

REVIEW ARTICLE

Harnessing benzamides as plant stress inhibitors, growth promoters and in management of crop resilience—A review

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DNA repair; PARP inhibitors; PARylation; plant biotechnology; stress management.

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ABSTRACT

Benzamides have emerged as potent stress inhibitors and growth promoters in plant biotechnology, particularly in the management of crop resilience. This review delves into the mechanisms of action, applications, and potential benefits of benzamides, especially focusing on their role as poly(ADP-ribose) polymerase (PARP) inhibitors. Benzamides modulate stress responses by inhibiting PARP activity, which is crucial for DNA repair and maintaining genomic stability. This inhibition prevents excessive poly(ADP-ribosylation), conserving cellular energy and enhancing stress tolerance. Additionally, benzamides promote alternative DNA repair pathways, contributing to the timely repair of DNA lesions and reducing mutation accumulation. In plant stress management, classical PARP inhibitors like 3-methoxybenzamide (3-MBA) and 3-aminobenzamide (3-AB) have demonstrated efficacy in enhancing resistance to abiotic stresses, improving plant growth, and increasing transformation efficiency. This review also highlights the antimicrobial, herbicidal, and insecticidal properties of benzamides, which enhance plant defence mechanisms against various pests and diseases. In summary, benzamides offer multiple approaches to enhancing crop resilience and stress management, with significant implications for sustainable agriculture.

INTRODUCTION

Stress management is a critical aspect of crop resilience, particularly in the context of changing environmental conditions and increasing biotic and abiotic stresses (Janni *et al.* 2019). Crops face numerous challenges, including drought, salinity, and attack by pests and diseases, all of which can significantly impact their productivity, with resultant effects on food security and metabolite production for pharmaceuticals. Enhancing stress tolerance in crops is essential for ensuring sustainable agricultural practices and mitigating the adverse effects of environmental stressors on crop yield and quality. By harnessing benzamides as stress inhibitors, researchers have developed innovative strategies for managing stress and improving crop resilience in plant biotechnology.

In crop production, benzamides have been found to inhibit poly(ADP-ribosylation) (PARylation), which is crucial for DNA repair and genomic stability (Guastafierro *et al.* 2008a). By regulating poly(ADP-ribose) polymerase (PARP) activity, benzamides may assist in maintaining the epigenetic state responsible for DNA methylation, which is vital for gene expression and regulation. The inhibition of PARylation could potentially enhance plant growth regulation and the overall genomic integrity. This could potentially shift the balance from PARP-mediated single-strand break repair (SSBR) toward alternative mechanisms such as nucleotide excision repair (NER) or homologous recombination (HR), a modulation that could potentially enhance genomic stability and influence

epigenetic regulation related to DNA methylation. In *Arabidopsis thaliana*, PARP1 and PARP2 catalyse PARylation upon DNA strand break detection, resulting in the recruitment of repair proteins such as XRCC1 (X-ray repair cross-complementing protein 1) that facilitate base excision repair (BER) and SSBR (Guastafierro *et al.* 2008b; Kalisch *et al.* 2021). This repair machinery can loosen the chromatin and may initiate the assembly of repair complexes at the sites of DNA damage (Dantzer *et al.* 1999; Kim *et al.* 2005). Thus, benzamide-mediated inhibition of PARP activity not only reduces PARylation but can also further slow the repair process by the BER/SSBR pathway (Haince *et al.* 2008; Pascal 2018). Beyond this repair shift, PARylation can influence chromatin remodelling and epigenetic regulation, such as the maintenance of DNA methylation marks key in gene expression and regulation (Guastafierro *et al.* 2008a; Kalisch *et al.* 2021). This means that benzamide-induced inhibition of PARP activity can stabilize epigenetic states by lowering PARylation targeted at chromatin re-modellers, which will in turn promote genomic integrity and appropriate gene regulation during development and stress response (Sousa *et al.* 2012).

In this review, we explore the mechanisms of benzamides' action, their agricultural applications in plant stress and disease management, impact on plant growth and development, challenges, and future perspectives. By exploring the role of benzamides in stress management and crop resilience, we aim to provide insights into the potential of benzamides in revolutionizing agriculture.

