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Characteristics of synbiotics and lactobionic acid

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ABSTRACT

This analysis delves into the combined advantages of synbiotics - a mix of probiotics and prebiotics, in supporting gut health and overall wellness. Synbiotics have displayed potential in enhancing function reducing inflammation and promoting digestion. Research has indicated their effectiveness in managing conditions like rheumatoid arthritis decline in adults, non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes. Despite their advantages, synbiotics encounter obstacles related to stability and effectiveness, particularly regarding the compatibility of components and the viability of strains. Lactobionic acid (LBA) an acid derived from lactose emerges as an addition to synbiotic formulations due to its antioxidant properties as well as its ability to stabilize and preserve. This examination underscores the benefits of incorporating LBA to enhance the stability and effectiveness of synbiotics urging exploration, through clinical trials to optimize formulation and assess their health impacts. This article is a review of the latest literature in the field of knowledge about synbiotics and lactobionic acid, which can provide a source of growth for probiotic microorganisms. The data presented and discussed in this narrative review were obtained from PubMed, ScienceDirect Scopus (Elsevier) and Web of Science (restricted to the years , 2002 to 2024 with the key words: probiotic, prebiotic and lactobionic acid).

1. Introduction

In the field of functional foods and nutraceuticals, synbiotics have been gaining attention for their health benefits. Synbiotics - a combination of probiotics and prebiotics offers a way to support gastrointestinal health and overall wellbeing (De Vrese & Schrezenmeir, 2008). Probiotics are microorganisms that provide health advantages when consumed in quantities (FAO/WHO, 2002) while prebiotics are non-digestible food components that help beneficial bacteria grow in the colon (De Vrese & Schrezenmeir, 2008). By incorporating prebiotics, synbiotic formulations aim to improve the survival, colonization and function of strains in a synergistic manner (Pandey et al., 2015).

Lactobionic acid has emerged as an option, among prebiotics due to its unique qualities such as antioxidant effects and compatibility with probiotic bacteria (Slavin, 2013). This compound, derived from lactose and gluconic acid possesses both antibacterial properties making it a desirable ingredient for preparations (Green et al., 2009). However, concerns exist regarding the stability of products containing acid and probiotic bacteria especially during storage and passage, through the gastrointestinal tract.

The article gathers knowledge from recent years on synbiotic and lactobionic acid and also probiotics and prebiotics, and highlights of lactobionic acid in the health promoting importance. Understanding the importance of maintaining the effectiveness and safety of preparations is essential. Various factors, like pH levels, temperature variations, exposure to oxygen and the interactions between bacteria and prebiotic substrates can affect the viability and functionality of microorganisms. These factors ultimately influence the health benefits provided by products (Alonso et al., 2013). Therefore conducting an analysis on the stability of preparations containing lactobionic acid and probiotic bacteria is necessary to uncover the underlying mechanisms and improve formulation strategies for better product performance.

This article is a review of the latest literature in the field of knowledge about probiotics, prebiotics and lactobionic acid, which can provide a source of growth for probiotic microorganisms. The purpose of the article is to present the latest knowledge in this field.

2. Synbiotics

Synbiotics, a combination of probiotics and prebiotics work together to support gut health and overall wellbeing. By blending these two supplements, synbiotics can have a synergistic impact on gut flora leading to improved immune response, reduced inflammation and better digestion. Various studies have shown the benefits of synbiotics in

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treating a range of health conditions. For instance, Esmaeili et al. (2020) found that synbiotic supplementation increased gut microbiota diversity and decreased inflammation in patients with arthritis. Similarly, research by Kim et al. (2021) revealed that synbiotics helped enhance cognitive performance and reduce oxidative stress in elderly individuals.

In a study by Figueroa-González (2010), an experiment was conducted using *Lactobacillus casei strain Shirota* combined with the OligomateTM to evaluate synbiotic effects of this combination. Another study by Bielecka et al. (2002) investigated the impact of combining *Bifidobacterium longum* with oligofructose as a prebiotic on gut health using a rat model *in vivo*. Additionally, Crittenden et al. (2001) conducted an experiment combining *Bifidobacterium lactis* LaftiTM B94 with starch to assess the synbiotic interaction, *in vitro*.

Asahara et al. (2001) investigated how the interaction between *Bifidobacterium breve* strain Yakult and galacto-oligosaccharides impacted mice in a setting. The main goal was to understand the effects of this combination on the gut bacteria of the mice. Morelli et al. (2003) carried out a study using *Lactobacillus gasseri*, inulin and other oligosaccharides to assess their influence on human gut health. Meanwhile Liong and Shah (2005) conducted research using *Lactobacillus* ATCC 4962 along with mannitol, fructo-oligosaccharides and inulin to examine their synbiotic effects under controlled conditions. Chen et al. (2007) focused on understanding how *Lactobacillus sakei* JCM interacted with fructo-oligosaccharides and trehalose in a setup to uncover their effects. Lastly Pan et al. (2009) evaluated the impact of combining *Lactobacillus plantarum* and *Lactobacillus acidophilus* with xylo- and fructo- oligosaccharides, within a controlled laboratory environment.

The impact of synbiotics, on non-alcoholic fatty liver disease (NAFLD) was explored in a separate study conducted by Eslamparast et al. (2014) revealing that synbiotics decreased liver fat and improved liver function in NAFLD patients. Likewise, research by Jiang et al. (2022) demonstrated that synbiotics aided type 2 diabetes patients in managing blood glucose levels, body weight and blood lipid profiles. In essence, synbiotics present an approach to boosting gut health and overall wellbeing. The combined action of probiotics and prebiotics on the gut microbiome could lead to better digestion, improved immune system response and decreased inflammation (Table 1). However further researches are needed to fully understand their effect on the human body.

Table 1
Commonly used synbiotics.

Synbiotic		Type of experiment	Reference
Probiotic	**Prebiotic**		
Lactobacillus casei strain Shirota	Oligomate™	*In vitro*	Figueroa-González (2010)
Bifidobacterium longum	Oligofructose	*In vivo* (rats)	Bielecka et al. (2002)
Bifidobacterium lactis Lafti™ B94	Resistant starch	*In vitro*	Crittenden et al. (2001)
Bifidobacterium breve strain Yakult	Galacto-oligosaccharides	*In vivo* (mice)	Asahara et al. (2001)
Lactobacillus gasseri	Inulin, and unspecified oligosaccharides	*In vivo* (humans)	Morelli et al. (2003)
Lactobacillus acidophilus ATCC 4962	Manitol, fructo-oligosaccharides, and inulin	*In vitro*	Liong and Shah (2005)
Lactobacillus sakei JCM	Fructo-oligosaccharides and trehalose	*In vitro*	Chen et al. (2007)
Lactobacillus plantarum and L. *acidophilus*	Xylo- and fructo-oligosaccharides	*In vitro*	Pan et al. (2009)

2.1.1. Challenges affecting stability of synbiotics

Despite the advantages associated with synbiotics, they encounter challenges that affect their stability, efficacy and safety. Issues such as synbiotics formulation, survival of probiotic strains, the stability of prebiotic components and managing interactions between probiotics and prebiotics are some of these significant hurdles (Pandey et al., 2015). Ensuring compatibility between strains and prebiotic components to support the growth of beneficial bacteria in the gut stands out as a key challenge, in developing synbiotics.

