Synergistic Integration of Probiotics and Nanotechnology: Advanced Therapeutic Strategies for Geriatric Drug Delivery, Hyperthermia, and Wound Management

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ABSTRACT

The convergence of probiotic science and nanotechnology offers a paradigm-shifting strategy for managing age-related health conditions, with specialized applications in targeted drug delivery, hyperthermia treatment, and chronic wound care. This comprehensive review examines the collaborative potential of probiotic-derived gold nanoparticles (AuNPs) and nano-encapsulation platforms in augmenting therapeutic outcomes for elderly patients. Probiotic-synthesized AuNPs exhibit substantial anti-inflammatory properties through suppression of NF-κB/MAPK signaling cascades, markedly decreasing pro-inflammatory cytokine production in both cellular and animal models. Nano-encapsulation methodologies employing chitosan, PLGA, and electrospun nanofibers safeguard probiotic viability under adverse gastrointestinal conditions while facilitating regulated release and site-specific delivery. These sophisticated platforms demonstrate considerable potential in photothermal treatment, tissue regeneration, and gut microbiome regulation, providing enhanced bioavailability and diminished toxicity relative to conventional approaches. Nevertheless, challenges related to mass production capabilities, regulatory endorsements, and extended stability require resolution prior to clinical implementation. The merger of probiotic technology with advanced nanotechnology introduces an innovative framework for creating personalized, biologically responsive treatments targeting chronic inflammation, multidrug-resistant infections, and metabolic disorders associated with aging.

Keywords: *Probiotic-engineered nanoparticles, gold nanoparticles, targeted drug delivery, photothermal therapy, tissue regeneration, geriatric medicine*.

1. *INTRODUCTION*

The elderly demographic, consisting of individuals aged 65 years and older, confronts unique health challenges due to physiological alterations and increased susceptibility to various diseases (Kadam, Dalai et al. 2025). United Nations data indicate that the global population over 65 years reached 761 million in 2021, with projections estimating growth to 1.6 billion by 2050 (Nations 2023). The aging process contributes to numerous disorders and heightens vulnerability to multiple diseases. Common conditions *among older adults include chronic constipation, osteoarthritis, chronic obstructive pulmonary disease, dementia, diabetes mellitus, hypertension, depression, hearing impairment, cataracts, spinal pain, frailty, urinary incontinence, delirium, falls, and pressure injuries (Kadam, Dalai et al. 2025). Chronic wounds, encompassing diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), and pressure ulcers, present substantial public health concerns, especially for elderly individuals and those with diabetes mellitus (Raffetto, Ligi et al. 2020, McDermott, Fang et al. 2023). Epidemiological studies reveal that chronic wounds affect approximately 2.21 per 1000 individuals in developed countries, while DFUs impact up to 25% of diabetic patients and account for 85% of diabetes-related amputations worldwide (Sen 2021, McDermott, Fang et al. 2023). These wounds frequently persist due to compromised healing mechanisms, persistent inflammation, oxidative damage, and infections from multidrug-resistant pathogens, rendering conventional antibiotic and antiseptic treatments largely ineffective (Ung and Chodosh 2021, Aswathanarayan, Rao et al. 2022, Malone and Schultz 2022, Diban, Di Lodovico et al. 2023, Cavallo, Sivori et al. 2024). This situation creates a pressing need for advanced, biologically responsive therapies capable of simultaneously addressing infection and promoting tissue regeneration (Kolimi, Narala et al. 2022, Pironi, Cuerda et al. 2023, Kavyani, Ahmadi et al. 2024). The composition of gut microbiota in older adults undergoes modifications influenced by multiple factors, including age, dietary patterns, lifestyle choices, medication use, immune status, geographical distribution, and comorbid conditions (Komanduri, Gondalia et al. 2019). Nutritional habits play a pivotal role in shaping the gut microbial community. Alterations in eating behaviors, reduced dietary fiber consumption, and changes in nutrient assimilation can significantly affect microbial composition (Vural, Avery et al. 2020). Alongside reduced microbial diversity, there is a documented decline in microbiota-derived metabolites. This reduction may be linked to various aging-related processes including diminished appetite, weakness, weight loss, cognitive decline, hypertension, vitamin D deficiency, diabetes, arthritis, and muscle mass reduction (Berridge 2017, Cani and Jordan 2018, Tsugawa, Ogawa et al. 2018). Probiotics have emerged as a promising therapeutic alternative due to their ability to modulate immune responses, inhibit pathogenic biofilm formation, and produce antibacterial and antioxidant metabolites (Pironi, Cuerda et al. 2023, Bădăluță, Curuțiu et al. 2024, Kavyani, Ahmadi et al. 2024). Probiotics are microorganisms that colonize the host's intestinal tract and confer health benefits by enhancing digestive processes and suppressing harmful bacterial growth. They are also recognized for their beneficial regulatory effects on various host systems, including the immune and nervous systems (Varvara and Vodnar 2024). However, their clinical application is constrained by limited viability, sensitivity to environmental conditions, and brief retention at wound sites (Bădăluță, Curuțiu et al. 2024). Challenges such as poor survival and reduced efficacy under harsh gastrointestinal conditions restrict their therapeutic potential (Kadam, Dalai et al. 2025). Certain probiotic strains can effectively reduce gold ions to produce biocompatible gold nanoparticles, offering an environmentally sustainable approach for tailoring their properties for medical applications (Liu, Perumalsamy et al. 2020, Mikhailova 2021, Kim, Wang et al. 2024, Sarani, Roostaee et al. 2024). Advanced nanotechnology can overcome these limitations by enhancing probiotic efficacy through nano-*