MECHANISMS OF BENZAMIDE ACTION

Mechanism of action in relation to poly(ADP-ribose)ation/PARYlation

Poly(ADP-ribose)ation is a rapid and transient post-translational protein modification that was described first in mammalian cells (Hassa *et al.* 2006). PARPs are key enzymes involved in poly(ADP-ribose)ation, with distinct roles in mammalian and plant systems (Wang *et al.* 1995). In mammals, PARPs have been implicated in DNA repair, chromatin remodelling, and cell death pathways (Bueren *et al.* 2011). Activated by the sensing of DNA strand breaks, poly(ADP-ribose) polymerase1 (PARP1) transfers ADP-ribose units onto itself and other target proteins using NAD⁺ as a substrate. Subsequently, DNA damage responses and other cellular responses are initiated. In plants, poly(ADP-ribose) polymerases (PARPs) have also been implicated in responses to DNA damage (Rissel & Peiter 2019). They play a crucial role in stress signalling, defence responses, and developmental processes (Perez-Lamigueiro & Alvarez-Gonzalez 2004). Over-activation of PARPs can cause a rapid breakdown of the NAD⁺ and ATP pools (Rissel & Peiter 2019). Consequently, resynthesis of NAD⁺ is stimulated, whereby three (NAD⁺ salvage pathway) to five (de novo synthesis) molecules of ATP are used for each molecule of NAD⁺ (De Block *et al.* 2005). As a result, the cellular ATP is depleted which leads to necrotic cell death (Fig. 1). It can therefore be expected that PARP inhibitors can decrease the degree of abiotic stress and cell death triggered by this process while the plant can use other forms of DNA repair that consume less energy than poly(ADP-ribose)ation (Heym *et al.* 2012; Schulz *et al.* 2012). PARP inhibitors are more robust than the genetic abolition of PARP gene expression (Rissel & Peiter 2019). The differential functions of PARPs in mammalian and plant systems highlight the complexity of poly

(ADP-ribose)ation-mediated processes and the need to elucidate the specific roles of PARPs in plant stress responses for effective crop management.

Poly(ADP-ribose)ation inhibition by benzamides

Benzamides have emerged as promising inhibitors in plant biotechnology, particularly in the context of stress management in crops. These compounds have shown potential in inhibiting stress-related pathways and enhancing crop resilience. For instance, benzamide derivatives have been explored for their inhibitory effects on programmed cell death pathways, indicating a role in modulating stress responses (Teng *et al.* 2008).

Benzamides in plants have a beneficial effect through the inhibition of PARYlation, primarily by modulating the activation and potential over-activation of PARPs (Campi *et al.* 2011). This inhibition can lead to the prevention of excessive PARYlation, which is crucial for maintaining genomic stability and DNA repair processes. By regulating PARP activity, benzamides may help preserve the integrity of DNA, preventing aberrant PARYlation-induced signalling that could lead to cell death or genomic instability. Furthermore, benzamides have been associated with controlling energy depletion and necrotic cell death in plants (Liang *et al.* 2006). This mechanism could potentially contribute to the elimination of damaged cells, thereby enhancing overall plant health and stress responses.

Mechanism of action in relation to DNA repair modulation

In terms of DNA repair modulation, benzamides promote alternative DNA repair mechanisms in plants, such as nucleotide excision repair (NER) and homologous recombination (HR) (Vitale *et al.* 2022). By enhancing the efficiency of these repair pathways, benzamides aid in the timely and accurate

