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Review Article

Integrating CRISPR-driven pheromones and RNAi production – Possible "savior" for the management of *Nilaparvata lugens* in rice paddy fields

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Abstract - The brown planthopper (*Nilaparvata lugens*) is a serious pest affecting rice production worldwide, causing economic losses and challenges to food security. Traditional and conventional approaches relied on synthetic insecticides, which have led to increased pest resistance and environmental concerns, highlighting the need for sustainable alternatives. A comprehensive management strategy for *N. lugens* that effectively integrates pheromone-targeted approaches and RNA interference (RNAi) has not yet been reported. This review discussed innovative strategies integrating pheromone-targeted and RNAi-induced biopesticides, enhanced by CRISPR technology. Pheromones, particularly sex pheromones, can disrupt mating behaviours, offering a non-toxic alternative to reduce pest populations sustainably. RNAi biopesticides offer a targeted approach by silencing essential genes related to the pest's survival and reproduction, minimizing off-target effects and environmental impacts, presenting a precision-based alternative to conventional pesticides. Additionally, CRISPR technology enhances these strategies by enabling the synthesis of pheromones independent of the insect host and facilitating the delivery of RNAi constructs, potentially leading to the pest-resistant rice varieties. Ultimately, a thorough understanding of the biological and ecological aspects of *N. lugens* is crucial for evaluating current research on pheromone and RNAi applications within integrated pest management (IPM) frameworks. The challenges and opportunities presented by these innovative approaches necessitate interdisciplinary research to optimize their effectiveness while addressing regulatory and public acceptance concerns. These insights can significantly advance agricultural practices and enhance food security amid rising pest pressures, ultimately ensuring both food security and environmental sustainability.

Keywords: *Nilaparvata lugens*, pheromone-targeted management, RNA interference (RNAi) biopesticides, CRISPR technology, integrated pest management (IPM)

1. Introduction

Rice (*Oryza sativa*) is a vital staple crop for over half of the world's population, cultivated extensively across various regions, in Asia, Sub-Saharan Africa, and South America, amongst the largest consumers (USDA, 2023). It is reported that more than 800 insect species live in rice ecosystems, which around 100 species are recognized as pest causing considerable damage (Oo et al., 2020). In rice agroecosystem, insect groups can be categorized based on their functional diversity into three main categories: insect pests, natural enemies, and neutral insects, such as pollinators (Isnawan & Ramadhanti, 2021). Major pests include armyworms, rice bugs, black bugs, cutworms, field crickets, grasshoppers, leafhoppers, mealybugs and planthopper. These pests collectively pose significant threats to agricultural productivity by causing direct damage to crops, reducing yields, and increasing the need for costly pest management interventions (Ane, 2016). Moreover, the practice of applying high rates of nitrogen fertilizer to boost rice production can inadvertently intensify pest outbreaks. This occurs because enhanced nutritional quality improves pests' longevity, fecundity, and growth rates while simultaneously weakening the plants' defenses against these pests (Horgan et al., 2021; Li et al., 2021). Uncontrolled pest infestation significantly affects rice production and yield losses. Research indicates that diseases like sheath blight, brown spot, and leaf blast can cause regional yield losses between 1% and 10%. The brown planthopper (*Nilaparvata lugens*), yellow stem borer (*Scirpophaga incertulas),* and leaf folder (*Cnaphalocrocis medinalis*), which collectively contribute to substantial yield losses, estimated at 31.5%, i.e., only in Asia. Among insect pests, stem borers are especially concerning, as they can lead to white heads and result in an estimated yield loss of about 2.3%. When accounting for the overall impact of various pests, the combined mean yield loss is approximately 37.2% at a regional attainable yield of 5.5 tonnes per hectare, with potential losses varying from 24% to 41% depending on specific conditions (Savary et al., 2000). Furthermore, it is reported that diseases account for about 10% of annual rice production losses, translating to approximately 2.5 million tonnes, underscoring the critical impact of pest management on food security (Prakash et al., 2014). However, despite the concern of popular stem borer, the *N. lugens* is also one of the most destructive, causing extensive damage to rice crops globally.