encapsulation, controlled delivery, and improved bioavailability (Karpagam, Balamuralikrishnan et al. 2022). Nanotechnology-based delivery systems address these constraints by protecting probiotics from degradation, enhancing site-specific delivery, and enabling controlled, stimulus-responsive release (Alhodieb, Barkat et al. 2022, Palani, Vijayakumar et al. 2024, Xie, Gao et al. 2025). Gold nanoparticles (AuNPs) demonstrate considerable promise as biomedical materials due to their high biocompatibility, adjustable size and morphology, and excellent drug delivery capabilities, among other unique physicochemical properties (Kim, Wang et al. 2024, Zomorodimanesh, Razavi et al. 2024). The facility of surface modification permits precise control over their characteristics, enabling customized applications in drug delivery and imaging (Sadeghi, Amini et al. 2015, Abdelkawi, Slim et al. 2023). Nanoparticle biofabrication denotes the synthesis process utilizing the inherent biochemical pathways of microorganisms, plants, or other biological systems (Zhang, Ma et al. 2020). The integration of probiotics and nanotechnology represents an innovative and transformative approach to promoting healthy aging, facilitating the development of novel therapeutic interventions. This review investigates the synergistic potential of probiotics and advanced nanotechnology in addressing health concerns related to aging. It emphasizes significant advancements in probiotic formulations, nano-based delivery systems, and their combined effects on gastrointestinal health, immune function, and neurological protection (Kadam, Dalai et al. 2025). Additionally, it assesses their roles in drug delivery, hyperthermia treatment, wound healing, and overall health improvement in elderly populations, incorporating insights from contemporary research.

2. Review of Methods and Technologies

2.1. Probiotic-mediated Synthesis of Nanoparticles

Nanoparticle biofabrication refers to the synthesis process utilizing the intrinsic biochemical pathways of microorganisms, plants, or other biological entities (Zhang, Ma et al. 2020). With growing emphasis on health-oriented applications, the utilization of probiotics for gold nanoparticle synthesis has attracted considerable attention (Dhandapani, Xu et al. 2021). Probiotic strains can efficiently reduce gold ions to generate biocompatible gold nanoparticles, providing a sustainable methodology for customizing their properties, particularly for medical applications (Kim, Wang et al. 2024). For example, probiotic-mediated AuNPs were produced using gold salt and lysates from Bifidobacterium animalis subsp. lactis (Kim, Wang et al. 2024). Similarly, non-covalent loading of ginsenoside compound K (CK) onto gold nanoparticles (DCY51 T -AuCKNps) was accomplished through one-pot biosynthesis using Lactobacillus kimchicus DCY51 T, a probiotic strain isolated from Korean kimchi (Markus, Mathiyalagan et al. 2016). Nanoparticle formation was indicated by a color transition of the reaction solution to purple, with subsequent collection of synthesized nanoparticles via centrifugation (Kim, Wang et al. 2024). The precise mechanism of green synthesis remains incompletely understood, although several reports have documented intracellular AuNP synthesis by Lactobacillus species (Iravani 2014). It has been hypothesized that exopolysaccharides (EPS) and NADH-dependent oxidoreductases secreted by microorganisms onto bacterial membranes facilitate gold ion reduction, while membrane phospholipids, *organic acids, and amino acid residues within cells provide stabilization of nanoparticle carboxylate groups through electrostatic interactions (Nair and Pradeep 2002).*

2. ***2.2. Characterization Techniques***

3. *Biosynthesized nanoparticles were characterized using various analytical and spectroscopic methods (Yeo, Joshua et al. 2017). Absorption spectra of nanoparticle solutions were acquired using UV-visible spectrophotometry (Kim, Wang et al. 2024). Furthermore, Fourier transform infrared (FT-IR) spectroscopy, field emission transmission electron microscopy (FE-TEM), biological transmission electron microscopy (Bio-TEM), and X-ray diffraction (XRD) were employed to determine the morphology, dimensions, and crystalline characteristics of synthesized nanoparticles (Kim, Wang et al. 2024). Dynamic light scattering (DLS) particle analysis was used to assess size distribution, stability, and dispersion properties of the nanoparticles (Kim, Wang et al. 2024). XRD analysis confirmed the crystalline nature of biologically synthesized nanoparticles, revealing distinct lattice planes identified as (111, 200, 220, and 311) (Haiss, Thanh et al. 2007, Kim, Perumalsamy et al. 2019, Jeong, Liu et al. 2020, Kim, Wang et al. 2024). Elemental mapping verified the presence of gold (Au), with the red color indicating the detected signal for gold elements (Kim, Wang et al. 2024). Selected area electron diffraction (SAED) patterns confirmed the crystalline structure with identified lattice planes (111, 200, 220, and 311) (Dhandapani, Wang et al. 2023). Energy-dispersive X-ray (EDX) spectra showed several peaks corresponding to gold elements, with an additional peak at 8 keV attributable to the copper grid used for analysis (Dhandapani, Xu et al. 2021, Kim, Wang et al. 2024).*