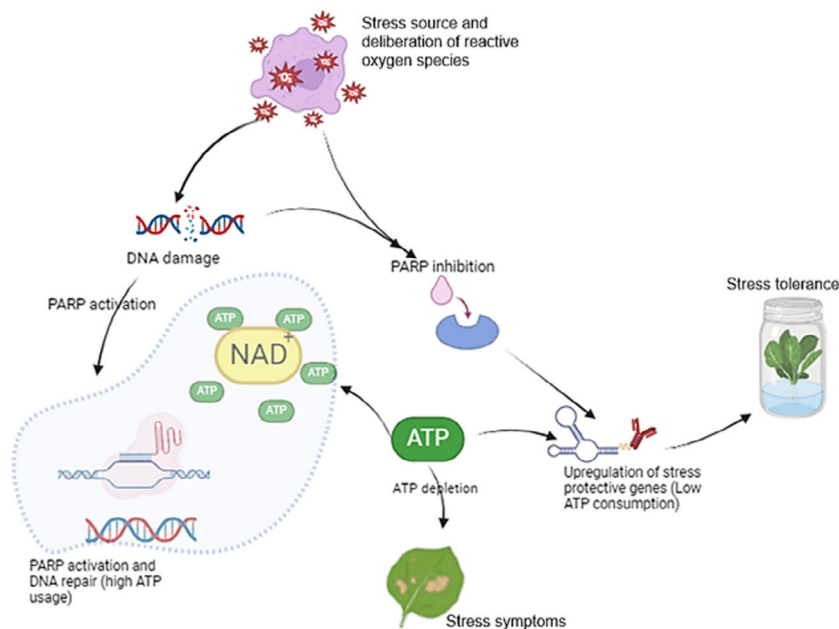


Fig. 1. A hypothetical relationship between stress and PARP enzyme activation and inhibition. Addition of PARP inhibitors leads to cell energy reserves, upregulation of stress protective genes, and increased stress tolerance.

repair of DNA lesions, thereby reducing the accumulation of mutations and maintaining genomic stability. Additionally, benzamides have been reported to influence the role of DNA repair processes in plants, particularly in the context of genome stability and stress responses (Krasileva 2019). These compounds are known inhibitors of poly(ADP-ribose) polymerase (PARP), a key enzyme involved in the base excision repair (BER) pathway (Guastafierro *et al.* 2008b; Pascal 2018). By inhibiting PARP activity, benzamides suppress the BER pathway and thereby reduce the repair of single-strand breaks via this mechanism (Kim *et al.* 2005). This inhibition triggers a compensatory shift toward alternative repair mechanisms, such as NER and homologous recombination (HR) (Haince *et al.* 2008; Bryant *et al.* 2009). NER becomes more prominent in handling bulky DNA lesions, while HR plays a critical role in the error-free repair of double-strand breaks, especially during replication stress (Scully *et al.* 2019; Marteiijn *et al.* 2014; see Fig. 2). This modulation of DNA repair pathway preference can enhance genome surveillance and stability under stress conditions by favouring high-fidelity repair processes (Kalisch *et al.* 2021). As a result, benzamides may

contribute to improved plant resilience by facilitating more robust responses to genotoxic stress and maintaining genome integrity under adverse environmental conditions (Desset *et al.* 2019).

APPLICATIONS OF BENZAMIDES IN PLANT STRESS MANAGEMENT

Classical PARP inhibitors

Table 1 provides details on some benzamides and their derivatives, together with known beneficial effects on plant growth and development. For example, 3-methoxybenzamide (3-MBA) has been identified as a stress inhibitor and classical PARP inhibitor in plants. Research has shown that 3-MBA can influence stress responses in plants by modifying rates of homologous recombination (Adams-Phillips *et al.* 2009). Studies have also demonstrated that 3-MBA can block the induction of betacyanin biosynthesis (involved in oxidative stress) in red beet callus lines without affecting cell growth, indicating its potential involvement in stress pathway regulation (Girod &