1.1 Geographical distribution of *N. lugens*

N. lugens live in many parts of the world where rice is a staple food for millions of people (Bottrell et al., 2012). *N. lugens* was reported to be native or originated from Southeast Asia, where countries such as Thailand, Vietnam, Indonesia, and the Philippines report high populations, especially during the wet season when rice cultivation is at its peak. Prior to 1975, the insect primarily inhabited certain state in Southern Asia. However, in 1995, it had extended its presence to Odisha, West Bengal, and Assam, and by 2000, it further spread to Chhattisgarh, Bihar, Jharkhand, and Uttar Pradesh (Krishnaiah & Varma, 2011). Meanwhile India and Bangladesh face considerable threats, particularly in regions with climatic conditions conducive to its proliferation. The pest is also prevalent in East Asia, notably in China and Japan, where it can inflict severe damage to rice crops during outbreaks (IRRI, 1979). Furthermore, *N. lugens* has been reported in certain areas of Africa, particularly Madagascar, where rice cultivation is expanding. The pest's ability to thrive in diverse environments makes it a persistent challenge for rice farmers, necessitating effective management strategies to mitigate its impact on rice production. The geographical distribution of *N. lugens* is influenced by climate, availability of host plants, and agricultural practices. Warmer temperatures and high humidity levels favor the pest's development and reproduction, leading to increased populations during certain seasons. Research indicates that the potential overwintering areas for *N. lugens* are projected to expand poleward, particularly into mid-latitude regions, which could facilitate its establishment in new areas previously unsuitable for overwintering. This shift raises concerns about its impact on local rice production systems, as the planthopper is known to cause severe damage to rice crops during outbreaks. Furthermore, studies have documented an increase in the ecological suitability for *N. lugens* in regions such as Northern China, Korea, and Japan, suggesting that these areas may become new hotspots for planthopper populations in the future (Hong et al., 2024; Tyagi et al., 2022). The expansion of its range is closely linked to changes in climate conditions that allow for greater survival and reproduction rates in these temperate zones. In addition, in recent years, it has caused extensive damage in countries such as India, Indonesia, and the Philippines, with estimated losses exceeding US$300 million due to both direct feeding damage and the transmission of the grassy stunt disease. The *N. lugens's* ability to rapidly increase in population and its unpredictability in infestation patterns have made it a primary concern for rice farmers globally (Dyck & Thomas, 2023). Since the late 1990s, this pest has developed into a significant threat across all rice-growing regions, causing yield losses that can soar to 60% (Jena et al., 2018). This global spread highlights the adaptability of *N. lugens* to various climatic and agricultural conditions, underscoring the urgent need for effective pest management strategies.

1.2 Life cycle and morphological characteristics of *N. lugens*

The *N. lugens* life cycle consists of incomplete metamorphosis, which is three main stages: egg, nymph and adult (Figure 1A). During the egg stage, adult female *N. lugens* lay eggs on the leaves and stems of rice plants. The eggs are elongated and whitish in color. They are usually in rows or clusters, sticking to each other with a sticky substance produced by the female *N. lugens*. The egg incubation period lasts around 7 to 10 days, depending on the environmental conditions (faster at a temperature of 25-30°C). For the nymph stage, they go through five instars or developmental stages. At first, the nymph is wingless and pale yellow. When they change instar, they become darker and grow wings. The duration of the nymphal stage varies from 16 to 25 days. Finally, during the adult stage, upon reaching the fifth instar, the nymph transforms into an adult *N. lugens*. Within 4 to 6 days, adult is to be then able to reproduce again. Adult *N. lugens* has several distinct morphological features; elongated body measuring about 3 to 4 mm in length, slender body with brownish brown color, a pair of thin and transparent wings, the head of the insect has compound eyes; hind legs long and suitable for jumping, with visible veins; long antennae, which help in the senses and have a mouth to suck the rice plant called a stylet bundle (stylet bundle) (Figure 1B). It penetrates the rice phloem, eats the rice sap, and causes damage or death to the rice plant directly.

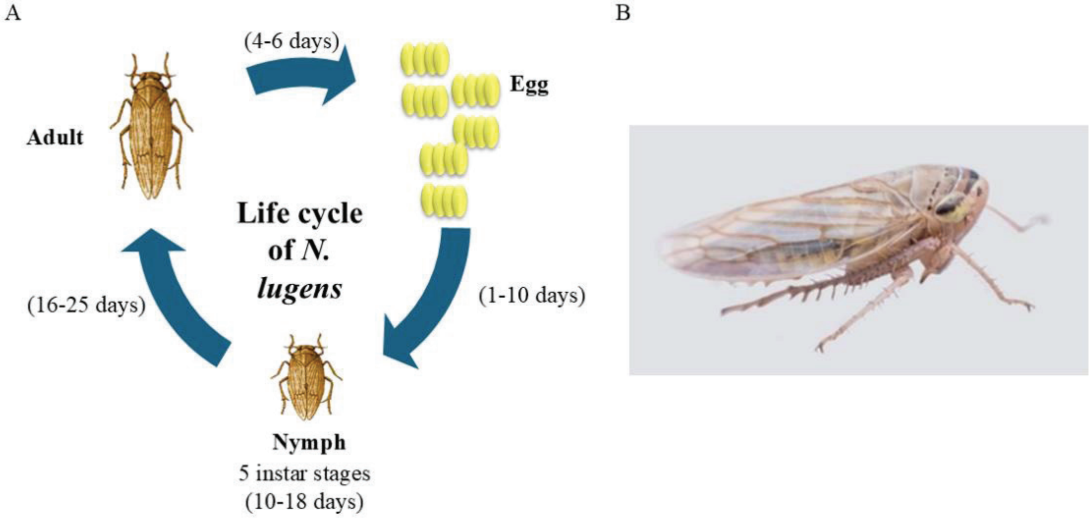

Figure 1. A) Life cycle of *N. lugens*, B) Morphology of adult *N. lugens*. (Syngenta, 2023).

Mating behaviour in *N. lugens* involves an acoustic signal called "swarming". Male *N. lugens* produce vibration calls or mating songs by rapidly vibrating their wings to attract the attention of female (Shi et al., 2021). The female responds to the call, and mating occurs on rice plants or even in flight (aerial mating). After mating, females lay their eggs on suitable surfaces of rice plants (EFSA Panel on Plant Health et al., 2023). *N. lugens* exhibits a strong preference for certain rice varieties as its primary host. They are particularly attracted to young rice plants and tender shoots because they contain phloem sap of rice plants with high levels of sucrose and low levels of silicon (He et al., 2015; Kikuta et al., 2015). Certain rice varieties show varying degrees of susceptibility or resistance to *N. lugens* attack. Genetic factors, such as the presence of specific *Bph* genes, mainly contribute to the resistance of certain rice types (Jena & Kim, 2010). These genes confer mechanisms like antibiosis and antixenosis, which prevent or lessen the impact of *N. lugens* infestation. For instance, a comparative study on multiple rice genotypes uncovered that the known resistant variety Ptb33 markedly reduced egg-laying rate, their survival, nymph number and inhibited the *N. lugens* population compared to the highly vulnerable TN1 variety (Wang et al., 2000).