4. ***Table 1: Characterization techniques for biosynthesized probiotic-mediated nanoparticles.***

Technique	*Abbreviation*	*Purpose*	*Key Findings*	*Reference*
Ultraviolet-Visible Spectrophotometry	UV-Vis	Analysis of optical properties and surface plasmon resonance	Confirmation of nanoparticle formation by color change and specific absorption peaks	(Kim, Wang et al. 2024)
Fourier Transform Infrared Spectroscopy	FT-IR	Identification of functional groups and biomolecules	Detection of organic capping agents on nanoparticle surface	(Kim, Wang et al. 2024)
Field Emission Transmission Electron Microscopy	FE-TEM	Morphological characterization and size determination	Visualization of nanoparticle shape, size, and distribution	(Kim, Wang et al. 2024)
Biological Transmission Electron Microscopy	Bio-TEM	Biological interaction and cellular uptake studies	Observation of nanoparticle-cell interactions	(Kim, Wang et al. 2024)

X-ray Diffraction	XRD	Crystalline structure analysis	Identification of lattice planes (111, 200, 220, 311) confirming crystalline nature	(Haiss, Thanh et al. 2007; Kim, Perumalsamy et al. 2019; Jeong, Liu et al. 2020)
Dynamic Light Scattering	DLS	Size distribution and stability assessment	Determination of hydrodynamic size and polydispersity index	(Kim, Wang et al. 2024)
Energy-Dispersive X-ray Spectroscopy	EDX	Elemental composition analysis	Confirmation of gold element presence with characteristic peaks	(Dhandapani, Xu et al. 2021; Kim, Wang et al. 2024)
Selected Area Electron Diffraction	SAED	Crystalline structure confirmation	Identification of lattice planes (111, 200, 220, 311)	(Dhandapani, Wang et al. 2023)

2.3. Nano-encapsulation and Delivery Systems

Probiotic encapsulation within nanoparticles protects them from harsh gastrointestinal conditions and external variables such as oxygen, temperature fluctuations, and light during storage and handling, thereby enhancing their survival and efficacy (Razavi, Janfaza et al. 2021). Various nanoencapsulation techniques have been developed, including nanoemulsions, polyelectrolyte complexation, spray-dried or freeze-dried nanobeads, and electrospun nanofibers (Bazzaz, Abbasi et al. 2025). For instance, microcapsules composed of gum Arabic and alginate containing Bifidobacterium bacteria, along with inulin-containing poly(lactic-co-glycolic acid) (PLGA) nanoparticles, served as nutrient sources for bacteria during storage (Kadam, Dalai et al. 2025). Electrospun nanofibers provide an advanced platform that mimics the human skin's extracellular matrix, offering both structural support and controlled probiotic release. These nanofibers provide high porosity and surface area, promoting gas exchange, moisture retention, and cell migration all essential factors in wound healing (Keshvardoostchokami, Majidi et al. 2020). Nanotechnology enables combinations of probiotics with bioactive medications. Co-encapsulation of probiotics and other therapeutic compounds in nanoparticles produces synergistic effects that promote health. Nanotechnology-based biosensors can rapidly detect and quantify probiotic bacteria. These biosensors can monitor probiotic levels in food products, supplements, and biological samples for quality control and efficacy assessment (Kadam, Dalai et al. 2025).

2.4. Functional Nanocarriers

Chitosan a natural polysaccharide derived from chitin has generated significant interest in wound healing applications due to its inherent antibacterial, biodegradable, and biocompatible properties (Mawazi, Kumar et al. 2024, Nasaj, Chehelgerdi et al. 2024). Nanoscale chitosan exhibits higher *surface-area-to-volume ratios, facilitating improved interaction with biological tissues and more efficient drug delivery (Hosseini, Naghib et al. 2024). Poly(lactic-co-glycolic acid) (PLGA), a biodegradable and biocompatible copolymer, is widely used in drug delivery systems due to its favorable degradation kinetics and capacity to encapsulate various therapeutic compounds (Makadia and Siegel 2011). PLGA nanoparticles have been employed in wound healing applications to enhance stability, controlled release, and targeted delivery of bioactive agents (Swain, Karri et al. 2025). Microneedle (MN) patches containing live probiotics represent another advanced delivery system that can penetrate the stratum corneum without reaching deeper nerve-rich areas, providing a minimally invasive and highly targeted delivery method (Jin, Lu et al. 2024, Sen, Poddar et al. 2024). Liposomes and solid lipid nanoparticles (SLNs) have shown potential for encapsulating both live probiotics and postbiotic components (Tannock and Rotin 1989). A recent study developed liposome-encapsulated L. rhamnosus GG, demonstrating prolonged bacterial viability and enhanced adhesion to keratinocytes in vitro (Jin, Lu et al. 2024). Dendrimers highly branched, tree-like polymers represent another emerging system with high loading capacity and surface functionalization potential (Joshi, Joshi et al. 2023, Kumar, Shahvej et al. 2025).*

