






# Baculoviruses as bioinsecticides: Evolution of *in vivo* production and future perspectives

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**ABSTRACT.** Baculoviruses are entomopathogenic agents widely used in the biological control of insect pests, standing out for their high specificity, biosafety, and efficacy. *In vivo* production in host larvae remains a relevant strategy due to its low cost and technical simplicity. The present study consists of a narrative review of the scientific literature, with a qualitative and analytical approach, aimed at synthesizing recent advances in the *in vivo* production of Baculoviruses for use as bioinsecticides. The literature search was conducted in the Scopus, Web of Science, PubMed, and Google Scholar databases, covering publications from January 2021 to March 2025. The synthesis of recent literature highlights technological trends including optimization of host rearing, infection protocols, formulation strategies for stability, and molecular characterization. Advances in genetic engineering aimed at increasing virulence and recombinant protein production are also discussed, as well as market potential, regulatory perspectives, and persistent challenges such as process standardization, scalability, and integration with computational and automation tools. This work provides an updated and comprehensive overview, contributing to the development of more effective and sustainable bioinsecticides.

**Key words:** Biological control; bioinput; genetic engineering; commercial applications.

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## INTRODUCTION

The growth of the global population and the consequent demand for food place significant pressure on agricultural systems to ensure food security. In this context, agricultural pests represent a substantial threat, being responsible for significant losses in the production of essential crops. It is estimated that more than 10,000 species of insects cause considerable damage to plantations worldwide (Martínez-Balardi *et al.*, 2025).

Traditionally, chemical control has been the primary strategy to combat these pests. However, the excessive use of synthetic pesticides has resulted in serious environmental problems, such as soil and water contamination, in addition to risks to human health and the development of resistance by pests. In this scenario, baculoviruses emerge as a promising and ecological alternative, offering highly specific, safe, and sustainable biological control (Chaudhary *et al.*, 2024).

Baculoviruses belong to the family

*Baculoviridae* and are double-stranded DNA viruses that primarily infect insects, most notably those in the orders Lepidoptera, Hymenoptera, and Coleoptera. Their host specificity and environmental safety make them ideal for integrated pest management (IPM) programs. Furthermore, they offer advantages such as the absence of toxicity to non-target organisms and the ability to degrade rapidly in the environment (Rohrmann, 2013).

Since the 1970s, with the identification of the first commercial baculovirus, the use of these viruses has expanded. Significant advances have been made in mass production, both *in vivo* and *in vitro*, and in the development of formulations that increase field efficacy and environmental persistence. Technologies such as microencapsulation and UV protectants have been employed to improve the stability of baculovirus-based products (Wilson *et al.*, 2020).

The occurrence of insect populations with lower susceptibility to baculoviruses constitutes a relevant challenge for the sustainability of this control strategy, although it is less frequent than the resistance observed for synthetic chemical insecticides. Additionally, the

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efficacy of these biological agents can be significantly influenced by environmental factors, such as temperature and humidity, which affect their stability and infectious activity (García-Munguía et al., 2025).

The global market for baculovirus-based products has shown growth in recent years, especially in regions such as Latin America and Asia, where more favorable regulatory policies have encouraged their use. However, in regions like the European Union, regulatory barriers still represent a significant obstacle to large-scale adoption (Martínez-Balardi et al., 2025).

This review aims to provide a comprehensive overview of baculoviruses as microbial pesticides, exploring their potential, challenges, and market landscape. By integrating this information, we seek to highlight their role as effective and sustainable alternatives to chemical pesticides in modern agriculture, contributing to the reduction of pesticide residues and environmental impact.

## MATERIALS AND METHODS

The present study consists of a narrative literature review with a qualitative and analytical approach. To ensure greater methodological transparency, a structured bibliographic search was conducted in the Scopus, Web of Science, PubMed, and Google Scholar databases, covering publications from January 2021 to March 2025. The search strategy utilized combinations of keywords such as “baculoviruses”, “*in vivo* production”, “bioinsecticide”, “host rearing”, “infection protocols”, and “genetic engineering”, employing Boolean operators (AND, OR) to refine the results.

