Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Postbiotics

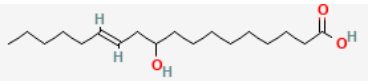
Evidence Summary

Postbiotics are microbial-derived products that can modulate microbiome-host interactions in a manner beneficial to the host. They show good safety, but efficacy has been limited in clinical studies to date.

Neuroprotective Benefit: By modulating the gut-brain axis, postbiotics have the potential to alter neurotransmitters involved in mood and cognition and mitigate neuroinflammation, but clear benefits have not yet been apparent in clinical studies.

Aging and related health concerns: By altering the activity of the microbiome and immune responses, postbiotics may mitigate the risk and intensity of infectious and allergic ailments, as well as improve glucose homeostasis.

Safety: Because they do not contain live organisms, postbiotics do not carry the same rare risks associated with probiotics. They have generally been safe in clinical studies, though some formulations could potentiate inflammatory responses in children.

Availability: OTC	**Dose**: No clinically validated doses or strains have been approved for therapeutic treatment.	**HYA** **Chemical formula:** $C_{18}H_{34}O_3$ **MW**: 298.5 g/mol  Source: PubChem
Half-life: Varies	**BBB**: Varies	
Clinical trials: Postbiotics have been tested in primarily small RCTs (range n=10s-100s) for gastrointestinal indications, allergies, respiratory illness, obesity, eczema, skin aging/acne, dry eye, and stress/anxiety.	**Observational studies**: The health benefits of the Mediterranean diet have been associated with the production of microbial derived metabolites.	

What is it?

In 2021, the International Scientific Association of Probiotics and Prebiotics (ISAPP) established a consensus definition of postbiotics as a "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" [1]. These include "inactivated microbial cells or cell components, with or without metabolites. Postbiotics do not currently fall within a particular regulatory category by the FDA, and will likely be regulated on a case by case basis depending on the composition and intended purpose of the postbiotic. Postbiotics have been described using a variety of terminologies, including paraprobiotics, metabiotics, ghost probiotics, non-viable probiotics, and pseudoprobiotics [2]. The major classes recognized by the World Health Organization are paraprobiotics, which are comprised of non-viable microbial cells, and fermented infant formulae, which is obtained by the fermentation of food by lactic acid–producing microbes, and includes microbial-derived metabolites, but no viable microbial cells. Evidence from preclinical and clinical probiotic studies finding that heat-killed or non-viable preparations of microorganisms could induce similar or superior health-related effects compared to supplementation with live strains (probiotics) has spurred interest in the development of postbiotics [1]. It has come to be appreciated that most probiotic strains do not become established into the host following consumption, but rather exert their effects by modifying the properties of the resident commensals. A variety of microbial-derived bioactive compounds have been identified, including short chain fatty acids (SCFAs), plasmalogens, antimicrobial bacteriocins, exopolysaccharides, teichoic acids, and vitamins [3]. The therapeutic potential of postbiotics is not well understood, as this is an emerging area of research. Most studies to date have been in preclinical

models, though there have been an increasing number of clinical studies in recent years. These have primarily been small studies lacking rigorous endpoints. The formulations of the postbiotics are tailored to the desired physiological effects, including the regulation of the gastrointestinal system, boosting immunity to combat pathogens, regulating metabolism, and regulating mood. To date, there are no postbiotic preparations that have been clinically proven to prevent or treat any specific disease.

Neuroprotective Benefit: By modulating the gut-brain axis, postbiotics have the potential to alter neurotransmitters involved in mood and cognition and mitigate neuroinflammation, but clear benefits have not yet been apparent in clinical studies.

Types of evidence:

- 3 clinical trials testing postbiotics for mood/mental health
- 1 clinical trial testing plasmalogens in Alzheimer's disease
- 1 observational study assessing the impact of microbial-derived metabolites on AD biomarkers
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

The gut-brain axis is a critical mechanism by which the microorganisms of the gut microbiome can influence brain function [4]. The fermentation of fiber-rich prebiotic foods by the microbes results in the production of metabolites, which are a form of postbiotic. The type of metabolites produced depends on the strains of bacteria or fungi, as well as the type of food source. The brain protective benefits from many foods, such as polyphenol-rich fruits and vegetables, are at least partially derived from the metabolites produced by the gut microbiome. Due to differences in the composition of the microbiome across individuals, the ability of people to obtain benefit from different types of 'healthy' foods is highly variable. For example, variability in the metabolite profile following coffee consumption was found to be driven largely by differences in gut microbe-derived metabolites [5]. This suggests that modification of the gut microbiome could enhance the health benefits of functional foods. We currently do not have easy and effective ways to specifically isolate and transfer the majority of the strains found in the human microbiota, so it is not yet possible to obtain all of the beneficial strains through commercial probiotic preparations. An alternative approach is to supplement directly with the brain protective metabolites or with compounds that can alter the functional properties and secretory profiles of existing gut microbes toward a more neuroprotective state.

