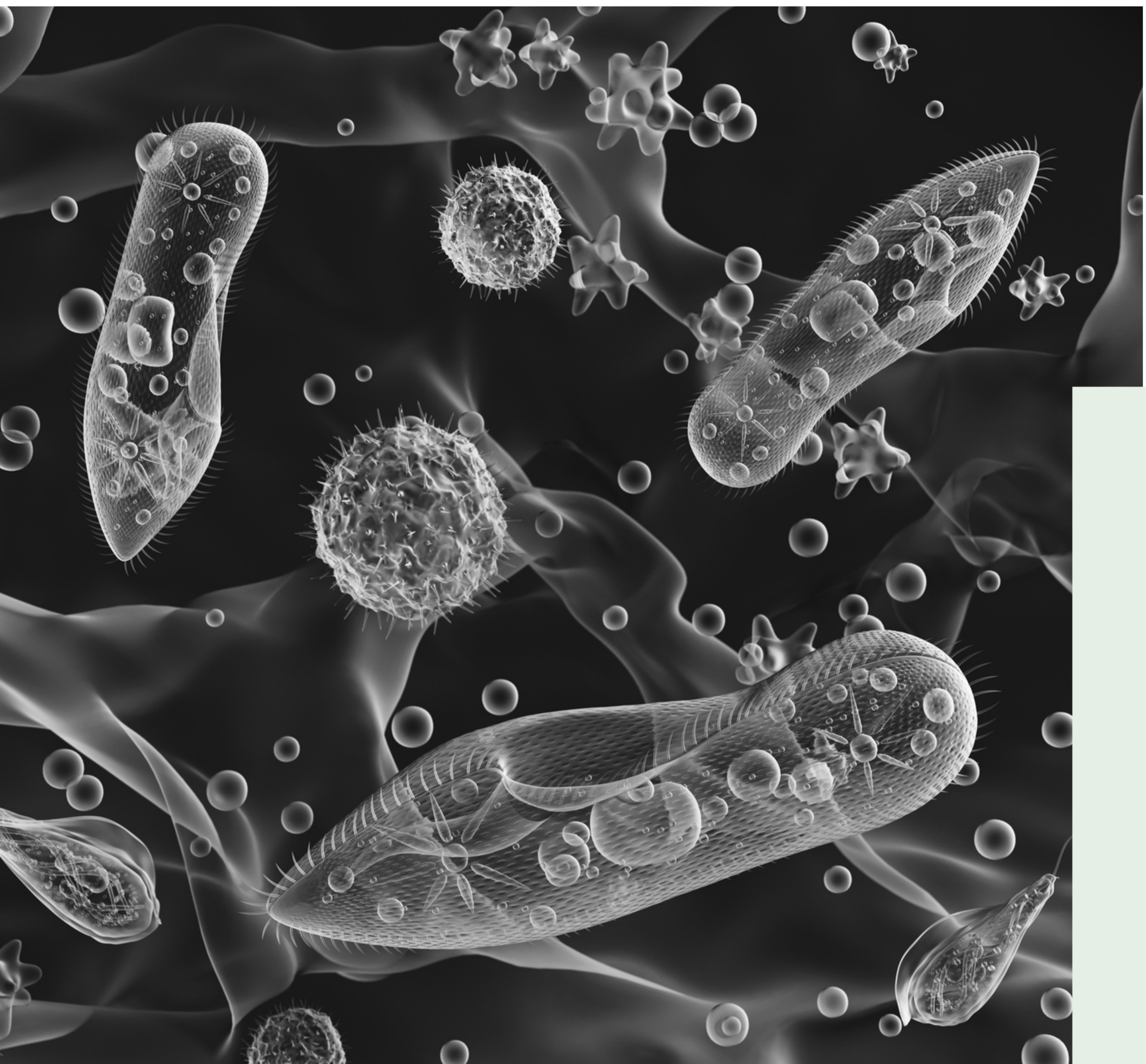
GLOBAL PREBIOTIC ASSOCIATION

SYNBIOTICS

WHITE PAPER

PREPARED BY THE GLOBAL PREBIOTIC ASSOCIATION



OVERVIEW

The word synbiotic originated from the Greek prefix 'syn,' meaning 'with; together,' and the suffix 'biotic,' meaning 'of or relating to life.'

