2026 Volume: 02 Issue: 01 www.ijrpa.com ISSN 2456-9995 Review Article

International Journal Research Publication Analysis

Page: 01-21

PRODUCTIZING MICROBIAL BIOLOGICALS: FORMULATION AND MANUFACTURING STRATEGIES FOR FIELD-READY AGRICULTURE

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Received: 27 November 2025
Article Revised: 17 December 2025
Published on: 07 January 2026

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DOI: https://doi-doi.org/101555/ijrpa.6958

ABSTRACT

The global transition toward sustainable agriculture has intensified interest in microbial biologicals—including biopesticides, biofertilizers, and biostimulants—as viable alternatives to synthetic agrochemicals. Although substantial progress has been achieved in microbial strain discovery and laboratory-scale efficacy, large-scale adoption remains constrained by formulation instability, limited shelf life, inconsistent field performance, manufacturing bottlenecks, and fragmented regulatory frameworks. These challenges have slowed the translation of promising microbial innovations into reliable, commercially scalable agricultural inputs. This review provides a critical and integrative analysis of recent advances in formulation science, industrial-scale fermentation, quality control systems, and regulatory pathways governing microbial biologicals. Particular emphasis is placed on formulation technologies—ranging from conventional wettable powders and granules to oil-based systems, microencapsulation, and emerging nano-enabled delivery platforms—and their role in enhancing microbial viability, environmental resilience, and field persistence. Key manufacturing considerations, including fermentation optimization, pilot-scale validation, downstream processing, and batch-to-batch consistency, are examined to bridge laboratory research with industrial production realities. Comparative evaluation of regulatory frameworks across major markets, including the European Union, United Kingdom, and India, highlights persistent challenges related to data requirements, approval timelines, and global harmonization. Emerging trends such as microbial consortia, artificial intelligence–assisted formulation and process optimization, and precision delivery systems are discussed

as transformative strategies to improve efficacy, scalability, and commercial reliability. By synthesizing scientific, industrial, and regulatory perspectives, this review identifies critical gaps and proposes a practical framework to accelerate the development of robust, scalable, and field-effective microbial biologicals. The insights presented aim to support researchers, manufacturers, and policymakers in advancing microbial technologies as integral components of sustainable and resilient agricultural systems.

KEYWORDS: Microbial biologicals; biopesticides; biofertilizers; biostimulants; formulation and delivery systems; fermentation scale-up; regulatory compliance; sustainable agriculture.

1. INTRODUCTION

The intensification of global agriculture over the past five decades has relied heavily on synthetic pesticides and fertilizers to sustain crop productivity. While these inputs have contributed to short-term yield gains, their prolonged and indiscriminate use has generated serious agronomic, environmental, and societal challenges, including rapid evolution of pest resistance, degradation of soil and aquatic ecosystems, accumulation of chemical residues in food chains, and adverse effects on non-target organisms and human health (Chandler et al., 2011; Glare et al., 2012; Wend et al., 2024). These concerns, combined with increasingly stringent regulatory restrictions and growing consumer demand for residue-free food, have intensified the search for safer, biologically based alternatives compatible with sustainable and climate-resilient agricultural systems.

In this context, microbial biologicals—encompassing biopesticides, biofertilizers, and biostimulants—have emerged as central components of modern sustainable agriculture and integrated pest management (IPM) strategies. Microbial biopesticides derived from bacteria, fungi, and viruses offer highly specific control of insect pests, plant pathogens, and weeds while minimizing impacts on non-target organisms and ecosystems (Lacey et al., 2015). Similarly, microbial biofertilizers and biostimulants enhance nutrient use efficiency, soil health, and plant resilience through mechanisms such as biological nitrogen fixation, phosphorus solubilization, phytohormone modulation, and induction of systemic resistance (Vessey, 2003; Bhattacharyya and Jha, 2012; du Jardin, 2015). The multifunctional nature of many microbial products—operating simultaneously as crop protectants, growth promoters, and stress mitigators—has further expanded their appeal across diverse cropping systems.

Despite strong scientific validation and rapid market growth, the field-level reliability and large-scale adoption of microbial biologicals remain limited. A persistent gap exists between laboratory or greenhouse efficacy and consistent performance under farmer-managed field conditions. This gap is primarily attributed to formulation instability, short shelf life, sensitivity to environmental stressors, inconsistent manufacturing quality, and fragmented regulatory frameworks (Mantzoukas and Grammatikopoulos, 2020; Mishra et al., 2023). Many promising microbial strains fail to progress beyond experimental stages not due to insufficient biological activity, but because they cannot be translated into shelf-stable, scalable, and regulatory-compliant products.

