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Chemosensitization: A Promising Strategy for Management of Pesticide Resistance

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Pesticide resistance has emerged as a critical challenge in modern agriculture, threatening not only crop productivity and food security but also environmental sustainability. Resistance occurs when pest populations adapt to withstand the effects of pesticides, which causes these chemical controls to become progressively less effective. This creates a severe obstacle to pest management and drives a vicious cycle: continued reliance on pesticides accelerates resistance, forcing increased pesticide use, rising control costs, and reduced efficacy.

The agricultural sector faces the complex dual challenge of controlling pests efficiently to feed an expanding global population while simultaneously reducing environmental and human health risks. Improper use of pesticides, limited adoption of diversified management, and agricultural intensification through monocropping all create favourable conditions for pest multiplication (Campos et al., 2019). To address this, Integrated Pest Management (IPM) incorporates biological agents, crop rotation, and need-based chemical applications (Rauf, 2024; Awad, 2023).

Furthermore, emerging technologies like chemosensitization show robust potential to enhance precision pest management programs. By co-applying a natural or low-toxicity compound with conventional pesticides, chemosensitization directly targets and disables the pest's innate resistance mechanisms, such as cellular efflux pumps or stress response systems (Campbell et al., 2012; Dhandapani et al., 2022). This synergistic disruption renders previously resistant pest populations highly susceptible to chemical treatments, thereby restoring the efficacy of failing agrochemicals (Dzhavakhiya et al., 2012). Consequently, this approach allows for significant reductions in the required dosages of toxic pesticides, extending their commercial lifespan while strictly adhering to IPM goals of minimizing environmental residues and protecting non-target organisms (Campbell et al., 2012; Dzhavakhiya et al., 2012).

The Concept and Impact of Pesticide Resistance

Pesticide Resistance

The Insecticide Resistance Action Committee (IRAC) formally defines pesticide resistance as a heritable change in the sensitivity of a pest population, which is reflected in the repeated failure of a product to achieve expected control when used according to label recommendations. Key factors driving this include:

- **Genetic variation:** Resistance originates from the natural genetic diversity already present within pest communities. Specific mutations or pre-existing biological characteristics can equip certain individuals with the innate ability to withstand specific pesticides.

- **Selection pressure:** The repeated and intensive reliance on a single pesticide or a specific mode of action drives rapid evolutionary adaptation. This continuous exposure acts as a filter, eliminating susceptible pests and leaving only the highly resilient survivors to thrive.
- **Heritability:** Because these survival advantages are embedded in their DNA, they are readily passed down to subsequent generations. As a result, the offspring of resistant pests inherit the exact same protective traits, ensuring the continuation and expansion of the problem.
- **Gradual process:** The shift toward a fully resistant population occurs progressively rather than instantaneously. The speed of this evolutionary change is dictated by interacting variables such as chemical application frequency, the reproductive cycles of the pest, and broader ecological conditions.

Impacts of Pesticide Resistance

The phenomenon of pesticide resistance severely disrupts agricultural frameworks, ecological balance, and worldwide food stability. As standard chemical treatments lose their efficacy, growers are often compelled to apply higher volumes or switch to more hazardous alternatives, which inevitably drives up production costs. The impacts of pesticide resistance can be categorized into several key areas:

Agricultural Productivity Losses: The most direct consequence of pesticide resistance is the decline in the effectiveness of pest control measures, which negatively affects crop productivity. Pesticides are essential for protecting crops from insects, weeds, and diseases, but their efficacy diminishes as resistance develops, leaving farmers with limited control options.

- **Rise in pest populations:** Resistant individuals survive pesticide treatments, resulting in larger and more persistent pest populations that continue to damage crops and reduce yields. For instance, resistance in the Colorado potato beetle has significantly reduced the success of conventional insecticides, leading to notable losses in potato production (Cohen et al., 2008).
- **Secondary pest outbreaks:** Excessive reliance on a single pesticide can disturb ecological balance, allowing non-target pests to multiply. These secondary pests can further harm crops and lower productivity, as seen in cotton systems where aphid outbreaks increased following broad-spectrum insecticide use.

