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Review

MICROENCAPSULATED PROBIOTICS FOR NEURODEGENERATIVE DISORDERS: HARNESSING FERMENTATION AND TARGETED DELIVERY ALONG THE GUT-BRAIN AXIS-A REVIEW

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Abstract

Neurodegenerative disorders (NDDs) such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis are characterized by progressive neuronal loss, neuroinflammation, and cognitive and motor decline. Recent research highlights the significant role of the gut–brain axis (GBA) in the development and progression of these disorders. Gut microbiota imbalance (dysbiosis) contributes to neuroinflammatory processes, making microbiome-based therapies a promising approach. Probiotics, particularly Lactobacillus and Bifidobacterium species, exhibit neuroprotective effects by modulating gut microbiota, enhancing intestinal barrier function, and producing beneficial neuroactive metabolites. However, their survival is often compromised during processing and gastrointestinal transit. Microencapsulation technologies such as spray drying, extrusion, ionotropic gelation, and nanoencapsulation improve probiotic stability, viability, and targeted intestinal delivery. Advanced delivery strategies further enhance gut–brain communication and therapeutic outcomes. This review summarizes fermentation-based probiotic production, microencapsulation techniques, formulation challenges, and future strategies for developing effective probiotic-based therapies for neurodegenerative disorders.

Keywords: Probiotics, Microencapsulation, Fermentation, Neurodegenerative disorders.

1. Introduction

Neurodegenerative disorders (NDDs) are characterized by the progressive degeneration and death of neurons, resulting in cognitive decline, motor dysfunction and behavioral changes. Representative NDDs include dementia-type Alzheimer's disease (AD), Parkinson's disease (PD), motor neuron diseases, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disease, multiple system atrophy, tauopathies, and prion diseases. Although NDDs share common pathological features, such as protein aggregation, oxidative stress and neuroinflammation, their exact underlying mechanisms have not been elucidated due to their significant complexity.(1) Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer health benefits to the host, according to the WHO/FAO. Probiotics are typically non-pathogenic bacteria or yeasts that help maintain or restore a balanced gut microbiota and provide physiological benefits when consumed in sufficient amounts. The most common probiotic strains come from lactobacillus, bifidobacterium, and certain yeasts such as saccharomyces.(2) The gut–brain axis (GBA) refers to the communication between the gut microbiota and the brain and involves multiple physiological processes that are strategic points in maintaining the homeostasis of the gastrointestinal (GI) tract, central nervous system (CNS) and microbial systems. Gut microbiota variations impact probiotic treatments' efficacy, with Lactobacillus and Bifidobacterium strains promising for alleviating Alzheimer's symptoms by restoring gut microbial diversity and decreasing neuroinflammation.(3) Encapsulation is a method for delivering therapeutics and bioactive compounds by enclosing nano, micro, or millimeter-scaled particles in a matrix or layer. By encapsulating bioactive compounds, they are delivered precisely to specific sites in the body, increasing stability, therapeutic efficacy, and bioavailability and minimizing the side effects. The survival rate of probiotics is affected by many complex factors, including ions, oxidative stress, osmotic pressure, nutrient depletion, and their passage through the GI tract. When choosing the optimum encapsulation method for probiotics, a number of factors must be considered to ensure that probiotics can survive the encapsulation process, storage conditions and ingestion, as well as controlled release into the gut at the appropriate time.(4)

2.Neurodegenerative Disorders: Overview

Neurodegenerative disorders involve the progressive loss of neuron function and structure in the brain and spinal cord. These conditions lead to cognitive, motor, and behavioral impairments that worsen over time.(5)

Types of neurodegenerative disorders

Alzheimer's disease: Memory loss and cognitive decline from cortical atrophy.

Parkinson's disease: Dopaminergic neuron loss causing tremors and rigidity.

Huntington's disease: Genetic mutation leads to striatal degeneration(the progressive breakdown of neurons in the striatum) and chorea(a state of excessive, spontaneous movements).