Based on research conducted by Piqué et al. (2019), the specific probiotic strains and prebiotic elements used, play a role in determining the success of synbiotics. Another challenge lies in ensuring the viability of strains during the production, storage and delivery of synbiotics. Environmental factors such as temperature, pH levels and oxygen concentrations can influence the survival rates and effectiveness of probiotic strains (Slavin, 2013). Therefore, it is essential to employ the right manufacturing and storage methods to maintain the vitality of these strains. The use of microencapsulation technology has been shown to enhance the viability of probiotic microorganisms (Koh et al., 2022).

Moreover, maintaining stability in synbiotic compositions can be challenging due to issues with prebiotic components. Prebiotics often consist of complex carbohydrates that are prone to degradation during storage and digestion. Hence, selecting prebiotics like fructooligosaccharides (FOS) and inulin's which are resistant to deterioration is important. Research by Koh et al. (2022) suggests that various forms of encapsulation can improve the stability of prebiotics.

Furthermore, interactions between probiotics and prebiotics can affect the stability and efficacy of synbiotics. Through physical and chemical interactions between them, probiotics and prebiotics have the potential to impact each others viability and functionality. To fully harness the combined benefits of synbiotics, understanding the interactions between probiotics and prebiotics in these products is essential. The importance of grasping how probiotics and prebiotics interact within synbiotics and their potential impacts on well being was emphasized in a study conducted by Slavin, 2013.

2.2. Lactobionic acid

Lactobionic acid (LBA) is a gluconic acid derivative that consists of a lactose molecule linked to a gluconic acid molecule through a -glycosidic link. Derived from lactose, a sugar found in milk, LBA is a polyhydroxy acid (Green et al., 2009). Recognized for its biocompatibility, biodegradability, nontoxicity as well as its chelating, amphiphilic and antioxidant properties, LBA exhibits a significant number of recently found biological activities and holds significant therapeutic potential. Belonging to the aldobionic family of acids, along with maltobionic acid and cellobionic acid (Pezzotti & Therisod, 2006). LBA has approximately 2 kcal/g calorie content categorizing it as a low calorie sweetener (Schaafsma, 2008). Chemically composed of one galactose molecule linked to one gluconic acid molecule *via* ether - like linkage and possessing multiple functional groups (8 hydroxyl groups), LBA offers diverse applications due, to its unique properties. The molecular weight of LBA is 358.3 and its pKa value is 3.6 (Armarego & Chai, 2009).

2.2.1. Applications of lactobionic acid in the food industry

In the food industry there is a growing trend, among consumers towards healthy eating habits leading to the development of functional foods like dairy products with probiotic and prebiotic properties (Balthazar et al., 2018; Ferrão et al., 2016; Silva et al., 2018). Many indigestible carbohydrates, including those derived from lactose are being used as prebiotics (Seki & Saito, 2012). Among them is lactobionic acid (LBA), a byproduct of oxidation that may possess prebiotic qualities (Alonso et al., 2013; Gutierrez et al., 2012). By contrast, lactobionic acid

appears to be a less commonly used prebiotic for both Lactobacilli and Bifidobacteria. However lactobionic acid has been suggested to improve gut health. *In vitro* tests show selected species/strains of Bifidobacteria and Lactobacilli can metabolise lactobionic acid as substrate for growth (Adebola et al., 2014). A key and surprising observation in study of Adebola et al. (2014) is the poor utilization of inulin as a carbon source by Lactobacilli species given the widespread use of inulin as a prebiotic in commercial preparations. By contrast lactulose was more utilized by the probiotics both L. *acidophilus* NCFM and L. *reuteri* NCIMB 11951 with growth comparable to that in the presence of glucose for all concentrations used. However, lactobionic acid supported the growth of L. *reuteri* NCIMB 11951 at concentrations up to 2.5 % (pH 5) (Adebola et al., 2014). However, very little has been reported on the incorporation of lactobionic acid in synbiotic applications with probiotics. The prebiotics may also enhance probiotic growth by lowering the gut pH to an optimal level, a factor influenced by the physicochemical properties of the bile acids. Another possibility is that high concentrations of certain prebiotics may decrease the solubility of the bile acids which may decrease toxicity (Oe & Kimura, 2011). The food industry's interest in LBA is driven by its health benefits and its abilities as a stabilizer, gelling agent and acidifier (Alonso et al., 2013).

The structure and physicochemical properties of LBA open up a wide range of present and potential future applications. One prominent use of LBA in the food industry is as a food preservative. Cao et al. (2019) found that LBA has antibacterial properties, against *Staphylococcus aureus* while the study by Chen and Zhong (2017) revealed that LBA enhances the synergistic effectiveness of nisin and thymol against *Listeria monocytogenes*. Due to these attributes LBA is considered an alternative to chemical preservatives like benzoates and sorbates which are known to pose health risks. Research has shown that LBA is effective in preserving a wide range of foods such as meat, fish and yogurt (Kiryu et al., 2012).

In addition to its preservation properties, LBA has been utilized as a functional ingredient in a range of food products. It is commonly included in meals and beverages due its antioxidant benefits (Goderska, 2019). Studies have indicated that LBA offers protection against oxidative stress, which is associated with a number of chronic conditions (Charloux et al., 1995). Manufacturers have incorporated LBA into the production processes to enhance the antioxidant capacities of foods, like yogurt and juice (Marques et al., 2020).

LBA serves other purposes such as, aging inhibitor in bread (FDA, 2011), acidifier for fermented milk products (Faergemand et al., 2012), an antioxidant, stabilizer or gelling agent in desserts (Oe & Kimura, 2011). LAB enhances the functional and sensory quality of food by reducing unwanted milliard browning reactions and products during cooking (Merrill & Singh, 2011), and enhacing flavor in meals and beverages (Walter et al., 2011).

In cosmetic and skincare products, LBA is valued for its high antioxidant properties that neutralizes free radicals, protect against UV damage and stop oxidative stress (Tasić-Kostov et al., 2012). LBA also possesses important moisturizing properties, which helps to increase the skin's hydration levels and reduce the appearance of fine lines and wrinkles (Green et al., 2006). Its ability to chelate metal ions, like calcium and magnesium contributes to the stability and shelf life of food and medicinal products. Food and medicinal items have better stability and shelf lives because it can chelate metal ions like calcium and magnesium (Cardoso et al., 2019). LBA is risk-free for usage in a variety of applications because of its non-toxic and biocompatible nature (Green et al., 2009). They have shown potential in applications especially in drug delivery systems. Studies by researchers such as Lin et al. (2009), Zheng et al. (2012) and Yang et al. (2010) have explored how LBA provide a biocompatible and targetable method for delivering DNA and bioactive molecules.