Increased Costs for Farmers: Managing resistance imposes substantial financial burdens due to increased pesticide usage and the need for alternative strategies. Farmers may need to apply pesticides more frequently or at higher doses to maintain control.

- **Higher input costs:** Resistance often forces a shift to newer or more potent (and expensive) pesticides. Additionally, rotating or combining chemicals further increases expenditure.
- **Reduced profitability:** Rising input costs, coupled with potential yield losses, can significantly reduce farm income, especially for smallholders with limited financial capacity.

Environmental Implications: Pesticide resistance intensifies reliance on chemical inputs, leading to serious environmental concerns.

- **Environmental contamination:** Increased pesticide application can result in soil and water pollution through leaching and drift, adversely affecting ecosystems and beneficial organisms such as pollinators and soil microbes (Geiger et al., 2010) [8].
- **Harm to non-target organisms:** Overuse of pesticides negatively impacts beneficial species, including natural enemies of pests, birds, and aquatic organisms. The decline of pollinators like bees and predators like ladybirds disrupts natural pest regulation and pollination services.
- **Resistance in beneficial species:** Not only pests but also beneficial organisms may develop resistance, weakening biological control systems and reducing ecosystem stability.

Public Health Risks: Pesticide resistance can indirectly threaten human health by encouraging the use of stronger and potentially more hazardous chemicals.

- **Increased toxicity risks:** The need for more potent pesticides raises exposure risks for farmers, agricultural workers, and consumers, potentially leading to acute poisoning or chronic health issues, including cancer (Zhao et al., 2017) [19].
- **Higher pesticide residues in food:** Greater pesticide use may result in increased residue levels in food products, posing potential health hazards, especially when safety thresholds are exceeded.

Threat to Global Food Security

Resistance undermines the ability to protect crops effectively, thereby contributing to food insecurity.

- **Decline in crop yields:** Ineffective pest control leads to increased crop damage and reduced yields, particularly in regions heavily dependent on chemical pesticides.
- **Reliance on unsustainable practices:** Widespread resistance can reinforce dependence on chemical-intensive agriculture, limiting the adoption of sustainable and eco-friendly farming practices necessary for long-term food security (Altieri et al., 2015).

Socioeconomic Effects: The broader socioeconomic impacts are particularly severe for small-scale farmers in developing countries.

- **Increased economic burden:** Farmers face rising costs due to expensive pesticides or the adoption of IPM practices that require additional investments in knowledge, labor, and resources.
- **Greater vulnerability:** Escalating costs and declining yields can lead to financial instability, forcing some farmers—especially smallholders—to abandon farming altogether.

Factors Contributing to Pesticide Resistance

Pesticide resistance is a multifaceted phenomenon shaped by biological, ecological, and management-related factors. A clear understanding of these factors is essential for designing effective resistance management strategies. The major factors for pesticide resistance are:

- **Overdependence on Chemical Pesticides:** The excessive and repeated use of pesticides imposes strong selection pressure on pest populations, where most pests are eliminated but a few with resistant traits survive and reproduce. The continuous reliance on chemical control has led to resistance against multiple insecticide groups (Hu, 2020; Lu et al., 2024).
- **Sub-lethal Doses and Improper Application:** The application of pesticides at doses insufficient to kill pests or using flawed application practices allows pests to survive, adapt, and evolve resistance. Incorrect dosage, poor timing, or uneven application significantly reduces effectiveness of pesticides (Rauf, 2024).
- **Lack of Crop and Pesticide Rotation**: The absence of crop rotation supports the persistence of specific pest populations, while failing to rotate pesticide modes of action limits variability in selection pressure, accelerating resistance development (Washim et al., 2024).
- **Limited Awareness and Farmer Training:** The lack of sufficient knowledge regarding proper pesticide use, recommended guidelines for dosage and timing, and a lack of awareness about IPM practices severely aggravate pesticide resistance development (Awad, 2023).
- **High Reproductive Potential of Pests**: Pests with short life cycles and high reproductive rates tend to develop resistance more rapidly because faster reproduction increases genetic variability. The high reproductive rate of the aphid species *Aphis gossypii*, coupled with its ability to develop resistance to insecticides, has made it a persistent pest in cotton fields (Bass et al., 2014; Croft & Van de Baan, 1988).
- **Environmental Factors and Pest Migration:** The higher temperatures and extended growing seasons driven by climate change promote faster pest reproduction, thereby

