




Utilization of Bacterial Enzymes for Cellulose and Hemicelluloses Degradations: Medical and Industrial Benefits

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Cellulose and hemicellulose, which are essential structural components of plant cell walls, are key renewable resources for various biotechnological applications. Bacterial enzymes can degrade these polysaccharides and have emerged as efficient, eco-friendly alternatives to chemical methods, offering significant advantages in industrial processes and medical therapies. This review explores bacterial enzymes, such as cellulases and hemicellulases, which break down cellulose and hemicellulose—two major components of plant cell walls—and their mechanisms of action in both industrial and medical applications. These enzymes offer an eco-friendly alternative to chemical processes, contributing significantly to sustainability by reducing chemical usage and improving biofuel yields. Beyond industrial applications, bacterial enzymes contribute to medical innovations such as targeted drug delivery systems and wound healing, with potential for treating chronic diseases like diabetes and inflammatory bowel disorders. These are currently being tested in clinical settings to enhance therapeutic outcomes. Advances in synthetic biology, which involves designing new biological parts and systems, enzyme engineering, the modification of enzymes to improve their function, and microbial consortia design have further enhanced the efficiency and versatility of these enzymes, making them indispensable in modern biotechnology. Future research focusing on optimizing enzyme stability, catalytic efficiency, and substrate specificity will drive innovations in both industrial sustainability and transformative medical applications.

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INTRODUCTION

Cellulose and hemicelluloses are primary structural components of the plant cell wall and major renewable carbon sources suitable for various applications. Cellulose, a β -(1 \rightarrow 4)-linked D-glucose polymer, forms crystalline microfibrils that enhance cell wall strength (Pattathil *et al.* 2015). Its high polymerization degree and hydrogen bonding make enzymatic degradation challenging, thus limiting biotechnological applications

(McCann and Carpita 2008). In contrast, hemicellulose, a branched polysaccharide of xylose, mannose, arabinose, and galactose, is amorphous and are more easily hydrolyzed, influencing cell wall rigidity and porosity (Scheller and Ulvskov 2010). Their proportions vary by plant species: woody biomass contains up to 50% cellulose and 20% to 35% hemicelluloses, while grasses have lower cellulose and higher hemicelluloses contents (Krasznai *et al.* 2018). Enzymatic degradation of cellulose and hemicelluloses supports the carbon cycle and enables bioethanol, oligosaccharide, and bioactive compound production. Lignocellulosic substrates, such as wood, straw, and agricultural residues, are composed of tightly bound cellulose, hemicelluloses, and lignin. These materials exhibit resistance to enzymatic degradation, a property known as recalcitrance, due to their complex, rigid structure and strong intermolecular interactions. This recalcitrance necessitates the use of advanced enzyme cocktails, pretreatment technologies, and synthetic biology approaches for efficient biomass hydrolysis (Bichot *et al.* 2018). Beyond industry, bacterial enzymes degrading cellulose and hemicelluloses have medical applications. Hemicellulases influence gut microbiota metabolism, affecting digestion, and immune function, while hydrolysis products such as xylooligosaccharides offer prebiotic benefits (Jana *et al.* 2021). Bacterial enzymes are not only pivotal in industrial processes such as biofuel production, paper processing, and environmental bioremediation (Makky and Abdel-Ghany 2009; Al-Rajhi *et al.* 2022, 2024), but also exhibit critical medical applications, including targeted drug delivery systems, modulation of gut microbiota, and advanced wound healing therapies. These medical applications stem from their unique ability to degrade complex polysaccharides, highlighting a crucial overlap between industrial efficiency and therapeutic innovation.