Recent advances in formulation science, fermentation technology, quality assurance systems, and regulatory science have begun to address these long-standing constraints. Innovations such as oil-based formulations, microencapsulation, controlled-release carriers, and improved drying technologies have significantly enhanced microbial viability, environmental resilience, and persistence after application (Knowles, 2008; Croda Agriculture, 2022). Concurrently, progress in industrial fermentation, pilot-scale validation, and digital process monitoring has improved batch consistency and production efficiency, facilitating commercialization at scale (El-Sayed et al., 2023). Regulatory frameworks are also evolving, with increased recognition of microbial products as distinct from synthetic chemicals and growing efforts toward international harmonization (FAO, 2018; OECD, 2014; Byreddy, 2024).

However, most existing reviews address these advances in isolation, focusing either on microbial ecology, strain efficacy, formulation chemistry, or regulatory aspects independently. There remains a critical need for an integrated, product-centric synthesis that connects biological performance with formulation robustness, manufacturing scalability, quality control, and regulatory acceptance—factors that ultimately determine commercial success and farmer adoption.

Accordingly, this review provides a critical and integrative analysis of microbial biologicals across the full innovation-to-deployment continuum. Emphasis is placed on formulation technologies, industrial-scale fermentation and downstream processing, quality assurance systems, and comparative regulatory frameworks. Emerging strategies—including microbial consortia, nano-enabled delivery systems, artificial intelligence–assisted process optimization, and precision agriculture integration—are evaluated for their potential to overcome persistent limitations. By synthesizing scientific, industrial, and regulatory

perspectives, this review aims to identify structural bottlenecks, highlight scalable solutions, and propose a practical framework for advancing microbial biologicals from promising alternatives to reliable, mainstream agricultural inputs.

2. Historical Development of Microbial Biologicals

The historical development of microbial biologicals dates back to the late nineteenth and early twentieth centuries, when early scientific observations revealed the potential of microorganisms as natural regulators of pest populations. Among the earliest and most influential breakthroughs was the discovery and commercialization of *Bacillus thuringiensis* (*B. thuringiensis*), which became the first widely successful microbial insecticide (Bharti and Ibrahim, 2020). The identification of insecticidal crystalline (Cry) δ-endotoxins produced by *B. thuringiensis* represented a paradigm shift in pest control, as these proteins exhibited remarkable specificity toward target insect orders while posing minimal risks to non-target organisms, humans, and the environment (Chandler *et al.*, 2011; Glare *et al.*, 2012).

During the mid-twentieth century, advancements in fermentation and mass-culturing technologies enabled large-scale production of *B. thuringiensis*-based formulations, facilitating their widespread adoption in forestry, vegetable, and field crops (Bharti and Ibrahim, 2020). These early commercial successes provided proof of concept for microbial pest control at industrial scale and stimulated systematic exploration of microbial diversity for agricultural applications (Lacey *et al.*, 2015).

Parallel research efforts led to the development of viral biopesticides, particularly nucleopolyhedroviruses (NPVs) and granuloviruses, which demonstrated high host specificity and effectiveness against lepidopteran pests. Despite their ecological advantages, viral biopesticides faced limitations related to slow speed of action, ultraviolet sensitivity, and production costs, which restricted their broader commercial adoption (Mishra *et al.*, 2023).

Fungal biopesticides gained prominence in the latter half of the twentieth century, with entomopathogenic fungi such as *Beauveria bassiana* and *Metarhizium anisopliae* emerging as versatile microbial control agents. These fungi offered several advantages, including the ability to infect multiple insect life stages through direct cuticle penetration, adaptability to diverse environmental conditions, and compatibility with organic and low-input farming systems (Khan *et al.*, 2024). Their successful deployment in greenhouse and field environments further expanded the scope of microbial pest management beyond bacterial agents.

In addition to insect control, increasing attention was directed toward microbial agents targeting plant pathogens and improving soil health. Fungal antagonists such as *Trichoderma* spp. emerged as multifunctional biologicals capable of suppressing soil-borne pathogens through mycoparasitism, antibiosis, and competitive exclusion, while simultaneously enhancing plant growth and inducing systemic resistance (Harman *et al.*, 2004; Woo *et al.*, 2014). This multifunctionality positioned *Trichoderma*-based products at the intersection of biopesticides, biofertilizers, and biostimulants.

The evolution of microbial biologicals has been closely linked to progress in fermentation technology, formulation science, and regulatory recognition. Early products often suffered from short shelf life, low spore viability, and inconsistent field performance; however, improvements in carrier materials, drying processes, encapsulation techniques, and quality control standards have substantially enhanced product stability and efficacy (Mantzoukas and Grammatikopoulos, 2020; Croda Agriculture, 2022). This gradual transition from empirical applications to scientifically optimized and regulated products has paved the way for the integration of microbial biologicals into modern sustainable agriculture and IPM programs worldwide.