accelerating resistance evolution. Additionally, the migration of pests from untreated areas introduces resistant genes into new populations.

Strategies for Managing Pesticide Resistance

Effective management requires integrated approaches to restrict the development and spread of pesticide resistance.The following strategies are useful for pesticide management :

- **Integrated Pest Management (IPM):** Integrated Pest Management (IPM) is a comprehensive approach that integrates multiple control methods to reduce dependence on chemical pesticides and thereby minimize resistance development. It combines cultural, biological, mechanical, and chemical methods, with strong emphasis on monitoring and informed decision-making.
- **Rotation and Combination of Pesticides:** Alternating pesticides with different modes of action is an effective way to slow resistance evolution. This approach reduces the likelihood of pests adapting to a single chemical.

✓ **Mode of action rotation**: Different pesticides target pests through varied biochemical pathways, lowering the risk of resistance buildup.

✓ **Sequential or combination use:** Switching or combining pesticides with diverse mechanisms helps minimize cross-resistance.

- **Use of Biopesticides:** Biopesticides provide a safer alternative to conventional chemicals and often act through unique mechanisms, thereby lowering resistance risk.

Types of biopesticides:

✓ **Microbial pesticides:** Include organisms like Bacillus thuringiensis (Bt) that produce toxins specific to certain insect pests.

✓ **Botanical pesticides:** Plant-derived compounds such as neem oil and pyrethrins that are relatively eco-friendly.

✓ **Biochemical pesticides:** Substances like pheromones that interfere with pest behavior, such as mating disruption.

- **Biological control:** The use of natural enemies—predators, parasitoids, and pathogens—offers sustainable, long-term pest suppression and complements other management strategies. The adoption of Bt crops (e.g., Bt cotton and Bt maize) has effectively controlled pests like cotton bollworm and European corn borer while reducing reliance on chemical insecticides (Tabashnik et al., 2008)
- **Adoption of Genetically Modified (GM) Crops:** GM crops expressing insecticidal proteins, such as Bt cotton and Bt maize, reduce pesticide dependency by providing built-in pest resistance (Tabashnik et al., 2008).

Modern Approach: Chemosensitization

Chemosensitization is an emerging concept in agriculture that involves the use of specific compounds to restore or enhance the susceptibility of resistant pests to pesticides. Chemosensitization is a biological and pharmacological strategy where a secondary, often weakly active or non-toxic agent (the "chemosensitizer") is co-administered with a primary chemical agent (such as a chemotherapeutic drug or commercial fungicide). The chemosensitizer functions by disabling or bypassing the target organism's innate or acquired defense mechanisms, thereby restoring or significantly enhancing the target's susceptibility to the primary chemical.

Molecular Pathways That Influence Chemosensitivity

Chemotherapeutic agents induce cancer cell death primarily through mechanisms such as necrosis, apoptosis, and autophagy. Among these, apoptosis (programmed cell death) is the most desirable outcome, as necrosis can damage surrounding tissues, while autophagy often helps cells survive under stress conditions. Therefore, the success of chemotherapy largely depends on the ability of cancer cells to undergo apoptosis in response to treatment. However, several barriers reduce drug effectiveness. One major limitation is the overexpression of anti-apoptotic molecules within cancer cells. Additionally, prolonged exposure to chemotherapeutic agents often leads to the development of chemoresistance. Many drugs not only activate apoptotic pathways but also unintentionally trigger survival

signaling pathways, which further contribute to resistance. Multiple mechanisms disrupt apoptotic signaling, including overexpression of anti-apoptotic genes, suppression of pro-apoptotic genes, alterations in the p53 pathway, and activation of cell survival pathways. These molecular changes collectively reduce the sensitivity of cancer cells to chemotherapy.