To date, clinical trials testing the psychoactive capacity of postbiotic preparations have focused on features of mental health, such as depression and anxiety, rather than on cognitive performance. An RCT testing heat-killed *Lactobacillus helveticus* MCC1848 powder on the mood states of healthy adults (n=58) found that four weeks of treatment with the postbiotic improved Profile of Mood States 2 (POMS 2) scores on positive mood states, but had no effect on negative mood states, fatigue, or sleep quality [6]. An RCT (NCT04452253-sub-project 1) testing 300 mg capsules of heat-killed *L. paracasei* PS23 for eight weeks found that the postbiotic reduced cortisol levels, relative to placebo, in a population of stressed clinical nurses (n=70), but other stress-related biomarkers and anxiety scores were not significantly different [7]. An RCT testing the effect of two tablets/day containing heat-inactivated, washed *Lactobacillus gasseri* CP2305 (1×10^{10} bacterial cells) for 24 weeks on stress-related symptoms in 60 young adults found that, relative to placebo, the postbiotic improved sleep quality measures, such as sleep latency and delta power, based on the Pittsburgh Sleep Quality Index and single-channel sleep electroencephalograms. The effects on sleep and anxiety may be related to the changes seen in the profile of the gut microbiota, including an increase in the SCFA n-valeric acid, which is associated with GABA and sleep facilitation [8].

Human research to suggest benefits to patients with dementia:

Postbiotics include a wide array of microbe derived products. While products specifically marketed as postbiotics have not yet been clinically tested in dementia patients, some compounds which fall under the category of postbiotics have been tested. Most notably are plasmologens, which are a type of phospholipid found in cell membranes, have been tested in patients with mild cognitive impairment (MCI) or mild Alzheimer's disease (AD) [9]. However, since this study used plasmologens purified from scallops rather than from microbes, these plasmologens would not be considered postbiotics per se. In the RCT including 276 patients, there were no significant effects on cognition on the total study population, as measured by the Mini Mental State Examination-Japanese (MMSE-J) or Wechsler Memory Scale-Revised (WMS-R), following 24 weeks of 1 mg/day plasmologens [10].

The composition of the gut microbiome has been shown to be altered in AD patients. This can potentially impact the production of microbe-derived neuroprotective metabolites in response to a dietary intervention. One study found that the microbiome (bacterial) and mycobiome (fungal) signatures differed between participants with and without cognitive impairment, and that some of the microbial-derived metabolites were associated with AD biomarkers [11; 12]. The microbiome/mycobiome and their metabolite profiles, such as the production of SCFAs, were found to

be differentially affected in response to different six-week dietary interventions, namely the Mediterranean-ketogenic diet and the American Heart Association diet. Furthermore, the microbiome/mycobiome effects of the dietary interventions differed between individuals with and without cognitive impairment. In this study, the Mediterranean-ketogenic diet led to a shift in the metabolite profile toward the increased production of butyrate and propionate, resulting in a favorable effect on AD biomarkers. This suggests that an analysis of fecal/urinary microbe-derived metabolites may facilitate the optimization of neuroprotective diets. It has not yet been established whether direct supplementation with these microbial-derived metabolites would produce a similarly protective effect in patient populations.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Psychobiotics: A variety of gut microbiome-derived metabolites have been identified which can have psychoactive properties through the regulation of neurotransmission [13]. Preclinical studies have found that microbial metabolites can impact a variety of neurotransmitter systems which regulate cognition, such as acetylcholine, as well as mood, such as GABA and serotonin.

Short chain fatty acids: SCFAs are the best characterized microbe-derived metabolites with functional properties in the host. The most common SCFAs, butyrate, acetate, and propionate, make up around 90% of colon produced microbial metabolites [14]. These SCFAs exert a wide variety of effects both locally in the gut, and systemically. They can cross the BBB and have been detected in human cerebrospinal fluid (CSF) at concentrations in the range of 0–171 µM for acetate, 0–6 µM for propionate, and 0–2.8 µM for butyrate [15]. Systemic levels of SCFAs have been found to be lower in AD patients [15]. A similar reduction has been seen in animal models of AD, which may be related to alterations to the composition and activities of the gut microbiome. Supplementation with butyrate-producing bacterial strains has been shown to boost neuroprotective butyrate levels in rodent models [16]. Supplementation directly with the physiological levels of postbiotic sodium butyrate has shown similar protective effects, such as the induction of neural growth factors (i.e. BDNF), reduction of Aβ and tau pathology, and the enhancement of learning and memory performance in these preclinical models [16]. SCFAs also have immunomodulatory effects. It has not yet been established whether direct supplementation with exogenous SCFAs can exert similar neuroprotective benefits in humans, or whether particular postbiotic formulations can stimulate the production of neuroprotective metabolites to physiologically relevant levels and induce clinically meaningful effects.