3. Formulation Technologies

Formulation technology is a critical determinant of the commercial success of microbial biologicals, as it directly influences microbial viability, shelf life, ease of application, and consistency of field performance. Unlike synthetic agrochemicals, microbial agents are living entities that are highly sensitive to environmental stressors such as temperature fluctuations, desiccation, ultraviolet (UV) radiation, and oxidative damage. Consequently, the formulation matrix must not only act as a delivery vehicle but also provide physical and physiological protection to ensure microbial survival from production to field application (Glare *et al.*, 2012; Lacey *et al.*, 2015).

3.1.Conventional Formulation Systems

Conventional formulations such as wettable powders (WP), water-dispersible granules (WG), suspension concentrates (SC), and dust formulations have historically dominated the microbial biopesticide market due to their relatively low production costs and compatibility with existing agricultural spraying equipment (Bharti and Ibrahim, 2020). These formulations typically employ inert carriers such as talc, kaolin, lignite, or starch-based materials to stabilize microbial propagules, particularly spores and conidia. Wettable powders remain widely used for fungal biopesticides owing to their simplicity and ease of large-scale

manufacturing; however, they often suffer from poor shelf stability, moisture sensitivity, dust formation, and reduced microbial viability during storage (Croda Agriculture, 2022; Mishra *et al.*, 2023).

Water-dispersible granules and suspension concentrates offer improvements over traditional powders by reducing operator exposure, improving flowability, and enhancing dosing accuracy. Nevertheless, these formulations can still be vulnerable to sedimentation, agglomeration, and loss of viability when exposed to prolonged storage or unfavorable environmental conditions (Wend et al., 2024). As a result, their performance in open-field conditions may vary considerably, particularly under high-temperature or high-UV environments.

3.2.Oil-Based and Emulsion Formulations

Oil dispersion (OD) and oil-in-water emulsion formulations have gained increasing attention as advanced delivery systems for microbial biologicals. Oil-based formulations provide several functional advantages, including improved adhesion to leaf surfaces, reduced wash-off by rainfall, and enhanced protection against desiccation and UV radiation (Khan *et al.*, 2024). Vegetable oils, mineral oils, and biodegradable ester-based oils are commonly employed as carriers, often in combination with emulsifiers and stabilizers to maintain formulation homogeneity.

For entomopathogenic fungi such as *Beauveria bassiana* and *Metarhizium anisopliae*, oil formulations have been shown to significantly improve conidial germination, infectivity, and persistence on plant surfaces compared to aqueous formulations (Lacey *et al.*, 2015; Mishra *et al.*, 2023). These attributes make oil-based systems particularly suitable for foliar applications in arid and semi-arid regions, where rapid desiccation limits the effectiveness of water-based sprays.

3.3. Microencapsulation and Controlled-Release Technologies

Microencapsulation represents one of the most promising formulation strategies for enhancing the stability and field performance of microbial biologicals. Encapsulation techniques using polymeric matrices, alginate beads, starch derivatives, or lipid-based capsules can physically shield microbial cells or spores from environmental stress while enabling controlled release at the target site (Glare *et al.*, 2012; Khan *et al.*, 2024). Encapsulated formulations have demonstrated superior shelf life, improved thermal tolerance, and enhanced resistance to UV degradation, which are key limitations of conventional formulations.

In addition to protection, microencapsulation can facilitate the co-formulation of microbial consortia or the integration of nutrients, adjuvants, and protectants within a single delivery system. This multifunctionality is particularly relevant for products positioned at the interface of biopesticides, biofertilizers, and biostimulants, where sustained microbial activity in the rhizosphere or phyllosphere is required for optimal performance (Woo *et al.*, 2014; du Jardin, 2015).

3.4.Role of Additives and Carriers

The selection of suitable carriers, adjuvants, and stabilizers is fundamental to formulation performance. Protective additives such as UV absorbers, antioxidants, humectants, and osmoprotectants are frequently incorporated to enhance microbial survival during storage and after application (Croda Agriculture, 2022). Carriers derived from organic and biodegradable materials are increasingly favored to align formulation design with environmental sustainability and regulatory acceptance.

For biofertilizers and biostimulants, carrier materials play a dual role by not only maintaining microbial viability but also supporting colonization and persistence in the rhizosphere. Advances in carrier engineering have enabled improved microbial attachment to seeds and roots, thereby enhancing nutrient uptake efficiency and plant growth responses under field conditions (Bhattacharyya and Jha, 2012; FNCA, 2019).

4. Challenges and Future Directions in Formulation Design

Despite substantial progress, formulation of microbial biologicals remains a complex and product-specific challenge. Variability in microbial physiology, sensitivity to processing stresses, and interactions with formulation components necessitate tailored formulation strategies for different microbial taxa. Furthermore, scalability, cost-effectiveness, and regulatory compliance must be considered alongside biological performance to ensure successful commercialization (Mantzoukas and Grammatikopoulos, 2020).