5. ***Table 2: Comparison of various nanocarriers for probiotic delivery and wound healing applications.***

Nanocarrier Type	*Material Properties*	*Advantages*	*Limitations*	*Key Applications*	*Reference*
Chitosan nanoparticles	Natural polysaccharide, biodegradable, biocompatible	Antibacterial properties, mucoadhesive, enhances permeability	Limited solubility at neutral pH, variable viscosity	Wound healing, oral delivery, controlled release	(Mawazi, Kumar et al. 2024; Nasaj, Chehelgerdi et al. 2024; Hosseini, Naghib et al. 2024)
PLGA nanoparticles	Biodegradable copolymer, FDA-approved	Controlled release, tunable degradation kinetics, protects payload	Acidic degradation products, potential inflammation	Drug delivery, wound healing, bioactive compound encapsulation	(Makadia and Siegel 2011; Swain, Karri et al. 2025; Kadam, Dalai et al. 2025)
Liposomes	Phospholipid bilayers, amphiphilic nature	High encapsulation efficiency, protects both hydrophilic/hydrophobic compounds	Stability issues, short shelf life, manufacturing complexity	Probiotic encapsulation, drug delivery, enhanced adhesion	(Tannock and Rotin 1989; Jin, Lu et al. 2024)

Solid Lipid Nanoparticles	Lipid matrix, solid at room temperature	Improved stability, controlled release, scalable production	Low drug loading, potential gelation	Probiotic and postbiotic delivery, topical applications	(Tannock and Rotin 1989)
Dendrimers	Branched, tree-like polymers	High loading capacity, surface functionalization, monodisperse	Complex synthesis, potential toxicity	Targeted delivery, imaging, functionalized systems	(Joshi, Joshi et al. 2023; Kumar, Shahvej et al. 2025)
Microneedle Patches	Polymer-based arrays	Minimally invasive, bypasses barriers, targeted delivery	Limited drug loading, mechanical strength concerns	Transdermal probiotic delivery, wound healing	(Jin, Lu et al. 2024; Sen, Poddar et al. 2024; Zhang, Liu et al. 2025)
Electrospun nanofibers	Polymer fibers, high surface area	Mimics extracellular matrix, high porosity, controlled release	Production scalability, fiber uniformity challenges	Wound dressing, tissue engineering, probiotic delivery	(Keshvardoostchokami, Majidi et al. 2020; Razavi, Janfaza et al. 2021)

2.5. Stability and Drug Loading

Nanoparticle stability under varying pH and ionic strength conditions represents a crucial criterion for biomedical applications (Kim, Perumalsamy et al. 2019). Zeta potential evaluation of Bifi-CKAuNPs yielded a value of -40.33 mV, with a polydispersity index of 0.10, indicating favorable solution stability (Kim, Wang et al. 2024). Drug loading efficiency, determined by liquid chromatography-mass spectrometry (LC-MS), was calculated at approximately 11.03% for DCY51 T -AuCKNps (Singh, Singh et al. 2017). The quantity of CK loaded onto nanoparticles was quantified by LC-MS, and released drug was analyzed by mass spectrometry to determine molecular weight. DCY51 T -AuNps and DCY51 T -AuCKNps demonstrated stability in aqueous suspension across a wide pH range (pH 2-10) when adjusted with 0.1 M HCl and 0.2 M NaOH at room temperature (Kim, Perumalsamy et al. 2019). Additionally, DCY51 T -AuCKNps were suspended in various electrolyte conditions (10^{-1} to 10^{-5} M) through NaCl addition. The absence of changes in surface plasmon resonance (SPR) peaks and bands, measured by UV-visible spectrophotometry after incubation, indicates colloidal stability under all tested conditions (Kim, Perumalsamy et al. 2019).

6. Table 3: Stability parameters and drug loading efficiency of probiotic-mediated nanoparticles.

Nanoparticle Type	*Zeta Potential (mV)*	*Polydispersity Index (PDI)*	*Drug Loading Efficiency (%)*	*Stability Conditions Tested*	*Key Stability Findings*
Bifi-CKAuNPs	-40.33	0.10	Not specified	Solution stability	Excellent colloidal stability, monodisperse distribution
DCY51 T -AuCKNps	Not specified	Not specified	11.03%	pH range (2-10), various electrolyte conditions (10^{-1} to 10^{-5} M)	Stable under all tested conditions, no change in SPR peaks
DCY51 T -AuNps	Not specified	Not specified	Not specified	pH range (2-10)	Maintained stability across broad pH range
Spray-dried probiotic nanocapsules	Variable	Variable	Variable	25°C for 6 months storage	30-40% viability retention in standard packaging
Liposome-encapsulated L. rhamnosus GG	Not specified	Not specified	Not specified	In vitro conditions	Prolonged bacterial viability, enhanced keratinocyte adhesion
Nanoparticle Type	Zeta Potential (mV)	Polydispersity Index (PDI)	Drug Loading Efficiency (%)	Stability Conditions Tested	Key Stability Findings

7.

