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Regulatory Approval and Market Adoption of Bt-based Biopesticides

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Abstract Bt biopesticides are known for their insecticidal properties and have been widely used in agriculture to reduce reliance on chemical pesticides and promote sustainable farming practices. Bt-based biopesticides are a promising alternative to chemical pesticides and have shown significant success in controlling pests and diseases, increasing crop yields, reducing environmental impact, and providing environmental and economic benefits. However, their market adoption is influenced by regulatory frameworks, potential drug resistance development, and environmental factors. The regulatory approval process for these biopesticides varies by region and often involves rigorous safety and effectiveness assessments. Studies have shown that Bt crops can affect soil enzyme activity and microbial ecology, requiring careful biosafety evaluation. Ongoing research and development, as well as rigorous regulation, are essential to maximize the benefits of Bt biopesticides and mitigate the risks associated with them. The purpose of this study was to investigate the regulatory approval process and market adoption of biopesticides based on *Bacillus thuringiensis* (Bt).
Keywords *Bacillus thuringiensis*; Biopesticides; Regulatory approval; Market adoption; Pest resistance

1 Introduction

Bacillus thuringiensis (Bt) is a Gram-positive, soil-dwelling bacterium that has been extensively utilized in agriculture due to its insecticidal properties (Bravo et al., 2011). The primary mode of action of Bt involves the production of crystalline inclusions containing proteins known as δ-endotoxins or Cry proteins during sporulation (Sanahuja et al., 2011). These proteins exhibit specific insecticidal activities against various insect pests, particularly lepidopteran and coleopteran larvae, making Bt the most widely used biopesticide globally (Kumar et al., 2008; Sanchis and Bourguet, 2011). Bt-based biopesticides can be applied in various forms, including sprays and transgenic crops expressing Bt *cry* genes, which have been developed to enhance crop protection and reduce reliance on chemical insecticides (Sanchis and Bourguet, 2011; Wafa et al., 2020).

The adoption of Bt-based biopesticides has significant implications for sustainable agriculture and environmental safety. Regulatory approval is crucial to ensure that these biopesticides are safe for human health and the environment. The rigorous evaluation process includes assessing the potential ecological risks, such as the impact on non-target organisms and the development of insect resistance (Kumar et al., 2008; Li et al., 2022). Market adoption of Bt-based biopesticides is influenced by public perception, regulatory frameworks, and the demonstrated efficacy of these products in pest management. Despite some biosafety concerns and ethical issues, the area under Bt transgenic crops is rapidly increasing, with several countries adopting these technologies to enhance agricultural productivity and reduce the environmental footprint of pest control (Kumar et al., 2008; Wafa et al., 2020).

This study reviews the historical development and current status of Bt-based biopesticides in various regions; evaluates the regulatory frameworks governing the approval of Bt-based biopesticides and their implications for market adoption; assesses the environmental and economic impacts of Bt-based biopesticides, including their role in integrated pest management and resistance management strategies and identify the challenges and opportunities associated with the broader adoption of Bt-based biopesticides in sustainable agriculture. By addressing these objectives, the study seeks to provide a comprehensive understanding of the factors influencing the regulatory approval and market adoption of Bt-based biopesticides, thereby contributing to the development of more effective and sustainable pest management practices.

2 Overview of Bt-based Biopesticides

2.1 Development and mechanism of Bt biopesticides

Bacillus thuringiensis (Bt) is a naturally occurring entomopathogenic soil bacterium that has been utilized as a biopesticide for over a century. The primary insecticidal components of Bt are crystal (Cry) proteins, which are produced during the sporulation phase of the bacterium. These proteins are highly specific to certain insect pests and are safe for non-target organisms, including humans (Kang et al., 2021). The mechanism of action involves the ingestion of Bt spores and Cry proteins by the target insect larvae, leading to the disruption of the gut cells, causing the insect to stop feeding and eventually die (Zhang et al., 2014). Recent advancements have focused on enhancing the efficacy of Bt biopesticides through genetic engineering and the development of nanopesticides, which improve delivery and reduce the required dosage (Devi et al., 2019; Li et al., 2022).