The following inclusion criteria were adopted: (i) peer-reviewed scientific articles; (ii) studies directly related to the *in vivo* production of baculoviruses for agricultural application; and (iii) publications available in full in English, Portuguese, or Spanish. Original articles, review articles, and relevant technical reports were considered. Theses and dissertations were included when they presented original methodological or technical contributions not yet published in indexed journals.

The selection process involved an initial analysis of titles and abstracts to verify thematic relevance, followed by a full reading of the selected studies. Duplicate works, those out of thematic scope, or those that did not present relevant methodological data were excluded from the final analysis. The analysis focused on the methodological approaches employed, production protocols, technological innovations, molecular characterization strategies, regulatory aspects, and market perspectives. There was no restriction regarding the country of origin of the

publications, seeking to encompass a broad and representative view of recent advances in the field.

### History and evolution of baculoviruses

Baculoviruses are naturally occurring entomopathogenic agents that primarily infect insects of the orders Lepidoptera, Hymenoptera, and Diptera. The empirical use of extracts from dead insects for agricultural pest control dates back more than a century, but the systematic scientific study of these viruses began in the early 20th century, when researchers began to recognize their viral nature and their potential as bioinsecticides (Boucias and Pendland, 1998).

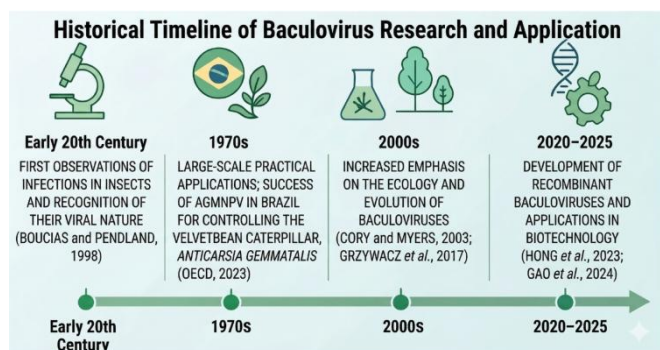
The 1970s marked the beginning of large-scale practical application of baculoviruses, especially in Latin America. In Brazil, the control program for the velvetbean caterpillar (*Anticarsia gemmatalis*) using the “*Anticarsia gemmatalis* multiple nucleopolyhedrovirus” (AgMNPV) was a global milestone in viral biocontrol. This initiative resulted in millions of hectares treated and demonstrated the feasibility of partially replacing chemical insecticides with biological agents (OECD, 2023).

During the 1980s and 1990s, technological advances allowed for the improvement of the *in vivo* production process, optimizing parameters such as larval diet, population density, and environmental conditions, which increased viral yield. Furthermore, the registration of commercial products, such as the *Cydia pomonella granulovirus* (CpGV) for the control of the codling moth, consolidated the role of baculoviruses as bioinsecticides of global relevance (Lacey et al., 2015).

At the beginning of the 21st century, the focus of research expanded to include the genetic diversity and evolutionary stability of these viruses. Cory and Myers (2003) highlighted the importance of baculovirus ecology and evolution for maintaining field efficacy, while Grzywacz et al. (2017) addressed challenges related to natural variability and the formulation of more stable and durable products. These studies reinforced the need to understand evolutionary dynamics and virus-host interactions to enhance their application.

In recent years, advances in molecular biology and genomics have significantly broadened the possibilities for baculovirus use. Next-generation sequencing (NGS) technologies have enabled the characterization of genomic variability and the identification of mutations associated with loss of virulence. Additionally, the development of genetically modified baculoviruses with toxin genes or specific regulatory proteins has increased infection speed and mortality in target pests, making these viruses versatile tools for both biocontrol and biotechnology (Gao et al., 2024; Hong et al., 2023).

