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Review

Targeting cell death processes for insect pest control: a promising but still underexploited strategy☆

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Cell death-related processes are fundamental to insect physiology, playing essential roles in development, immune response, and metamorphosis, thereby maintaining tissue and organism's homeostasis. Among the various cell death mechanisms, apoptosis is crucial for sculpting tissues, eliminating damaged or infected cells, and limiting pathogen replication. In parallel, autophagy serves as a self-recycling process that facilitates nutrient allocation, stress resilience, and remodeling of larval structures during development but, in specific contexts, can be associated with cell death. Beyond their physiological importance, apoptosis and autophagy have emerged as attractive targets for pest control. To this purpose, two strategies can be envisaged: i) inducing cell death in key tissues using natural or synthetic compounds to compromise insects' physiology and ii) manipulating apoptotic and autophagic signaling pathways through chemical or genetic tools, such as RNA interference (RNAi) or clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 systems, to impair development and immunity, thus reducing insect survival and fitness. Harnessing these cell death pathways offers promising new avenues for controlling insect pests and vector-borne diseases. However, further research is needed to improve the specificity, efficacy, and environmental safety of these approaches.

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Introduction

Cell death-related processes are fundamental biological mechanisms regulating insect growth and development, tissue homeostasis, and immunity [1]. In insects, apoptosis and autophagy are the predominant and best-characterized cell-death and recycling processes involved in metamorphosis, tissue remodeling, and responses to infection and stress [1]. Apoptosis is a caspase-directed cascade that ensures the selective removal of old, damaged, or infected cells, resulting in tissue remodeling and resistance to infections. In contrast, autophagy is a dynamic recycling process permitting metabolic adaptation and stress resistance by degradation and reuse of cellular constituents. Under certain conditions, autophagy can also act as a mediator of cell death (autophagy-dependent cell death) [1,2].

Recent evidence has highlighted the potential of apoptosis and autophagy as targets for the management of insect pests and disease vectors. These mechanisms represent attractive targets because (i) they are essential for insect development and immunity, and thus crucial for survival, (ii) molecules capable of modulating these processes are known and available, and (iii) potential targets whose expression can be altered using specific molecular tools have already been identified. In this setting, synthetic or natural molecules that interfere with

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these cellular pathways have been proposed as possible control agents [3,4]. Moreover, breakthroughs in molecular entomology and functional genomics may provide opportunities to develop selective and targeted strategies for insect pest control using RNA interference (RNAi) and CRISPR-based gene editing to perturb apoptosis and autophagy [5–7].

This review explores the role of apoptosis and autophagy in insect physiological processes, their intricate regulatory mechanisms, and the exploitation of this knowledge to develop effective strategies for controlling insect pests. In particular, it synthesizes recent advances in harnessing these pathways as precision-tailored tools for insect control and weighs broader ecological and evolutionary implications. It also outlines key research priorities and future directions to translate these approaches into sustainable, high-precision pest control tools for agriculture and public health.

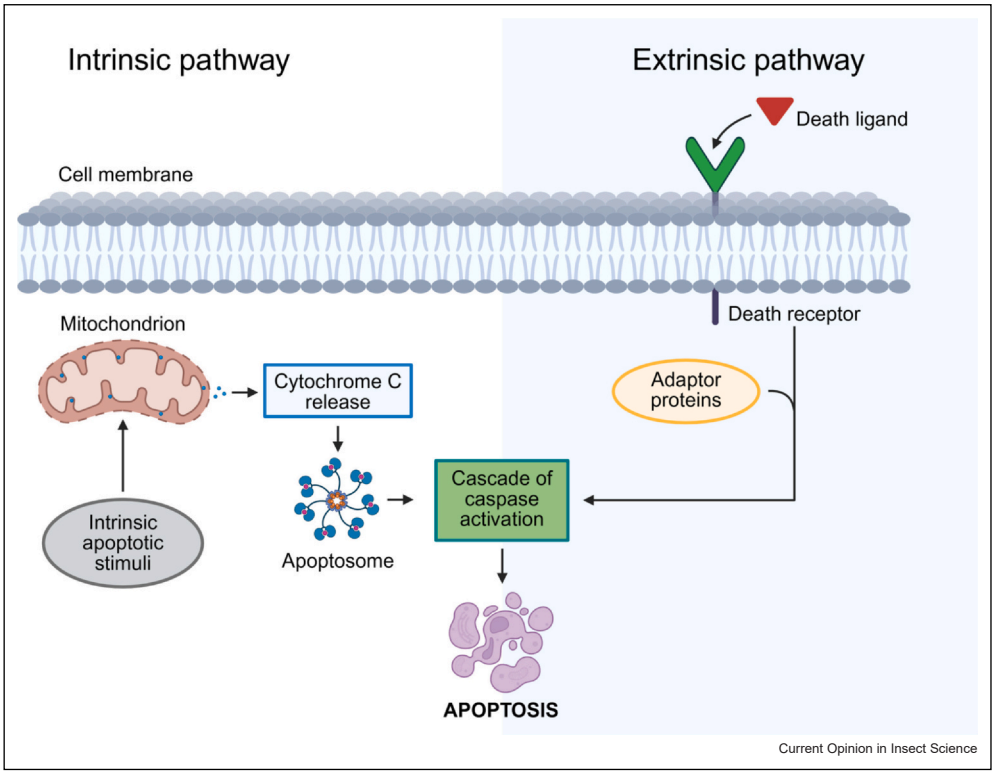
Cell death processes in insects: biological roles and regulatory pathways

