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Research review paper

Plant secondary metabolites against biotic stresses for sustainable crop protection

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ABSTRACT

Sustainable agriculture practices are indispensable for achieving a hunger-free world, especially as the global population continues to expand. Biotic stresses, such as pathogens, insects, and pests, severely threaten global food security and crop productivity. Traditional chemical pesticides, while effective, can lead to environmental degradation and increase pest resistance over time. Plant-derived natural products such as secondary metabolites like alkaloids, terpenoids, phenolics, and phytoalexins offer promising alternatives due to their ability to enhance plant immunity and inhibit pest activity. Recent advances in molecular biology and biotechnology have improved our understanding of how these natural compounds function at the cellular level, activating specific plant defense through complex biochemical pathways regulated by various transcription factors (TFs) such as MYB, WRKY, bHLH, bZIP, NAC, and AP2/ERF. Advancements in multi-omics approaches, including genomics, transcriptomics, proteomics, and metabolomics, have significantly improved the understanding of the regulatory networks that govern PSM synthesis. These integrative approaches have led to the discovery of novel insights into plant responses to biotic stresses, identifying key regulatory genes and pathways involved in plant defense. Advanced technologies like CRISPR/Cas9-mediated gene editing allow precise manipulation of PSM pathways, further enhancing plant resistance. Understanding the complex interaction between PSMs, TFs, and biotic stress responses not only advances our knowledge of plant biology but also provides feasible strategies for developing crops with improved resistance to pests and diseases, contributing to sustainable agriculture and food security. This review emphasizes the crucial role of PSMs, their biosynthetic pathways, the regulatory influence of TFs, and their potential applications in enhancing plant defense and sustainability. It also highlights the astounding potential of multi-omics approaches to discover gene functions and the metabolic engineering of genes associated with secondary metabolite biosynthesis. Taken together, this review provides new insights into research opportunities for enhancing biotic stress tolerance in crops through utilizing plant secondary metabolites.

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1. Introduction

As global agricultural systems contend with increasing pressures from biotic stresses such as pathogens, insect pests, and weeds, the need for sustainable and eco-friendly crop protection strategies has become more urgent than ever (Altieri et al., 2024; Singh et al., 2023a). Biotic stresses, including a wide array of organisms, such as fungi, bacteria, viruses, nematodes, and weeds, which adversely affect plant growth and development, collectively contribute to significant crop yield losses and compromised quality (Altieri et al., 2024; Kaur et al., 2022a; Nawaz et al., 2023; Singh et al., 2023a). Alarmingly, the global economic loss attributed to pathogens and pests alone is estimated at approximately $220 billion annually, posing a direct threat to food security and regional economies (Singh et al., 2023a). While traditional chemical pesticides have historically been effective in controlling biotic stresses, their overuse has raised critical concerns about environmental degradation, the emergence of pesticide-resistant pests, and harmful effects on non-target organisms, including humans (Ayilara et al., 2023; Devi et al., 2022). These challenges have catalyzed interest in alternative strategies, particularly plant-derived natural products, as a means of enhancing crop resilience.

Plants, as sessile organisms, have evolved intricate defense mechanisms to counteract biotic threats, primarily relying on secondary metabolites (plant specialized metabolites or PSMs), a diverse group of chemical compounds, including alkaloids, terpenoids, phenolic compounds, flavonoids, and glucosinolates, which are critical components of plant immunity, each exhibiting distinct biological activities essential for mitigating biotic stresses, including pests, pathogens, and herbivores (Ahanger et al., 2020; Al-Khayri et al., 2023; Anjali et al., 2023; Mishra et al., 2020; Salam et al., 2023; Sun and Fernie, 2024). To date, approximately 200,000 plant secondary metabolites have been identified, with nearly half subjected to experimental investigation (Rogowska-van der Molen et al., 2023). Most of the secondary metabolites are not directly involved in basic growth and development but are essential for survival under stress conditions (Isah, 2019; Venkataraman and Hefferon, 2023). These compounds, induced upon pathogen attack, serve as toxic deterrents or signaling molecules, enabling plants to counteract attackers by repelling or inhibiting them or by attracting their natural enemies, thereby safeguarding physiological functions and ensuring survival under both biotic and abiotic stresses (Zhan et al., 2022; Adhikary and Dasgupta, 2023). For instance, alkaloids, characterized by their bitter taste and ability to disrupt protein function and nervous system activity, deter herbivores effectively (Matsuura and Fett-Neto, 2015). Meanwhile, terpenoids and phenolic compounds provide antimicrobial defense, preventing pathogen invasion and colonization (Ahanger et al., 2020; Thakur et al., 2019). Beyond direct defense, PSMs serve broader ecological roles, such as repelling pests, signaling symbiotic interactions, and modifying the host-associated microbial community (Pang et al., 2021). The dynamic interactions between plants and their environments, including their biotic interactions with pathogens, pests, and mutualistic organisms, profoundly influence secondary metabolism. These interactions alter the expression of plant hormones and secondary metabolite pathways, enabling plants to mount tailored defense responses (Mishra et al., 2020). Under biotic stress, plants activate intricate signaling networks that stimulate the biosynthesis of secondary metabolites, which are pivotal in maintaining homeostasis (Adhikary and Dasgupta, 2023). For instance, pathogen infection triggers the accumulation of specific secondary metabolites such as alkaloids, flavonoids, glucosinolates, and terpenoids that exhibit antimicrobial properties, disrupting pathogen growth and colonization (Pang et al., 2021). Similarly, insect herbivory induces the production of a suite of toxic metabolites, including steroidal compounds, terpenes, phenols, indoles, and nitrogenous chemicals, which deter herbivores by inhibiting their growth and reproduction or attracting their natural enemies (Rodriguez-Saona and Frost, 2010; Orre et al., 2010). Emerging studies suggest that pathogens not only trigger these metabolites but also manipulate their accumulation to influence plant defense outcomes (Mishra et al., 2020). Despite extensive research, the intricate regulatory networks governing pathogen-induced secondary metabolite production remain underexplored.

Transcription factors (TFs) play a central role in orchestrating these stress responses by binding to *cis*-elements in gene promoters, mediating protein-DNA interactions, and regulating gene expression patterns associated with secondary metabolism, thereby managing biotic stress responses (Chowdhary et al., 2023; Meraj et al., 2020; Weidemüller et al., 2021). Manipulating TFs at both transcriptional and post-transcriptional levels holds significant promise for genetic modification and molecular breeding aimed at enhancing the synthesis of secondary metabolites to enhance the production of defense metabolites for improved crop resilience. The emergence of molecular biology, genetic engineering, and omics technologies has transformed our understanding of secondary metabolism. Recent advancements in functional genomics, including metabolomics, proteomics, transcriptomics, and epigenomics, have significantly enhanced our ability to identify and characterize secondary metabolites along with their regulatory genes. Multi-omics approaches offer comprehensive insights into the distribution and diversity of biosynthetic gene clusters (BGCs) as well as their developmental dynamics (Alami et al., 2022). These cutting-edge technologies facilitate an in-depth understanding of the structural and functional features of secondary metabolites and their biosynthetic pathways, uncovering previously hidden regulatory mechanisms (Anjali et al., 2023). Metabolic engineering technologies can be used to modify regulatory genes and major enzymes to redirect or augment the synthesis of plant secondary metabolites (Razzaq et al., 2023). Whole-genome sequencing and genome-wide association studies (GWAS) now enable the mapping of biosynthetic pathways and identification of regulatory genes critical for secondary metabolite production (Das et al., 2024; Mipeshwaree Devi et al., 2023; Singh et al., 2022). These advances have unlocked the potential to enhance plant secondary metabolite synthesis through precise genetic modifications. For example, overexpressing pathway-specific genes increases the production of compounds with insect-repellent or antimicrobial properties (War et al., 2019; Zhang et al., 2020). Similarly, CRISPR/Cas9-mediated genome editing offers unparalleled accuracy in targeting genes involved in secondary metabolite biosynthesis, facilitating the development of crops with enhanced resistance to biotic stresses (Das et al., 2024; Zhang et al., 2020). Therefore, investigating the biosynthesis, regulation, and functions of plant secondary metabolites is crucial for understanding the complex mechanisms underlying plant defense responses to biotic stresses.

By leveraging these advancements, researchers are reengineering plant defense systems to bolster innate immunity, promoting not only higher yields but also reducing reliance on synthetic pesticides. This integrative approach harnessing natural plant defenses for crop protection represents a sustainable and ecologically friendly strategy for modern agriculture. This review examines recent breakthroughs in the understanding of PSMs as biotic stress resistance molecules, focusing on innovative strategies like metabolic engineering, gene editing, and breeding programs to develop resilient crops. By integrating scientific advancements with practical applications, we aim to illustrate how plant-derived metabolites are shaping the future of agriculture and sustainable food systems. Expanding our understanding of these processes through integrative approaches, including transcriptomics, metabolomics, and advanced genetic engineering, holds promise for developing crops with enhanced resistance to biotic stresses, paving the way for sustainable and resilient agricultural systems.

2. Secondary metabolites related to plant defense against biotic stress

Plants produce a diverse range of secondary metabolites that are indispensable for their survival, ecological interactions, and adaptation to environmental challenges. Once considered mere metabolic

byproducts, these compounds are now recognized for their critical roles in plant growth, development, and responses to biotic and abiotic stresses (Ramawat and Goyal, 2020; Wink and Schimmer, 2018). Derived from primary metabolites, secondary metabolites gain their structural and functional diversity through enzymatic modifications such as hydroxylation, methylation, glycosylation, and acylation (Wang et al., 2019). This biochemical flexibility enables plants to mediate intricate ecological interactions, enhancing their fitness and resilience.

Secondary metabolites serve as key agents in plant defense, deterring herbivores and pathogens, while also functioning as signaling molecules in processes like pollination and host-pathogen communication. These compounds are integral to plant-plant interactions, allelopathy, and mutualistic relationships with beneficial organisms (Ramawat and Goyal, 2020). Over 400 million years of co-evolution with herbivores has driven plants to develop sophisticated defensive strategies, including physical barriers (e.g., cuticles and spines) and chemical deterrents (e.g., alkaloids and antifeedants), while herbivores concurrently evolved countermeasures, such as detoxification mechanisms (Mithoefer and Boland, 2012; Ramawat and Goyal, 2020). For instance, *Argemone* species utilize prickles and alkaloid-rich resin as a dual defense mechanism against herbivores, illustrating the dynamic nature of this evolutionary arms race that underscores the ongoing innovation in plant defense systems (Suissa and Barton, 2018).