Immunoregulation: Microbial-derived products, including cell components and metabolites, are involved in training the immune system to protect commensal species and fight off pathogenic species, and appear to be particularly involved in the regulation of innate immunity, including microglia [17]. Depending on the context, postbiotics can have anti-inflammatory effects, or they can promote immune system activation.

APOE4 interactions: Not established.

Aging and related health concerns: By altering the activity of the microbiome and immune responses, postbiotics may mitigate the risk and intensity of infectious and allergic ailments, as well as improve glucose homeostasis.

Types of evidence:

- 1 systematic review of clinical trials testing postbiotics in atopic dermatitis
- 1 systematic review of clinical trials testing postbiotics in infectious diseases in children
- 12 clinical trials testing postbiotics for respiratory indications
- 6 clinical trials testing postbiotics on measures of metabolic health
- 6 clinical trials testing postbiotics on gastrointestinal indications in adults
- 4 clinical trials testing postbiotics for acne
- 3 clinical trials testing postbiotics for skin aging
- 2 clinical trials testing postbiotics on measures of immunity
- 1 clinical trial testing postbiotics in dry eye disease
- 2 observational studies assessing the impact of microbial-derived metabolites on cardiovascular health
- Numerous laboratory studies

Metabolic disease: POTENTIAL BENEFIT

Metabolic syndrome has been associated with dysbiosis of the gut microbiome, resulting in altered metabolite profiles and chronic inflammation. Preclinical studies and a limited number of clinical studies suggest that postbiotics may help improve metabolic parameters by altering the composition and/or functional profile of the gut microbiome.

A pilot RCT in 32 participants with obesity and insulin resistance tested the impact of 10^{10} colony forming units (CFUs) live or pasteurized *Akkermansia muciniphila*, a bacterial strain which has been inversely associated with obesity, on metabolic parameters over a three-month period [18]. The

pasteurized *A. muciniphila* treatment led to improved insulin sensitivity (+28.62±7.02%, P=0.002), reduced insulinemia (-34.08±7.12%, P=0.006), reduced plasma total cholesterol (-8.68±2.38%, P=0.02), and reduced gamma-glutamyl transferase (-24.11±5.55%, P=0.009), relative to placebo. These protective effects were not seen with live *A. muciniphila* treatment.

An RCT (NCT02921217) testing capsules of live or heat-killed *Bifidobacterium animalis* subsp. *lactis* CECT8145 (10^{10} CFUs) for three months in abdominally obese individuals (n=135) found a significant reduction in visceral fat area, waist circumference, waist to height ratio, and conicity index, relative to placebo, for the heat-killed postbiotic bacteria, but only a non-significant trend toward reduction with the live probiotic [19]. There were also reductions in diastolic blood pressure and insulin resistance based on the HOMA-IR with the postbiotic. The effects were more pronounced in women. This postbiotic is manufactured by Archer Daniels Midland Company, and sold commercially as BPL1® HT.

An RCT (NCT03630588) in 120 abdominally obese participants testing the effect of 50 mg/day of seafood sticks enriched with 10^{10} CFUs of heat-inactivated *Bifidobacterium animalis* subsp. *lactis* CECT8145, 370 mg/day omega 3, and 1.7 g/day inulin for 12 weeks found that this postbiotic containing food source reduced insulin levels by −5.25 mg/dL and HOMA-IR, a measure of insulin resistance, by −1.33 [20]. The changes in these glycemic parameters were associated with changes in the profile of the gut microbiome.

HYA (10-hydroxy-cis-12-octadecenoic acid) is a microbial derived fatty acid produced from linoleic acid. HYA™ is being developed as a postbiotic by Noster. It has been shown to improve insulin resistance by promoting the secretion of GLP-1 via the activation of the G-protein coupled receptor GPR40/120, and to protect against obesity via stimulation of the appetite suppressing hormone PYY, in preclinical models [21]. HYA™ has also been shown to reduce postprandial blood glucose spikes and visceral fat mass in pilot clinical trials [22; 23; 24](Company website). In a dose finding trial (n=60), supplements containing 1,000 mg or 2,000 mg HYA reduced blood glucose levels 30 minutes (127.8±21.9 mg/dL and 117.7±13.8 mg/dL, respectively, vs. 151.3±17.5 mg/dL) and 60 minutes (134.9±21.9 mg/dL and 131.9±22.4 mg/dL, respectively, vs. 146.2±31.2 mg/dL) following a meal, relative to placebo. A similar effect was seen with 30 minutes postprandial blood glucose in a separate confirmatory trial (n=60) with a 300 mg HYA containing supplement (144.9±22.0 mg/dL vs. 161.6±16.5 mg/dL). In an RCT (n=56), participants taking 900 mg HYA per day in the form of three tablets, three times per day, prior to meals, showed a statistically significant decrease in abdominal fat area (from 127.6±45.5 cm^2 to 117.1±43.6 cm^2) within 12 weeks, relative to placebo (from 129.1±49.0 cm^2 to 128.4±46.0 cm^2).