In the field of nanoparticle diagnostics using LBA as a surface coating material has been found to improve the properties of nanoparticles enhancing stability, biocompatibility, cellular internalization and dispersibility (Bahadur et al., 2009). In addition, LBA plays an important role in tissue regeneration by acting as a bio-functionalization agents in biomaterials or biocompatible scaffolds for tissue engineering purposes (Fan et al., 2010; Feng et al., 2009; Qiu et al., 2012; Yang et al., 2002). LBA is used as a component in conjunction with erythromycin for treating bacteremia and, in formulations containing chlorhexidine as discussed by Werle et al. (2002). In the field of surfactants, LBA's iron binding and emulsifying properties make it a good choice for creating surfactants derived from sugar or as a component in eco detergents as outlined by Gerling (1998). LBA is also widely used in skincare products due to its therapeutic effects. It proves effective in managing skin conditions like atopic dermatitis and rosacea while also serving as a treatment for acne, anti-aging and promoting keratinization. Furthermore it provides antioxidant benefits, moisturizes the skin, exfoliates gently and helps retain moisture. These advantages are backed by research from Briden and Green (2006)B, Hatano et al. (2009), Decker and Graber (2012,) Green et al. (2008, 2009), and Yu and Van Scott (2004).

The mechanism of action of lactobionic acid on *Staphylococcus aureus* as a Gram-positive bacterium and on *Pseudomonas fluorescens* as a Gram-negative bacterium. In both cases, observed effects include induction of oxidative stress, loss of membrane integrity, inhibition of metabolic pathways, protein synthesis, and DNA repair. Besides, on Gram-negative bacteria an increase in the permeability of the outer membrane that causes hypoosmotic shock was observed (Sáez-Orviz et al., 2022).

Antimicrobial mechanism of lactobionic acid against *Shewanell baltica* and *Shewanella putrefaciens* and its application on refrigerated shrimp was described by Zhang et al. (2023). It was observed 2MIC of LBA for 3 h only for *S. putrefaciens* and 1 MIC for *S. baltica*. For either bacterium, the MIC and MBC was 8 mg/mL and 16 mg/mL respectively. LBA exhibited an excellent effect on the preservation of shrimp by inhibiting of bacteria growth and delaying melanosis.

Fan, He, et al. (2022) analyzed inhibitory effect of lactobionic acid on *Vibrio Parahaemoliticus* planktonic cells and biofilms. It is pathogenic bacteria associated in born illness. The aim of them studies was to investigate the inhibitory effect of LBA on *Vibrio Parahaemoliticus* planktonic cells and biofilms. Authors concluded that LBA has antimicrobial and antibacterial effect against *Vibrio parahemaliticus*. The MIC and MBCs of LAB against this two analyzed strain was 4 mg/mL. This finding indicate that LBA can be applied as the potential alternative for controlling planktonic *V. parahemaliticus* and the biofilms.

2.2.2. Production of lactobionic acid

Various methods used for the synthesis of LBA for industrial purposes involve chemical, electrochemical, biocatalytic, and heterogeneous catalytic oxidations of lactose (Gutierrez et al., 2012). Beginning with the electrolytic method and catalytic hydrogenation techniques (Glattfeld & Schimpff, 1935; Isbell, 1933), the methods for obtaining LBA has advanced to the biotechnological mechanisms (Stodola & Lockwood, 1947), which is thought to be the most appropriate for its production in the future when it reaches a stable upscale. LBA is now not only produced from lactose, but also from additional carbon sources such as maltose, isomaltose, and whey, which have been successfully explored in biotechnological pathways (Cardoso et al., 2019; Goderska et al., 2014; Goderska et al., 2015).

Wu et al. (2022) use *P.fragi* NL20W for the production of lactobionic acid from whey. So they identified a new strain with high lactobionic acid production and they conclude that the potential An efficient approach of this strain in this upgrading of cheese was fully exploited. An efficient approach was developed for improving of lactobionic acid titer and yield even the substrate up to 300 g/L. In batch fermentation using a 3 L of bioreactor the lactobionic acid producing from whey powder containing 300 g/L lactose reached 3.09 g /L/h with the yield of 100 %.

While chemical synthesis remains the method for producing LBA using expensive metal catalysts and generating unwanted byproducts (Murzina et al., 2008), enzymatic oxidation of lactose offers an alternative with a high conversion rate. However, this approach faces

challenges with enzyme deactivation requiring enzymes and costly co-factors (Oh et al., 2020). Another option involves fermentation of whey to oxidize lactose into LBA utilizing *Pseudomonas* species such as *Pseudomonas taetrolens* or other bacteria, like *Burkholderia cepacia, Zymomonas mobilis,* or *Acetobacter orientalis* (Alonso et al., 2013; Sarenkova & Ciprovica, 2018). This eco-friendly method produces no harmful byproducts. However, expensive purification processes are required for the LBA produced through microbial fermentation (Alonso et al., 2013). Delagustin et al. (2019) have produced also lactobionic acid by *Zymomonas moblis*. The stability and stress test were performed to evaluated the stability against pH, temperature and oxidation. Concerning the forced degradation studies, lactobionate salt and lactobionic acid remained stable against wide range of pH and temperature of 60 °C and 90 °C and also against UV lights. This study brings new information regarding to chemical stability of sodium potassium and calcium lactobionate and lactobionic acid compounds.

2.3. Probiotics

The groundwork for probiotics was laid by Elie Metchnikoff, a scientist and future Nobel laureate working at the Pasteur Institute in Paris (Gasbarrini Giovanni et al., 2016). Metchnikoff's early investigations focused on understanding how these microbes could improve health while Louis Pasteur identified the microorganisms for fermentation processes. He observed that regular consumption of fermented dairy products such as yogurt was associated with increased longevity, among populations. He linked this discovery to the *bacillus*, identified by a 27 year Bulgarian physician named Stamen Grigorov. He suggested that *lactobacilli* could counteract the effects of digestion contributing to illness and aging (Gasbarrini et al., 2016). Metchnikoff's scientific theory paved the way, for Europe's dairy industry in France through the use of fermented milk from *Bacillus bulgaricus* (Gasbarrini et al., 2016). In 2013 an expert consensus document defined "probiotic" as microorganisms that when consumed in quantities positively impact health (Hill et al., 2014).

Probiotics are commonly found in supplements and fermented foods existing in forms such as lactic acid bacteria, *bifidobacteria* and yeasts. Lactic acid bacteria (LAB) a type of Gram bacteria are widely used in producing fermented foods, like yogurt, cheese and sourdough bread. LAB encompasses species including *Lactobacillus*, *Streptococcus* and *Enterococcus* (Makarova et al., 2006). Due to the breakdown of carbohydrates, these bacteria produce acid giving fermented foods their tangy taste. The benefits of lactic acid bacteria (LAB) are well documented including promoting gut health boosting function and reducing infection risks (Olivares et al., 2007). For example studies have shown that *Lactobacillus rhamnosus GG* can help repair permeability issues, caused by cow milk exposure or rotavirus infections and may shorten the duration of rotavirus induced diarrhea, traveler's diarrhea and antibiotic related diarrhea (Kaur et al., 2002). *Lactobacillus casei* is known for easing diarrhea symptoms enhancing gut responses relieving Crohns disease symptoms (Kaur et al., 2002;Itsaranuwat et al., 2003 ; Shah, 2007). Moreover *Lactobacillus casei Shirota* has been found to prevent bacterial induced diarrhea and reduce the recurrence rate of superficial bladder cancer post-surgery (Itsaranuwat et al., 2003; Shah, 2007).