Cell death in insects encompasses tightly regulated processes that determine cell fate in development, immunity, and stress adaptation [1,2]. Apoptosis is involved in developmental transitions and is essential during metamorphosis to eliminate or remodel larval tissues and organs [1]. For instance, apoptosis configures the nervous system in the fruit fly *Drosophila melanogaster*, establishing synaptic relationships, while apoptosis of larval muscles, midgut cells, and silk glands allows body reshaping in the silkworm *Bombyx mori* during development [1]. It also plays a key role in immune defense by eliminating pathogen-infected cells [2]. On the other hand, although autophagy contributes to organ remodeling during metamorphosis [1], it is also involved in insect survival, especially under stress conditions. For example, autophagy is induced by starvation in the fat body of the kissing bug *Rhodnius prolixus*, thus permitting the recycling of stored lipids and proteins, and maintaining energy homeostasis [8]. This mechanism also confers resistance against bacterial and viral infection, as demonstrated in *D. melanogaster*, where the activation of autophagy regulatory genes suppresses bacterial growth [2,9]. In addition, apoptosis and autophagy act in a coordinated manner influencing cell fate decisions [10–13]. For example, prolonged autophagy has the ability to suppress the apoptotic cascade in *D. melanogaster* hemocytes, while apoptosis-resistant cells preferentially upregulate autophagy [10,13]. This evidence suggests that autophagy in specific cells and conditions can counteract apoptosis and highlights a feedback loop between these two processes. Such bidirectional regulation is not exclusive to immunity, but it is also seen in other contexts like reproduction, where autophagy and apoptosis ensure proper gametogenesis [14].

Apoptosis and autophagy are controlled by conserved, yet plastic, molecular networks [15]. While fundamental components of apoptosis are generally shared among animals, their regulation and execution can vary significantly across insect orders due to evolutionary divergence and ecological adaptations, with gene duplications and pseudogenization contributing to shape the apoptotic repertoires. In *D. melanogaster*, apoptosis is mediated by a well-characterized intrinsic pathway, as in other metazoans (Figure 1). The main components of the apoptotic pathway in *D. melanogaster* are outlined in Figure 2 [11]. In relation to evolutionary divergence and diversification of apoptotic profiles across insect taxa, mosquitoes show expanded caspase gene families [11]. These duplications may represent lineage-specific adaptations, but their precise roles remain unclear. Lepidoptera retain a conserved apoptotic core similar to *D. melanogaster*, but differ in regulation. In fact, unlike *D. melanogaster*, cytochrome c release is essential for caspase activation. Additionally, *Bm*IAP1 (*B. mori* inhibitor of apoptosis 1) inhibits the initiator caspase but not effector caspases, indicating mechanistic divergence [16,17]. The pea aphid *Acyrthosiphon pisum* exhibits unique caspase duplications, such as two Dronc paralogs with distinct motifs and possible functional divergence, and expanded inhibitor of apoptosis protein (IAP) families. Similar IAP expansions and novel domain combinations have been found across all aphid genomes, suggesting lineage-specific apoptotic regulation [11,18]. The whole scenario in insects is further complicated by the increasingly recognized nonapoptotic roles of insect caspases; for example, Dronc is involved in neuroblast regulation in *D. melanogaster*, Dredd contributes to innate immunity through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, mediating antimicrobial peptide expression, and similar immune-related functions have been observed in other insects, such as the yellow fever mosquito *Aedes aegypti* and the red flour beetle *Tribolium castaneum* [12].

