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CHEMOSENSITIZATION: A NEW HOPE FOR OVERCOMING FUNGICIDE RESISTANCE IN CROP PROTECTION

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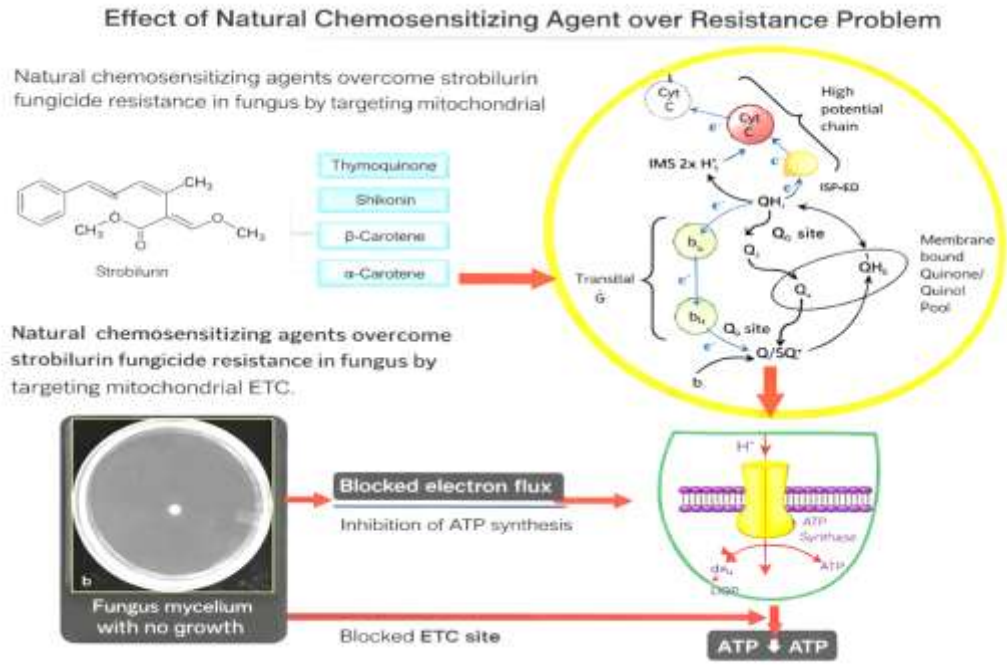
Abstract *The chemical method of pest control is the most reliable in crop protection for high yield and better quality of produce. In agriculture, more than 200 fungicides are in use and have different modes of action. The number of registered fungicides is based more on the above. New generation fungicides such as triazoles or azoles, methoxy acrylates group, etc., are used against phytopathogenic fungi and significantly control the most severe diseases. Despite multiple applications of these fungicides in the same growing season, they are needed for the management of these pathogens. But application at these doses promotes the development of resistance and is detrimental to the environment. That can make any fungicide costly, as it does not last very long for the farmers. Several trials have been done at higher doses, causing biomagnification as well as bioconcentration. Which is also not sustainable from any point of view. So in search of different sustainable ways to overcome these resistance problems. One of the rational ways is to use chemosensitization, where natural compounds help to increase the antifungal activity of modern fungicides to solve these acute problems. It is the combination of synthetic or commercial fungicides with non- or marginal natural compounds that synergistically increases the efficacy of the target fungicides. Generally, the target of a chemosensitizing agent differs from commercial or known fungicides in both biochemical and structural ways. Chemosensitization is eco-friendly in terms of reducing doses of fungicides. In this review, chemo-sensitization helps to cross the bottlenecks of resistant problems against modern fungicide groups when they are co-applied with natural metabolites or secondary plant metabolites. We must understand the problem and mechanism of resistance development in the fungus as well.*



Graphical Abstract

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Introduction

Chemosensitization is a strategy that combines a conventional antifungal drug or fungicide with a second compound, called a chemosensitizer, to increase the efficacy of the drug or fungicide. Chemosensitizers can also overcome the resistance of fungal pathogens to commercial drugs or fungicides. These chemosensitizers are, by definition, safe compounds and, when co-applied with a commercial antifungal agent, can result in a synergistic antifungal interaction. Therefore, this approach can provide a safe measure of improving the efficacy of conventional antifungal agents, resulting in lower dosages for antifungal treatment (Campbell et al., 2012; Dzhavakhiya et al., 2012).

Resistance development in any fungus is generally biological, whenever any fungus develops resistance against any fungicide by showing the capability of adapting to continuous change in the environment. In the modern world, most of the scientists are fighting against the development of resistance, which is the reason for the establishment of FRAC in 1994. New-generation groups of fungicides are fighting against the most destructive pathogens. For example, if you see triazole groups, they are DMI inhibitors by inhibiting the 14α-demethylase, which belongs to cytochrome p450. This enzyme helps to break the 14 α methyl group from lanosterol, where lanosterol is the precursor of ergosterine, whereas 14 α methyl accumulates due to the reduction of enzymes is 14 α methyl concentration, increase causing oxidative stress causes damage to the membrane, and consequently death of the fungus cell in methoxy acrylate groups are QoI by blocking if ubiquinone oxidase between cyt bc1 and cyt b. So basically they inhibit mitochondrial respiration by inhibiting electron transfer between cyt b and cytochrome c, resulting in a reduction of ATP synthesis, causing deficiency of energy in fungus cells, resulting in fungi static reaction (Ma and Michailides, 2005; Shkel' et al., 2013; Balba, 2007). When new systemic and contact fungicides came into the market with single-site action, including modern fungicide groups, then more development of resistance by the fungus and newly developed fungicides became active in two or three years. To solve the problem, farmers started using higher doses and frequent application, which aggravated the problem by the accumulation of that fungicide in the plant and soil, stimulating resistance. It is also found that the development of resistance in strobilurin due to ubiquinone oxidase is encoded with mitochondrial DNA (Wood and Hollomon, 2003).

The term "chemosensitization" was originally used in the medical community as a strategy to counter the development of resistance in cancer cells to anticancer drugs. The resistance mechanisms to anticancer drugs are almost parallel to those developed by fungal pathogens against fungicides. Cancer cells develop resistance through mutations of target enzyme genes, overexpression of target enzymes, upregulation of genes controlling efflux pumps, production of enzymes that detoxify the anticancer drugs, and DNA repair (Shabbits et al., 2003; Kim et al., 2015; Dhandapani et al., 2022). When a chemosensitization agent is co-applied with an anticancer drug, it stresses or debilitates the cancer cells, allowing the anticancer drug to be effective again. Chemosensitization agents aid in lowering the dosages of the anticancer drug, overcoming resistant cancer cells, and reducing the negative side effects by avoiding toxicity to non-target cells.

Generations of Chemosensitizers

Research has extensively focused on overcoming multidrug resistance (MDR) in cancer by targeting ATP-binding cassette (ABC) transporters. These transporters actively efflux drugs from cells, thereby diminishing the efficacy of therapeutic agents. Chemosensitizers are compounds specifically designed to inhibit these transporters, facilitating increased intracellular drug accumulation and restoring the effectiveness of chemotherapeutic agents (Wu et al., 2011). Based on their affinity, specificity, and toxicity profiles, chemosensitizers are classified into distinct generations (Palmeira et al., 2012).

First-Generation Chemosensitizers

The first generation includes drugs that were previously approved for clinical use, later identified for their ABC transporter inhibitory activity. These include calcium channel blockers such as verapamil, immunosuppressants such as cyclosporine A, and antimalarial agents such as quinine (Tsuruo et al., 1981; Krishna and Mayer, 2001; Karthikeyan and Hoti, 2015). However, these compounds were not initially designed as chemosensitizers, and their primary pharmacological activities imposed several limitations. They exhibited low specificity and weak affinity for ABC transporters, necessitating high doses to achieve effectiveness, which resulted in significant toxicity to normal cells and undesirable side effects, thereby restricting their clinical applicability (Shiraga et al., 2001).