A network pharmacology study constructed a microbiota–substrate–metabolite–target network for obesity interventions [25]. *Lactobacillus paracasei* JS1 was identified as a probiotic strain that can

produce the postbiotic equol, an isoflavone-derived metabolite, which may protect against obesity through the inhibition of IL-6.
The presence or absence of these networks across individuals may explain some of the heterogeneity in responses to dietary interventions. Urinary microbial phenolic metabolites were found to be positively associated with ideal cardiovascular health (ICVH) score in response to the Mediterranean diet in a sub study of 200 participants from the PREDIMED trial [26]. The microbial phenolic metabolite urolithin B glucuronide was associated with lower levels of LDL-c. This suggests that higher production of microbial phenolic metabolites enhances the cardioprotective benefits of the Mediterranean diet, such that postbiotic interventions which promote the production of these metabolites could augment the health benefits of various diets.

Irritable bowel syndrome: POTENTIAL BENEFIT
The majority of clinical trials testing postbiotic interventions to date have been for intestinal conditions with the goal of improving intestinal barrier integrity and reducing inflammation by regulating or rebalancing the gut microbiome.
Oral capsules of non-viable, heat-inactivated *Bifidobacterium bifidum* MIMBb75 (SYN-HI-001) were tested in an RCT in 443 patients with IBS for eight weeks [27]. The postbiotic treatment led to a reduction in IBS symptoms in a greater proportion of participants relative to placebo (43% vs 21%; RR:1.7, 95% CI 1.3 to 2.4).
Lacteol®, a postbiotic from Adare Biome, which is comprised of inactivated *Lactobacillus* LB plus fermented culture medium, reduced rates of fecal incontinence, pain, and bloating in a study of 297 patients with diarrhea-predominant IBS. Bactistatin® includes metabolites derived from *Bacillus subtilis* VKPM V-2335 [28]. It has been found to contain appreciable quantities of palmitic, stearic, myristic, palmitoleic, pentadecanoic, lauric, capric, margaric and lignoceric acids, 18 chemical elements, as well as numerous compounds which inhibit pathogens [29]. While the details are not available, it has been reported that Bactistatin® altered the gut microbiome composition, reduced pathogenic species, and improved gut barrier function in clinical and preclinical studies [28].
Hylak® forte, a postbiotic liquid containing metabolites derived from *Lactobacillus acidophilus* (DSM 4149), *Lactobacillus helveticus* (DSM 4183), *Escherichia coli* (DSM 4087) and *Enterococcus faecalis* (DSM 4086), is designed to inhibit the growth of pathogenic bacteria by lowering the intestinal pH [30]. It has shown efficacy in reducing enteritis and the duration of salmonella excretion in infants, and treating intestinal dysbacteriosis in patients with chronic gastritis [31; 32]. Gas chromatography analysis indicated that the major bacterial metabolites contained in this postbiotic include the SCFAs formic acid in the range of 39.33 ppm (90% CI 36.50 to 42.17) to 48.33 ppm (90% CI 45.91 to 50.76), and acetic acid

(415.67 ppm, 90% CI 385.93 to 445.41), as well as vitamin B1 (0.029 mg/100 g), monosaccharides and disaccharides (2.767 g/100 g), glutamic acid, and glutamine (0.047 g/100 g) [30]. Acetate is expected to be the primary mediator of therapeutic benefit to the gastrointestinal system in this preparation.
ReFerm® (Profermin®), is a postbiotic product of oat gruel fermented with *Lactobacillus plantarum* 299v [33]. A study in 30 patients with moderate to severe IBS, found that treatment with this postbiotic for 14 days improved gut barrier function based on biopsy analysis and *ex vivo* assays. Significant improvement in clinical symptoms was not seen relative to placebo, which may be related to the enema mode of administration used in this study.