1.3 Damage caused by *N. lugens*

As mentioned above *N. lugens* adult stages feed on rice plants by sucking sap or sap from the phloem, leading to the extraction of plant fluids, reducing plant nutrients, weakening and disrupting the immune system of rice plants (Zhu et al., 2020). This causes stunted growth and yellowing of leaves and ultimately reduces grain production and quality. Severe infestations can result in desiccation and death of rice plants, leading to significant yield losses. Severe infestations can cause a phenomenon called "hopperburn", a condition characterized by maximum wilting and drying (Figure 2). Yield loss varies depending on the intensity and duration of the attack, as well as the resistance level of the rice variety.

Figure 2. The phenomenon of "hopperburn" in rice fields due to the drying of rice plants infested with *N. lugens* (IRRI, 2023).

N. lugens also acts as a vector to spread plant viruses, including Rice Ragged Stunt Virus (RRSV) and Rice Grassy Stunt Virus (RGSV), which worsen rice growth and yield (Cabauatan et al., 2009). They employ specific mechanisms to enhance viral transmission through persistent-propagative mechanisms, primarily by invading the midgut epithelium, crossing the basal lamina into visceral muscles, and then spreading into the hemolymph. This leads to systemic viral spread, and interaction with salivary glands during feeding on rice plants (Na Phatthalung & Tangkananond, 2021). They acquire this virus from infected plants and spread it to healthy plants while feeding, exacerbating the damage caused by the insects. Plants infected with the virus show symptoms such as stunting, mosaic pattern, and yellowing, reducing grain quality, which leads to more severe yield loss (Kurniawati et al., 2023).

1.4 The need for an effective pest management strategy: Integrated pest management (IPM)

Integrated Pest Management (IPM) is a combined strategy that effectively controls pest populations while minimizing environmental impact and reducing reliance on chemical pesticides. It involves the integration of various strategies, including cultural, biological and chemical control methods, to achieve long-term pest reduction (Kogan, 1998). Figure 3 illustrates the stages of control when managing pest infestation in any global agricultural area.

Due to uncontrolled *N. lugens* infestation, traditional or cultural pest control methods have shown limited effectiveness in controlling *N. lugens* infestation, leading to significant yield loss. In addition, the use of synthetic pesticides with chemical control has resulted in resistance to *N. lugens* and has raised environmental concerns. The efficacy is likewise poor. Therefore, by integrating the biotechnology approach may pave a way to improve the IPM strategy in managing these pests (Alemu, 2020). In recent years, advances in biotechnology have opened new avenues for insect pest management. Genetic engineering and RNAi specifically offer targeted and specific pest control methods (Andrade & Hunter, 2016). This approach has the potential to disrupt the reproductive and physiological processes of *N. lugens*, reducing populations and

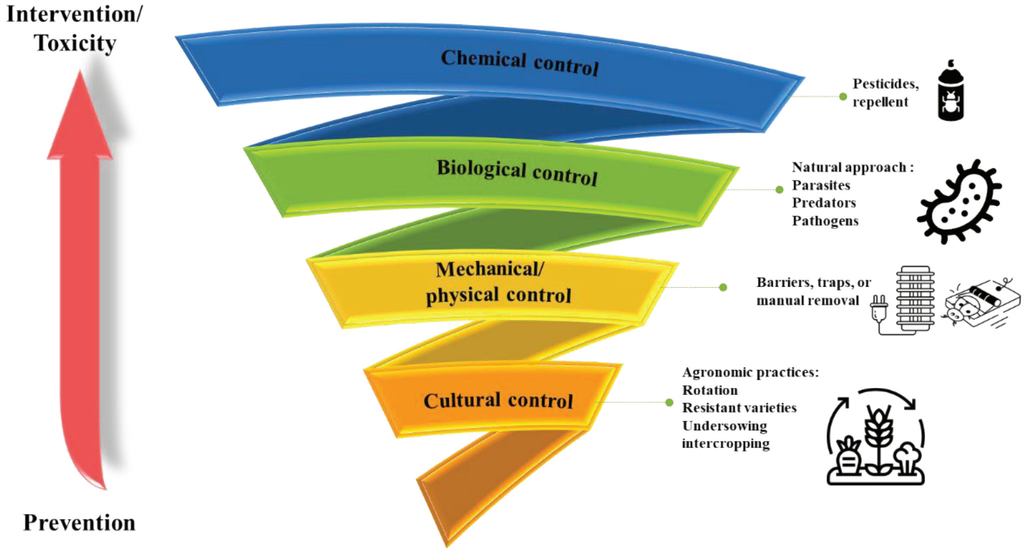

Figure 3. Integrated Pest Management (IPM); graphic guideline illustrating global agricultural practices that are often used worldwide.