Beyond their ecological importance, secondary metabolites have significant therapeutic and industrial applications. Compounds such as alkaloids, flavonoids, and polyphenols are vital sources of natural drugs, anticancer agents, antibiotics, allelopathic chemicals, and functional additives in food and cosmetics (Sharma et al., 2022). Their roles as UV protectants, signaling molecules, and deterrents to predators further highlight their versatility (Chen et al., 2022a; Wink, 2016). This dual importance in plant defense and human utility has driven extensive research into their biosynthesis, regulation, and application. The structural and functional complexity of secondary metabolites reflects their evolutionary significance, mediating ecological interactions that enhance plant survivability and fecundity (Kariñho-Betancourt, 2019). As these compounds continue to inspire advancements in agricultural biotechnology, they underscore the intricate interplay between plants and their environment, offering vast potential for sustainable innovations.

A wide range of SMs, including approximately 12,000 alkaloids,

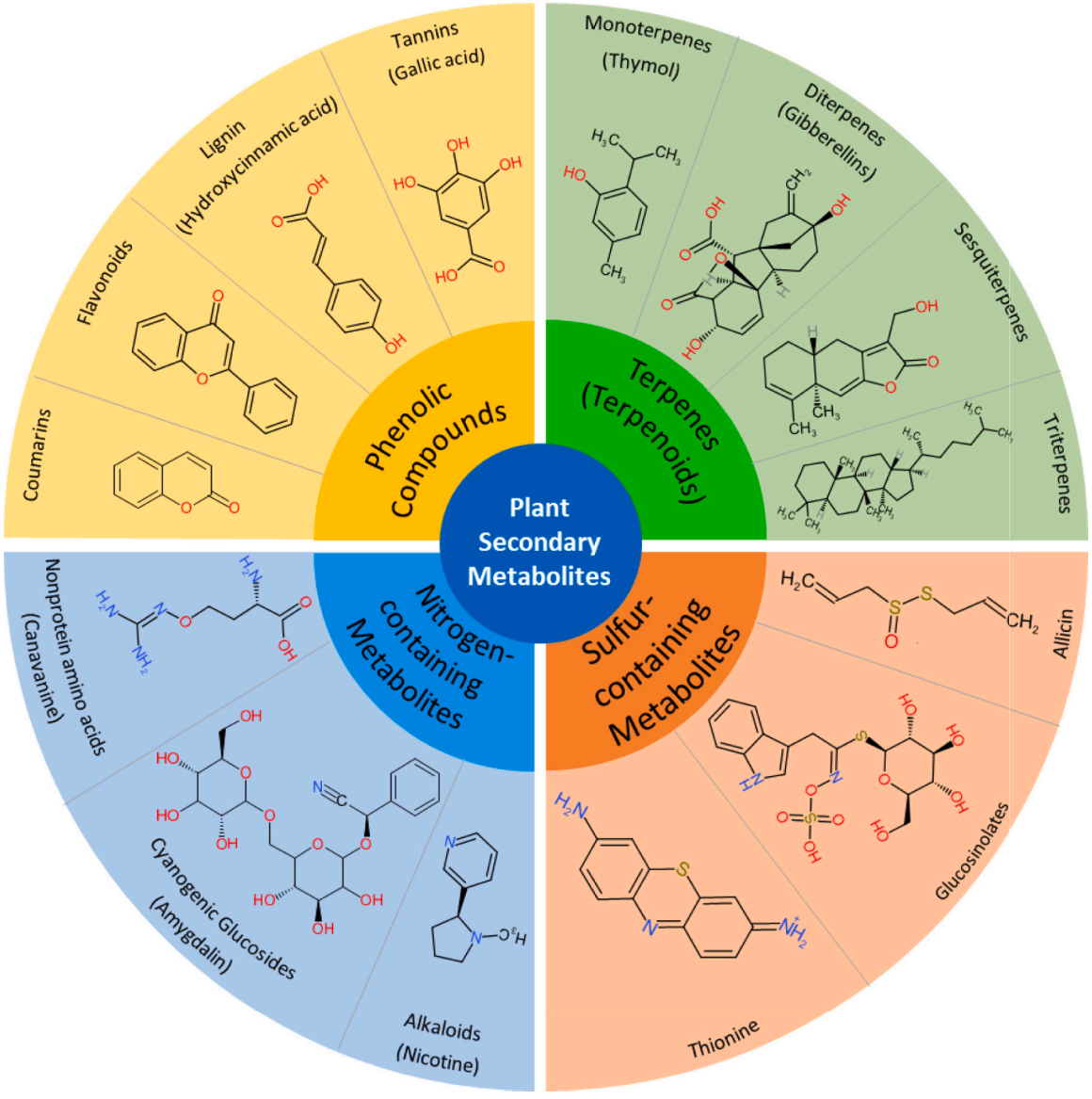

Fig. 1. Major types of plant secondary metabolites with their chemical structure.

8000 phenylpropanoids, and 40,000 terpenoids, can be synthesized by plants (Elshafie et al., 2023; Shiade et al., 2024). These compounds are often specific to certain taxa, with concentrations varying among populations, individual plants, and even across tissues and organs (Ritmejerytė et al., 2020). Plant secondary metabolites can be biogenically classified into four main groups, including phenolic compounds, terpenes/terpenoids, nitrogen-containing metabolites, and sulfur-containing metabolites, which are further subdivided based on structural features and substituent patterns (Fig. 1) (Al-Khayri et al., 2023; Divekar et al., 2022; Jan et al., 2021; Sharma et al., 2022; Shiade et al., 2024).

Among these, terpenes represent the most structurally and functionally diverse class of plant secondary metabolites (PSMs), encompassing over 50,000 distinct compounds (Bhonwong et al., 2009; Shiade et al., 2024). These lipid-soluble compounds are derived from isoprene (2-methyl-1,3-butadiene) units, forming carbon backbones that may undergo thousands of structural modifications, leading to highly varied structures such as acyclic, monocyclic, and polycyclic forms (Christianson, 2017; Sharma et al., 2022). Terpenoids are synthesized in specialized plant tissues, such as the epidermal cells of leaves and roots, and accumulate in secretory structures like resin ducts, lactifers, and glandular trichomes (Zunjarrao et al., 2020). Their biosynthesis is influenced by developmental stage, tissue type, and environmental conditions, with higher concentrations often observed in reproductive parts, particularly during flowering, as well as in young vegetative tissues such as leaves (Li et al., 2020c; Li et al., 2023b; Shiade et al., 2024). For instance, *Malus domestica* and *Prunus avium* exhibit elevated terpene levels in flowers, while young leaves generally contain higher terpene levels than mature leaves (Anjali et al., 2023). Notably, variations in localization within a tissue, as seen in *Pinus ponderosa* needles, can influence herbivore feeding behavior, highlighting the ecological specificity of terpenoid functions (Zunjarrao et al., 2020). Terpenoids play vital roles in plant adaptation by attracting pollinators, deterring herbivores, and protecting against microbial pathogens (Abbas et al., 2017; Aharoni et al., 2005). Many terpenoid compounds, including benzoxazinoids, iridoids, and volatile mono- and sesquiterpenes such as α-bisabolene, β-caryophyllene, and 1,8-cineole, are implicated in direct defense mechanisms (Divekar et al., 2022; Shiade et al., 2024). In roots, terpenoids such as 1,8-cineole and (*E*)-β-caryophyllene also contribute to resistance against soil borne pathogens (Zunjarrao et al., 2020). Furthermore, their neurotoxic effects on insects, including acetylcholine esterase inhibition leading to anoxia and death, underscore their protective utility (Zunjarrao et al., 2020). Phytoalexins, a subclass of terpenoids, play critical roles in plant immunity. For example, rice (*Oryza sativa*) synthesizes diterpenoid phytoalexins such as momilactones, oryzalexins, and phytocassanes in response to pathogen exposure. Genetic studies have identified over 20 genes involved in their biosynthesis, confirming their role in enhancing resistance to diverse pathogens (Block et al., 2019; Schmelz et al., 2014; Toyomasu et al., 2014). Mutants deficient in these compounds, such as cps4-tos lines, show increased susceptibility to pathogens, validating their defensive function (Toyomasu et al., 2014). Additionally, terpenoid-mediated defense mechanisms have been demonstrated in ornamental plants such as *Chrysanthemum morifolium*, where terpenes like 1,8-cineole and γ-muurolene negatively correlate with susceptibility to *Alternaria tenuissima* (He et al., 2022). Resistant cultivars emit fewer terpenoid volatiles upon pathogen attack, suggesting that these compounds function as modulators of pathogen-induced responses (He et al., 2023). The structural distinction between terpenes and terpenoids lies in the presence of oxygen-containing functional groups in terpenoids, formed through oxidation or methyl group rearrangement (Sharma et al., 2022). These modifications generate diverse functional groups, including alcohols, aldehydes, ketones, carboxylic acids, and esters, further diversifying their roles in plant physiology and ecology (Dev, 1989). Terpenes play critical roles at the molecular and cellular levels. Diterpenes such as phytol and abietic acid stabilize cell membranes and exhibit antimicrobial properties (Priyanka et al., 2021). Triterpenes, including sterols, enhance membrane integrity and regulate pathogen interactions (Thimmappa et al., 2014). Triterpenoid glycosides, such as saponins, act as potent antifeedants and antidigestive agents against herbivorous insects (Cárdenas et al., 2019a; Tian et al., 2020). These compounds deter insects from feeding on plant tissues by triggering unpleasant sensory responses, such as bitterness or irritation. This discourages herbivores from consuming the plant. They can also interfere with the insect's digestive process, making it difficult for them to digest the plant material. This can lead to reduced growth, development, and ultimately mortality (Qasim et al., 2019). Terpenes are precursors for key phytohormones such as gibberellins and brassinosteroids, which contribute to growth and developmental regulation (Aharoni et al., 2005). Additionally, they are responsible for characteristic aromas and pigments, playing crucial roles in species-specific ecological interactions (Bhonwong et al., 2009). Terpenoids exemplify the intricate interplay between structural diversity and ecological functionality in plant secondary metabolism. Their multifaceted roles in growth regulation, stress adaptation, and defense make them indispensable for plant survival. Advances in understanding terpenoid biosynthesis and function have profound implications for agriculture and biotechnology, offering potential solutions for enhancing crop resilience and developing sustainable pest management strategies.