Diarrhea: POTENTIAL BENEFIT
Postbiotics have been tested and shown efficacy in small clinical trials for the treatment or prevention of diarrhea in both adult and pediatric populations [9].
Adults: A trial in 137 adults with chronic diarrhea comparing the efficacy of a four-week course of the postbiotic Lacteol Fort, distributed by Amsco Healthcare, which is comprised of lyophilized, heat-killed *Lactobacillus acidophilus* LB, relative to live *lactobacilli* in the form of Lacidophilin tablets (probiotic) found that the postbiotic was more effective in reducing bowel frequency and improving clinical symptoms [34]. Similarly, an exploratory study including 184 adults taking antibiotics found that co-administration of Lacetol Fort postbiotics reduced the incidence of antibiotic associated diarrhea and bloating [9].
Children: Therapeutic supplementation with heat-killed *Lactobacillus acidophilus* LB was found to be effective in reducing the duration of diarrhea in children (Mean Difference [MD]: −20.31 hours, 95% CI −27.06 to −13.57) based on four RCTs including 224 participants [35]. Preventative supplementation with cow's milk fermented with heat-treated *Lactobacillus paracasei* CBA L74 reduced the rates of diarrhea (Relative Risk [RR]: 0.51, 95% CI 0.37 to 0.71) and gastroenteritis in children aged 12-48 months (n=503) in two RCTs [35].

Allergies/Respiratory illness: POTENTIAL BENEFIT
Heat-killed *Lactobacillus plantarum* L-137, a strain isolated from fermented food, has been shown to induce Th1 immune responses through the induction of the cytokine IL-12. In an RCT including 60 healthy adults (mean age 56.3), participants took a 10 mg oral capsule containing heat-killed *L. plantarum* L-137, in the form of LP20 from House Wellness Foods, or placebo for 12 weeks. The treatment impacted immune responses, based on *ex vivo* assays from participant-derived peripheral blood mononuclear cells (PBMCs) [36]. LP20 treatment increased concanavalin A-induced cell proliferation, a marker of acquired immunity, altered the Th1:Th2 ratio in favor of a Th1 profile, and

improved quality of life measures. The boosting of the Th1 response may offer protection against allergies.

In an RCT testing live or heat-killed *Lactobacillus paracasi* 33 (two capsules/day; 5×10^9 colony-forming units/capsule) for 30 days in patients with house-dust-mite-induced allergic rhinitis (n=90), both the live and heat-killed bacteria similarly improved quality of life measures relative to placebo [37]. This suggests that benefits may be derived from the postbiotic effects of the bacteria.

del-IMMUNE-V®, a preparation of cell fragments derived from *Lactobacillus rhamnosus* DV - NRRLB68023 manufactured by Stellar Biotics, was tested in an RCT in preschool-age children with food allergies and bronchial asthma. A peer-reviewed publication is not yet available, but a company presentation indicates that treatment significantly increased serum levels of IFN-gamma and levels of salivary secreted IgA, while reducing serum levels of leukotrienes, relative to controls.

Treatment with LP20 (10 mg tablet containing heat-killed L. plantarum L-137) for 12 weeks reduced the incidence (47 cases vs. 35 cases), duration, and severity of upper respiratory tract infections relative to placebo in an RCT including 78 adults (mean age 50.6) [38]. LP20 (10 mg tablet containing heat-killed *L. plantarum* L-137) for eight weeks led to increased serum levels of IFN-β prior to administration of trivalent inactivated influenza vaccine, relative to placebo in an RCT including 16 healthy women (mean age 45.4) [39]. However, there were no clear differences in the seroresponse rate, seroprotection rate, or antibody titers between the groups following vaccination.

Other studies suggest that the immune stimulating responses of postbiotics may be more relevant in an elderly population [9]. An RCT testing the effect of heat-killed *Lactobacillus pentosus* strain b240 (4×10^9 cells) in a beverage formulation for 12 weeks on salivary secretory IgA in 80 elderly participants (71 ± 5 years old) found that b240 treatment increased the salivary secretory IgA secretion rate, suggestive of improved mucosal immunity [40]. In support of this, a separate RCT including 300 elderly adults, found that treatment with high dose (2×10^{10}) and low dose (2×10^9) b240 reduced the incidence of the common cold (29% vs. 34.8% vs. 47.3%) relative to placebo [41].

An RCT testing a jelly containing 10 billion heat-killed *L. paracasei* MCC1849 cells, a postbiotic preparation from Morinaga Milk (Japan) currently known as LAC-Shield, did not significantly impact immunological parameters or vaccine antigen levels following influenza vaccination (A/H1N1, A/H2N3 and B) in the total population of treated nursing home residents (n=42), relative to placebo [42]. However, participants in the oldest subgroup (≥85 years old) (n=27) treated with heat-killed *L. paracasei* MCC1849 showed an elevation of titers to the A/H1N1 and B antigens following vaccination, which was not seen in the placebo group. Since no cases of influenza occurred during the study, impacts to vaccine efficacy were not assessed.