Lactobacillus acidophilus releases acid that regulates pH levels and hinders the growth of harmful pathogens, like *Salmonella spp.* or certain *Escherichia coli* strains. It also increases antibody responses and seroconversion rates while lowering serum cholesterol levels (Gill & Prasad, 2008; Itsaranuwat et al., 2003; Shah, 2007). *Bifidobacteria*, a type of gram-positive bacteria commonly found in the stomach are often included in dairy products and dietary supplements as probiotics. *Bifidobacterium breve* enhances the system by boosting anti rotavirus IgA production or protection against influenza virus (Kaur et al., 2002). *Bifidobacterium bifidum* competes effectively for resources and space with bacteria thereby reducing diarrhea occurrences and improving antibody responses (Gill & Prasad, 2008; Itsaranuwat et al., 2003). *Bifidobacterium infantis* helps prevent both diarrhea and constipation (Fric, 2007), while *Bifidobacterium animalis* aids in regulating movements in constipated individuals and lowering the likelihood of diarrhea, among children and adults (Vasiljevic & Shah, 2008; de Vrese & Schrezenmeir, 2008). *Bifidobacteria* are responsible for producing short chain fatty acids which plays a role, in maintaining gut health and may have anti-inflammatory properties (Olivares et al., 2007).

Yeast, another type of microorganism commonly used in food as a probiotic includes *Saccharomyces boulardii*. This particular yeast strain is often found in supplements and has been shown to offer various health benefits, such as reducing the risk of *Clostridium difficile* infections and antibiotic related diarrhea (McFarland, 2010).

2.3.1. Mode of action of probiotics

The mechanism of action of probiotics is multifaceted. These live bacteria when consumed in amounts can confer health benefits to the host. Probiotics are commonly found in supplements and fermented foods. They interact with the host through pathways including modulating function, producing antimicrobial substances and competing with harmful microbes for resources.

2.3.1.1. Normalization and colonization of disturbed microbial communities in the intestine. One important aspect of probiotics is their ability to normalize and establish communities in the gut. Adhesion of bacteria to host surfaces is crucial for colonization as it hinders the removal of infections (Plaza Diaz et al. 2019). Various bacterial surface components have been documented, apart from pili, which are elongated organelles protruding from the surface of bacteria and serving as a group of structures involved in attaching bacteria to host cells (Plaza-Diaz et al., 2019).. Experimental studies involving children using probiotics have shown effects like restoring microbiota balance, promoting intestinal development, reducing pathogen presence and infections, and enhancing immune responses. However only a limited number of these studies specifically monitored changes in the microbiotas composition. Certain probiotic strains administered to children have exhibited potential in trials by lessening the severity of conditions like necrotizing enterocolitis (NEC), inflammatory bowel disease (IBD), hospital acquired and antibiotic associated diarrhea, colic and allergies (Hojsaki et al., 2018; Szajewska, 2016).

2.3.1.2. Bacteriocin production and pathogen exclusion through competition. According to Bermudez Brito et al. (2012), competitive exclusion occurs when a particular bacterial species outcompetes others for binding sites, in the system. The exact ways and important regulatory systems involved in the benefits remain somewhat unclear. One of the proposed methods for competing with pathogens includes, lowering the pH, competing for nutrients, and producing bacteriocin or bacteriocin like substances (Plaza Diaz et al., 2019). Bacteriocins are peptides created by *lactobacilli* and *bifidobacteria* that hinder the growth of some infections. Using probiotics to prevent or treat diseases is known as "colonization resistance" (Bermudaz Brito et al., 2012). Bacteriocins are compounds made up of 30–60 amino acids. These compounds target charged membrane vesicles on membranes to disrupt the proton motive force (Umu et al., 2017).

2.3.1.3. Enzymatic activities and volatile fatty acid production. The enzymatic actions of probiotics, in the gut lumen may impact the effects of these probiotics. *Lactobacilli* and *bifidobacteria* exhibit more than 20 enzymatic activities with galactosidase activity being the most common. Damage to the intestines occurs when intestinal bacterial glucuronidase breaks down glucuronidated metabolites into poisonous forms. Reduced glucuronidase activity in material has been linked to a presence of chemicals like carcinogens in the intestinal lumen (Kim & Jin, 2021). Probiotics alter the metabolism of bile acids in the gut impacting the absorption of cholesterol. Bacterial species, including probiotics

produce an enzyme called bile salt hydrolase (BSH) that may be involved in deconjugating salts (Bourgin et al., 2021).

Short chain fatty acids (SCFAs) play roles as signaling molecules for maintaining gut health and providing energy for enterocytes. Furthermore SCFAs can travel throughout the body, interact with cell receptors in tissues. The proof that supports the utilization of SCFAs in preventing and treating obesity and related issues with glucose metabolism and insulin resistance is increasing, from animal and laboratory studies (Canfora et al., 2015). SCFAs can engage with the SCFA receptors, G protein-coupled receptor (GPR) 41, and GPR43 to enhance the secretion of YY and glucagon like peptide 1 as noted by Canfora et al. (2015) and Hur and Lee (2015). This interaction can help improve the feeling of fullness. Additionally SCFAs might have an impact on GPR43 in adipose tissues, where they could potentially reduce inflammation and fat breakdown while increasing fat cell formation and leptin release. Propionate has the potential to improve the absorption of fatty acids by affecting angiopoietin-like 4, an inhibitor of lipoprotein lipase. Through their interaction, with the SCFA receptor GPR43, acetate and propionate may also decrease fat breakdown by lowering hormone-sensitive lipase phosphorylation (Canfora et al., 2015). Similarly, acetate, propionate and butyrate might stimulate adipogenesis *via* a pathway controlled by PPAR- mediated pathway, that could be influenced by a mechanism similar to GPR43. Furthermore, acetate, propionate and butyrate, particularly the latter two, have been suggested to inhibit the release of proinflammatory cytokines and chemokines, most likely by lowering the amount of infiltrating macrophages in the area (Canfora et al., 2015). Probiotics may be responsible for additional SCFA-related biological activities as a result of epigenetic changes, which might account for the probiotics' diverse array of anticarcinogenic properties (Kim et al., 2015).

2.3.1.4. Production of mucin and cell adhesion. When a microbial strain is labeled as a probiotic it needs to meet certain criteria, including adhering to the mucosa for effective colonization and interaction with the host (Bermudez-Brito et al., 2012). This connection plays a role in modifying responses and combating infections (Van Tassell & Miller, 2011; Yadav et al., 2017). Intestinal epithelial cells release mucin to prevent harmful microorganisms from adhering (Plaza-Diaz et al., 2019). According to research by Van Tassell and Miller (2011), a number of *Lactobacillus* proteins contain surface adhesins that aid in their attachment to the mucous layer as highlighted in research by.

2.3.1.5. Immune system modification. The gut microbiota influences the immune system by producing substances with inflammatory and immunomodulatory properties that can activate immune cells. Probiotic bacteria interact with epithelial cells, monocytes/macrophages and lymphocytes to generate these immunomodulatory effects (D'Amelio & Sassi, 2018). One of the mechanisms of probiotics is regulating the hosts response. Probiotics help maintain the intestinal balance, in the gut by controlling the immunological response and supporting the growth of T regs as mentioned by Giorgetti et al. (2015).

