NATURAL BIOPESTICIDES: A LITERATURE REVIEW ON BIOINSECTICIDES, BIOHERBICIDES, AND APPLIED MODELING

https://doi.org/10.22533/at.ed.835152512066

Data de aceite: 01/07/2025

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ABSTRACT: The expansion of Brazilian agribusiness has led to an increasing use of pesticides, resulting in environmental impacts, toxicological risks, and the development of resistance in target organisms. In this context, there is growing interest in sustainable alternatives for agricultural management, such as natural biopesticides. This chapter presents a comprehensive review of scientific literature on the use and development of biopesticides, with a particular focus on bioinsecticides and bioherbicides, as well as the role of computational modeling in this field. It discusses the main plant-derived compounds with insecticidal potential, including flavonoids, terpenoids, and glucosinolates, addressing their biological effects, mechanisms of action, and the most widely used extraction methods and efficiency evaluation techniques. Additionally, the chapter examines how computational modeling tools have contributed to predicting interactions between natural compounds and biological targets, facilitating the identification of promising molecules and optimizing the development of new biopesticides by reducing both time and costs. Despite their potential, the adoption of biopesticides still faces technical, regulatory, and economic challenges. The integration of basic research, technological innovation, and computational modeling is essential to enable the gradual replacement of synthetic pesticides with safer, more sustainable, and efficient solutions for agriculture.
KEYWORDS: Natural biopesticides; Plant-derived products; Computational modeling; Sustainable agriculture.

BIOPESTICIDAS NATURAIS: UMA REVISÃO DE LITERATURA SOBRE BIOINSETICIDAS, BIOHERBICIDAS E MODELAGEM APLICADA

RESUMO: O avanço do agronegócio brasileiro tem resultado em um uso crescente de agrotóxicos, gerando impactos ambientais, riscos toxicológicos e o desenvolvimento de resistência em organismos-alvo. Diante desse cenário, cresce o interesse por alternativas sustentáveis para o manejo agrícola, como os biopesticidas naturais. Este capítulo apresenta uma revisão da literatura científica sobre o uso e o desenvolvimento de biopesticidas, com foco especial em bioinseticidas e bioherbicidas, além de destacar o papel da modelagem computacional nesse processo. São discutidos os principais compostos vegetais com potencial inseticida, como flavonoides, terpenoides e glucosinolatos, abordando seus efeitos biológicos, mecanismos de ação e os métodos mais utilizados para sua extração e avaliação de eficiência. Também se analisa como as ferramentas de modelagem computacional têm contribuído para prever a interação entre compostos naturais e alvos biológicos, facilitando a identificação de moléculas promissoras e otimizando o desenvolvimento de novos biopesticidas, com redução de tempo e custos. Apesar de seu potencial, a adoção de biopesticidas ainda enfrenta desafios técnicos, regulatórios e econômicos. A integração entre pesquisa básica, inovação tecnológica e modelagem computacional é fundamental para viabilizar a substituição progressiva dos agrotóxicos sintéticos por soluções mais seguras, sustentáveis e eficientes para a agricultura.
PALAVRAS-CHAVE: Biopesticidas naturais; Produtos vegetais; Modelagem computacional; Agricultura sustentável.

INTRODUCTION

The rapid expansion of Brazilian agribusiness in recent years has established the country as one of the leading global players in food production. This growth has positioned Brazil among the largest grain suppliers in the international market, accounting for approximately half of the global output and reaching the status of the world's largest soybean producer in the 2024/2025 harvest (Artuzo *et al.*, 2018; Embrapa, 2025). As a consequence of this process, Brazil-currently the largest consumer of pesticides worldwide-approved the registration of 505 new pesticide products in 2023 alone, according to data from the Ministério da Agricultura e Pecuária, highlighting the increasing intensification of pesticide use within the national agricultural sector (Agência Brasil, 2023).