Apoptotic Pathways in Chemosensitivity

Cell death is initiated through two major apoptotic pathways:

1. Extrinsic Pathway (Death Receptor-Mediated)

This pathway is activated when ligands bind to death receptors (DRs) on the cell surface. This interaction triggers activation of caspases, leading to DNA fragmentation and cell death. Besides caspases, other proteases such as cathepsins, calpains, granzymes, and proteasomes also contribute to apoptosis.

2. Intrinsic Pathway (Mitochondrial Pathway)

This pathway involves mitochondrial signaling, where cytochrome c release leads to the formation of a complex with Apaf-1 and procaspase-9, activating downstream caspases. It can be triggered by factors like p53 activation or Bid cleavage. Most chemotherapeutic drugs primarily act through this pathway.

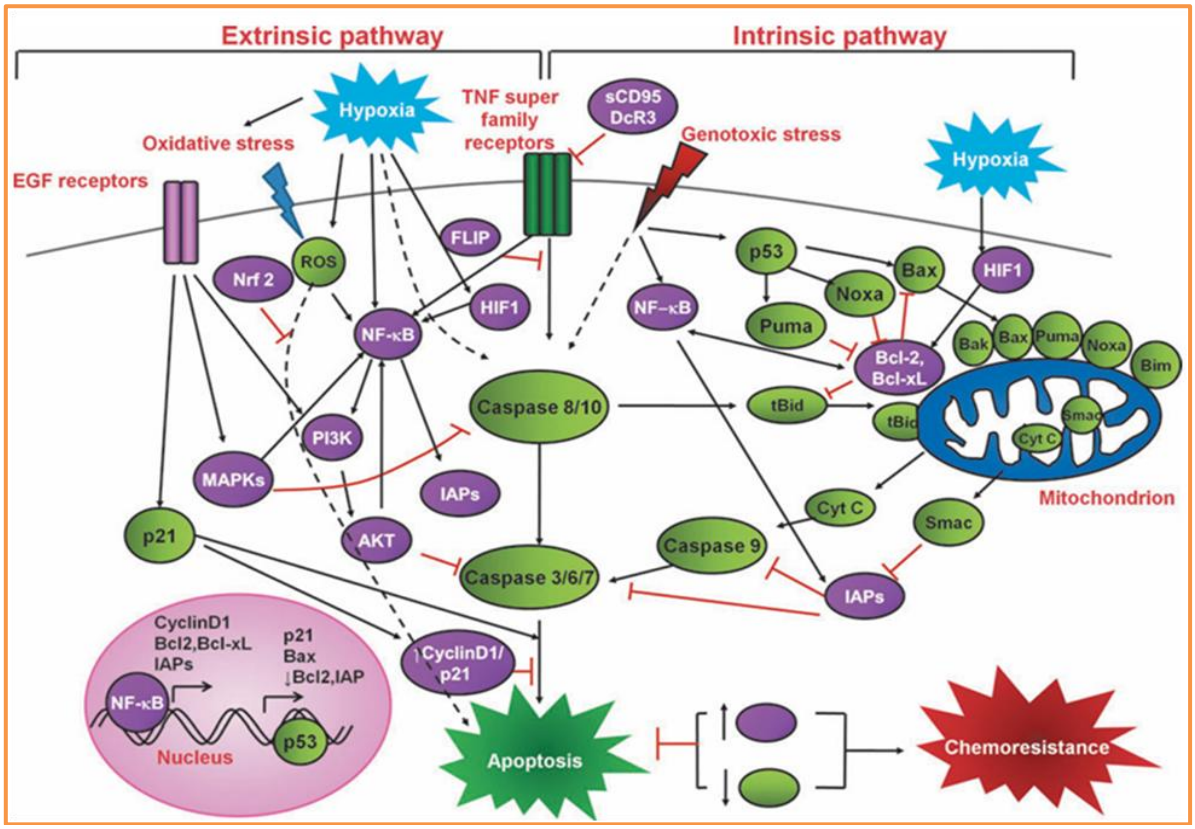

FIG. 1. Signaling intermediates regulating apoptosis and chemoresistance. Signaling events and key regulators of apoptosis involved in chemoresistance (Vinod *et al* ., 2013)