Emerging trends in formulation research include nano-enabled delivery systems, smart carriers responsive to environmental cues, and AI-assisted optimization of formulation components to predict stability and field performance (Wend et al., 2024). Continued integration of formulation science with microbial ecology and industrial biotechnology will be essential for translating laboratory innovations into robust, farmer-friendly products capable of delivering consistent benefits under diverse agricultural conditions (Table 1).

Table 1. Comparative Analysis of Microbial Biological Formulation Types.

Formulation Type	Typical Carriers / Systems	Key Advantages	Major Limitations	Suitable Microbial Products	Typical Shelf-life
Wettable Powder (WP)	Talc, kaolin, lignite, starch	Low cost; simple manufacturing; easy scale-up	Dust formation; moisture sensitivity; reduced shelf life	*Trichoderma sp.*, *Bacillus sp.*, biofertilizers	6–12 months
Water-Dispersible Granules (WG/WDG)	Granulated inert carriers	Improved handling; reduced inhalation risk; uniform dosing	Higher production cost; limited UV protection	Fungal and bacterial biopesticides	12–24 months
Suspension Concentrate (SC)	Aqueous dispersions with stabilizers	No dust; good sprayability; uniform application	Sedimentation; microbial stress during storage	*Bacillus thuringiensis*, PGPR	6–12 months
Oil Dispersion (OD)	Vegetable/mineral oils, emulsifiers	Enhanced adhesion; UV protection; reduced desiccation	Compatibility issues; higher formulation complexity	*Beauveria*, *Metarhizium*	12–18 months
Emulsion (Oil-in-Water)	Oil + surfactant systems	Improved persistence; rainfastness	Emulsion instability; cost	Entomopathogenic fungi	6–12 months
Granular (GR)	Clay, corncob, organic granules	Soil persistence; targeted delivery	Slower action; bulky application	Soil-applied biofertilizers, nematodes	12–36 months
Microencapsulated	Alginate, starch, polymers	Extended shelf life; UV & thermal protection; controlled release	High cost; complex scale-up	High-value biopesticides, consortia	18–36 months
Liquid Bioformulations	Nutrient broth + stabilizers	Easy application; rapid microbial activation	Short shelf life; contamination risk	PGPR, biofertilizers	3–6 months
Seed Coating / Pelleting	Polymers, adhesives,	Targeted rhizosphere	Limited microbial	*Rhizobium*, PGPR,	6–12 month

	biochar	delivery; reduced dosage	load; storage sensitivity	*Trichoderma*	s
Nano-enabled Formulations	Nano-carriers, liposomes	Precision delivery; enhanced efficacy	Regulatory uncertainty; cost	Next-generation microbial products	12–24 months

Notes:

- Shelf-life depends on temperature, moisture, and formulation quality.
- Microencapsulated and granular forms generally show the longest stability due to physical protection.
- Liquid and wettable powders are most sensitive to storage conditions.
- Conventional formulations dominate due to low cost and scalability, but suffer from short shelf life and environmental sensitivity.
- Advanced systems such as oil-based and encapsulated formulations significantly improve field persistence and efficacy, especially under harsh climatic conditions.
- Microencapsulation and nano-delivery systems represent emerging solutions, although cost and regulatory acceptance remain barriers to widespread adoption.

5. Scale-Up and Manufacturing of Microbial Biologicals

The commercialization of microbial biopesticides, biofertilizers, and biostimulants relies heavily on robust, reproducible, and economically viable scale-up and manufacturing processes. Laboratory-scale production focuses on strain selection and proof-of-concept efficacy, whereas industrial production demands consistent biomass yield, product stability, batch-to-batch uniformity, and regulatory compliance. Translating laboratory protocols into pilot- and commercial-scale operations represents a critical bottleneck in the microbial biological value chain (Ravensberg, 2011; El-Sayed et al., 2023).

5.1.Fermentation Strategies and Process Optimization

Fermentation is the core upstream process in microbial manufacturing. Optimization is essential to achieve high cell density, spore yield, and metabolite production while maintaining microbial efficacy. Key parameters—such as aeration, agitation, dissolved oxygen, pH, temperature, and nutrient composition—must be carefully controlled and scaled to ensure physiological equivalence across production volumes (Stanbury et al., 2017). Inadequate oxygen transfer or excessive shear stress during scale-up can substantially reduce

microbial viability, sporulation efficiency, or metabolite production, particularly for filamentous fungi and spore-forming bacteria (El-Sayed et al., 2023).

Batch, fed-batch, and continuous fermentation modes are employed depending on the microbial species and product requirements. Fed-batch fermentation is commonly favored for *Bacillus* spp. and fungal biopesticides because it allows controlled nutrient feeding, prevents catabolite repression, and enhances spore or metabolite yields (Tripathi, 2019). Advances in bioreactor design—including optimized impeller configurations and real-time process monitoring—further enable precise control of critical parameters at industrial scale.