The yeast-based postbiotic Epicor®, a dried *Saccharomyces cerevisiae* fermentate manufactured by Cargill, reduced the incidence and duration of cold or flu-like symptoms, relative to placebo, in a 12-week trial of 116 participants (mean age 44±11) [43]. Another 12-week trial testing EpiCor® (500 mg) in 116 participants who did not receive the seasonal flu vaccine found a significant reduction in the incidence, but not in the duration or severity of cold or flu-like symptoms, relative to placebo [44]. EpiCor (500 mg) was also shown to reduce nasal congestion and rhinorrhea, as well as elevate salivary IgA levels, relative to placebo, in a trial of 96 adults with allergic rhinitis conducted during a 12-week period with elevated pollen counts [45]. Elevated saliva secretory IgA and reduced pollen allergies were also seen with EpiCor® in a five-week placebo controlled and eight week open-label extension study in 22 healthy adults [46]. These results likely stem from the immunomodulatory effects of this postbiotic preparation. A single 500 mg dose of EpiCor was found to transiently shift the profile and activation status of circulating lymphocytes, most notably an increase in CD25+ activated NK cells, in a population of young and middle-aged adults (n=12), which is consistent with the effects seen in preclinical studies [47].

Immunity: POTENTIAL BENEFIT

A variety of commercially available postbiotics claim to have immunity boosting effects. These are most commonly related to preclinical studies, though there have been some human studies, most of which did not rigorously examine immune function, but instead looked at measures such as numbers of sick days. A few, such as those described in the respiratory illness section, combined wellness measures with immunity markers, typically salivary secretory IgA.

Lactococcus lactis subsp. lactis JCM 5805, also called *Lactococcus lactis* strain Plasma, commercially available as IMMUSE™ (LC-Plasma) from Kyowa Hakko, has been shown to activate plasmacytoid dendritic cells (pDCs) and induce type I and III interferons, mediators of antiviral immunity, via TLR9 stimulation in preclinical studies. In a trial of 31 healthy athletic adults, CD86, a marker of pDC activation was elevated in those treated with LC-Plasma compared to those receiving placebo for 14 days [48]. LC-Plasma treated individuals also reported lower levels of fatigue. Similar effects on CD86 pDCs and fatigue were seen in a separate study including 51 male athletes [49]. A trial of 54 volunteers examined whether LC-Plasma could impact the salivary shedding of herpesviruses HHV-6 and HHV-7, which can reactivate in response to stress [50]. There were no significant differences in shedding rates in the overall population, but effects were seen when stratified by age. Participants under age 40 had higher rates of HHV-6 shedding, and this subpopulation showed lower HHV-6 DNA loads with LC-Plasma treatment.

Atopic dermatitis: POTENTIAL MINOR BENEFIT IN ADULTS

Alterations to the gut microbiome have been observed in patients with atopic dermatitis, also known as eczema, which may play a role in the manifestation of this inflammatory skin disorder. A systematic review including nine RCTs (n=512 participants) found that non-viable oral Lactobacillus postbiotics were associated with an improvement in clinical symptoms in adults, but not in pediatric populations [51]. The effects in pediatric studies were highly variable depending on age, bacterial strain, and dosage. Additionally, the trials in adults were all conduced in Japan, whereas the trials in children were conducted in various countries in Europe and East Asia, such that heterogeneity in microbiomes may have also contributed to the variability in responses to the postbiotic interventions. These results are consistent with what has been observed with probiotics. The studies in adults observed a decline in clinical symptoms based on the SCORAD index, but these symptomatic changes were not necessarily associated with changes in inflammatory markers or reductions in topical steroid use during the study period. The postbiotics tested in adults included heat-killed *L. paracasei* K71 and heat-*killed L. acidophilus* L-92.

Skin aging/health: POTENTIAL BENEFIT

Postbiotics are starting to be incorporated into skin care products touted to improve the appearance and health of skin. The skin microbiome varies across different regions of the body and changes throughout the lifespan. Dysbiosis of the skin microbiome can impact epithelial barrier integrity, resulting in inflammation and reduced moisture retention [52]. The effects on the skin microbiome and health have not been rigorously tested for the vast majority of postbiotic containing products currently on the market, however, there are an increasing number of clinical trials testing postbiotic formulations for skin-related indications.