The intensive use of synthetic pesticides in agriculture has raised serious environmental, social, and economic concerns. The release of these potentially hazardous chemical compounds into the environment can lead to the contamination of food, soil, and water bodies, as well as negative impacts on biodiversity. In this context, continuous monitoring is essential, both for detecting pesticide residues and for assessing their adverse effects on non-target organisms (Hess and Nodari, 2022).

In this context, there is growing interest in more sustainable alternatives, such as biopesticides, which employ living organisms or natural substances for the control of agricultural pests, resulting in lower environmental and toxicological impacts.

Over the past five years, the biopesticide sector in Brazil has shown an average annual growth rate of 45%, significantly surpassing the 6% growth observed in the conventional pesticide market. In 2022, agricultural areas managed with biological control practices totaled approximately 70 million hectares, according to data from Embrapa (2024), reflecting the substantial expansion of this sector and its increasing competitive potential compared to conventional technologies.

In light of this context, the objective of this study is to conduct a literature review on the development and application of natural biopesticides, with emphasis on bioinsecticides, bioherbicides, and the use of computational modeling as a supporting tool for research and innovation in this field.

NATURAL BIOINSECTICIDES

Bioinsecticides, also known as biological products, are technologies used to control insect pests in agricultural crops (Valicente, 1994). Although chemical control remains the primary strategy for pest management in agriculture-mainly due to its immediate effectiveness, the intensive and continuous use of pesticides has been linked to several negative impacts. These include the accumulation of toxic residues in food intended for human and animal consumption, the contamination of natural resources such as soil and water, and the increased resistance of pest insect populations to the active ingredients used (Campos *et al.*, 2014).

In response to these challenges, sustainable alternatives have gained increasing attention, with biological control standing out among them. This strategy is based on ecological interactions in which humans compete with pests for natural resources, such as cultivated plants and agricultural production. Additionally, biological control relies on the action of natural agents that serve as human allies and natural enemies of pests. In this context, natural resources-whether of plant or animal origin, managed or unmanaged-are considered positive externalities that directly contribute to human well-being (Fontes; Pires; Sujii, 2020).

One of the most extensively studied natural pest control strategies is the use of neem oil (*Azadirachta indica*), who's physiological and sublethal effects have been widely documented in various pest insect species. Duarte *et al.* (2019) observed that diets containing *A. indica* oil prolonged the larval and pupal stages, reduced pupal weight, and resulted in adults with deformed wings. Additionally, insects exposed to the treatment exhibited lower fecundity and reduced survival rates. Although these sublethal effects do not cause immediate mortality, they can significantly compromise the reproductive success of target populations, contributing to long-term population control.

In addition to neem oil, other plant extracts have also shown promising bioinsecticidal potential. In a study conducted by Spochacz *et al.* (2021), the efficacy of *Solanum nigrum* berry extract was evaluated for the control of the greater wax moth (*Galleria mellonella*). The incorporation of the extract into the insect diet led to a reduction in protein, lipid, and carbohydrate levels in the hemolymph, as well as causing ultrastructural damage to the fat body and midgut tissues. These physiological and morphological effects reinforce the insecticidal potential of the bioactive compounds present in *S. nigrum*.

Furthermore, plant-based insecticides are obtained from extracts containing substances produced through the secondary metabolism of plants. According to chemical and ecological studies, these compounds play a crucial role in plant defense during interactions with insects (Viglianco *et al.*, 2008). Specific flavonoids and isoflavonoids, for instance, can directly interfere with insect feeding, development, or reproduction. In this regard, Graça *et al.* (2016) demonstrated that treating soybean cultivars with *cis*-jasmone increased the levels of genistein and daidzein-compounds that negatively affected the growth of the stink bug *Euschistus heros*, particularly in the resistant Dowling cultivar.