Phenolic compounds represent another structurally diverse group of secondary metabolites in plants, encompassing an estimated 10,000 distinct compounds (Divekar et al., 2022). These compounds are defined by the presence of a hydroxyl group attached to an aromatic phenyl ring. This structural framework underpins their classification into various subcategories, including simple phenols (e.g., hydroxybenzoic acid derivatives), catechol melanins, flavonoids, stilbenes, lignins, and condensed tannins, enabling them to perform diverse biological functions within plants (Divekar et al., 2022). Phenolic compounds are generally categorized into six main groups: coumarins, lignins, furanocoumarins, flavonoids, isoflavonoids, and tannins. Coumarins are characterized by the integration of benzene and α-pyrone rings and are widely distributed across vascular plants, with over 1300 types identified. They play a key defensive role against herbivores and fungi (Gan et al., 2019; Shiade et al., 2024). Lignin, the second most abundant biopolymer after cellulose, is vital for providing structural toughness and resistance to biotic and abiotic stresses (Jan et al., 2021). Furanocoumarins, predominantly found in the Rutaceae and Apiaceae families, exhibit phototoxicity upon activation by UV-A radiation, providing protection against herbivores and pathogens (Mazid et al., 2011; Upadhyay et al., 2024). Flavonoids, which constitute over 9000 compounds, represent the most diverse group of phenolics and serve critical functions in defense, pigmentation, UV protection, and signaling (Jan et al., 2021; Divekar et al., 2022). These compounds are synthesized across various plant tissues and developmental stages, with specific types such as anthocyanins, aurones, and flavonols contributing to floral pigmentation and fragrance, thereby attracting pollinators and facilitating reproductive success (Sharma et al., 2022). Isoflavonoids, a specialized group of flavonoids predominantly found in leguminous plants, are central to nitrogen fixation and plant-microbe interactions (Jan et al., 2021). Tannins, another critical class of phenolics, are categorized into condensed and hydrolyzable types and play essential roles in herbivore deterrence by forming complexes with proteins, inhibiting digestive enzymes, and reducing the digestibility of plant tissues (Barbehenn and Constabel, 2011). These compounds are predominantly found in the leaves of woody plants such as Fabaceae, Fagaceae, Myrtaceae, and Polygonaceae, serving as a defense mechanism against pests and pathogens (Ramawat and Goyal, 2020). Early flavonoids, such as chalcones and flavanones, were identified in the Silurian period alongside the rise of bryophytes, while anthocyanins and proanthocyanins developed concurrently with vascular plants and flowering species, respectively (Sharma et al., 2022). Lignins, which appeared alongside tracheophytes during the Silurian period,

contributed significantly to structural rigidity and mechanical strength in plants, enabling the formation of woody tissues. These compounds also possess anti-nutritive properties, deterring herbivorous insects (Ramawat and Goyal, 2020). Tannins emerged later during the Carboniferous period, providing seed protection and serving as pest deterrents in gymnosperms and angiosperms (Zunjarrao et al., 2020). Phenolic compounds exhibit remarkable structural diversity, ranging from simple molecules to complex polymers with varied functional groups such as hydroxyl, alkoxy, and acetyl groups. This diversity extends to their classification into flavonoids and non-flavonoid compounds, with further subdivisions based on phenolic unit number, linkage types, and substituent patterns (Sharma et al., 2022). Their synthesis and localization are tightly regulated by developmental stages, tissue types, and environmental stimuli, reflecting their multifaceted roles in plant survival and adaptation.

Nitrogen-containing secondary metabolites (N-SMs) constitute a critical class of plant defense compounds, encompassing alkaloids, cyanogenic glycosides, glucosinolates, and nonprotein amino acids. Most N-SMs are biosynthetically derived from amino acids, providing plants with a diverse arsenal for ecological interactions, including defense against herbivores and pathogens. Alkaloids are among the largest and most structurally diverse classes of secondary metabolites, with over 12,000 derivatives identified to date (Divekar et al., 2022; Yue et al., 2022). These nitrogenous compounds, often bitter-tasting, are found in about 20% of flowering plant species and are concentrated in specific plant parts such as leaves, bark, and roots (Singh et al., 2023b). Alkaloids are broadly classified into three categories based on their biosynthetic origin: true alkaloids (e.g., nicotine, atropine), pseudoalkaloids (e.g., caffeine, solanidine), and protoalkaloids (e.g., mescaline). True and pseudoalkaloids are amino acid derivatives, while protoalkaloids are not. Most alkaloids possess basic nitrogen atoms and often include oxygen, sulfur, or halogens, contributing to their structural diversity (Yue et al., 2022). Heterocyclic alkaloids predominate, although non-heterocyclic variants also exist. Their biosynthesis involves amino acids like tryptophan, tyrosine, and lysine, resulting in a range of structures with significant pharmacological properties, including effects on the central nervous system (Singh et al., 2023b). Alkaloids exhibit remarkable biological activities, functioning as natural toxins that interfere with neuronal signal transduction, DNA replication, protein synthesis, and enzymatic activities, thereby deterring herbivory (Shiade et al., 2024). Notable examples include caffeine, morphine, and capsaicin, the latter being responsible for the characteristic pungency of chili peppers (Sharma et al., 2022). Glucosinolates are sulfur- and nitrogen-containing β-thioglucosides of N-hydroximinosulfate esters derived from glucose and amino acids. Predominantly found in the order Capparales and the genus *Drypetes* (Euphorbiaceae), these compounds are well-studied in *Brassica napus* for their role in herbivore resistance (Agerbirk and Olsen, 2012). Upon tissue disruption, glucosinolates interact with myrosinase enzymes, producing toxic isothiocyanates that deter insect herbivory (Zunjarrao et al., 2020). Evolutionarily, glucosinolates are hypothesized to have originated from cyanogenic glucosides, facilitated by mutations in aldoxime-metabolizing enzymes of the cytochrome P450 family (Møller et al., 2016). Cyanogenic glycosides, another significant N-SM class, are O-β-glycosides of α-hydroxynitriles derived from protein and nonprotein amino acids. Stored in plant tissues, these glycosides release toxic hydrogen cyanide upon enzymatic hydrolysis, serving as a robust defense mechanism against herbivores (Vetter, 2017). Nonprotein amino acids are alkylated or functionally substituted derivatives of protein amino acids. These compounds exhibit diverse structural features due to the presence of various functional groups, such as amino, carboxylic, hydroxyl, and thiol groups, and serve critical roles in plant defense and survival (Blažević et al., 2020). The ecological role of N-SMs extends beyond defense; they also assist plants in resource allocation and reproductive success. Structurally diverse and highly reactive, these compounds frequently form water-soluble salts with acids, enhancing their functional versatility (Divekar et al., 2022; Yue et al., 2022). Thus, nitrogen-containing secondary metabolites represent a critical aspect of plant survival strategies and ecological interactions. Their structural diversity and multifunctionality underline their significance in plant biochemistry, ecology, and potential applications in advanced molecular strategies.

Sulfur-containing compounds represent a significant class of low-molecular-weight PSMs, characterized by their structural diversity and vital roles in defense and signaling (Castro et al., 2023). These compounds, often recognized by their distinctive odors, are critical in plant defense against herbivores and pathogens, alongside their therapeutic and medicinal implications. Glucosinolates, which incorporate both sulfur and nitrogen atoms, consist of a β-D-thioglucose group linked to an N-hydroximinosulfate ester with variable side chains derived from amino acids. Upon enzymatic hydrolysis, they generate isothiocyanates with potent bioactivities, such as sinigrin converting to allyl isothiocyanate and glucotropaeolin to benzyl isothiocyanate (Agerbirk and Olsen, 2012). These compounds are vital in defense, particularly against herbivores and pathogens, and not only function as direct defense compounds but also influence the biosynthesis of other secondary metabolites. For example, indole glucosinolate mutants exhibit altered phenylpropanoid levels due to changes in transcriptional regulation mediated by enzymes like CYP83B1 and transcriptional complexes such as MED5 (Kim et al., 2015; Kim et al., 2020a, 2020b; Erb and Kliebenstein, 2020). Lectins are profusely found in leguminous crops and secreted as a defense strategy against coleopteran, lepidopteran, and homopteran insects (Rauf et al., 2019; War et al., 2012). It damages insect tissues by interfering with carbohydrates, lipid, and protein metabolism, as well as hormonal and defensive positions, which retards insect and pest growth. Plants communicate with a particular carbohydrate when sucking insects begin to invade, and they initiate defense mechanisms by producing mannose-binding lectins. For example, lectins effectively defend aphids in *Arum maculatum* L. In response to various stresses, plant elicitors stimulate lectins (Saddique et al., 2018). Lectins like *Phaseolus hemagglutinin* (PHA) from kidney bean seeds, *Galanthus nivalis* (snowdrop lectin, GNA) from snowdrops, and *wheat germ agglutinin* (WGA) from wheat germ are extensively researched due to their chemical properties and insect toxicity (Al-Khayri et al., 2023). Phytoalexins, a diverse group of inducible PSMs including sulfur-containing compounds, accumulate temporarily in plants under biotic and abiotic stresses. Notable examples include camalexins, brassinin, and rapalexin, which contain sulfur atoms in their structures. These low-molecular-weight antibiotics exhibit antimicrobial properties, enhancing plant resilience against pathogenic attacks (Ahuja et al., 2012; Zhou et al., 2022). Defensins are cationic, cysteine-rich antimicrobial peptides with a conserved β-sheet fold and disulfide-linked cysteines. They exhibit both antimicrobial activity and immune signaling roles, acting as essential components of plant defenses against biotic stress. Defensins are categorized into α-, β-, and θ-types based on cysteine disulfide pairing, further highlighting their structural versatility (Sharma et al., 2022). Thionins are small, cysteine-rich peptides found in various plant tissues, displaying potent antimicrobial activity. These peptides, consisting of 45–47 amino acids with multiple disulfide bonds, disrupt the membranes of pathogens, thereby safeguarding plants against bacteria, fungi, and yeast. Representative examples include crambin and viscotoxins, critical to plant immune responses (Hayes and Bleakley, 2018; Odintsova et al., 2018). Furthermore, aldoximes, intermediates in glucosinolate biosynthesis, modulate phenolic compound accumulation, underscoring the intricate regulatory networks between sulfur-containing and phenolic pathways (Kim et al., 2020a, 2020b). These compounds, predominantly found in taxonomic groups like Brassicaceae, are crucial for protein synthesis and nitrogen metabolism. Their abundance within vacuoles aids in efficient resource allocation and stress mitigation. Sulfur availability directly impacts plant health and the effectiveness of these metabolites, emphasizing their ecological importance (Bloem et al., 2007; Takahashi et al., 2023). Overall, sulfur-containing secondary metabolites serve as indispensable components of

plant defense, particularly under biotic stress. Their multifunctional roles, spanning direct antimicrobial activity, signaling, and metabolic regulation, highlight their importance in plant adaptation and survival in hostile environments. However, further research integrating multi-omics approaches and advanced pathway engineering can enhance the understanding and utilization of PSMs. The following section explores how these metabolites perform vital roles in biotic stress tolerance, bridging their structural diversity with their functional applications in sustainable crop protection.