Amyotrophic lateral sclerosis (ALS): Motor neuron death resulting in muscle weakness.(6)

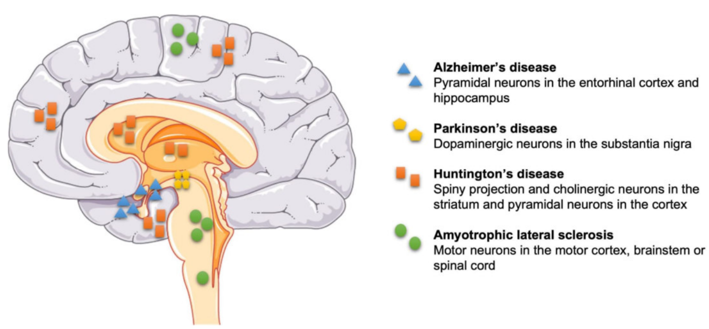


Image-1: Types of neurodegerative disorders

3.Early signs of Neurodegenerative Disorders

- For cognitive issues like memory loss and disorientation
- Motor changes such as tremors or stiffness and behavioral shifts including sleep problems.
- Early detection supports better management.(7)

4. Gut-Brain Axis in Neurodegenerative Disorders

The gut–brain axis (GBA) is a complex bidirectional communication network that connects the gut and brain. It involves neural, immune and endocrine communication pathways between the Gastrointestinal (GI) tract and the CNS.(8) This complex interplay allows continuous biochemical interference between the gastrointestinal tract and brain, with profound implications for both neurological health and disease. This axis consists of several key components, including the gut microbiome, intestinal barrier, vagus nerve and immune system. These components interact through chemical, neurological and immune signals that directly or indirectly affect brain the health and function.(9) Furthermore, the gut microbiome is involved in the production of various neuroactive compounds, including neurotransmitters and short-chain fatty acids, which can be directly influence brain function. Understanding these interactions is crucial for developing novel therapeutic strategies that target the gut microbiome to prevent or mitigate neurodegenerative diseases.(10)