Autophagy is an ancient cellular degradation process, likely originated during eukaryogenesis [15]. It involves autophagosome formation on the endoplasmic reticulum, followed by fusion with lysosomes. This process is coordinated by a core set of about 20 Atg (autophagy-related) proteins grouped into functional complexes. These genes are widely conserved in eukaryotes, while components involved in selective autophagy (i.e. a specific type of autophagy, mediated by specialized receptors and adaptor proteins, that targets and degrades specific cargos within the cell) show more species-specific distribution [13,19]. In species such as *D. melanogaster* and *B. mori*, autophagy is regulated transcriptionally and post-translationally by 20-hydroxyecdysone (20E) and by nutrient supply, highlighting the close link among autophagy, development, and nutritional status of the insect [1,13] (Figure 3).

Figure 1



Schematic overview of intrinsic and extrinsic apoptotic pathways. Left (Intrinsic pathway): Intracellular apoptotic stimuli (e.g. DNA damage, oxidative stress) induce mitochondrial outer membrane permeabilization, resulting in cytochrome c release into the cytosol. Cytochrome c triggers the assembly and activation of the apoptosome and initiator caspases, which in turn activate effector caspases, leading to apoptosis. Right (extrinsic pathway): External death ligands bind to cell surface transmembrane death receptors, leading to the recruitment of adaptor proteins. This event triggers the same caspase cascade as the intrinsic pathway, driving apoptotic cell death.

A key aspect that deserves great attention in this context is the group of proteins indicated as potential molecular links between autophagy and apoptosis. In fact, as highlighted above, these two pathways frequently interact, with overlapping regulators such as Atg5, p62, p53, and members of the Bcl-2 family, influencing the outcome toward survival or death. In particular, the cleavage of Atg5 appears crucial to promote the switch from autophagy to apoptosis in the midgut of the cotton bollworm *Helicoverpa armigera* [20]. In addition, new evidence in the tobacco whitefly *Bemisia tabaci* suggests that factors like phosphatidylethanolamine-binding protein (PEBP) control this balance between apoptosis and autophagy in arboviral infections to limit virus persistence, making PEBP a potential candidate for applications in future pest management practices [11,21]. This evidence, together with other findings discussed in the next section, indicates that the dissection of molecular mechanisms underlying apoptosis and autophagy in insects may help identify potential targets for pest control.

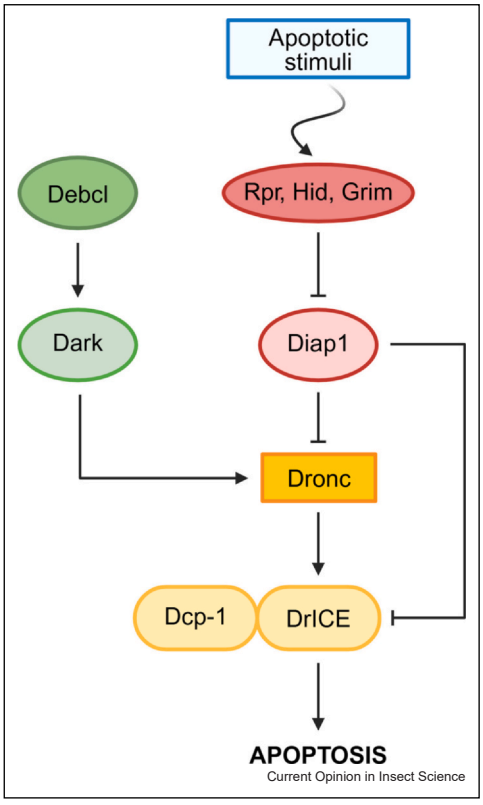
Targeting cell death pathways for pest control

Targeting and/or manipulating apoptotic and autophagic pathways in insects with selected control agents and molecular tools holds promise for the development of innovative pest control strategies.

Botanical compounds

Botanical insecticides represent a class of environmentally sustainable pest control agents that act through diverse biochemical and cellular mechanisms. Among them, azadirachtin, pyrethrins, and curcumin have been shown to induce cell death—mainly apoptosis and autophagy—in insects [4]. Most available data derive from studies on dipteran and lepidopteran cell lines, although *in vivo* evidence, particularly with azadirachtin, supports its capacity to disrupt midgut tissue structure and function in the tobacco cutworm *Spodoptera litura*, impairing digestion and larval development [22]. Mechanistic studies indicate that azadirachtin triggers both intrinsic (mitochondrial) and extrinsic apoptotic pathways and may also induce autophagic cell death [23]. Notably, this effect involves the