Second-Generation Chemosensitizers

To address the limitations associated with first-generation compounds, second-generation chemosensitizers were developed through structural modifications of earlier drugs. Examples include dexverapamil, an R-enantiomer of verapamil, and PSC833 (valspodar), a derivative of cyclosporine A. Such compounds have shown an enhanced ability to sensitize MDR cancer cells in vitro. Nevertheless, they still presented toxicity in animal studies and were linked to drug–drug interactions during clinical trials due to the inhibition of cytochrome P450 enzymes (Nawrath and Raschack, 1987; Pirker et al., 1990; Abdallah et al., 2015; Klinkhammer et al., 2009). Consequently, despite their improvements, clinical success remained limited.

Third-Generation Chemosensitizers

Advances in quantitative structure–activity relationship (QSAR) studies and combinatorial chemistry have facilitated the development of third-generation chemosensitizers. These compounds are specifically engineered 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 demonstrated promising biological activity, resulting in enhanced drug accumulation and reduced adverse effects (Toppmeyer et al., 2002; Yanagisawa et al., 1999; Avendaño and Menéndez, 2015). However, clinical studies have indicated that many of these compounds display dual or broad interactions with multiple ABC transporters, which compromises their selectivity and hinders their effectiveness in targeting specific resistance mechanisms.

Fourth-Generation Chemosensitizers (Natural Products)

In light of the limitations associated with earlier generations, natural products have emerged as promising fourth-generation chemosensitizers. Their substantial structural diversity, improved biocompatibility, and relatively low toxicity render them suitable candidates for overcoming multidrug resistance (MDR). These compounds are often employed in combination with conventional chemotherapeutic agents to enhance drug efficacy and restore sensitivity in resistant cancer cells. Dietary phytochemicals, including curcumin, quercetin, and kaempferol, have demonstrated the ability 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, exhibit robust chemosensitizing properties and have been successfully utilized in clinical settings (Huang, 2007; Abraham et al., 2010).

These natural chemosensitizers encompass a variety of chemical classes, including flavonoids, coumarins, and terpenoids, and primarily target key efflux transporters such as ABCB1, ABCC1, and ABCG2. Their multi-targeted mechanism of action, coupled with a lower toxicity profile, positions them as highly promising candidates for future development in the realm of overcoming drug resistance.

Pathways and Mechanisms of Antifungal Resistance

Similarly, chemosensitization can be a useful strategy to manage plant pathogenic fungi. The use of chemosensitizing agents could help overcome resistance to commercial fungicides. Chemosensitizing agents function by stressing or debilitating the defense of the fungus, increasing its sensitivity to commercial fungicides (Kim et al., 2015). A fundamental characteristic of a chemosensitizing agent is that while it aids in augmenting fungicide efficacy, it presents little fungicidal activity when applied alone (Campbell et al., 2012). With the limited number of fungicides available today, chemosensitizing agents could play a role in plant disease management strategies (**Figure 1**).

Antifungal resistance in Candida involves several complex pathways and mechanisms. Resistance to azoles is often due to mutations in ERG11 or ERG6, or alterations in the ergosterol biosynthetic pathway, and is mediated by multidrug transporters through efflux pumps. Resistance to polyenes can occur due to mutations in ERG3 or ERG6, which decrease the affinity for ergosterol binding (Figure 2). Echinocandin resistance is typically caused by alterations in the affinity of echinocandins for β-1,3-glucan synthase (FKS1 and FKS2). Resistance to 5-fluorocytosine arises from defects in cytosine permease or a deficiency in enzymes involved in the metabolism of 5-FC. Allylamines and thiocarbamates resistance mechanisms include the inhibition of squalene epoxidase (ERG1). Efflux pumps, which are mediated by efflux pump transporters, also play a significant role in antifungal resistance. These pathways highlight the intricate nature of antifungal resistance mechanisms in Candida (Dhandapani et al., 2022).

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 and 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:

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.

Role of 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:

a) Increased levels of soluble receptors (e.g., sCD95, DcR3) that block ligand binding (Ugurel et al., 2001).
b) Elevated expression of anti-apoptotic proteins like c-FLIP, which inhibits caspase-8 activation (Kim et al., 2008).
c) 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).

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.

Role of Intrinsic Pathway in Chemoresistance

a) 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).
b) Bcl-2 Family Proteins: The Bcl-2 protein family regulates mitochondrial membrane integrity and apoptosis.
c) Anti-apoptotic members (e.g., Bcl-2, Bcl-xL, Mcl-1) promote cell survival.
d) 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).

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.

a) Moderate ROS levels induce apoptosis.
b) 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).

Mechanism of Action

Inhibition of efflux pumps

Efflux pumps in fungi, such as those in *C. albicans*, *A. fumigatus*, and *Cryptococcus neoformans*, actively expel antifungal agents, reducing their intracellular concentration and effectiveness. By inhibiting these pumps, chemosensitizing agents can enhance the efficacy of antifungal drugs. The two main families of efflux pump proteins in fungi are indeed the ABC (ATP-binding cassette) proteins and the MFS (Major Facilitator Superfamily) transporters. A study found that Verapamil, a calcium channel blocker, inhibits the efflux pumps in *C. albicans*, specifically the Cdr1p efflux pump, leading to increased intracellular accumulation of fluconazole. This results in a synergistic effect, enhancing the antifungal activity of fluconazole against C. albicans (Vega-Chacón et al., 2021).

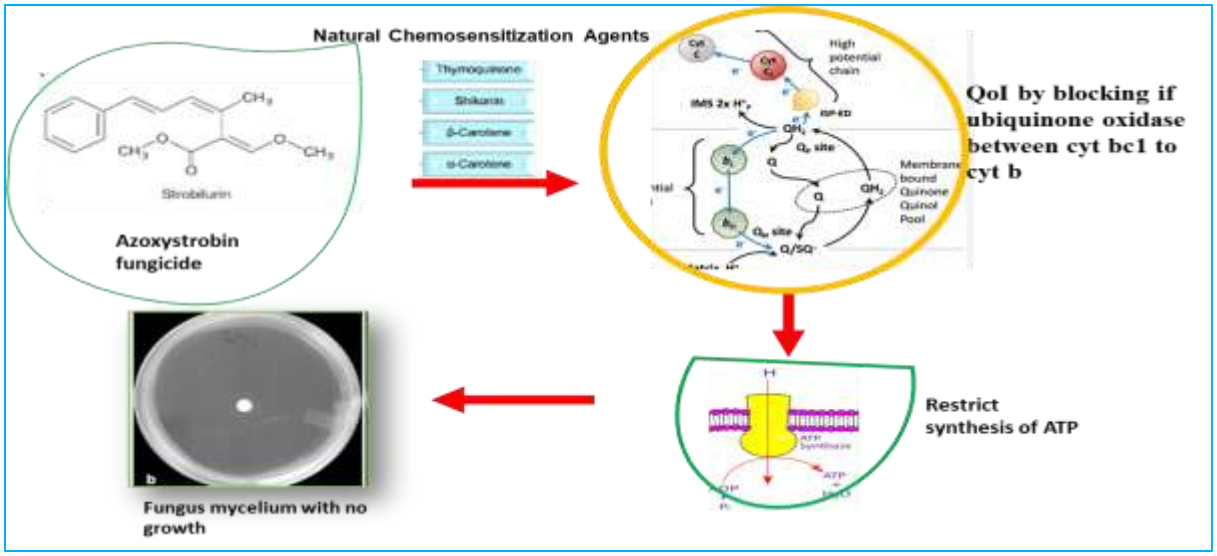

Figure 1 Effect of a natural chemosensitizing agent on the resistance problem

Mn-SOD (mitochondrial superoxide dismutase) as Target

There are studies suggesting that the combination of strobilurins with certain compounds, particularly berberine and veratraldehyde, increased the antifungal effect on various fungi. One such experiment aimed to test the increase in antifungal properties of strobilurins in combination with berberine hemisulfate and various phenolic compounds, was carried out in a specific strain of Saccharomyces cerevisiae lacking the Mn-SOD gene (sod2\Δ), which was highly sensitive to berberine and veratraldehyde, indicating the potential targeting of Mn-SOD by these compounds.