5. PROBIOTICS AND THEIR NEUROPROTECTIVE MECHANISMS

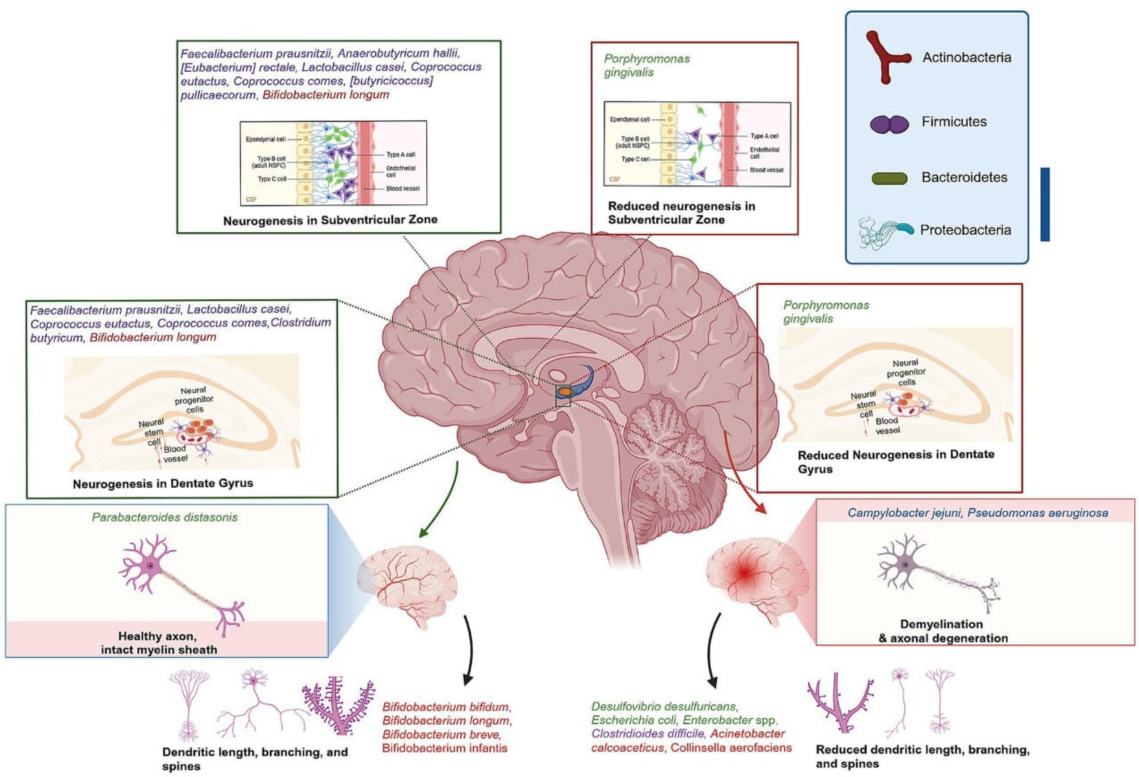


Image-2:Probiotics and their neuroprotective mechanisms

6. Fermentation Process for Probiotic Production &Enhancement

Probiotic fermentation produces viable lactic acid bacteria, such as *Lactobacillus* and *Bifidobacterium,* through controlled microbial growth for pharmaceutical applications. Enhancement focuses on optimizing biomass, metabolites and viability through precise bioprocess parameters.(11)

Fermentation produces probiotics through controlled microbial growth, primarily lactic acid bacteria (LAB), converting sugars into lactic acid and other metabolites. This process enhances food preservation, flavor and health benefits like gut health support.(12)

6.1. Fermentation Phases

Lacto-fermentation starts with salt brine (salt+water) killing harmful bacteria like Klebsielleae while favoring good bacteria. Leuconostoc species then dominate, creating an oxygen-free, acidic environment with gas production. Lactobacillus strains (e.g., L. plantarum) finish the process, lowering pH further for probiotic stability.(13)

6.2. Microbial Pathways

Homofermentative LAB convert glucose directly to lactic acid via glycolysis. Heterofermentative paths yield lactic acid, ethanol and carbon di oxide, supporting diverse strains. Later stages may include yeast-driven alcoholic fermentation transitioning to acetic acid production(14)

6.3. Parameters

Temperature: Ranges 30-42°C, ideally ~37°C for LAB; balances rapid growth against survival in drying processes.(15)

pH: Start at neutral (6.5–7.0), allow drop to 5.0–5.5 via lactic acid production; use buffers or alkali addition to prevent excessive acidity inhibiting viability.(16)

Other Factors: Moderate agitation improves nutrient diffusion without shear damage. Anaerobic conditions for most strains; Media with glucose/yeast extract maximizes biomass.

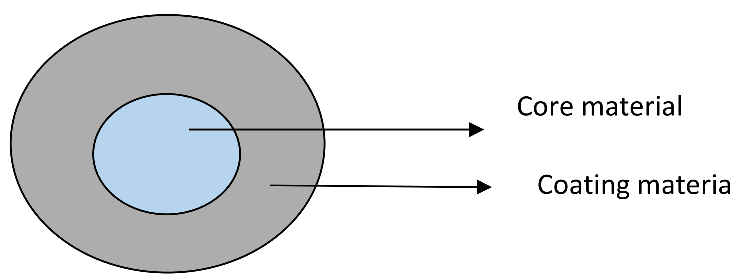
Duration: 12-48 hours to stationary phase, with cryoprotectants for preservation. (17)

7. MICROENCAPSULATION TECHNIQUES FOR PROBIOTIC PROTECTION AND DELIVERY

Microencapsulation is a process in which solid, liquid or gaseous materials are enclosed within thin polymeric coatings to form small particles known as microcapsules. The coating acts as a protective barrier, preventing degradation and controlling the release of the core material at a desired time or site. The size of microcapsules typically ranges from a few micrometers to a few millemeters.(18)