2.2 Types and applications

Bt-based biopesticides are available in various formulations, including liquid, powder, and granules, to cater to different agricultural needs. These formulations are used in a wide range of crops, including vegetables, fruits, and ornamental plants, as well as in forestry and mosquito control (Sansinenea, 2016; Devi et al., 2019). The versatility of Bt biopesticides is further enhanced by the development of transgenic crops that express Bt proteins, providing continuous protection against pests (Kang et al., 2021; Li et al., 2022). Additionally, innovative approaches such as the integration of Bt with RNA interference (RNAi) technology are being explored to manage resistance in pests and improve the sustainability of Bt products (Kang et al., 2021).

2.3 Benefits and limitations

Bt-based biopesticides offer several benefits over chemical pesticides, including specificity to target pests, safety for non-target organisms, and minimal environmental impact (Gupta and Dikshit, 2010; Sansinenea, 2016; Devi et al., 2019). They are considered a key component of integrated pest management (IPM) strategies and are gaining acceptance worldwide due to their eco-friendly nature (Sansinenea, 2016). However, there are limitations to their widespread adoption. These include the development of resistance in target pests, the need for stable delivery systems, and the higher production and formulation costs compared to chemical pesticides (Brar et al., 2006; Devi et al., 2019; Kang et al., 2021). Additionally, regulatory challenges and the need for farmer education on the effective use of biopesticides are significant barriers to market adoption (Gupta and Dikshit, 2010; Sansinenea, 2016).

In summary, Bt-based biopesticides represent a promising and environmentally sustainable alternative to chemical pesticides. Continued research and development, along with supportive regulatory frameworks, are essential to overcoming the current limitations and enhancing the adoption of these biopesticides in modern agriculture.

3 Regulatory Approval Process

3.1 International regulatory frameworks

The regulatory approval process for Bt-based biopesticides varies significantly across different international frameworks. In the European Union, the regulation of biopesticides falls under the Pesticide Regulation (EC) No. 1107/2009, which encourages the use of less harmful active substances. Despite the potential benefits, manufacturers face challenges due to stringent approval and registration processes, which are similar to those for synthetic pesticides (Villaverde et al., 2014). In contrast, the global market for biopesticides is growing, but the regulatory landscape remains complex, with different countries having varying requirements for data on chemistry, bioefficacy, toxicity, and packaging (Gupta and Dikshit, 2010; Sansinenea, 2016).

3.2 National regulatory processes

National regulatory processes for Bt-based biopesticides also exhibit considerable diversity. In India, for instance, the Central Insecticides Board and Registration Committee (CIBRC) oversees the registration of biopesticides. As of 2017, numerous microbial species and formulations have been registered, including various strains of *Bacillus thuringiensis* (Bt) (Kumar et al., 2019). However, the registration process is rigorous, requiring comprehensive data on the product's efficacy and safety. Similarly, in other countries, regulatory bodies impose strict guidelines to ensure the safe use of biopesticides, often mirroring the requirements for synthetic pesticides (Gupta and Dikshit, 2010; Rodríguez et al., 2019).

3.3 Comparative analysis of approval procedures

A comparative analysis of the approval procedures reveals both commonalities and differences across international and national frameworks. For instance, while the European Union and India both require extensive data on the safety and efficacy of biopesticides, the specific requirements and the stringency of the approval process can vary. The European framework, under Regulation (EC) No. 1107/2009, emphasizes zonal evaluations and cut-off criteria, which can complicate the approval process for biopesticides (Villaverde et al., 2014). In India, the focus is on ensuring that biopesticides meet the same rigorous standards as synthetic pesticides, which includes detailed assessments of their chemistry and bioefficacy (Gupta and Dikshit, 2010; Kumar et al., 2019).

Moreover, the regulatory innovation in some countries has led to the development of new policy spaces and proactive stances by regulatory agencies to promote the use of biopesticides. This is evident in the efforts to streamline the approval processes and reduce the regulatory burden on manufacturers, thereby encouraging the adoption of more sustainable pest control methods (Greaves, 2009).

In summary, while there is a global trend towards the increased use of biopesticides, the regulatory approval processes remain complex and varied. Harmonizing these processes and reducing the regulatory burden could facilitate the broader adoption of Bt-based biopesticides, contributing to more sustainable agricultural practices (Greaves, 2009; Villaverde et al., 2014; Sansinenea, 2016; Kumar et al., 2019).