3. Discussion

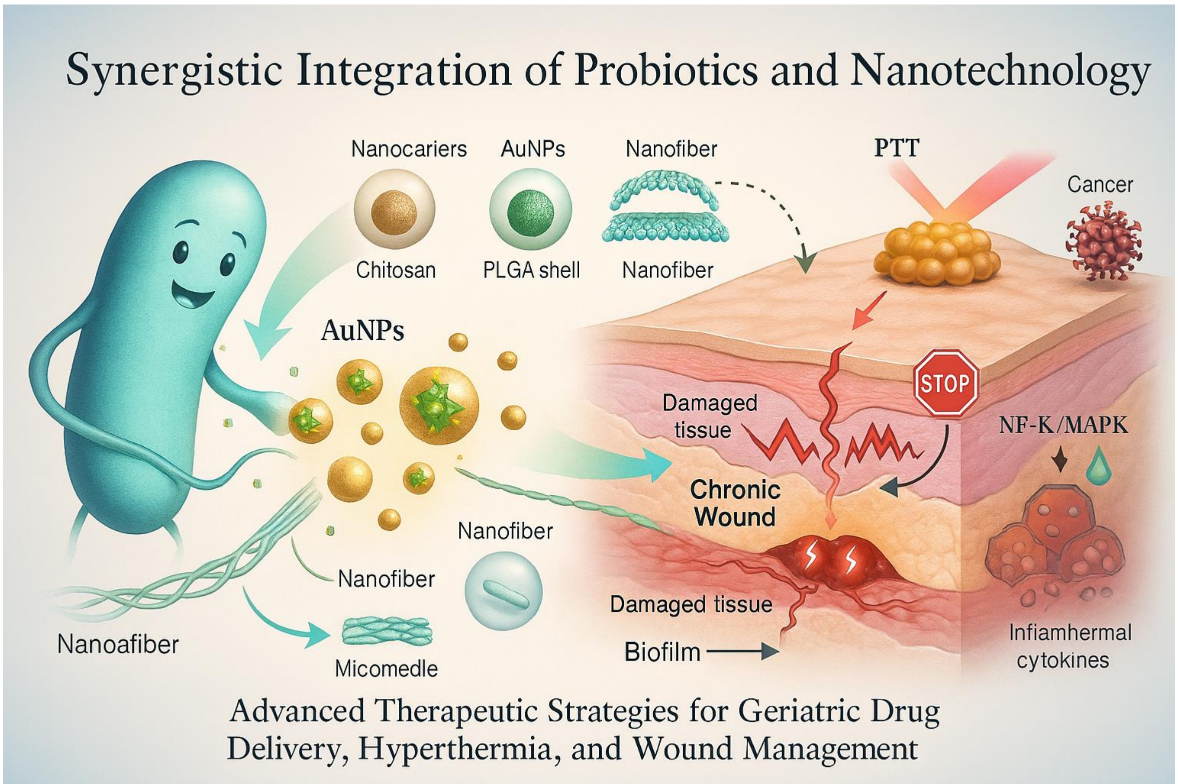
The integration of probiotics and nanotechnology represents a fundamental shift in biomedical applications, offering synergistic benefits that exceed the capabilities of either component alone. This convergence proves particularly impactful in drug delivery, hyperthermia treatment, wound healing, and overall health enhancement for elderly populations. In drug delivery, this combination addresses critical limitations of bioactive compounds. For example, the relatively low bioavailability of ginsenoside compound K (CK) restricts its effective delivery and action within biological systems (Kim, Wang et al. 2024). Probiotic-mediated synthesis of gold nanoparticles (AuNPs) emerges as a promising strategy to overcome these challenges (Kim, Wang et al. 2024). Research involving biofabrication of gold *nanoparticles using probiotic strains from Korean kimchi for photothermal cancer therapy suggests the feasibility of utilizing probiotics for synthesizing anticancer gold nanoparticles (Balusamy, Karuppaiah et al. 2022, Kim, Wang et al. 2024). Similarly, ginsenoside CK was non-covalently bioconjugated to probiotic-mediated DCY51 T -AuNps, improving its aqueous dispersibility and anticancer effects (Mathiyalagan, Subramaniyam et al. 2014). The substantial drug loading capacity of gold nanoparticles stems from their extensive surface area, facilitating effective encapsulation of drug molecules (Wang, Mathiyalagan et al. 2016, Hassan, Sharma et al. 2022). This synergy enhances targeted delivery, as the ease of surface modification enables attachment of ligands for specific recognition of target cells or tissues (Jazayeri, Amani et al. 2016, Nejati, Dadashpour et al. 2022, Kim, Wang et al. 2024). In hyperthermia applications, particularly photothermal therapy (PTT), the combination demonstrates remarkable efficacy. PTT represents a recently developed advanced therapeutic strategy that utilizes near-infrared laser-absorbing agents to generate heat for thermal ablation of cancer cells upon NIR irradiation (Shanmugam, Selvakumar et al. 2014). DCY51 T -AuCKNps functioned as potent photothermal therapy agents with synergistic chemotherapeutic effects for cancer treatment (Kautzka, Clement et al. 2017). Following laser treatment, DCY51 T -AuCKNps showed enhanced cell apoptosis in A549, HT29, and AGS cells compared to cells treated with DCY51 T -AuCKNps alone (Fröhlich 2012). PTT efficacy depends on the conversion of light to heat by photothermal agents, particularly nanoscale agents (Kim, Perumalsamy et al. 2019). This approach offers distinct advantages in cancer therapy, including enhanced specificity, reduced invasiveness, and precise spatiotemporal selectivity (Hu, Fang et al. 2014). For wound healing, the synergy provides a multifaceted strategy to address the complex pathophysiology of chronic wounds. Probiotics inhibit pathogenic biofilms and generate antibacterial and antioxidant metabolites (Das, Pradhan et al. 2022, Pironi, Cuerda et al. 2023, Bădăluță, Curuțiu et al. 2024, Kavyani, Ahmadi et al. 2024, Petrariu, Barbu et al. 2024). However, nanotechnology-based delivery systems address limitations by protecting probiotics from degradation, enhancing site-specific delivery, and enabling controlled, stimulus-responsive release (Alhodieb, Barkat et al. 2022, Palani, Vijayakumar et al. 2024, Xie, Gao et al. 2025). Encapsulation techniques using materials such as chitosan, PLGA, liposomes, nanogels, nanofibers, and microneedles have demonstrated significant success in improving wound healing outcomes in preclinical and clinical models (Ayu, Ha et al. 2021, Grzywaczyk, Zdarta et al. 2021, Wei, Zhou et al. 2021, Alhodieb, Barkat et al. 2022, Jin, Lu et al. 2024, Kaya, Bianchi et al. 2024, Palani, Vijayakumar et al. 2024, Thirumalai, Girigoswami et al. 2024, Zhang, Liu et al. 2025). A Lactobacillus (formerly classified under Lactobacillus genus) microneedle patch outperformed standard topical antibiotics, achieving 85% complete wound closure within one week (Zhang, Liu et al. 2025). Similarly, chitosan nanoparticles loaded with cell-free supernatants of Lacticaseibacillus