3. Role of plant secondary metabolites in biotic stress tolerance

Plants produce secondary metabolites as part of their defense mechanisms against diverse biotic stresses. Under stress conditions, these metabolites accumulate to high levels and act as signaling molecules, enhancing the expression of genes involved in plant defense pathways. Additionally, they confer resilience to plants, enabling them to withstand harsh environments (Kumari et al., 2024; Sun and Fernie, 2024). To date, a variety of plant secondary metabolites have been discovered for their roles in defending against pathogens and pests (Table 1). These defenses typically operate through direct or indirect mechanisms (Fig. 2), linked to specific biosynthetic pathways that synthesize these metabolites.

3.1. Indirect defense mechanism of PSMs

3.1.1. Allelopathic role of secondary metabolites

Allelopathy involves the release of low-molecular-weight secondary metabolites into the environment, affecting the growth and development of neighboring plants and microbes, thus playing a crucial role in plant defense (Latif et al., 2017). Plant secondary metabolites, particularly alkaloids, terpenoids, and phenolic compounds, act as phytotoxins that influence the development of nearby plants by suppressing their seed germination, root growth, and other physiological processes (Anjali et al., 2023). Moreover, several insect pest, including *Bemisia tabaci*, *Callosobruchus maculatus*, *Sitophilus zeamais*, *Simulium* spp., *Amrasca biguttula*, *Spodoptera litura*, and different species of parasitic nematodes, i.e., *Meloidogyne* spp., *Helicotylenchus* spp., and *Pratylenchus* spp., are suppressed by secondary metabolites, including phenolic acids, flavonoids, pyrrolizidine alkaloids, and terpenoids found in plant extracts of *Chromolaena odorata* (Kato-Noguchi and Kato, 2023). Additionally, Hussain et al. (2022) observed that several allelochemicals, for instance, phenolic acids, flavonoids, benzoxazinones, and phenoxazinones extracted from several wheat genotypes, significantly restrain various weeds, i.e., *Avena fatua*, *Chenopodium album*, *Bromus japonicus*, *Portulaca oleracea*, and *Lolium rigidum*. The development of numerous monocot and dicot plants was inhibited by cuminaldehyde, derived from *Cuminum cyminum* L. (Sunohara et al., 2021), while oats produce a potent allelochemical, Avenicin, with anti-pathogen activity (Latif et al., 2017). Procyanidins produced by *Fallopia* spp. have been suggested to influence the nitrogen cycle indirectly by inhibiting microbial denitrification processes, which could limit nitrogen availability to invasive plant species (Bardon et al., 2016). However, further studies are needed to clarify the extent and ecological implications of this interaction.

3.1.2. Secondary metabolites as attractants of predator enemies

Plants employ various defensive strategies in response to herbivory, including the production of secondary metabolites that attract natural enemies of herbivores, with herbivore-induced plant volatiles (HIPVs) playing a key role in this indirect defense mechanism (Ode, 2022). HIPVs include amino acid and fatty acid derivatives, phenylpropanoids/benzenoids, and terpenoids (War et al., 2011). When plants detect particular elicitors or effectors, they are able to activate defenses that are specific to insects since they can differentiate between physical injury and damage caused by insect feeding. Additionally, this detection aids plants in differentiating between various herbivore species, allowing for the release of various HIPV blends that may draw in the herbivore's natural enemies (Qian et al., 2024). Cotton plants follow an efficient indirect defense strategy when they are infected with *Agrotis segetum*. They produce volatile chemicals that lure the natural enemy, *Microplitis mediator* (Li et al., 2022a). HIPVs released by potato and cucumber plants infected with aphids and caterpillars attract ants (Schettino et al., 2017), and Arabidopsis infested with these pests draws parasitoids like *Diadegma semiclausum* (Kroes et al., 2017). Moreover, various secondary metabolites found in extrafloral nectaries of plants also draw ants and protect them from herbivore attacks (Gish et al., 2016).

3.1.3. Secondary metabolites act as cellular barriers

Secondary metabolites have an impact on wound and post-injury healing by strengthening the plant cell wall. Plants accumulate different secondary metabolites, such as lignin, suberin, cutin, or callose, to increase the strength of their cell walls in order to heal wounds caused by insect and pest damage (Batsale et al., 2021). Both lignin and suberin act as cellular barriers against pathogen invasion. Lignin strengthens cell walls by preventing the penetration of enzymes and toxins from pathogens, while suberin, a hydrophobic barrier in Casparian strips, regulates nutrient and water transport and reinforces cell walls in response to root nematode attacks. For instance, suberin deposition in Arabidopsis periderm has been observed to limit damage from nematodes and enhance resistance to soil-borne pathogens (Holbein et al., 2019; Chen et al., 2022b; Yadav and Chattopadhyay, 2023). Similarly, *Hypericum perforatum* produces the phenolic compound xanthone from exodermis and endodermis with antimicrobial properties that protect plants from soil-borne pathogens and predators (Tocci et al., 2018). Suberin accumulates in the periderm of Arabidopsis to repair the endodermis after damage by nematodes (Maron, 2019). Suberin also confers antimicrobial and antifungal properties in addition to cellular barriers when conjugated with hydrocinnamic acid derivatives (HCAAs). HCAAs are also defensive compounds that work efficiently to prevent pathogen infection by strengthening the cell wall and slowing cell wall degradation (Liu et al., 2022a).

3.1.4. Secondary metabolites act as plant defense regulators

Secondary metabolites, such as glucosinolates, terpenes, benzoxazinoids, green-leaf volatiles, and aromatics, have the potential to regulate plant defense strategies against different biotic stresses (Divekar et al., 2022; Erb and Kliebenstein, 2020). Plant glucosinolates, along with genes PEN2 and PEN3, significantly modulate callose plug production in the cell wall of the wounded area caused by pathogen attack, which prevents further pathogen entry (Clay et al., 2009). Additionally, Johansson et al. (2014) identified that the genes PEN1, PEN2, and PEN3 are crucial for cell wall-based defense against the non-adapted powdery mildew *Blumeria graminis* f. sp. *hordei* (Bgh) in Arabidopsis. Coumaroyltyramine and coumaroyltryptamine boost PR1 gene activation and callose deposition in *Arabidopsis thaliana* (Macoy et al., 2022). Stomatal closure can inhibit bacterial invasion and reduce bacterial infection, whereas campesterol, sinigrin, ferulic acid, sitosterol, quercetin, and the glucosinolate-myrosinase system have significant impacts on the regulation of stomatal closure (Al-Khayri et al., 2023).

3.1.5. Secondary metabolites to deter pathogens and herbivores

3.1.5.1. Feeding deterrents. Antifeedants are allomone compounds that primarily restrict the feeding of stored products and suppress the development of pests without directly killing them (Kaczmarek et al., 2018). Generally, they work through mechanisms involved in chemosensory-based food aversion. While it is true that certain compounds from the Meliaceae family and limonoids from *Croton jatrophoides* have shown potential as feeding deterrents for insects, it should be noted that the effectiveness of these compounds may vary based on the species of the insects and their individual feeding preferences. The

Table 1
Secondary metabolites in plants for controlling different pests and pathogens.

