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Review

Cyclodextrins in Probiotic Protection and Microbiome Modulation: From Carrier Systems to Synbiotic Design

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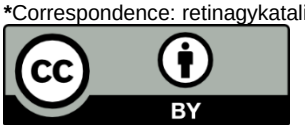

Abstract

Cyclodextrin-based micro- and nanocarriers are increasingly being explored as versatile tools for improving the stability and delivery of probiotic microorganisms, addressing persistent challenges such as acid and bile sensitivity, oxidative stress, and processing-related losses. A wide range of micro- and nano-encapsulation strategies, including spray drying, extrusion, coacervation, freeze-drying, and electrospinning, have been developed to enhance probiotic viability and gastrointestinal performance. Within this technological landscape, cyclodextrins offer distinctive advantages due to their ability to form multifunctional carrier matrices and stabilize sensitive bioactive components through both inclusion and non-inclusion interactions.

Beyond their role as formulation excipients, emerging evidence indicates that certain cyclodextrins may also exhibit prebiotic-like properties, selectively stimulating beneficial microorganisms such as Bifidobacterium, Lactobacillus, Akkermansia, and Bacteroides, while modulating gut microbial metabolism. This combination of carrier functionality and potential biological activity suggests a conceptual framework for synbiotic design in which cyclodextrins could both protect probiotics and influence the intestinal environment following release.

Advances in cyclodextrin-based hydrogels, nanosponges, and hybrid polymer systems further illustrate opportunities for colon-targeted delivery, microbiota-responsive degradation by resident bacteria such as Bacteroides spp., and controlled release; however, most probiotic-specific applications remain at an exploratory stage. Key challenges related to large-scale manufacturing, microbial viability, safety assessment, and regulatory harmonization remain unresolved.

Rather than presenting a finalized technology, this review integrates evidence from food science, pharmaceutical research, and microbiome studies to highlight cyclodextrin-enabled probiotic formulation as an emerging research domain. By delineating current opportunities and limitations, the work aims to stimulate interdisciplinary investigation into the potential role of cyclodextrins in future probiotic and synbiotic systems.

1. Introduction

The concept of probiotics has undergone significant refinement since its earliest formulations. Classical definitions, such as that of Schrezenmeir and de Vrese describe probiotics as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host” (1). The probiotic concept has evolved from early observations on fermented foods to an evidence-based framework recognizing probiotics as modulators of gut ecology, immune function, and metabolic homeostasis (2,3).

Clinically, probiotics are now recognized for their diverse functional roles in digestion, immune regulation, and metabolic pathways. Quigley (4) highlights their interactions with host physiology and with prebiotics, emphasizing synergy in shaping gastrointestinal health. Despite these potential benefits, several critical challenges limit probiotic efficacy. These include poor survival in the acidic gastric environment, sensitivity to bile salts, oxygen, and temperature, as well as stresses encountered during food processing and storage. Such vulnerabilities have greatly accelerated interest in micro- and nanoformulation techniques designed to protect probiotic cells, enhance viability, and improve targeted delivery - approaches thoroughly discussed in recent works such as Kiprono (5) and Rajam & Subramanian (6).

Parallel to the evolution of probiotic science, the concept of prebiotics has also expanded considerably. Prebiotics are now broadly defined as substrates selectively utilized by host microorganisms that confer health benefits. Yoo et al. (7) provide a comprehensive overview of prebiotic types - including oligosaccharides, fibers, and emerging carbohydrate structures - and their capacity to modulate the gut microbiome. Mechanistically, classical and newly described pathways encompass short-chain fatty acid (SCFA) production, immune modulation, and reinforcement of the intestinal barrier, as reviewed by Smolinska et al. (8) and Bock et al. (9). These insights underline

the multi-layered interactions between diet-derived substrates and microbial communities.

Among emerging prebiotic candidates, cyclodextrins (CDs) have gained particular scientific attention. CDs are cyclic oligosaccharides composed of α-(1-4)-linked glucopyranose units, forming hydrophobic cavities capable of hosting various guest molecules. Detailed structural and chemical analyses by Spiridon & Anghel (10) describe the three principal natural CDs - α-, β-, and γ-cyclodextrin - and their numerous derivatives, which differ in cavity size, substitution pattern, and physicochemical properties. Beyond classical inclusion complexation, cyclodextrins are increasingly recognized to stabilize guest molecules via non-inclusion mechanisms, contributing to improved solubility, stability, and bioavailability in advanced nano-delivery systems (11). Beyond their carrier functionality, a growing body of evidence suggests that CDs themselves may exhibit prebiotic activity (12–14). This dual identity - functioning both as a delivery system and as a fermentable substrate - positions CDs as a unique bridge between probiotic stabilization technologies and prebiotic functionality.

This review seeks to highlight intersections among recent advances in probiotics, prebiotics, and cyclodextrins, and to propose potential avenues for future research.