4 Risk Assessment for Bt-based Biopesticides

4.1 Environmental risk assessment

The environmental risk assessment of Bt-based biopesticides involves evaluating their impact on non-target organisms, soil health, and overall ecosystem stability. Studies have shown that Bt proteins, which are the active components in Bt biopesticides, can be released into the soil through root exudates, pollen, and plant residues, potentially affecting soil microbial diversity and physical-chemical properties (Figure 1) (Li et al., 2022). Additionally, the nonmonotonic dose-response observed in *Daphnia magn*a suggests that even low concentrations of Bt biopesticides can have significant effects on non-target aquatic organisms, challenging the assumption of their universal safety (Machado et al., 2017). Regulatory frameworks must therefore ensure comprehensive environmental safety evaluations, including the potential for gene flow and the stability of gene expression in genetically modified Bt crops (Then et al., 2022).

4.2 Health and safety risk assessment

Health and safety risk assessments for Bt-based biopesticides focus on their potential impacts on human and animal health. The introduction of new food safety regulations in the European Union has highlighted the need for stringent safety criteria for biopesticides, similar to those applied to synthetic pesticides (Czaja et al., 2015). Despite the general perception of biopesticides as safer alternatives, there are concerns regarding the stability and safety of Bt toxins produced in genetically engineered crops, such as Bt cowpea, which necessitate thorough evaluations to ensure food safety (Then et al., 2022). Moreover, the development of RNAi-based biopesticides, which involve the use of double-stranded RNA (dsRNA), requires careful consideration of their health impacts, although current evidence suggests minimal risks to human health (Figure 2) (Fletcher et al., 2020).

4.3 Socioeconomic risk assessment

The socioeconomic risk assessment of Bt-based biopesticides involves analyzing their market adoption, regulatory challenges, and potential benefits to agriculture and public health. The market share of biopesticides remains relatively low, partly due to the stringent regulatory requirements and the need for extensive data on chemistry, bioefficacy, and toxicity for registration (Gupta and Dikshit, 2010). In India, for example, the adoption of biopesticides is hindered by regulatory barriers and the need for farmer education to maximize their benefits (Kumar et al., 2019). However, the increasing demand for organic farming and residue-free commodities is expected to drive the adoption of biopesticides, offering significant benefits to sustainable agriculture and public health programs (Gupta and Dikshit, 2010; Villaverde et al., 2014). Regulatory frameworks that facilitate the approval and registration of biopesticides, while ensuring their safety and efficacy, are crucial for their widespread adoption and integration into integrated pest management (IPM) programs (Matten et al., 2008).

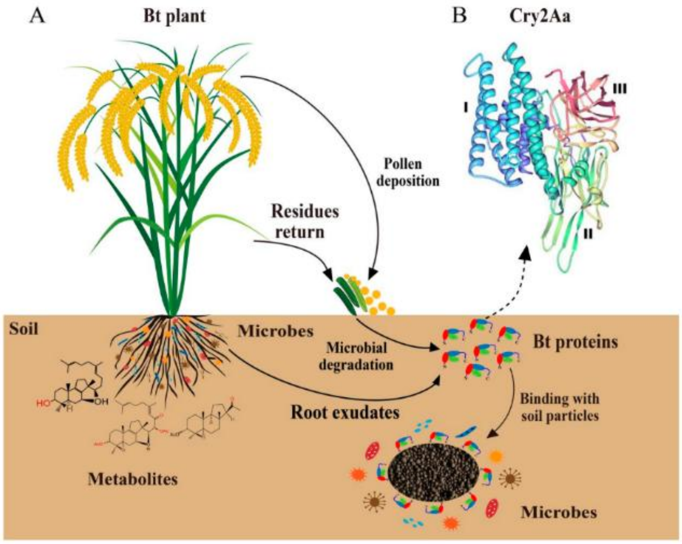

Figure 1 Environmental behaviors of Bt protein (A) and its three-dimensional structures (B). I, II, and III: domains I, II, and III (Adopted from Li et al., 2022)

Image caption: Residual accumulated Bt proteins in the environment exceed the consumption by insect larvae and degradation by environmental factors, leading to potential impacts on the abundances, community structures, and functions of natural soil microbial communities. Domain I (the pore-forming domain) is located at the N-terminal of the Cry active protein and consists of a bundle of seven antiparallel α-helices. The domain is cleaved by proteolytic enzymes during toxin activation and is associated with toxins entering cell membranes and pore formation. Domain II (the central domain) comprises three antiparallel β-folds and is a receptor recognition and binding site that determines the specificity of insecticidal protein targets. Domain III (the galactose-binding domain) comprises two antiparallel β-folds and is related to receptor binding and pore formation (Adopted from Li et al., 2022)