Class	Compound(s)/ pathway	Plant species	Target pathogen	Mode of Actions	Reference
Flavonoid	Polymethoxylated flavonoids (PMFs)	*Citrus* spp.	*Penicillium digitatum*	Inhibited spore germination and mycelial growth and effectively control the growth of *P. digitatum*	(Guo et al., 2023)
	Rutin	*Solanum lycopersicum*	*Botrytis cinerea*	Enhances tomato resistance by initiating the generation of ROS and phosphorylation of MPKs related genes expression during the initial phase of invasion by *B. cinerea*	(Zhao et al., 2023)
	O-methylflavonoids	*Zea mays*	*Fusarium graminearum* and *Fusarium verticillioides*	Inhibited the growth of two maize pathogens, *Fusarium graminearum* and *F. verticillioides*	(Förster et al., 2022)
	Polymethoxylated flavonoids (PMFs)	*Citrus* spp.	*Penicillium italicum*	Antifungal activity against *P. italicum* by disrupting cell membrane integrity and permeability	(Guo et al., 2022)
	Tangeretin	*Oryza sativa*	*Magnaporthe oryzae*	Delayed the formation of *M. oryzae* appressoria and blocks the development of blast lesions on rice plants	(Liang et al., 2021a)
	Methoxylchalcones	*Hordeum vulgare*	*Bipolaris sorokiniana* and *Fusarium graminearum*	Inhibited conidial germination of *B. sorokiniana* and *F. graminearum*, thereby indicating these compounds possessed antifungal activity	(Ube et al., 2021)
	Tangeretin	*Citrus reticulata*	*Aspergillus niger*	Reduced the chitin production which change the cytomembrane permeability and the fragility of cell walls	(Wu et al., 2014)
Phenolics	Rutin and chlorogenic acid	*Rosa hybrida*	*Podosphaera pannosa*	Reduced conidial germination and appressorium formation of *P. pannosa*	(Shetty et al., 2011)
	Ferulic acid	*Amorphophallus muelleri*	*Fusarium solani*	Inhibited the growth of *F. solani*, thereby reducing the harm caused by it	(Gao et al., 2023a)
	Ferulic acid, gallic acid, 4-hydroxybenzoic acid, ellagic acid, and pyrogallol	*Rhaphiolepis indica*	*Fusarium verticillioides, Rhizoctonia solani,* and *Aphis gossypii*	Antifungal activity against *F. verticillioides* and *R. solani* and diminished the nymph's production and their total reproductive rate of *A. gossypii*	(Khamis et al., 2023)
	Chlorogenic acid and caffeic acid	*Citrullus lanatus*	*Fusarium oxysporum* f. sp. *niveum* (FON)	Inhabited the conidial germination and growth of FON	(Ling et al., 2013)
	Quercetin, luteolin aglycons, tyrosol, rutin, oleuropein, *p*-coumaric acid, luteolin-7-glucoside, and catechin	*Olea europaea*	*Phytophthora megasperma* and *Cylindrocarpon destructans*	Affected the growth, morphology and ultrastructure of *P. megasperma* and *C. destructans*	(Báidez et al., 2006)
Phenylpropanoid	α-phenylcinnamic acid	*Camellia sinensis*	*Colletotrichum gloeosporioides*	Inhibited conidia germination and appressorium formation of *C. gloeosporioides*	(Zhang et al., 2022a)
Flavonone	Pinocembroside	*Ficus hirta*	*Penicillium italicum*	Suppressed postharvest blue mold by direct inhibition of *P. italicum* mycelial growth via membrane-targeting mechanism	(Chen et al., 2020a)
Isoflavone/ stilbenoid	Daidzein, genistein, coumestrol, and resveratrol	*Phaseolus vulgaris*	*Pseudomonas savastanoi* pv. *phaseolicola*	Inhibited *P. savastanoi* pv. *phaseolicola* growth	(Cooper et al., 2022)
Stilbenoid	Pterostilbene	*Vitis vinifera*	*Botrytis cinerea*	Suppressed the development of gray mold in table grapes through loss of plasma membrane integrity	(Xu et al., 2022)
	Resveratrol	*Vitis* spp.	*Botrytis cinerea*	Suppressed the mycelial growth and conidia germination of *B. cinerea*	(Xu et al., 2018)
Alkaloid	α-solanine	*Fragaria ananassa*	*Curvularia trifolii*	Inhibit the growth and development of fungal spores	(Xu et al., 2023a)
	Camalexin	*Arabidopsis thaliana*	*Plasmodiophora brassicae*	Reduced the development of pathogen	(Lemarié et al., 2015)
	Camalexin	*Arabidopsis thaliana*	*Myzus persicae*	Antimicrobial activity	(Kettles et al., 2013)
Terpenoid	Diterpenoid phytoalexins	*Oryza sativa*	*Meloidogyne graminicola*		(Desmedt et al., 2022)
	α-humulene, α-phellandrene, α-pinene, caryophyllene oxide, and eugenol	*Cinnamomum verum, Syzygium aromaticum*	*Sitophilus granarius*	Terpenoids were toxic and repellent to adult *S. granarius*	(Plata-Rueda et al., 2018)

(*continued on next page*)

Table 1 (*continued*)

Class	Compound(s)/ pathway	Plant species	Target pathogen	Mode of Actions	Reference
Monoterpene	Geraniol	*Oryza sativa*	*Xanthomonas oryzae* pv. *oryzae* (*Xoo*)	Inhibited the growth of *Xoo* by suppressing the expression of the cell division-related genes of *Xoo*	(Kiyama et al., 2021)
	(*S*)-limonene	*Oryza sativa*	*Xanthomonas oryzae* pv. *oryzae* (*Xoo*)	Inhibited the growth of *Xoo*	(Lee et al., 2016)
	β-ocimene	*Nicotiana tabacum*	*Macrosiphum euphorbiae*	Decreased number of aphids settled, number newborn nymphs, and weight of aphids feeding as well as attracted more parasitoids	(Cascone et al., 2015)
	(−)-α-pinene, (−)-β-pinene, (+)-3-carene, myrcene, (+)- and (−)-limonene, terpinolene, α-terpineol, terpinen-4-ol, 1,8-cineole, and bornyl acetate	*Picea abies*	*Heterobasidion parviporum*	Inhibited mycelial growth through complex functions such as biodegradation	(Kusumoto et al., 2014)
	β-pinene	*Poncirus trifoliata*, *Citrus paradisi*	*Steinernema diaprepesi*		(Ali et al., 2011)
	Thymol, citronellal, and alpha-terpineol	*Nicotiana tabacum*	*Spodoptera litura*	Act as acute toxicity and feeding deterrence	(Hummelbrunner and Isman, 2001)
Diterpene/ Diterpenoid	Rhizathalene	*Arabidopsis thaliana*	*Bradysia* spp	Act as antifeedants	(Vaughan et al., 2013)
	Epoxydolabranol	*Zea mays*	*Fusarium graminearum* and *Fusarium verticillioides*	Inhibited the growth of *F. graminearum* and *F. verticillioides*	(Mafu et al., 2018)
Triterpene glycosides	3-*O*-*α*-$_L$-rhamnopyranosyl asiatic acid, macranthoside A, *α*-hederin, and ilekudinoside D	*Trevesia palmata*	*Magnaporthe oryzae* and *Botrytis cinerea*	Antifungal, antifeedants, and antidigestive activities	(Kim et al., 2018)
Sesquiterpenoids	β-caryophyllene	*Arabidopsis thaliana*	*Diaphorina citri*	Repellent effect on *D. citri*	(Alquézar et al., 2017)
	β-costic acid	*Zea mays*	*Aspergillus parasiticus, Cochliobolus heterostrophus*, *Fusarium graminearum*, *Fusarium verticillioides*, and *Rhizopus microsporus*	Inhibited the growth of *A. parasiticus, C. heterostrophus*, *F. graminearum, F. verticillioides,* and *R. microsporus*	(Ding et al., 2017)
Saponin	Sapindoside B, hederagenin-pentosylhexoside, and oleanolic acid-hexosyl-deoxyhexosyl-hexoside	*Sapindus mukorossi*	*Venturia inaequalis* and *Botrytis cinerea*	Inhibited the mycelial growth of *V. inaequalis* and *B. cinerea*	(Porsche et al., 2018)
	Aginoside	*Allium nigrum*	*Botrytis squamosa*, *Colletotrichum gloeosporioides*, *Fusarium verticillioides*, *Fusarium oxysporum* f. sp. *cepae*, *Fusarium oxysporum* f. sp. *radicis-lycopersici*, *Fusarium oxysporum* f. sp. *lycopersici*	Antifungal activity	(Mostafa et al., 2013)
	α-tomatine	*Solanum lycopersicum*	*Fusarium oxysporum*	Killed sensitive cells by binding to cell membranes followed by leakage of cell components	(Ito et al., 2007)
Coumarin	Scopoletin	*Glycine max*	*Phakopsora pachyrhizi* (*Pp*)	Suppressed the formation of *Pp* pre-infection structures and penetration of the plant, resulted protected soybean from *Pp* infection	(Beyer et al., 2019)
	Scopoletin	*Nicotiana tabacum*	*Botrytis cinerea*	Suppressed pathogenesis-related proteins accumulation and the capacity of the mycelium	(El Oirdi et al., 2010)
Lignans	Erythro-austrobailignan-6, meso-dihydroguaiaretic acid, and nectandrin-B	*Myristica fragrans*	*Alternaria alternata*, *Colletotrichum coccodes*, *Colletotricum gloeosporioides*, and *Magnaporthe grisea*	Suppressed the development of rice blast, wheat leaf rust, barley powdery mildew, and tomato late blight disease causing agents	(Cho et al., 2007)
Cyanogenic glucoside	Linamarin and lotaustralin	*Lotus japonicus*	*Zygaena filipendulae*	Hampered feeding preferences which affect the growth and development	(Zagrobelny et al., 2007)
Steroidal glycoside	Torvoside K	*Solanum torvum*	*Aspergillus flavus* and *Fusarium verticillioides*	Inhibited the growth of *A. flavus* and *F. verticillioides*	(Abhishek et al., 2015)

Meliaceae family produces azadirachtin, azadiradione, azadirone, salannin, salannol, methyl angolensate, gedunin, and 7-deacetyl gedunin, while *Croton jatrophoides* produces several limonoids, i.e., dumsenin, dumnin, musiduol, musidunin, umketol, zumsenol, and zumsenin with feeding deterrent properties (Lin et al., 2021). Pyrethrins are another important feeding deterrent against various sucking insects, providing effective protection for plants (Kojima et al., 2022).

3.1.5.2. Oviposition deterrents. In response to insect oviposition, plants undergo metabolic changes that disrupt the reproductive cycle of herbivorous pests. These responses often include the production of ovicidal substances, localized hypersensitive-like reactions, or neoplasm formation, which collectively impair egg viability or deter further egg-laying (Kumari and Kaushik, 2016). For instance, specific secondary metabolites such as coumarin and rutin in cabbage and ginsenosides in *Panax ginseng* alter the plant's surface chemistry and signaling pathways, making them less attractive to pests like *Pieris rapae* (Zhang et al., 2017). Similarly, azadirachtin, heptanal, and eucalyptol act as oviposition