2. Search Strategy

Literature was identified through Web of Science, PubMed, Scopus, and Google Scholar using the keywords "cyclodextrin", "probiotic", and "prebiotic". Publications from 2000 onward were considered, and relevant articles were selected according to their relevance to the scope of this review.

3. Results

3.1. Micro- and Nanoformulation of Probiotics

The incorporation of probiotics into food and pharmaceutical delivery systems is constrained by their susceptibility to environmental stresses, including gastric acidity, bile salts, oxidative degradation, and thermal inactivation. These factors collectively reduce viability during processing, storage, and gastrointestinal transit, emphasizing the need for encapsulation technologies that can establish protective microenvironments for sensitive probiotic strains (15,16).

Among the available microencapsulation methods, spray drying remains the most extensively applied technique due to its scalability, economic feasibility, and capacity to integrate diverse wall materials while maintaining moderate cell viability (6). Alternative encapsulation methods, including extrusion, emulsification, and coacervation, further improve probiotic survival by providing protective hydrogel or polymer matrices (17). Clinical translation of such microencapsulation strategies is reflected in the work of Gąsiorowska et al. (18), who demonstrate the feasibility of combining microencapsulated sodium butyrate with probiotic strains and short-chain fructooligosaccharides, thereby highlighting the potential of encapsulation approaches for stabilizing multi-component probiotic formulations in vivo.

Low-temperature encapsulation approaches such as freeze drying and electrospinning provide additional benefits for thermally sensitive microorganisms. Cryoprotectants and polymeric carriers strongly influence structural integrity, microcapsule morphology, and long-term stability under storage. Electrospinning is particularly promising for generating nano- to microscale fibrous matrices with large surface areas, which can modulate release kinetics while affording robust protection from harsh gastrointestinal conditions. (15,19).

More recently, probiotic formulations incorporating nanostructured components have gained increasing attention for their capacity to enhance stability, mucosal interaction, and site-specific intestinal release. Importantly, such “nanoencapsulation” strategies do not imply that the probiotic cells themselves are reduced to nanoscale dimensions; rather, nanoscale carriers, coatings, or internal matrix architectures are employed to impart functional advantages to inherently micrometer-sized microorganisms. Lipid nanoparticles, polymeric nanocarriers, and multilayered nano-coatings can effectively shield probiotics against extreme acidity, bile exposure, and oxidative stress while enabling controlled or stimuli-responsive delivery (20,21). In the context of gastrointestinal disorders, delivery systems integrating nano- and microscale structural features have shown particular promise. Lopes et al. (22) report that such hierarchically organized carriers significantly improve probiotic survival during upper gastrointestinal transit and facilitate targeted colon delivery, positioning nanostructured encapsulation approaches as a powerful means of modulating intestinal inflammation without altering probiotic cell size.

Collectively, encapsulation strategies employing micro- and nanoscale structural elements expand the formulation toolbox for stabilizing probiotics and optimizing their

bioavailability. The selection of an appropriate approach must reconcile multiple constraints, including thermal sensitivity, oxygen tolerance, process robustness, economic feasibility, and desired release profiles. Accumulating evidence indicates that hydrogel bead systems, freeze-dried matrices, spray-coated particles, and nanostructured carriers each confer distinct and complementary advantages for tailoring probiotic delivery in functional food, nutritional, and therapeutic applications.

3.2. Cyclodextrins and Probiotics

3.2.1. Cyclodextrin-Based Carriers

Extensive pharmaceutical research suggests a solid technological basis that may be leveraged for the formulation of probiotic systems incorporating cyclodextrins. Polymerized CD architectures - such as nanosponges, nanospheres, and hydrogels - are characterized by high loading capacity and tunable degradation behavior, properties that could be advantageous in the design of probiotic formulations. Ji et al. (11) describe a range of CD-based nanosponges, metal-organic frameworks (MOFs), and nanogels developed for controlled drug release, while Omidian et al. (23) report hybrid CD hydrogels capable of regulating water uptake and enabling sustained release.

Because the colon is the principal site of probiotic colonization and activity, particular interest has focused on CD-based systems designed for colon-targeted delivery. Sharma et al. (24) report β-CD-derived mucoadhesive hydrogels that undergo microbiota-dependent degradation, particularly through enzymatic cleavage by Bacteroides species, thereby enabling site-specific carrier activation and controlled release.

3.2.2. Cyclodextrins as Prebiotic Components of Synbiotic Systems

Although cyclodextrins are primarily recognized as pharmaceutical excipients and carrier materials, growing evidence suggests that certain CDs may also exert biologically relevant prebiotic effects. This observation has stimulated interest in their incorporation into synbiotic systems, where a single component may simultaneously contribute to probiotic protection and microbiota modulation.