Synbiotics have received considerable interest in recent years as modulators of the gut microbiome and contributors to health. While initially synbiotics included two main components, a probiotic and a prebiotic, more recently, synbiotics are being formulated to combine two or more probiotics, prebiotics, and postbiotics.

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (Hill et al., 2014). Prebiotics are compounds or ingredients utilized by the microbiota that produce a health or performance benefit (GPA, 2024).

Postbiotics are preparations of inanimate microorganism or their components that confer a health benefit on the host (Salminen et al., 2021). As such, synbiotics offer a dual approach to optimize gut microbiome and confer various health benefits more than the standalone ingredients.

DEFINITION:

The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines a synbiotic to be "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).

Following closely, the Global Prebiotic Association (GPA), defines synbiotics as "mixtures of live or inanimate microorganisms co-administered with substrate(s) selectively utilized by either the co-administered microorganism or the host indigenous microorganisms, conferring a health or performance benefit."

GPA's synbiotic definition aims to be more inclusive, market facing, and science based. The term "inanimate" was added to capture postbiotic combinations and makes synbiotic status to be more attainable. The action of co-administration was included to emphasize that the two components – prebiotic and probiotic – are taken together.

These changes make GPA's definition more comprehensive in terms of product innovations, while still retaining the rigorous scientific substantiation aspect.

COMPLEMENTARY SYNBIOTICS:

Synbiotics are commonly formulated as either complementary or synergistic. Complementary synbiotics consist of a live or inanimate microorganism independently chosen from the co-administered substrate(s), with each component working towards a separate effect or health benefit, which in ideal scenarios, is additive. As such, the substrate or the prebiotic component of the synbiotic formula may not necessarily be selectively used by the co-administered microorganism, but rather by other members of the microbiota.

Similarly, the live or inanimate microorganism component may not necessarily benefit from the combined substrate and may not even be capable of using or fermenting it (Krumbeck et al., 2018). The two ingredients may act independently but must meet minimum dosage requirements, as substantiated by scientific evidence, to achieve one or more health benefits (Nguyen et al., 2022). Most synbiotics used in clinical research are formulated as complementary.

SYNERGISTIC SYNBIOTICS:

In contrast, synergistic synbiotics consist of a live or inanimate microorganism specifically stimulated by the co-administered substrate (Gomez Quintero et al., 2022). Synergistic synbiotics are formulated so that the substrate primarily supports the growth or activity of the ingested microorganism but may also enrich or support other gut microbiota members (Swanson et al., 2020). The ideal scenario would be for the components to enhance each other's therapeutic and nutritional value (Nguyen et al, 2022). Additionally, the benefit of synergistic synbiotics is providing both the strain and the substrate, bypassing variability in how the microbiota responds in different individuals (Krumbeck et al., 2018) and necessitating less of each component than required in complementary synbiotic combinations.

Nonetheless, numerous reasons, including convenience, ease of formulation, and simplicity of experimental design, make complementary synbiotics a favourite over synergistic synbiotics (Gomez Quintero et al., 2022). The experimental challenge to demonstrate the efficacy of a synergistic synbiotic in clinical trials makes nearly all commercial synbiotics formulated as complementary (Nguyen et al., 2022). As such, preclinical models such as the Simulator of the Human Intestinal Microbial Ecosystem (SHIME) may be useful to provide preliminary data on synergistic synbiotics (Van de Wiele, et al., 2015).

Complementary and synergistic formulations require testing the synbiotic effect in the target host, conveying a health benefit. While it is unnecessary in the same study to demonstrate selective utilization of the substrate by the live or inanimate microorganisms in complementary synbiotics, synergistic synbiotics require this demonstration of selective utilization and health benefits.

GPA DEFINES COMPLEMENTARY AND SYNERGISTIC SYNBIOTICS AS:

COMPLEMENTARY SYNBIOTICS

"Comprise one or more live or inanimate microorganisms co-administered with a substrate that independently work in the formulation to generate a health benefit that is additive."