rhamnosus achieved over 95% inhibition of both mono- and dual-species biofilms without inducing resistance in vitro (Kaya, Bianchi et al. 2024). Regarding health enhancement in elderly populations, the combined approach targets age-related physiological decline. Probiotics play a crucial role in maintaining gut homeostasis, reducing inflammation, and supporting metabolic functions (Kadam, Dalai et al. 2025). Nanotechnology enhances* *intestinal epithelial absorption of probiotics, improving bioavailability. Nanoparticles facilitate probiotic bacteria passage through the intestinal barrier, enhancing their medicinal effects. This is particularly important for geriatric patients, as alterations in digestive and nutrient absorption processes in the gastrointestinal tract impact gut microbiome composition. The integration of probiotics and nanotechnology shows promise for personalized geriatric healthcare (Razavi, Janfaza et al. 2021). Comparative analysis of studies reveals a consistent theme: the probiotic component provides biological activity and targeting specificity, while the nanomaterial enhances stability, bioavailability, and enables external control. For instance, Bifi-CKAuNPs exhibited minimal cytotoxicity while significantly reducing LPS-induced NO and ROS production, along with decreased mRNA expression of pro-inflammatory cytokines in cells (Kim, Wang et al. 2024). Similarly, DCY51 T -AuCKNps demonstrated slightly higher cytotoxicity compared to ginsenoside CK treatment in cancer cells (Castro Aceituno, Ahn et al. 2016). In wound care, probiotic-nano hybrids promote epithelialization, ensure balanced cytokine environments, counteract microbial resistance, and facilitate granulation tissue development (Chhabra, Tyagi et al. 2016, Virijević, Živanović et al. 2024). The mechanistic synergy operates at multiple levels. First, probiotics facilitate green synthesis of well-characterized, biocompatible nanoparticles (Kim, Perumalsamy et al. 2019, Kim, Wang et al. 2024). Second, nano-encapsulation protects fragile probiotic cells or bioactive metabolites from degradation in harsh environments (Kadam, Dalai et al. 2025, Umekar, Chaudhary et al. 2025). Third, functionalized nanoparticles can enhance targeting and retention of probiotics to specific sites, such as inflamed tissues or tumors, leveraging the enhanced permeability and retention (EPR) effect (Upadhyaya, Singh et al. 2015, Umekar, Chaudhary et al. 2025). Finally, external stimuli like light or pH can trigger on-demand release of therapeutic agents, creating powerful combination therapies (Kim, Perumalsamy et al. 2019, Umekar, Chaudhary et al. 2025). The anti-inflammatory activity of ginsenoside CK has been extensively documented, suggesting that Bifi-CKAuNPs are expected to exhibit enhanced anti-inflammatory efficacy as nanocarriers through synergistic effects produced by ginsenoside CK (Ahn, Siddiqi et al. 2016). In vivo experiments showed that Bifi-CKAuNPs significantly reduced inflammation in lung, kidney, and liver tissues of mice without toxicity (Kim, Wang et al. 2024). The anti-inflammatory activity of Bifi-CKAuNPs was mediated through inhibition of NF-κB/MAPK signal transduction, a well-established critical pathway in inflammation pathogenesis (Ahn, Siddiqi et al. 2016, Dhandapani, Wang et al. 2023, Yi, Li et al. 2023). The potential of Bifi-CKAuNPs to regulate ROS and NO levels in cells indicates they may offer promising therapeutic options for inflammatory and oxidative-stress-related diseases (Kim, Wang et al. 2024). Validating molecular mechanisms is crucial for unraveling intricate cellular and molecular processes influenced by treatments (Wang, Moon et al. 2022, Kim, Wang et al. 2024). This confirmation provides insights into specific pathways and signaling cascades affected by treatments, establishing precise understanding of their effects (Kim, Wang et al. 2024). This discussion emphasizes the significant potential of combining probiotic functionality with nanotechnological innovation to create advanced therapeutic platforms* *capable of addressing complex medical challenges, particularly those prevalent in aging global populations.*