Figure 2



Intrinsic apoptotic pathway in *D. melanogaster*. Activation of apoptosis begins with the assembly of the apoptosome via the adaptor protein Dark, which recruits and activates the initiator caspase Dronc. Activated Dronc then activates the effector caspases (DrICE and Dcp-1), culminating in cell death. While Bcl-2-like proteins (Debcl) play a limited role in this species, IAPs, particularly DIAP1, are key negative regulators, counteracted by Reaper, Hid, and Grim. Notably, *D. melanogaster* lacks a clear extrinsic apoptotic pathway, and cytochrome c is not required for apoptosome formation—unlike in mammals and other insect groups.

suppression of phosphoinositide 3-kinase/protein kinase B/target of rapamycin (PI3K/AKT/TOR) survival signaling and cleavage of Atg5, a molecular event that could facilitate the transition from autophagy to apoptosis under cellular stress [24]. While these findings highlight the potential of botanical compounds to induce cell death in insects, further research integrating transcriptomic, proteomic, and functional analyses is needed to clarify their mode of action and improve their selectivity and efficacy in pest control strategies.

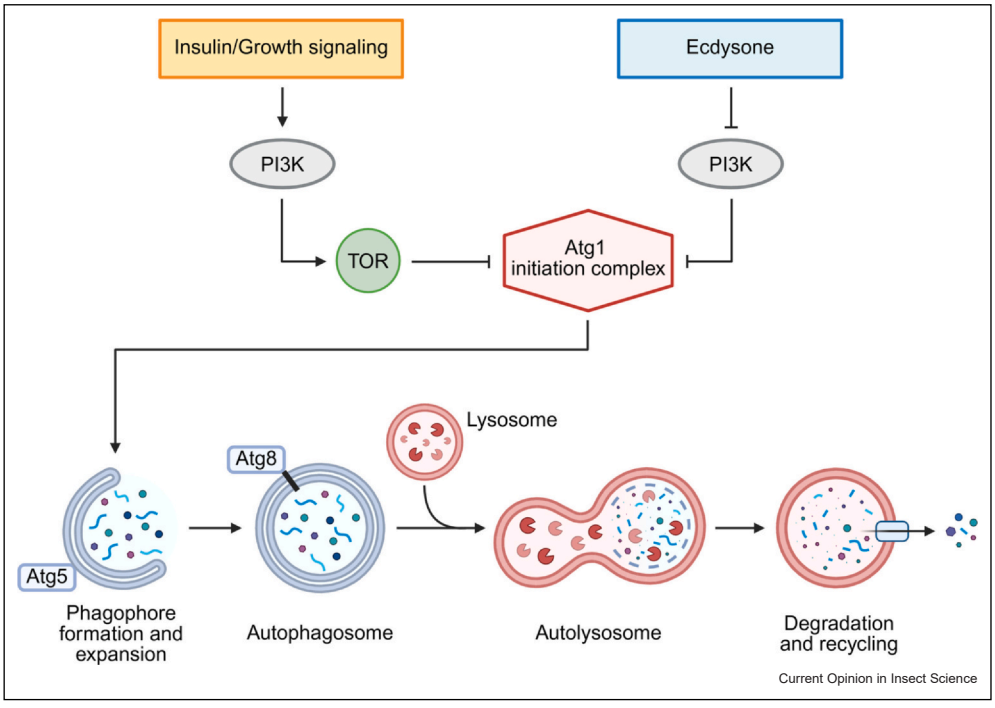
Revisiting *Bacillus thuringiensis* mode of action: cell death beyond lysis