Ferment filtrates derived from the actinobacteria species, *Epidermidibacterium Keratini* EPI-7, which was prevalent in women in their twenties, was previously found to modulate the activity of matrix metalloproteases (MMPs) in photo-aged human dermal fibroblasts [53]. The application of the postbiotic to the skin of Korean women (n=55) in their 20s, 50s, or over 60 years of age for three weeks, altered the composition of the skin microbiome, including the abundance of *Cutibacterium*, *Clostridium*, and *Prevotella*. The EPI-7 postbiotics also led to significant improvements in skin hydration, and elasticity, while reducing redness and hyperpigmentation.

A topical cream containing sonicated *Streptococcus thermophilus* was found to improve the ceramide composition of the outer layer of the epidermis in 20 healthy Caucasian women aged 68 ± 3 years old following two weeks of treatment [54]. The increase in ceramide levels and skin barrier function was driven by the sphingomyelinase (SMase) activity of the *S. thermophilus* extract.

A cream containing CLS02021, a postbiotic extract including metabolites derived from *Lactobacillus plantarum* AN057, *Lactobacillus casei* AN177, and *Streptococcus thermophilus* AN157, developed by Ambiome labs, was tested for four weeks in 47 volunteers in Bosnia and Herzegovina [55]. The treatment was associated with improvements in skin moisture, elasticity, pore size, and wrinkle depth. The metabolites thought to be mediating these effects include lipoteichoic acid, hyaluronic acid, lactic acid, and SMase.

Acne vulgaris is an inflammatory skin condition driven by the bacteria *Propionibacterium acnes.* A variety of probiotic and postbiotic preparations have been tested as an alternative to antibiotics to reduce the abundance of *P. acnes*.
A postbiotic extract derived from the co-fermentation of collagen with the probiotic strains *Lactobacillus acidophilus* TYCA06, *Lactobacillus salivarius* AP-32, and *Bifidobacterium animalis* subsp. *lactis* CP-9, was formulated into a facial gel [56]. In a study with 11 participants, treatment with the postbiotic gel for four weeks significantly reduced skin inflammation, redness, acne lesions, and brown spots.
A lotion containing a fermented lysate derived from *Lactiplantibacillus plantarum* VHProbi® E15 was tested in 22 participants with mild to moderate acne [57]. The postbiotic treatment led to a reduction in the proportion of facial acne lesions and sebum production over the four-week study. Similar results were seen in a study (n=20) testing a postbiotic derived from *Lactiplantibacillus plantarum* VHProbi® V22 [58]. Treatment with LC-Plasma, a *Lactococcus lactis* strain Plasma postbiotic, reduced the overgrowth of *P. acnes* and reduced erythema in a clinical trial of healthy women in Japan (n=70) [59].

Dry Eye: POTENTIAL BENEFIT
Dysbiosis of the gut and/or ocular microbiome may promote the infiltration of immune cells, resulting in ocular inflammation and immune-mediated dry eye [60]. An RCT in 40 women with dry eye disease tested postbiotic and probiotic formulations of *Latilactobacillus sakei*, in the forms of ophthalmic bacterial lysate drops (4%) and oral capsules (5 billion colony-forming units), respectively (NCT04938908) [61]. The postbiotic drops led to improvement on clinical measures relative to placebo, including the change in Ocular Surface Disease Index (active -16.257 ± 1.020 vs. placebo -8.082 ± 1.075), the change in Tear Break-up Time (4.456 ± 0.616 vs. 0.740 ± 0.651), and change in Schirmer I tests (5.897 ± 0.531 vs. 1.117 ± 0.561). These were associated with a reduction in the tear levels of pro-inflammatory cytokines, including IL-6, TNFα, and IFN-γ. In contrast, no significant clinical or immunological improvements were seen with the probiotic formulation.

Cancer: POTENTIAL BENEFIT (Preclinical)

Postbiotic compounds have been associated with anti-cancer properties in a variety of preclinical studies [62; 63]. Thus far, there is limited evidence regarding the clinical benefit for the majority of postbiotics, but there are some preliminary studies suggesting that at least some postbiotics may help potentiate anti-tumor immune responses in anti-cancer vaccines [63]. The metabiotic supplement, del-IMMUNE-V® from Stellar Biotics, is currently being tested in a Phase 1 trial as a nutritional supplement adjuvant to surgery in stage III colorectal cancer patients to reduce inflammation and aid recovery (Press release).

Senescence: POTENTIAL BENEFIT (Preclinical)
Long term administration of heat-killed *Lactococcus lactis* subsp. *lactis* strain Plasma (LC-Plasma) (1 mg/day), which has been shown to stimulate stimulated plasmacytoid dendritic cells, promoted the induction activity of IFN-α and increased the naïve T cell ratio in the senescence accelerated SAMP1 mouse strain [64; 65]. Additionally, LC-Plasma reduced age-associated skin thinning and muscle loss, resulting in a decreased senescence score at 47 weeks of age in SAMP10 mice. Treatment with LC-Plasma improved the survival rate at 82 weeks (93.75% vs 62.5%) in SAMP6 mice. The extended survival was associated with dendritic cell activation, and reduced levels of IL-1β, a mediator of age-related chronic inflammation.

