

## UNDERSTANDING PROBIOTICS, PREBIOTICS, SYNBIOTICS, AND POSTBIOTICS: A COMPREHENSIVE REVIEW OF THE NEWEST DEFINITIONS, SELECTED STRAINS AND PRODUCTS

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Submitted on 29 April 2025, accepted on 25 September 2025

**Abstract:** In recent years the field of probiotics, prebiotics, synbiotics and postbiotics has been extensively studied. Preparations including live and inanimate microorganisms, their parts and substances that selectively stimulate their growth, are promising in treatment or amelioration of symptoms in many diseases. The aftermath of the COVID-19 pandemic has forced us to face complications such as post-acute COVID-19 syndrome and a general decrease in population immunity, for which treatment with probiotics, prebiotics, synbiotics and postbiotics is promising. The use of such preparations can have a positive effect on the immune system and has also shown positive effects in major depressive disorder. Due to the rapid development in the field a lot of confusion and misconceptions emerged, especially regarding the use of terms and definitions. This article aims to present a clear classification of these products according to International Scientific Association of Probiotics and Prebiotics (ISAPP) guidelines as well as basic mechanisms of action and efficacy of selected preparations. Authors of this article use the term 'biotic(s)' to refer collectively to probiotics, prebiotics, synbiotics and postbiotics. While this term has not been officially established, it is used by other authors in the scientific literature. The taxonomic nomenclature used in this article has been updated according to the most recent taxonomic reclassification.

1. Introduction. 2. Current classification and nomenclature for biotics. 2.1. Probiotics 2.2. Prebiotics. 2.3. Synbiotics. 2.4. Postbiotics. 3. Navigating synonyms: challenges in biotics nomenclature. 3.1. Biotics complementary mode of action and health benefits. 3.2. Molecular pathways. 3.3. Single vs multiple-strain probiotics. 3.4. Efficacy and regulatory framework of biotics. 3.5. Future perspectives.

**Keywords:** probiotics, prebiotics, synbiotics, postbiotics, next-generation probiotics, live biotherapeutic products;

### 1. Introduction

The practice of using fermentation in food preparation and preservation dates back far in the history of human species across the globe. Despite the widespread use, it was no earlier than the beginning of 20th century that Metchnikoff proposed the beneficial value of consuming fermented foods and associated these benefits with lactic acid bacteria (LAB) (Metchnikoff, 1907; Markowiak and Śliżewska, 2017). Since then, the idea of beneficial influence of bacteria on humans has

been extensively investigated by scientists, ultimately leading to the formulation of the term 'probiotic' in 1954 and its first definition in 1965 (Vergin, 1954; Lilly and Stillwell, 1965). The development in the field of probiotics, which also led to formulation of new definitions for other biotics, has created some misconceptions regarding the understanding and proper use of these terms.

The field of biotics is characterized by a variety of terms that frequently denote the same idea. Although the concept of probiotics is widely understood and ac-

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#### Cite as:

Understanding Probiotics, Prebiotics, Synbiotics, and Postbiotics: A Comprehensive Review of The Newest Definitions, Selected Strains and Products, Woźniak A. et al. ADV MICROBIOL-NY, 2025, 64, 3, 160-181, <https://doi.org/10.2478/am-2025-0013>

cepted, other biotics such as synbiotics or postbiotics encounter challenges due to the lack of clear understanding and the presence of synonymous terms and definitions. Therefore, the International Scientific Association for Probiotics and Prebiotics (ISAPP) was founded to bring together expert scientists in the field. ISAPP proposed four terms and their definitions in 2014, 2017, 2020 and 2021 to create a unified nomenclature, respectively: probiotic, prebiotic, synbiotic and postbiotic (Table I). The establishment of each term, definition, and clear guidelines was preceded by a convention of a panel of experts. Most of the authors in the field assert that the nomenclature and definitions provided by ISAPP most accurately describe all microorganism-derived products and substrates that are selectively utilized by microorganisms, conferring a health benefit (Hill et al. 2014; Gibson et al. 2017; Swanson et al. 2020; Salminen et al. 2021). In this paper the authors aim to compile the most current definitions of all biotics according to ISAPP recommendations and present them clearly, highlighting the differences and connections. Additionally, authors discuss modes of action of biotics and characterize selected probiotic strains.

## 2. Current classification and nomenclature for biotics

### 2.1. Probiotics

The term “probiotic” was first used by Vergin in 1954 in the paper “Anti-und Probiotika” (Vergin, 1954). Lilly and Stilwell presented first definition, describing probiotics as a growth-promoting factors produced

by one microorganism that exert beneficial effects on another microorganism (Lilly and Stillwell, 1965). The most recent definition was proposed by the FAO/WHO in 2001 and was accepted, with minor grammatical change, by ISAPP in 2014 as: “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” (FAO/WHO, 2001; Hill et al., 2014). This definition is clear and rarely misused. The ISAPP has published clear guidelines that precisely define whether the definition is applicable – Table I and Figure I (Hill et al., 2014).

One of the first described probiotic strains was *Lactobacillus bulgaricus*, isolated by Grigorov in 1905 (Lee et al. 2024). In 1985 Gorbach and Goldin isolated and described *Lactobacillus rhamnosus* GG (for more probiotic strains and their health benefits see Table II). Following the reclassification of the *Lactobacillus* genus, this strain was renamed to *Lacticaseibacillus rhamnosus* GG (Stage et al. 2020; Zheng et al. 2020).

When defining a probiotic one should determine whether beneficial effects are species-specific or strain-specific. This association can be defined in respect of the claims for a certain probiotic. If the claims exceed core benefits, then the probiotic should be defined at strain level. Core benefits allow for generalization of certain effects or mode of action present at species level. Examples of such benefits include colonization resistance, short-chain fatty acids (SCFA) production, vitamins synthesis or direct antagonism (Beane et al., 2021; O’riordan et al., 2022; Zhang et al., 2022; Caballero-Flores et al., 2023). For more distinct effects such as neurological, endocrinological and immunological effects, a strain-specific relation should be applied accordingly (Hill et al., 2014).

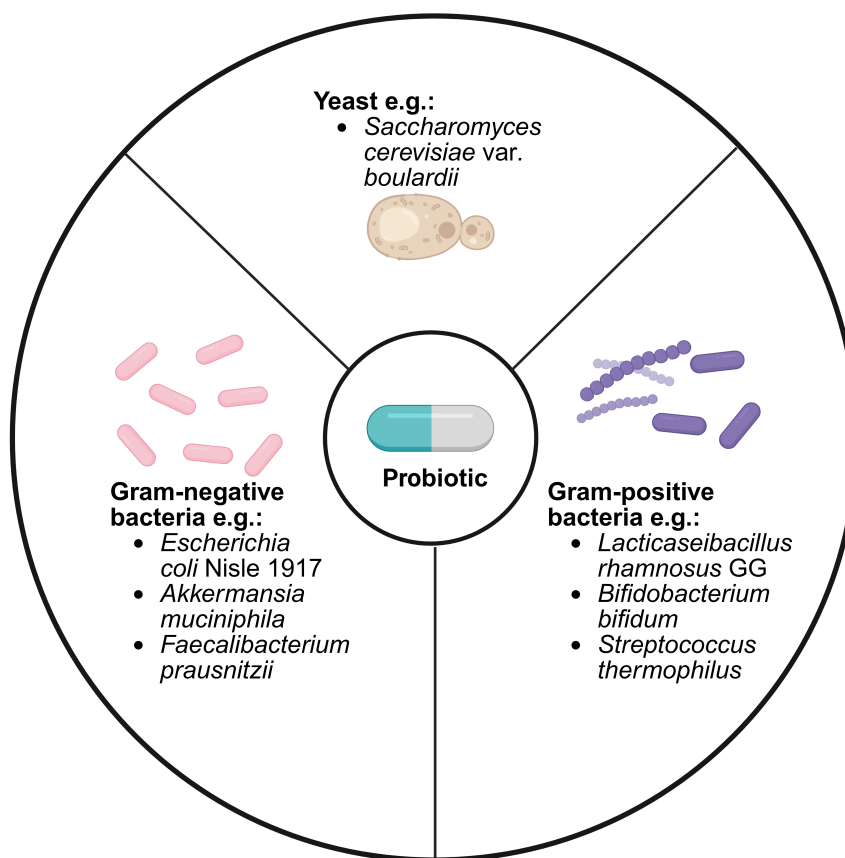
**Table I.** Current classification and nomenclature of biotics according to ISAPP.

