The Concept of Postbiotics

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In 2021, the International Scientific Association for Probiotics and Prebiotics (ISAPP) defined a postbiotic as “a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host”. This definition of postbiotic requires that the whole or components of inactivated microbes be present, with or without metabolic end products. The definition proposed by ISAPP is comprehensive enough to allow the development of postbiotics from different microorganisms, to be applied in different body sites, encouraging innovation in a promising area for any regulatory category and for companion or production animals, and plant or human health. From a technological perspective, probiotic products may contain inanimate microorganisms, which have the potential to impart a health benefit. However, their contribution to health in most cases has not been established, even if at least one probiotic has been shown to confer the same health benefit by live or inanimate cells.

postbiotics probiotics International Scientific Association for Probiotics and Prebiotics ISAPP

1. Introduction

Cell viability has long been regarded as important for a probiotic to confer a health benefit. However, it has been long recognized that non-viable microbes, their cell components, and their metabolites also can impact health. A number of different terms can be found in the published research to address these preparations: non-viable probiotics, heat-killed probiotics, tyndallized probiotics, cell lysates, paraprobiotics, ghostbiotics and postbiotics [1]. In mid-2021, a definition of postbiotics was proposed by the International Scientific Association of Probiotics and Prebiotics (ISAPP), stating that a postbiotic is a “preparation of inanimate microorganisms and/or their components that confers a health benefit on the host” [1]. This definition was debated for more than one year by a consensus panel composed of scientists with different backgrounds and perspectives. Usage of this term has grown over recent years, but until 2021, no consensus definition had been published, and indeed, many different conceptualizations of this term were in use. This precise, well-considered definition provides a basis for clarity and accuracy in communications about postbiotics, to the benefit of scientists, industry and regulators.

2. Postbiotic Definition

Postbiotic is a term derived from the Greek for ‘post’, meaning after, and ‘bios’, meaning life. Further, the ‘biotic’ family of terms (probiotics, prebiotics, synbiotics and postbiotics) coalesces around microbes (or their substrates) (**Table 1**). Therefore, the term postbiotic appropriately refers to substances derived after the microorganisms are no longer alive, or, in other words, inanimate, dead or inactivated. The microbes comprising a postbiotic may be inanimate, intact cells or may be structural fragments of microbes, such as cell walls. Many preparations of

postbiotics also retain microbe-produced substances, such as metabolites, proteins, or peptides, which may contribute to the overall health effect conferred by a postbiotic, but such components are not essential to a postbiotic. A postbiotic must be derived from a well-defined microorganism or combination of microorganisms for which genomic sequences are known and prepared using a delineated technological process of biomass production and inactivation, which can be reliably reproduced.

Table 1. Definitions of 'biotics' family of substances put forward by consensus panels convened by ISAPP. Note that all substances have been defined in a manner that does not restrict target host, target benefit, regulatory category, site of action on the body or specific mechanism of action. All substances must be safe for their intended use and properly identified/characterized, with a documented health benefit.

Term (Example)	Definition	SIMPLE Way to Conceptualize	Note
Probiotic (*Bifidobacterium animalis* subsp. *lactis* BB-12 [2])	Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [3]	Live microbes that are beneficial for the host health	Identity must be confirmed through genome sequencing. An efficacious dose of viable probiotics must be preserved through the end of shelf life.
Prebiotic (Inulin, FOS, or GOS [4])	A substrate that is selectively utilized by host microorganisms conferring a health benefit on the host [5]	"Food" for beneficial microbes residing in or on the host that provide a health benefit	Not all fibers are prebiotics. Candidate prebiotics include substances such as polyphenols, which are not fibers.
Synbiotic (*B. lactis* BB-12 + inulin [6])	A mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host [7]	Probiotic + Prebiotic, defined as a complementary synbiotic	Two types of synbiotics have been defined: complementary and synergistic. A synergistic synbiotic contains a live microbe (not necessarily a proven probiotic) and a substrate (not necessarily a proven prebiotic) that it can use for growth.
Postbiotic (heat-killed *Akkermansia mucinophila* ATCC BAA-835 [8])	Preparation of inanimate microorganisms and/or their components that confers a health benefit on the host [1]	Intact non-viable microbes or cell fragments, with or without metabolites that provide a health benefit	Purified metabolites do not qualify as postbiotics