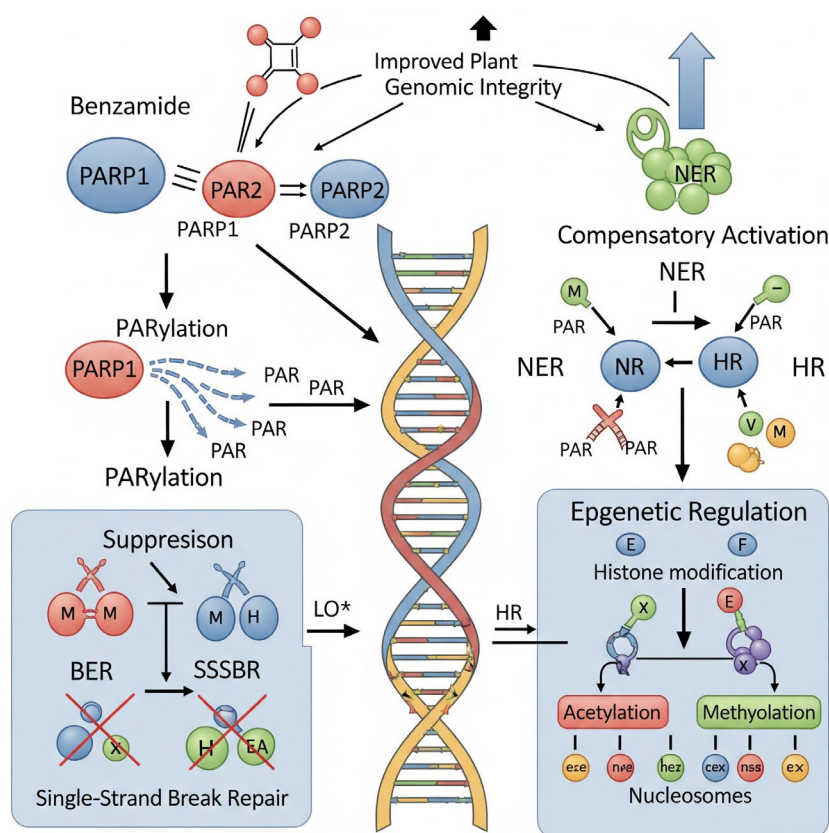


Fig. 2. Benzamide-mediated inhibition of poly(ADP-ribose) polymerase (PARP) modulates DNA repair pathway choice and epigenetic regulation in *Arabidopsis thaliana*. PARP1 and PARP2 enzymes detect DNA strand breaks and catalyse poly(ADP-ribosylation) (PARylation), which recruits repair proteins such as XRCC1 (X-ray repair cross-complementing protein 1) to facilitate base excision repair (BER) and single-strand break repair (SSBR). Benzamides inhibit PARP activity, reducing PARylation and suppressing BER/SSBR. This leads to compensatory activation of nucleotide excision repair (NER) to resolve bulky DNA lesions, and homologous recombination (HR) for accurate repair of double-strand breaks, thereby enhancing genomic stability. PARylation also regulates chromatin remodelling and DNA methylation, key for epigenetic control. Inhibition by benzamides stabilizes epigenetic marks, contributing to appropriate gene regulation and improved stress resilience. Legend keys: PARP1/2: Poly(ADP-ribose) polymerase 1 and 2; PARylation (PAR): Poly(ADP-ribosylation), a post-translational modification; BER: Base excision repair; SSSBR: Single-strand break repair; NER: Nucleotide excision repair; HR: Homologous recombination; Blue arrows: DNA repair signalling and pathway activation.

Table 1. Some examples of benzamides, their derivatives, and reported beneficial effects on plant growth and development.