Name	ISAPP definition	Examples	Examples of commercial products	Reference
<b>Probiotic</b>	Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.	<i>Lactobacillus acidophilus</i> DSM 20079, <i>Lactiplantibacillus plantarum</i> 299v, <i>Bifidobacterium longum</i> subsp. <i>infantis</i> UCD272, <i>Saccharomyces boulardii</i> CNCM I-745	Vivomixx® Lacidofil® Enterol®	Hill et al., 2014
<b>Prebiotic</b>	A substrate that is selectively utilized by host microorganisms conferring a health benefit.	galactooligosaccharides (GOS), fructooligosaccharides (FOS), Inulin	Orafti® Inulin NutraFlora® FOS BLF®100	Gibson et al., 2017

<b>Synbiotic</b>	A mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host.	<i>Lactiplantibacillus plantarum</i> ATCC 202195 and fructooligosaccharides (FOS)	Ther-Biotic® Synbiotic Acidolac® Baby Multilac®	Swanson et al., 2020; Kleerebezem and Führen, 2024
<b>Postbiotic</b>	Preparation of inanimate microorganisms and/or their components that confers a health benefit on the host.	pasteurized <i>Akkermansia muciniphila</i> Muc <sup>T</sup>  heat-killed <i>Lacticaseibacillus paracasei</i> MCC1849	SANPROBI® Premium EpiCor® BPL1™ Postbiotic	Salminen et al., 2021; Kato et al., 2024

The strain-specific effects of a probiotics can also extend to mental health benefits leading to the formulation of a term ‘psychobiotic’. Psychobiotics are promising therapeutics for diseases such as schizophrenia, depression, autism spectrum disorder, Alzheimer’s disease, Parkinson’s disease, or Tourette syndrome (Logan and Katzman, 2005; Liu et al., 2019; Munawar et al., 2021; Sharma et al., 2021). Examples of psychobiotics include *Lactiplantibacillus plantarum* PS128 which has been used to ameliorate some autism symptoms (Liu et al. 2019); four probiotic strains (*Bifidobacterium*

*infantis* Bi-26, *Lacticaseibacillus rhamnosus* HN001, *Bifidobacterium lactis* BL-04, and *Lacticaseibacillus paracasei* LPC-37) administered together with FOS which positively affected the children with autism spectrum disorder (ASD), contributing to behavioural and gastrointestinal (GI) tract improvement (Wang et al. 2020); and *Bifidobacterium breve* CCFM1025 which attenuates psychiatric and gastrointestinal abnormalities in patients with major depression disorder (Tian et al. 2022).



**Figure 1.** Classification of microorganisms constituting probiotics with representative examples. Created in BioRender.

Classifying psychobiotics as a separate group contradicts the goal of unifying and simplifying scientific nomenclature. There is no unified definition of psychobiotic, but most authors describe psychobiotics as probiotics with the specific characteristic that their claimed health benefits are associated with mental health (Magalhães-Guedes, 2022; Zhu et al., 2023; Chiano et al., 2024). Based on this common understanding, they should be identified as a specific type of probiotic or sub-group/sub-class rather than a separate group of biotics. Some authors expand the definition of psychobiotic to include “any exogenous influence whose effect on the brain is bacterially mediated” encompassing prebiotics as well (Sarkar et al., 2016, 2020; Warda et al., 2019). The authors of this paper disagree with such an approach, as it broadens the concept of psychobiotic to include any biotic or any substance beyond the field of biotics. This approach makes it unclear as to what a psychobiotic might be composed of, allowing for the possibility that two entirely different preparations could share the same name. Psychobiotics should be understood as “probiotic bacteria that benefit mental health when consumed in adequate amounts” (Dziedzic et al. 2024).

An important aspect of probiotics is the incorporation of genetically modified microorganisms (GMMs) (Ma et al. 2022). Each strain’s safety must be assessed regardless of the modification (Zhou et al. 2020). Genetic engineering and tools such as CRISPR/Cas9 facilitate the development of GMMs (Wu et al. 2021; Chen et al. 2025). ZBiotics’ is one of the few probiotics based on GMMs and the first to become commercially available. It was designed to ameliorate the hangover symptoms, using *Bacillus subtilis* modified with the acetaldehyde dehydrogenase gene derived from *Cu-priavidus necator* (Esawie et al. 2025). This probiotic also has potential for addressing type 2 diabetes mellitus and non-alcoholic steatohepatitis (Saad et al. 2024; Esawie et al. 2025). It has been proposed that GMMs should be excluded from probiotics, with next-generation probiotics (NGP) and live biotherapeutic products (LBP) taking on that role (O’Toole et al. 2017).

Warda et al. proposed that the definition of probiotics should also include inactivated microorganisms (Warda et al., 2019). Inanimate bacterial cells fall un-

der the definition of postbiotic and used to be referred to as ‘heat-killed probiotics’, ‘paraprobiotics’ and other synonymous names, prior to the consensus statement on the definition of postbiotics (Salminen et al., 2021). Nevertheless, creating a new classification that includes components for which definitions have already been coined and for which clear classification have been established, is unnecessary and hinders the development in the field of biotics. All microorganisms, their products and substrates for selective utilization can be described using four basic and defined terms (probiotic, prebiotic, synbiotic and postbiotic) or the appropriate chemical name of isolated metabolite. Thus, creating a new definition seems unnecessary (Hill et al. 2014; Gibson et al. 2017; Swanson et al. 2020; Salminen et al. 2021).

## 2.2. Prebiotics

The concept of prebiotics was introduced in 1995 by Gibson and Roberfroid. Initially the following definition was proposed “A prebiotic is a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon and thus improves host health” (Gibson and Roberfroid, 1995). In this initial understanding prebiotics were exclusively connected with GI tract, as they only referred to food ingredients. Further development of the concept led to the formulation of a new definition: “a substrate that is selectively utilized by host microorganisms conferring a health benefit” (Gibson et al., 2017). This change broadened the idea of prebiotics, allowing for substances other than carbohydrates, which do not have to be present in food and can be applied to body sites other than GI tract, to be classified as prebiotics.

An important aspect of a prebiotics is their selectivity, which was highlighted in the initial definition and persists in the most recent understanding of the term. Selectivity differentiates the prebiotics from dietary fibre and other substances that affect the microbiota in non-selective manner. While the dietary fibre is not digested by the host, sharing this characteristic with prebiotics, it can be utilized by gut microbiota in general. Prebiotics, however, are utilized only by given

group or groups of microorganisms, which, along with the health benefit, ought to be proven experimentally (Hutkins et al. 2024). The beneficial aspects of prebiotics include increased abundance of beneficial microbiota e.g. *Bifidobacterium spp.* which produce metabolites such as SCFA (Lai et al. 2023). The effect does not have to be direct as long as the health benefit is obtained. An example of this is the ‘cross-feeding effect’, where the production of a beneficial product, positively affecting host health, results of interaction between two microorganisms induced by a prebiotic (Culp and Goodman 2023). Such interaction has been observed between *Bifidobacterium longum* PT4 and *Bacteroides ovatus* HM222. When xylan was used as a carbon source, the *B. longum* PT4 showed an increased growth in the presence of *B. ovatus* HM222, indicating potential cross-feeding effect (Vega-Sagardía et al. 2023).

The most common prebiotics are galactooligosaccharides (GOS), fructooligosaccharides (FOS) or inulin (Flaujac Lafontaine et al. 2020). Candidates for prebiotics are constantly being researched, with human milk oligosaccharides (HMO) being an example. Human milk oligosaccharides play an important role in early stages of gut microbiota development. HMO are selectively metabolized by *Bifidobacteriaceae* and especially *Bifidobacterium longum* subsp. *infantis*. They can also prevent pathogen adhesion, making HMO very promising candidates for prebiotic (Okburan and Kıziler, 2023).