This analysis confirmed that the compounds (berberine and veratraldehyde) target Mn-SOD. Strobilurin activity was heightened in several species of Aspergilli and *Penicillium expansum* when combined with berberine or veratrald

ehyde at specified concentrations. The compounds (berberine and veratraldehyde) also prevented specific mutations in Aspergillus fumigatus (s ak *A* Δ and m pk *C* Δ) from evading the toxicity induced by fludioxonil, a phenylpyrrole fungicide potentiated by the MAPK pathway (Kim et al., 2007).

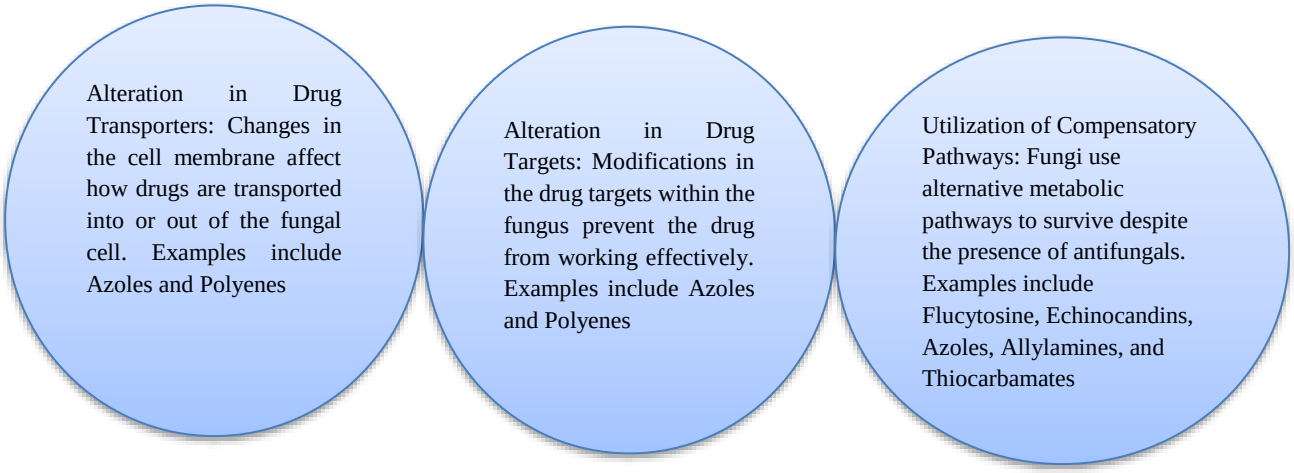

Figure 2 Pathways of Antifungal Resistance

Hsp90 as Target

Targeting Hsp90 (Heat Shock Protein 90), a molecular chaperone, plays a crucial role in maintaining protein homeostasis and regulating stress responses in cells. It has emerged as a promising strategy to combat antifungal drug resistance and enhance treatment efficacy. This is because Hsp90 plays a crucial role in fungal resistance to azoles and echinocandins, and is also involved in the PKC pathway that regulates the stress response to cell wall integrity (LaFayette et al., 2010).

Chitin synthase inhibitor

Some compounds specifically target the stress-response systems of pathogens, thereby enhancing their sensitivity to fungicides. Recent strategies for enhancing antifungal treatments found that chemosensitization can significantly boost the effectiveness of conventional drugs by targeting specific cellular systems, making fungal pathogens more vulnerable to these drugs (Dhandapani et al., 2022). For example, the fungus *Aspergillus giganteus* produces an antifungal protein (AFP). AFP induces

cell wall stress by disturbing plasma membrane integrity and inhibiting chitin synthesis in sensitive fungi. Hence, it increases the effectiveness of antifungal drugs against various fungal pathogens and can be used as a chemosensitizer to improve the performance of commercial antifungal treatments.

Generation of ROS (Reactive Oxygen Species)

Several compounds focus on the stress response system of pathogens and increase sensitivity towards fungicides; Such a strategy is known as chemosensitization. When any putative chemosensitizer is selected, it basically breaks the fungal oxidative stress response system, so the fungus is not protected by reactive oxygen species after disruption of the system. Various phenolic compounds increase the sensitivity of fungi. In one study, Dzhavakhiya et al., (2012) showed that two benzo analogs, 4-hydroxybenzaldehyde (4-HBA) and 2,3-dihydroxybenzaldehyde (2,3-DBA), and the natural phenolic compound thymol (2-isopropyl-5-methylphenol) showed significant improvement in the fungicidal bioefficacy of triazole and strobilurin fungicides. Their results also suggested that these chemosensitizers possibly attack the oxidative stress-response systems common to various fungi, such as Mn-SOD (mitochondrial superoxide dismutase) and the MAPK pathway.

7-chlorotetrazolo[5,1-c] benzo[1,2,4]triazine (CTBT) is a synthetic chemosensitizing agent that enhances the antifungal activity of drugs such as fluconazole (FLU) and itraconazole. Its mode of action involves inducing oxidative stress and targeting mitochondria, without relying on traditional mechanisms of multidrug resistance. This makes CTBT a promising compound for the development of new antifungal therapies, particularly in combination with existing antifungal agents (Cernicka et al., 2007; Batova et al., 2010). Photodynamic therapy (PDT) is a novel approach that utilizes synthetic compounds to augment th antimycotic activity of drugs. These compounds are designed to react with visible light, resulting in the production of reactive oxygen species (ROS). The generated ROS can enhance the antimicrobial activity of PDT agents, making them potential candidates for the treatment of cutaneous or mucocutaneous mycoses (Mizuno et al., 2011; Chabrier-Roselló et al., 2008).

Types of Chemosensitizing Agents Used in Agriculture

Insecticide Synergists

Synergists are a highly effective class of chemosensitizers employed in insect pest management, playing a crucial role in inhibiting metabolic detoxification enzymes (Table 1).

Table 1 Insecticide synergists as chemosensitizers

Synergist	Chemical Class	Primary Target Enzyme	Synergized Insecticide Classes
Piperonyl butoxide (PBO)	Methylenedioxyphenyl (MDP)	Cytochrome P450 monooxygenases	Pyrethroids, carbamates, and neonicotinoids
Sesamex	Lignan (natural)	P450s, esterases	Pyrethroids, organophosphates
Sesamolin	Lignan (natural)	P450s	Pyrethroids
Sulfoxide	Synthetic	Mixed function oxidases	Various
Tribufos (DEF)	Organophosphate	Esterases	Organophosphates, carbamates
Dietholate	Thiocarbamate	P450s	Organophosphates
Propyl isome	Synthetic	Mixed function oxidases	Pyrethroids, carbamates
Bucarpolate	Synthetic	P450s	Various
Octachlorodipropyl ether (S2)	Halogenated ether	P450s	Pyrethroids

Fungal Chemosensitizers

Fungal pathogens present distinct challenges, and the strategy of chemosensitization demonstrates considerable potential in enhancing the effectiveness of commercial fungicides (**Table 2**).