2.3.1.6. Modulation of cytokine and sIgA production. sIgA, an antibody transporter found on the epitheliums surface and produced by intestinal B cells plays a key role in transporting IgA dimers to epithelial cell surfaces. Research indicates that probiotics can enhance sIgA synthesis thereby improving barrier function (Wang et al., 2016). Probiotics also influence cells in the gut leading to the production of certain cytokines. According to Kwon et al. (2010), probiotic therapy that boosts DCs and T regs production is beneficial for managing inflammatory immune conditions.

2.3.1.7. Interplay with the gut-brain axis. The health of children and their short and long term behavior have been associated with interactions between the intestinal microbiota, brain gut communication system and genetic receptors influenced by microbiota activity (Tillisch et al., 2013). Although the neural, endocrine, and immunologic mechanisms underlying the effects of the gut intestinal microbiota on the central nervous system are multifactorial (Ong et al., 2018), these effects are thought to primarily occur *via* the generation of bacterial metabolites. These effects are believed to be mediated through the production of neuroactive compounds by gut bacteria, such as dopamine, gamma aminobutyric acid (GABA) histamine, acetylcholine and tryptophan which plays a role in serotonin synthesis. Short chain fatty acids (SCFAs) also influence neuronal excitability.

In summary, probiotics exert their effects through interactions with the system of the host, production of substances, and competition with harmful microbes for nutrients and attachment sites.

2.3.2. Expected probiotic characteristics

A prospective probiotic strain is anticipated to possess a number of desirable traits in order to exercise its positive effects. The ones currently determined by *in vitro* tests are: acid and bile tolerance, which appears to be essential for oral administration, adhesion to mucosal and epithelial surfaces, an important property for successful immune modulation, competitive exclusion of pathogens, prevention of pathogen adhesion and colonization.

The colony forming units per gram of the finished product is a crucial criterion, and probiotic dosage levels should be based on those that have been shown effective in human research. It is generally agreed upon that probiotic products should contain a concentration of 10^6 CFU/mL or gram with an intake of approximately 10^8 to 10^9 probiotic microorganisms needed for the desired probiotic effect to be transferred to the consumer. Information on minimum effective concentrations is still limited. Additionally strains must thrive in both commercial environments while maintaining viability during storage (Kechagia et al., 2013; Sanders, 2008). Viability is essential for functionality as it improves processes, like adherence reduces gut permeability and modulates the system (Galdeano & Perdigón, 2004). Some research studies have indicated that not all probiotic benefits are tied to viability as certain health effects could stem from the cell wall components or DNA of bacteria. This suggests that maintaining growth during production might be more crucial, than viability for some strains (Lahtinen, 2012; Salminen et al., 1998).

2.3.3. Stability of probiotics and prebiotics

Regarding the stability of probiotics and prebiotics, a significant challenge lies in their stability and viability during storage and processing. Factors like pH, temperature, moisture levels and exposure to substances can impact their survival and function. Adverse environmental conditions during processing and storage can greatly diminish their efficacy and viability (Champagne et al., 2018). The conditions that probiotics may face during storage are: unstable pH, relative humidity, elevated temperature, oxygen, hydrogen, peroxides and in the gut: mouth-enzymes, mastication, mucin, mineral ions; stomach-gastric acid (pH 1–3), mineral ions. Enzymes (lipase, protease), churning; small intestine-bile acid, peristalsis, enzymes |(lipases, proteases, amylases); colon-gut microbiota, enzymes, peristalsis (Yao et al., 2020). Similar concerns about stability also apply to prebiotics when it comes to processing and storage to maintain their effectiveness, as food components. The effectiveness of prebiotics can also diminish when exposed to temperatures related processes like drying or extrusion or storage in adverse environments (Misra et al., 2022).

2.3.4. Microencapsulation of probiotics

The process of microencapsulation of probiotics involves enclosing substances within a barrier to shield them from environmental stresses such as heat, light and moisture (Misra et al., 2022). By employing microencapsulation technology, the stability and efficacy of prebiotics and probiotics in food products can be enhanced. Through encapsulation, prebiotics and probiotics are safeguarded from the conditions

within the system ensuring their safe passage, to the colon (Jafari et al., 2008). The success of the microencapsulation process relies heavily on the selection of materials, for encapsulation (Table 1). Common substances used for encapsulation include lipids, polysaccharides and proteins (Jafari et al., 2008). Various methods can be employed to microencapsulate prebiotics and probiotics such as extrusion spray drying, spray freezing and emulsification (Misra et al., 2022). Among these methods spray drying stands out as the favored due to its simplicity cost effectiveness and scalability (Gbassi & Vandamme, 2012).

Alginate is utilized to deliver *Lactococcus lactis* (*L. lactis*) in the form of microgels which enhance its resilience against harsh factors (Yeung et al., 2016). *Bifidobacterium* BB 12 (B. BB 12) also employs alginate-based microgels to boost viability in conditions mimicking the tract and during storage. This method allows for controlled release of probiotics (Holkem et al., 2017, 2016). Similarly, *Lactobacillus rhamnosus* GG (LGG) is introduced using pectin in microgels to enhance survival within a gastrointestinal environment (Li et al., 2016). Researchers have found that *Lactobacillus plantarum* (*L. plantarum*) can be stored in potato starch (PRS) microgels to help counter the effects of chronic lead toxicity in mice as shown by Muhammad et al. (2018). Another study by Gonzalez Ferrero et al. (2018) demonstrated that encapsulating this probiotic in soybean protein simple microparticles can enhance its stability during storage and passage through the tract.

Furthermore, *Bifidobacterium longum* and various *Lactobacillus* strains were successfully delivered using alginate and chitosan in core shell microgels aiming to improve their survival rates within an environment and target the colon effectively as evidenced by studies conducted by Trabelsi et al. (2014) and Yeung et al. (2016). Similarly, *Bifidobacterium bifidum* has been enclosed in zein and alginate core shell microgels to enhance its survival rate within a gastrointestinal environment while exhibiting resistance to gastric juice (Riaz et al., 2019). Moreover, *Lactobacillus rhamnosus* GG (LGG) was administered using polyalginate and polyelectrolyte core shell microgels to enhance its survival rate and metabolic activity during its journey through the tract as indicated by Eshrati et al. (2018). Another approach involved encapsulating *Lactobacillus acidophilus* in whey protein and alginate core shell microgels to improve its viability during high temperature storage periods and digestion, within the system as detailed by de Araujo Etchepare et al. (2020). Furthermore *Lactobacillus salivarius* Li01 is incorporated into gelatin and alginate within biopolymer microgels to enhance its survival during extended high temperature storage and digestion, in the gastrointestinal tract (Yao et al., 2017).