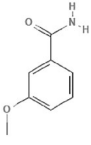
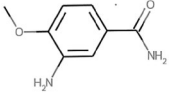
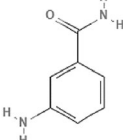
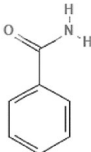
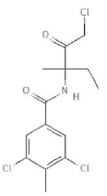
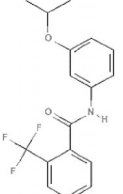
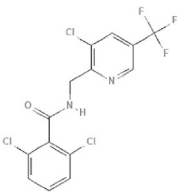
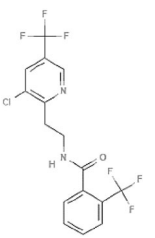
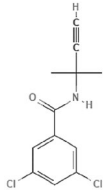
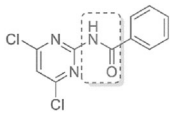
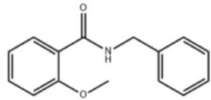
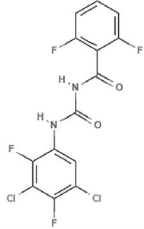
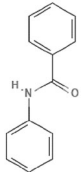
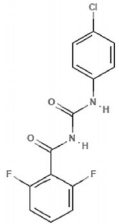
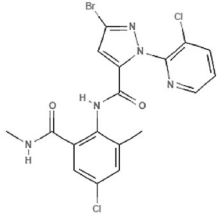
benzamide compound/ derivative	category	structure	reported effect/function	references
3-Methoxybenzamide	PARP inhibitor		Reported for its inhibitory effects on essential bacterial cell division proteins, suggesting potential applications in crop protection and disease management in amaranth. Improved plant growth, microtubularization, and transformation efficiency in <i>Solanum tuberosum</i>	Lü <i>et al.</i> 1999; Chetty <i>et al.</i> 2020
3-Amino-4-methoxybenzamide	PARP inhibitor		An inhibitor of poly(ADP-ribosylation) and shown to enhance plant resistance to abiotic stresses, such as high light and oxidative damage	Briggs <i>et al.</i> 2017
3-Aminobenzamide	PARP inhibitor		This PARP inhibitor modulates gene expression related to stress responses in plants, including antiviral defence mechanisms Reported for inhibition of oxidative stress in <i>Catharanthus roseus</i>	Berglund <i>et al.</i> 1996; Teng <i>et al.</i> 2008; Motaung 2020; Spechenkova <i>et al.</i> 2023
Benzylamide III	Antimicrobial		Has antimicrobial properties, particularly against <i>P. aeruginosa</i> , suggesting its potential in enhancing plant defence mechanisms against pathogens	Vlasov <i>et al.</i> 2022
Zoxamide	Antimicrobial		A benzamide and anti-tubulin fungicide used commercially against oomycete development in crops Prevents blight and downy mildew by interfering with nuclear division	Podhorniak 2014; Freitas <i>et al.</i> 2022
Flutolanil	Antimicrobial		Hinders fungal mycelium growth especially <i>Rhizoctonia solani</i> , thus reducing disease severity	Teng <i>et al.</i> 2019
Fluopicolide	Antimicrobial		Targets oomycetes that harm a wide array of crops	Wen 2023
Fluopyram	Antimicrobial		A pyridinyl-ethyl-benzamide fungicide effective as a succinate dehydrogenase inhibitor, impeding ATP synthesis in fungal mitochondrial respiratory chain	Xie <i>et al.</i> 2022; Freitas <i>et al.</i> 2022

Table 1. (Continued)

benzamide compound/ derivative	category	structure	reported effect/function	references
N-(1,1-dimethylpropynyl)-3,5-dichlorobenzamide	Herbicide		Also known as propyzamide, and used as a systemic post-emergent herbicide for control of grass and broadleaf weeds in a wide range or variety of fruit and root crops.	Smith <i>et al.</i> 1971
N-(4,6-Dichloropyrimidine-2-Yl)Benzamide	Herbicide safener		Protective effect on metolachlor injury in rice seedlings	Zheng <i>et al.</i> 2018
N-benzyl-2-methoxybenzamide	Herbicide		Interferes with the carotenoid biosynthesis pathway	Zhang <i>et al.</i> 2021
Teflubenzuron	Insecticide		N-[(3,5-dichloro-2,4-difluorophenyl)carbamoyl]-2,6-difluorobenzamide. Acts as a chitin synthesis inhibitor effective against fish lice	Mayer <i>et al.</i> 2013
N-phenylbenzamide	Insecticide		Act as antagonists (channel blockers) for insect γ -Aminobutyric acid receptors (GABARs) by binding to their receptor site	Ozoe <i>et al.</i> 2013; Yu <i>et al.</i> 2021
Diflubenzuron	Insecticide		Interferes with chitin deposition by oral absorption. Used on soya bean, citrus, tea, vegetables and mushrooms	Nahorniak <i>et al.</i> 2005
Chlorantraniliprole	Insecticide		A novel anthranilic diamide insecticide with low risk to mammals. Replacing other insecticides due to its effectiveness	Elbert <i>et al.</i> 2008