5.2.Pilot-Scale Production and Process Validation

Pilot-scale production serves as an essential bridge between laboratory research and full-scale manufacturing. It allows validation of fermentation kinetics, downstream processing, and formulation compatibility under conditions closely resembling commercial operations. Pilot-scale studies are also required to demonstrate production reproducibility, process robustness, and product equivalence for regulatory approval (Ravensberg, 2011; Tripathi, 2019).

Optimization at the pilot scale focuses on minimizing batch-to-batch variability while maintaining microbial identity, purity, and potency. Parameters such as harvest timing, cell concentration, and drying conditions are fine-tuned for consistent product quality. Pilot-scale trials also facilitate cost modeling and identification of scale-related bottlenecks, including foam formation, oxygen limitation, or contamination risks, which may not be apparent at laboratory scale (El-Sayed et al., 2023).

5.3.Downstream Processing and Formulation Integration

Downstream processing—including biomass separation, concentration, stabilization, and drying—is critical for final product quality. Techniques such as centrifugation, filtration, spray drying, and freeze-drying are selected based on microbial sensitivity and formulation requirements. Drying processes must preserve microbial viability while achieving moisture content suitable for long-term storage (Knowles, 2008).

Integration of downstream processing with formulation development enhances microbial survival during storage. Protective agents such as sugars, polymers, and antioxidants are frequently added to improve stability and compatibility with final formulations (Mishra et al., 2023).

5.4.Quality Control and Batch Consistency

Quality assurance (QA) and quality control (QC) systems are indispensable to ensure product consistency and regulatory compliance. Key quality attributes include microbial identity,

viable cell or spore count, absence of contaminants, and stability over the declared shelf life. Standard operating procedures (SOPs) for in-process and final product testing are developed during pilot-scale production and validated prior to commercial manufacture (FAO/WHO, 2018).

Batch-to-batch variability remains a significant challenge, especially when production spans multiple facilities. Implementation of Good Manufacturing Practices (GMP), statistical process control, and digital fermentation monitoring tools has improved reproducibility and traceability in recent years (El-Sayed et al., 2023).

5.5.Manufacturing Challenges and Emerging Trends

Despite advances, large-scale microbial production faces challenges such as high production costs, sensitivity to processing stresses, and limited infrastructure in certain regions. Addressing these issues requires innovations in strain improvement, process intensification, and automation (Table 2 & Fig 1).

Emerging trends include process analytical technologies (PAT), artificial intelligence-assisted fermentation control, and modular bioprocessing platforms designed for rapid scale-up and decentralized production. These innovations promise reduced production variability, lower costs, and faster translation of microbial biologicals from research to field applications (Wend et al., 2024).

Table 2. Fermentation Modes for Microbial Production: Advantages and Challenges.

Fermentation Mode	Advantages	Challenges	Typical Applications
Batch	Simple, low contamination risk, easy control	Limited productivity, nutrient depletion	Small-scale biopesticides, lab studies
Fed-batch	Controlled nutrient feeding, high spore/metabolite yield, prevents catabolite repression	Requires monitoring and control, complex operation	*Bacillus* spp., fungal biopesticides
Continuous	Constant product output, efficient resource use	High contamination risk, complex design	Specialized metabolite production, industrial enzymes

Concept:

Lab-Scale (strain selection & proof-of-concept)

↓

Pilot-Scale (fermentation validation, downstream processing, QA)

↓

Process Optimization (fermentation parameters, harvest timing, drying)

↓

Industrial-Scale Manufacturing (GMP compliance, batch consistency, formulation integration)

↓

Commercial Product (QA/QC approved, shelf-stable, field-ready)

Figure 1. Workflow of Microbial Bioproduct Scale-Up

6. Quality Control and Standardization

Quality control (QC) and standardization are indispensable components of microbial bioproduct development, ensuring that products are safe, consistent, and effective from batch to batch and throughout their shelf life. A robust quality assurance (QA) framework encompasses defined specifications, validated testing procedures, and ongoing monitoring protocols that collectively uphold product integrity and regulatory compliance across the manufacturing lifecycle (FAO 2018; FNCA 2019).

6.1.Regulatory Guidelines and Standards

International and regional regulatory bodies provide standardized protocols for microbial pesticide quality specifications and testing. The Food and Agriculture Organization (FAO) and World Health Organization (WHO) have published guidelines outlining requirements, analytical methods, and safety standards for microbial pesticides (FAO 2018). Similarly, biofertilizer quality assurance guidelines, such as those developed by the Forum for Nuclear Cooperation in Asia (FNCA 2019), provide reference procedures for quantification of beneficial microorganisms, contamination limits, and carrier quality, supporting consistent field efficacy.