4. Challenges and Future Perspectives

Despite the promising therapeutic potential of probiotic-nanotechnology hybrids, several significant challenges must be addressed before widespread clinical translation can be realized. Ensuring probiotic viability and metabolic activity throughout encapsulation, storage, and delivery processes represents a fundamental concern. Probiotics are encapsulated using techniques including spray drying, freeze-drying, or nanoprecipitation; however, shear stress, heat, and drying processes can reduce viability (Kandasamy and Naveen 2022, Meena, Taneja et al. 2023). A second major challenge involves scalability and cost considerations. While laboratory-scale probiotic formulations show substantial clinical benefits, scaling to commercial production requires additional technical and economic considerations. Ensuring safety and consistency in nanoparticle size and bioactivity necessitates infrastructure with quality control adhering to Good Manufacturing Practice (GMP) standards (D'Amico, Cavaliere et al. 2025). Furthermore, obtaining regulatory approval for probiotic nanomedicine remains challenging. Unlike pharmaceuticals, probiotics are sometimes classified as food supplements or biologics, leading to regulatory inconsistencies across different countries. The integration of nanotechnology adds complexity to classification, safety evaluation, and approval processes. Additionally, preclinical studies should address host-probiotic interactions and long-term nanomaterial biocompatibility (Medhi 2022). Examining immunological risks is also essential. While probiotics are generally recognized as safe (GRAS), the potential for dysbiosis or adverse immune reactions, particularly in immunocompromised individuals, should not be overlooked. Occasional cases of bacteremia and fungemia have been documented, mainly in patients undergoing live microbial therapy. Nanoformulations might further influence host responses by altering microbial adhesion characteristics or translocation behavior (Kothari, Patel et al. 2019, Umekar, Chaudhary et al. 2025). Ensuring stability and shelf life is crucial for probiotic-based nanotherapeutics, particularly in environments lacking cold chain distribution. Studies indicate that spray-dried nanocapsules using trehalose or skim milk as cryoprotectants exhibit superior thermal stability compared to in vitro experiments. However, when stored in standard packaging, they retain only 30-40% viability after 6 months at 25°C. This viability reduction not only diminishes probiotic counts but also affects bio-efficacy, potentially limiting therapeutic effectiveness (Nag and Das 2013, OĞUZ 2022). The inherent toxicity of polymers and residual solvents may cause immunological responses that endanger environmental and public health. In complex biological systems, nanoparticles can generate pro-oxidant species, potentially leading to uncontrolled levels of reactive oxygen species (ROS), reactive nitrogen species (RNS), and free radicals (Kadam, Dalai et al. 2025). Looking toward the future, probiotic nanotechnology holds potential to transform wound healthcare, particularly in precision medicine and advanced therapeutics (Dudhat 2025). The future of probiotic nanotechnology appears promising, with development of microbiome-targeted approaches to *customize wound care (Abouelela and Helmy 2024, Dudhat 2025). Chronic wounds can vary depending on the bacterial composition of host microbiota (Abouelela and Helmy 2024, Mihai, Bălăceanu-Gurău et al. 2024). Using next-generation sequencing and microbiome profiling, future probiotic formulations could be customized to specific local microflora, aiming to selectively reduce dysbiotic bacteria and restore microbial balance in infected wounds (Abouelela and Helmy 2024). The integration of biosensing technologies into probiotic delivery systems is rapidly advancing. Smart wound dressings equipped with biosensors can detect changes in glucose, pH, reactive oxygen species, or pro-inflammatory cytokines and respond accordingly (Chen, Wang et al. 2023). The combination of artificial intelligence (AI) with probiotic nanomedicine could significantly impact chronic wound management. AI-driven platforms can analyze imaging, sensor, and microbiome data to forecast wound progression, recommend optimal treatment strategies, and evaluate probiotic effectiveness in real-time. Initial clinical models using machine-learning algorithms have shown approximately 92% accuracy in identifying healing trajectories (Umekar, Chaudhary et al. 2025). However, integrating these findings into clinical practice requires controlled trials, thorough validation, and regulatory alignment (D'Urso and Broccolo 2024, Encarnação, Manuel et al. 2024). Several early-phase