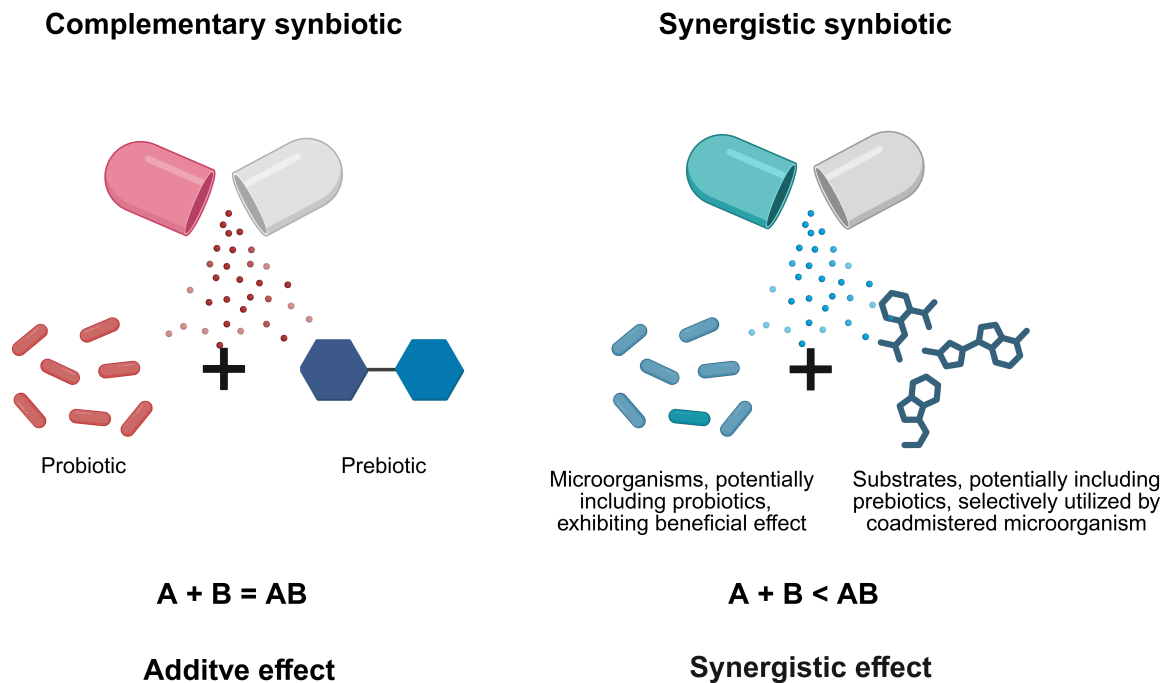
To conclude, the most important characteristic of prebiotics are: being non-digestible by host, selectively stimulating the growth and/or the activity of a group of microorganisms, conferring health benefit to the host (Jenkins and Mason 2022).

### 2.3. Synbiotics

The concept of synbiotics emerged alongside prebiotics. It was the same article where Gibson and Roberfroid defined prebiotics, they also proposed the concept of the synbiotics as the combination of probiotics and prebiotics (Gibson and Roberfroid 1995). The initial definition described synbiotics as: “a mixture of probiotics and prebiotics that beneficially affects the host by improving the survival and implantation of live

microbial dietary supplements in the gastrointestinal tract, by selectively stimulating the growth and/or by activating the metabolism of one or a limited number of health-promoting bacteria and thus improving host welfare” (Gibson and Roberfroid, 1995).

The definition was updated by ISAPP in 2020, describing synbiotics as: “a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host” (Swanson et al., 2020). The updated and simplified definition broadens the understanding of the term. Combination of prebiotics and probiotics are still referred to as synbiotics, specifically as complementary synbiotics - Figure 2. Such products are not designed to work exclusively together, they are administered together but each component must be a defined biotic separately (with all the requirement for each accordingly). The effect of complementary synbiotic is no greater than when the components of the synbiotic are administered separately. Updating the definition allowed for the concept of a synergistic synbiotics to emerge. Elements of such synbiotics do not have to be a predefined prebiotics and probiotics. The microorganism and the substance used in the formulation depend on one another in such way that, when used separately, they exert much weaker or no health benefit. Such approach allows for a development of new synbiotics, components of which haven't necessarily been used previously in other biotics. It is also important to note that in the most recent definition of synbiotics, the understanding of host microorganism both refers to autochthonous and allochthonous microbiota, latter administered in synbiotics or probiotics (Swanson et al., 2020). This is crucial since microorganisms present in synergistic synbiotic formulations might lack the ability to colonize the gut (Walter et al. 2018). Most commercially available synbiotics are complementary (Gomez Quintero et al. 2022). To the best of authors' knowledge, no synergistic synbiotic formulations are currently available on the market. However, *ex vivo* studies have demonstrated the potential of synergistic synbiotics, highlighting the need for further research, particularly through *in vivo* investigations (De Bruyn et al., 2024; Ghyselincx et al., 2024).



**Figure 2.** Comparative characteristics of complementary and synergistic synbiotics. Created in BioRender.

#### 2.4. Postbiotics

Probiotics, in addition to mandatory presence of live microorganism, naturally contain dead cells. For a long time, the influence of dead microorganisms in probiotics has been overlooked. Since the potential of inanimate cells to confer a health benefit in host has been recognized, multiple names to describe such preparations have emerged in the literature. Examples include: ‘heat-killed probiotics’, ‘paraprobiotics’, ‘tyndallized probiotics’ and ‘postbiotics’ (Barros et al. 2021; Ding et al. 2021; Boyte et al. 2023; Bolzon et al. 2024). In 2019, ISAPP reviewed existing names describing preparations containing dead microorganism cells and, two years later, published the consensus statement on the definition of postbiotics: “preparation of inanimate microorganisms and/or their components that confers a health benefit on the host” (Salminen et al., 2021).

The term “postbiotic” is coherent with other defined biotics and well describes the characteristics of the preparation - Figure 3. It is important to distinguish vaccines, which can include dead microorganism cells, and purified metabolites of microorganisms from postbiotics. Vaccines and metabolites do not fall under the definition of postbiotic. Metabolites can be present in postbiotic preparations but only together with dead cells and/or their parts (Salminen et al.,

2021). Microbial metabolites can be named according to their chemical structure or origin, thus creating additional definitions such as: “compounds produced by the microbial metabolism, namely postbiotics” seems unnecessary (Puccetti et al. 2020).

Postbiotics, unlike vaccines, do not aim to provide post-vaccination immunity (Aggarwal et al. 2022). While they can affect the immune system, their effects differ fundamentally from those induced by vaccines (Shukla and Shah 2018). Moreover, postbiotics are not designed to prevent any specific diseases, which is the primary purpose for vaccines. For these reasons, associating postbiotics with vaccines is both incorrect and misleading (Salva et al. 2021; Prygiel et al. 2022).

Even though the clear definition of postbiotics has been proposed, authors still use synonymic names, such as: paraprobiotics (Lee et al., 2023; Mudaliar et al., 2024), heat-killed probiotics (Poaty Ditengou et al., 2023; Yoon et al., 2024), tyndallized probiotics (Bolzon et al., 2024). These multiple terms often describe the same concept, yet some involve modified definitions. For instance, “paraprobiotics, which contain inactivated nonviable probiotics” (Docampo et al., 2024). This understanding narrows the potential of inanimate microorganisms that could be used in preparations, since they would have to be also identified as probiotics, which is not obligatory for postbiotic preparations.

This narrow understanding also excludes metabolites and cell parts, which are included in the broader postbiotic definition (Vinderola et al. 2022).

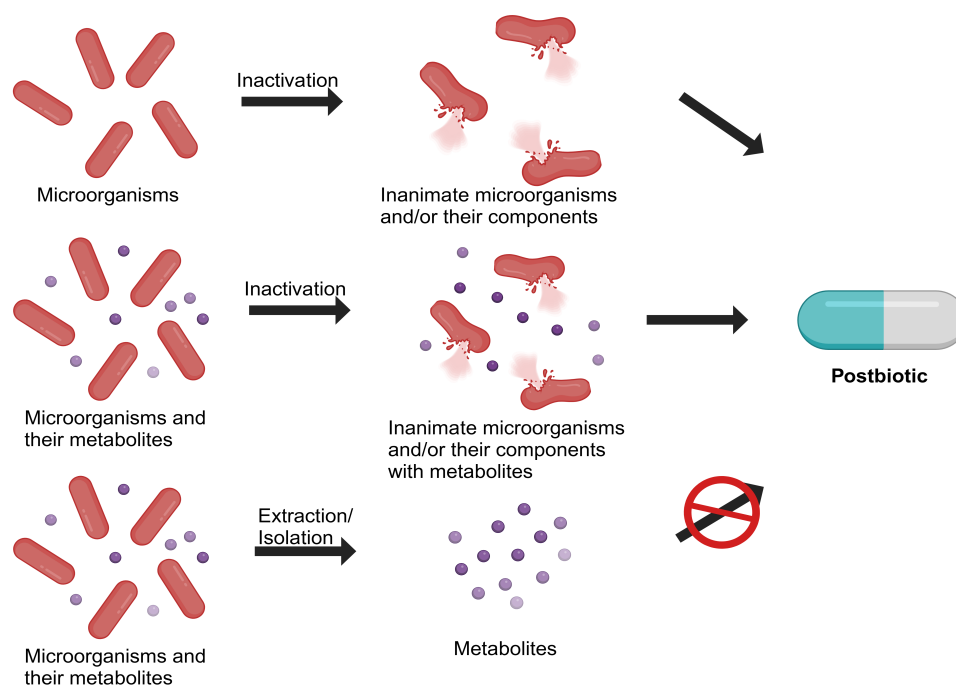
The term ‘heat-killed probiotics’, used for preparations containing dead microorganism cells that provide a health benefit on the host is also problematic. Probiotics, according to their well understood and widespread definition must contain: “live microorganisms that, when administered in adequate amounts” (Hill et al., 2014). Hence, the use of the name probiotic for microorganisms that have been heat-killed seems inappropriate. The inconsistent use of multiple names for the same definition is highly unfavourable and hampers the development of postbiotics (Vinderola et al. 2024).

