus allowing them to interact and stimulate the proliferation of T and NK lymphocytes to regulate the immune response [24]. On the other hand, EPS isolated from *Lactobacillus plantarum* in tofu can enhance the phagocytic potential of macrophages by indirectly inducing the secretion of nitric oxide (NO), and at the same time, this EPS can stimulate the proliferation of lymphocytes, thus enhancing human immunity [25].

EPS produced from lactic acid bacteria can have beneficial effects on human health [26]. It can protect and regulate the healthy environment of gastrointestinal tract and promote the formation of biofilm. Further, EPS can absorb cholesterol to reduce the incidence of cardiovascular disease, inhibit the formation of pathogenic biofilms, and regulate the adhesion of intestinal epithelial cells [26].

Enzymes: Antioxidant enzymes are a defense method produced by microorganisms in order to resist the damage caused by reactive oxygen species (ROS) [23]. Reactive oxygen species are closely related to human aging, which can damage proteins, lipids and even nucleic acids [27] and the way that microbes fight ROS is usually through antioxidant enzymes, which are metabolites of microorganisms and are also a class of postbiotics [28]. In fact, antioxidant enzymes are a general term that includes glutathione peroxidase, peroxide dismutase, catalase and so on [23]. Previous study showed antioxidant enzymes have been proved to have high antioxidant activity *in vitro* [28]. Malondialdehyde (MDA) is considered as the final product of lipid peroxidation, and its content is related to aging and oxidative damage [29]. After feeding lambs with Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPX) for a period of time, Izuddin [30] found that the serum MDA content of lambs fed with antioxidant enzyme for a long time was lower than that of lambs fed without antioxidant enzyme. This demonstrates that adding the epigenin of peroxidase to the diet can reduce the degree of lipid peroxidation.

Intestinal inflammation will make immune cells contact with inflammatory tissues, thus producing a large number of reactive oxygen species [31]. In the short term, reactive oxygen species will not damage intestinal cells [32]. On the contrary, intestinal cells in the environment of high concentration of reactive oxygen species will release antioxidant enzymes, so that the oxygen in the environment can achieve a dynamic balance and prevent the damage of cells by reactive oxygen species [32]. However, if the cells are exposed to a high concentration of Reactive Oxygen Species (ROS) for a long time, such as chronic diseases such as chronic gastroenteritis, the cells cannot release antioxidant enzymes for a long time, and the oxygen in the environment will become unbalanced, which will lead to the intestinal barrier and epithelial cells gradually being destroyed by ROS [32]. Tomusiak-Plebanek [33] fed mice with intestinal inflammation with peroxide dismutase for 18 days and found that the intestinal inflammation of mice was significantly alleviated, indicating that the antioxidant enzyme has potential food and drug applications.

DISCUSSION

Future remarks

The emergence of postbiotics has broken the dominant position of probiotics and prebiotics in regulating human health in the past decades. Although it was only formally defined last year, some research on its benefits to the human body has been going on for years. At present, the number of postbiotics discovered by human fermentation bacteria is very large, including essential nutrients, short chain fatty acids, glutathione, antimicrobial peptides, phenyllactic acid, D-amino acid, phytoestrogens, flavuric acid, enzymes and so on [34]. These postbiotics can provide the human body with different functions, short chain fatty acid can inhibit the proliferation of intestinal pathogenic bacteria, butyric acid, in particular, it can not only inhibit the excessive breeding of bacteria, as well as the main energy of intestinal epithelial cells, on the other hand butyrate can be used as an immune factors, indirectly involved in the immune response [20,22]. Glutathione is a powerful antioxidant that helps the body flush out harmful substances while also strengthening the immune system [35]. Antibacterial peptides fight pathogens with high drug resistance, phenyllactic acid maintains an acid-base balance in the gut, and fulvic acid binds to minerals consumed by the body to transport them into cells [36-38]. Enzymes have very strong antioxidant properties, which are commonly used to fight intestinal inflammation and the damage that reactive oxygen species can do to human cells [23]. Vitamin A, an essential nutrient, can increase inflammation levels in patients, which is considered harmful, but studies have shown that appropriate Reactive Oxygen Species (ROS) in the body are beneficial to health and longevity, while excessive use of antioxidants may cause a sharp decrease in ROS levels and thus affect human health [39,40]. So as a postbiotic, vitamin A is in a very special place. Vitamin E, on the other hand, acts as an antioxidant and, like enzymes, protects against damage to human cells by reactive oxygen species, reducing oxidative stress levels [39]. Vitamin E also protects adrenal cortical cells from DNA breaks caused by peroxides [39]. Vitamin K is the only fat-soluble vitamin other than the B vitamins that can be directly involved in energy metabolism as a coenzyme [41].

As we all know, post-probiotics are produced by probiotics through fermentation, so in the same way, pathogens can also produce toxic postbiotics [34]. Therefore, in terms of food application of postbiotics, manufacturers should know how to distinguish between probiotics and pathogens to ensure food safety [34]. However, even postbiotics, which are produced by probiotics, are not exactly good for you. For example, vitamin A, as mentioned above, does not reduce the level of inflammation in patients, but causes further inflammation [39]. Vitamin E, on the other hand, inhibits insulin release by inhibiting insulin sensitivity, which increases after moderate exercise [42]. Vitamin E intake in people who also have type-2 diabetes can lead to increased blood pressure [43]. Compared to food products with probiotics, products containing postbiotics are safer and applicable to a wider range of people, because postbiotics are not living microbes and probiotics are living microbes. Teenagers or infants with incomplete immune systems may have adverse reactions or bacterial infections when they take probiotics, so post-prebiotics food products have a very broad development prospect [23,44-51].

CONCLUSION

In closing, postbiotics are metabolites synthesised by probiotic microorganisms, including antioxidants, enzymes, exopolysaccharides, short chain fatty acids and vitamins. They exert numerous bioactivities that allow them to modulate inflammatory response to toxicants, pathogens and oxidants. Antioxidant activity, antimicrobial properties and interference with T cell-mediated inflammation are their key mechanisms.

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