minimizing crop damage. Based on the literature search, there does not appear to be any published paper that specifically combines pheromone-targeted approaches with RNAi strategies for managing *N. lugens*. While studies are exploring CRISPR/Cas9 and RNAi technologies independently in the context of pest management, and some discussing the use of pheromones, the integration of these methods into a cohesive strategy for controlling *N. lugens* has not yet been documented in the literature. Briefly, CRISPR technology, which stands for Clustered Regularly Interspaced Short Palindromic Repeats, has revolutionized genome editing, offering an accurate, efficient, and cost-effective method for modifying DNA sequences. This system, derived from the bacterial immune response against viruses, employs a guide RNA (gRNA) to direct the Cas9 enzyme to a specific DNA sequence, enabling targeted cuts or modifications (Makarova et al., 2011; Pickar-Oliver & Gersbach, 2019). CRISPR has diverse applications across various fields. In medicine, for instance, CRISPR-based treatments, which repair mutations to restore normal gene activity, are being explored for hereditary illnesses such as sickle cell anemia and hemophilia (Kansal, 2024). In agriculture, CRISPR has facilitated the development of drought-resistant crops and allergen-free foods by precisely altering plant genomes (Ahmad et al., 2023). Moreover, in biotechnology, it has been applied to engineer microorganisms for biofuel production and bioremediation (Hassanien et al., 2023). Thus, this review will comprehensively be discussed on the integration of these methods in management of *N. lugens* infestation.

2. Pheromone-targeted approach

Pheromone-targeted pest control has emerged as a promising approach in modern agriculture, offering a sustainable and eco-friendly alternative to conventional pesticides. Pheromone-targeted approaches in agriculture utilize insect pheromones to manage pest populations through methods such as mating disruption and mass trapping. Pheromones are chemicals released by insects to communicate with each other. They play an important role in attracting mates, marking territory, aggregation, host location and alarm signalling (Abd El-Ghany, 2020). One of the key advantages of this method is its specificity. Pheromones are species-specific, meaning they are recognized and responded to only by individuals of the same species (Sorensen & Baker, 2014). When exogenous pheromones are applied to crops, the insects become confused and are unable to locate one another to mate and reproduce (Figure 4). Because they are species-specific, biodegradable substances that don't destroy biodiversity or promote the emergence of resistance, pheromones are appealing. By utilizing synthetic versions of these pheromones, researchers and farmers can effectively disrupt the mating cycles of target pest species, leading to a decline in their populations without adversely affecting beneficial insects or the environment. Moreover, the use of pheromones in pest control reduces the reliance on conventional pesticides, which can leave chemical residues in agricultural products and the environment. By minimizing the use of these chemicals, pheromone-targeted approaches contribute to the production of safer, more sustainable agricultural products that are in high demand by consumers.

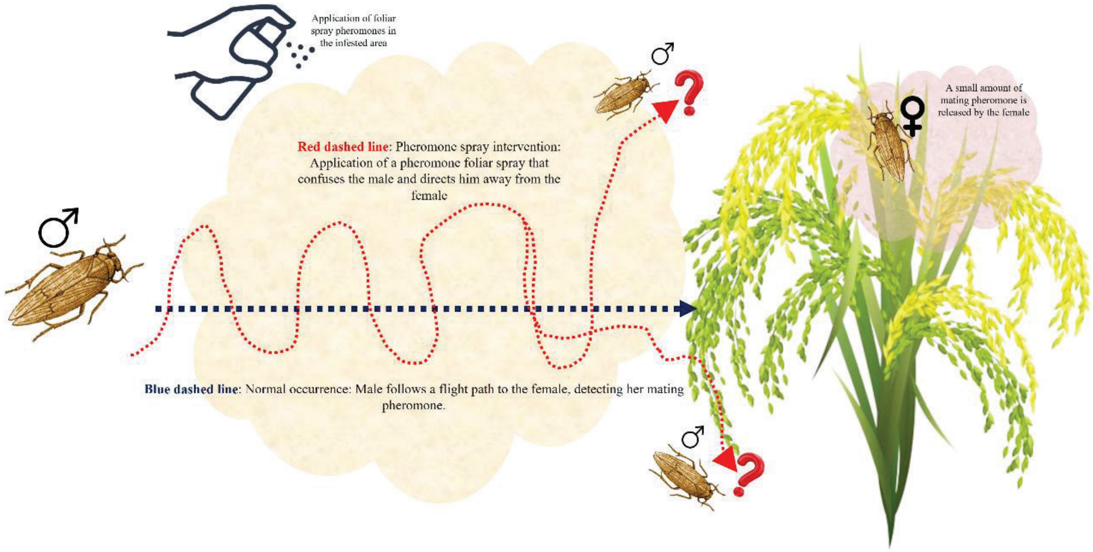

Figure 4. Exogenous pheromone application confuses males, misdirecting them away from female *N. lugens* for reproduction and leading to a reduction in population.