As mentioned above, the microorganisms used in postbiotic preparations do not have to be classified as probiotics, though they have to be clearly defined. This is important in context of the safety of use such as the presence of genes conferring antibiotic resistance (Daniali et al. 2020). The method of inactivation is yet another important aspect of postbiotics. Different methods of inactivation may influence the cells in different ways, thereby altering the characteristics of the final product (Zhong et al., 2024). Inactivation methods can broadly be categorized into two groups: thermal and non-thermal (Zhu et al., 2025). The use of temperature, in methods such as sterilization, pasteurization, freeze drying or spray drying, remain the most used due to standardized procedures and relatively

low operational costs (Rafique et al., 2023). However, these approaches have notable limitations, as they may compromise beneficial cellular properties during the inactivation process (Sun et al., 2023). Non-thermal inactivation methods include UV, ultrasonic sterilization, high-pressure, pulsed electric field, irradiation, supercritical carbon dioxide and exposure to extreme pH conditions (Zhu et al., 2025). Those physical and chemical methods allow heat-labile elements to retain their bioactivity (Zhong et al., 2022). The use of inanimate microorganisms may also enable researchers to use genetically modified organisms, as the safety of use when microorganisms are administered in non-viable form is superior (Salminen et al., 2021).

One of the challenges in development of postbiotic preparations is the evaluation of number of cells and/or their parts present in the preparation. Establishing the CFU by plating method is prone to undervaluation of the cells present, as this technique omits dead cells. Flow cytometry (FCM) seems to be more applicable, as it can differentiate live and dead cells (Bolzon et al., 2024).

Though postbiotics face challenges, they can be superior to probiotics. Probiotic shelf life is a problem due to the mandatory presence of live microorganisms at declared concentration. The use of dead cells in postbiotics eliminates the problem of CFU fluctuations during shelf life, proposing a good alternative (Salminen et al., 2021).



**Figure 3.** Postbiotic components vs. independent metabolites (Salminen et al. 2021; Vinderola et al. 2024). Created in BioRender.

### 3. Navigating synonyms: challenges in biotics nomenclature

The field of biotics is rife with synonymous terms and definitions, which hinder its development. Stakeholders may overlook significant literature related to the given topic due to the presence of multiple names, especially when they are not familiar with all the existing synonyms. The ISAPP has presented four names (probiotic, prebiotic, synbiotic and postbiotic), definitions and clear guidelines for each. Nonetheless, as highlighted above, incoherent nomenclature remains prevalent (Warda et al. 2019; Lee et al. 2023; Yoon et al. 2024).

There are three terms in the field that authors find particularly important to discuss: psychobiotic, next-generation probiotic (NGP) and live biotherapeutic product (LBP). The term 'psychobiotic' is commonly used in the literature to refer to a product providing health benefits regarding the nervous system and which has potential in treatment of neurological disorders (Cheng et al. 2019; Munawar et al. 2021; Sharma et al. 2021). However, the authors of this article believe that the proposed definition of psychobiotic does not present enough differences to justify it as a separate biotic (Zhu et al. 2023; Chiano et al. 2024). The distinction merely narrows the health benefit to the mental health, thus psychobiotics fall under the broader definition of probiotics (Hill et al. 2014). Since this issue has already been addressed in relation to probiotics, the discussion will now focus on NGP and LBP.

NGPs are described as new microbial strains isolated using culture independent methods, primarily genome sequencing. There is no unified and common definition; authors only often present differences between NGPs and conventional probiotics (Singh and Natraj, 2021; Abouelela and Helmy, 2024). Al-Fakhry and Elekhawy are one of few authors proposing the definition for NGP: "living microbes identified on the base of comparative microbiome investigations which confer health advantages to their host when taken to suitable extents" (Al-Fakhry and Elekhawy, 2024). This definition only narrows down the potential source of NGP, which is not restricted in any way by current definition of probiotic. The only difference that authors of this paper find compelling enough to consider the NGP as a separate group of biotics is the personalization of the preparations (Singh and Natraj 2021).

Live biotherapeutic product (LBP) is a term coined in the USA by Food and Drug Administration (FDA),

to regulate the field of probiotics. It can be defined as: "a biological product that: 1) contains live organisms, such as bacteria; 2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and 3) is not a vaccine" (FDA, 2016). LBPs share more similarities with NGPs rather than with conventional probiotics. The context of application in treatment of a given disease, as stated in the second part of the definition, is crucial in the understanding the differences. Microorganisms do not have to exhibit specific health claim to be considered probiotics. According to the most recent probiotic definition, it is sufficient to demonstrate safety of use and general health benefits for the host, proven through human studies (Hill et al., 2014). Therefore, the terms LBP and probiotic cannot be used interchangeably, despite their similarities.

For stakeholders outside of the USA, the use of the term LBP may seem unjustified, given the presence of four biotics defined by ISAPP. Regardless, the term LBP is also used in EU, where its regulatory framework has been established in 2018 (Ph. Eur. 2018). Since probiotics are only required to demonstrate a general health benefit, the term LBP has been adopted to refer to products intended for the treatment or prevention of disease (Franciosa et al. 2023). This can be confusing since in Poland (member of EU) there are probiotics already functioning as drugs that aim to treat or prevent disease, which is not excluded by the ISAPP definition of probiotic (Hill et al., 2014; Ruszkowski et al. 2018).

#### 3.1. Biotics complementary mode of action and health benefits

The interactions between probiotics, prebiotics, synbiotics, and postbiotics are complex and synergistic, lying in their complementary roles. As described before prebiotics enhance the growth of probiotics, synbiotics optimize the combined effects of probiotics and prebiotics, and postbiotics offer additional health benefits through their bioactive compounds. This interconnected relationship helps maintain a balanced gut microbiome, supports immune function, and improves overall health (see Figure 4).

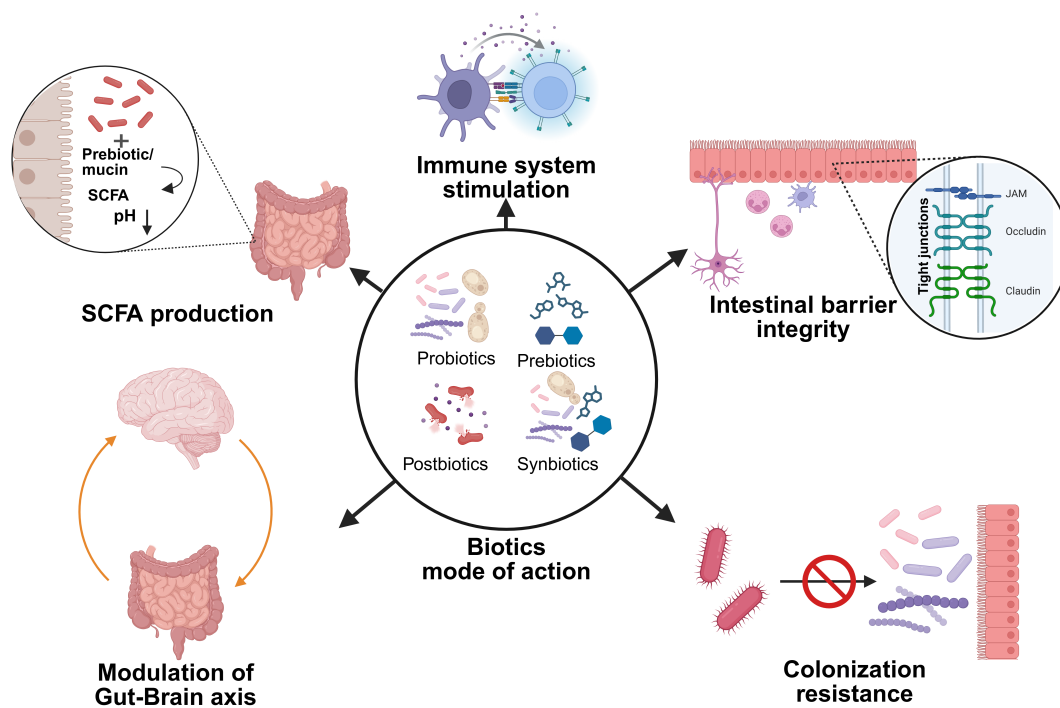
The efficacy of biotics has been demonstrated in numerous randomised controlled trials (Andresen et al. 2020; Łukasik et al. 2022; Srivastava et al. 2024; Lau et al. 2024). Some biotics have been registered as drugs (see Table III and IV), further proving their effective-

ness. Although the positive effects of biotics are extensively studied, their direct mechanisms of action are often not fully understood. Human microbiota plays an important role in health and diseases, yet its complexity makes creating representative models to study the relations very challenging (El-Sayed et al. 2021; Rios Garza et al. 2023).