Bacterial enzymes provide an eco-friendly alternative to chemical processes, reducing environmental toxicity and supporting sustainability in industries such as biofuel production and paper processing. Bacteria decompose plant biomass using specialized enzymes, unlike fungi that degrade lignocellulose extracellularly. Key bacterial genera include *Clostridium*, *Cellulomonas*, *Bacillus*, and *Actinobacteria*. These produce endoglucanases, exoglucanases, β -glucosidases, and hemicellulases including xylanases and mannanases. The cellulosome, a multiprotein complex in anaerobic bacteria such as *Clostridium thermocellum*, enhances enzymatic synergy. Metabolic engineering and synthetic biology have optimized bacterial enzyme systems for efficient biomass deconstruction (Puentes-Téllez and Falcao Salles 2018). These enzymes are crucial in biofuel production, where hydrolysis efficiency impacts ethanol yields, and hemicellulose-derived sugars are converted into chemicals such as furfural and lactic acid (Saini *et al.* 2022). This review examines bacterial enzymes in cellulose and hemicelluloses degradation, emphasizing their biochemical complexity, industrial, and medical applications. It also addresses advancements in enzyme engineering and future directions for sustainable biotechnology.

STRUCTURE AND COMPOSITION OF CELLULOSE AND HEMICELLULOSES

Molecular Structure of Cellulose

Cellulose, the most abundant biopolymer, is a linear polysaccharide of β -D-glucopyranose units linked by β -(1 \rightarrow 4) glycosidic bonds. Its extensive hydrogen bonding forms a crystalline structure, enhancing rigidity and mechanical strength in plant cell walls (Wohlert *et al.* 2022). The extensive hydrogen bonding between cellulose chains

creates a tightly packed crystalline network that hinders enzyme accessibility, making cellulose highly resistant to enzymatic degradation. Cellulose's degree of polymerization (DP), which refers to the number of glucose units in the chain, influences its crystallinity and resistance to enzymatic degradation. Higher DP values are associated with increased crystallinity and greater resistance, making enzymatic hydrolysis more challenging. Amorphous regions provide enzymatic access points, facilitating degradation by bacterial cellulases, crucial for optimizing enzyme formulations in industrial applications (Poletto *et al.* 2014). Cellulose exists in several allomorphic forms, with Cellulose I being the most common. Other polymorphs (Cellulose II, III, and IV) result from chemical or thermal treatments, influencing enzymatic susceptibility. Mercerization-induced conversion of Cellulose I to Cellulose II enhances bacterial cellulase accessibility, a feature leveraged in biorefinery processes (Ciolacu *et al.* 2012).

Hemicellulose Structure and Enzymatic Degradation

Hemicellulose, a branched polysaccharide, cross-links with cellulose and lignin but it is more enzymatically accessible due to its lower molecular weight and reduced hydrogen bonding. Its types—xylans (hardwoods, cereals), mannans (softwoods, legumes), glucuronoxylans (hardwoods, herbaceous plants), and arabinoxylans (grasses, cereals)—vary in structure and hydrolysis susceptibility. The structural variability of hemicelluloses, such as xylans, mannans, and arabinoxylans, influences their susceptibility to enzymatic degradation, with certain types requiring specific enzymes for efficient hydrolysis. Interactions with cellulose and lignin hinder degradation, necessitating pretreatments to improve enzyme accessibility. Pretreatments such as alkali extraction significantly enhance hemicellulose degradation by disrupting hemicellulose-lignin interactions and solubilizing hemicellulose components, thus increasing their susceptibility to enzymatic attack. Alkali pretreatment methods, including sodium hydroxide (NaOH) treatment, effectively break ester linkages and remove acetyl groups from hemicellulose structures, thereby exposing polysaccharide backbones to bacterial hemicellulases and enhancing the efficiency of subsequent enzymatic hydrolysis. These pretreatments are crucial in various industrial processes, including biofuel production and pulp manufacturing, where maximizing enzyme accessibility and substrate hydrolysis is essential for economic feasibility and sustainability.

Genetic engineering strategies have also been utilized to enhance microbial hemicellulases, thereby further optimizing their applications in both industrial and medical contexts. Cellulose, with rigid β -(1 \rightarrow 4)-glycosidic linkages and strong hydrogen bonding, resists hydrolysis and requires endoglucanases, exoglucanases, and β -glucosidases for its breakdown. Hemicelluloses, with diverse linkages, requires xylanases (breaking xylose backbones) (Gupta *et al.* 2022), mannanase (hydrolyzing mannose-rich polysaccharides) (Capetti *et al.* 2023), acetyl xylan esterases (removing acetyl groups) (Malgas *et al.* 2019), and feruloyl esterases (degrading ferulic acid cross-links) (Rafeeq *et al.* 2022). Ester, acetyl, and uronic acid groups affect hemicellulose biodegradability (Martins *et al.* 2024). Figure 1 illustrates hemicellulose's structural organization and key components. This hierarchical representation highlights the structural complexity and diverse linkage patterns present within hemicelluloses. Understanding these details is critical for designing efficient enzymatic strategies and targeted pretreatment methods, facilitating improved bacterial enzyme accessibility for enhanced polysaccharide degradation in both industrial and medical applications.