2.1 Application for *N. lugens* management

In the case of *N. lugens*, the female emits a special pheromone mixture to attract the male to mate. In pest management, by producing large quantities of pheromones, it becomes a tool to manipulate the behaviour of male *N. lugens*, disrupting their mating patterns and behavior, thus reducing their reproduction rate (Benelli et al., 2019; Witzgall et al., 2010). The use of pheromone traps or dispensers in the field aims to attract *N. lugens* from plants or attract them to certain areas as a control measure. To date, none of these approaches have been used against a reported *N. lugens* attack. This approach offers a targeted and environmentally friendly alternative to traditional insecticides, as it specifically targets *N. lugens* without harming other beneficial organisms. Additionally, plant traps and pheromone traps are non-toxic approaches that can be integrated into IPM programs to manage *N. lugens* infestation. Trap plants are attractive alternative host plants and can divert pests from the main rice crop, reducing the level of infestation (Sarkar et al., 2018). Pheromone traps, on the other hand, use synthetic sex pheromones to attract and trap male *N. lugens*, disrupting their reproductive cycle. These techniques have shown effective results in reducing pest populations and can be effectively integrated into IPM strategies.

2.2 Application of genetic engineering techniques using CRISPR technology for pheromone production

Traditionally, pheromones are extracted from natural sources, such as insects or plants, where availability and scalability are limited. Extraction methods often require large quantities of starting materials and require labour (Cortes Ortiz et al., 2016). These factors lead to challenges in meeting the demand for pheromones in pest management programs. Genetic engineering techniques including gene cloning, transformation, genome editing techniques (gene editing) such as CRISPR-Cas9 appear as promising platforms to produce pheromones on a larger scale (Wani et al., 2022). Yeast species such as *Saccharomyces cerevisiae* can be genetically modified to express biosynthetic genes responsible for pheromone production (Petkevicius et al., 2020; Williams et al., 2016). Yeast offers several advantages, such as the ease of genetic manipulation, ease of propagation, and the ability to produce complex molecules (Wagner & Alper, 2016). This leads to the production and secretion of pheromones into the surrounding environment (Figure 5).

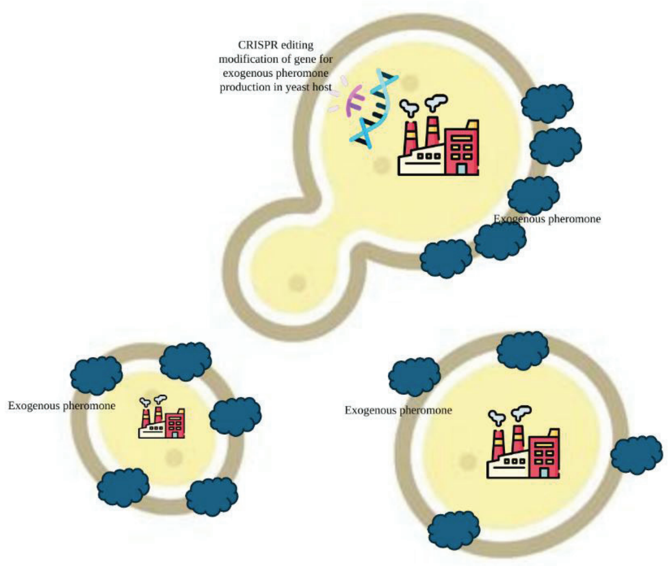

Figure 5. Exogenous pheromones production in yeast as a host using genetic engineering approaches.

Therefore, researchers can create production systems that produce consistent quality and purity, are controllable, cost-effective and can be easily manufactured to meet the demands for large-scale applications. Additionally, this approach reduces the need to extract pheromones directly from insects, which can be burdensome and disruptive to the environment. Researchers have successfully introduced the gene responsible for pheromone synthesis into yeast and demonstrated insect pheromone production (Table 1). These studies have focused on optimizing the production process, increasing yields, and evaluating the attractiveness and efficacy of engineered pheromones in yeast.

Table 1. Studies on pheromone production in engineered yeast.

Insect/ pest species	Pheromone biosynthesis pathway	Yeast host	Yield of pheromone produced	Reference(s)
Helicoverpa armigera	Z)-11-Hexadecenal (Z11–16: Ald) and (Z)-9-hexadecenal (Z9–16: Ald)	*Saccharomyces cerevisiae*	22.7 mg/L and 45.9 mg/L respectively	(Jiang et al., 2022)
Lepidoptera (*moth*)	fatty acyl-CoA desaturases and fatty acyl-CoA reductases	*Yarrowia lipolytica*	NS	(Petkevicius et al., 2022)
European corn borer (ECB), *Ostrinia nubilalis*	(Z)-11-tetradecenol (Z11-14: OH)	*Yarrowia lipolytica*	188.1 ± 13.4 mg/L	(Petkevicius et al., 2021)
Helicoverpa armigera	(Z)-hexadec-11-en-1-ol and (Z)-tetradec-9-en-1-ol,	*Yarrowia lipolytica*		(Holkenbrink et al., 2020)
Oriental fruit moth, *Grapholita molesta*	Desaturase (Gm-DES) and terminal reduction catalyzed by fatty acyl reductase (Gm-FAR)	*Saccharomyces cerevisiae*	NS	(Vatanparast & Kim, 2019)
Turnip moth, *Agrotis segetum*	Fatty-Acyl Desaturase and a Fatty-Acyl Reductase	*Saccharomyces cerevisiae*	NS	(Hagström et al., 2013)
Cabbage looper moth, *Trichoplusia ni*	Desaturation of coenzyme-A esters of saturated fatty acids	*Saccharomyces cerevisiae*	NS	(Knipple et al., 1998)

Note: *NS; not specified in the literature.