SYNERGISTIC SYNBIOTICS

"Comprise a substrate that is utilized selectively by the co-administered live or inanimate microorganisms, yielding a significant combined benefit."

HOW TO FORMULATE SYNBIOTIC PRODUCTS?

Synbiotics are commonly formulated using one or more different microbial strains combined with one or more prebiotic ingredients" (Swanson et al., 2020). Most prebiotics used in synbiotic formulations are "established" prebiotics (e.g., FOS, GOS, and inulin), which have been extensively studied for their prebiotic effect. There is growing interest, however, around including "novel" (e.g., polyphenols) and "emerging" (e.g., yeast hydrolysates) prebiotics in synbiotic formulations (Sharma & Padwad, 2020), which corresponds to more research and increasing evidence of their prebiotic effect.

Moving forward, synbiotics will be formulated using a combination of one or more prebiotics, probiotics, and postbiotics at clinically tested efficacious doses, providing one or more health benefits (Beteri et al., 2024; Nguyen et al., 2022). The formulation components may be selected to achieve a specific endpoint or health benefit. Challenges arise in the absence of rational strategies currently available to assess the synbiotic potential of the formulation before clinical testing (Gomez Quintero et al., 2022), specifically for synergistic synbiotics, where both components must be shown to work together and lead to gut microbiome modulation and health benefits.

Nonetheless, several criteria are necessary to formulate synbiotics, which include:

I. SELECTION OF THE SYNBIOTIC COMPONENTS: The identity of the individual components must be known, including a scientifically validated name and a fully designated strain for the live microorganism.

II. SELECTION OF THE FORMULATION TYPE: The utilization of the substrate by the host's indigenous microorganisms (complementary) or the co-administered microorganism (synergistic) must be substantiated with preclinical or clinical evidence.

III. DOSE SELECTION: An appropriate dose and composition must be selected as supported by preclinical and clinical data.

IV. SAFETY TESTING: Safety of the individual components and combination thereof.

V. EFFICACY TESTING: Measurable and reproducible health benefits demonstrated in the target host as supported by valid preclinical and clinical data.

VI. QUALITY TESTING: The stability of the live microorganism and its viability during the product's shelf life under different storage conditions must be verified.

While these are the main criteria for formulating synbiotics, other factors such as the formulation type, manufacturing processes, and the regulatory landscape in the market of interest are also important when developing a new synbiotic product.

PREBIOTICS USED IN THE FORMULATION OF SYNBIOTICS

Numerous prebiotic types have been clinically studied in human subjects as part of a synbiotic formulation. These include acacia gum, fructooligosaccharides (FOS), galactooligosaccharides (GOS), xylooligosaccharides (XOS), isomaltooligosaccharides (IMOs), guar gum, human milk oligosaccharides (HMO), inulin, lactulose, polyphenols, psyllium, resistant starch (RS), and mixtures of these. Other prebiotic types, such as yeast hydrolysates, pectin, beta-glucan, and arabinoxylan, have animal studies on their synbiotic use, but no human clinical trials have examined their potential in synbiotic formulations yet.

In terms of dose, the prebiotic component of a complementary synbiotic must be at a dose previously shown in the literature to be effective (see Table 1). Prebiotics used in synbiotic formulations have been used at doses ranging from as little as 100 mg up to as much as 68 g per day. In the case of synergistic synbiotics, the dose used for the prebiotic component should only be sufficient for its selective utilization by the live microorganism, resulting in a clinically demonstrated health benefit, which must be superior to the individual components' effect.

TABLE 1:

Clinically Tested Doses of Different Prebiotic Types in Synbiotic Formulations Reported in Scientific Literature.

Prebiotic Type	Dose (g)
FOS	0.1-15
GOS	2.8-20
Inulin	3.2-30
Acacia Gum	5-30
HMOs	2-20
IMOs	10-68
Polyphenols	0.5-1.5
RS	6-30
XOS	1.4-8

HEALTH BENEFITS OF SYNBIOTICS

Over the last decade, research of innovative synbiotic formulations has significantly increased, combining prebiotics, probiotics, and postbiotics to support human and animal health. While most synbiotics act in one of a few mechanisms, including gut microbiota modulation, gut barrier function improvement, inflammation and immune modulation, and metabolite production such as short-chain fatty acids, the ultimate result is a variety of health benefits. The following are some examples.