human trials are currently underway to evaluate safety and effectiveness of probiotic nano-formulations for different wound types, including diabetic foot ulcers, pressure ulcers, and burn injuries (Ezhilarasu, Vishalli et al. 2020). In the near future, we can anticipate convergence of biotechnology, materials science, and digital health to create multifunctional programmable probiotic systems capable of responding to wound dynamics in real-time. Next-generation wound therapies will not only treat infections or inflammation but will also possess capabilities for diagnosis, response, and regeneration in real-time (Ezhilarasu, Vishalli et al. 2020). For extensive industrial utilization of Bifi-CKAuNPs, additional investigations, including clinical trials, are essential to thoroughly examine their impact on human health, with particular emphasis on safety considerations. These inquiries will be undertaken in forthcoming research (Kim, Wang et al. 2024). Naturally derived nanomaterials are gaining increased attention compared to chemically synthesized materials, as the final products can offer greater sustainability, lower toxicity, improved functionality, and enhanced bioactivity (Kadam, Dalai et al. 2025). Economic analysis indicated that although probiotic dressings could potentially reduce long-term clinical costs, their initial expense remains 1.5 to 2 times higher than standard treatments (Machado, Ribeiro et al. 2025). A 2022 report by the European Medicines Agency (EMA) highlighted the necessity for a unified regulatory framework to manage combined formulations involving both microbial and nanomaterial components (Medhi 2022). Recent work further emphasizes the importance of lyo-protectants and stabilizing agents in preserving probiotic viability during nano-delivery formulation. In various PEO-based nanofiber systems, species-specific efficacy of excipients was observed: sucrose best preserved Lactobacillus jensenii, while dextran and trehalose were most protective for Staphylococcus and Stenotrophomonas isolates (Grilc, Stojanov et al. 2025). As of this summer, ongoing research is investigating use of oxygen* *scavengers and smart packaging to enhance shelf stability, though this might affect functionality (Umekar, Chaudhary et al. 2025). A murine study revealed mild lymphocytic infiltration and increased IL-17 expression in wounds treated with L. rhamnosus nanofibers (Hadian, Bagood et al. 2019). These results underscore the importance of conducting individual risk-benefit analyses and evaluating product-specific toxicity (Hadian, Bagood et al. 2019, Kothari, Patel et al. 2019, Xuan, Ju et al. 2023).*

5. Conclusion

The convergence of probiotics and nanotechnology represents a paradigm-shifting advancement in biomedical science, particularly within geriatric care. As comprehensively reviewed, this unique synergy offers innovative solutions to overcome the inherent limitations of conventional therapies. Probiotic-synthesized gold nanoparticles (e.g., Bifi-CKAuNPs) have demonstrated remarkable anti-inflammatory potential in both in vitro and in vivo models, achieved through the inhibition of key signaling pathways such as NF-κB/MAPK and a significant reduction in pro-inflammatory cytokines. Concurrently, advanced nano-encapsulation systems utilizing materials like chitosan, PLGA, and electrospun nanofibers not only protect probiotic viability under harsh gastrointestinal conditions but also enable controlled release and targeted delivery, thereby substantially enhancing bioavailability. The applications of this combined technology spanning targeted drug delivery, optical hyperthermia (photothermal therapy), wound repair, and gut microbiome modulation hold unprecedented promise for treating complex age-related conditions, including chronic inflammation, multidrug-resistant infections, and metabolic disorders. However, the translation from laboratory research to clinical practice necessitates overcoming significant challenges related to manufacturing scalability, ensuring long-term stability, meeting complex regulatory requirements, and conducting comprehensive toxicological studies and clinical trials. Looking forward, the integration of this technology with artificial intelligence, biosensors, and personalized medicine based on individual microbiome profiles will open new horizons for developing the next generation of intelligent, responsive, and bio-adaptive therapeutics. In summary, while a long path remains to fully realize this potential, the amalgamation of probiotics and nanotechnology undoubtedly constitutes a promising and transformative strategy for enhancing the health of the aging population in the era of advanced medicine.



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