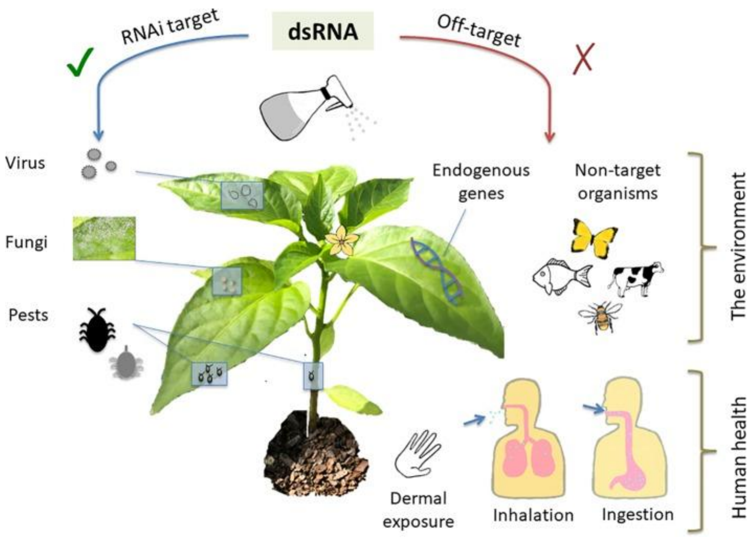

Figure 2 As a crop protection measure, topically-applied dsRNA should be effective against specific pests and pathogens while avoiding unintended adverse consequences (Adopted from Fletcher et al., 2020)

Image caption: Topically applied double-stranded RNA (dsRNA) can be used to generate resistance to pathogenic viruses and fungi, and pests such as insects. Off-target impacts to be avoided include silencing of crucial host plant and other non-target organism genes. Potential routes of exposure to humans including operators applying the dsRNA along with consumers of treated products could occur via dermal exposure, inhalation, and ingestion (Adopted from Fletcher et al., 2020)

5 Market Adoption of Bt-based Biopesticides

5.1 Factors influencing market adoption

The market adoption of Bt-based biopesticides is influenced by several factors, including regulatory frameworks, farmer awareness, and the perceived efficacy of these products. Regulatory barriers are a significant challenge, as biopesticides are often subjected to the same stringent regulations as chemical pesticides, which can be costly and time-consuming to navigate (Chandler et al., 2011; Sansinenea, 2016; Keswani et al., 2019). Additionally, the lack of awareness and education among farmers about the benefits and proper use of biopesticides hampers their adoption. Farmers often perceive biopesticides as less effective compared to chemical pesticides, which further slows their market penetration (Marrone, 2007; Marrone, 2019; Kumar et al., 2019).

5.2 Case studies of successful adoption

Despite these challenges, there have been successful cases of Bt-based biopesticide adoption. For instance, in India, several Bt-based products have been registered and are being used effectively against various pests. Over 30 products based on *Bacillus thuringiensis* (Bt) subsp. *kurstaki* are registered for use against bollworms and other lepidopterans, while products based on Bt subsp. *israelensis* and Bt subsp. *sphaericus* are used against mosquitoes (Kumar et al., 2019). These successful adoptions are often driven by strong regulatory support, effective farmer education programs, and the integration of biopesticides into Integrated Pest Management (IPM) systems (Gupta and Dikshit, 2010; Sansinenea, 2016).

5.3 Barriers to market entry

The primary barriers to market entry for Bt-based biopesticides include stringent regulatory requirements, high costs of registration, and the need for extensive efficacy data (Chandler et al., 2011; Balog et al., 2017; Keswani et al., 2019). In the European Union, for example, the complex regulatory environment has resulted in fewer biopesticide-active substances being registered compared to other regions like the United States and India (Balog et al., 2017). Additionally, the perception of biopesticides as less effective and more expensive than chemical pesticides further impedes their market entry (Marrone, 2007; Marrone, 2019). Overcoming these barriers requires coordinated efforts between policymakers, researchers, and industry stakeholders to streamline regulatory processes and enhance farmer education and support systems.