Prior to settling on the definition of postbiotic, the ISAPP panel considered other definitions that had been previously published (**Table 2**), as well as the Greek derivation of the word. Most published definitions of postbiotic focused on metabolites or factors produced by microbes. Some also included dead or inactivated microbes. Other stipulations in some definitions were problematic. For example, the requirement that a postbiotic should be produced from a probiotic places capricious restrictions on a postbiotic. A probiotic by definition must meet specific

criteria, including a documented health benefit [9]. It is not clear what the value is of stipulating that the starting material for a postbiotic must in itself be proven to be a probiotic, when a postbiotic is so different from a probiotic and an established health benefit for a live microbe does not predict a benefit in an inactivated form. Such a definition would also be a barrier to innovation as the research path should first establish that a microbe is a probiotic, or restrict the starting microbe to already established probiotics, and then go on to meet the criteria for a postbiotic when the latter should be sufficient. Further, definitions that focused on metabolites from probiotics were problematic as, by that definition, a metabolite produced by a probiotic could be a postbiotic, whereas the chemically identical metabolite produced by a microbe not established to be a probiotic would not be. Another concern about some previous definitions is the absence of a clear requirement for a health benefit. If no health benefit is specified, then it is uncertain what value is added by the use of a postbiotic. Some definitions were unclear if the postbiotic was to be administered to a target host or could instead be produced in situ via the normal activities of resident or administered microorganisms. Definitions that do not distinguish between a product that is administered and substances that are produced in situ have an unclear path to translation into foods, feeds and other final products. Finally, other definitions stipulated that postbiotics target only the gut lumen [10], leaving out the possibility of applying postbiotics to other surfaces, such as the vagina or the skin. Taken together, the previously published definitions of postbiotic were deemed to be vague and lacking consideration of important, practical factors. Further exciting new research in the area of potential health benefits of inactivated microbes has accumulated. Hence, the ISAPP consensus panel focused on the inanimate microbe, not on their metabolic outputs. Opposition to the ISAPP definition was levied shortly after its publication [11], and the corresponding reply refuting the criticism was also published [12].

Table 2. Published definitions of postbiotics (adapted from [12]; [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/), accessed on 22 February 2022)).

Definition	Microbial Cells/Cell Components Included?	Metabolites Included in the Absence of Cells/Cell Components?	Scope Limited to Substances Produced by a Probiotic?	Health Benefit Required?	Is In Situ Production of 'Postbiotic' Sufficient?
Any factor resulting from the metabolic activity of a probiotic or any released molecule capable of conferring beneficial effects to the host in a direct or indirect way [10]	No	Yes	Yes	No	Yes
Soluble factors (products or metabolic byproducts), secreted by live bacteria, or released after bacterial lysis, such as enzymes, peptides, teichoic acids, peptidoglycan-derived	No	Yes	No	No	Yes

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muropeptides, polysaccharides, cell surface proteins, and organic acids [13]					
Compounds produced by microorganisms released from food components or microbial constituents, including non-viable cells that, when administered in adequate amounts, promote health and well-being [14]	Yes (not required)	Yes	No	Yes	No
Non-viable metabolites produced by probiotics that exert biological effects on the hosts [15]	No	Yes	Yes	No *	Yes
Non-viable bacterial products or metabolic byproducts from probiotic microorganisms that have positive effects on the host or microbiota [16]	No	Yes	Yes	No **	Yes
Functional bioactive compounds, generated in a matrix during fermentation, which may be used to promote health [17]	No	Yes	No	Yes	No
Preparation of inanimate microorganisms and/or their components that confers a health benefit on the host [1]	Yes (required)	No	No	Yes	No

* Biological, but not health effects, stipulated. ** A health benefit is not specifically stipulated.