Key Quality Attributes and Testing Protocols

Core quality attributes for microbial products include:

- **Viable cell or spore count:** Minimum colony-forming units (CFU) per unit to ensure biological efficacy.

- **Microbial purity:** Absence of unwanted microorganisms or contaminants that could compromise safety or performance.
- **Identity and strain confirmation:** Verification of the intended microbial strain using phenotypic and molecular methods.
- **Shelf-life stability:** Sustained viability and activity under defined storage conditions throughout the declared product life.
- **Physicochemical parameters:** pH, moisture content, and carrier integrity appropriate for the product type and formulation (Knowles 2008; Mishra et al. 2023).

For example, national standards for biofertilizers require specific CFU thresholds (typically $\geq 10^7$–10^8 CFU/g), defined pH ranges, and absence of contaminating organisms at specified dilutions to maintain consistent efficacy (FNCA 2019; Studocu 2023).

6.2.In-Process and Final Controls

QC begins during upstream fermentation with in-process monitoring of viable counts and contamination risk to ensure batch consistency. Post-fermentation, products undergo rigorous evaluation of viability, strain identity, and stability under storage and transport conditions. Analytical methods range from standard plate counts to advanced molecular techniques, such as PCR, for precise strain verification (Mishra et al. 2023).

6.3.Standardization and Harmonization Challenges

Despite established guidelines, global standardization remains challenging. Recent regulatory frameworks, such as the European Union Fertilizer Regulation (EU 2019/1009), integrate microbial biostimulants and biofertilizers under unified quality requirements, including microbial content and labeling standards (European Commission 2019). Harmonization across regions improves market acceptance, though differences in national regulations still pose challenges for manufacturers.

6.4.Integration of QA/QC in Manufacturing

Quality control is integrated across production stages—from raw material verification and in-process monitoring to final product release and shelf-life stability testing. Implementation of Good Manufacturing Practices (GMP), well-defined standard operating procedures (SOPs), and digital monitoring tools enhances traceability, minimizes batch-to-batch variability, and ensures compliance with both regulatory and commercial standards (FAO 2018; FNCA 2019). Robust QA/QC systems reinforce product reliability, maintain regulatory compliance, and strengthen user confidence in microbial bioproducts.

7. Regulatory Frameworks

Microbial biopesticides are subject to rigorous regulatory oversight to ensure their safety, efficacy, and environmental compatibility. In the European Union, these products are regulated under Regulation (EC) No. 1107/2009, which mandates the submission of comprehensive dossiers detailing microbial identity, mode of action, toxicology, environmental fate, residue profiles, and risk assessments for non-target organisms (Byreddy 2024; HSE 2023). The approval process in the EU is typically multi-tiered, involving evaluation at both the active substance level by the European Food Safety Authority (EFSA) and at the formulated product level by member states. Emphasis is placed on standardized testing protocols, including acute and chronic toxicity, ecotoxicology, and efficacy trials under field conditions, to ensure that microbial biopesticides do not pose risks to humans, animals, or the environment.

Comparative regulatory assessments indicate that approval processes in countries such as India are relatively less stringent, with a primary focus on microbial identification, minimum efficacy testing, and safety for applicators and crops. However, Indian regulations have been evolving to align more closely with international standards, incorporating requirements for standardized microbial counts, quality control, and environmental safety data (Kumar et al. 2024). These reforms aim to facilitate global market access and enable Indian microbial biopesticides to meet export requirements in regions with strict regulatory oversight, including the EU and North America.

Global harmonization of microbial biopesticide regulations remains a key objective, as regulatory frameworks vary widely in terms of dossier requirements, risk assessment methodologies, and timelines. Efforts by international organizations, such as the FAO, OECD, and WHO, advocate for standardized testing protocols, guidance on strain characterization, and risk assessment frameworks to streamline approvals while maintaining safety and efficacy (Byreddy 2024). Harmonized regulations not only support international trade but also incentivize research and development by reducing duplicative testing and regulatory uncertainty.

In addition to regulatory approval, post-market surveillance and compliance monitoring are increasingly emphasized to track product quality, efficacy, and environmental impact throughout the product’s lifecycle. Such frameworks ensure that microbial biopesticides maintain consistent performance in the field while adhering to safety and environmental standards. The evolution of regulatory systems, particularly in emerging markets, reflects a

growing recognition of the importance of science-based, standardized evaluation to support sustainable agriculture and promote the adoption of microbial biocontrol agents globally.

8. Challenges and Future Directions

Despite significant technological progress, several persistent challenges continue to limit the widespread adoption of microbial biopesticides in sustainable agriculture. One of the most critical constraints is limited shelf life, as many microbial strains are highly sensitive to storage conditions, desiccation, temperature fluctuations, and ultraviolet radiation. Maintaining adequate viable cell or spore counts while preserving functional activity throughout storage and distribution remains a major bottleneck for large-scale commercialization (Mishra et al., 2023; Mantzoukas and Grammatikopoulos, 2020).