The use of yeast engineering for pheromone production offers several advantages, including scalability, cost-effectiveness, and the ability to produce pheromones with high purity and consistency. Genetic engineering techniques also allow modification of pheromone components to optimize their attractiveness and effectiveness in pest management strategies.

3. RNA interference (RNAi)-induced biopesticide

RNA interference (RNAi) is a biological process that controls gene expression by silencing certain genes (Leung & Whittaker, 2005). RNAi enables silencing of specific genes by introducing small RNA molecules, known as small interfering RNA (siRNA), which combine with complementary RNA molecules that bind to and degrade messenger RNA (mRNA) target genes thereby preventing the translation of target genes into functional proteins (Agrawal et al., 2003). RNAi offers promising biotechnological tools for targeting and disrupting the expression of specific genes in *N. lugens*. Various virulence genes have been identified in *N. lugens*, contributing to its ability to attack and damage rice plants (Ji et al., 2013; Xiao et al., 2015). These genes encode proteins involved in processes such as nutrition, detoxification, or immune evasion. By targeting important genes involved in insect survival or virulence, RNAi can inhibit important physiological processes such as molting, reproduction, immune response, thereby reducing insect and population survival and minimizing damage to crops. Several studies have shown success in identifying *N. lugens* virulence genes and using RNAi to control *N. lugens* in a laboratory setting (Rout et al., 2023; Wang et al., 2015). Such as 7,860 differently expressed genes, including those related to metabolism and immunology, were found in fat bodies from virulent and avirulent *N. lugens* populations using transcriptome analysis. These genes are essential for virulence adaptation to resistant rice types like Mudgo (*Bph1*) (Yu et al., 2014). Another study, involving RNAi targeting three *NICstF* genes implicated in molting and reproduction resulted in fatal phenotypes and decreased survival rates in *N. lugens* nymphs (Jing et al., 2024). Furthermore, *N. lugens's* genome-wide analysis of alternative gene-splicing revealed a total of 27,880 alternative splicing events corresponding to 9,787 multi-exon genes were detected that are key virulence-associated genes that may be inhibited by RNAi to hinder the pest's abilities to overcome rice resistance (Liu et al., 2021). These findings underscore the potential of RNAi-based strategies to target virulence mechanisms in *N. lugens*, paving the way for effective pest management solutions. While, CRISPR technology have shown effective findings in manipulating *N. lugens* genes for pest management (Table 2), Xue and colleagues, reported that they target the eye pigmentation genes (*NI-cn* and *NI-w*) led to noticeable phenotypic changes, demonstrating the precision of CRISPR-mediated mutagenesis (Xue et al., 2018). Furthermore, the CRISPR knockout of *NICYP6CS1* gene (a detoxifying gene of *N. lugens*) cause insecticide resistance to the pest (Zhang et al., 2023). Additionally, another study targeted the gustatory receptor gene (*NlugGr23a*), which caused male sterility by disrupting sperm development, offering a potential molecular target for genetic pest control (Zhang et al., 2023). These studies highlight CRISPR as complementary tools for managing pest populations while minimizing environmental impact.

Table 2. CRISPR applications in *N. lugens*.

Gene targeted	Function	Findings	References
NI-cn (Cinnabar) & *NI-w* (White)	Eye pigmentation	Germ-line mutations resulted in bright red compound eyes and ocelli, heritably transmitted to the G1 generation. Mosaic eyes with white and lightly pigmented ommatidia; mutant rate of up to 27.3%.	(Xue et al., 2018).
NlCYP6CS1	Cytochrome P450-mediated detoxification	Increased susceptibility to insecticides like imidacloprid, nitenpyram, and thiamethoxam by 2.3- to 7-fold; reduced survival and reproduction.	(Zhang et al., 2023)
NlugGr23a	Gustatory receptor (male fertility)	Knockout caused male sterility due to arrested sperm development prior to pronucleus formation, reducing female fertility after mating.	(Zhang et al., 2023).

Table 3 indicated the RNAi application for *N. lugens*. Using RNAi technology, scientist are able to silence essential genes like *NICPSF30,* which lead to impaired hormonal pathways in *N. lugens*, subsequently halting their growth and causing mortality (Jing et al., 2024). Next, RNAi targeting metamorphosis-related genes (*NIE93* and *NIKr-h1*) disrupted the balance between ecdysone and juvenile hormone signaling, preventing proper development (Li et al., 2018). On the other hand, the autophagy-related gene *NIATG3* was also targeted, significantly reducing survival and fecundity in *N. lugens* (Ye et al., 2021). Another study focused on the *NITOR* gene, which, when knocked down, reduced male fertility by impairing spermatogenesis (Zhuo et al., 2017). Therefore, the application of RNAi-based approaches in pest management has great potential for selective and environmentally friendly control of *N. lugens*. However, more research is needed to optimize delivery methods and ensure efficient management under field conditions.

Table 3. RNAi Applications in *N. lugens*.

