PURINA Institute

Advancing Science for Pet Health

UNDERSTANDING POSTBIOTICS
and Their Effects on Gastrointestinal and Host Health

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The gastrointestinal (GI) tract is a complex ecosystem in which the resident microbiota and the host interact in numerous ways to establish and maintain a functional barrier that protects the host from attack and infection by pathogens and ingested substances to which the host is continually exposed. A growing body of evidence has shown that the resident microbiota also play many active, beneficial roles in host health. Optimal microbiome health supports digestive, metabolic, and local and systemic immune function as well as intestinal and extra-intestinal health.

Diet has a profound impact on health, including gut health and the health and resilience of the microbiome. Nutritional interventions with “biotics” such as prebiotics, probiotics, synbiotics (combinations of pre- and probiotics), postbiotics, and combinations of biotics offer numerous opportunities to positively impact host health.

CONTENTS

WHAT ARE POSTBIOTICS?

Unlike other biotics, postbiotics are not yet universally defined. The International Scientific Association for Probiotics and Prebiotics (ISAPP) convened an expert panel that published a consensus document regarding the definition of postbiotics.[1] Prior to the 2021 ISAPP consensus statement, there were 6 different definitions of postbiotics in the scientific literature.[2] The ISAPP consensus definition for postbiotic is "a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host," indicating two primary parts: 1) inanimate cells and/or cell components; 2) with or without metabolites.[1,3] See ***Table 1*** for ISAPP definitions of prebiotics, probiotics, synbiotics, and postbiotics.

According to ISAPP, the term "postbiotic" is derived from the Greek language, with "post" indicating "after" and "biotic" meaning "living thing;" therefore, a postbiotic is something that was alive but is now in its "after life" phase and inanimate.[3] Many of the beneficial effects of probiotics with viable microorganisms may also be observed when administering the same microorganisms after they have been killed/inactivated (i.e., as postbiotics) – both live and dead microorganisms can serve as biological response modifiers.[1,4-8]

The ISAPP definition of a postbiotic includes the following criteria:[1-3,9-11]

- Postbiotics do not contain live microorganisms but must be derived from (a) living microorganism(s) and their inactivation must be confirmed.
- Postbiotics are not simply dead/inanimate probiotics; postbiotics are deliberately inanimate and a postbiotic's efficacy must be separately established.
- Postbiotics are consumed or applied; the term does not apply to metabolites or products produced *in situ* (e.g., as part of normal microbiome function or in response to administration of a prebiotic, probiotic, or synbiotic).
- Semi-purified or purified metabolites in the absence of cellular components do not qualify as postbiotics because dead microbes or microbial cell fragments or structures must be present to qualify as a postbiotic.
- A postbiotic should be sufficiently characterized to allow for reproducibility and adequate quality control. The source microorganism must be clearly identified, and the inactivation process described in detail.
- The safety of the postbiotic has been assured.
- The health benefit must be supported by a well-designed intervention trial in the target host at the appropriate dose.

Other terms that have been used, but are now considered outdated and seceded by the ISAPP definition, include paraprobiotics, parapsychobiotics, inactivated probiotics, non-viable probiotics, ghost probiotics, metabiotics, biogenics, cell-free supernatants, Tyndallized probiotics, and bacterial lysates.[1,5,12-17]

Controversy in the definition of postbiotics

There is dispute regarding ISAPP's requirement that dead microbes or microbial cell fragments or structures must be present to qualify as a postbiotic.[2,3,11,12] Previous definitions of postbiotics did not have this requirement, and considered cell-free supernatants and purified metabolites to be postbiotics.[5,12,16] In this monograph, the ISAPP definition of postbiotic has been applied.

Table 1: Definitions according to the International Scientific Association for Probiotics and Prebiotics (ISAPP)[1,18-20]

Category	Prebiotic	Probiotic	Synbiotic	Postbiotic
ISAPP Definition	A substrate that is selectively utilized by host microorganisms conferring a health benefit on the host	Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host	A mixture, comprising live microorganisms and substrate(s) selectively utilized by host microorganisms, that confers a health benefit on the host	A preparation of inanimate microorganisms and/or their components that confers a health benefit on the host
Publication	Gibson et al., 2017	Hill et al., 2014	Swanson et al., 2020	Salminen et al., 2021
Contains Viable Microorganisms	No	Yes	Yes	No*

*some live cells may remain after the inactivation step of postbiotic production, but would be expected to be negligible.