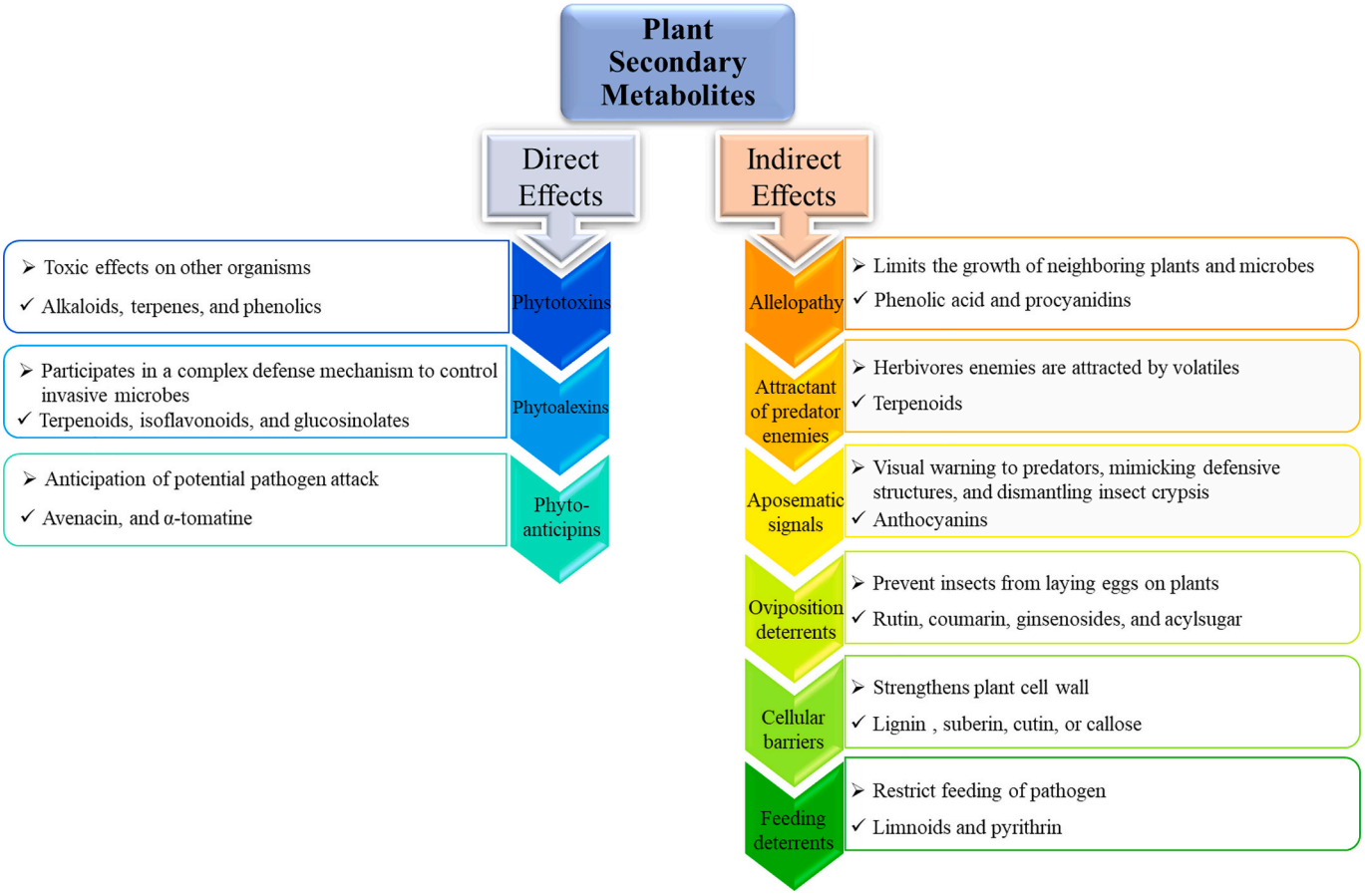

Fig. 2. Direct and indirect effects of plant secondary metabolites under biotic stress.

deterrents against potato tuber moth, *Phthorimaea operculella* (Ma and Xiao, 2013), and acylsugar against tobacco thrips, *Frankliniella fusca*, whitefly *Bemisia tabaci*, and western flower thrips, *Frankliniella occidentalis* (Ben-Mahmoud et al., 2018). Moreover, ostholes showed potential oviposition deterrents against *Tetranychus urticae*, *Myzus persicae*, and *Bactrocera dorsalis* (Dong et al., 2023). However, plants can also change their odor and leaf surface chemistry, which can serve as an indirect defense against egg deposition by attracting antagonists of the insect eggs. These changes in odor and leaf surface chemistry can also help disrupt the life cycle of insects (Rani, 2015). These defense mechanisms highlight the dynamic interplay between plant metabolism and pest behavior in mitigating biotic stress.

3.1.5.3. As aposematic signals. Aposematic coloration is a visual signal whose signal environment during the interaction has a significant impact on both transmission and reception (Arenas et al., 2014). The signal environment can influence the effectiveness of aposematic coloration in deterring predators (Skelhorn et al., 2016). The presence of other visually striking organisms in the environment can either enhance or diminish the deterrent effect. The phenomenon of aposematic coloration, which is widely recognized in animals, received minimal attention in plants before 2001. Plants with bright colors, such as red, orange, or yellow, often serve as a warning to predators or make plants unpalatable to them. This adaptation serves as a natural defense mechanism, as predators learn to associate the coloration with negative traits (Prudic et al., 2007). For example, anthocyanin-rich leaves' red color is believed to repel herbivores due to their vibrant color, which indicates a significant metabolic investment in toxic chemicals. Anthocyanin is responsible for the red color of spring leaves, which acts as a deterrent against herbivores, particularly lepidopteran and coleopteran insects (Chen et al., 2021). Moreover, they contribute to mimicking defensive structures, dismantling insect crypsis, and concealing plant components against their backgrounds (Lev-Yadun and Gould, 2008).

3.2. Direct defense mechanism of PSMs

3.2.1. Phytotoxins

Phytotoxins are plant-derived compounds with toxic effects on other organisms, produced as a defense mechanism against herbivores and pathogens or to compete with other plants for resources (Kocyigit et al., 2023). Phytotoxins have a significant impact on various organisms in different ways, including inhibiting growth, causing organ damage, or even leading to death. There are various classes of phytotoxins, such as alkaloids, terpenes, and phenolics, each with its own unique chemical structure and mode of toxicity. Plants naturally produce phytochemicals, also known as phytotoxins, to protect themselves against a variety of threats, including bacteria, fungi, insects, and predators. Herbivores can be killed or severely damaged by phytotoxins due to their lethal cytotoxic and neurotoxic effects (Friday, 2019). The cyanogenic glycosides found in cassava, sorghum, linamarin, lotaustralin, and amygdalin, as well as taxiphyllin from bamboo shoots, are released after herbivore attack and combine with β-glucosidase to form sugars and cyanohydrin, which then break down spontaneously to form HCN, a potent neurotoxin that hinders cellular respiration (Vetter, 2017). Other powerful plant-based toxins that alter herbivore metabolism and enzymatic pathways include alkaloids such as caffeine found in beverages like coffee, tea, and cocoa; nicotine from tobacco; and morphine and codeine from opium poppy (Matsuura and Fett-Neto, 2015). Phytotoxins have significant implications for agriculture as they can impact crop yield and quality (Cui et al., 2024). Discussing the potential use of phytotoxins in crop protection strategies or exploring ways to mitigate their negative effects

on agricultural productivity could be an interesting avenue to explore. While primarily produced as a defense mechanism against herbivory, some phytotoxins can inadvertently affect non-target organisms like beneficial insects or soil microorganisms (Gostin and Popescu, 2024).

3.2.2. Phytoalexins and Phytoanticipins

Phytoalexins are low-molecular-weight antimicrobial compounds synthesized by plants in response to biotic and abiotic stresses, playing a pivotal role in defending against invasive microbes (Table 2) (Ahuja et al., 2012). These compounds are produced rapidly and accumulate at infection sites, exemplifying a localized reaction to pathogenic attacks (Hammerschmidt, 1999; Li et al., 2023b). Interestingly, phytoalexins are often unique to specific plant families, reflecting evolutionary specialization. For example, isoflavonoids are characteristic of legumes, while glucosinolates are specific to the Cruciferae family. Distinctive phytoalexins, such as phaseolin in beans, gossypol in cotton, glyceollin in soybeans, rishitin in potatoes, pisatin in peas, and capsidiol in pepper, further highlight the diversity of these defensive metabolites (Al-Khayri et al., 2023). When under attack, plants swiftly synthesize and accumulate phytoalexins, disrupting the pathogen's metabolism, cell wall synthesis, or other vital processes (Li et al., 2023a). Additionally, these compounds can trigger other defense mechanisms, such as the hypersensitive response, which involves localized cell death to contain the infection (Chang et al., 2011). Phytoalexins are indispensable components of plant defense, exemplifying the sophistication of plant immune strategies. By integrating rapid synthesis and multifaceted mechanisms, they play a critical role in maintaining plant health under stress (Pérez-Clemente et al., 2013). Their continued study holds great potential for developing innovative strategies to enhance crop resistance to diseases. The dual function of phytoalexins, direct pathogen inhibition and

Table 2
List of the different phytoalexins identified in plants against various pathogens.