TABLE 2: Health Benefits of Synbiotics

GASTROINTESTINAL	**Gastrointestinal Microbiome Health:**	Synbiotics help maintain the microbial population naturally residing in the gut and various other locations in the body, including the skin, respiratory tract, and urogenital tract, contributing to health-supporting benefits. A recent randomized, double-blinded, placebo-controlled study investigated the effects of 12-week supplementation of a complementary formulation with prebiotics and postbiotics at 5 g/day (containing 32% konjac glucomannan, 60% GOS, and 8% exopolysaccharides from *Bifidobacterium breve*) or placebo (cellulose microcrystalline) on gut health, metabolic function, and diet in 53 prediabetic volunteers. Significant improvement was reported in gut microbiota alpha diversity, butyrate-producing bacteria, and reductions in hemoglobin A1c (HbA1c) and fasting blood glucose (FBG) levels (Beteri et al., 2024). Another study utilizing a synbiotic supplement (containing 2.75 g GOS and 15 x 10^9 colony forming units (CFUs) proprietary strains of *Lactobacillus acidophilus*, *B. lactis*, *B. longum*, *B. bifidum*) with weight loss program and low-carbohydrate, high-protein, reduced-energy diet for three months in 20 subjects increased the abundance and richness of gut bacteria associated with positive health effects, such as bifidobacteria and lactobacilli growth (Sergeev et al., 2020).
	Constipation:	A synbiotic supplement (60 mg FOS and 5 x 10^9 CFUs *L. acidophilus* and *B. longum*) taken twice per day for 60 days in chronic kidney patients on hemodialysis in a randomized, double-blinded, placebo-controlled trial significantly improved constipation symptoms and constipation-related quality of life compared to placebo (Lydia et al., 2022). Another study demonstrated that a synbiotic (containing 1996.57 mg fiber, polydextrose, FOS, and GOS with 4 x 10^9 CFUs *L. casei*, *L. rhamnosus*, *L. plantarum*, and *B. lactis*) consumed for four weeks in children with functional constipation had significant improvements in the weekly number of defecations, abdominal pain, and painful defecation compared to placebo (Baştürk et al., 2017).
METABOLIC	**Weight Management:**	A synbiotic formula containing *L. fermentum* strains K7-Lb1, K8-Lb1, and K11-Lb3 and 10 g of acacia gum showed a significant change in visceral adipose tissue, liver steatosis grade, and constipation score as compared to placebo when taken for three months in 180 individuals with abdominal overweight (Laue et al., 2023). Significant reductions were also reported in the visceral fat area and total fat area with a test beverage containing 1 × 10^{10} CFUs of *B. animalis* subsp. *lactis* GCL2505 per 100 g and 2.0 g of inulin per 100 g ingested for 12 weeks (Baba et al., 2023).
	Lipid Profile Reduction:	Synbiotics and prebiotics positively modulate numerous lipid profile components, including FBG, HbA1c, low-density lipoprotein, high-density lipoprotein, and triglycerides compared to placebo (Mahboobi et al., 2018).

HEALTH BENEFITS OF SYNBIOTICS (CONT.)