6 Strategies to Enhance Market Adoption

6.1 Policy and regulatory recommendations

To enhance the market adoption of Bt-based biopesticides, it is crucial to streamline and adapt regulatory frameworks to better accommodate these products. Current regulations often mirror those for chemical pesticides, which can be unnecessarily stringent for biopesticides. Simplifying the registration process and providing clear guidelines specific to biopesticides can facilitate quicker market entry and wider adoption (Gupta and Dikshit, 2010; Sansinenea, 2016; Damalas and Koutroubas, 2018). Additionally, offering incentives for the development and registration of low-risk biopesticides can encourage innovation and investment in this sector (Greaves, 2009; Damalas and Koutroubas, 2018). Regulatory bodies should also consider adopting a more proactive stance, negotiating new policy spaces, and promoting the use of biopesticides through executive interventions (Greaves, 2009).

6.2 Public awareness and education

Increasing public awareness and education about the benefits and safety of Bt-based biopesticides is essential for their market adoption. Farmers and consumers need to be informed about the environmental and health advantages of biopesticides compared to chemical pesticides (Ayele, 2005; Gupta and Dikshit, 2010). Extension services and demonstration projects can play a significant role in this regard, showcasing the efficacy and safety of Bt biopesticides in real-world settings (Ayele, 2005). Educational campaigns should also address common misconceptions and provide training on the proper use and integration of biopesticides into pest management programs (Marrone, 2019). By building confidence and knowledge among stakeholders, the adoption of Bt-based biopesticides can be significantly enhanced.

6.3 Innovation and product development

Innovation in the formulation and delivery of Bt-based biopesticides is critical to overcoming existing challenges and improving their market appeal. Advances in nanotechnology and microencapsulation can enhance the stability, efficacy, and shelf-life of biopesticide products, making them more competitive with chemical pesticides (Damalas and Koutroubas, 2018; Devi et al., 2019; Hernandez-Tenorio et al., 2022). Research and development should focus on creating formulations that are more resistant to environmental degradation and have extended field persistence (Devi et al., 2019; Hernandez-Tenorio et al., 2022). Additionally, integrating biopesticides into broader pest management systems, such as Integrated Pest Management (IPM), can optimize their use and demonstrate their effectiveness in combination with other control methods (Ayele, 2005; Fletcher et al., 2020). By continuously improving product performance and delivery mechanisms, the market adoption of Bt-based biopesticides can be significantly boosted.

7 Comparative Analysis of Global Practices

7.1 Best practices in regulatory approval

The regulatory approval processes for biopesticides vary significantly across different regions, impacting the availability and adoption of these products. In the United States, the regulatory framework is relatively streamlined, allowing for a higher number of biopesticide-active substances to be registered compared to the European Union (EU). The complexity of EU regulations has resulted in fewer biopesticide products being available in the market, which is a stark contrast to the more flexible regulatory environments in the United States, India, Brazil, and China (Balog et al., 2017). In Canada, the regulatory landscape has evolved over the years, with significant increases in the registration of microbial biopesticides due to proactive government policies and industry collaboration (Bailey et al., 2010).

7.2 Successful market adoption strategies

Successful market adoption of biopesticides is often driven by a combination of regulatory support, public awareness, and industry innovation. In North America, which holds the largest market share of biopesticides at 44%, the growth is supported by favorable regulatory conditions and increasing public and political support for sustainable agricultural practices (Bailey et al., 2010). In India, despite the vast potential for biopesticides, market adoption remains low at 2.5% of the total pesticide market. This is attributed to the need for greater farmer education and awareness about the benefits of biopesticides, as well as the development of more robust regulatory guidelines for the registration of genetically modified biopesticides (Gupta and Dikshit, 2010).

7.3 Lessons learned from different regions

Different regions offer valuable lessons in the regulatory approval and market adoption of biopesticides. The EU's stringent regulatory framework highlights the need for balancing safety and innovation to avoid stifling market growth (Balog et al., 2017). The United States and Canada demonstrate the benefits of a supportive regulatory environment that encourages the development and registration of new biopesticide products (Bailey et al., 2010; Balog et al., 2017). India's experience underscores the importance of education and awareness in driving market adoption, as well as the necessity for clear and comprehensive regulatory guidelines (Gupta and Dikshit, 2010). These insights can inform global strategies to enhance the adoption and effectiveness of biopesticides in sustainable agriculture.