Another major limitation is variable field performance, which arises from environmental heterogeneity, soil physicochemical properties, climatic variability, and complex interactions with native microbial communities. Products demonstrating strong efficacy under laboratory or greenhouse conditions frequently exhibit inconsistent results under field conditions, undermining farmer confidence and slowing market acceptance (Khan et al., 2024; Lacey et al., 2015).

Production- and commercialization-related challenges further complicate adoption. Scale-up from laboratory or pilot-scale fermentation to industrial manufacturing often results in reduced microbial viability due to shear stress, oxygen limitation, foaming, and contamination risks. In addition, high production costs, limited infrastructure in certain regions, and fragmented regulatory requirements across countries can delay market entry and restrict international trade (El-Sayed et al., 2023; Byreddy, 2024; Kumar et al., 2024).

Emerging innovations offer promising solutions to these constraints. Microbial consortia, consisting of functionally complementary strains, can enhance field efficacy through synergistic biocontrol, nutrient mobilization, and stress tolerance, while reducing variability across agroecological zones (Mishra et al., 2023; Woo et al., 2014). Nano-enabled delivery systems and advanced encapsulation technologies provide improved protection against environmental stressors, controlled release of active microbes, and enhanced adhesion to plant and soil surfaces, thereby extending shelf life and improving consistency under field conditions (Kah et al., 2018; Khan et al., 2024).

Artificial intelligence (AI) and machine learning approaches are increasingly being applied to optimize fermentation parameters, formulation composition, and application strategies. By integrating large datasets on microbial physiology, environmental conditions, and field

performance, AI-assisted tools can reduce empirical trial-and-error approaches and accelerate the development of reliable, scalable microbial products (Wend et al., 2024; Mishra et al., 2023).

Future research should focus on strain improvement through adaptive evolution or targeted genetic approaches, development of modular and decentralized production platforms, and integration of microbial biopesticides into precision agriculture systems. Such strategies aim to enhance reliability, reduce costs, and improve adoption, supporting the broader transition toward resilient and eco-friendly crop protection systems.

9. Critical Synthesis and Author Perspective: What Is Failing, What Must Change, and What Will Succeed

Despite extensive research and increasing commercial interest, the field of microbial biologicals continues to struggle with a fundamental disconnect between laboratory success and field-level reliability. A critical examination of the literature reveals that many reported advances emphasize biological efficacy under controlled conditions while underestimating formulation robustness, manufacturing scalability, and environmental variability. This imbalance has resulted in a proliferation of products that perform well in experimental settings but fail to deliver consistent outcomes under commercial farming conditions.

9.1 What Is Failing: Structural Limitations in Current Development Paradigms

A major failure in current microbial bioproduct development lies in the overreliance on strain-centric screening approaches. Numerous studies focus on identifying highly potent microbial strains without parallel evaluation of formulation compatibility, shelf-life stability, or manufacturability. As a result, many promising strains are unsuitable for industrial production or rapidly lose viability during storage and transport. The persistence of short-lived liquid formulations and moisture-sensitive powders in commercial markets reflects this disconnect between biological potential and product engineering.

Another critical limitation is the assumption that laboratory-scale fermentation performance can be directly extrapolated to industrial-scale production. In practice, scale-up often introduces oxygen transfer limitations, shear stress, and metabolic shifts that compromise spore quality and biological efficacy. These factors are frequently underreported in the literature, creating an overly optimistic perception of scalability that does not reflect industrial realities.

Field performance variability represents a further systemic failure. Many microbial products are evaluated in narrowly defined agroclimatic conditions, leading to efficacy claims that do

not translate across soil types, cropping systems, or climatic zones. This has contributed to inconsistent farmer experiences and erosion of confidence in microbial solutions.

9.2 What Must Change: From Strain Discovery to Product-Centric Design

For microbial biologicals to achieve consistent commercial success, the development paradigm must shift from strain discovery–driven research toward **product-centric design**. Formulation science should be integrated at the earliest stages of strain selection, with microbial candidates evaluated not only for biological activity but also for tolerance to drying, encapsulation, carrier materials, and long-term storage.

Manufacturing considerations must similarly be embedded early in development pipelines. Fermentation strategies should prioritize robustness, reproducibility, and cost-efficiency rather than maximal laboratory yield alone. Pilot-scale validation and process stress testing should be reported more transparently in academic literature to bridge the gap between research and commercialization.

Regulatory science must also evolve to accommodate emerging technologies such as microbial consortia and nano-enabled delivery systems. Current regulatory frameworks are largely designed for single-strain products and often fail to capture synergistic interactions or formulation-driven modes of action, creating uncertainty for innovators and regulators alike.