Zrýd 1991). The application of 3-MBA has been associated with increased frequencies of homologous recombination in *Arabidopsis thaliana* and *Nicotiana tabacum* (Puchta *et al.* 1995). Additionally, investigations have revealed that 3-MBA inhibits ADP-ribosyltransferase, resulting in the

suppression of cell division in *Bacillus subtilis*, illustrating its impact on stress-related cellular processes (Ohashi *et al.* 1999). Moreover, reduction of PARP activity in *A. thaliana* through chemical inhibitors or gene silencing has been shown to inhibit cell death and enhance tolerance to abiotic stresses such as high

light intensity, drought, and heat (Block *et al.* 2004). Treatment with 3-MBA or another PARP inhibitor, 3-aminobenzamide (3AB), has been linked to enhanced resistance to abiotic stresses like high light and oxidative damage in *A. thaliana* (Briggs *et al.* 2017). A particularly notable effect of 3-MBA is improved plant growth, microtuberization, and transformation efficiency recorded in *Solanum tuberosum* (Chetty *et al.* 2020). These findings underscore the crucial role of PARP inhibitors like 3-MBA in regulating stress responses and supporting plant survival under adverse environmental conditions.

The 3-aminobenzamide (3-AB) is also a well-known inhibitor of PARP with various roles in stress management and cellular protection. Research has shown that 3-AB can modulate stress responses and cellular processes in different biological contexts (Curtin & Szabó 2013). In plants, 3-AB has demonstrated potential in enhancing stress tolerance and regulating stress-induced pathways, leading to increased resistance to stressors (Thomas *et al.* 2016). Moreover, 3-AB has been associated with protecting cells from apoptosis by inactivating glyceraldehyde-3-phosphate dehydrogenase, a key enzyme in glycolysis (Colussi *et al.* 2000). The inhibition of PARP by 3-AB has been associated with plant antiviral defence mechanisms, particularly where PARP1 interacts with the Cajal body protein coilin and salicylic acid-mediated responses (Spechenkova *et al.* 2023).

Apart from PARP inhibition, benzamides also attracted attention for their potential applications as protease inhibitors. These play a crucial role in plants under stresses like drought, salt, and freezing (Sabotić & Kos 2012). These inhibitors are involved in regulating proteolytic systems and can enhance plant defence mechanisms against both biotic and abiotic stresses (Liu *et al.* 2024). Studies have also shown that proteolytic enzymes and their inhibitors are essential in biological processes, including the degradation of metabolic proteins and the regulation of cellular protein catabolism under environmental stress (Mangena 2022).

Benzamides as antimicrobials, herbicides, and insecticides in plant stress management

Benzamides have been shown to disrupt essential bacterial proteins like FtsZ, which are crucial for cell division (Stokes *et al.* 2013). They and their derivatives also exhibit antimicrobial activity against pathogens such as *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), and *Candida albicans* (ATCC 885–653) (Vlasov *et al.* 2022), highlighting their potential to enhance plant defence and serve as valuable antimicrobial agents in agriculture.

Fungicides derived from benzamides are essential in safeguarding crops against various fungal diseases. These include formulations like zoxamide, flutolanil, fluopicolide, and fluopyram, commonly used for their efficacy in inhibiting fungal attacks in crops (Podhorniak 2014; Freitas *et al.* 2022). Zoxamide prevents blight in potato and downy mildew in grape by interfering with the pathogen's nuclear division (Podhorniak 2014). Flutolanil is employed to hinder fungal mycelium growth, thus reducing disease severity in peanut and rice (Teng *et al.* 2019). Fluopicolide, developed by Bayer Crop Science, targets oomycetes that harm a wide array of crops (Wen 2023). Fluopyram, a pyridinyl-ethyl-benzamide fungicide, effectively controls various crop pathogens (Xie

et al. 2022). These fungicides work by targeting specific fungal mechanisms. Fluopyram, for instance, acts as a succinate dehydrogenase inhibitor, impeding ATP synthesis in the fungal mitochondrial respiratory chain (Freitas *et al.* 2022). Additionally, pyrazol-5-yl-benzamide derivatives have been crafted as potential succinate dehydrogenase inhibitors, displaying promising antifungal properties against destructive crop pathogenic fungi (Cheng *et al.* 2022). In agricultural practice, benzamide fungicides are often combined with others that have distinct modes of action to enhance efficacy and delay resistance development, such as the use of zoxamide in combination with cymoxanil and mancozeb for effective control of blight diseases in tomato (Saha *et al.* 2017). Growers may rotate between fungicides like mefenoxam, azoxystrobin, mandipropamid, and fluopicolide, each from different chemical groups, to effectively combat diseases (Pintore *et al.* 2016).

