



EDITORIAL

Metabiotics: do we need a new definition?**Metabióticos: ¿necesitamos una nueva definición?**

It is a well-established fact that when a microbe grows in a laboratory, industrial culture medium, or in nature, it produces a range of metabolites with a plethora of biological activities, whether studied as single purified-metabolites, a combination of them or the whole package of synthesized metabolites, generally referred to as cell-free supernatant. The chemical nature of these compounds will be intrinsically related to the environmental growth conditions. In fact, the type of nutrients, temperature and pH during growth, water activity, harvesting time, and even the co-culture with other microbes significantly impact the profile of metabolites produced. Some metabolites have been clearly identified and were fully characterized, such as lactic acid, nisin, surfactin, among many others. In other cases, cell-free supernatants are used to study their biological activities, making it impossible to link a specific biological effect or health benefit to a defined metabolite.

The term *biotic* has been used in science to refer to living things and derivatives. Many prefixes have been added to the term biotic to form a growing family of biotic terms such as probiotics, psychobiotics, paraprobiotics, parapsychobiotics, immunobiotics, postbiotics, pharmabiotics, globobiotics, and the list could go on almost forever. In 2022, an opinion letter titled "The Never-Ending List in the Family of Biotics" addressed this issue.¹ For some of these terms, consensus definitions were proposed and pushed forward. However, for other terms, a clear definition is lacking, and moreover, there are some terms that overlap in meaning, creating confusion and misunderstanding among stakeholders (academics, industry, health professionals, consumers and regulators). The proper use of terms and definitions is key for a common understanding of any topic. The importance of having clear definitions that are quickly adopted and well implemented by all stakeholders has been very nicely addressed for the term prebiotics, for example, by Hutkins et al.,²

As an example, a metabolite of interest for its anti-inflammatory capacity in the gut is butyric acid. Butyric acid is commonly referred to as a postbiotic, "a metabo-

lite produced by a probiotic", according to some opinions. The point of view of considering metabolites as postbiotics, and the weaknesses and limitations of this approach, has been the focus of recent publications.³ Existing nomenclature can be used in the case of simple, fully characterized metabolites, such as butyrate, or collective names such as filtrates or cell-free supernatants can be used for more complex preparations of unpurified metabolites. This approach prevents the confusing situation where a microbe-derived metabolite or metabolite mixture is called a 'postbiotic', but an identical chemically synthesized preparation is not. Some authors have proposed the use of the term '*metabiotics*' to collectively refer to metabolites able to confer a health benefit.³ Other authors have suggested that metabiotics are the structural components of probiotic microorganisms and/or their metabolites and/or signalling molecules with a determined (known) chemical structure that can optimize host-specific physiological functions, regulator, metabolic and/or behavior reactions connected with the activity of host indigenous microbiota.⁴ Thus, metabiotics would have some advantages because of their exact chemical structure, precise dose, proved safety and long shelf-life. However, requiring that a metabiotic be derived from a probiotic may impose barriers to development, as you are forced to conduct two clinical trials: the first to demonstrate that the producing strain is a probiotic, and the second to prove that the metabiotic should confer a health benefit. Any new definition should be carefully considered, without imposing unnecessary burdens to development. A metabiotic could be produced by any microbes if the product is safe and effective, irrespective of the nature of the producing microbe, be it a probiotic or not.

However, a careful and thorough expert debate aiming to differentiate any new terminology from existing definitions should be undertaken before introducing a new term and its definition. In some cases, the introduction of a new term and definition may bring more drawbacks than solutions to the field of interest. In this sense, it is worth mentioning the number of researchers and academic groups around the world such as the International Scientific Association for

Probiotics and Prebiotics (ISAPP), which has been actively engaged in proposing terms and definitions since its foundation in 2002. This association of academics and industrial scientists is involved in basic and applied research on probiotics, prebiotics, synbiotics, postbiotics, fermented foods and the microbiome, for both human and animal health.

Although some disagreement exists among the broader scientific community regarding some of the definitions, it is important to underline principles to neither unnecessarily limit future innovations, restrict potential mechanisms of action, or artificially restrain their scope (i.e., host, regulatory category, mechanism, site of action, etc.). Moreover, this type of discussion requires the demonstration of a health benefit on a target host; otherwise, what is the value of these new biotic substances? Of course, fermented foods are the exception to this criterion, because the value of consuming them, even in the absence of an established health benefit, is evident.

Many published definitions, including previous ones for postbiotics,³ are untenable because they do not recognize these principles. There may also be a tendency to rely on historical uses of terms, rather than describe what is justified by current scientific knowledge. A good example of this is provided by the first definition of probiotics, published in 1965, namely "substances secreted by one microorganism that stimulate another microorganism",⁵ which is far from the current definition of "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host".⁶

In this context, many purified metabolites, or undefined mixtures of metabolites have been shown to exert health benefits when administered in adequate amounts. Since "postbiotics" would not be the right term for them, is it timely to propose a new collective name? Is metabiotics the right term? What would be a proper definition? Time will tell.

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