Most currently available postbiotics are derived from probiotic strains, but this is not a requirement.[1,9,11] The efficacy of the postbiotic may differ from that of its parent source,[15] and a postbiotic cannot be presumed safe and effective because the microorganism from which it is sourced has been demonstrated safe and effective; the postbiotic's beneficial effects and safety must be demonstrated in the target host.[1,21] Similarly, the effects of a postbiotic cannot be fully predicted by the effects of its source.[22]

Postbiotic effects can arise from the dead cells, the cell walls and cell fractions, pili, and the metabolites in the extracellular medium.[1,4,5,23]

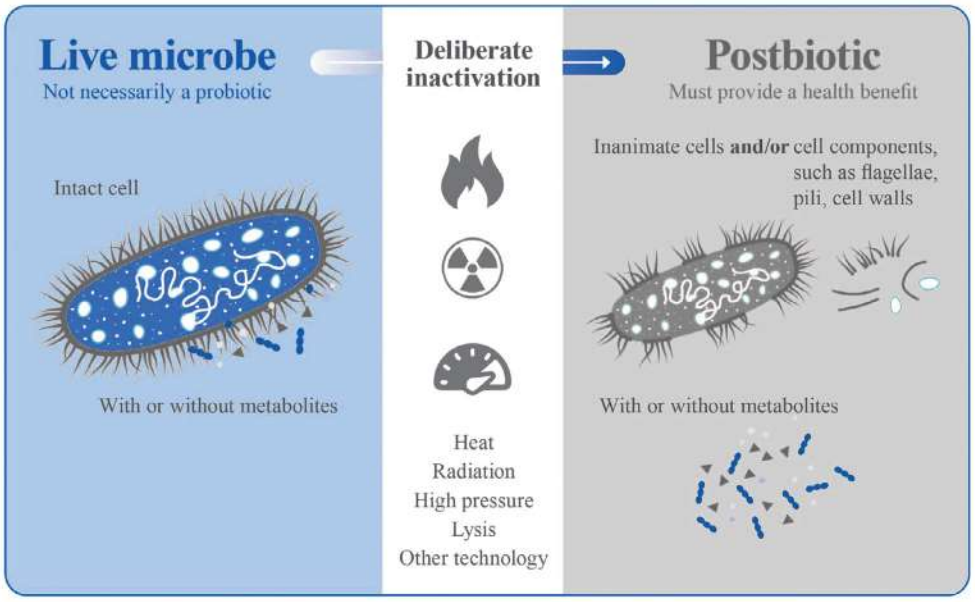


Figure 1: Further clarification of the ISAPP definition of postbiotic, from Vinderola et al.[3]

Postbiotics are highly diverse in their composition and may include bioactive substances that range from single molecules to an entire mixture of fermentation products.[1,6] Examples of bioactive components (cellular biomass; cell fragments or disrupted cells) and metabolites that may play roles in the effects of postbiotics are listed below. The presence of these components and metabolites varies widely based on the parent source as well as the composition of the postbiotic.[1,5,24,25] Some of these products are secreted by live bacteria prior to inactivation and remain in the medium (the matrix surrounding the bacteria), while others are released into the environment during bacterial lysis.[5]

- Adhesins
- B vitamins
- Bacteriocins
- Beta-glucans
- Cell homogenates and cell surface proteins
- Endo- and exo-polysaccharides
- Enzymes
- Lipopolysaccharides
- Lipoteichoic acids (LTAs)
- Organic acids
- Peptides
- Peptidoglycans and peptidoglycan-derived muropeptides
- Plasmalogens
- Polyamines
- Quorum sensing molecules
- Short-chain fatty acids
- Teichoic acids
- Urolithin A and B

PRODUCTION OF POSTBIOTICS

Postbiotics may be derived from bacteria, yeast, or fungi. Most postbiotics to date are derived from *Lactobacillus* and *Bifidobacterium* bacterial strains, but *Streptococcus* and *Faecalibacterium* species as well as *Akkermansia muciniphila*, *Eubacterium hallii*, and the yeast *Saccharomyces boulardii* have also been used as sources.[1,5]