The utilization of benzamides as herbicides in crop protection dates to 1971. One of the early compounds, N-(1,1-dimethylpropynyl)-3,5-dichlorobenzamide, was employed to eliminate quackgrass (*Agropyron repens*) by inhibiting the growth of its meristematic regions. This inhibition was associated with an increase in cellulase levels and several disruptive changes in the meristematic, nodal, and internodal tissues of quackgrass rhizomes (Smith *et al.* 1971). Following this, more recent discoveries have led to the synthesis of additional compounds, such as N-(4,6-Dichloropyrimidine-2-Yl) benzamide, a herbicide safener and antifungal agent shown to be protective for rice seedlings (Zheng *et al.* 2018). Recently, approximately 67 N-benzyl-2-methoxybenzamide derivatives have been synthesized, with three of these compounds demonstrating 100% inhibition of the weeds *Abutilon theophrasti* and *Amaranthus retroflexus* (Zhang *et al.* 2021). Furthermore, (thio)benzamide herbicides, which inhibit photosystem system II, represent the latest advances in herbicide development (Pereira *et al.* 2022). Continuous formulation of new antimicrobial and herbicidal compounds is crucial to prevent the development of resistance that can arise from prolonged use of the same chemistries.

Benzamide derivatives have also been explored for their insecticidal properties and potential applications as insect growth regulators. Among the earliest used compounds, diflubenuron has been applied to control insects and parasites in forests and field crops (Nahorniak *et al.* 2005). Similarly, N-acylamino-benzamides have been identified as potent insecticides (Raves *et al.* 2008), and chlorantraniliprole, introduced shortly thereafter, emerged as a novel anthranilic diamide insecticide valued for its effectiveness and low toxicity to mammals (Elbert *et al.* 2008). Teflubenzuron, another benzamide, acts as a chitin synthesis inhibitor effective against fish lice and other pests (Mayer *et al.* 2013).

In more recent developments, benzamides substituted with pyridine-linked 1,2,4-oxadiazole have been designed and synthesized for their insecticidal properties (Yang *et al.* 2020), while N-phenylbenzamide derivatives bearing a trifluoromethylpyrimidine moiety have demonstrated strong insecticidal activity (Yu *et al.* 2021). Further investigations into benzodioxole-6-benzamide derivatives have revealed their inhibitory effects on insect chitinases, as in the case of Asian corn borer (*Ostrinia furnacalis*), and notable insecticidal potential against both *O. furnacalis* and the diamondback moth

(*Plutella xylostella*) larvae (Misra *et al.* 2021; Jin *et al.* 2023; Bakry 2024).

These benzamide compounds not only act as direct insecticides but also serve as insect growth regulators, targeting pests like the white mango scale insect (*Aulacaspis tubercularis*) by disrupting their development and reproduction (Bakry 2024). This targeted approach helps reduce insect populations and minimize crop damage (Misra *et al.* 2021; Okolle *et al.* 2022). Additionally, certain benzamide derivatives are compatible with other agrochemical classes, such as strobilurins and phosphonates, enabling their use in integrated pest and disease management (IPM) strategies (Schmitt *et al.* 2021). Within the broader framework of IPM, which emphasizes the combined use of diverse pest control methods, including targeted chemical applications, benzamide compounds present a promising alternative to neonicotinoid insecticides. Their specificity toward certain insect pests, along with a reduced risk to non-target organisms and the environment, highlights their value in promoting more sustainable and ecologically responsible crop protection practices (Furlan & Kreutzweiser 2014).