One of the earliest indications of such a role is provided by Pranckutė et al. (25), who demonstrate that α-cyclodextrin serves as a selective substrate for specific probiotic microorganisms. In their study, Lactococcus lactis subsp. lactis efficiently utilizes α-

cyclodextrin and exhibits enhanced antibacterial activity, suggesting that cyclodextrins may directly support the growth and functionality of selected beneficial bacteria.

Subsequent investigations extend these observations beyond individual strains to broader microbiome-level effects. Experimental studies show that α-cyclodextrin can influence gut microbial composition and metabolic activity, promoting the growth of beneficial bacterial groups while increasing short-chain fatty acid production (12,26,27). In parallel, Gościniak et al. (13) report that selected cyclodextrins stimulate Bifidobacterium species and favorably affect microbial fermentation patterns. More recently, Varut et al. (14) report that α- and β-cyclodextrin derivatives may contribute to the expansion of beneficial genera such as Lactobacillus and Akkermansia, further supporting the concept that cyclodextrins participate in microbiome modulation beyond their technological functions.

At the same time, cyclodextrins may enhance probiotic performance through formulation-related mechanisms. Although probiotic cells themselves generally do not enter the cyclodextrin cavity, CDs can stabilize co-encapsulated compounds, reduce moisture-related degradation, and improve the physicochemical properties of carrier matrices. Singh et al. (28) demonstrate that native cyclodextrins significantly improve the viability and encapsulation efficiency of Lactobacillus rhamnosus GG, resulting in enhanced storage stability and greater survival under simulated gastrointestinal conditions. These findings suggest that cyclodextrins support probiotics both indirectly through carrier functionality and directly through prebiotic effects.

The combination of these properties stimulates the development of practical synbiotic formulations. For example, Mohammadi et al. (29) develop a fermented dairy beverage containing microencapsulated Lactobacillus plantarum and Lactobacillus acidophilus in a β-cyclodextrin-containing system combined with β-glucan. Such studies illustrate how cyclodextrins can be integrated into multifunctional formulations designed to improve probiotic stability while simultaneously contributing to microbial ecosystem support.

Taken together, the progression of evidence from selective microbial utilization to microbiome modulation and applied formulation studies supports an emerging concept of cyclodextrins as dual-function excipients. Within this framework, cyclodextrins may not only protect probiotics during processing, storage, and gastrointestinal transit, but may also contribute to a more favorable intestinal environment after release. Although the clinical significance of these combined effects remains to be fully established,

cyclodextrins represent promising building blocks for the next generation of synbiotic delivery systems.

3.2.3. Challenges and Future Perspectives of Cyclodextrin-Containing Probiotic Delivery Systems

In the food sector, CDs are already used to improve the stability and shelf life of selected bioactive compounds (30,31), providing a conceptual - though not yet fully validated - basis for their extension to probiotic delivery systems.

Beyond conventional delivery concepts, cyclodextrins are increasingly discussed in the context of synbiotic and postbiotic systems, where they may provide combined technological and nutritional functions. Emerging research on microbiome-related axes, such as gut-brain and gut-skin interactions, points to possible future applications, including dermatological and cosmetic formulations (32,33). Nevertheless, the translation of these concepts into robust probiotic products remains at an early stage.

Despite these prospects, several limitations must be carefully addressed. Scale-up of CD-containing probiotic systems is challenged by variability in encapsulation efficiency, maintenance of microbial viability, and cost control (34)n addition, comprehensive toxicological evaluation is essential, given reported dose-dependent effects (14) and the membrane-active properties of certain cyclodextrins (35). Regulatory uncertainty further complicates development, as harmonized standards for probiotics, prebiotics, and combined formulations are still lacking (3).

Looking forward, CD-based probiotic delivery may benefit from incremental advances rather than disruptive transformations. Personalized, microbiome-informed formulation strategies and synbiotic systems combining CDs with live probiotics represent promising but still speculative. Overall, continued interdisciplinary research will be required to determine whether CD-based carriers can be translated into safe, scalable, and regulatory-compliant probiotic technologies.

4. Conclusion

Cyclodextrin-based micro- and nanocarriers represent a versatile yet still insufficiently explored platform at the intersection of food science, pharmaceutical technology, and microbiome research. Their well-established structural and physicochemical properties support a rational extension toward probiotic stabilization and delivery, while

accumulating evidence suggests that selected cyclodextrins may also exert prebiotic-like effects.

Importantly, probiotic-specific applications of cyclodextrins remain largely exploratory, with significant challenges related to formulation design, microbial viability, safety, scalability, and regulatory acceptance. At the same time, advances in cyclodextrin-based hydrogels, nanosponges, and responsive carrier systems provide a promising foundation for further investigation. By framing cyclodextrin-enabled probiotic formulation as an emerging research domain, this review aims to stimulate interdisciplinary efforts to critically assess its feasibility, limitations, and potential contribution to future probiotic and synbiotic technologies.

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