The production of postbiotics involves rendering the cells of the microorganism inanimate by physical (e.g., heat, irradiation, pressure, etc.) or chemical means (e.g., acid deactivation).[5] Although this is commonly called inactivation, the term "inactive" is often interpreted as ineffective or inert and does not apply to the bioactive postbiotic.[1] The inactivation process can have a notable influence on the composition of the postbiotic as well as its nutritional value, sensory characteristics, and flavor.[1]

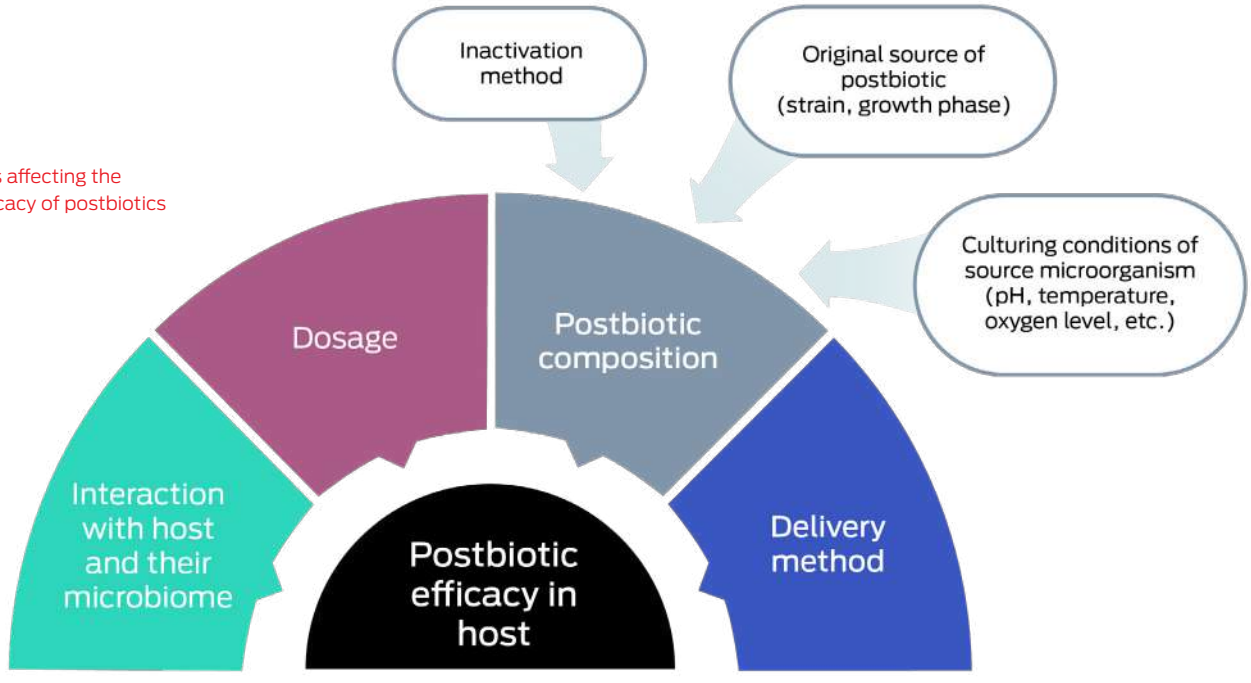


Figure 2: Factors affecting the variability and efficacy of postbiotics

PHYSIOLOGICAL AND POTENTIAL CLINICAL EFFECTS OF POSTBIOTICS

The mechanisms of action of postbiotics have not been fully elucidated.[5,6] The variation in postbiotics' effects depends on their composition, with some postbiotics having more profound clinical effects in one or more of these categories compared to other postbiotics.