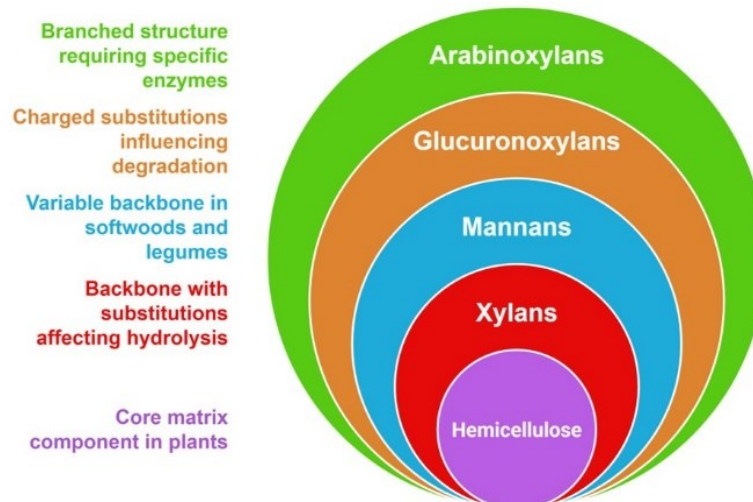


Fig. 1. Structural representation of hemicellulose showing its diverse backbone and side-chain compositions, including xylans, mannans, and glucuronoxylans. This figure illustrates the complexity and heterogeneity of hemicellulose, which contributes to the variation in enzymatic degradation pathways.

BACTERIAL ENZYMES FOR CELLULOSE AND HEMICELLULOSES DEGRADATION

Classification of Bacterial Enzymes

Bacteria utilize a range of enzymes to break down cellulose and hemicelluloses, which are categorized into cellulases, hemicellulases, and accessory enzymes. Cellulases, including endoglucanases, exoglucanases, and β -glucosidases, hydrolyze cellulose into fermentable sugars. Hemicellulases such as xylanases, mannanases, and arabinanases target hemicellulose backbones, while accessory enzymes such as acetyl xylan esterases and feruloyl esterases remove side-chain modifications that hinder degradation (Shrivastava 2020). Figure 2 illustrates the roles of glycoside hydrolases (GHs), carbohydrate esterases (CEs), polysaccharide lyases (PLs), and auxiliary activity enzymes (AAs) in biomass degradation. Lytic polysaccharide monooxygenases (LPMOs) further enhance cellulose breakdown, facilitating efficient biomass conversion. The visual overview underscores the collaborative roles of these enzyme families in decomposing complex polysaccharides, demonstrating their combined efficacy and specialization. This figure emphasizes how synergistic enzyme interactions significantly improve the efficiency of biomass conversion, directly supporting the broader applicability of bacterial enzymes in biotechnological processes.