SUMMARY OF KEY FINDINGS

Benzamides offer varying applications in plant stress management by enhancing crop resilience, protecting against biotic stressors, and enabling innovative biotechnological solutions. They improve tolerance to abiotic stresses, such as drought, salinity and heat, through inhibition of poly(ADP-ribose) polymerase (PARP) activity and the activation of alternative DNA repair pathways (De Block *et al.* 2005).

Beyond abiotic stress, benzamides demonstrate strong antimicrobial activity by targeting essential microbial proteins such as FtsZ and have been shown to be effective against *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), and *Candida albicans* (ATCC 885–653) (Stokes *et al.* 2013; Vlasov *et al.* 2022). Their fungicidal derivatives, such as zoxamide, flutolanil, fluopicolide, and fluopyram, disrupt key fungal processes including nuclear division and mitochondrial respiration (Podhorniak 2014; Teng *et al.* 2019; Freitas *et al.* 2022; Xie *et al.* 2022; Wen 2023), providing targeted protection against blights, mildews, and soilborne diseases.

As herbicides, benzamides have been employed since the 1970s, initially to control quackgrass through inhibition of meristematic growth (Smith *et al.* 1971). More recently, compounds like N-(4,6-Dichloropyrimidine-2-Yl) benzamide and various N-benzyl-2-methoxybenzamides have shown selective action against weeds such as *Abutilon theophrasti* and *Amaranthus retroflexus* (Zheng *et al.* 2018; Zhang *et al.* 2021). Newer (thio)benzamide formulations targeting photosystem II mark a further advance in this class (Pereira *et al.* 2022).

In terms of insecticidal roles, benzamide derivatives including diflubenzuron, teflubenzuron, and chlorantraniliprole have long been used to manage pests by inhibiting chitin synthesis or acting as anthranilic diamides with low mammalian toxicity (Nahorniak *et al.* 2005; Elbert *et al.* 2008; Mayer *et al.* 2013). The integration of benzamide derivatives into crop protection and breeding strategies presents a significant opportunity for biotechnological innovation. By combining their antimicrobial, herbicidal, and insecticidal properties, benzamides contribute to the development of broad-spectrum agricultural products

with potential to improve crop productivity, sustainability, and resilience under diverse stress conditions.

CHALLENGES AND PROSPECTS

Despite the promising potential of benzamides as stress inhibitors and enhancers of crop resilience, several gaps remain in current knowledge that future research must address. While benzamides have been shown to inhibit PARP activity and influence stress responses, the precise molecular pathways and interactions involved are not fully understood. Detailed molecular studies using advanced techniques like transcriptomics, proteomics, and metabolomics are needed to unravel the specific pathways and gene networks modulated by benzamides in plant stress responses. Additionally, the specificity and selectivity of different benzamide derivatives in targeting various stress-related pathways in plants are not well characterized. Understanding the structure–activity relationships and identifying the most effective derivatives for specific stress conditions would enhance their application in crop biotechnology. Research should focus on exploring and optimizing various benzamide derivatives to enhance their efficacy and specificity in targeting stress-related pathways.

Although benzamides have not yet been specifically tested in the context of plant biotechnology applications, such as somatic embryogenesis or epigenetic modification, the positive effects observed with other small-molecule epigenetic tools suggest strong potential for benzamide analogues to play similar roles. Their chemical structures could, in theory, be adapted to function as methyl donors or chromatin modifiers if appropriately designed or screened, representing a promising frontier for further research in epimutagenic breeding and stress-resilient crop development.

The long-term effects of benzamide application on plant health, growth, and yield under field conditions remain largely unexplored. Extensive field trials are needed to evaluate the practical benefits and potential risks of prolonged benzamide use, ensuring the sustainability of their application in agriculture. Furthermore, the environmental impact of benzamide use, including potential effects on non-target organisms and soil health, has not been thoroughly investigated. Research into the ecological consequences of benzamide application is necessary to ensure environmentally sustainable practices. This will provide an opportunity to develop environmentally friendly benzamide formulations.

AUTHOR CONTRIBUTIONS

MJK: Writing original draft, TEM: reviewing and editing, SOA: reviewing, editing, and sourcing funding.

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