Chemical nature	Phytoalexins	Host	Pathogens	Reference
Flavonoids	Sakuranetin	*Oryza sativa*	*Magnaporthe oryzae*	(Jiang et al., 2024; Hasegawa et al., 2014)
	Xilonenin	*Zea mays*	*Fusarium graminearum* and *Fusarium verticillioides*	(Förster et al., 2022)
	Tangeretin	*Oryza sativa*	*Magnaporthe oryzae*	(Liang et al., 2021a)
	3-deoxyanthocyanidin	*Saccharum officinarum*	*Colletotrichum falcatum*	(Nandakumar et al., 2021)
	3-deoxyanthocynidin	*Sorghum bicolor*	*Fusarium* spp.	(Nida et al., 2021)
	Methoxylchalcones	*Hordeum vulgare*	*Bipolaris sorokiniana* and *Fusarium graminearum*	(Ube et al., 2021)
	Sakuranetin	*Oryza sativa*	*Rhizoctonia solani* and *Pyricularia oryzae*	(Katsumata et al., 2018; Katsumata et al., 2017)
	3-deoxyanthocyanidin	*Sorghum bicolor*	*Puccinia purpurea* and *Colletotrichum sublineolum*	(Schnippenkoetter et al., 2017)
	3-deoxyanthocyanidin	*Sorghum bicolor*	*Colletotrichum sublineolum* and *Cochliobolus heterostrophus*	(Liu et al., 2010)
Isoflavonoids	Genistein	*Phaseolus vulgaris*	*Pseudomonas savastanoi* pv. *phaseolicola*	(Cooper et al., 2024)
	Glyceollin	*Glycine Soja*	*Heterodera glycines*	(Yasmin et al., 2024)
	Daidzein and genistein	*Phaseolus vulgaris*	*Pseudomonas savastanoi* pv. *phaseolicola*	(Cooper et al., 2022)
	Glyceollin	*Glycine max*	*Fusarium solani*	(Abdul and Al-Muwayhi, 2020)
	Glyceollin	*Glycine max*	*Phytophthora sojae*	(Jahan et al., 2020)
	Medicarpin and 7,4′-dihydroxyflavone	*Medicago sativa*	*Fusarium oxysporum* f. sp. *medicaginis*	(Gill et al., 2018)
	Pisatin	*Pisum sativum*	*Nectria haematococca*	(Coleman et al., 2011)
Phenolics	Biphenyl	*Sorbus pohuashanensis*	*Alternaria Tenuis*	(Song et al., 2021)
Terpenoids	Kauralexin	*Zea mays*	*Cercospora zeina*	(Meyer et al., 2017)
	ent-10-oxodepressin	*Oryza sativa*	*Magnaporthe oryzae*	(Liang et al., 2021b; Inoue et al., 2013)
	Momilactone A	*Oryza sativa*	*Magnaporthe oryzae*	(Imai et al., 2012)
	Kauralexins A3 and B3	*Zea mays*	*Ostrinia nubilalis, Colletotrichum graminicola,* and *Rhizopus microsporus*	(Schmelz et al., 2011)
	Zealexins and Kauralexin	*Zea mays*	*Fusarium verticillioides*	(Veenstra et al., 2018)
	ent-10-oxodepressin	*Oryza sativa*	*Magnaporthe oryzae*	
	Momilactone A and B	*Oryza sativa*	*Magnaporthe oryzae*	(Hasegawa et al., 2010)
	Phytocassane	*Oryza sativa*	*Magnaporthe grisea*	(Umemura et al., 2003)
	Capsidiol	*Capsicum annuum*	*Colletotrichum scovillei*	(Baba et al., 2020)
	Capsidiol	*Capsicum* spp.	*Phytophthora infestans*	(Lee et al., 2017)
	Capsidiol 3-acetate	*Nicotiana benthamiana*	*Potato Virus X*	(Li et al., 2015a)
	Capsidiol	*Nicotiana attenuata*	*Botrytis cinerea* and *Phytophthora nicotianae*	(El Oirdi et al., 2010)
Stilbenoids	Resveratrol	*Phaseolus vulgaris*	*Pseudomonas savastanoi* pv. *phaseolicola*	(Cooper et al., 2022)
	Resveratrol	*Vitis amurensis*	*Agrobacterium rhizogenes*	(Kiselev et al., 2007)
Coumarins	Scopoletin	*Nicotiana attenuata*	*Alternaria alternata*	(Sun et al., 2014)
	Scopoletin	*Nicotiana attenuata*	*Botrytis cinerea* and *Phytophthora nicotianae*	(El Oirdi et al., 2010)
	Coumarin and furanocoumarin	*Citrus* spp.	*Phytophthora citrophthora*, *Phytophthora sojae*, *Botrytis cinerea*, *Alternaria alternata*, and *Sclerotinia sclerotiorum*	(Dugrand-Judek et al., 2015)
Indole phytoalexins	Brassilexin and spirobrassinin	*Brassica napus*	*Pseudomonas aeruginosa*	(Cook et al., 2022)
	Camalexin and indole-3-carboxylic acid	*Arabidopsis thaliana*	*Plectosphaerella cucumerina* and *Colletotrichum tropicale*	(Pastorczyk et al., 2020)
	Camalexin, indol-3-ylmethylamine, and indole-3-carboxylic acid	*Arabidopsis thaliana*	*Pseudomonas syringae*	(Stahl et al., 2016)
	Camalexin	*Arabidopsis thaliana* and *Solanum lycopersicum*	*Ralstonia solanacearum*	(Lin et al., 2014)
	spirobrassinin, cyclobrassinin, and rutalexin	*Brassica rapa* and *Brassica napus*	*Albugo candida*	(Pedras et al., 2008)

activation of additional plant defenses, illustrates their critical role in maintaining plant health under biotic stress. By integrating rapid synthesis and multifaceted mechanisms, these compounds exemplify the sophistication of plant immune strategies.

Phytoanticipins are a type of constitutive defense compound produced by plants in anticipation of potential pathogen attacks or other biotic stresses. Unlike phytoalexins, which are synthesized in response to pathogen invasions, phytoanticipins are constitutively present in plants and serve as pre-existing defense mechanisms. The innate immune system of the plant includes these compounds, which serve to deter or inhibit pathogens before they can establish an infection. Many plants have phytoanticipins, such as α-tomatine in tomatoes and avenacin in oats (Oros and Kállai, 2019). Phytoanticipins can include diverse secondary metabolites, including alkaloids, phenolics, terpenoids, and glucosinolates, among others. They may accumulate in different plant tissues, such as seeds, stems, leaves, and roots. Phytoanticipins can act through various mechanisms, including antimicrobial activity, inhibition of pathogen enzymes, and interference with pathogen cell structures (Tiku, 2020). Future research into their biosynthesis and functionality may unlock innovative strategies for enhancing crop resistance to pests and diseases.

4. Biosynthetic pathways of secondary metabolites: insights and integration for enhanced stress resistance

The biosynthetic pathways of secondary metabolites are activated in plants under stress conditions and are intricately linked to primary metabolism, forming a dynamic network of chemical transformations that enable adaptation to biotic stresses (Eulgem and Somssich, 2007; Ramawat and Goyal, 2020). Recent advances in genomic analysis have facilitated the identification and characterization of the genes and enzymes associated with secondary metabolite biosynthesis in different plant species through the utilization of high-throughput techniques such as genome wide association study, whole-genome sequencing and resequencing (Amjad et al., 2024; Naqvi et al., 2024; Xu et al., 2023b). Metabolites are transported through different cells and cellular compartments of plants, regulating the synthesis of specific metabolites within distinct cells or tissues. The activation and transcription of genes involved in secondary metabolite biosynthesis are governed by transcription factors (TFs), which also oversee the storage and transport of these metabolites (Divekar et al., 2022). While most biosynthetic pathways occur in the cytoplasm, terpenes such as monoterpenes, diterpenes, carotenoids, and phytols, along with alkaloids like caffeine and coniine, are synthesized in the chloroplast. Conversely, compounds like dolichol, sesquiterpenes, and sterols are synthesized in the cytosol or endoplasmic reticulum (Kutchan, 2005; Wink and Schimmer, 2018).

Key SM classes, such as phenolics, terpenes, and nitrogen- and sulfur-containing compounds, follow distinct biosynthetic pathways (Fig. 3). Phenolics primarily originate from the shikimate pathway, where shikimic acid, derived from erythrose-4-phosphate and phosphoenolpyruvate, serves as a precursor. The shikimate and tricarboxylic acid (TCA) cycles generate essential precursors, including fatty acids, amino acids, acetyl-CoA, and sugars, which undergo modifications such as methylation, glycosylation, hydroxylation, oxidation, and acylation. These metabolic processes diversify the structures of secondary metabolites (Divekar et al., 2022; Wink and Schimmer, 2018). Shikimate pathway