Table 2 Chemosensitizers active against different fungi

Chemo-sensitizer	Natural Source	Target Pathway	Synergized Fungicide	Target Pathogen	Fold Enhancement
Cinnamaldehyde	Cinnamon bark	β-1,3-glucan synthase (cell wall)	Various phenolics (eugenol, quercetin, catechin)	Wood-decaying fungi	>100-fold
Octylgallate (OG)	Gallic acid derivative	Oxidative stress response	Fludioxonil, kresoxim-methyl (strobilurin)	*Penicillium expansum, Aspergillus flavus*	Significant
2,5-Dihydroxybenzoic acid	Plant phenolic	Glutathione homeostasis	Fludioxonil	*A. flavus*	~100-fold
Berberine	Coptis chinensis (goldthread)	Mitochondrial Mn-SOD, oxidative stress	Strobilurins, fludioxonil	*A. flavus, A. fumigatus*	Substantial

2,3-Dihydroxybenzaldehyde	Synthetic analog	HOG1 MAPK signaling	Strobilurins, antimycin A	*A. flavus, P. expansum*	Moderate to high
Salicylaldehyde	Plant-derived	HOG1 osmotic/oxidative stress pathway	Strobilurins	*A. flavus*	Moderate
Long-chain alkyl gallates	Gallic acid esters	Heat sensitization (lowers thermal tolerance)	Heat treatment	Seed-borne pathogens	Enables lower temperature sanitation

Biological/Biocontrol-Derived Chemosensitizers

Lee et al. (2017) demonstrated that *Bacillus amyloliquefaciens* JCK-12 produces a combination of iturin A, fengycin, and surfactin, which work together to effectively inhibit the germination of *Fusarium graminearum* spores. Interestingly, while fengycin exhibited weak antifungal activity on its own, it significantly enhanced the efficacy of iturin A. This interaction serves as an example of chemosensitization among biological control agents (**Table 3**)

Table 3 Biocontrol Chemosensitizers

Agent	Source	Mechanism	Application
Iturin A + Fengycin	*Bacillus amyloliquefaciens* JCK-12	Synergistic membrane disruption	*Fusarium graminearum* control, mycotoxin (DON) reduction
Surfactin	*Bacillus subtilis*	Enhances iturin A penetration	Fungal spore germination inhibition
Cyclic lipopeptides (CLPs)	*Bacillus* spp.	Disruption of fungal cell membranes + inhibition of toxin biosynthesis genes	Fusarium head blight (FHB) management

Chemosensitization Agents

Cinnamaldehyde

Cinnamaldehyde is likely the most well-known natural plant product used as a chemosensitization agent against plant pathogenic fungi (Copping and Duke, 2007) (Table 4). The compound is a yellow oily liquid with a cinnamon odor and has been used to flavor foods and beverages (Figure 1). Cinnamaldehyde has been shown to have fungicidal properties against wood-decaying fungi (Yen and Chang, 2008), as well as antibacterial properties (Lee and Ahn, 1998; Friedman et al., 2002). It has inhibitory effects on ATPases, cell wall biosynthesis, and alteration of cell membrane integrity (Usta et al., 2003; Kyu-Ho et al., 2000). Cinnamaldehyde has been shown to reduce spore germination in *Aspergillus flavus* (Xie et al., 2004). It has also demonstrated chemosensitizing effects on the human fungal pathogen *Candida* species (Shreaz et al., 2016).

Thymol

Thymol, another natural plant product derived from *Thymus vulgaris* oil, is believed to disrupt fungal cell membrane integrity by reducing ergosterol content (Pinto et al., 2006). Thymol was used in a study as a chemosensitization agent co-applied with azoxystrobin in an effort to manage *Stagonospora nodorum* and *Phoma glomerata* (Dzhavakhiya et al., 2012). The results showed that the percentage of *S. nodorum* growth inhibition using thymol (10 ppm) alone was 1.1%, azoxystrobin alone was 14.8%, but when both compounds were co-applied, the inhibition was 40.9% (Dzhavakhiya et al., 2012).

Table 4 Chemosensitizing agents

COMPOUND	Active Agent	Target Enzyme	Enzyme/Receptor Action	Reference
Thymol	*Thymus vulgaris*	Ergosterol	Disrupts cell membrane integrity	Pinto et al., 2006
Cinnamaldehyde	Cinnamon	ATPases	Inhibits ATPases, cell wall biosynthesis, and alters cell membrane integrity	Usta et al., 2003, Kyu-Ho et al., 2000, Xie et al., 2004
Octyl Gallate	Benzo derivative	Cell wall	Disrupts cell wall integrity	Kim et al., 2014a
Salicylaldehyde	Benzo derivative	MAPK pathway	Targets MAPK pathway	Levin, 2005, Kim et al., 2011

Kojic Acid	*Aspergillus, Penicillium*	Tyrosinase	Inhibits tyrosinase, important in melanin biosynthesis	Chee and Lee, 2003; Kim and Chan, 2014
2,3-DHBA	Benzaldehyde	Fludioxonil resistance	Overcomes fludioxonil resistance	Kim et al., 2010b
Berberine	Plant alkaloid	Mn-SOD	Targets Mn-SOD, enhances fungicide activity	Kim et al., 2007
Veratraldehyde	Phenolic compound	Mn-SOD	Targets Mn-SOD, enhances fungicide activity	Kim et al., 2007
4-Hydroxybenzaldehyde	Benzaldehyde	Various enzymes	Enhances fungicide efficacy	Faria et al., 2011
Fengycin	*Bacillus amyloliquefaciens*	Cell membrane	Disrupts cell membrane integrity	Kim et al., 2017
Iturin A	*Bacillus subtilis*	Cell membrane	Disrupts cell membrane integrity	Ongena et al., 2007
Surfactin	*Bacillus subtilis*	Cell membrane	Disrupts cell membrane integrity	Ongena et al., 2007
Resveratrol	Grapes, berries	Various enzymes	Inhibits fungal growth, enhances fungicide activity	Adrian et al., 1998
Quercetin	Various plants	Various enzymes	Inhibits fungal growth, enhances fungicide activity	Cushnie and Lamb, 2005
Gallic Acid	Various plants	Various enzymes	Inhibits fungal growth, enhances fungicide activity	Borges et al., 2013
Curcumin	Turmeric	Various enzymes	Inhibits fungal growth, enhances fungicide activity	Kim et al., 2015
Catechin	Green tea	Various enzymes	Inhibits fungal growth, enhances fungicide activity	Friedman et al., 2002
Eugenol	Clove oil	Cell membrane	Disrupts cell membrane integrity	Devi et al., 2010, Ahmad et al., 2010
Carvacrol	Oregano oil	Cell membrane	Disrupts cell membrane integrity	Lambert and Barley, 2001
Allicin	Garlic	Various enzymes	Inhibits fungal growth, enhances fungicide activity	Ankri and Mirelman, 1999
Thymoquinone	*Nigella sativa*	Various enzymes	Inhibits fungal growth, enhances fungicide activity	Gali-Muhtasib et al., 2015
Limonene	Citrus fruits	Cell membrane	Disrupts cell membrane integrity	Fisher and Meunier, 2008
Menthol	Peppermint	Cell membrane	Disrupts cell membrane integrity	Inouye et al., 2001
Camphor	Camphor tree	Cell membrane	Disrupts cell membrane integrity	Silva et al., 2003
Saponins	Various plants	Cell membrane	Disrupts cell membrane integrity	Osbourn, 1996
Tannins	Various plants	Various enzymes	Inhibits fungal growth, enhances fungicide activity	Scalbert, 1991
Gingerol	Ginger	Various enzymes	Inhibits fungal growth, enhances fungicide activity	Singh et al., 2009
Capsaicin	Chili peppers	Various enzymes	Inhibits fungal growth, enhances fungicide activity	Dorantes et al., 2000
Piperine	Black pepper	Various enzymes	Inhibits fungal growth, enhances fungicide activity	Srinivasan, 2007

Benzo Derivatives and Natural Plant Products

In the study, benzo derivatives and natural plant products have been successfully utilized as chemosensitization agents to manage *Aspergillus*. The benzo analog used was octyl gallate, which has a mode of action that disrupts the fungal cell wall integrity. The minimum inhibitory concentration (MIC) was lowered from 0.35 mM to 0.05 mM when octyl gallate was co-applied with kresoxin methyl (strobulurin) to inhibit *A. fumigatus*. Importantly, the MIC of the chemosensitization agents that were applied alone resulted in minimal growth inhibition. Octyl gallate has been shown to possess antifungal activity, but not enough to be a stand-alone fungicide (Kim et al., 2014a).