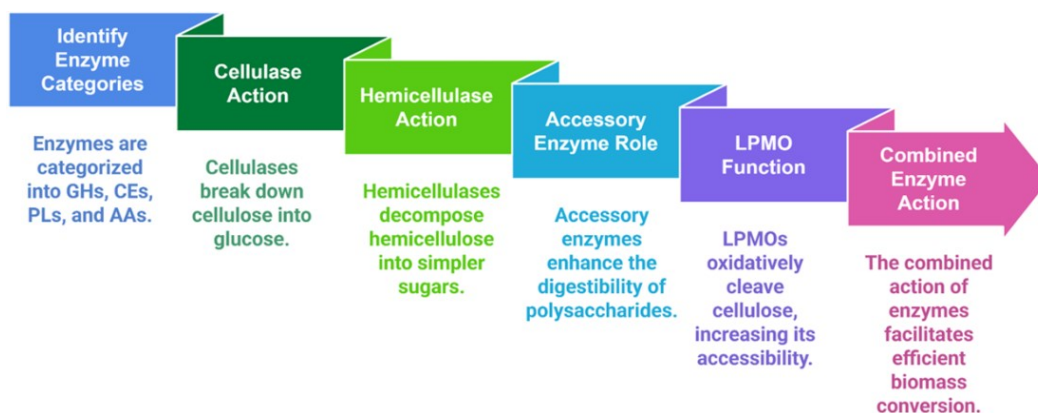


Fig. 2. Bacterial enzymes such as cellulases and xylanases break down plant polysaccharides, highlighting the specific enzymatic actions on cellulose and hemicellulose. The figure emphasizes how different enzyme classes (e.g., endoglucanases, exoglucanases, β -glucosidases) collaborate to hydrolyze complex plant biomass into simpler sugars.

Key Enzymatic Mechanisms

Bacterial enzymatic degradation of cellulose and hemicelluloses is a highly coordinated process involving synergistic enzyme interactions. Endoglucanases randomly cleave internal β -(1 \rightarrow 4) bonds in amorphous cellulose, creating new polymer-chain ends for further hydrolysis. Exoglucanases, in contrast, release cellobiose by acting on the termini of cellulose chains, which are subsequently converted into glucose by β -glucosidases, ensuring complete hydrolysis [*Mechanistic Insights into Bacterial Cellulolytic Systems*]. Hemicellulase activity is similarly multifaceted, with xylanases attacking β -(1 \rightarrow 4) linkages in xylan backbones, while α -L-arabinofuranosidases and glucuronidases hydrolyze the side-chain substitutions to enhance substrate accessibility (Sun *et al.* 2021). Figure 3 highlights key enzymatic mechanisms that improve biomass degradation. This schematic clearly demonstrates the complementary actions of different bacterial enzymes, including endoglucanases, exoglucanases, and accessory enzymes. By illustrating the distinct yet cooperative roles of these enzymes, the figure emphasizes the importance of enzyme synergy in optimizing the hydrolysis of cellulose and hemicelluloses, a crucial consideration for maximizing effectiveness in industrial and medical enzyme applications.

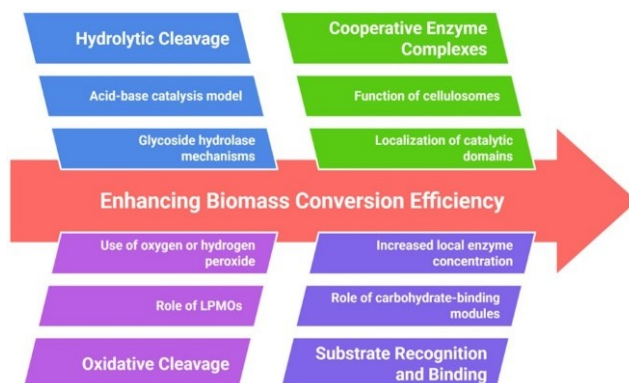


Fig. 3. Mechanistic overview of enzymatic degradation of lignocellulosic biomass by bacterial enzymes. The figure shows how the synergistic action of glycoside hydrolases, carbohydrate esterases, and auxiliary enzymes contributes to the efficient breakdown of cellulose and hemicellulose, enabling applications in biofuel production and bioremediation.