The entomopathogen *B. thuringiensis* (*Bt*) produces insecticidal proteins that are used both as spray formulations and by expressing them in genetically modified crops, offering a targeted approach to pest control that is considered safe for humans and nontarget organisms [25]. Cry proteins—produced during the sporulation phase of the bacterial life cycle—are the most studied *Bt* toxins. They bind to specific receptors in the apical membrane of midgut cells and form pores that lead to cell lysis, disruption of gut integrity, transit of gut-resident bacteria into the hemolymph, and ultimately insect death by septicemia [26]. However, a few studies showed that the death effect triggered by these toxins is more complex and may involve the induction of cell death processes as well. The first study on this topic dates back to 2006 [27]. Using a cultured cell line, the authors showed that the binding of Cry1Ab toxin to the cadherin receptor induces cell death, suggesting an alternative *Bt* mode of action, independent of binding to other receptors and pore formation. More recently, Cry1Ac has been reported to induce autophagy in the midgut epithelium of *H. armigera* larvae [28]. Interestingly, inhibition of autophagy by specific inhibitors or RNAi resulted in delayed cell death triggered by the toxin, suggesting a direct participation of autophagy in the death response after toxin ingestion. These findings open up the possibility of manipulating the autophagic pathway to enhance the toxicity of *Bt* toxins. In a few studies, an upregulation of caspase-encoding transcripts following *Bt* intoxication has been observed [29–31]. However, in the western corn rootworm *Diabrotica virgifera*, this phenomenon coincides with the upregulation of IAP-encoding transcripts, suggesting a possible balance between pro- and anti-apoptotic signals and underscoring the need for additional investigations to clarify the involvement of the apoptotic pathway in the *Bt* mode of action [29]. In the tobacco hornworm *Manduca sexta*, the upregulation of transcripts encoding caspases is dependent on the administered toxin dose [31]. Furthermore, sublethal exposure of Vip3 toxins (produced by *Bt* during its vegetative growth phase) to *S. exigua* causes the activation of apoptosis in midgut tissues [30]. These findings suggest that toxin dose affects the triggered mechanism, ultimately leading to insect death. Moreover, sublethal doses may activate apoptosis, potentially as a host defense mechanism necessary to renew the damaged epithelial layer. In this context, strategies aimed at inhibiting the apoptotic response could enhance *Bt* toxicity at low doses.

Gene silencing and genome editing strategies targeting cell death pathways

Recent progress in molecular entomology and in the application of RNAi and CRISPR genome editing to insects offers the opportunity to precisely modulate the expression of specific genes, enabling highly targeted approaches for pest control with minimal off-target effects and reduced ecological impacts. Silencing or knockout strategies could leverage the specific physiological roles of autophagy and apoptosis to develop tailored pest control approaches. The ultimate goal is to induce cell death in targeted tissues, thereby compromising vital physiological functions and leading to insect

Figure 3



Schematic overview of autophagy initiation and execution in insects. Under nutrient-rich conditions, insulin/growth factor signaling activates TOR (Target of Rapamycin), which inhibits Atg1 and suppresses autophagy; conversely, in the absence of nutrients, TOR suppression is relieved, and autophagy is set in motion by recruiting Atg proteins. The levels of ecdysone increase during development, leading to downregulation of PI3K signaling, thereby activating autophagy. After nucleation of the phagophore, it progressively expands, forming an autophagosome that engulfs the target material for degradation. Fusion of autophagosome with lysosomes leads to the breakdown of the cargo by hydrolytic enzymes, and the resulting products are recycled back to the cytoplasm. Atg5 participates in phagophore formation and expansion, whereas Atg8 is involved in autophagosome formation, cargo recruitment, and cargo degradation.

mortality, or to manipulate these pathways to disrupt essential developmental and metabolic processes, ultimately reducing insect survival and fitness. There are several studies conducted on different insect species about the effective RNAi-mediated silencing of both apoptotic and autophagic genes. Among apoptotic regulators, multiple studies converged on *IAP* genes as specific targets for pest control due to their essential roles in cell survival and developmental processes across various insect species [6,32]. In *T. castaneum*, RNAi-mediated knockdown of *TcIAP1* and *TcIAP5* resulted in lethal phenotypes due to an impairment of apoptosis regulation and alterations in the development [6]. Similarly, dsRNA targeting *Diap1* in dipteran pests (*Musca domestica* and *Delia radicum*) induced dose-dependent larval mortality and increased caspase activity, although oral delivery was ineffective in adults, likely due to degradation by nucleases. Interspecies RNAi effects were observed—with *M. domestica* larvae responding to *D. radicum* Diap1 dsRNA—suggesting that even partial sequence identity (15 bp) can elicit off-target effects [33]. However, broader studies using dsIAPs across multiple insect species demonstrated that treatments are generally target-specific: no significant gene silencing or phenotypic consequences were observed in nontarget species or in closely related species with high sequence similarity [34]. The utility of *IAP* gene silencing has also been explored in the Asian long-horned beetle *Anoplophora glabripennis*, where dsRNA targeting this gene resulted in 100% mortality in both larvae and adults [35]. Importantly, oral delivery using heat-killed bacteria expressing dsRNA provided protection against environmental degradation, making this approach more feasible for field applications. In contrast, RNAi-based control of mosquitoes via *IAP* gene knockdown has yielded inconsistent results. In particular, although dsIAP1 induced apoptotic morphology in cultured cells, neither microinjection nor topical application produced significant mortality *in vivo*, challenging the effectiveness of IAP targeting in adult mosquitoes and suggesting species- and stage-specific variability in RNAi susceptibility [36]. In addition to apoptosis-related targets, genes involved in autophagy, such as *ATG3*, also represent potential candidates for RNAi-based pest control. In particular, in the brown planthopper *Nilaparvata lugens*, *NlATG3* silencing resulted in complete nymphal

mortality, molting defects, and severely reduced fecundity and egg viability [7]. These findings support the potential of targeting apoptotic and autophagic pathways via RNAi, though delivery methods, life stage, and species-specific responses remain critical issues for field implementation.