COGNITIVE	**Psychiatric Disease Symptom Alleviation (e.g., Anxiety, Depression, Panic):**	Recent and accumulating evidence of the microbiota-gut-brain bidirectional connection points toward alterations in the gut microbiota, which impact the central nervous system and vice versa (Freijy et al., 2023; Fuloria et al., 2022; Methiwala et al., 2021). A synbiotic formula containing 5 g each of FOS, GOS, and inulin with 2.7 x 10^7 CFUs/g each of freeze-dried *L. acidophilus* strain T16, *B. bifidum* strain BIA-6, *B. lactis* strain BIA-7, and *B. longum* strain BIA-8 supplemented for 12 weeks resulted in a significant decrease in clinical depression symptoms and increase in serum brain-derived neurotrophic factor levels (Haghighat et al., 2021).
ANTI-INFLAMMATORY AND IMMUNOMODULATORY	**Polycystic Ovarian Syndrome (PCOS):**	The supplementation of 2 g synbiotic sachets containing 0.5 g of FOS and 10^{11} spores of *Bacillus coagulans* (GBI-30), 10^{10} CFUs of *L. rhamnosus*, and 10^{10} of *L. helveticus*) for 12 weeks significantly improved numerous health-related quality of life scores, including emotional, body hair, weight, and fertility as compared to placebo in 52 women with PCOS (Hariri et al., 2024).
	Postoperative Complications:	A synergistic synbiotic formulation containing 1 g of inulin and 2.5 x 10^{10} CFUs of *L. acidophilus, B. lactis, L. plantarum, L. paracasei, B. breve, S. thermophilus, L. salivarius,* and *B. longum* consumed daily for 2 weeks significantly decreased inflammatory cytokines, elevated CD8+T cell proportion, interferon-gamma (IFN γ) expression, and the rate of postoperative complications, including anastomotic leakage, diarrhea, and abdominal distension (Maher et al., 2024).
	Sepsis:	A randomized, double-blinded, placebo-controlled trial of an oral synbiotic composed of 150 mg of FOS and ~10^9 of *L. plantarum* ATCC strain 202195 showed a significant reduction in the combination of sepsis and death, culture-positive and culture-negative sepsis, and the incidence of respiratory tract infections compared to placebo (maltodextrin) in rural Indian newborns (Panigrahi et al., 2017).
ANTINEOPLASTIC	**Chemotherapy-Induced Side Effects:**	A synbiotic supplement containing 21 g of FOS and 1x10^9 CFUs of *L. rhamnosus*, *L. casei*, *L. acidophilus*, *L. bulgaricus*, *B. breve*, *B. longum*, *L. helveticus*, *L. lactis*, *L. paraplantarum*, *B. bifidum*, *Streptococcus thermophilus* and *L. gasseri* supplemented twice per day for 8 weeks by 74 inpatient females with breast cancer significantly decreased the severity of chemotherapy (Adriamycin + Cyclophosphamide) complications, including abnormal defecation and fatigue, compared to the placebo. Synbiotics also improved nausea/vomiting and anorexia, but the decrease was not statistically significant compared to the placebo (Khazaei et al., 2023). Another randomized, double-blinded clinical trial investigated the effects of a synbiotic supplement on chemotherapy-induced diarrhea, nausea, vomiting, and constipation in children with acute lymphoblastic leukemia receiving maintenance chemotherapy. The synbiotic contained FOS as the prebiotic and *L. casei*, *L. acidophilus*, *L. rhamnosus*, *L. bulgaricus*, *B. breve*, *B. longum*, and *S. thermophilus* as the probiotics. It was administered at 5 x 10^9 CFUs twice/day for 7 days. The incidence of diarrhea and constipation was significantly reduced 3 days after the synbiotic supplement intake compared to the placebo (Eghbali et al., 2023).

POTENTIAL CLAIMS

As previously discussed, synbiotic formulations have shown various health benefits in human clinical trials. These include benefits for the gastrointestinal, metabolic, cognitive, inflammatory, and immune systems. These benefits may result from the individual components' mechanisms of action or their combination and interaction as part of the synbiotic formulations.

Synbiotics are an emerging category in the regulatory landscape and different jurisdictions may vary in how they regulate synbiotics and synbiotic-related claims. Furthermore, the specific claims permissible for different synbiotic formulations may differ based on factors such as the different components used, whether the formulation is complementary or synergistic, the strain of live microorganisms, the type of substrates, and whether the product is a functional food, dietary supplement, etc. These claims may include inflammation management, lipid profile reduction, weight management, antineoplastic effects, immune function support, surgical infection management, gastrointestinal health support, cognitive health enhancement, skin health, healthy aging, and general health and wellbeing.

The claims permitted for synbiotic products largely depend on acceptable claims language and/or pre-cleared claims for the individual components in each marketed jurisdiction. While synbiotics are not considered nutrients and cannot carry nutrient content claims, these claims are commonly used and approved in most jurisdictions for the individual synbiotic components like prebiotic dietary fibers, where the nutrient has an established Daily Value (DV) that it can be compared to (e.g., "high in fiber").