Lactobacillus casei can be enclosed in starch and alginate biopolymer microgels, which not only boost viability in a simulated gastrointestinal environment but also serve as potential prebiotics enabling the loading of more probiotic cells (Pankasemsuk et al., 2016). Gelatin gum transglutaminase are used to encapsulate *Lactobacillus acidophilus* within biopolymer microcapsules for increased encapsulation efficiency and improved resistance and viability during simulated gastrointestinal passage and storage heat treatment (Da Silva et al., 2019). *Pediococcus pentosaceus* Li05 employs alginate, gelatin and MgO nanoparticles in gastric microgels to fill pores while providing antacid effects (Yao et al., 2018). *Bifidobacterium pseudocatenulatum* G7 is delivered through gastric microgels containing alginate, $CaCO_3$ and $Mg(OH)_2$, for antacid purposes (Gu et al., 2019). Additionally *Lactobacillus rhamnosus* is enclosed in gastric microgels comprising alginate, CNCs and lecithin to enhance survival within a gastrointestinal tract environment while filling pores within the microgels (Huq et al., 2017).

LGG can be enclosed within alginate and EDTA in pH microgels, for controlled release as discussed by Zheng et al. (2017). To safeguard cells in temperatures and during GI passage *Lactobacillus fermentum* is delivered using oligosaccharides and alginate in nutrient enriched microgels (Liao et al., 2019). Furthermore, *Lactobacillus casei* can also be transported utilizing alginate and sea buckthorn in nutrient enriched microgels to shield probiotics during heat treatment and GI transit as proposed by Pop et al. (2017). According to Anselmo et al. (2016), *Bacillus coagulans* is preserved using alginate and chitosan through a layer by layer application directly on cell surfaces to enhance protection during GIT transit while promoting adhesion and growth within the intestines.

Despite the benefits of microencapsulation techniques, challenges persist. One major obstacle is the risk of viability loss for prebiotics and probiotics throughout the encapsulation process as highlighted by Jafari et al. (2008). Additionally the selection of encapsulation materials may influence the stability of prebiotics and probiotics during processing, storage as their release, within the digestive system according to Gbassi and Vandamme (2012). Therefore, in order to ensure that prebiotics and probiotics function as intended in food products, it is crucial to select the materials for encapsulation and optimize the parameters of the encapsulation process.

2.3.5. Health benefits of probiotics

Research increasingly supports the notion that probiotics offer health benefits, such as promoting gut health, boosting the immune system, reducing blood cholesterol levels and potentially preventing cancer. These specific health advantages associated with probiotic strains are influenced by factors discussed earlier. Probiotics have demonstrated effectiveness in treating health conditions, preventing diarrhea caused by antibiotics and aiding in lactose digestion. However, there is evidence to support their use for other medical issues..

2.3.5.1. Diarrhea associated with antibiotics. When natural gut bacteria are disrupted by antibiotics, it can lead to the growth of bacteria and also result in mild or severe episodes of diarrhea as a side effect of antibiotic treatment. This can manifest as conditions, like colitis or non-specific diarrhea. Recent research shows that taking probiotics like L. *rhamnosus, L. casei* and *S. boulardii* can also lower the chances of developing this health condition. This conclusion comes from an analysis that looked at how probiotics help, in preventing and treating antibiotic related diarrhea (Kechagia et al., 2013).

2.3.5.2. Contagious diarrhea. The health benefits of probiotics are widely recognized, in treating and preventing contagious diarrhea. Rotavirus is a cause of infantile diarrhea and a significant factor in infant mortality worldwide. Adding probiotics to infant foods has been used to both treat illnesses and prevent infections. Clinical studies have demonstrated that probiotics like L. *rhamnosus* GG, *L. reuteri, L. casei* Shirota and *B. animalis* Bb12 can reduce the duration of acute rotavirus diarrhea effectively (Shah, 2007; Mrukowicz, 2001; Isolauri et al., 2002).

2.3.5.3. Intolerance to lactose. Lactose intolerance stems from a deficiency in beta galactosidase which hinders the breakdown of lactose into glucose and galactose monosaccharides. When undigested lactose reaches the intestine, bacterial enzymes break it down leading to diarrhea. Strains, like *S. thermophilus* and L. *delbrueckii ssp* - bulgarian style traditional yogurt preparations are believed to be more beneficial, in this regard partly due to their beta galactosidase activity. Improved lactose metabolism is considered a health advantage of probiotics (De Vrese et al., 2001; Levri et al., 2005).

2.3.5.4. Allergies and probiotics. This interaction is proposed to be influenced by strains more than others and at specific concentrations. Research suggests that early exposure to bacteria could help protect against allergies with probiotics serving as an alternative to the stimulation necessary for the developing immune systems of young children. Additionally they support the function of the mucosal barrier, which is believed to aid in controlling responses. Studies have noted differences in gut microbiota between children with allergies and those without indicating a link between gut flora and allergic conditions (Ouwehand

et al., 2001; Salminen et al., 1998). Probiotic effects seem impactful on food allergies and atopic dermatitis. Recent studies involving breastfed infants with atopic eczema revealed that *Bifidobacterium lactis* and *Lactobacillus rhamnosus* GG were effective, in reducing the severity of the condition. Furthermore research has indicated that giving L. *rhamnosus* GG to mothers, with a family history of atopic eczema, allergic rhinitis or asthma can help prevent atopic eczema in high risk infants (Isolauri et al. 2000).

2.3.5.5. Additional health benefits. Probiotic bacteria have been linked to health benefits such, as reducing cancer risk. Studies have shown that certain *Lactobacillus* and *Bifidobacterium spp.* reduce the levels of carcinogenetic enzymes produced by colonic flora by restoring intestinal permeability and microflora balance, producing antimutagenic organic acids, and boosting the host's immune system (Hirayama & Rafter, 1999; Kumar et al., 2010). The exact mechanisms are still being studied. Also, research suggests that foods containing probiotic bacteria may help control blood pressure and prevent coronary heart disease by reducing serum cholesterol levels. The production of fermentation end products, direct cholesterol assimilation, interference with gastrointestinal cholesterol absorption, and an antihypertensive influence on systemic blood lipid levels are some of the proposed processes (Sanders, 1999). Finally, probiotic strains added to dairy products have been found to help women with bacterial vaginosis achieve better treatment results. This is most likely because they promote the healthy vaginal *lactobacilli* microbiome (Mogha & Prajapati, 2016).

2.4. Prebiotics

Long before such nutrients had definitions, it was thought that some nutrients, including carbohydrates, could alter the gut microbiota. The 1980s and the beginning of the 1990s saw reports on the bifidogenic properties of inulin, oligofructose (produced from inulin), fructooligosaccharides (FOS) synthesized from sucrose, as well as galactose- and xylose-containing oligosaccharides (Ito et al., 1990; Okazaki et al., 1990; Tanaka et al., 1983). In the 1950's, researchers found that human breast milk contained a substance called the "bifidus factor," which promoted the growth of *bifidobacteria*, in babies (Gyorgy et al., 1954). Further studies revealed that this factor consisted of oligosaccharides and glycans (Coppa et al., 2004; Kitaoka et al., 2005). While oligosaccharides were present in cow's milk and dairy products, their physiological role remained unclear (Holsinger, 1988). Thousands of years ago, fermentable fibers like fructans likely played a role in the diets of humans (Leach et al., 2006).

The concept of prebiotics was introduced by Gibson and Roberfroid in 1995 defining it as "a nondigestible food ingredient that beneficially affects the host by specifically encouraging the growth and/or activity of one or a limited number of bacteria in the colon, and thereby improves host health" (LC database, 2007). Even though the initial definition has been revised times, the core elements have mostly stayed consistent over time (Gibson et al., 2004; Gibson et al., 2010; Pineiro et al., 2008; Reid et al., 2003).