Unlike RNAi, the exploration of CRISPR to target apoptotic or autophagic pathways is still in its infancy. To the best of our knowledge, only two studies—performed on lepidopteran cell lines or —are available, proving the feasibility of using this approach to manipulate cell death processes. CRISPR-mediated knockout of Sf-Caspase-1 gene in Sf9 cells inhibits apoptosis when they are infected by baculovirus [37]. Moreover, knockout of ganglioside-induced differentiation-associated protein 2 in the silkworm led to an increased expression of autophagic and apoptotic genes, affecting insect development and lifespan [38].

Synergistic integration of RNAi and CRISPR is also in the pipeline for insect pest management. While RNAi induces temporary, short-term gene silencing, CRISPR induces permanent genome editing for a lifelong effect. A notable example of the combined use of RNAi and CRISPR is provided by Koo's study [39], which used CRISPR to deactivate dsRNase in the gut of the fall armyworm *Spodoptera frugiperda*, increasing the mortality in dsIAP-fed larvae. One of the promising approaches for integration is RNAi-primed CRISPR editing, where RNAi is employed to silence DNA repair genes, enhancing the efficiency of CRISPR-mediated mutations [40]. Another new concept is the use of RNAi as a reversible 'off-switch' for CRISPR-based gene drives, allowing tighter control of genetic alterations. In addition, using RNAi and CRISPR to target autophagy and apoptosis regulators/inducers, or the processes themselves, can increase mortality effects and reduce the chance of resistance development [41].

Despite its promise, the wide-scale application of gene-silencing technology must be preceded by a thorough environmental risk assessment [42]. Attention should be given to off-target effects since improperly designed RNAi or CRISPR constructs could impact non-target species, potentially disturbing ecological balance [43,44]. Additionally, insect pests may become resistant to such interventions as observed for chemical insecticides. This risk can be mitigated by targeting several fundamental genes simultaneously, thereby hindering the insects from developing resistance [45]. A further aspect that deserves careful consideration —and remains a major bottleneck for the large-scale implementation of these technologies— is the delivery of the active molecules [46,47]. Effective oral delivery, which is the simplest and potentially scalable strategy, requires not only protection of the molecules from environmental degradation but also the ability to reach the target sites, which are often located within the hemocoel. This entails preventing degradation within the gut lumen and enabling the molecules to successfully cross the intestinal barrier. Nevertheless, taken together, these approaches require strict international regulations as well as comprehensive risk-benefit analyses to ensure safety and public acceptance.

Proof-of-concept demonstrations

Laboratory and pot-scale studies provide direct proof-of-concept that activating cell death increases insect mortality. RNAi knockdown of *IAP* genes caused pronounced apoptosis and ~91–100% larval mortality in *T. castaneum* [6]. In experiments with dsRNA silencing of *IAP* genes, cross-species toxicity was minimal, indicating target specificity of the approach (for instance, no effect on non-target insects) [36]. In the Colorado potato beetle *Leptinotarsa decemlineata*, dsRNA silencing *IAP* genes reduced feeding and raised larval mortality; moreover, bacterially-expressed dsRNA applied as a spray on potato foliage protected plants in pot trials [32]. Botanical adjuvants can likewise potentiate lethality. For example, curcumin, when combined with avermectin, synergistically enhanced activity against *S. litura* in pot experiments and induced autophagic cell death in *S. frugiperda* Sf9 cells through PI3K/AKT/TOR inhibition [48]. *B. thuringiensis* Cry toxins induced midgut epithelial disruption accompanied by caspase activation and classical apoptotic hallmarks, which collectively contributed to larval death in Lepidoptera [49]. Finally, RNAi targeting caspases or key autophagy genes resulted in significant mortality across multiple pest species in laboratory assays, demonstrating genetic proof-of-concept for cell death-based control strategies [50]. While most evidence remains laboratory-based, pot trials and dietary delivery suggest promising translatability, underscoring the need for further validation under field-relevant conditions.