DIVERSITY OF CELLULOLYTIC AND HEMICELLULOLYTIC BACTERIA

Bacterial Strains in Cellulose and Hemicelluloses Degradation

Bacteria capable of degrading cellulose and hemicelluloses are diverse, spanning various taxonomic groups and ecological niches. They play a crucial role in natural biomass turnover, breaking down plant material in soil, aquatic environments, and the guts of herbivores. Key cellulolytic and hemicellulolytic genera include *Clostridium*, *Cellulomonas*, *Bacillus*, *Paenibacillus*, and *Actinobacteria*, each having specialized enzymatic systems suited to their environments. Anaerobic bacteria such as *Clostridium thermocellum* use cellulosomes—multi-enzyme complexes that enhance substrate binding and hydrolysis. In contrast, aerobic bacteria such as *Cellulomonas fimi* and *Bacillus subtilis* secrete free cellulases and hemicellulases, allowing flexible degradation strategies. Oxygen availability significantly affects the degradation efficiency. Anaerobic bacteria, commonly found in deep soils, marine sediments, and ruminant digestive tracts, rely on cellulosomes to enhance enzyme synergy under oxygen-deprived conditions. Aerobic bacteria utilize secreted enzyme systems with endoglucanases, exoglucanases, and accessory enzymes, offering broad substrate accessibility but sometimes lower the efficiency. However, aerobic species like *Thermobifida fusca* and *Bacillus licheniformis* produce thermostable cellulases that outperform anaerobic enzymes in high-temperature industrial processes, highlighting the versatility of bacterial degradation strategies.

Table 1. Comparative Summary of Bacterial Genera, Associated Enzymes, Target Polysaccharides, Notable Features, and their Key Industrial or Medical Applications

Bacterial Genus	Key Enzymes	Polysaccharide Target	Notable Features	Industrial/Medical Applications
<i>Clostridium</i>	Cellulases (endoglucanases, exoglucanases, β -glucosidases)	Cellulose	Anaerobic, highly efficient in cellulose hydrolysis	Biofuel production, anaerobic digestion
<i>Bacillus</i>	Xylanases, β -glucanases, cellulases	Cellulose, hemicellulose	Thermostable enzymes, suitable for industrial conditions	Pulp and paper, animal feed, textile, medical textiles
<i>Cellulomonas</i>	Cellulases, hemicellulases	Cellulose, hemicellulose	Facultative anaerobe, efficient in complete saccharification	Bioethanol, enzyme formulation
<i>Actinobacteria</i>	Mannanases, xylanases, β -xylosidases	Hemicellulose	High enzyme diversity, effective in lignocellulose breakdown	Waste bioremediation, soil amendment
<i>Thermobifida</i>	Thermostable cellulases and hemicellulases	Cellulose, hemicellulose	Operates at high temperature, suitable for harsh conditions	Composting, textile, bioreactor systems
<i>Streptomyces</i>	Endoxylanases, β -glucosidases	Hemicellulose	Produces multiple enzymes with synergistic actions	Prebiotics, pharmaceutical enzyme formulations

Genomics and Consortia in Biomass Degradation

Genomic advancements have uncovered the genetic blueprints of cellulolytic and hemicellulolytic bacteria, identifying gene clusters for glycoside hydrolases and novel enzymes with industrial potential (You *et al.* 2023). Polysaccharide utilization loci (PULs), particularly in *Bacteroidetes*, encode hydrolytic enzymes, binding proteins, and transport systems, enabling bacteria to adapt to plant biomass complexity. Transcriptomic analyses reveal regulatory mechanisms like catabolite repression and quorum sensing, while horizontal gene transfer (HGT) has allowed non-cellulolytic bacteria to acquire lignocellulolytic traits, opening new avenues in synthetic biology. Plant biomass degradation often depends on cooperative microbial consortia found in compost, soil, and ruminant guts, where species specialize in different degradation steps. Engineered consortia, such as *Clostridium thermocellum* (cellulosome producer) paired with *Bacillus subtilis* (hemicellulase producer), enhance degradation efficiency. Advances in metabolic modeling and synthetic biology enable the design of tailored consortia, with computational tools predicting metabolic interactions to optimize enzyme production and minimize resource competition, improving industrial biomass conversion.

INDUSTRIAL APPLICATIONS OF BACTERIAL ENZYMES

Biofuel Production and Biorefinery Applications

Bacterial enzymes play a key role in biofuel production and biorefinery processes by hydrolyzing lignocellulosic biomass into fermentable sugars for bioethanol, biobutanol, and other advanced biofuels. *Clostridium thermocellum*, a thermophilic anaerobe, excels in consolidated bioprocessing (CBP), combining enzymatic hydrolysis and fermentation in a single step (Periyasamy *et al.* 2023). Metabolic engineering has optimized bacterial strains like *Bacillus subtilis* to enhance cellulase production, boosting sugar yields from agricultural residues such as corn stover and wheat straw (Vadala *et al.* 2021). Additionally, microbial consortia of cellulolytic and hemicellulolytic bacteria facilitate biogas (methane) production through anaerobic digestion, where synergistic interactions accelerate polysaccharide breakdown for renewable energy generation (Sahil *et al.* 2023).