Salicylaldehyde

Salicylaldehyde is another benzo analog that targets the mitogen-activated protein kinase (MAPK) pathway (Levin, 2005). It is another promising candidate CA when co-applied with antimycin A or kresoxim-methyl against *Aspergillus* spp. Chemosensitizing activity of salicylaldehyde combined with inhibitors of mitochondrial respiration, antimycin A or kresoxin-methyl, resulted in complete inhibition of fungal growth of *A. flavus* and *A. parasiticus* (Kim et al., 2011).

Kojic Acid

Natural compounds produced by fungi to inhibit the growth of other encroaching fungi are also chemosensitizing agents. Kojic acid is produced by *Aspergillus* and *Penicillium* spp. (Rodrigues et al., 2014). It acts by inhibiting the enzyme tyrosinase, which is an important enzyme in melanin biosynthesis (Chee and Lee, 2003). MIC was 1.3 to 2.4 times lower when the compounds were applied independently, as compared to when kojic acid was co-applied in vitro with H_2O_2 (Kim and Chan, 2014). Mutations in the *Z. tritici* gene encoding a polyketide synthase (PKS1) involved in melanin biosynthesis were linked to higher melanized colonies as well as DMI resistance (Lendenmann et al., 2015). This finding suggests the melanin biosynthesis pathway may be another possible target for chemosensitization agents.

Thymol and Benzaldehydes

Thymol (2-isopropyl-5-methylphenol), 4-hydroxybenzaldehyde (4-HBA), and 2,3-dihydroxybenzaldehyde (2,3-DHBA) are putative chemosensitizers. Two of the aforementioned benzaldehydes are effective chemosensitizers for *Candida, Aspergillus*, and *Penicillium* strains and species (Faria et al., 2011). 2,3-DHBA acted as a chemosensitizing agent to overcome fludioxonil resistance of *P. expansum*, commonly referred to as blue mold of apples, in vitro (Kim et al., 2010b). Thymol, a natural monoterpene derivative of cymene from *Thymus vulgaris* oil, is believed to disrupt fungal cell membrane integrity by reducing ergosterol content (Pinto et al., 2006). In another study, the potential of 6-demethylmevinolin (6-DMM) to enhance the sensitivity of plant pathogenic fungi to fungicides. Using Petri plate and microplate bioassays, 6-DMM was shown to affect colony growth and conidial germination of fungi such as *A. solani*, *A. alternata*, *Parastagonospora nodorum*, *Rhizoctonia solani*, and four *Fusarium* species (*F. avenaceum*, *F. culmorum*, *F. oxysporum*, and *F. graminearum*). The study determined non- or marginally toxic concentrations of 6-DMM suitable for sensitizing effects. For instance, the growth inhibition of *S. nodorum* increased significantly when 6-DMM was co-applied with triazole- and strobilurin-based fungicides. This approach suggested that 6-DMM could be used to reduce fungicide dosages, mitigate environmental impact, and manage fungicide resistance in plant pathogens (Shcherbakova et al., 2020).

Fusarium head blight (FHB) caused by *Fusarium graminearum* leads to significant crop losses and contamination with mycotoxins, posing risks to human and animal health. This study investigates the chemosensitization of *F. graminearum* to chemical fungicides using cyclic lipopeptides (CLPs) produced by *Bacillus amyloliquefaciens* strain JCK-12. Out of 500 bacterial strains isolated from soil, *B. amyloliquefaciens* JCK-12 showed strong antifungal activity and was identified as a potential biocontrol agent. The strain produces several CLPs, including iturin A, fengycin, and surfactin. Iturin A inhibited spore germination of *F. graminearum* by 70%, while a mixture of iturin A, fengycin, and surfactin exhibited a remarkable synergistic inhibitory effect, reducing spore germination by 90%. The fermentation broth and formulation of *B. amyloliquefaciens* JCK-12 reduced the incidence of FHB in wheat by 60% under field conditions. Co-application of *B. amyloliquefaciens* JCK-12 and chemical fungicides resulted in synergistic antifungal effects, increasing disease control efficacy by 50% compared to fungicides alone under greenhouse conditions. The synergistic effect is likely due to cell wall damage and altered cell membrane permeability in the fungi caused by the CLP mixtures, leading to increased sensitivity of *F. graminearum* to fungicides. This study suggests that *B. amyloliquefaciens* JCK-12 could be used as a biocontrol agent or chemosensitizer to enhance the efficacy of chemical fungicides in controlling FHB and reducing mycotoxin contamination in crops (Kim et al., 2017; Ongena et al., 2007).

Eugenol and Methyleugenol

In vitro synergy of eugenol and methyleugenol with fluconazole against clinical *Candida* isolates. The combined antifungal effects of eugenol (EUG) and methyleugenol (MEUG) with fluconazole (FLC) against clinical *Candida* isolates (Ahmad et al., 2010). The researchers tested 64 FLC-sensitive and 34 FLC-resistant clinical *Candida* isolates using checkerboard microdilution assays to determine the fractional inhibitory concentration indices (FICIs). The results showed high synergism between FLC and both EUG and MEUG, with MEUG demonstrating the greatest

synergy. Notably, FLC-resistant *Candida* isolates were highly sensitive to both EUG and MEUG, and no antagonistic activity was observed. These findings suggest that EUG and MEUG have significant potential as antifungal agents, enhancing the efficacy of FLC, particularly against FLC-resistant *Candida* infections.

Conclusion

Chemosensitization represents a promising strategy to enhance the efficacy of conventional antifungal agents and manage resistance in fungal pathogens. By combining antifungal drugs or fungicides with chemosensitizers, it is possible to achieve synergistic effects that lower the required dosages and overcome resistance mechanisms. This approach, initially developed to counter resistant cancer cells, has shown potential in plant pathology as well, particularly in managing plant pathogenic fungi. Natural compounds such as cinnamaldehyde and thymol have demonstrated significant chemosensitizing effects, making them valuable tools in agricultural and medical applications. The use of benzo derivatives like octyl gallate and salicylaldehyde further highlights the versatility of chemosensitization agents in targeting various fungal pathogens. Additionally, compounds like kojic acid and putative chemosensitizers such as 4-hydroxybenzaldehyde and 2,3-dihydroxybenzaldehyde offer new avenues for research and application.

The combination of strobilurins with phenolic compounds like berberine and veratraldehyde has shown increased antifungal activity, suggesting that targeting stress-response systems of pathogens can enhance their sensitivity to fungicides. This multifaceted approach underscores the potential of chemosensitization in developing more effective and sustainable antifungal treatments. Co-application of sensitizing agents with agricultural fungicides could retard the emergence of plant diseases using decreased dosage rates, while reducing the number of treatments, making fungicide applications more economically sound. Another potential advantage of using chemosensitizers in agriculture is the opening of new avenues for solving the problem of emerging fungicide-resistant mutants. Until now, the most common way to control resistance to fungicides has been by increasing dosages until they are effective. Chemosensitization agents (CAs) are compounds that have little to no antifungal activity, but may increase the efficacy of commercial fungicides when co-applied. CAs could lead to better management of diseases and reduced production costs. Overall, chemosensitization offers a promising avenue for improving antifungal efficacy and managing resistance, with significant implications for both agricultural and medical fields.