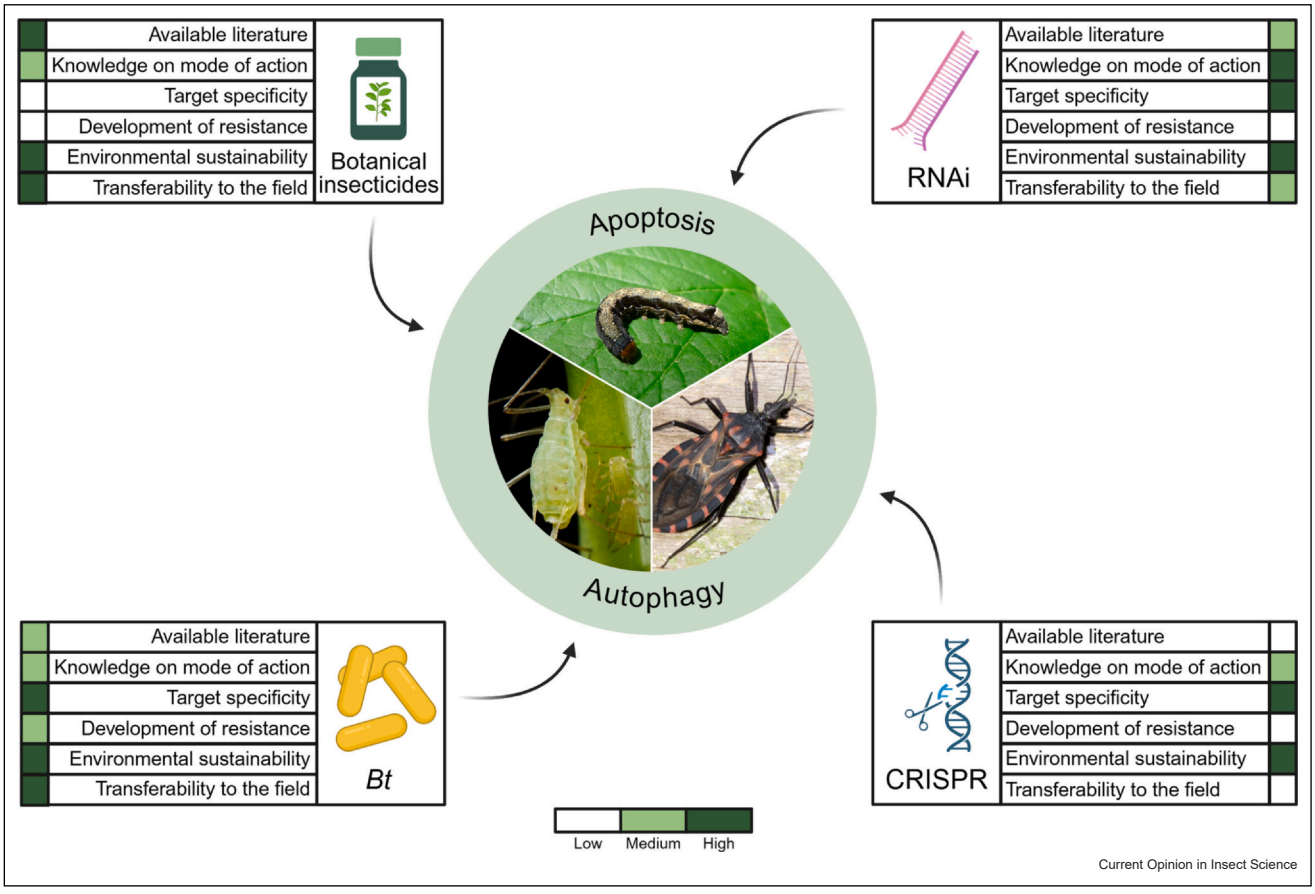
Challenges and perspectives in leveraging cell death for insect pest control

Autophagic and apoptotic pathways may offer novel targets for insect pest control; however, challenges related to long-term efficacy, environmental safety, and regulatory approval must be carefully considered (Figure 4).

Can insects develop resistance to cell death manipulation?