7.1 Materials Involved In Microencapsulation

In this process, each particle or droplet (core) is surrounded by a continuous film (shell) of polymeric material to form microcapsules. The polymer coating helps protect the core and allow for targeted or controlled release of the active substance when exposed to specific conditions.(19)



7.2. Core Materials

The core material is the substance that needs to be coated. It can be either solid or liquid and may include active ingredients, stabilizers, dilutents, excipients or release-rate modifiers. The core may contain dispersed or dissolved substances depending on the intended use and formulation requirements.(20)

7.3. Coating Materials

The coating material forms the outer shell of the microcapsule.

It must be:

Chemically compatible and non-reactive with the core,strong,flexible and impermeable, stable and capable of forming a cohesive film.

E.g. Coating materials:

- Gums: Gum arabic, sodium alginate, carragenan
- Carbohydrates: Starch, dextran, sucrose
- Celluloses: Carboxymethylcellulose, methycellulose.
- Lipids: Bees wax, stearic acid, phospholipids.
- Proteins: Gelatin, albumin.(21)

8.An Overview of Microencapsulation Techniques

Microencapsulation can be achieved through various techniques, each designed to control the encapsulation and release of active materials effectively.

A. Spray drying:

Spray drying is a technique in which a feed solution—containing the core material and a wall material—is atomized into a fine mist inside a drying chamber. Hot air is then applied to rapidly evaporate the solvent, converting the mist into dry powder. The core material becomes entrapped within the dried particles, forming microcapsules. This method is widely used for microencapsulation due to its efficiency and scalability. However, despite its many advantages, some studies have also highlighted certain drawbacks of the spray-drying process.(22)

B. Spray cooling:

Spray cooling is an encapsulation method very similar to spray drying, but instead of hot air it uses cold air to solidify the droplets. A mixture of core and wall material is atomized into a mist inside a chamber where cold air flows, causing the microdroplets to solidify into microencapsulated powder. This technique has strong potential for large-scale production. It has been successfully used to microencapsulate tocopherols in a lipid matrix with up to 90% efficiency, as well as iron, iodine, and vitamin A in hydrogenated palm oil for salt fortification, yielding highly stable microcapsules.(23)

C. Coacervation:

This process involves forming a polymer-rich layer around the core by changing temperature, PH or ionic strength. The resulting coacervates encapsulate the core material, commonly used for hydrophilic molecules. Sodium alginate and calcium chloride are often used to form calcium alginate microcapsules through ionic gelation.(24)

D. Fluidized bed coating:

Fluidized bed coating is an encapsulation method in which coating material is sprayed onto the fluidized core material. Here, the core material is fluidized by application of air, onto which a coating material is sprayed. In this method of encapsulation, coating efficiency of the wall material is dependent on various parameters like feed rate of the wall material, atomization pressure of the nozzle, inlet air temperature, and velocity.(25)

E. Extrusion:

Extrusion technology for microencapsulation can be used for producing highly dense microcapsules. To use this method, the core and the wall material should be immiscible. Here, the core and the wall materials are passed in such a way that the wall material surrounds the core and they are passed through concentric nozzles, thus, forming droplets containing the core surrounded by the wall material.(26)

F. Emulsification:

Encapsulation using emulsification technique is done by dispersing the core in an organic solvent, containing the wall material. The dispersion is then emulsified in the oil or water, to which emulsion stabilizer is added. Encapsulation of the core occurs by formation of a compact polymer layer around it, by evaporation of the organic solvent. This is one of the frequently used techniques of encapsulation as the procedures involved are very simple. This technique is widely used for encapsulating enzymes and microorganisms.(27)

G. Cyclodextrin inclusion:

Cyclodextrins are cyclic oligosaccharides, capable of forming inclusion complexes with many organic compounds. Cyclodextrins have an internal nonpolar cavity and hydroxyl groups on the surface.Form inclusion complexes with hydrophobic compounds through hydrophobic,dipole-dipole and van der waals interactions. This technique enhances the solubility, stability and bioavailability of poorly soluble substances.(28)