References

Abdallah, HM, Al-Abd, AM, El-Dine, RS, and El-Halawany, AM (2015). P-glycoprotein inhibitors of natural origin as potential tumor chemo-sensitizers: A review. *Journal of Advanced Research*, **6**(1), 45-62. https://doi.org/10.1016/j.jare.2014.11.008

Abraham, I., Jain, S., Wu, CP, Khanfar, MA, Kuang, Y., Dai, CL, and Chen, ZS (2010). Marine sponge-derived sipholane triterpenoids reverse P-glycoprotein (ABCB1)-mediated multidrug resistance in cancer cells. *Biochemical Pharmacology*, **80**(10), 1497-1506. https://doi.org/10.1016/j.bcp.2010.08.001

Adrian, M., Rajaei, H., Jeandet, P., Veneau, J., and Bessis, R. (1998). Resveratrol oxidation in *Botrytis cinerea* conidia. *Phytopathology*, **88**(5), 472-476. https://doi.org/10.1049/phyto.1998.88.5.472

Ahmad, A., Khan, A., Khan, LA, and Manzoor, N. (2010). In vitro synergy of eugenol and methyleugenol with fluconazole against clinical *Candida* isolates. *Journal of Medical Microbiology*, **59**(10), 1178-1184. https://doi.org/10.1099/jmm.0.020693-0

Ankri, S., and Mirelman, D. (1999). Antimicrobial properties of allicin from garlic. *Microbes and Infection*, **1**(2), 125-129. https://doi.org/10.1016/S1286-4579(99)80003-3

Avendaño, C., and Menéndez, JC (2015). Chapter 14 - Drugs that modulate resistance to antitumor agents. *Medicinal Chemistry of Anticancer Drugs* (Second Edition), pp. 655-700. Elsevier. https://doi.org/10.1016/B978-0-12-818549-0.00007-8

Balba, H. (2007). Review of strobilurin fungicide chemicals. *Journal of Environmental Science and Health, Part B*, **42**(4), 441-451. https://doi.org/10.1080/03601230701316465

Batova, M., Klobucnikova, V., Oblasova, Z., Gregan, J., Zahradnik, P., Hapala, I., and Schüller, C. (2010). Chemogenomic and transcriptome analysis identifies the mode of action of the chemosensitizing agent CTBT. *BMC Genomics*, **11**, 1-16. (Article number: 295). https://doi.org/10.1186/1471-2164-11-153

Borges, A., Ferreira, C., Saavedra, MJ, and Simões, M. (2013). Antibacterial activity and mode of action of ferulic and gallic acids against pathogenic bacteria. *Microbial Drug Resistance*, **19**(4), 256-265. https://doi.org/10.1089/mdr.2012.0244

Campbell, B., Chan, K., and Kim, JH (2012). Chemosensitization as a means to augment commercial antifungal agents. *Frontiers in Microbiology*, **3**, 79. https://doi.org/10.3389/fmicb.2012.00079

Castino, R., Peracchio, C., Salini, A., Nicotra, G., Trincheri, NF, Demoz, M., Valente, G., and Isidoro, C. (2009). Chemotherapy drug response in ovarian cancer cells strictly depends on a cathepsin D-Bax activation loop. *Journal of Cellular and Molecular Medicine*, **13**(6), 1096–

1109. https://doi.org/10.1111/j.1582-4934.2008.00435.x

Cernicka, J., Kozovska, Z., Hnatova, M., Valachovic, M., Hapala, I., Riedl, Z., and Subik, J. (2007). Chemosensitisation of drug-resistant and drug-sensitive yeast cells to antifungals. *International Journal of Antimicrobial Agents*, **29**(2), 170-178. https://doi.org/10.1016/j.ijantimicag.2006.08.037

Chabrier-Roselló, Y., Foster, TH, Mitra, S., and Haidaris, CG (2008). Respiratory deficiency enhances the sensitivity of the pathogenic fungus *Candida* to photodynamic treatment. *Photochemistry and Photobiology*, **84**(5), 1141-1148. https://doi.org/10.1111/j.1751-1097.2007.00280.x

Chee, HY, and Lee, EH (2003). Fungistatic activity of kojic acid against human pathogenic fungi and inhibition of melanin-production in *Cryptococcus neoformans*. *Mycobiology*, **31**(4), 248-250. https://doi.org/10.4489/MYCO.2003.31.4.248

Copping, LG, and Duke, SO (2007). Natural products that have been used commercially as crop protection agents. *Pest Management Science*, 63(6), 524-554. https://doi.org/10.1002/ps.1378

Cushnie, TT, and Lamb, AJ (2005). Antimicrobial activity of flavonoids. *International Journal of Antimicrobial Agents*, **26**(5), 343-356. https://doi.org/10.1016/j.ijantimicag.2005.09.002

Devi, KP, Nisha, SA, Sakthivel, R., and Pandian, SK (2010). Eugenol acts as an antibacterial agent against *Salmonella typhi* by disrupting the cellular membrane. *Journal of Ethnopharmacology*, **130**(1), 107-115. https://doi.org/10.1016/j.jep.2010.04.025

Dhandapani, K., Sivarajan, K., Ravindhiran, R., and Sekar, JN (2022). Fungal infections as an uprising threat to human health: Chemosensitization of fungal pathogens with AFP. *Frontiers in Cellular and Infection Microbiology*, **12**, 887971. https://doi.org/10.3389/fcimb.2022.887971

Dorantes, L., Colmenero, R., Hernandez, H., Mota, L., Jaramillo, ME, Fernandez, E., and Solano, C. (2000). Inhibition of growth of some foodborne pathogenic bacteria by *Capsicum annum* extracts. *International Journal of Food Microbiology*, **57**(1-2), 125-128. https://doi.org/10.1016/S0168-1605(00)00216-6

Dzhavakhiya, V., Shcherbakova, L., Semina, Y., Zhemchuzhina, N., and Campbell, B. (2012). Chemosensitization of plant pathogenic fungi to agricultural fungicides. *Frontiers in Microbiology*, **3**, 87. https://doi.org/10.3389/fmicb.2012.00087

El-Dairy, WS (2003). The role of p53 in chemosensitivity and radiosensitivity. *Oncogene*, **22**(47), 7486–7495. https://doi.org/10.1038/sj.onc.1206949

Faria, NCG, Kim, JH, Gonçalves, LAP, Martins, M., Chan, KL, and Campbell, BC (2011). Enhanced activity of antifungal drugs using natural phenolics against yeast strains of *Candida* and *Cryptococcus*. *Letters in Applied Microbiology*, **52**(5), 506–513. https://doi.org/10.1111/j.1472-765X.2011.03032.x

Fisher, N., and Meunier, B. (2008). Molecular basis of resistance to cytochrome bc1 inhibitors. *FEMS Yeast Research*, **8**(2), 183-192. https://doi.org/10.1111/j.1567-1364.2007.00328.x

Friedman, M., Henika, PR, and Mandrell, RE (2002). Bactericidal activities of plant essential oils and constituents against foodborne pathogenic bacteria in relation to 4-hydroxybenzoate content. *Journal of Food Protection*, **65**(10), 1545-1560. https://doi.org/10.4315/0362-028X-65.10.1545

Gali-Muhtasib, H., Hmadi, R., Kareh, M., Tohme, R., and Darwiche, N. (2015). Cell death mechanisms of plant-derived anticancer drugs: beyond apoptosis. *Apoptosis*, **20**(12), 1531-1562. https://doi.org/10.1007/s10495-015-1169-2

Huang, Y. (2007). Pharmacogenetics/genomics of membrane transporters in cancer chemotherapy. *Cancer and Metastasis Reviews*, **26**(1), 183-201. https://doi.org/10.1007/s10555-007-9050-6

Inouye, S., Takizawa, T., and Yamaguchi, H. (2001). Antibacterial activity of essential oils against respiratory tract pathogens by gaseous contact. *Journal of Antimicrobial Chemotherapy*, **47**(5), 565-573. https://doi.org/10.1093/jac/47.5.565