One of the biggest challenges for apoptosis- and autophagy-targeting approaches is the potential evolution of resistance [51]. Just as insects develop resistance to insecticides and RNAi-based treatments, they might activate compensation mechanisms preventing the manipulation of such cell death pathways. Studies on *D. melanogaster* and *B. mori* indicate that apoptosis and autophagy are partially regulated by common mediators,

Figure 4



Comparison of cell death-targeted pest control strategies. The central circle highlights the two key cell death-related processes occurring in insects and some representative pest species. Surrounding panels summarize the four tools targeting these pathways: (1) Botanical insecticides (e.g. azadirachtin and pyrethrins), (2) RNAi, (3) CRISPR-based gene editing, and (4) *B. thuringiensis* (*Bt*) toxins. For each approach, six evaluation criteria are rated from low (white) to high (dark green), according to the scoring scale.

which can potentially enable insects to reallocate these pathways as an adaptation to selection pressure [52,53]. Furthermore, as autophagy is generally a cytoprotective stress response, its inhibition may trigger alternative survival responses [13]. Further studies need to concentrate on identifying evolutionary constraints on such pathways to ascertain if they can be repeatedly targeted without causing rapid resistance development. However, it is important to emphasize that autophagic and apoptotic pathways may provide new potential targets for the control of pest insects, and the manipulation of these pathways may also have the potential to enhance the virulence of entomopathogens.

Balancing specificity with ecological safety

The presence of common molecular elements among insects raises concerns about the specificity of apoptosis- and autophagy-targeting strategies [13,18]. RNAi-based insecticides, for example, have demonstrated unintended off-target effects [54]. To improve molecular specificity, advanced approaches such as CRISPR gene editing and large-scale screenings for target identification are essential [55]. Developing species-specific RNAi and employing genetic engineering of entomopathogens (e.g. modified baculoviruses or entomopathogenic fungi that modulate host apoptotic pathways) [56] to design pest-selective apoptosis inducers could significantly enhance precision while minimizing impacts on biodiversity [54]. Nonetheless, comprehensive risk assessments in accordance with current regulations are necessary to ensure safety and public acceptance. This is especially true for CRISPR-based applications, which, despite an evolving regulatory framework, are currently classified in Europe as genetically modified organism-generating technologies and regulated accordingly. In this context, self-limiting or reversible kill-switch CRISPR gene drives represent promising tools to address concerns about the uncontrolled spread of genetic alterations, offering a more ethically acceptable and controlled approach for regulating insect populations.

Compatibility with current pest control practices

Although cell death-based technologies might be effective as standalone solutions, they could be included in Integrated Pest Management strategies to maximize pest control outcomes and delay resistance. Moreover, genetic engineering of entomopathogenic fungi and baculoviruses to selectively modulate apoptotic mechanisms in host insects with higher specificity and reduced dependence on chemical pesticides is one of the newer strategies [57,58]. Field deployment needs to be rigorously screened for effectiveness, cost, and effects on non-target species. The regulatory framework also needs to be modified to permit such novel control methods for their effective use in agriculture and public health.

Future directions: toward the next generation of insect control

The development of apoptosis- and autophagy-based pest management requires the completion of basic research lacunae in nonmodel insects. Although *D. melanogaster* and *B. mori* are excellent model systems, the majority of agricultural and medically important insect species have limited genomic and transcriptomic information. Moreover, death processes with unique combinations of morphological features (and likely peculiar regulatory mechanisms) have been reported in certain species [59]. Thus, comparative genomics and functional analysis will be central to the identification of lineage-specific regulatory elements that can be exploited for species-specific use.

Another major challenge lies in bridging lab-scale results with effective field practices, which requires robust delivery systems and thorough validation under real-world conditions. Finally, regulatory frameworks should evolve alongside technological advances to ensure that new pest management strategies are both scientifically sound and environmentally sustainable. Addressing these issues, together with challenges related to specificity and resistance, is essential for advancing sustainable and scalable pest control solutions that target and modulate cell death-related pathways.

Conclusions

Harnessing cell death pathways as a tool for pest control is an innovative approach that can expand the available strategies to reduce crop loss as well as the transmission of insect-borne diseases, but it will depend on stringent validation, environmental risk assessment, and close coordination with other control measures. The bipotential role of apoptosis and autophagy in cell survival and cell death demands highly sensitive interventions that avoid resistance emergence as well as off-target effects. Hopefully, the need to integrate different control procedures, the development of suitable delivery methods effective in the field, the revision of the regulatory framework, and the increasing environmental awareness will act as a driving force for the development of sustainable, high-precision insect pest control strategies, in alignment with the One Health principles.

CRediT authorship contribution statement

G. Tettamanti: Conceptualization, Writing – original draft, Writing – review & editing. **M. Casartelli:** Writing – review & editing. **A. Mohamed:** Writing – original draft, Writing – review & editing. **U. Toprak:** Writing – review & editing. **D. Bruno:** Writing – review & editing. **L. Tian:** Writing – review & editing.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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