A. Role of Intrinsic Pathway in Chemoresistance

- **p53 Pathway Alterations**: The tumor suppressor protein p53 plays a central role in regulating apoptosis. It induces cell cycle arrest, DNA repair, or apoptosis under stress conditions. Many anticancer drugs rely on functional p53 to trigger apoptosis. However, mutations, deletions, or inactivation of p53 impair this process, leading to resistance against drugs such as doxorubicin, cisplatin, 5-fluorouracil, and etoposide (El-Deiry, 2003). In some cases, mutant p53 may even promote resistance by activating genes like EGFR and MDR1 (Lanyi et al., 1998).
- **Bcl-2 Family Proteins:** The Bcl-2 protein family regulates mitochondrial membrane integrity and apoptosis.
- Anti-apoptotic members (e.g., Bcl-2, Bcl-xL, Mcl-1) promote cell survival.
- Pro-apoptotic members (e.g., Bax, Bak, Bim, Bid, PUMA, Noxa) promote cell death.

Overexpression of anti-apoptotic proteins, particularly Bcl-2, is strongly associated with resistance to several chemotherapeutic drugs (Weller et al., 1995). Conversely, inhibition of these proteins or activation of pro-apoptotic factors can restore drug sensitivity. Deficiencies in key apoptotic proteins such as Bax and Apaf-1 also contribute to resistance (Castino et al., 2009; Tan et al., 2011). MicroRNAs and ROS Certain microRNAs (e.g., miR-10b) suppress pro-apoptotic proteins and enhance resistance (Nishida et al., 2012). Reactive oxygen species (ROS) also play a dual role—while moderate levels promote apoptosis, adaptive responses to oxidative stress can protect cancer cells and induce resistance (Pervaiz & Clement, 2004).

B. Extrinsic Pathway and Chemoresistance

The extrinsic pathway involves death receptors such as CD95 (Fas), TNFR1, TRAIL-R1, and TRAIL-R2, along with their ligands (FasL, TNF-α, TRAIL). These interactions activate caspases and induce apoptosis. However, resistance can arise due to:

- Increased levels of soluble receptors (e.g., sCD95, DcR3) that block ligand binding (Ugurel et al., 2001).
- Elevated expression of anti-apoptotic proteins like c-FLIP, which inhibits caspase-8 activation (Kim et al., 2008).
- Enhanced activity of kinases such as CK2, which promote survival signaling (Ravi & Bedi, 2002; Llobet et al., 2008).

c-FLIP, in particular, plays a major role in blocking apoptosis and contributing to TRAIL resistance in cancer cells (Kim et al., 2008).

C. Role of Signalling Pathways and ROS in Chemoresistance

Signaling pathways such as NF-κB and PI3K are activated downstream of death receptors and contribute to resistance by promoting cell survival. ROS act as important signaling molecules:

- High ROS levels may cause necrosis.
- Moderate ROS levels induce apoptosis.
- Adaptive responses to ROS help cancer cells survive and develop resistance (Pervaiz & Clement, 2004).

Many chemotherapeutic drugs generate oxidative stress, but cancer cells often adapt through redox-regulating pathways, thereby reducing drug effectiveness (Conklin, 2004). Activation of NF-κB signaling is particularly important in mediating ROS-induced chemoresistance (Morgan & Liu, 2011).