Postbiotics are most frequently classified by function/benefit.[1,5,8,26]

Figure 3: Functional benefits of postbiotics

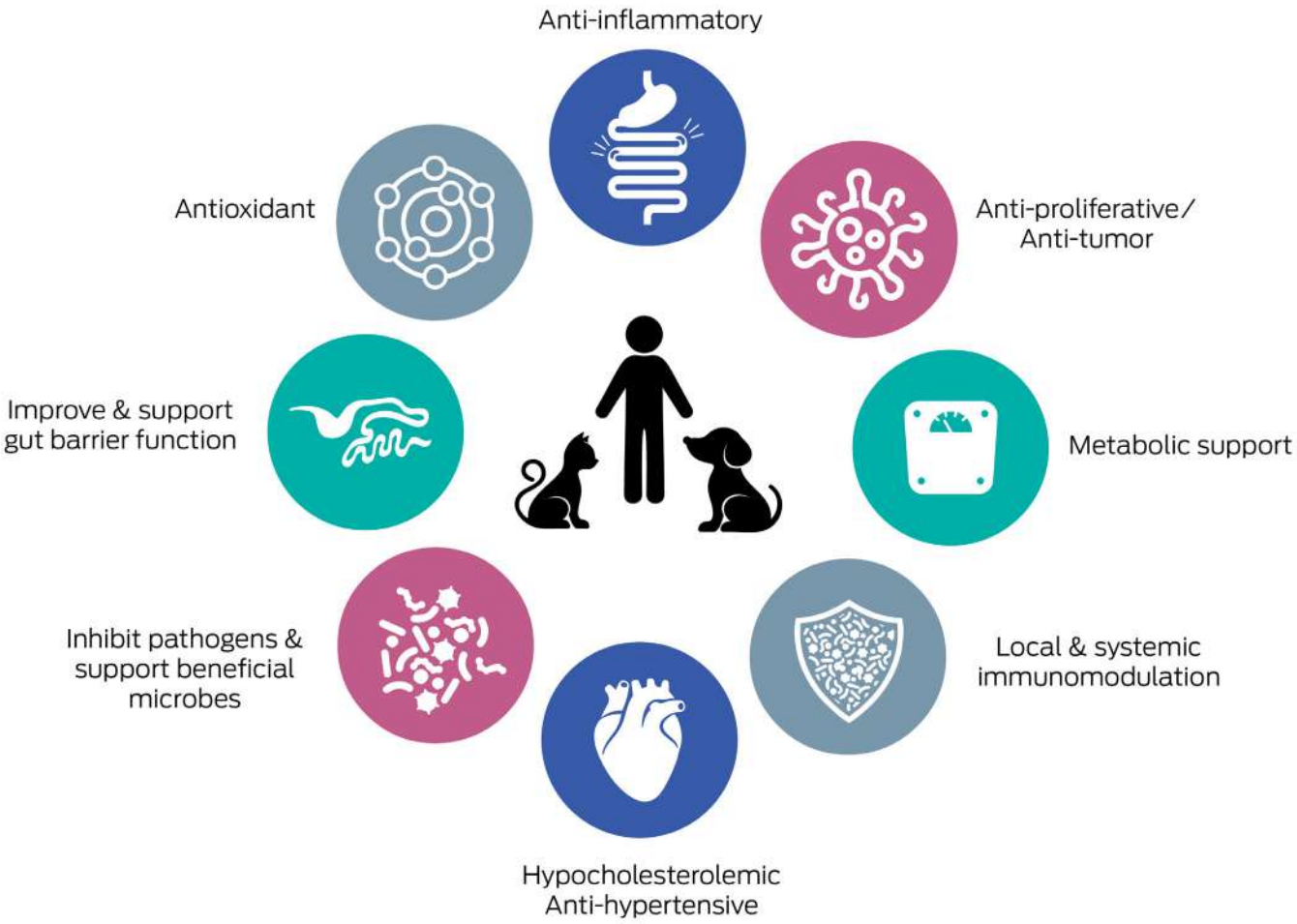
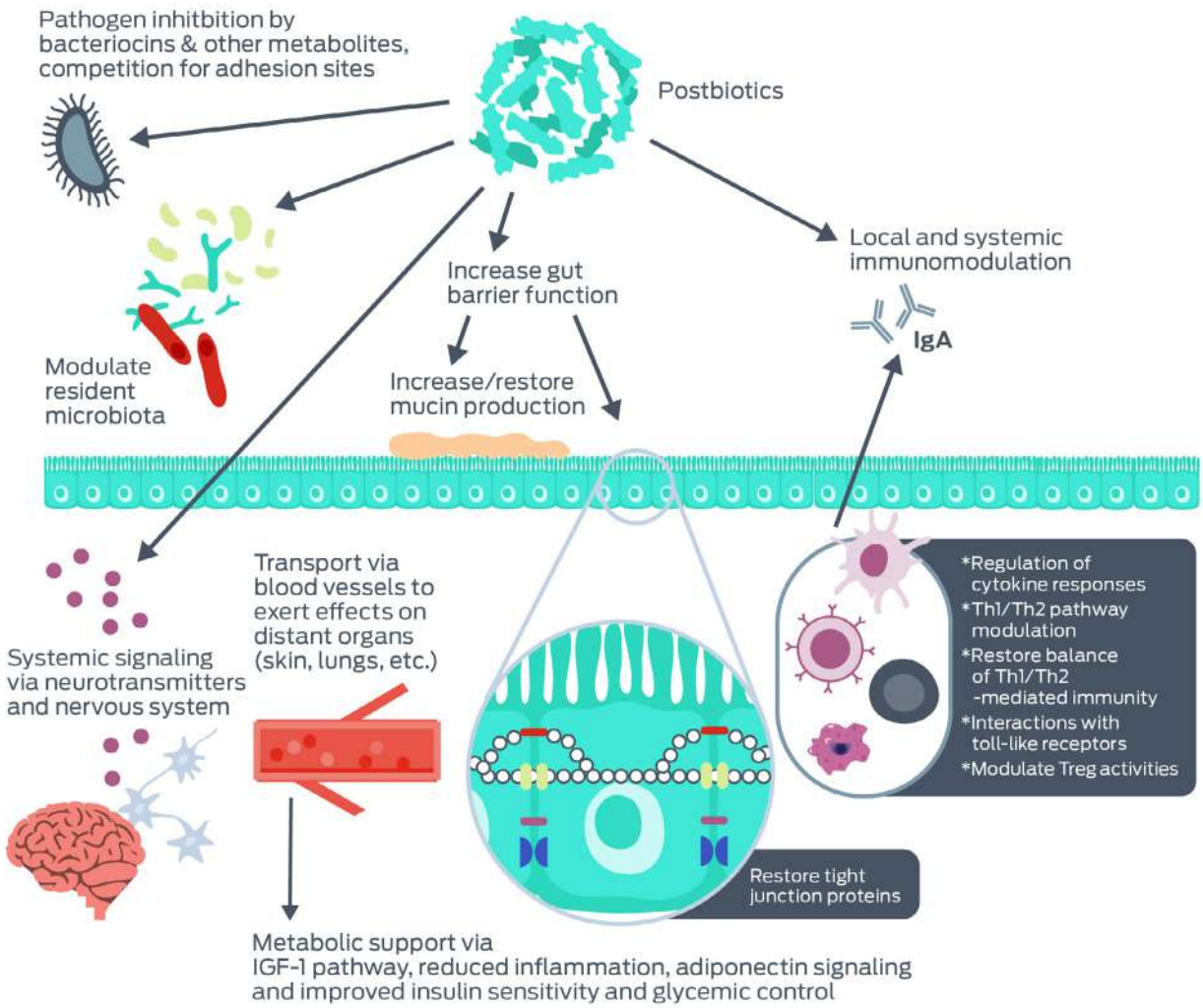