The bidirectional gut-brain axis plays an important role in maintaining homeostasis. The dysfunction of the axis has been shown in diseases such as irritable bowel syndrome (IBS), major depressive disorder or ASD (Socała et al. 2021; Hillestad et al. 2022). Administration of probiotics can positively influence the abnormal functioning of the axis through both direct and indirect interactions. Production of bioactive compounds such as serotonin or SCFA and interaction with enteric and autonomic nervous system, are possible ways in which probiotics can positively affect the axis (Mayer et al. 2022). The high abundance of microbiota in various body sites, particularly in the colon, is the principle behind the colonization resistance. In health, body sites are colonized by symbiotic microorganisms, inhibiting the colonization of pathogens – Figure 4 (Caballero-Flores et al. 2023). When this state is disturbed, body sites can be colonized by pathogens, leading to disease. Administration of probiotics can prevent the colonization of pathogens and help restore proper microbiota by colonizing the body

sites themselves and/or promoting the colonization of other commensal microorganisms (Osbelt et al. 2021; Zheng et al. 2021; Gao et al. 2021). Prebiotics may also positively affect the integrity of the barrier by influencing the microbiota composition, significantly increasing the abundance of beneficial bacteria (Mellai et al. 2024).

Microorganisms present in GI tract are responsible for production and synthesis of various compounds, such as serotonin, gamma-aminobutyric acid (GABA), SCFA and vitamins (Beane et al. 2021; Socała et al. 2021; O’riordan et al. 2022). When the composition of microbiota is altered, an imbalance described as dysbiosis can occur. Administration of probiotics and their ability to produce SCFA, which lower the pH in the gut, can prevent the colonization of pathogens – Figure 4. SCFA are also used by the colonocytes as a source of energy (O’riordan et al. 2022). Postbiotics and synbiotics can also help in restoring the proper microbial composition e.g. by increasing the abundance of the *Faecalibacterium*, *Anaerobutyricum* and *Lactobacillales*, respectively (Jung et al. 2022; Srivastava et al. 2024; Naghibi et al. 2024). The microbiota plays crucial role in tryptophan and serotonin metabolism (Roth et al. 2021). Use of biotics can help maintain the proper balance, preventing dysbiosis, and when such imbalances occur, probiotics can help restore the balance (El-Sayed et al. 2021; He et al. 2022).



**Figure 4.** Basic mode of action of biotics. Created in BioRender.

The integrity of intestinal barrier is another very important aspect, which can be positively affected by biotics. In health, properly functioning barrier prevents the pathogens from penetrating the intestine wall and entering other body sites. Biotic administration, such as synbiotics, can enhance the integrity of the barrier by decreasing the level of pro-inflammatory biomarkers and increasing anti-inflammatory cytokines (Li et al. 2023). Mucin layer present in intestines prevents the direct contact of microorganisms with epithelial cells (Di Tommaso et al. 2021). Lack or thinning of this layer, observed in diseases e.g. inflammatory bowel disease (IBD), leads to constant stimulation of immune system as epithelial cells are directly exposed to microbial antigens. As a result, inflammation is observed and the integrity of the intestinal barrier is disrupted (Aleman et al. 2023). Mucin degradation is generally considered as a pathogenicity factor, but probiotic microorganism can use this ability to set an equilibrium between the mucin degradation and host production of mucin (Markowska and Kiersztan 2021). Products of mucin degradation, such as SCFA, can be beneficial to host. SCFA promote the tight junction formation, directly affecting the integrity of intestinal barrier (Hays et al. 2024). Constant immune system interactions with multiple microbial antigens, due to a disrupted intestinal barrier, negatively affect the host and can lead to diseases such as leaky gut syndrome (Chae et al. 2024). However, the interactions between the immune system and microorganisms are not always unfavourable. Postbiotic preparations can positively affect the activity of immune cells, thereby boosting host immunity (Kato et al. 2024).

While biotics offer a wide range of health benefits, the administration of probiotics and synbiotics can be associated with certain risks in immunocompromised individuals (Katkowska et al., 2021). In such populations, conditions like sepsis or endocarditis have been reported (Rahman et al., 2023; Eze et al., 2024). A promising alternative to mitigate these risks is the use of postbiotics (Figure 3). Preparations containing inanimate microorganisms, with or without their metabolites, do not carry the same risk associated with the intake of live microbes found in probiotics and synbiotics. Nevertheless, safety considerations remain essential, as components such as cell wall fragments or membrane elements e.g., endotoxin A (a part of the outer membrane in Gram-negative bacteria), may still raise significant safety concerns (Salminen et al., 2021; Vinderola et al., 2022). Changing the legal sta-

tus of probiotics to medicinal products could further enhance their safety profile, as any contraindications, supported by clinical trials, would be required to be clearly disclosed.

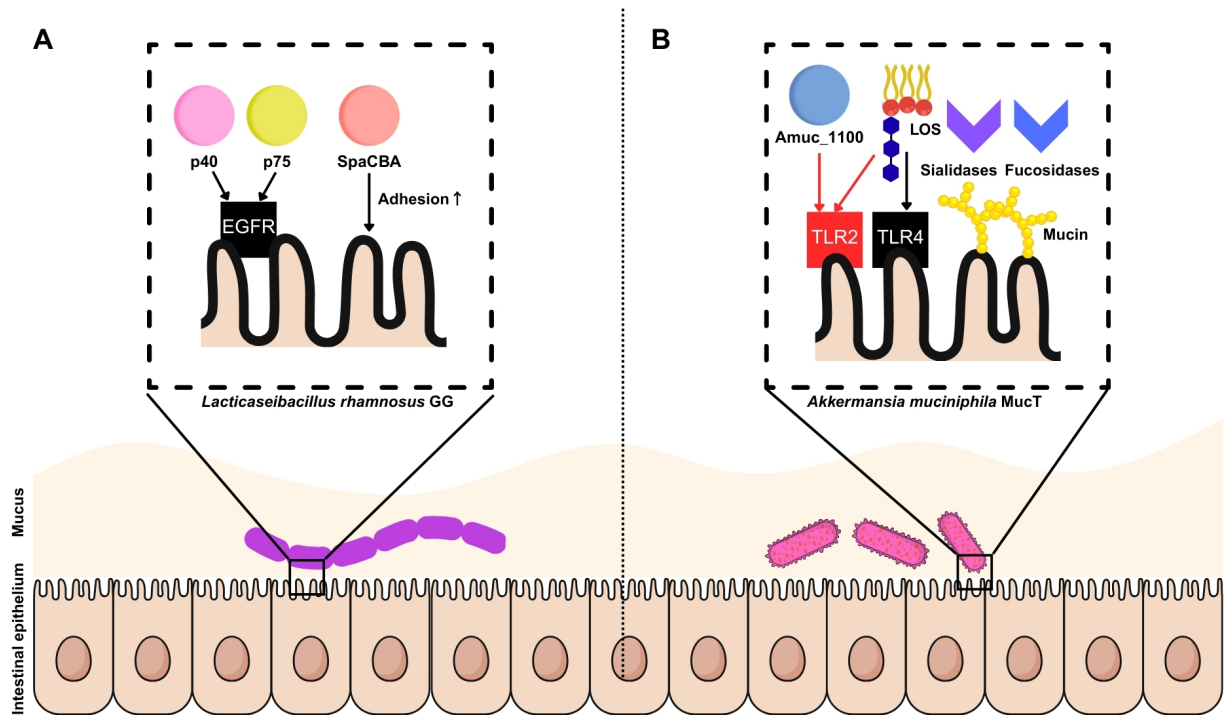
### 3.2. Molecular pathways

As mentioned before, biotics can interact with host in various ways. In this section, we present two examples of probiotic-host interactions, focusing on *L. rhamnosus* GG and *A. muciniphila* MucT. The former strain represents conventional probiotics and the latter serves as an example of novel probiotic strain.