**Figure 1.** Timeline of the evolution and applications of baculoviruses. Illustration generated by artificial intelligence (Gemini, Google).



The trajectory of baculoviruses, from the first empirical experiments to commercial and recombinant bioinsecticides, reflects a continuous evolution marked by scientific, technological, and productive advancements. Currently, these viruses remain a sustainable and effective alternative in integrated pest management, with growing potential in a market that progressively seeks to replace chemical pesticides (Martínez-Balerdi et al., 2025) (Figure 1).

### Biological characteristics and mode of action of baculoviruses

Baculoviruses are double-stranded DNA (dsDNA) viruses with circular genomes ranging between 80 and 180 kbp, encapsulated in enveloped nucleocapsids and protected by a crystalline protein matrix called an occlusion body (OB) (Rohrmann, 2013). These viruses belong to the family *Baculoviridae*, subdivided into four genera: *Alphabaculovirus* (infecting Lepidoptera), *Betabaculovirus* (lepidopteran granuloviruses), *Gammabaculovirus* (infecting Hymenoptera), and *Deltabaculovirus* (infecting Diptera) (Jehle et al., 2006).

The infection begins when susceptible insect larvae ingest the occlusion bodies present on the surface of contaminated leaves. In the alkaline midgut of the insect, the protein matrix of the OBs dissolves, releasing occlusion-derived virus (ODV) particles, which penetrate the intestinal epithelial cells and release the viral DNA into the nucleus (Rohrmann, 2013). Initial replication generates budded virus (BV) particles, responsible for the systemic dissemination of the virus throughout the host tissues (Kokusho et al., 2025).

During the infection cycle, the baculovirus manipulates the host's metabolism and behavior, promoting the suspension of feeding, the delay of metamorphosis, and, in the final stages, the liquefaction of the larva's body, which facilitates the release of new OBs into the environment. This process includes behavioral alterations, such as the tendency of infected larvae to climb to the top of plants before death—a phenomenon known as "tree-top disease" or "climbing

behavior," which increases the dispersal of the virus over the canopy (Zhu et al., 2025).

Baculoviruses possess a set of highly conserved genes, termed core genes, responsible for essential functions such as replication, transcription, assembly, and viral occlusion. However, genetic diversity among species and strains is broad and reflects evolutionary adaptations to different hosts. Furthermore, many baculoviruses contain accessory genes acquired through horizontal transfer, providing ecological advantages, such as the production of enzymes that degrade the cuticle or suppress the insect's immune responses (Ferrelli and Salvador, 2023).

Understanding these mechanisms has been essential for the development of biotechnological applications, including the use of the baculovirus expression vector system (BEVS) in the production of recombinant proteins, vaccines, and therapeutic viruses. Thus, the detailed study of the life cycle and virus-host interactions continues to be fundamental both for the advancement of biological control and for the expansion of baculovirus use in modern biotechnology (Martínez-Balerdi et al., 2025).

### *In vivo* production strategies for baculoviruses

*In vivo* production of baculoviruses remains the predominant method for generating viral bioinsecticides on a commercial scale. This system is based on the infection of susceptible host larvae, which serve as natural bioreactors, allowing for viral replication and the formation of highly infectious OBs. Despite the development of *in vitro* techniques, the operational simplicity and high productivity in terms of OBs per unit of biomass still make the *in vivo* method economically competitive for several baculovirus species of agricultural importance (Beperet et al., 2023).

Several biological and environmental factors influence the efficiency of the production process. Infection success depends primarily on host susceptibility, viral dose, and the larval stage at the time of inoculation. In general, third- or fourth-instar larvae show better performance, as they combine an appropriate balance between biomass and permissiveness to infection. Additionally, parameters such as temperature, photoperiod, and the nutritional quality of the diet directly affect viral replication and OB formation (OECD, 2023).