A typical diet often contains a variety of prebiotic carbohydrates. For example inulin type fructans are found in little amounts in grains like wheat but are present in considerable amount in foods such as chicory root, Jerusalem artichoke, and garlic (van Loo et al., 1995). Other carbohydrates like psyllium, galactomannan, lactosucrose, lactobionic acid, isomaltooligosaccharides, xilooligosaccharides, arabinooligosaccharides and soybean oligosaccharides (McFarlane et al., 2006) can be found in a balanced diet and have been demonstrated to have prebiotic effects (Guarino et al., 2020). Furthermore substances like polyphenols and polyunsaturated fatty acids that convert to corresponding conjugated fatty acids may also be included in the definition of prebiotics based on the ISAPP consensus statement (Gibson et al., 2017), if they present compelling evidence in the host organism (Lunet et al., 2005; Yoo & Kim, 2016).

Although all dietary fibers have dietary impact, but not all dietary fibers have prebiotic effects. The term "dietary fiber" was first used in 1953 and over the years these fibers have been associated with health benefits such as promoting regular bowel movements increasing stool weight and preventing diseases (Slavin, 2013). In today's world, the connection between fibers and reducing metabolic and cardiovascular issues like diabetes, obesity and cancer is well established (Slavin, 2013). To distinguish between fibers and prebiotics it's important to note that certain glycosidic linkages in some polysaccharides like cellulose, hemicelluloses, mucilage, pectin and lignin cannot be broken down by human enzymes. These undigestible fibers are often partially fermented in the gut. Some dietary fibers can act as prebiotics by promoting the growth or activity of gut bacteria associated with health (Roberfroid, 2008).

Swennen et al. (2006) proposed that ideal prebiotics should have several qualities. They should work effectively at low doses, be selectively and easily metabolized by beneficial bacteria, like *Bifidobacterium* and *Lactobacillus* species without causing gas or common side effects. Persistence through the colon is essential, particularly with a high molecular weight, allowing them to reach the lower digestive system. Prebiotics can be customized for uses by adjusting their viscosities based on molecular weights and linkages, while stability during storage and processing is ensured by structures like 1–6 linkages and pyranosyl sugar rings. The best prebiotics should selectively influence the microflora, suppressing harmful microorganisms ones and supporting beneficial bacteria. They should also offer varying sweetness levels depending on their monosaccharide composition allowing for taste profiles without the need for additional sweeteners.

The following is a succinct summary of the known modes of action of common prebiotics - fructans, GOS, and lactulose:

1. Fructan: One key effect of consuming fructans on the gut system is modulating intestinal microflora. Research have demonstrated that inulin exerts a favorable effect on the level of *F. prausnitzii* and *Anaerostipes sp.* in the intestine, which may explain some of the butyrogenic effects resulting from it when ingested (Dewulf et al., 2013; Ramirez-Farias et al., 2017; Vandeputte et al., 2017). It has been proven that consuming vegetables rich, in inulin type fructans for a period of two weeks led to a 3.8 increase in the *Bifidobacterium* genus. Specifically at species level, there was an increase in *B. longum* subsp. *longum*, as slight increase in *B. pseudocatenulatum*, *B. bifidum* and *B. adolescentis* (Salazar et al., 2015, Ramirez-Farias et al., 2008). These results align with studies linking the consumption of inulin Jerusalem artichokes to higher levels of *Bifidobacterium* (Ramnani et al., 2010). Additionally inulin has been found to lower the production of radicals (H_2O_2) and protect the human colon mucosa from damage caused by lipopolysaccharides (Ramirez Farias et al., 2017).
2. GOS: In terms of GOS and their effects on the system there is currently limited data on their modes of action. Many bacteria containing the enzyme - galactosidase are capable of metabolizing GOS. Research conducted indicates that *in vitro* GOS exhibit more selectivity for growth particularly within the *Bifidobacterium* species compared to plant derived GOS (Brummer et al., 2015; Vulevic et al., 2004). Notably a combination of GOS has been shown to have an impact on immunological regulation. In a study involving older participants, it was found that taking GOS supplements led to an increase in the immune regulatory cytokine IL-10 and a significant decrease in IL-1 production compared to a placebo (Vulevic et al., 2015). Moreover, research has shown that this GOS blend can enhance the function of Natural Killer (NK) cells and elevate the levels of IL-8 and C-reactive protein in the blood (Vulevic et al., 2015). Furthermore, an *in vivo* experiment indicated that supplementing mice with GOS improved their lipid metabolism without a favorable effect on their glucose metabolism. It also resulted in an

enrichment of alloprevotella, bacteroides and parasutterella in the mouse microbiota (Cheng et al., 2018).

3. Lactulose: Lactulose has been used for therapeutic purposes since 1957. It is referred to as the "bifidus factor" due to its ability to increase *Bifidobacteria* levels (Petuely, 1957). Studies have shown that doses of lactulose ranging from 3 g for two weeks (Terada et al., 2009), 10 g for six weeks (Bouhnik et al., 2004) to 20 g for four weeks (Ballongue et al., 1997) do not exhibit bifidogenic effects on humans.
4. Furthermore, recent advancements have led to the discovery of new prebiotic compounds. These substances include xilooligosaccharides, soybean oligosaccharides, isomaltooligosaccharides, lactobionic acid, resistant starch and polyphenols (McFarlane et al., 2006; Zaman & Sarbini, 2016; Slavin, 2013).

2.4.1. Health benefits of prebiotics

The health benefits of prebiotics are well documented with evidence showing their impacts on immunity enhancement, digestive health promotion and reduction in the risk of conditions such as type 2 diabetes, cardiovascular diseases and certain cancers (Delzenne & Cani, 2005; Roberfroid, 2007). Moreover, prebiotics have been associated with mood regulation and cognitive function as reported by Schmidt et al. (2015). One proposed mechanism for these benefits is the production of short chain fatty acids with inflammatory properties by gut bacteria that serve as an energy source for colon cells (Cani et al., 2009). Other potential pathways involve modifications in the gut bacteria composition and function along with the release of gut hormones that impact metabolism and appetite regulation. The following section elaborates, on the health advantages offered by prebiotics. The health benefits linked to primary and secondary metabolites produced from the direct or indirect fermentation of certain substances have been extensively studied (Carlson et al., 2018). When amino acids, carbohydrates and other nutrients that are not absorbed in the intestine are fermented, short chain fatty acids (SCFAs) with 6 carbon atoms are produced by the gut microbiota (Carlson et al., 2018). The colon produces 90–95 % of SCFAs, primarily acetate, propionate and butyrate. Acetate is a source of energy for muscles (Wong et al., 2006), and it accounts for more than half of the SCFAs present in human feces (Louis et al., 2007). Inflammatory responses pathways in GI disorders like ulcerative colitis have been linked to propionate and butyrate. Studies have shown that fermenting inulin - type fructans can increase concentrations in urine hippurate (Dewulf et al., 2013). Hippurate is a microbial co-metabolite produced by mammals, with lower levels observed in obese individuals compared to lean individuals and in diabetics compared to non diabetics as indicated by research studies (Calvani et al., 2010; Salek et al., 2007; Cashman, 2002). In view of inulins fermenting properties, higher levels of hippurate in urine is considered advantageous (Dewulf et al., 2013).