In a healthy gut, microorganisms rarely interact directly with the intestinal epithelium, with Payer's Patches being one of the few exceptions. This is primarily due to the protective mucin layer covering the epithelial surface. *L. rhamnosus* GG secretes proteins (most notably p40 and p75) that contribute to host health, with p40 exerting a more pronounced effect. p40 activates the epidermal growth factor receptor, leading to reduced apoptosis and enhanced mucus production – Figure 5A. These effects collectively strengthen intestinal barrier integrity, which is essential in maintaining homeostasis (Leser and Baker, 2024). Although indirect interactions via secreted proteins are critical, direct contact also plays a role. The expression of *SpaCBA* operon, encoding *SpaCBA* pili, by *L. rhamnosus* GG facilitates adhesion to host cells, thereby preventing pathogen adhesion through colonization resistance – Figure 5A (Spacova et al., 2020). Additionally, molecular interactions of *L. rhamnosus* GG with enterocytes can inhibit the formation of reactive oxygen species (ROS) and chloride ion excretion, counteracting two key pathogenic mechanisms of rotavirus infection (Buccigrossi et al., 2022). *A. muciniphila* MucT interacts with host via Amuc\_1100 pili protein, which is recognized by Toll-like receptor 2 (TLR2) and lipooligosaccharide (LOS), which engages both TLR2 and Toll-like receptor 4 (TLR4) (Segers and de Vos, 2023; Garcia-Vello et al., 2024). These interactions enhance the transepithelial electrical resistance (TEER) and stimulate the production of anti-inflammatory cytokines such as IL-10, improving intestinal barrier integrity – Figure 5B (Ottman et al., 2017). *A. muciniphila* MucT indirect interactions are mediated by extracellular vesicles (EV) which also activate TLR2 and TLR4. The heat stable nature of LOS, EV and other components e.g. ornithine lipids, underscores its potential as a postbiotic (Garcia-Vello et

al., 2024; Ioannou et al., 2024). Another key aspect of this Gram-negative bacterium is mucin degradation. Through the activity of various fucosidases and sial-

idases, *A. muciniphila* effectively degrades mucin, thus stimulating its turnover and promoting the growth of other beneficial microorganisms (Shuoker et al., 2023).



**Figure 5.** Selected molecular mechanisms by which two probiotic strains, A - *Lactocaseibacillus rhamnosus* GG and B - *Akkermansia muciniphila* MucT, interact with host intestinal epithelium. Panel A illustrates *L. rhamnosus* GG indirect interactions mediated by p40 and p75, which interact with EGFR, as well as direct interactions induced by SpaCBA. Panel B illustrates *A. muciniphila* MucT direct and indirect interactions, the former shown as Amuc\_1100 and LOS interactions with TLR2 and TLR4, the latter as sialidases and fucosidases degrading mucin.

Legend: Amuc\_1100 - *A. muciniphila* MucT pilus protein; LOS - lipooligosaccharide; TLR2 - Toll-like receptor 2; TLR4 - Toll-like receptor 4; p40/p75 - *L. rhamnosus* GG secreted proteins; EGFR - epidermal growth factor receptor; SpaCBA - *L. rhamnosus* GG pilus protein.

### 3.3. Single vs. multiple-strain probiotics

The difference in efficacy between multiple-strain probiotics and single-strain probiotics is not clear and seems to depend on the given strain(s) and their estimated outcomes rather than a general rule (Ouweland et al. 2018). A meta-analysis conducted by McFarland shows that a two-strain probiotic containing *L. rhamnosus* GG and *B. lactis* Bb12, was more effective in eradicating the *H. pylori* than either strain alone. It was also found that single strain probiotic, containing *L. rhamnosus* GG was more effective in preventing necrotizing enterocolitis (NEC) compared with multiple strain probiotic containing the same strain. In cases of antibiotic-associated diarrhoea (AAD), atopic dermatitis/eczema, atopic dermatitis/allergy, upper respira-

tory tract infection (URTI), irritable bowel syndrome (IBS), there were no significant differences between single and multiple strain probiotics, whether the formulations were found to be effective or ineffective (McFarland, 2021). Another meta-analysis has shown superior effect of multiple strain probiotics in prevention of NEC (Morgan et al., 2020). Niu and Xiao's meta-analysis shows the superior effect of multiple strain probiotics in treatment of IBS, yet there are limitations to the study due to heterogeneity of RCTs (Niu and Xiao, 2020).

Evaluating the efficacy of single and multiple-strain probiotics is difficult, even when addressing the treatment or prevention of a specific disease. The number of papers that evaluate the differences between single and multiple-strain probiotics for the same strains is

limited. The differences in study design of RCTs (e.g. duration of treatment, dose), considering the same strain in different formulations, often prevent obtaining valuable data (McFarland 2021). Probiotics in multiple-strain formulations can exert additive, synergistic or antagonistic effects (Kwoji et al., 2021). Therefore, further research is needed to evaluate the efficacy of these formulations compared to corresponding single strain formulations, separately for a specific disease.

### 3.4. Efficacy and regulatory framework of biotics

Many clinical trials demonstrate the effectiveness of probiotics, prebiotics, synbiotics and postbiotics in various diseases (see Table II). Such use is particularly promising for diseases where current therapies prove to be ineffective or require long-term treatment. Given the critical role of the microbiota-gut-brain axis, biotics hold significant potential for managing psychiatric disorders, which are currently one of the major health challenges facing humanity (Soc ala et al. 2021).

The recent recognition that inanimate microorganisms can confer health benefits on the host, along with the unified definition of postbiotics presented by ISAPP, has facilitated studies and clinical trials for postbiotics (Salminen et al. 2021). Srivastava et al. studied the safety and efficacy of *Bifidobacterium longum* CECT 7347 as both a probiotic and postbiotic, the latter obtained through heat-treatment of the strain. The study proved safety and efficacy of both preparations, indicating that *Bifidobacterium longum* CECT 7347, in either form, is a good candidate for reducing the severity of IBS symptoms (Srivastava et al. 2024). The approach of studying the same strain in both probiotic and postbiotic formulation is uncommon and makes the study significant. The results show that postbiotics can be as effective as probiotics. In some aspects, postbiotics can be superior to probiotics, including better storage and safety standards (Ma et al. 2023; da Silva Vale et al. 2023).

The legal aspect of biotics is important considering their development and future. Regulations to classify a given biotic as a pharmaceutical or food supplement directly correspond to the quality of the product and its effectiveness. Currently the terms probiotic, prebiotic and synbiotic are overused (it is not the case for postbiotic since the term is novel). Many products, ranging from foods to personal care items, claim to contain probiotics. However, such statements are often not verified, due to the legal characteristics of these products. It is also important to acknowledge that the presence of

live microorganisms in the product (e.g. in yogurt) is not enough to identify the product as a probiotic. Microorganisms present in such products must confer a proven health benefit to be considered probiotics (Hill et al. 2014).

The regulatory framework for probiotics is not homogenous across European Union. In Poland probiotics can be considered pharmaceuticals, food supplements and dietary foods for special medical purposes (Ruszkowski et al. 2018). In Poland there are only a few biotics registered as drugs – Table III and IV. Most of the biotics available commercially are food supplements, which do not undergo the strict regulations applied for drugs (Sionek and Ko ozyn-Krajewska 2019).

In the USA, the FDA coined a new term, the live biotherapeutic product (LBP), to regulate the field of probiotics. The issue with this approach is that LBP can only refer to probiotics and synbiotics, as by the definition, LBP must contain live microorganisms (FDA 2016). To address postbiotics or prebiotics in a similar way, new term(s) must be coined, or LBP definition has to be modified.

The legal aspect of biotics is crucial in implementing safe and effective products that customers can trust. In addition to conducting the necessary studies to evaluate the safety and efficacy of probiotics, prebiotics, synbiotics, and postbiotics, it is important that the regulatory framework and laws adapt to the latest scientific literature, ensuring the access to high-quality products. The unification of the terms, such as those presented by ISAPP, should also be considered to enhance the customers knowledge (Liang et al. 2024).

**Table II.** Examples of health benefits demonstrated by probiotics, prebiotics, synbiotics and postbiotics in clinical trials.