Natural bioinsecticides represent a highly promising alternative to traditional chemical pest control methods. Their main advantages include lower environmental impact and reduced risks to human and animal health (Mossa *et.,* 2018; Hertlein *et.,* 2010). Additionally, many of these products act sublethally, affecting pest growth, development, and reproduction, thereby contributing to the ecological balance of agricultural systems in a more sustainable manner. Nevertheless, significant challenges remain, such as formulation standardization, active compound stability, and production costs. Overcoming these limitations is essential to enable the large-scale adoption of bioinsecticides and their effective integration into integrated pest management programs.

DEVELOPMENT OF NATURAL BIOINSECTICIDES

The development process of natural bioinsecticides involves several interdisciplinary stages, ranging from the identification of plant species with insecticidal potential to the final formulation of stable and effective products for agricultural applications. Initially, screening of extracts or isolated compounds is conducted through laboratory assays to evaluate toxic, repellent, or sublethal effects on various target pests. Once bioactive compounds are identified, these products are optimized in terms of concentration, application method, and chemical stability. Furthermore, field studies are essential to validate the efficacy of bioinsecticides under real environmental conditions, ensuring their viability and performance across different cultivation environments.

There are several methods used to extract bioactive substances from plants, with the most common being maceration, reflux, and the use of the Soxhlet apparatus. In maceration, the plant material is immersed in a solvent and left to rest for several days at room temperature, with occasional stirring to release the compounds. Reflux and Soxhlet, on the other hand, use heat to facilitate the extraction process. The key difference between these two methods is that Soxhlet causes the solvent to evaporate, condense, and recirculate repeatedly over the plant, improving the extraction of heat-resistant compounds and making the process more efficient (Tzanova *et al*., 2020). These techniques are considered simple and effective, applicable to a wide range of samples with high yields, but their selectivity depends on the solvent used.

The choice of solvent for extracting bioactive compounds depends on the type of plant material, the polarity of the compounds of interest, and the methodology used. One of the methods commonly employed to test the efficacy of plant extracts against pests is the feeding bioassay, as exemplified by the study of Llanos, Arango, and Giraldo (2008), in which insects are fed grains treated with plant extracts, and mortality is observed at different time intervals. This type of assay allows the evaluation of toxic and sublethal effects of the compounds on the insect life cycle, serving as a crucial step in the development of natural bioinsecticides.

According to National Health Surveillance Agency (Anvisa, 2020), the toxicological regulation of biological products, such as bioinsecticides, in Brazil is now governed by specific guidelines outlined in Technical Notes 10/2020 and 11/2020. Technical Note 10/2020 addresses the toxicological classification of biological products concerning acute toxicity, while Technical Note 11/2020 provides guidance for the development of labels and package inserts, considering the characteristics of these products.

According to the Anvisa, the toxicological evaluation of biological products can be conducted through the submission of a complete toxicological dossier or, when the product complies with previously approved Reference Specifications (RS), this requirement can be waived, thereby streamlining the regulatory process (Anvisa, 2020).

Thus, the development of natural bioinsecticides requires an integrated approach across fields such as phytochemistry, entomology, agronomy, and formulation technology. Progress in this area may provide safer, more environmentally friendly, and effective alternatives for agricultural pest control, contributing to more resilient and sustainable production systems.

NATURAL BIOHERBICIDES

Natural bioherbicides are products used to control weeds, differing from synthetic herbicides by being derived from living organisms, such as plants, fungi, or bacteria. In many plant species, the natural herbicidal effect is linked to the release of secondary metabolites, which are substances produced by the plant that are not directly related to its growth but can influence the development of surrounding plants (Mousavi *et al.*, 2021).

Natural substances capable of inhibiting weed growth have garnered significant scientific interest, particularly in the search for more sustainable alternatives to synthetic herbicides. Therefore, these compounds are being studied as a foundation for the development of new natural herbicides, as they are often considered less harmful to the environment and exhibit good biodegradability (Lima *et al.*, 2018).

For many years, weed control was carried out through practices such as soil solarization, manual removal, crop rotation, planting delay, as well as the use of traps and soil amendments. Although these strategies provide some level of control, they are often insufficient in the face of the increasing resistance of weeds, especially after more than 50 years of intensive herbicide use (Masi *et al.*, 2020).