However, jurisdiction-specific regulations may require pre-market confirmation and approval from the respective regulatory agency. Health and Structure-Function claims may also be used in certain jurisdictions such as the United States and Canada, depending on the source and substantiating evidence, adhering to country-specific regulations. While some claim types may be permissible in different jurisdictions based on different regulatory submissions, no specific pre-approved regulatory documents are currently available for synbiotics. To make claims on a synbiotic product, a company must follow region-specific requirements for scientific substantiation through credible and rigorous clinical trials to establish safety, efficacy, and quality at the selected dose of each component in the formulation, ensuring each component complies with jurisdiction-specific regulatory guidelines.

OPPORTUNITIES IN THE SYNBIOTIC SPACE

Synbiotics show great promise as dietary interventions in humans and animals, used for health support and disease prevention. Their efficacy arises from their main mechanism of action in influencing the gut microbial ecology, while their safety has been confirmed in numerous studies in healthy and diseased populations including non-alcoholic fatty liver disease, chronic kidney disease, metabolic diseases, autoimmune diseases, gastrointestinal conditions, and various cancers (Nguyen et al., 2022).

While traditional oligosaccharide-based prebiotics have been commonly used in synbiotic formulations, there has been a growing interest in the use of novel and emerging prebiotics, including polyphenols. Synbiotics consisting of multi-strain probiotics have been found to provide more benefits in modulating the gut microbiota compared to single-strain probiotics (Fallah & Mahdavi, 2023). Recently, there has been a trend toward the use of second-generation synbiotics, which focus on utilizing a variety of prebiotic agents based on their physiological effects and functional capacities rather than their microbial targets (Sharma & Padwad, 2020).

With many synbiotic formulations being possible using different combinations of probiotics, prebiotics, and postbiotics, the main challenge is ensuring that the formulation is efficacious, providing health benefits at a specific dose. New approaches such as microencapsulation offer an exciting way to address this challenge (Jiménez-Villeda et al., 2023).

For instance, formulating probiotics in a dried, powdered form may reduce the stress on the bacteria, improving their survival in the host's acidic gastrointestinal gateway. Microencapsulation can further enhance probiotic cell survival and optimize gut deliverability by providing a protective coat (Nguyen et al., 2022). This protective coating shields the formulation components and enhances their interaction and availability at the appropriate region of the gastrointestinal tract (Goderska & Kozlowski, 2021; Jiménez-Villeda et al., 2023), which is especially beneficial in synergistic synbiotic formulations, where the formulation components are interdependent to achieve a significant combined health benefit.

Synbiotics can be utilized in dietary supplements, functional foods and beverages, and personalized nutrition, where the product is tailored based on individual microbiome profiles and ingredient efficacy and stability requirements are met. While various age groups may benefit from consuming synbiotics, these dietary interventions may be particularly beneficial for the elderly, as gut microbiota diversity tends to decrease with age. This demographic often experiences numerous comorbidities, which can impact their quality of life. As such, synbiotics, along with probiotics, prebiotics, and postbiotics, may serve as non-invasive treatments to combat the inflammatory conditions and compromised immunity associated with aging (Ale & Binetti, 2021).

The global synbiotic market was estimated at USD 638.2 million in 2023, growing at a compound annual growth rate of 7.5% between 2023-2033, projected to reach USD 1.12 billion in 2033 (Future Market Insights, 2023).

CONCLUSIONS

Primarily, the beneficial effects of synbiotics largely depend on the success of combining two or more "biotic" components, maintaining the stability and viability of the individual ingredients, and resulting in one or more benefits.

Exploring different combinations of substrates and strains of live microorganisms for an ideal combination is encouraged. Synbiotic formulations offer a broad array of health benefits, which may be via the synergistic route of boosting one area or a holistic approach towards a multitude of benefits where each component acts independently to confer a different health benefit.

Nonetheless, dosage selection is crucial as meeting minimum dosage may not be adequate for a physiologically detectable health effect while increasing the dose requires substantiating evidence of safety and tolerability in the host. Lastly, the success of market entry for such products depends on the regulatory landscape of each jurisdiction, which determines the approved claims and labeling requirements.

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