8 Challenges and Future Directions

8.1 Technical and methodological challenges

The development and deployment of Bt-based biopesticides face several technical and methodological challenges. One significant issue is the degradation of bioactive components due to environmental factors such as air, light, and temperature, which can reduce the efficacy of biopesticides (Hernandez-Tenorio et al., 2022). Additionally, the production and formulation costs of Bt biopesticides are often high, which can limit their marketability and widespread use (Brar et al., 2006). The variability in regulations across different countries also poses a challenge, as it complicates the registration and approval process for new biopesticide products (Soetopo and Alouw, 2023).

Furthermore, the development of resistance in target pests, such as the diamondback moth, necessitates the integration of new biotechnological techniques like RNA interference (RNAi) to manage resistance effectively (Kang et al., 2021).

8.2 Knowledge gaps and research needs

There are several knowledge gaps and research needs that must be addressed to enhance the effectiveness and adoption of Bt-based biopesticides. One critical area is the need for more research on the long-term environmental impacts of biopesticides, including their effects on non-target organisms and ecosystems (Gupta and Dikshit, 2010). Additionally, there is a need for more studies on the stability and delivery mechanisms of RNAi-based biopesticides to ensure their effectiveness and longevity in the field (Fletcher et al., 2020). Research on the optimization of biopesticide formulations, including the use of nanotechnology to improve bioefficacy and field persistence, is also essential (Devi et al., 2019). Moreover, there is a need for more comprehensive studies on the socio-economic factors that influence the adoption of biopesticides by farmers, particularly in developing countries (Ayele, 2005).

8.3 Future trends and innovations

The future of Bt-based biopesticides lies in the integration of advanced technologies and innovative approaches to overcome existing challenges. One promising trend is the use of nanotechnology to develop nano-Bt formulations that offer higher efficacy, efficient delivery, and increased field persistence (Devi et al., 2019). Another innovative approach is the combination of Bt with RNAi to manage resistance in target pests, providing a new mode of action that complements existing Bt products (Kang et al., 2021). Additionally, there is a growing interest in the development of biopesticides that can be incorporated into integrated pest management (IPM) systems, which can enhance their effectiveness and sustainability (Sansinenea, 2016). The adoption of public-private partnerships and institutional arrangements for the transfer of research knowledge to the private sector can also facilitate the development and commercialization of new biopesticide products (Ayele, 2005). Finally, the reduction of regulatory barriers and the harmonization of biopesticide registration processes across different countries can promote the global adoption of Bt-based biopesticides (Soetopo and Alouw, 2023).

9 Concluding Remarks

The research on *Bacillus thuringiensis* (Bt)-based biopesticides highlights several critical points regarding their regulatory approval and market adoption. Bt biopesticides have been recognized for their specificity and effectiveness against target pests, making them a valuable component of integrated pest management (IPM) strategies. Despite their advantages, the adoption of Bt biopesticides has been slow due to factors such as cost-performance issues compared to synthetic pesticides and complex regulatory environments. However, the global market for biopesticides is growing, driven by increasing environmental safety concerns and advancements in biotechnological methods, such as genetic modification and nanoformulations, which enhance the efficacy and persistence of Bt products.

Effective regulatory and market strategies are crucial for the broader adoption of Bt-based biopesticides. The regulatory landscape varies significantly across regions, with some countries having more streamlined processes than others. For instance, the European Union has a more complex registration process compared to the United States, India, Brazil, or China, which can hinder the commercialization of new biopesticide products. In India, despite the presence of a regulatory framework, issues such as quality control and limited large-scale production facilities pose challenges. In China, the Bt biopesticide industry has seen significant growth due to well-established mass production and market development strategies. Therefore, harmonizing regulatory requirements and providing incentives for low-risk biopesticides could facilitate their market entry and adoption.

Future research should focus on several key areas to enhance the regulatory approval and market adoption of Bt-based biopesticides. Firstly, continued research into genetic modification and nanoformulations can improve the efficacy, delivery, and persistence of Bt biopesticides, making them more competitive with synthetic pesticides. Secondly, efforts should be made to harmonize regulatory requirements across different regions to streamline the approval process for new biopesticide products. Thirdly, investment in domestic fermentation technologies and improved quality control measures can address production challenges, particularly in regions like India. Fourthly, increasing awareness among farmers about the benefits of biopesticides and providing education on their use can enhance adoption rates. Besides, more field research is needed to assess the effectiveness of new Bt strains and formulations under diverse cropping systems and environmental conditions. By addressing these areas, the potential of Bt-based biopesticides can be fully realized, contributing to sustainable agricultural practices and reduced reliance on chemical pesticides.

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Conflict of Interest Disclosure
The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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