Gene Targeted	Function	Findings	References
NICPSF30	mRNA processing	Severe developmental defects, disrupted molting, increased mortality, and hormonal regulation impairment.	(Jing et al., 2024)
NIE93 & *NIKr-h1*	Ecdysone signaling (metamorphosis) & juvenile hormone signaling	Prevented nymph-adult transition, causing supernumerary nymphal instars. Precocious formation of incomplete adult features; mutual repression with *NIE93*.	(Li et al., 2018)
NIATG3	Autophagy regulation	Inhibited survival and fecundity, significantly reducing the total number of eggs laid per female.	(Ye et al., 2021)
NITOR	Protein synthesis regulation	Reduced fertility in male *N. lugens* by impairing spermatogenesis and sperm quality.	(Zhuo et al., 2017)

4. Ethical and regulatory considerations

The integration of CRISPR-driven pheromones and RNAi production for managing *N. lugens* in rice paddy fields raises several ethical and regulatory considerations that must be addressed to ensure responsible implementation (Figure 6). One key ethical standpoint is the need for informed consent and transparency; stakeholders, including farmers and consumers, must be fully informed about the nature, potential risks and their intended effect and any possible unintended consequences associated with these biopesticides as it involves genetic modification approaches, such as CRISPR. This aligns with ethical standards emphasizing voluntary informed consent, which is crucial for maintaining public trust as well as their perception and ensuring ethical compliance in agricultural biotechnology (Lockwood, 2004). Additionally, the environmental impact of introducing genetically modified organisms (GMOs) into ecosystems is crucial to be assessed to prevent unintended consequences on non-target species including beneficial insects and other organisms within the ecosystem to ensure ecological balance (Caradus, 2022; Devos et al., 2016). Engaging with communities and stakeholders is essential to address public perception concerns regarding genetically engineered organisms and biopesticides, fostering transparency in research and development to build trust (Shams et al., 2024; Singh et al., 2024). Long-term ecological balance should be prioritized to avoid unintended consequences. Moreover, the implications for food security must be carefully considered; any new technology should enhance sustainable agricultural practices without compromising crop yields (Qaim, 2020). Transparency in food labelling is also essential, as consumers should be informed if products have been treated with biopesticides derived from genetic technologies (Fărcaș, 2024). Equity and accessibility are also critical ethical considerations, as there is a risk that advanced biotechnological solutions may be monopolized by large agribusinesses, exacerbating inequalities in agricultural productivity and resource access (Schurman & Munro, 2013). Policies should promote inclusivity and support for marginalized farming communities to ensure that smallholder farmers can benefit from these innovations (Diao et al., 2023). Furthermore, the welfare of any organisms affected using these biopesticides should be evaluated to minimize suffering. Ethical frameworks should guide these evaluations, prioritizing ecological integrity alongside agricultural productivity (Gjerris et al., 2023).

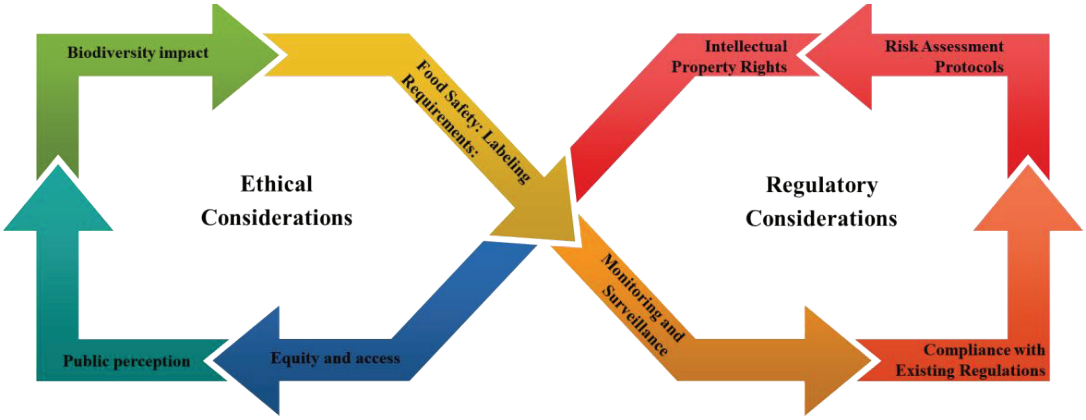

Figure 6. Proposed ethical and regulatory considerations for CRISPR-driven pheromone and RNAi biopesticides.

From the regulatory perspective, adherence to existing frameworks governing genetically modified organisms (GMOs) and biopesticides is vital, as regulations vary by country due to normally existing frameworks often treat biopesticides similarly to conventional pesticides, which can hinder the approval process for innovative solutions like CRISPR-driven pheromones and RNAi. Regulatory bodies, such as the EPA in the United States, need to adapt their guidelines to account for the unique characteristics of biopesticides, including their mode of action and environmental impact. This adaptation may involve establishing specific data requirements for registration, including assessments of potential off-target effects and long-term ecological consequences (NASEM, 2016). Thorough risk assessments must be conducted to evaluate potential environmental and health impacts, including studies on the stability and persistence of pheromones and RNAi in the environment. The registration of biopesticides typically requires extensive data on efficacy, safety, and environmental impact. Establishing protocols for monitoring the effects of these biopesticides on both target and non-target species post-release is necessary, along with reporting mechanisms for any adverse effects that may arise during agricultural practices (Arora et al., 2016; Greaves, 2009). Intellectual property rights present another layer of complexity; addressing patent issues and ensuring fair use of genetic technologies will be important to protect farmer rights and access to these biopesticides (Hashimy & Benjamin, 2024). Finally, aligning with international frameworks, international harmonization of regulations is essential given the global nature of agricultural markets. Collaboration between countries to share data and best practices can facilitate faster approval processes and broader acceptance of innovative pest management strategies (Handford et al., 2015; Yeung et al., 2017). Finally, robust monitoring and post-market surveillance systems are necessary to track the effectiveness of biopesticides and any adverse effects on non-target organisms and ecosystems once they are in use (EFSA Panel on Genetically Modified Organisms et al., 2020). Regulatory agencies must implement these systems to ensure compliance with safety standards and to address any emerging issues promptly. Overall, addressing these ethical and regulatory considerations is crucial for the responsible deployment of innovative biopesticide strategies in agriculture that prioritizes environmental sustainability, food security, and social equity will be essential for the successful implementation of these innovative strategies.