Composition	Classification	Health benefits	Daily dose and duration	Reference
<i>Lactiplantibacillus plantarum</i> PS128	Probiotic	Amelioration of symptoms in children with ASD, such as: - disruptive and rule breaking behaviours - hyperactivity/impulsivity	3x10 <sup>10</sup> CFU for 28 days	Liu et al., 2019
<i>Bifidobacterium bifidum</i> BGN4 <i>Bifidobacterium longum</i> BORI	Probiotic	- stress alleviation - mental flexibility - beneficial changes in microbiota	1x10 <sup>9</sup> CFU 1x10 <sup>9</sup> CFU for 12 weeks	Kim et al., 2020
<i>Lactocaseibacillus rhamnosus</i> ŁOCK 0900 <i>Lactocaseibacillus rhamnosus</i> ŁOCK 0908 <i>Lactocaseibacillus casei</i> ŁOCK 0918	Probiotic	Significant improvement in atopic dermatitis symptom severity	1x10 <sup>9</sup> CFU for 3 months	Cukrowska et al., 2021
<i>Bifidobacterium bifidum</i> W23 <i>Bifidobacterium lactis</i> W51 <i>Lactobacillus acidophilus</i> W37 <i>Lactobacillus acidophilus</i> W55 <i>Lactocaseibacillus paracasei</i> W20 <i>Lactiplantibacillus plantarum</i> W62 <i>Lactocaseibacillus rhamnosus</i> W71 <i>Ligilactobacillus salivarius</i> W24	Probiotic	Reduced risk of diarrhoea during and 7 days after antibiotic treatment	1x10 <sup>10</sup> CFU during antibiotic treatment + 7 days	Łukasik et al., 2022
<i>Bacillus subtilis</i> BS50	Probiotic	Alleviation of gas-related gastrointestinal symptoms	2x10 <sup>9</sup> CFU for 6 weeks	Garvey et al., 2022
<i>Bacillus subtilis</i> MB40	Probiotic	Elimination of <i>Staphylococcus aureus</i> without altering the microbiota	1x10 <sup>10</sup> CFU for 30 days	Piewngam et al., 2023
<i>Lactocaseibacillus rhamnosus</i> CECT 30031, <i>Arthrospira platensis</i> BEA_IDA_0074B	Probiotic	Significant reduction in the severity of acne vulgaris	1x10 <sup>9</sup> CFU for 12 weeks	Eguren et al., 2024
<i>Escherichia coli</i> Nissle 1917	Probiotic	Potential use of engineered <i>E. coli</i> Nissle 1917 in adenoma diagnosis and therapy of colorectal cancer	1x10 <sup>9</sup> CFU for 14 days	Gurbatri et al., 2024
<i>Saccharomyces boulardii</i> CNCM I-745	Probiotic	In patients with SIBO, associated with dietary advice: - Improved digestive symptoms - restoration of the intestinal microbiota	500 mg for 15 days	Bustos Fernández, Man and Lasa, 2023
<i>Streptococcus thermophilus</i> BT01	Probiotic	Reduction of urease activity in faecal samples	1x10 <sup>11</sup> aFU for 1 week	Martinović et al., 2023
<i>Lactobacillus crispatus</i> DSM32717 DSM32720, DSM32718, DSM32716	Probiotic	Reduction of the signs and symptoms of bacterial vaginosis - significant increase in the lactobacilli counts in the vagina - lowered combined score of the amount of discharge and itching/irritation in vulvovaginal candidiasis	3x10 <sup>10</sup> CFU for 3 months	Māndar et al., 2023
<i>Lactobacillus acidophilus</i> <i>Lactiplantibacillus plantarum</i> <i>Bifidobacterium lactis</i> <i>Saccharomyces boulardii</i> (LactoLevure®)	Probiotic	- positive effects on glycaemic and lipid parameters - improvements in measures of adiposity in individuals with Type 2 Diabetes	1,75x10 <sup>9</sup> CFU 0,5x10 <sup>9</sup> CFU 1,75x10 <sup>9</sup> CFU 1,5x10 <sup>9</sup> CFU for 6 months	Zikou et al., 2023
<i>Lactocaseibacillus rhamnosus</i> GG	Probiotic	Beneficial modulation of gut and skin microbiome	1x10 <sup>10</sup> CFU for 12 weeks	Carucci et al., 2022

Composition	Classification	Health benefits	Daily dose and duration	Reference
<i>Bifidobacterium longum</i> CECT 7347	Probiotic	Reducing IBS symptom severity	1x10 <sup>9</sup> for 84 days	Srivastava et al., 2024
<i>Opuntia ficus-indica</i> extract (Odia <sup>TM</sup> )	Prebiotic	Positive modulation of gut microbiota composition: - significant reduction in the <i>Firmicutes</i> to <i>Bacteroidetes</i> ratio - significant increase in relative abundances of beneficial bacteria - significant reduction in pro-inflammatory bacteria	300 mg for 8 weeks	Mellai et al., 2024
Inulin and oligofructose	Prebiotic	- significant improvement in frailty and renal function - increases in protein levels, body fat percentage, walking speed, grip strength - elevation in gut probiotic count - induced alterations in microbial metabolite expression levels among the older population	15 g for 3 months	Yang et al., 2024
Yeast mannan	Prebiotic	- An increase in the frequency and volume of bowel movements - accelerated transition to deep sleep stage and lengthened duration	1,1 g for 4 weeks	Tanihiro et al., 2024
<i>Bifidobacterium adolescentis</i> , <i>Bifidobacterium bifidum</i> , <i>Bifidobacterium longum</i> and galactooligosaccharides, xylooligosaccharides, resistant dextrin (SIM01)	Synbiotic	Alleviation of multiple symptoms of PACS	2x10 <sup>10</sup> CFU for 6 months*	Lau et al., 2024
<i>Bifidobacterium lactis</i> HN019, <i>Lactocaseibacillus rhamnosus</i> HN001 and fructooligosaccharide	Synbiotic	Decrease in pro-inflammatory biomarkers (CRP and IFN- $\gamma$ ) and increased anti-inflammatory cytokine (IL-10 and sIgA)	1,5x10 <sup>8</sup> CFU 7,5x10 <sup>7</sup> CFU and 500 mg for 8 weeks	Li et al., 2023
<i>Lactocaseibacillus rhamnosus</i> FloraActive <sup>TM</sup> 19070-2, <i>Lactobacillus acidophilus</i> DSMZ 32418, <i>Bifidobacterium lactis</i> DSMZ 32269, <i>Bifidobacterium longum</i> DSMZ 32946, <i>Bifidobacterium bifidum</i> DSMZ 32403 and fructooligosaccharides	Synbiotic	Significant amelioration in: - feeling of incomplete bowel movements - flatulence - pain - stool pressure and diarrheal stools	1,96x10 <sup>9</sup> CFU  9,80x10 <sup>8</sup> CFU 5,88x10 <sup>9</sup> CFU 5,88x10 <sup>8</sup> CFU  5,88x10 <sup>8</sup> CFU and 1,894 g for 8 weeks	Skrzydło-Radomańska et al., 2020
<i>Lactobacillus acidophilus</i> La-14, <i>Lactiplantibacillus plantarum</i> Lp-115, <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> CBG-C10 and fructooligosaccharide (LactominPlus <sup>®</sup> )	Synbiotic	- improvement in the degree of formed stool - decrease in faecal calprotectin level - increase in <i>Lactobacillales</i>	2,9x10 <sup>7</sup> CFU 4,7x10 <sup>7</sup> CFU 2,4x10 <sup>7</sup> CFU and 1,2 g for 8 weeks	Jung et al., 2022
<i>Bifidobacterium bifidum</i> MIMBb75	Postbiotic	Alleviating IBS and its symptoms	1x10 <sup>9</sup> cells for 8 weeks	Andresen, Gschossmann and Layer, 2020

Composition	Classification	Health benefits	Daily dose and duration	Reference
<i>Limosilactobacillus reuteri</i> DSM17648 (Pylopass)	Postbiotic	Improved effectiveness of <i>Helicobacter pylori</i> eradication therapy in patients with functional dyspepsia	2x10 <sup>10</sup> cells for 28 days	Ivashkin et al., 2024
<i>Bifidobacterium longum</i> CECT 7347	Postbiotic	- decreased total and non-HDL cholesterol - significant increase in the abundance of the genera <i>Faecalibacterium</i> and <i>Anaerobutyricum</i> - reduced IBS symptom severity	2,5x10 <sup>9</sup> cells for 8 or 12 weeks	Naghibi et al., 2024; Srivastava et al., 2024
<i>Akkermansia muciniphila</i> HB05	Postbiotic	Significant increase in muscle strength among individuals aged 60 years or older	1x10 <sup>10</sup> cells for 12 weeks	Kang et al., 2024
<i>Lactocaseibacillus paracasei</i> MCC1849	Postbiotic	- increasing plasmacytoid dendritic cells activity - beneficial effects on immune cells in healthy adults	5x10 <sup>10</sup> cells for 4 weeks	Kato et al., 2024

Legend: ASD – autism spectrum disorder, SIBO - small intestinal bacterial overgrowth, PACS - post-acute COVID-19 syndrome, CRP - C-reactive protein, IFN- $\gamma$  - interferon gamma, IL-10 - interleukin-10, sIgA - secretory immunoglobulin A, IBS – irritable bowel syndrome, non-HDL - non-high-density lipoprotein, CFU – colony forming unit, aFU - active fluorescent unit, \*- no data for prebiotic dose.