Generations of Chemosensitizers

A significant amount of research has focused on overcoming multidrug resistance (MDR) in cancer by targeting ATP-binding cassette (ABC) transporters, which actively efflux drugs out of cells and reduce therapeutic efficacy. Chemosensitizers are compounds designed to inhibit these transporters, thereby increasing intracellular drug accumulation and restoring the effectiveness of chemotherapeutic agents (Wu et al., 2011). Based on their affinity, specificity, and toxicity profiles, chemosensitizers have been broadly classified into different generations (Palmeira et al., 2012).

- **First-Generation Chemosensitizers**

The first generation consisted of already approved drugs that were later identified to possess ABC transporter inhibitory activity. These included calcium channel blockers like **verapamil**, immunosuppressants such as **cyclosporine A**, and antimalarial drugs like **quinine** (Tsuruo et al., 1981; Krishna and Mayer, 2001; Karthikeyan and Hoti, 2015).

However, these compounds were not originally designed as chemosensitizers, and their primary pharmacological actions led to several limitations. They exhibited **low specificity and weak affinity** toward ABC transporters, requiring high doses for effectiveness. This resulted in **significant toxicity to normal cells** and undesirable side effects, limiting their clinical applicability (Shiraga et al., 2001).

- **Second-Generation Chemosensitizers**

To address the shortcomings of first-generation compounds, second-generation chemosensitizers were developed through structural modification of earlier drugs. Examples

include **dexverapamil** (an R-enantiomer of verapamil) and **PSC833 (valspodar)**, a derivative of cyclosporine A.

These compounds demonstrated improved ability to sensitize MDR cancer cells in vitro. However, they still exhibited **toxicity in animal studies** and were associated with **drug–drug interactions** during clinical trials due to inhibition of cytochrome P450 enzymes (Nawrath and Raschack, 1987; Pirker et al., 1990; Abdallah et al., 2015; Klinkhammer et al., 2009). Thus, despite improvements, their clinical success remained limited.

- **Third-Generation Chemosensitizers**

Advances in **quantitative structure–activity relationship (QSAR)** studies and combinatorial chemistry facilitated the development of third-generation chemosensitizers. These compounds were specifically designed to exhibit **high affinity for P-glycoprotein (P-gp)**, improved specificity, and reduced toxicity.

Notable examples include **tariquidar (XR9576)**, **zosuquidar (LY335979)**, **laniquidar (R1010933)**, **elacridar (GF120918)**, and **biricodar (VX-710)**. These agents showed promising activity with enhanced drug accumulation and reduced adverse effects (Toppmeyer et al., 2002; Yanagisawa et al., 1999; Avendaño and Menéndez, 2015).

However, clinical studies revealed that many of these compounds exhibited **dual or broad interactions with multiple ABC transporters**, reducing their selectivity and limiting their effectiveness in targeting specific resistance mechanisms.

- **Fourth-Generation Chemosensitizers (Natural Products)**

Due to the limitations of earlier generations, natural products have emerged as promising fourth-generation chemosensitizers. Their **high structural diversity, better biocompatibility, and relatively low toxicity** make them suitable candidates for overcoming multidrug resistance (MDR). These compounds are often used in combination with chemotherapeutic agents to enhance drug efficacy and restore sensitivity in resistant cells.

Dietary phytochemicals such as **curcumin, quercetin, and kaempferol** have been shown to inhibit ABC transporters, particularly ABCB1, thereby increasing intracellular drug accumulation and reversing MDR in cancer cells (Limtrakul et al., 2005). In addition to plant-derived compounds, certain natural products of marine and microbial origin, such as **trabectedin and cytarabine**, also exhibit strong chemosensitizing properties and have been successfully utilized in clinical settings (Huang, 2007; Abraham et al., 2010).

These natural chemosensitizers belong to diverse chemical classes, including **flavonoids, coumarins, and terpenoids**, and primarily target key efflux transporters such as **ABCB1, ABCC1, and ABCG2**. Their multi-targeted mode of action and lower toxicity profile make them highly promising for future development in overcoming drug resistance.