5. Integrated pest management (IPM) strategies: Combining pheromone, RNAi, and CRISPR approaches

The ongoing threat posed by *N. lugens* requires the development and implementation of effective pest management strategies. An integrated strategy that combines pheromone lures, RNAi biopesticides, and CRISPR technology could provide a comprehensive solution to managing *N. lugens* (Figure 7). By integrating exogenous pheromones into trap forms, this mechanical or physical prevention approach can effectively monitor and reduce pest numbers. However, despite its advantages, the pheromone-targeted method is not a standalone solution for pest control. In the event of a damaging infestation, chemical control measures, such as the application of pheromone sprays or RNAi biopesticides, are necessary to provide immediate relief from high pest populations (Kourti et al., 2017; Kumari et al., 2023). By combining these methods, farmers can achieve a more comprehensive and sustainable approach to pest management.

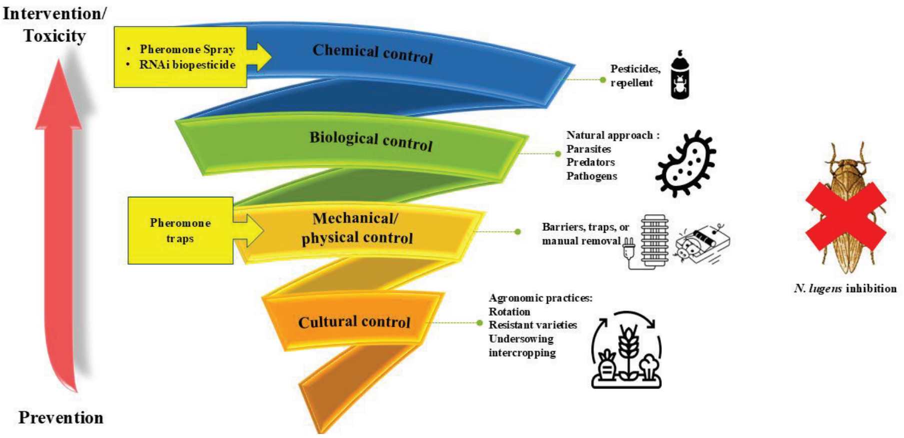

Figure 7. Understanding integration of pheromones and RNAi biopesticides against *N. lugens* infestation in paddy field crop.

6. Limitations, challenges and future directions

As research and technology continue to advance, the potential of pheromone-based pest control is expected to grow, contributing to the development of more sustainable and environmentally responsible agricultural practices. Despite the potential for *N. lugens* pheromone production using yeast engineering, several challenges need to be addressed. One of the challenges is to identify and optimize the genes involved in pheromone synthesis to ensure biologically active pheromone production. Factors such as gene expression levels, metabolic flux and precursor availability need to be optimized to maximize pheromone production (Löfstedt & Xia, 2021; Min et al., 2017). Balancing the expression of various genes involved in the pheromone biosynthesis pathway is important to ensure efficient production. Furthermore, introducing genes and foreign substances into yeast can affect its physiology. Expression of pheromone biosynthesis genes can alter cellular resources, leading to changes in yeast growth, metabolism, or stress response. Ensuring that engineered yeast strains remain stable throughout prolonged fermentation is essential for scaled-up pheromone production (Ferreira et al., 2024; Rizvi et al., 2021). Other challenges are to achieve high pheromone production yields to meet the demand for large-scale pest management applications, improve the attractiveness of engineered pheromones, and optimize delivery methods for effective pest control. Additionally, the development of a cost-effective and sustainable development system will be essential for the commercialization and widespread use of engineered yeast-based pheromone production in *N. lugens* pest management (Veres et al., 2020). Future research directions for *N. lugens* pest management involve further elucidating the mechanisms of RNAi in *N. lugens*, improving the delivery system to increase target specificity and efficiency, and evaluating the long-term ecological effects of RNAi on non-target organisms and the environment (Li et al., 2025; Zarrabian & Sherif, 2024). Addressing these challenges will contribute to the development of sustainable and environmentally friendly strategies for *N. lugens* management.

7. Conclusion

The integration of pheromone-targeted strategies, RNAi biopesticides, and CRISPR technology presents a promising pathway for sustainable management of *N. lugens*. Continued research is essential to optimize these approaches and ensure their efficacy in real-world agricultural settings.

Artificial intelligent declaration

The authors utilized QuillBot (https://quillbot.com/) for paraphrasing and grammar checks in the preparation of this work. Subsequently, the author(s) conducted a thorough review and editing process, taking full responsibility for the content of the publication.

Human/animal ethics declaration

This research did not involve human participants or animal subjects. No ethical approvals were required as the study was conducted without any interaction with humans or animals. The authors take full responsibility for the content of this publication.

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