The problem is exacerbated by the excessive and often inappropriate use of chemical pesticides, which not only contaminate food and the environment but also pose serious risks to human and animal health (Ahmad *et.,* 2024; Scorza *et.*, 2023). Studies show that prolonged exposure to pesticides has been linked to millions of deaths worldwide (Masi *et al.*, 2020), revealing a profound impact that extends far beyond the field.

DEVELOPMENT OF NATURAL BIOHERBICIDES

Recently, allelopathy has become one of the ecologically sound approaches for the development of bioherbicides, regarded as a safe alternative method. It influences the growth of weeds, which are considered one of the most significant agricultural pests, negatively affecting crops and, consequently, the quality of the fruits (Mona Adel, 2019).

The effects of allelopathy occur when one plant interferes with the growth of another, caused by chemical substances known as allelochemicals. These compounds are not part of the plant's basic functions, such as growth or reproduction, but are produced through a process known as secondary metabolism. According to Lima *et al.* (2018), it is in this metabolism that plants produce a variety of compounds with important ecological functions, such as defense against pests, attraction of pollinators, and, in this case, influencing other plants around them.

The Brassicaceae family, for example, which includes plants such as broccoli and cabbage, is known for producing large amounts of glucosinolates. These natural substances help protect against pests and diseases. When these plants are damaged, such as by cutting or insect feeding, glucosinolates come into contact with an enzyme called myrosinase, leading to the formation of compounds such as isothiocyanates, nitriles, and thiocyanates, which have strong toxic effects on other plants. As a result, several species from this family can inhibit the growth and germination of neighboring plants, demonstrating an interesting allelopathic effect.

This phenomenon can be intelligently applied in agriculture as a natural alternative to the use of chemical herbicides. In this way, it is possible to control weeds more sustainably, helping to maintain the balance of the agricultural ecosystem. The research by Salisbury *et al.* (2018) supports this idea, showing that glucosinolates and their derivatives are directly linked to the ability to suppress the development of other plant species.

MODELING APPLIED TO BIOPESTICIDES

Computational modeling has gained prominence in the research and development of natural biopesticides, especially bioinsecticides and bioherbicides derived from plant extracts. This approach aims to predict biological properties, environmental behavior, and the efficiency of formulations (Rodrigues *et al.*, 2021; Zhang *et al.*, 2022). Among the main techniques are molecular docking, molecular dynamics studies, and QSAR (Quantitative Structure-Activity Relationship), which allow the prediction of interactions and activities before laboratory testing, thus reducing costs and research time (Rodrigues et al., 2021; Zhang *et al.*, 2022; Menezes *et al.*, 2024).

Molecular Docking

It is a computational technique used to predict how two molecules, typically a ligand and a protein (receptor), interact with each other. The goal is to determine the preferred position and orientation of the ligand within the protein's active site, simulating their fit. This approach helps to understand the affinity and specificity of the binding (Morris *et al.*, 2009).

Molecular dynamics

Molecular dynamics is a computational method based on the principles of Classical Mechanics, used to simulate the movement of atoms and molecules over time. This technique provides information about the dynamic behavior of molecular systems at the atomic scale, allowing the study of the structural evolution of molecules and intermolecular interactions at the nanometric scale (Namba *et al.*, 2008; Brooks *et al.*, 2024).

QSAR (Quantitative Structure-Activity Relationship)

It is a computational technique that establishes quantitative relationships between the chemical and structural properties of molecules (descriptors) and their biological or physicochemical activity. These models allow the prediction of the behavior of untested compounds, optimizing the development of drugs and agrochemicals, such as biopesticides. The methodology has evolved from 2D linear models to more advanced approaches (3D to 7D), incorporating aspects such as molecular dynamics, solvation, and machine learning algorithms (Menezes, 2024).