9.3 What Is Promising—and Why These Approaches Are Likely to Succeed

Among emerging strategies, advanced formulation technologies represent the most immediate and impactful avenue for improving microbial product reliability. Oil-based formulations, microencapsulation, and controlled-release systems directly address the primary causes of field failure by protecting microbial viability against environmental stressors and enabling sustained activity at the target site. Unlike genetic modification or strain replacement, these approaches can often be applied to existing, well-characterized microbial agents, accelerating commercialization.

Microbial consortia offer another promising pathway, particularly when designed on the basis of functional complementarity rather than taxonomic diversity alone. Consortia that combine biocontrol activity with nutrient mobilization or stress tolerance are better positioned to buffer environmental variability and deliver consistent performance across diverse agroecological contexts.

The integration of artificial intelligence and data-driven optimization into fermentation control, formulation design, and field deployment represents a transformative opportunity. AI-assisted platforms enable predictive modeling of microbial behavior under variable

environmental and processing conditions, reducing empirical trial-and-error and supporting scalable, reproducible manufacturing.

Finally, alignment with precision agriculture systems—including targeted application, decision-support tools, and real-time environmental monitoring—offers a realistic pathway to improve microbial efficacy without requiring radical changes in microbial biology itself.

9.4 Author Outlook: A Realistic Path to Mainstream Adoption

The future success of microbial biologicals will not be determined by the discovery of ever more potent strains, but by the ability to deliver biologically effective, shelf-stable, and manufacturing-ready products that perform reliably under farmer-managed conditions. Progress will depend on interdisciplinary collaboration among microbiologists, formulation scientists, process engineers, and regulatory experts, supported by transparent reporting standards and harmonized regulatory frameworks.

Microbial biologicals should therefore be evaluated not as biological curiosities or niche alternatives, but as engineered agricultural inputs whose success depends on systems-level optimization. Approaches that integrate formulation robustness, scalable manufacturing, and data-driven deployment are most likely to transition microbial biologicals from promising alternatives into dependable, mainstream components of sustainable agriculture.

10. CONCLUSION

Microbial biologicals—comprising biopesticides, biofertilizers, and biostimulants—are increasingly recognized as essential technologies for achieving sustainable, low-input, and environmentally responsible agriculture. Decades of research have clearly established their potential to suppress pests and diseases, enhance nutrient use efficiency, improve soil health, and strengthen crop resilience while reducing dependence on synthetic agrochemicals (Chandler et al., 2011; Glare et al., 2012; Lacey et al., 2015). Yet, widespread adoption has been constrained not by biological inefficacy, but by challenges associated with formulation stability, manufacturing scalability, quality consistency, and regulatory complexity.

This review demonstrates that formulation science and industrial manufacturing are the primary determinants of commercial success for microbial biologicals. Conventional formulations, although cost-effective and widely used, often fail to adequately protect microbial viability under storage and field conditions, resulting in inconsistent efficacy and limited farmer confidence. In contrast, advanced delivery systems—such as oil-based formulations, microencapsulation, and controlled-release carriers—have shown clear

advantages in enhancing shelf life, environmental resilience, and field persistence. However, their broader adoption is constrained by higher production costs, scale-up complexity, and evolving regulatory expectations.

Equally critical are robust fermentation strategies, downstream processing protocols, and integrated quality control systems, which underpin batch-to-batch consistency, microbial purity, and compliance with national and international standards. The absence of harmonized regulatory frameworks across regions continues to pose barriers to global commercialization, emphasizing the need for science-based, risk-proportionate regulatory approaches that recognize the unique characteristics of microbial products.

Looking ahead, the convergence of microbial consortia design, nano-enabled formulation platforms, artificial intelligence–driven process optimization, and precision agriculture tools offers a realistic pathway to overcome long-standing limitations. These approaches shift the focus from isolated strain discovery toward systems-level optimization, enabling microbial biologicals to perform reliably across diverse agroecological conditions while remaining economically viable at scale.

Ultimately, the transition of microbial biologicals from niche solutions to dependable, mainstream agricultural inputs will depend on product-centric development paradigms that integrate biology, formulation engineering, manufacturing, and regulatory science from the earliest stages of innovation. Interdisciplinary collaboration, transparent reporting of scale-up and field performance, and continued regulatory harmonization will be essential to unlock the full potential of microbial technologies. When developed and deployed as engineered agricultural inputs rather than experimental alternatives, microbial biologicals can play a transformative role in advancing global food security, environmental sustainability, and climate-resilient farming systems.

ACKNOWLEDGMENTS

The authors express their sincere gratitude to the Head, Department of Biological Sciences, Rani Durgawati University, Jabalpur, Madhya Pradesh, for providing the necessary facilities and support to carry out this work. Financial assistance received from the Council of Scientific and Industrial Research (CSIR), Government of India, is gratefully acknowledged.

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