H. Ionotropic gelation method:

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogel beads also called as gelispheres. Gelispheres are spherical crosslinked hydrophilic polymeric entity capable of extensive gelation and swelling in simulated biological fluids and the release of drug through it controlled by polymer relaxation. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. The cations diffuse into the drug-loaded polymeric drops, forming a three-dimensional lattice of ionically crosslinked moiety. Biomolecules can also be loaded into these gelispheres under mild conditions to retain their three-dimensional structure.(29)

9. Targeted Delivery Systems Crossing the Gut-Brain Barrier

Targeted delivery systems targeting the gut-brain barrier (GBB) mark a promising advance in treating neurodegenerative diseases. They harness the gut-brain axis modulated by microbial signals to bypass blood-brain barrier using routes like intranasal administration or microbiome-enhanced transport.(30)

9.1. Gut-Brain Axis Overview

The GBB, distinct from the blood-brain barrier, facilitates communication through vagal nerves, microbial metabolites and immune pathways. Dysbiosis disrupts this axis, contributing to conditions like Parkinson's and Alzheimer's. Targeted delivery exploits short-chain fatty acids. (31)

9.2. Receptor-Mediated strategies

Receptor-mediated transcytosis employs transferring(or)insulin receptors, which are overexpressed on endothelial cells, by linking them to nanoparticles carrying gut-derived therapeutics. Transporter systems such as GLUT1(Glucose transporter type 1) facilitate the passage of glucose-mimicking prodrugs through active uptake mechanisms, demonstrating strong specificity in preclinical animal studies. These methods reduce off-target effects more effectively than passive diffusion strategies.(32)

9.3. Microbiome-Targeted Platforms

Silica nanoparticles encapsulate probiotic spores forGBMA(**Gamma-rhythmic Gain)** modulation, delivering neuroprotective agents like antioxidants. Composite hydrogels from pectin and proteins sustain release in the gut, influencing brain signaling via microbial fermentation products. Biomimetic nanosystems mimic gut-derived vesicles for non-invasive transit.(33)

10. FORMULATION CHALLENGES

- High temperatures (e.g., spray drying, cheese stretching) shear, low pH, and oxygen exposure can drastically reduce viable counts during manufacturing.(34)
- Wall materials must be food - grade, biodegradable and able to form a strong barrier to acid, bile, oxygen and moisture, while remaining compatible with the strain and not disrupting its metabolism.(35)
- Encapsulation method strongly affects particle size, morphology and dispersion extrusion gives large beads, while emulsion and spray systems can suffer from droplet coalescence, broad size distributions and solvent removal problems.(36)

11. FUTURE DIRECTION

Future directions in microencapsulated probiotics for neurodegenerative disorders focus on enhancing gut-brain axis modulation via advanced encapsulation for strains like Lactobacillus and Bifidobacterium. (37)

11.1. Emerging Strategies

Nanoencapsulation: Smaller particles improve bioavailability, stability against GI stress, and targeted brain delivery through microbiome signaling, addressing aggregation and scalability challenges. (38)

Strain-Specific Optimization: Tailor matrices for novel probiotics to reduce amyloid plaques andinflammation in Alzheimer's/Parkinson's.(39)

Synergistic Formulations: Combine with prebiotics or neurotransmitters to boost neuronal health and clinical translation.(40)

12. CONCLUSION

Microencapsulated probiotics hold transformative potential for neurodegenerative disorders by safeguarding viability through the GI tract and amplifying gut-brain axis benefits. Integrating nanoencapsulation, strain optimization, and synergistic delivery will overcome current hurdles, paving the way for scalable, clinically viable therapies that modulate neuroinflammation and pathology via microbiota signaling. These innovations promise enhanced patient outcomes in Alzheimer's and Parkinson's management.

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