APPLICATIONS OF MODELING IN BIOPESTICIDE RESEARCH

In the context of biopesticide research, computational modeling has been crucial for the screening and optimization of bioactive compounds. Molecular docking is widely used to predict the binding affinity between candidate molecules and their biological targets, elucidating potential mechanisms of action and providing structural foundations for the optimization and enhancement of the molecules (Morris *et al.*, 2009). Additionally, molecular dynamics simulations are applied to assess the stability and durability of interactions in dynamic environments. This approach enables a detailed evaluation of the structural variations and intermolecular interactions that occur over time (Karplus and McCammon, 2002; Brooks *et al.*, 2024; Slathia *et al.*, 2025).

The QSAR technique helps correlate quantitative molecular descriptors with observed biological activity, contributing to the selection of the most promising compounds to be subjected to experimental testing (Todeschini and Consonni, 2009).

Recent studies reinforce the effectiveness of these approaches. Daoui *et al.* (2022) used 3D-QSAR (CoMFA and CoMSIA), ADME-Tox analysis, and molecular docking to evaluate 27 semisynthesized triterpene derivatives from *Euphorbia*. The 3D-QSAR models showed good statistical results, enabling the design of 38 new molecules, four of which were selected as promising based on their properties and stable interactions with target proteins (MurE and EcR) through docking. The integrated methodology facilitated the rational identification of new biopesticides with antibacterial and insecticidal potential.

The study by Mangat *et al*. (2022) conducted a virtual screening of 98,072 natural compounds to identify inhibitors of the ecdysone receptor (BtEcR) in the whitefly (*Bemisia tabaci*). Molecular dynamics simulations of 50 ns were performed with the two most promising candidates, followed by the estimation of the binding free energy using the g_mmpbsa method, which confirmed their stability and reinforced their potential as insecticides. The integrated methodology enabled the rational selection of promising compounds for the environmental control of the pest.

Silva *et al*. (2024) applied bioinformatics tools in the analysis of 23 Bowman-Birk inhibitor (BBI) sequences in species from the *Phaseoleae* tribe, conducting physicochemical studies, phylogenetic analysis, three-dimensional modeling, and molecular docking simulations. The study allowed for the identification of conserved domains and interaction residues with insecticidal potential, highlighting the use of computational modeling in the screening of bioactive proteins for the development of natural biopesticides.

These examples highlight how integrated computational approaches have been effective in the screening and optimization of bioactive compounds with insecticidal potential. Rigorous validation through statistical metrics and realistic simulations strengthens the reliability of predictive models. Furthermore, the increasing incorporation of machine learning algorithms has enhanced the ability to predict environmental and toxicological properties, reinforcing the development of more effective, selective, and environmentally safe biopesticides.

CONCLUSIONS

In this context, natural bioinsecticides emerge as an efficient and sustainable solution, integrating different scientific fields for the development of products that are selective and less harmful to the environment. Although challenges such as product standardization and associated costs remain, research advancements point to a promising future in replacing traditional chemical pesticides with natural alternatives, promoting a more sustainable and balanced agriculture.

Based on the studies presented, it is evident that the use of natural bioherbicides, particularly those derived from allelopathic compounds such as glucosinolates found in the Brassicaceae family, represents a promising and ecologically viable alternative for weed management. In addition to reducing environmental impacts and health risks associated with synthetic herbicides, this strategy contributes to more sustainable agriculture, integrating ecological knowledge with efficient and safe agricultural practices.

Computational modeling, in turn, plays a strategic role in the rational development of biopesticides, enabling the virtual screening of bioactive compounds, the prediction of molecular interactions, and the estimation of pharmacokinetic and toxicological properties. Techniques such as molecular docking, molecular dynamics, and QSAR significantly contribute to optimizing the process of discovering new bio inputs, reducing the number of experimental assays, and accelerating technological innovation. In this regard, the integration of biotechnology and computational methods represents a promising approach for advancing sustainable solutions in agricultural crop protection and environmental conservation.

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