Figure 4: Illustration of potential mechanisms for postbiotic benefits



POSTBIOTICS BEYOND THE GUT

The effects of postbiotics are not limited to the gut; they can be as far-reaching as the effects of the microbiome itself.[1] In addition to GI and immunomodulatory benefits, postbiotics and microbial metabolites have shown some beneficial effects for atopic dermatitis,[27,28] respiratory tract immunity,[29,30] allergic rhinitis,[31] gingivitis,[32] wound healing,[33] sleep quality,[34] diabetic retinopathy,[35] and muscle strength and athletic endurance.[36]

ADVANTAGES OF POSTBIOTICS

Unlike probiotics, postbiotics are not comprised of live microorganisms and therefore they do not face some of the same challenges, such as surviving the environmental conditions within the GI tract or surviving the processes of manufacturing, packaging, transporting and storing the products.[4,5,8,21,31,37,38]

Because postbiotic function does not rely on live microorganisms, a benefit of postbiotic administration is there is no need to worry whether live microorganisms will survive the pet food manufacturing process.

- Effects do not depend on bacterial viability
- Longer shelf life
- Favorable absorption, metabolism, distribution, and excretion characteristics
- Resistant to mammalian enzymes
- Stable in digestive system environmental conditions
- Less dependent on ideal conditions to exert beneficial effects
- Do not compete with host microbiota for nutrient supply
- Can be administered concurrently with antibiotics without losing efficacy

Inflammatory bowel disease and chronic enteropathies are often associated with reduced barrier function and increased gut permeability, the combination of which potentially increases the risks of bacterial translocation – including translocation of probiotic microorganisms – as well as an abnormal inflammatory response to what would normally be non-invasive, harmless bacteria.[39] Although clinical cases of bacterial translocation and septicemia from probiotics are extremely rare,[40] the use of probiotics is frequently discouraged in patients with severely immunodeficiency and/or compromised intestinal barrier dysfunction; in contrast, postbiotics do not pose any risk of translocation, sepsis, or opportunistic infection because they are nonviable.[1,4,5,8,13,22,24,26,31,41] In addition, postbiotics cannot colonize the host and do not present the risk of possible transfer of antibiotic resistance genes.[5,11,31]

Many pet food ingredients that may be classified as postbiotics are already recognized as safe. However, regulatory frameworks regarding postbiotics are limited to date from a global perspective.[11]

Postbiotics may offer opportunities to reduce, or even replace, antimicrobial use in certain situations. Although antimicrobials can provide life-saving treatment of infection, they are not without potentially significant negative impact on microbiome and host health: antimicrobials alter gut microbial diversity and population, with some effects being transient while others are long-lasting.[42] An imbalanced, or dysbiotic, microbiome may induce metabolic and immunological disorders.[42] Antimicrobial administration can select for antimicrobial-resistant microorganisms that may transfer resistance genes, further propagating antimicrobial resistance.[42,43] In contrast, postbiotics may offer comparable benefits without the adverse effects of antimicrobial medications while offering the advantages described above.[42,43]

CLINICAL APPLICATIONS AND BENEFITS OF POSTBIOTICS

Postbiotics have been investigated in a number of species, and research is ongoing to determine optimal use of postbiotics for a range of uses.

- **In livestock and poultry species,** postbiotics have been shown to increase feed efficiency, growth performance, and quality of the products (e.g., eggs, meat) derived from animals as well as exert immunomodulatory effects.[44-52]
- **Human studies** have shown beneficial postbiotic effects for chronic diarrhea,[53,54] pediatric diarrhea,[55-57] respiratory infection,[29] and irritable bowel syndrome.[58,59]