2.4.2. Impact on mineral absorption

It is important to lower the risk of osteoporosis and bone fractures as statistics show that one out of eight individuals over 50 in the EU suffer spine fractures yearly and over 28 million Americans have osteoporosis or low bone mass (Cashman, 2002). A significant objective for maintaining bone structure among elderly populations is to enhance calcium bioavailability and absorption through the use of prebiotics (Whisner et al., 2013). Calcium absorption primarily occurs in the distal intestine, where different bacteria's chemical modifications and increased acid fermentation of prebiotic dietary fibers aid absorption (Carlson et al., 2018).

2.4.3. Impact on the fermentation of proteins

When fermentable carbohydrates is absent, protein fermentation can occur from endogenous or undigested protein sources leading to the production and accumulation of potentially harmful metabolites like sulfides, amines, ammonia and phenols (Windey et al., 2012). Without fermentable carbohydrates, the pH in the environment increases while SCFA concentration decreases, creating an ideal setting (the distal colon) for protein fermentation. This fermentation leads to the creation of branched chain fatty acids along with phenols and indoles that are unique to bacterial metabolism (Carlson et al., 2018). Increases in saccharolytic fermentation offer numerous potential health advantages over increases in proteolytic fermentation.

2.4.4. Changes in the numbers of pathogenic bacteria

Maintaining a healthy gut mucosa and microbiota is crucial to ward off infections like *E. coli, Salmonella spp., Campylobacter* and other harmful bacteria from infiltrating the GI tract, the gut mucosa and microbiota (Gibson & Wang, 1994). Gibson et al. (2005) outlined possible mechanisms; competition for scarce nutrients; antagonism by inhibitory peptides produced by lactic acid bacteria; acidic metabolic byproducts that reduce colonic pH below levels conducive for pathogenic bacteria; and reinforcement of the immune system.

2.4.5. Impact on the risk of allergies

The microbial diversity in the gut plays a significant role in various inflammatory conditions, including allergic conditions. Changes in gut colonization or reduced microbial diversity can impact these conditions (Prescott, 2013). According to Kalliomäki et al. (2001) and Sjögren et al. (2009), decreased levels of *lactobacilli* and *bifidobacteria* may be linked to allergic conditions in children under five years old. Researchers like Jeurink et al. (2013) have identified pathways highlighting the importance of oligosaccharides and their ability to modulate the immune system. The use of FOS/GOS supplement (8 g/L in hypoallergenic formula) has shown protective effects against allergies particularly in preventing eczema and rhinoconjunctivitis. Additionally research from the Cochrane report found that adding GOS/FOS (in a 9:1 ratio; 8 g/L added to cow milk based formula) reduced eczema among 1218 infants studied during early life stages (Osborn & Sinn, 2013).

2.4.6. Effects on the permeability of the gut barrier

Epithelial cells act as a cellular defense mechanism against the environment, lining the body's mucosal surfaces. Intestinal goblet cells produce mucins that form a gel barrier to prevent particles like bacteria from reaching the epithelial cell layer. The term "leaky gut" describes a condition where tight junctions responsible for maintaining the barrier mechanisms of the GI lining epithelial lining are compromised, potentially leading to increased occurrence of inflammation (Quigley, 2016; Turner, 2009).

The creation of SCFAs, from prebiotic dietary fiber can also enhance the function of the intestinal barrier (Carlson et al., 2018). Studies have shown that administering single or combined SCFA blends to rat caecal walls improved transepithelial electrical resistance and reduced indicators of paracellular transport indicators (Suzuki et al., 2008). Oligofructose has been found to promote specific changes in microbiota (*Bifidobacterium spp.*) leading to increased production of glucagon-like peptide-2 (GLP 2) which enhances gut barrier functions resulting in tighter junctions and decreased inflammation (Cani et al., 2009).

Strengthening GI barrier integrity may help reduce plasma lipopolysaccharide (LPS). LPS, common in gram-negative bacteria is an endotoxin produced by bacteria that acts as an inflammatory agent contributing to inflammatory metabolic disorders and diseases (Knaapen et al., 2013). The activation of Toll-like receptor 4 by LPS triggers the release of chemokines and cytokines that stimulate inflammation (Nakamura & Omaye, 2012). In comparison to maltodextrin, oligofructose-enriched inulin (10 g/d) has been shown to significantly lower plasma LPSs in women with type 2 diabetes (Dehghan et al., 2014).

2.4.7. Effect on the immune system's defense

Numerous cell types within the host's gastrointestinal tract play a crucial role in signaling and responding to the immune system. Prebiotics and the metabolites produced *via* fermentation have an impact on

TREG cells, effector T cells, natural killer cells, and B cells (Frei et al., 2015; Schley & Field, 2002). The metabolites produced by the fermentation of prebiotics, such as SCFAs, are most likely to blame for this, even if the precise processes by which they affect the immune system are unknown. According to research by Frei et al. (2015), butyrate in particular has been demonstrated to affect macrophages, T cells, and dendritic cells.

3. Conclusion and future directions

In conclusion, the analysis of synbiotic preparations with lactobionic acid (LBA) and probiotic bacteria shows promising prospects, for boosting gut health and overall wellness. Probiotics, prebiotics, and synbiotics offer a range of health benefits, including enhanced immune system, enhanced digestive well-being and decreased risks of chronic conditions like type 2 diabetes, heart disease and certain cancers.

The stability and efficacy of synbiotics pose challenges, including the compatibility of probiotic strains and prebiotic components, viability of probiotic strains during manufacturing and storage processes, stability of prebiotic elements, and interactions between probiotics and prebiotics. Nevertheless, advancements in production methods like microencapsulation technology, along with a comprehension of how probiotics interact with prebiotics present opportunities to address these obstacles.

Lactobionic acid (LBA) emerges as a promising component in synbiotic preparations due to its versatile properties, encompassing antioxidant effects, stabilizing capabilities, acidification traits, and preservative qualities. LBA not prolongs the shelf life and robustness of food items but also enhances their functional and sensory attributes. Moreover, the eco-friendly alternative for producing LBA through biotechnological means, like fermentation of whey offers sustainable options when compared to traditional chemical synthesis methods.

According to the insights presented in this review article, it is suggested to explore and optimize synbiotic formulations containing LBA and probiotic bacteria to improve their stability, effectiveness, and health advantages. Future studies should concentrate on investigating the potential synergistic effects of combining LBA with other prebiotics and probiotics to maximize their health promoting characteristics. Clinical trials need to be carried out to assess the efficiency and safety of synbiotic preparations, with LBA across populations, including individuals with specific health conditions or dietary preferences.

Overall, continued research and development in the realm of synbiotics with LBA show potential, for tackling global health issues and fostering well-being by enhancing gut health and nutrition.

Author Contribution

K.G.: Conceptualization, data curation, visualisation, writing—original draft, and writing—review and editing. P.O.O.: Writing part of original draft. All authors have read and agreed to the published version of the manuscript.

CRediT authorship contribution statement

Kamila Goderska: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Peace Oluwamuyiwa Obey:** Writing – original draft.

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Data availability

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