Karthikeyan, S., and Laxmanappa Hoti, S. (2015). Development of fourth generation ABC inhibitors from natural products to overcome cancer multidrug resistance. *Anti-Cancer Agents in Medicinal Chemistry*, **15**(5), 605-615. https://doi.org/10.2174/1871520615666150113103439

Kim, JH, and Chan, KL (2014). Augmenting the antifungal activity of an oxidizing agent with kojic acid. *Molecules*, **19**(11), 18448-18464. https://doi.org/10.3390/molecules191118448

Kim, JH, Campbell, BC, Mahoney, N., Chan, KL, and Molyneux, RJ (2011). Chemosensitization of aflatoxigenic fungi using salicylaldehyde. *Mycopathologia*, **171**(4), 291-298. https://doi.org/10.1007/s11046-010-9356-8

Kim, JH, Campbell, BC, Mahoney, N., Chan, KL, Molyneux, RJ, and Xiao, C.-L. (2010). Use of chemosensitization to overcome fludioxonil-resistance in *Penicillium expansum*. *Letters in Applied Microbiology*, **51**(2), 177–183. https://doi.org/10.1111/j.1472-765X.2010.02875.x

Kim, JH, Campbell, BC, Mahoney, N., Chan, KL, Molyneux, RJ, and May, GS (2007). Enhanced

activity of strobilurin and fludioxonil by using berberine and phenolic compounds. *Letters in Applied Microbiology*, **45**(2), 134-141. https://doi.org/10.1111/j.1472-765X.2007.02159.x

Kim, JH, Chan, KL, and McConnell, LL (2015). Augmenting the efficacy of fungal and mycotoxin control via chemosensitization. *Outlooks on Pest Management*, **26**(4), 171-175. https://doi.org/10.1564/v26_aug_08

Kim, JH, Mahoney, N., Chan, KL, Campbell, BC, Haff, RP, and Stanker, LH (2014). Use of benzo analogs to enhance antimycotic activity of kresoxim methyl. In *Global Health Issues of Aflatoxins in Food and Agriculture* (Vol. 5, No. **5**, pp. 96-111). https://doi.org/10.3389/fmicb.2014.00087

Kim, JY, Kim, EH, Park, SS, Lim, JH, Kwon, TK, and Choi, KS (2008). Quercetin sensitizes human hepatoma cells to TRAIL-induced apoptosis via Sp1-mediated DR5 up-regulation and proteasome-mediated c-FLIPS down-regulation. *Journal of Cellular Biochemistry*, **105**(6), 1386–1398. https://doi.org/10.1002/jcb.21958

Kim, K., Lee, Y., Ha, A., Kim, JI, Park, AR, Yu, NH, Son, H., Choi, GJ, Park, HW, Lee, CW, Lee, T., Lee, YW, and Kim, JC (2017). Chemosensitization of *Fusarium graminearum* to chemical fungicides using cyclic lipopeptides. *Frontiers in Plant Science*, **8**, 2010. https://doi.org/10.3389/fpls.2017.02010

Krishna, R., and Mayer, LD (2001). Multidrug resistance in cancer: mechanisms and reversal using modulators. *European Journal of Pharmaceutical Sciences*, **11**(4), 265-283. https://doi.org/10.1016/S0928-0987(00)00114-7

Kyu-Ho, BANG, Dong-Won, LEE, Hee-Moon, PARK, and Young-Ha, RHEE (2000). Inhibition of fungal cell wall synthesizing enzymes by trans-cinnamaldehyde. *Bioscience, Biotechnology, and Biochemistry*, **64**(5), 1061-1063. https://doi.org/10.1271/bbb.64.1061

LaFayette, SL, Collins, C., Zaas, AK, Schell, WA, Betancourt-Quiroz, M., Gunatilaka, AL, and Cowen, LE (2010). PKC signaling regulates drug resistance of the fungal pathogen *Candida albicans*. *PLoS Pathogens*, **6**(8), e1001069. https://doi.org/10.1371/journal.ppat.1001069

Lambert, MJ, and Barley, DE (2001). Research summary on the therapeutic relationship and psychotherapy outcome. *Psychotherapy: Theory, Research, Practice, Training*, **38**(4), 357-361. https://doi.org/10.1037/0033-3204.38.4.357

Lanyi, A., Deb, D., Seymour, RC, Ludes-Meyers, JH, Subler, MA, and Deb, S. (1998). "Gain of function" phenotype of tumor-derived mutant p53 requires the oligomerization/non-sequence-specific nucleic acid-binding domain. *Oncogene*, **16**(24), 3169–3176. https://doi.org/10.1038/sj.onc.1201857

Lee, HS, and Ahn, YJ (1998). Growth-inhibiting effects of *Cinnamomum cassia* bark-derived materials on human intestinal bacteria. *Journal of Agricultural and Food Chemistry*, **46**(1), 8-12. https://doi. org/10.1021/jf970548y

Lendenmann, MH, Croll, D., and McDonald, BA (2015). QTL mapping of fungicide sensitivity reveals novel genes and pleiotropy with melanization. *Fungal Genetics and Biology*, 80, 53-67.https://doi.org/10.1016/j.fgb.2015.05.001

Levin, DE (2005). Cell wall integrity signaling in *Saccharomyces cerevisiae*. *Microbiology and Molecular Biology Reviews*, **69**(2), 262-291. https://doi.org/10.1128/MMBR.69.2.262-291.2005

Llobet, D., Eritja, N., Encinas, M., Llecha, N., Yeramian, A., Pallares, J., Sorolla, A., Gonzalez-Tallada, FJ, Matias-Guiu, X., and Dolcet, X. (2008). CK2 controls TRAIL and Fas sensitivity by regulating FLIP levels in endometrial carcinoma cells. *Oncogene*, **27**(17), 2513–2524. https://doi.org/10.1038/sj.onc.1210924

Ma, Z., and Michailides, TJ (2005). Advances in understanding molecular mechanisms of fungicide resistance in phytopathogenic fungi. *Crop Protection*, **24**(10), 853-863. https://doi.org/10.1016/j.cropro.2005.01.011

Mizuno, K., Zhiyentayev, T., Huang, L., Khalil, S., Nasim, F., Tegos, GP, and Hamblin, MR (2011). Antimicrobial photodynamic therapy with functionalized fullerenes. *Journal of Nanomedicine & Nanotechnology*, 2(2), 1000114. https://doi.org/10.4172/2157-7439.1000109

Nawrath, H., and Raschack, M. (1987). Effects of (-)-desmethoxyverapamil on heart and vascular smooth muscle. *The Journal of Pharmacology and Experimental Therapeutics*, **242**(3), 1090-1097.https://doi.org/10.1016/S0022-3565(25)39159-7

Nishida, N., Yamashita, S., Mimori, K., Sudo, T., Tanaka, F., Shibata, K., Yamamoto, H., Ishii, H., Doki, Y., and Mori, M. (2012). MicroRNA-10b is a prognostic indicator in colorectal cancer and confers resistance to the chemotherapeutic agent 5-fluorouracil in colorectal cancer cells. *Annals of Surgical Oncology*, **19**(9), 3065–3071. https://doi.org/10.1245/s10434-012-2246-1

Ongena, M., Jourdan, E., Adam, A., Paquot, M., Brans, A., Joris, B., and Thonart, P. (2007). Surfactin and fengycin lipopeptides of *Bacillus subtilis* as elicitors of induced systemic resistance. *Environmental Microbiology*, **9**(4), 1084-1090. https://doi.org/10.1111/j.1462-2920.2006.01202.x

Osbourn, AE (1996). Preformed antimicrobial compounds and plant defense against fungal attack. *The Plant Cell*, **8**(10), 1821-1833. https://doi.org/10.1105/tpc.8.10.1821

Pervaiz, S., and Clement, MV (2004). Tumor intracellular redox status and drug resistance—serendipity or a causal relationship? *Current Pharmaceutical Design*, **10**(16), 1969–1977. https://doi.org/10.2174/1381612043384411