Mechanisms and Chemosensitization Agents in Agriculture

Chemosensitizers enhance drug accumulation through substrate competition, ATP-binding interference (Urbatsch et al., 1995), and membrane modulation (Ferte, 2000; Eytan, 2005). In plant pathology, this concept enables heavy dose reduction (Campbell et al., 2012). Key agricultural agents include:

Cinnamaldehyde

Among natural plant products, cinnamaldehyde is likely the most well-known chemosensitization agent used against plant pathogenic fungi (Copping & Duke, 2007). It exerts its effects by inhibiting ATPases, altering cell wall biosynthesis, and disrupting cell membrane integrity (Usta et al., 2003; Kyu-Ho et al., 2000; Xie et al., 2004). Specific data shows that cinnamaldehyde effectively reduces spore germination in the pathogen *Aspergillus flavus* (Xie et al., 2004) and exhibits chemosensitizing effects on the human fungal pathogen *Candida* spp. (Shreaz et al., 2016).

Thymol

Another natural plant product, thymol, derived from *Thymus vulgaris* oil, disrupts fungal cell membrane integrity by reducing the cell's ergosterol content (Pinto et al., 2006). The synergistic impact of thymol is well documented; for instance, when utilized as a chemosensitization agent to manage *Stagonospora nodorum*, an application of 10 ppm

thymol alone yielded a mere 1.1% growth inhibition, while the fungicide azoxystrobin alone yielded a 14.8% growth inhibition (Dzhavakhiya et al., 2012). However, when both compounds were co-applied, the total growth inhibition surged to 40.9%, a synergistic trend similarly observed in treatments on *Phoma glomerata* and *Alternaria alternata* (Dzhavakhiya et al., 2012).

Octyl Gallate

Benzo derivatives have also been utilized successfully as chemosensitization agents, primarily to manage *Aspergillus* species. Octyl gallate, a benzo analog, disrupts fungal cell wall integrity (Kim et al., 2014). Although it possesses some antifungal activity, it does not exert enough suppression to serve as a stand-alone fungicide (Kim et al., 2014). However, when octyl gallate was co-applied with the strobilurin fungicide kresoxim-methyl to inhibit *Aspergillus fumigatus*, the minimum inhibitory concentration (MIC) of the fungicide was drastically lowered from 0.35 mM down to 0.05 mM (Kim et al., 2014).

Salicylaldehyde

Another benzo analog, salicylaldehyde, targets the mitogen-activated protein kinase (MAPK) pathway (Levin et al., 2005). The chemosensitizing activity of salicylaldehyde, when combined with mitochondrial respiration inhibitors like antimycin A or kresoxim-methyl, resulted in the absolute and complete inhibition of fungal growth in both *Aspergillus flavus* and *Aspergillus parasiticus* (Kim et al., 2011).

Kojic Acid

Additionally, natural compounds produced by fungi to inhibit the growth of competing encroaching fungi act as highly effective chemosensitization candidates. Kojic acid, a compound produced by *Aspergillus* and *Penicillium* spp., acts by inhibiting the enzyme tyrosinase, which plays an essential role in melanin biosynthesis (Rodrigues et al., 2014; Chee et al., 2003). Targeting this pathway is valuable because mutations linked to higher melanized colonies have been associated with increased fungicide resistance (Lendenmann et al., 2015). When kojic acid was co-applied in vitro alongside hydrogen peroxide, the MIC required for fungal control was 1.3 to 2.4 times lower than when the respective compounds were applied independently (Kim et al., 2014).

Conclusion

Chemosensitization represents a highly promising and sustainable strategy to overcome the widespread challenge of pesticide resistance by enhancing the efficacy of existing agrochemicals. By explicitly targeting key cellular resistance mechanisms—such as multidrug efflux transporters and intracellular detoxification pathways—this approach restores pesticide sensitivity in resilient pest populations. Furthermore, chemosensitization enables significantly improved pest and pathogen control at highly reduced chemical dosages, thereby minimizing environmental contamination and delaying the continued evolutionary development of resistance in modern agriculture. Although still under research and limited field application, it holds potential as a supportive tool in resistance management strategies.

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