Paper and Pulp Industry

The paper and pulp sector, traditionally reliant on chemical pulping and bleaching processes, has increasingly adopted bacterial xylanases, laccases, and cellulases to improve efficiency and environmental sustainability. Xylanases, in particular, have proven indispensable in bleaching processes, significantly reducing the need for chlorine-based chemicals while maintaining fiber integrity (Almeida *et al.* 2022). Additionally, bacterial cellulases are employed to refine fiber properties, enhancing paper smoothness, tensile strength, and drainage efficiency during manufacturing. A noteworthy advancement involves thermostable and alkaline-tolerant bacterial xylanases, which have outperformed fungal counterparts in high-pH and high-temperature conditions, making them ideal for modern industrial-scale applications.

Textile Industry: Enzymatic Fabric Processing

Bacterial enzymes have replaced harsh chemicals in textile processing with eco-friendly alternatives. Cellulases improve fabric texture and durability through bio-

polishing, while alkaliphilic cellulases perform well in high-pH industrial settings (Korsa *et al.* 2023). In denim processing, cellulases, and laccases reduce water usage and fabric damage, replacing traditional stone-washing (de Souza Moreira *et al.* 2016). Xylanases and pectinases enhance dye uptake by removing impurities during scouring. Growing demand for sustainable fashion has driven research into bacterial proteases and oxidoreductases for biodegradable, low-impact textile treatments (Kundu *et al.* 2021).

Food and Beverage Industry: Enhancing Digestibility and Quality

Bacterial enzymes enhance food processing by improving digestibility, texture, and flavor. Xylanases, amylases, and pectinases streamline baking, brewing, and juice clarification, reducing processing time and enhancing consistency. *Bacillus*-derived xylanases improve wheat flour's rheology, boosting dough elasticity, and bread volume (Ben Hmad *et al.* 2024). Cellulases and pectinases increase juice yield and clarity while preserving antioxidants (de Souza and Kawaguti 2021). In brewing, β -glucanases reduce viscosity and improve filtration. Lactic acid bacteria with cellulolytic activity aid in fermenting foods, breaking down complex carbohydrates for better nutrient bioavailability and probiotic benefits (Lee *et al.* 2019).

Waste Management and Environmental Bioremediation

Bacterial enzymes play a key role in waste valorization and environmental remediation, addressing agricultural waste, plastic degradation, and effluent treatment. Cellulolytic and hemicellulolytic bacteria convert lignocellulosic waste into bio-based products, reducing landfill reliance (Nwankwo *et al.* 2021). Synthetic bacterial consortia and engineered strains degrade agro-industrial residues and synthetic polymers, contributing to bioplastics production and plastic waste reduction (Yeom *et al.* 2022). In wastewater treatment, bacterial cellulases and xylanases improve sludge decomposition and anaerobic digestion efficiency. Metagenomics-guided research has also uncovered extremophilic enzymes capable of degrading pollutants in harsh conditions (Tapadar *et al.* 2021).

Table 2. Summary of Key Bacterial Enzymes, their Substrate Targets, Enzymatic Activities, and Associated Industrial or Medical Applications

Enzyme	Substrate Target	Specific Activity	Key Industrial/Medical Applications
Endoglucanase	Amorphous cellulose	Cleaves internal β -1,4-glycosidic bonds, reducing chain length	Biofuel production, pulp processing, composting
Exoglucanase	Crystalline cellulose	Removes cellobiose units from chain ends	Textile processing, bioethanol conversion
β -Glucosidase	Cellobiose and short cellooligosaccharides	Converts cellobiose to glucose for microbial fermentation	Enhances saccharification efficiency in bioenergy systems
Xylanase	Xylan (a hemicellulose component)	Breaks down xylan backbone to xylo-oligosaccharides and xylose	Pulp and paper bleaching, animal feed, prebiotics production
β -Xylosidase	Xylo-	Releases xylose from	Biofuel and food

	oligosaccharides	xylo-oligosaccharides	industries
Mannanase	Mannans (hemicellulose)	Hydrolyzes mannose-containing polysaccharides	Oil extraction, detergent, and food processing
Laccase	Lignin and phenolic compounds	Oxidizes lignin-related substrates; improves cellulose accessibility	Textile dye degradation, wound healing (antioxidant enzyme systems)
Auxiliary Enzymes (e.g., LPMOs)	Cellulose and hemicellulose	Enhance cellulose degradation via oxidative cleavage of glycosidic bonds	Boosts enzymatic hydrolysis in biofuel systems and composting