Safety: Because they do not contain live organisms, postbiotics do not carry the same rare risks associated with probiotics. They have generally been safe in clinical studies, though some formulations could potentiate inflammatory responses in children.

Types of evidence:

- 2 systematic reviews
- 38 clinical trials
- Numerous laboratory studies

The safety profile of postbiotics is likely to vary depending on the composition of the postbiotic, as the potential antigenic nature of non-viable microorganisms is higher than for a preparation of their metabolites [1]. In the vast majority of clinical studies to date, postbiotics showed similar adverse event profiles relative to placebo treatments. Due to the potential immunostimulatory properties of some postbiotic preparations, inflammation-related side effects, such as the induction of chemokines, and vomiting have occurred, most frequently in young children [35].
Overall, the safety profile of postbiotics is expected to be stronger than for live microorganism containing probiotics, because having non-viable microbes or their metabolites eliminates the risk of

possible infection or colonization [1]. The lack of live organisms also reduces the risk of spoilage during transport and storage [66]. Theoretical complications include unanticipated interactions of the postbiotics with an individual's gut microbiome resulting in the production of metabolites with undesired/harmful properties, the disruption of exogenous metabolite-producing pathways, and the development of resistance [67].

One of the current challenges of postbiotics involves targeted delivery. Various delivery systems are being developed to ensure that the postbiotic products are able to reach the gut, or other intended microbiome intact. These include the use of gut microbiota-triggered release and delivery strategies, such as coating with polysaccharides or azo functional polymers, pH-dependent delivery systems, time dependent delivery systems, osmotic pressure-controlled systems, and nanoparticles [67]. For example, encapsulation with alginate, a prebiotic, was shown to improve the delivery of indole-3-propionic acid to the gut and offer therapeutic benefit in a rodent model of colitis [68].

Biomarkers are needed to verify that postbiotics are exerting physiologically meaningful effects on their intended targets [66]. The relevant biomarkers will vary depending on the postbiotic and may include measures such as changes in levels of circulating or excreted SCFAs, or changes to immune cell composition or function.

Drug interactions: Unlike probiotics, postbiotics should not be affected by antibiotics or antifungals. Postbiotic metabolites could potentially interact with the absorption or metabolism of certain drugs, though this is likely to be limited to specific drug-postbiotic combinations, as opposed to class effects.

Sources and dosing:

There are currently no approved or clinically validated postbiotic formulations or doses, though some have undergone clinical testing.
A variety of postbiotic products are now commercially available Postbiotics which have been tested in clinical trials include:
Gastrointestinal indications: Lacteol® from Adare Biome, Lacteol Fort from Amsco Healthcare, Hylak® forte made by Teva (Germany), Referm® from Nordic Reblance (Sweden), and Bactistatin® made by Stada (Germany).

Immune boosting: EpiCor® from Cargill, IMMUSE™ (LC-Plasma) from Kyowa Hakko, del-IMMUNE-V® from Stellar Biotics, LAC-Shield from Morinaga Milk (Japan), and LP20 from House Wellness Foods (Japan).
Metabolic indications: BPL1® HT from the Archer Daniels Midland Company, and HYA™ from Noster.

Research underway:

There are currently clinical trials underway testing oral postbiotics in macular atrophy (NCT05391074), postbiotics in macular degeneration (NCT05056025), pasteurized *Akkermansia muciniphila* in stressed health care workers (NCT05738746), a multi-strain postbiotic blend from the Archer Daniels Midland Company for moderate self-reported anxiety (NCT05562739), SlimBiotic (heat-inactivated *L. fermentum* K8 postbiotic) from Citruslabs for weight management and metabolic health outcomes (NCT05912699), a single strain live probiotic and heat-killed postbiotic from the Archer Daniels Midland Company in overweight and obese individuals (NCT05440630), a live probiotic and heat-killed postbiotic from the Archer Daniels Midland Company in overweight individuals (NCT05428137), the rapid immune modulating effects of EpiCor® from Cargill (NCT05819424), and two trials testing del-IMMUNE-V®, manufactured by Stellar Biotics, in patients with NAFLD (NCT05804422), and in patients with Type 2 Diabetes (NCT05770076).

Search terms:
Pubmed, Google: Postbiotics

- Alzheimer's disease, cognition

Websites visited for Postbiotics:

- Clinicaltrials.gov
- WebMD.com
- PubChem (HYA)
- ConsumerLab.com

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