Experimental infection is traditionally performed through the ingestion of leaves or artificial diets contaminated with a viral suspension. Alternatively, the droplet feeding technique has been widely employed—a method described and standardized in classic baculovirus bioassay studies (Hughes and Wood, 1981) and still extensively used in contemporary protocols for precise dose-response determination

(Lacey et al., 2015). In this approach, a small volume (usually 1–5  $\mu\text{L}$ ) of a suspension containing a concentration of OBs is offered individually to the larvae using a micropipette, often after a short fasting period to stimulate ingestion. This technique allows for greater control over the ingested dose and reduces experimental variability. After the larvae die, the material is collected, purified, and quantified for subsequent formulation, resulting in products ready for field application (Martínez-Balardi et al., 2025).

The *in vivo* system, however, presents challenges related to biological variability, colony maintenance, and industrial scaling. Dependence on living hosts makes the process sensitive to genetic and physiological variations in insect populations, which can affect product yield and stability. Furthermore, the continuous reuse of viral isolates may favor the selection of less virulent variants, requiring constant genetic monitoring of the strains (Sanches et al., 2021).

To mitigate these limitations, recent advances include the selection of more stable viral strains and highly susceptible hybrid hosts, as well as the use of molecular and genomic tools to identify mutations associated with loss of virulence (Martínez-Balardi et al., 2025). Modern colony control and formulation techniques have also been reducing operational costs and improving batch uniformity, bringing the *in vivo* system closer to the standards required by the modern biopesticide industry (OECD, 2023).

Thus, although *in vitro* methods have been gaining ground in baculovirus biotechnology—especially for recombinant protein production and specific industrial applications—*in vivo* production remains the primary practical and economically viable basis for commercial bioinsecticide formulations. This is particularly true in countries with limited or developing industrial infrastructure, where *in vitro* scaling costs still represent a significant hurdle (Moscardi, 1999; García-Munguía et al., 2025).

### ***In vitro* production strategies, molecular characterization, and genetic engineering**

The *in vitro* production of baculoviruses, using insect cell cultures, has developed significantly in recent decades, primarily for applications that require rigorous quality control and viral purity. This approach allows for the standardization of cultivation conditions, contamination control, and monitoring of the genomic integrity of the viruses. Recent studies demonstrate that next-generation sequencing (NGS) is fundamental to ensuring genetic stability during multiple replication cycles, preventing the loss of virulence or undesired alterations (Wang et al., 2024; Ning et al., 2016).

The genetic engineering of baculoviruses has expanded the possibilities for optimizing viral

production both *in vivo* and *in vitro*. Modifications to the genome can increase the replication rate, accelerate insect death, or allow for the expression of recombinant proteins of biotechnological interest. Techniques such as the insertion of genes encoding specific toxins, enzymes that facilitate host tissue degradation, or proteins that enhance viral replication have shown promising results (Martínez-Solís et al., 2019).

In *in vitro* systems, the use of insect cell cultures, such as the *Sf9* and *High Five* lineages, has allowed for improved baculovirus-mediated recombinant protein expression. Recent advances in the optimization of multiplicity of infection (MOI), cell density, and control of physicochemical parameters have contributed to increasing the yield and quality of the produced proteins (Hitchman et al., 2010). These progresses reinforce the importance of integrating *in vivo* and *in vitro* strategies to maximize the efficiency of the production system.

The integration of genetic engineering techniques with *in vitro* production also offers the opportunity to create more effective and specific bioinsecticides, allowing the application of baculoviruses in integrated pest management programs with greater safety for non-target organisms and lower environmental impact (Martínez-Balardi et al., 2025).

### **Applications of Baculoviruses**

Baculoviruses remain strategic tools for both biological pest control and biotechnology. Traditionally, the most relevant application is the management of agricultural insect pests, especially lepidopterans, offering safe and specific alternatives to chemical pesticides. The specificity of baculoviruses ensures the protection of non-target organisms, preserving natural enemies and ecosystem balance (Gelaye and Negash, 2023).