Pinto, E., Pina-Vaz, C., Salgueiro, L., Goncalves, MJ, Costa-de-Oliveira, S., Cavaleiro, C., Palmeira, A., Rodrigues, A., and Martinez-de-Oliveira, J. (2006). Antifungal activity of the essential oil of *Thymus pulegioides* on *Candida*, *Aspergillus* and dermatophyte species. *Journal of Medical Microbiology*, **55**(10), 1367–1373. https://doi.org/10.1099/jmm.0.46443-0

Pirker, R., Keilhauer, G., Raschack, M., Lechner, C., and Ludwig, H. (1990). Reversal of multi-drug resistance in human KB cell lines by structural analogs of verapamil. *International Journal of Cancer*, **45**(5), 916-919. https://doi.org/10.1002/ijc.2910450523

Ravi, R., and Bedi, A. (2002). Sensitization of tumor cells to Apo2 ligand/TRAIL-induced apoptosis by inhibition of casein kinase II. *Cancer Research*, **62**(15), 4180–4185. https://doi.org/10.1158/0008-5472.CAN-02-1545

Rodrigues, APD, Farias, LHS, Carvalho, ASC, Santos, AS, do Nascimento, JLM, and Silva, EO (2014). A novel function for kojic acid as antileishmanial agent. *PLoS ONE*, **9**(3), e91259. https://doi.org/10.1371/journal.pone.0091259

Scalbert, A. (1991). Antimicrobial properties of tannins. *Phytochemistry*, **30**(12), 3875-3883. https://doi.org/10.1016/0031-9422(91)83426-L

Shabbits, JA, Hu, Y., and Mayer, LD (2003). Tumor chemosensitization strategies based on apoptosis manipulations. *Molecular Cancer Therapeutics*, **2**(8), 805-813. https://pubmed.ncbi.nlm.nih.gov/12939471/

Shcherbakova, L., Kartashov, M., Statsyuk, N., Pasechnik, T., and Dzhavakhiya, V. (2020). Assessment of the sensitivity of some plant pathogenic fungi to 6-demethylmevinolin. *Antibiotics*, **9**(12), 842. https://doi.org/10.3390/antibiotics9120842

Shiraga, K., Sakaguchi, K., Senoh, T., Ohta, T., Ogawa, S., Sawayama, T., and Tsuji, T. (2001). Modulation of doxorubicin sensitivity by cyclosporine A in hepatocellular carcinoma cells. *Journal of Gastroenterology and Hepatology*, **16**(4), 460-466. https://doi.org/10.1046/j.1440-1746.2001.02457.x

Shkel', TV, Vasilevskaya, AV, Gilep, AA, Chernovetskii, MA, Luk'yanenko, IG, and Usanov, SA (2013). Structural features of cytochrome P450 11B1 (CYP11B1) from *Homo sapiens*. *Trudy Belorusskogo Gosudarstvennogo Universiteta*, **8**(1), 152-158. https://doi.org/10.1016/j.jsbmb.2013.04.002

Shreaz, S., Wani, WA, Behbehani, JM, Raja, V., Irshad, M., Karched, M., and Hun, LT (2016). Cinnamaldehyde and its derivatives, a novel class of antifungal agents. *Fitoterapia*, **112**, 116-131. https://doi.org/10.1016/j.fitote.2016.05.016

Silva, J., Abebe, W., Sousa, SM, Duarte, VG, Machado, MIL, and Matos, FJA (2003). Analgesic and anti-inflammatory effects of essential oils of *Eucalyptus*. *Journal of Ethnopharmacology*, **89**(2-3), 277-283. https://doi.org/10.1016/j.jep.2003.09.007

Singh, AB, Akanksha, SN, Maurya, R., and Srivastava, AK (2009). Anti-hyperglycaemic, lipid lowering and anti-oxidant properties of [6]-gingerol in db/db mice. *International Journal of Medical and Medical Sciences*, **1**(12), 536-544. https://doi.org/10.5897/IJMMS.9000122

Srinivasan, K. (2007). Black pepper and its pungent principle-piperine: a review of diverse physiological effects. *Critical Reviews in Food Science and Nutrition*, **47**(8), 735-748. https://doi.org/10.1080/10408390601062054

Tan, L., Kwok, RP, Shukla, A., Kshirsagar, M., Zhao, L., Opipari, AW, Jr., and Liu, JR (2011). Trichostatin A restores Apaf-1 function in chemoresistant ovarian cancer cells. *Cancer*, **117**(4), 784–794. https://doi.org/10.1002/cncr.25649

Toppmeyer, D., Seidman, AD, Pollak, M., Russell, C., Tkaczuk, K., Verma, S., and Demetri, GD (2002). Safety and efficacy of the multidrug resistance inhibitor biricodar in combination with paclitaxel. *Clinical Cancer Research*, **8**(3), 670-678. https://doi.org/10.1128/aac.48.11.4171-4176.2004

Tsuruo, T., Iida, H., Tsukagoshi, S., and Sakurai, Y. (1981). Overcoming of vincristine resistance in P388 leukemia through enhanced cytotoxicity by verapamil. *Cancer Research*, **41**(5), 1967-1972. https://api.semanticscholar.org/CorpusID:15484163

Ugurel, S., Rappl, G., Tilgen, W., and Reinhold, U. (2001). Increased soluble CD95 (sFas/CD95) serum level correlates with poor prognosis in melanoma patients. *Clinical Cancer Research*, **7**(5), 1282–1286. Online ISSN: 1557-3265

Usta, J., Kreydiyyeh, S., Barnabe, P., Bou-Moughlabay, Y., and Nakkash-Chmaisse, H. (2003). Effect of cinnamon and clove extracts and their main components on different types of ATPases. *Human & Experimental Toxicology*, **22**(7), 355-362. https://doi.org/10.1191/0960327103ht379oa

Vega-Chacón, Y., de Albuquerque, MC, Pavarina, AC, Goldman, GH, and Mima, EGDO (2021). Verapamil inhibits efflux pumps in *Candida albicans* and exhibits synergism with fluconazole. *Virulence*, **12**(1), 231-243. https://doi.org/10.1080/21505594.2020.1868814

Vinod, BS, Maliekal, TT, and Anto, RJ (2013). Phytochemicals as chemosensitizers: from molecular mechanism to clinical significance.

Antioxidants & Redox Signaling, **18**(11), 1307-1348. https://doi.org/10.1089/ars.2012.4573

Weller, M., Malipiero, U., Aguzzi, A., Reed, JC, and Fontana, A. (1995). Protooncogene bcl-2 gene transfer abrogates Fas/APO-1 antibody-mediated apoptosis of human malignant glioma cells and confers resistance to chemotherapeutic drugs. *The Journal of Clinical Investigation*, **95**(6), 2633–2643. https://doi.org/10.1172/JCI117965

Wood, PM, and Hollomon, DW (2003). A critical evaluation of the role of alternative oxidase in the performance of strobilurin fungicides. *Pest Management Science*, **59**(5), 499-511. https://doi.org/10.1002/ps.655

Xie, XM, Fang, JR, and Xu, Y. (2004). Study of antifungal effect of cinnamaldehyde and citral on *Aspergillus flavus*. *Food Science*, **25**(9),31-34. https://doi.org/10.3321/j.issn:10026630.2004.09.003

Yen, TB, and Chang, ST. (2008). Synergistic effects of cinnamaldehyde in combination with eugenol against wood decay fungi. *Bioresource Technology*,**99**(1),232–236. https://doi.org/10.1016/j.biortech.2006.11.022

Statements and Declarations

Authors' Contribution

KT and RK Conceptualization, data curation, writing - first draft, formal analysis, investigation, methodology; formal analysis, validation, data curation, software, writing - review and editing. PK and NAS provide guidance and assistance during the article. All authors made important contributions, reviewed, and approved the published version of the work.

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