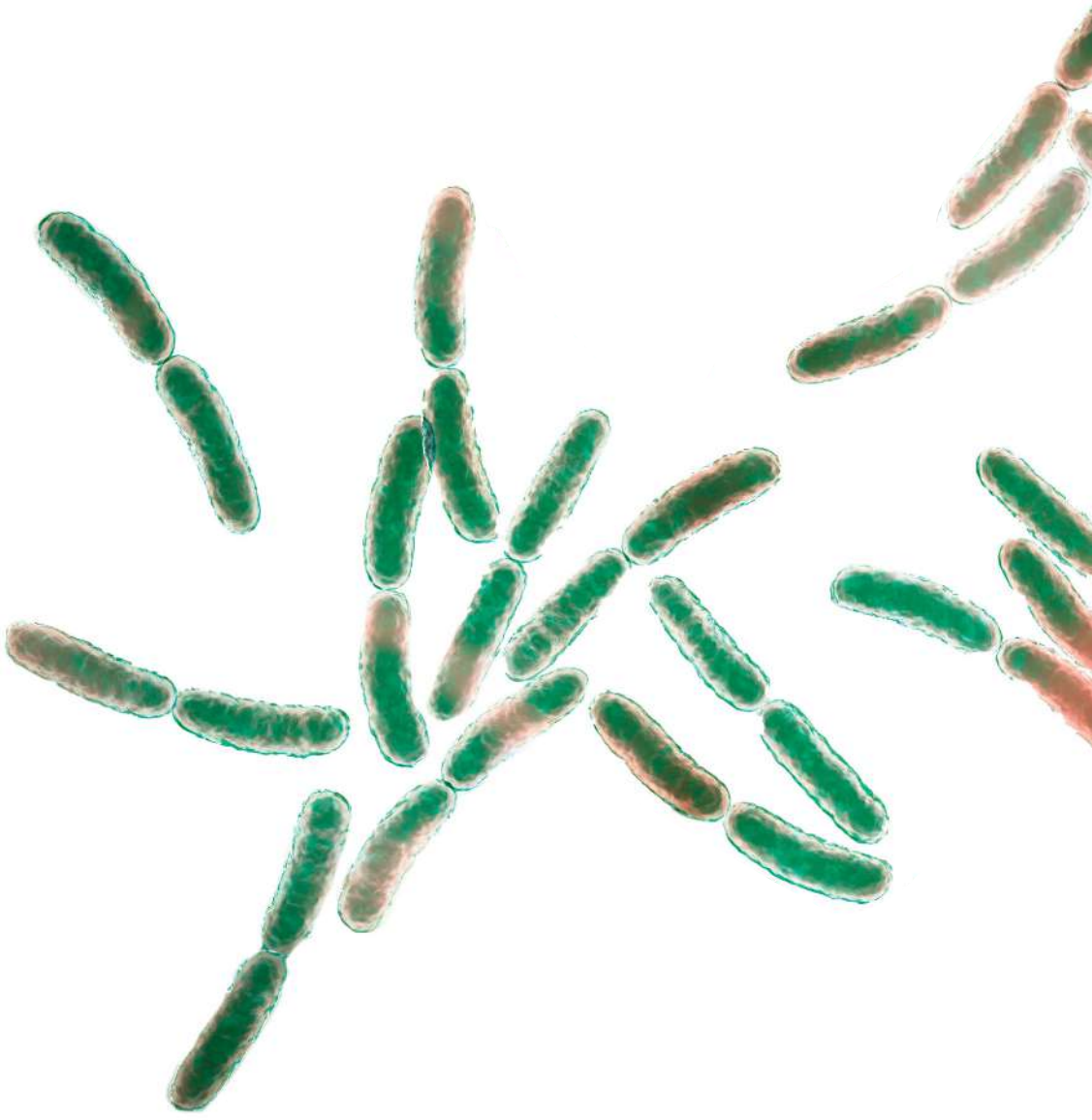
- **Industrial uses** include biopreservatives, stabilizers, emulsifiers, palatability enhancers, bacterial biofilm removers and inhibitors, and antimicrobial packaging methods.[5,60]

Postbiotics for companion animals

To date, the published research on postbiotics for companion animals is focused on postbiotics' effects in healthy animals. Observations in healthy pets include the following, depending on the postbiotic evaluated in the study:

- Immunomodulation, including stimulation of non-specific immune responses as well as cell-mediate immune responses; increased IgA production and interferon-γ secretion; and reduced TNF-α secretion in dogs[22,61-65]
- Increased fecal IgA, indicating an active gut immune system, in dogs and cats[22]
- Reductions of inflammatory cytokines in dogs (e.g., IL-18)[22]
- Improved response to mild, naturally occurring stress in dogs and cats[22]
- Increased microbiome diversity and resilience in dogs and cats[22]
- Improved stool quality in dogs exposed to mild transport stress[64,66,67]
- Increased antioxidant capacity in dogs[64-66]
- Increased skin sebum production in dogs[65]

Postbiotic research is still in its early stages and much remains to be learned about their composition, effects, and appropriate clinical uses. Postbiotics present many potential opportunities for improving health through functional benefits such as immunomodulation, metabolic support, improved gut barrier function, and anti-inflammatory and antioxidant effects. Postbiotics also offer advantages such as safety, stability, and long shelf life as well as the potential to reduce antimicrobial use for certain conditions.



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