**Table III.** Orally administered probiotics and postbiotics, commercially available in Poland and registered as drugs.

Name	Classification	Content per one capsule or sachet	Recommended use
Lakcid Forte - POLPHARMA S.A.	Probiotic	10x10 <sup>9</sup> CFU: - <i>Lactocaseibacillus rhamnosus</i> Pen (40%) - <i>Lactocaseibacillus rhamnosus</i> E/N (40%) - <i>Lactocaseibacillus rhamnosus</i> Oxy (20%)	Treatment of antibiotic-associated colitis, including pseudomembranous colitis; supportive treatment during and after antibiotic therapy; prevention of traveller's diarrhoea
Lakcid Entero - POLPHARMA S.A.	Probiotic	250 mg ( $\geq 10^{10}$ CFU/1 g) - <i>Saccharomyces cerevisiae</i> var. <i>boulardii</i>	Treatment of acute infectious diarrhoea, diarrhoea in IBS, AAD, recurrent <i>Clostridium difficile</i> diarrhoea; prevention of diarrhoea associated with enteral nutrition, traveller's diarrhoea, as an adjunct in treatment of <i>H. pylori</i>
Lacidofil - LALLEMAND S.A.S.	Probiotic	2x10 <sup>9</sup> CFU*: - <i>Lactocaseibacillus rhamnosus</i> R0011 - <i>Lactobacillus helveticus</i> R0052	Treatment of recurrent pseudomembranous colitis, supportive treatment during and after antibiotic therapy; prevention of traveller's diarrhoea
Enetrol – BIOCODEX	Probiotic	250 mg: - <i>Saccharomyces boulardii</i> CNCM I-745	Treatment of acute infectious diarrhoea, recurrent <i>Clostridium difficile</i> diarrhoea; prevention of diarrhoea associated with enteral nutrition, traveller's diarrhoea; as an adjunct in treatment in IBS diarrhoea
Lacteol Fort 340 mg - DSM-Firmenich Houdan SAS	Postbiotic	340 mg including: - Inactivated <i>Limosilactobacillus fermentum</i> and <i>Lactobacillus delbrueckii</i> – 10x10 <sup>9</sup> CFU - Fermented medium – 160 mg	Supportive treatment of diarrhoea
Trilac - Krotex Pharm	Probiotic	1,6x10 <sup>9</sup> CFU: - <i>Lactobacillus acidophilus</i> La-5 (37,5%) - <i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> Lb-Y27 (25%) - <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> Bb-12 (37,5%)	Treatment of antibiotic-associated colitis, including pseudomembranous colitis; prevention of traveller's diarrhoea; supportive treatment after antibiotic therapy

Legend: AAD – antibiotic-associated diarrhoea; CFU – colony forming unit; IBS – irritable bowel syndrome; \*- ratio for each strain has not been declared.

**Table IV.** Non-orally administered probiotics registered as drugs in Poland.

Name	Classification	Content per one capsule	Recommended use
Lakcid Intima – POLPHAR-MA S.A.	Probiotic	- <i>Lactobacillus gasseri</i> DSM 14869 $\geq 10^8$ CFU - <i>Lacticaseibacillus rhamnosus</i> DSM 14870 $\geq 10^8$ CFU	Preventive use to maintain or restore normal vaginal microbiota
Lactovaginal – BIOMED S.A.	Probiotic	- <i>Lacticaseibacillus rhamnosus</i> 573 $\geq 10^8$ CFU	Preventive use; treatment of vaginal discharge and inflammation of reproductive organs after the antibacterial, antitrichomonal, or antifungal treatment
inVag – BIOMED S.A.	Probiotic	$\geq 10^9$ CFU: - <i>Limosilactobacillus fermentum</i> 57A (25%) - <i>Lactiplantibacillus plantarum</i> 57B (25%) - <i>Lactobacillus gasseri</i> 57C (50%)	Prevention of genitourinary infections; supportive treatment in vaginitis, during and after antibiotic and/or antifungal treatment
Protrivagin – Verco S.A.	Probiotic	- <i>Lactiplantibacillus plantarum</i> P 17630 $10^8$ CFU	Normalization of the disrupted vaginal microbiota after antibiotic therapy for bacterial vaginosis; maintaining normal vaginal microbiota in recurrent infections

Legend: CFU – colony forming unit.

#### 4. Future perspectives

Biotics present great potential in treatment and prevention of multiple diseases. As mentioned in the previous paragraph, the regulatory framework can be a limiting factor for implementing novel therapeutics. Therefore, the future of biotics greatly depends on legal aspects (Cordailat-Simmons et al. 2020; Liang et al. 2024).

Some authors point out that individual differences in microbiota make the use of formulations with invariable composition unjustified (Lee et al. 2021). This has led to the idea of using personalized therapies. Such personalization could be achieved based on the presence of the characteristic microbiota. In 2011 the idea of enterotypes was proposed (Arumugam et al. 2011). The study distinguished three enterotypes based on specific relation of the present taxa. Since then, the idea of enterotypes has been studied. Multiple authors proposed a new insight on the topic, considering new classification, the influence of enterotypes on nutrition and probiotic intake (Costea et al. 2017; Liang et al. 2017; Chen et al. 2017; Song et al. 2020; Lee et al. 2021; Cerdó et al. 2022; Yuan et al. 2022) Although the idea of enterotypes is well established in the literature, novel reports show no basis for identifying such groups, thus

suggesting the absence of enterotypes in the human gut (Bulygin et al. 2023).

While the idea of enterotypes evolved and number of distinguished enterotypes has changed, the approach to question their existence in general, as presented by Bulygin et al., is novel and groundbreaking (Gorvitovskaia et al. 2016; Mobeen et al. 2018; Jiao et al. 2022; Bulygin et al. 2023). To the best of authors knowledge, the cited article is the only one that states the absence of enterotypes and supports this claim with data (Bulygin et al. 2023). The idea of enterotypes, understood as discrete clusters, was challenged earlier by Cheng and Ning, who proposed a more continuous understanding of the term (Cheng and Ning 2019).

Such cutting-edge approach, denying the existence of enterotypes, may be controversial given the fact that the idea of enterotype has been well established in the literature. Many clinical trials proved the correlation between the enterotypes and health (Christensen et al. 2020; Vallet et al. 2023; Jamieson et al. 2024).

As our understating of human microbiota constantly evolves, the idea of personalized therapies can be promising, even if enterotypes will be abandoned in their present understanding (Abouelela and Helmy 2024). Tools such as next-generation sequencing and machine learning help isolate potentially beneficial

microorganisms, by some classified as NGP, and at the same time provide more data for better understanding of the microbiota relations (Chollet et al. 2024; Hasnain et al. 2024). The field of biotics would greatly benefit from the unification of nomenclature, a problem this article directly addresses. The wide variety of terms used, often synonymous, hinders the understanding of the subject by stakeholders (Salminen et al. 2021). Biotics are promising in the treatment of various diseases, including civilization diseases, positively affecting general health, preventing colonization of the pathogens and dysbiosis (see Table II) (Logan and Katzman 2005; Maldonado Galdeano et al. 2019; Osbelt et al. 2021; Caballero-Flores et al. 2023).

Further research could focus on postbiotic inactivation methods. As shown, inanimate microorganisms and their metabolites exhibit great potential, which is often limited by the lack of efficient inactivation techniques, capable of preserving bioactive properties, while remaining cost-effective and scalable. Additionally, omics-driven approaches may be employed to identify novel probiotic candidates and to investigate the characteristics and potential applications of already selected strains. Characterization of individual microbiome using next-generation sequencing (NGS) can enable the development of personalized therapies. As shown, microorganism derived products such as secreted proteins can exert therapeutic effect. Studying the proteomics on both host and microbial level along with their interactions, may deepen our understanding of host-microbiome relationship, supporting the development of novel biotics. Evaluating the efficacy of biotics, such as differences between single- and multi-strain probiotics, safety considerations, and the regulatory framework, remains a critical area of research.

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#### Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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