Beyond pest control, baculoviruses have been widely explored as versatile biotechnological platforms, especially for the production of recombinant proteins. Their ability to infect insect cells and promote the correct folding of complex proteins enables the development of vaccines, monoclonal antibodies, and biopharmaceuticals. The versatility of this platform has also boosted applications in gene therapy, thanks to low immunogenicity and the ability to transduce mammalian cells without replication (Flock et al., 2024).

With the advancement of genetic engineering, baculoviruses can be modified to express specific toxins or proteins that increase virulence and efficacy against resistant pests, resulting in improved and faster-acting bioinsecticides. These applications have broadened the range of possibilities, making baculoviruses not only biological control agents

but also high-value-added biotechnological production platforms (Lin and Chen, 2023; Sari-Ak et al., 2023).

### Advantages of using Baculoviruses

The use of baculoviruses offers several advantages that make them an efficient and sustainable alternative to conventional pest control methods.

**Biosafety:** Studies confirm that baculoviruses are harmless to microorganisms, plants, vertebrates, and non-target insects, as they do not replicate in organisms that are not specific hosts. This qualifies them as low-environmental-risk agents, safe for large-scale applications (Martínez-Balerdi et al., 2025).

**Specificity:** Their high host specificity ensures that only target species are affected, preserving natural enemies of pests and maintaining ecological balance. This characteristic is especially important in complex agricultural ecosystems, where the indiscriminate use of chemical pesticides can cause environmental imbalances (Gelaye and Negash, 2023).

**Sustainability and Agricultural Compatibility:** Baculoviruses do not leave harmful chemical residues and can be applied using the same equipment used for conventional pesticides, reducing costs and facilitating integration with integrated pest management (IPM) programs. Furthermore, their use contributes to reducing environmental impact in tropical regions, where high temperatures favor the emergence and dispersal of pests (Martínez-Balerdi et al., 2025; Gelaye and Negash, 2023).

**Versatility:** Beyond pest control, their capacity for heterologous expression allows **baculoviruses** to produce recombinant proteins of pharmaceutical and industrial interest, adding economic and scientific value to the technology (Flock et al., 2024).

### Challenges and future perspectives

Despite recent advances, the *in vivo* production of baculoviruses still faces technical and biological challenges that must be overcome to optimize yield, quality, and applicability. One of these is the variability in yield; for instance, biological factors such as larval stage, insect density, and cannibalistic behavior can significantly affect viral production. Environmental conditions, such as temperature and humidity, also influence the replication rate and the release of viral particles (van Beek and Davis, 2016; Gelaye and Negash, 2023).

Recent technological advancements point toward the incorporation of automation and robotics systems in insect rearing and inoculation, allowing for the implementation of automated processes that promise to reduce labor demand and increase productivity (Martínez-Balerdi et al., 2025). Another relevant progress refers to the use of predictive modeling and

artificial intelligence tools, which enable the prediction of viral yield and the optimization of diets and cultivation conditions, enhancing the efficiency of the production process. Furthermore, improvements in biosafety stand out, including genetic monitoring strategies and contamination control, ensuring greater stability, traceability, and product quality, especially in biotechnological and biomedical applications (Gelaye and Negash, 2023).

Finally, genomic modifications through genetic engineering continue to broaden the potential of baculoviruses, whether to increase virulence, accelerate pest death, or optimize the production of high-value recombinant proteins (Flock et al., 2024; Lin et al., 2023). These challenges and perspectives indicate that the *in vivo* production of baculoviruses remains a dynamic area, with great potential for innovations that consolidate the technology as a sustainable and economically viable tool for biological control and applied biotechnology.

### Programs and examples in Brazil

Brazil is a global reference in the application of baculoviruses for the biological control of agricultural pests, with several successful programs demonstrating the viability and efficacy of this technology.