MEDICAL APPLICATIONS OF BACTERIAL ENZYMES

Enzyme-Based Drug Delivery Systems

Enzyme-responsive drug delivery has transformed targeted therapy by enabling controlled, site-specific drug release. Bacterial enzymes, with unique substrate specificity, play key roles in activating drugs or aiding their transport across biological barriers. β -glucuronidase-producing bacteria activate prodrugs in the colon for localized colorectal cancer treatment, reducing systemic side effects (Tapadar *et al.* 2021). Cellulases and hemicellulases in smart hydrogels control drug diffusion by modifying cellulose-based matrices, aiding chronic disease management like diabetes and inflammatory bowel disorders (Sobczak 2022). Additionally, bacterial lipases and proteases enhance nanocarrier drug delivery by improving bioavailability and reducing off-target effects, advancing precision medicine (Wang *et al.* 2022).

Role in Prebiotic and Gut Microbiome Modulation

Bacterial enzymes in the gut microbiome are essential for metabolic and immune balance. Hemicellulases and cellulases break down dietary fibers into short-chain fatty acids (SCFAs), supporting intestinal health (Peredo-Lovillo *et al.* 2020). Xylanases and arabinofuranosidases convert non-digestible polysaccharides into bioactive oligosaccharides, promoting beneficial bacteria like *Bifidobacteria* and *Lactobacilli*, enhancing gut barrier integrity, and reducing inflammation, with implications for preventing obesity and type 2 diabetes (Pyeon *et al.* 2024). Additionally, bacterial β -glucosidases aid in phytoestrogen metabolism, improving the bioavailability of plant compounds and influencing hormone-related conditions like menopausal symptoms and osteoporosis (Cady *et al.* 2020).

Bacterial Enzymes for Wound Healing

Bacterial enzymes are effective in treating chronic wounds and biofilm-associated infections resistant to antibiotics. Cellulases and hemicellulases aid in enzymatic debridement by gently degrading necrotic tissue, promoting healing in diabetic ulcers and pressure sores (de Amorim *et al.* 2022). Bacterial metalloproteases and serine proteases, from species like *Bacillus* and *Pseudomonas*, remodel extracellular matrix components, accelerating tissue regeneration, angiogenesis, and fibroblast migration while clearing infection-related debris (Xiang *et al.* 2024). These enzymes are promising for advanced wound care formulations.

CONCLUSION AND FUTURE PERSPECTIVES

Bacterial enzymes used for cellulose and hemicelluloses degradations have proven invaluable in both industrial and medical fields, contributing to biofuel production, bioremediation, and advanced medical therapies such as drug delivery and wound healing. Their substrate specificity, efficiency, and eco-friendliness underscore their potential to address pressing global challenges in sustainability and healthcare. Future efforts should prioritize enzyme engineering to enhance stability and catalytic performance under industrially relevant conditions. Additionally, advancements in metagenomics and synthetic biology will be crucial in discovering novel enzymes and optimizing microbial consortia for broader applications. Emerging technologies such as artificial intelligence-driven enzyme design, high-throughput screening methods, and genome editing techniques like CRISPR-Cas9 represent promising avenues for rapid advancement in bacterial enzyme innovation. An urgent need for research lies in developing enzymes capable of efficiently degrading synthetic polymers and complex waste materials, addressing global plastic pollution and waste management challenges. Collaborative interdisciplinary research integrating microbiology, biotechnology, bioinformatics, and materials science will be essential for realizing these breakthroughs, thereby driving the next generation of sustainable bacterial enzyme applications.

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Data Availability

All datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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