***Anticarsia gemmatalis* nucleopolyhedrovirus (AgMNPV):** Used to control the velvetbean caterpillar (*Anticarsia gemmatalis*), this was the largest bioinsecticide program using entomopathogenic viruses in the country, covering nearly 2 million hectares of soybean. Studies demonstrate that AgMNPV maintains high field efficacy, showing significant mortality in target larvae without affecting non-target insects (Castro, 2006; Gelaye and Negash, 2023).

***Spodoptera frugiperda* multiple nucleopolyhedrovirus (SfMNPV):** Aimed at controlling the fall armyworm (*Spodoptera frugiperda*), Brazilian companies have registered commercial products such as Cartuchovit and Vircontrol. Recent research indicates that densities of 50 to 100 larvae per container, maintained for up to 96 hours post-inoculation, optimize *in vivo* production without the need for individualization, increasing efficiency and reducing costs (van Beek and Davis, 2016; Martínez-Balerdi et al., 2025).

***Erinnyis ello* granulovirus (ErelGV):** Applied for the control of the cassava hornworm (*Erinnyis ello*), this program demonstrates that granuloviruses can be incorporated into integrated pest management systems, maintaining environmental safety and selectivity (Moscardi, 1999; Gelaye and Negash, 2023).

***Chrysodeixis includens* nucleopolyhedrovirus (ChinNPV) and *Condylorrhiza vestigialis* nucleopolyhedrovirus**

(CoveNPV): Ongoing studies have evaluated the development of commercial products for the control of these pest caterpillars, highlighting the importance of selecting specific isolates that maximize viral yield and reduce losses due to early liquefaction of the integument (Sanches *et al.*, 2021; Castro *et al.*, 2009).

***Helicoverpa armigera* nucleopolyhedrovirus (HearNPV)**: Applied in the control of the *H. armigera* caterpillar—considered a quarantine pest until 2013—this example illustrates the adaptation of baculovirus programs to new agricultural demands, reinforcing the flexibility of this technology across different crops and regions (Muraro *et al.*, 2022; Gelaye and Negash, 2023).

These examples illustrate Brazil's capacity to integrate baculovirus programs into sustainable management strategies with scalability, efficiency, and environmental preservation, serving as a model for other countries with similar challenges in tropical agriculture.

## CONCLUSION

The *in vivo* production of baculoviruses stands out as an efficient and sustainable strategy for biological pest control and advanced biotechnological applications. Mastery of this process has allowed for consistent results in terms of viral yield, product quality, and environmental safety, consolidating this approach as a viable alternative to the use of chemical insecticides.

Recent advances in host management techniques, formulations, and rearing conditions have expanded the productive potential and stability of the viruses, favoring their application in different agricultural contexts. In the Brazilian scenario, the large-scale use of baculoviruses demonstrates that the technology can be adapted to local conditions while maintaining efficiency and low environmental impact.

Despite this progress, challenges still need to be overcome, such as the standardization of production processes and the improvement of product stability during storage and application. The incorporation of emerging technologies, such as automation, bioinformatics, and genetic engineering, represents the next step toward optimizing production and broadening the reach of this biotechnology.

In summary, the *in vivo* production of baculoviruses represents a strategic tool for more sustainable agriculture, capable of uniting biological efficiency, economic viability, and technological innovation. Its continuous development tends to

strengthen the role of bioinsecticides in integrated pest management and the transition to more balanced and resilient agricultural systems.

In synthesis, this review highlighted that *in vivo* production of baculoviruses remains the primary model for obtaining commercial bioinsecticides, especially due to its economic viability and applicability in different production realities. Advances related to the optimization of infection protocols, host selection, molecular characterization, and the integration of tools such as automation, bioinformatics, and genetic engineering were emphasized. However, limitations associated with biological variability, industrial standardization, product stability, and regulatory requirements persist. Overcoming these challenges, combined with the incorporation of emerging technologies, will be decisive in consolidating and expanding the use of baculoviruses as a strategic tool in sustainable pest management.

## CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

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## DATA AVAILABILITY STATEMENT

This study is a review article and does not include original data. Therefore, no datasets were generated or deposited in repositories.

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