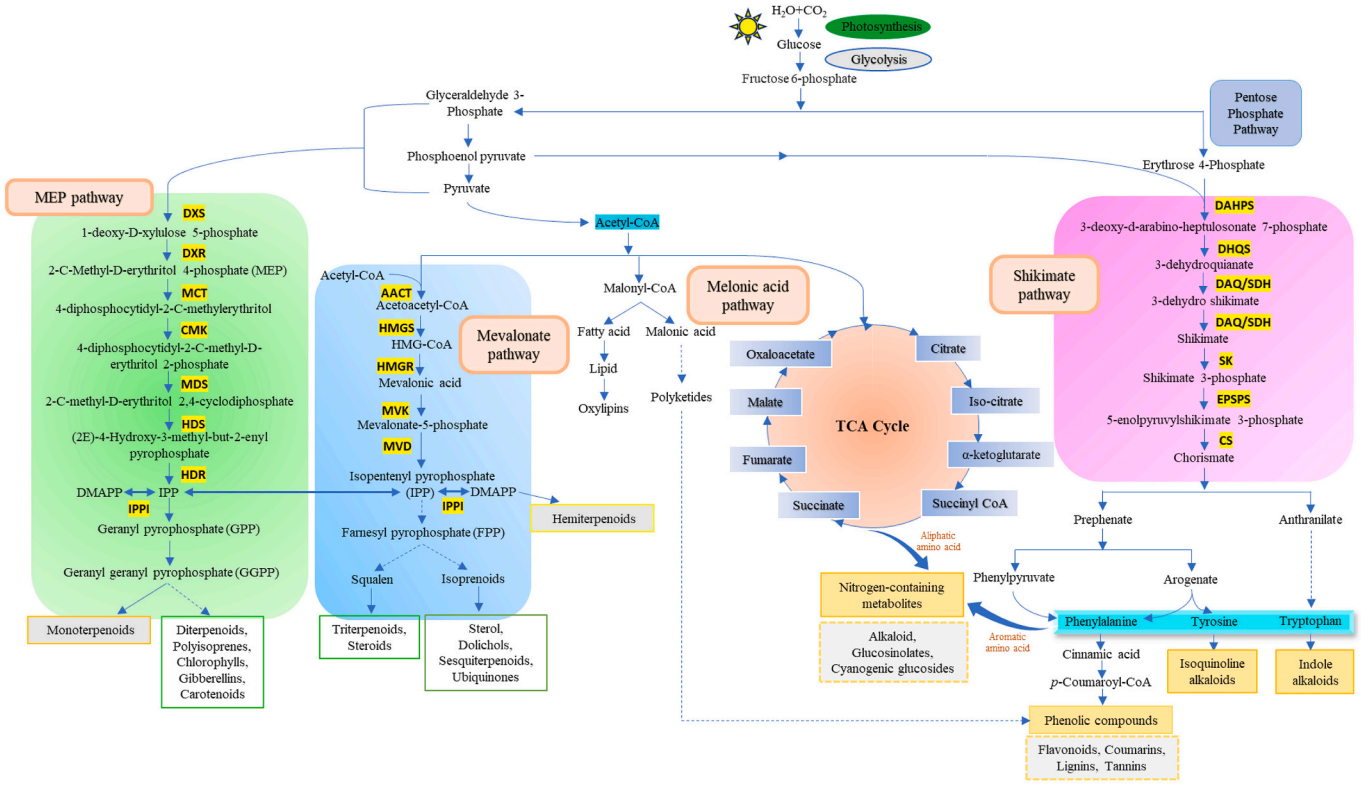

Fig. 3. Biosynthetic pathways plant secondary metabolites. Abbreviations: AACT, acetyl-CoA acetyltransferase; HMGS, 3-hydroxy-3-methylglutaryl-CoA synthase; HMGR, 3-hydroxy-3-methylglutaryl-CoA reductase; MVK, mevalonate kinase; MVD, mevalonate diphosphate decarboxylase; IPPI, isopentenyl diphosphate isomerase; DMAPP, dimethylallyl diphosphate; IPP, isopentenyl pyrophosphate; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; DXS, 1-deoxy-d-xylulose-5-phosphate synthase; DXR, 1-deoxy-d-xylulose-5-phosphate reductoisomerase; MCT, 4-diphosphocytidyl-2C-methyl-d-erythritol 4-phosphate synthase; CMK, 4-(cytidine-5′-diphospho)-2-C-methyl-d-erythritol kinase; MDS, 2C-methyl-d-erythritol 2,4-cyclodiphosphate synthase; HDS, 4-hydroxy-3-methylbut-2-enyl diphosphate synthase; HDR, 1-hydroxy-2-methyl-2-(*E*)-butenyl 4-diphosphate reductase; MEP, 2C-methylerythritol 4-phosphate; DAHPS, 3-Deoxy-D-arabinoheptulosonate 7-phosphate synthase; DHQS, 3-dehydroquinate synthase; DAQ, 3-dehydroquinate dehydratase; SDH, shikimate dehydrogenase; SK, shikimate kinase; EPSPS, 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase; and CS, chorismate synthase.

produces essential amino acids such as phenylalanine, tyrosine, and tryptophan, which are further utilized in the biosynthesis of lignins, flavonoids, and alkaloids (Ahuja et al., 2012; Yokoyama et al., 2021). Chorismate, the final product of the shikimate pathway, acts as a precursor for various metabolites and is regulated by enzymes such as isochorismate synthase and chorismate mutase (Ahuja et al., 2012; Divekar et al., 2022). Additionally, phenolics are synthesized via the malonic acid pathway in plants, fungi, and bacteria (Cheynier et al., 2013), with enzymes like phenylalanine ammonia-lyase (PAL) and chalcone synthase (CHS) playing pivotal roles under stress conditions (Amjad et al., 2024; Dehghan et al., 2014; Divekar et al., 2022). Another major class of secondary metabolites, terpenes are synthesized from isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). These structural units are produced via two distinct pathways i.e., the cytosolic mevalonate (MVA) pathway, which is acetyl-CoA derived, and the plastidial 2-*C*-methyl-D-erythritol-4-phosphate (MEP) pathway, derived from pyruvate (Basallo et al., 2023; Yokoyama et al., 2021). Terpenes are categorized based on the number of isoprene units and encompass compounds like monoterpenes, sesquiterpenes, and carotenoids. These compounds play critical roles in plant defense, phytocompounds synthesis, and environmental interactions (Divekar et al., 2022; Li et al., 2023b). Notably, the MEP pathway was first identified in *Escherichia coli*, and its plant homologs have since been characterized through genomic and biochemical studies (Rodriguez-Concepcion and Boronat, 2002). Nitrogen-containing secondary metabolites, derived from amino acids such as lysine, tyrosine, and tryptophan, are integral to plant stress responses. These include alkaloids and glucosinolates, which are synthesized via distinct, tightly regulated pathways. Their production is controlled at multiple levels, including transcriptional, post-transcriptional, and post-translational stages, ensuring precise accumulation in specific tissues (Kajla et al., 2023). Research has highlighted the importance of TFs in regulating SM biosynthesis, transfer, and storage, emphasizing the interplay between genetic and environmental factors in determining SM profiles (Jamwal et al., 2018; Nagegowda, 2010; Nagegowda and Gupta, 2020).). While the core steps in the biosynthesis of major secondary metabolite classes have been well-characterized, critical gaps remain in understanding how these pathways are regulated in response to biotic stresses. Specifically, the interaction between multiple biosynthetic pathways and the coordination of their regulation under stress conditions is a worthy area for exploration.

Recent advancements in multi-omics technologies, such as transcriptomics, metabolomics, and proteomics, have begun to unravel the complexity of these networks. For instance, transcriptomic studies have identified stress-inducible genes encoding key biosynthetic enzymes, such as chalcone synthase (CHS) in the flavonoid pathway and terpene synthase (TPS) in terpenoid biosynthesis (Jia et al., 2022; Wenkai et al., 2021). However, the integration of these transcriptomic findings with metabolomic profiles remains underexplored. Combining these datasets can illuminate how shifts in metabolic flux are coordinated during biotic stresses, offering insights into pathway prioritization under specific environmental conditions. Synthetic biology presents exciting possibilities for pathway engineering by reconstructing biosynthetic pathways in heterologous systems, identifying bottlenecks, and optimizing metabolite production (Aminian-Dehkordi et al., 2023). For instance, engineering yeast or bacteria to produce plant-specific secondary metabolites has uncovered novel regulatory elements that could be applied to crop improvement (Mipeshwaree Devi et al., 2023). Additionally, advances in genome editing, such as CRISPR/Cas9 and base editing, provide precise tools to modify key genes in biosynthetic pathways, enabling tailored responses to biotic stresses (Jan et al., 2021). Targeting regulatory genes and TFs offers the potential to modulate metabolic flux toward desired compounds (Al Aboud, 2024). This approach involves the overexpression of key enzymes and optimization of biosynthetic pathways to improve metabolite yield. For example, the overexpression of terpene synthases has successfully increased terpenoid production, simultaneously enhancing both plant resistance to herbivores and their commercial value (Dhandapani et al., 2020; Irmisch et al., 2014; Zhou and Pichersky, 2020). Furthermore, systems biology approaches integrating genomics, transcriptomics, proteomics, and metabolomics provide comprehensive insights into the regulatory networks underlying secondary metabolite biosynthesis (Khanijou et al., 2022). Coupled metabolomic and transcriptomic profiling can pinpoint critical metabolites and regulatory genes activated during biotic stress, which is invaluable for designing targeted genetic interventions (Aggarwal et al., 2024; Kulkarni et al., 2024). These approaches, combined with genetic tools, can sustainably increase the yield of SMs in crop plants (Divekar et al., 2022). Moreover, emerging evidence highlights significant crosstalk between metabolic pathways. For instance, intermediates from the phenylpropanoid pathway, which typically produces lignins and flavonoids, can be redirected to synthesize phytoalexins during pathogen attacks (Cesarino, 2019; Dong and Lin, 2020). This metabolic flexibility underscores the potential for engineering pathway "switches" to enhance the production of stress-specific metabolites. Such efforts require a deeper understanding of the transcriptional and enzymatic regulators modulating pathway interactions. Despite these advancements, challenges persist in decoding the intricate regulation of secondary metabolite pathways while avoiding unintended trade-offs in plant growth and development.

Future research must focus on integrating multi-omics data to unravel the complex interplay between primary and secondary metabolism. Developing robust biotechnological platforms for large-scale secondary metabolite production is vital for addressing global demands in sustainable agriculture. Innovations in genetic engineering, metabolic engineering, and omics technologies offer promising avenues for enhancing crop resilience against biotic stresses (Divekar et al., 2022). For instance, the ability to redirect metabolic pathways or optimize biosynthetic efficiency can lead to crops with enhanced resistance, reducing dependency on chemical pesticides and fostering sustainable agricultural practices. This perspective emphasizes the need to move beyond cataloging pathway components toward developing integrative models that connect gene expression, enzyme activity, and metabolite production under dynamic environmental conditions. By leveraging multi-omics and synthetic biology, biosynthetic pathways can be reimagined as adaptable networks that optimize plant resilience in real-time. Such insights have the potential to transform global agriculture, paving the way for crops with superior stress resistance and broader applications in sustainable crop production.

5. Transcriptional regulation of biotic stress responses for plant resilience

Transcription factors are crucial for plant secondary metabolite biosynthesis because they regulate the expression of genes in these pathways, enabling plants to produce specific defense compounds in response to biotic stresses (Table 3) (He et al., 2023). Plants have around 58 families of transcription factors (TFs), with six key TF families comprising WRKY, MYB, bHLH, bZIP, AP2/ERF, and NAC being particularly well-studied and recognized for their potential role in responses to biotic and abiotic stresses (Chowdhary et al., 2023; Liu et al., 2024a; Meraj et al., 2020; Rai et al., 2024). These key TF families play diverse regulatory roles, acting as either activators or repressors of gene expression to wield plant responses under stress conditions. Through binding to specific *cis*-acting elements of promoter regions of biosynthetic genes, they orchestrate complex transcriptional networks that enable plants to adapt and defend against various environmental challenges (Fig. 4) (Anjali et al., 2023; Jan et al., 2021; Kajla et al., 2023; Liu et al., 2024a). Understanding the regulatory mechanisms of these TFs is essential for uncovering their contributions to plant resilience and enhancing crop resistance through targeted genetic approaches.

Table 3
TFs mediated biotic stress response in plants through regulating secondary metabolites biosynthetic genes.

Family Name	Transcription Factors	Plant species	Metabolites	Target genes	Resistance against	Effect	References
MYB	GhMYB3D5	*Gossypium hirsutum*	Lignin	*GhPAL, GhC4H, Gh4CL,* and *GhPOD/ GhLAC*	*Verticillium dahliae*	GhMYB3D5 promoted lignin accumulation by improving the transcriptional levels of lignin biosynthesis genes, *GhPAL, GhC4H, Gh4CL,* and *GhPOD/ GhLAC* in cotton, thereby enhancing cotton *Verticillium* wilt resistance.	(Liu et al., 2024b)
	VqMYB15	*Vitis quinquangularis*	Stilbene	*STS*	*Uncinula necator*	Transient overexpression of VqNAC44 and VqMYB15 in grape leaves resulted in increased expression of the *STS* gene and increased production of stilbene compound, thereby enhancing resistance to disease.	Wang et al. (2024a)
	PpMYB308	*Prunus persica*	Flavonoids and phenolic compounds (neochlorogenic acid, chlorogenic acid, gallic acid, and rutin)	*PpPAL1* and *Pp4CL5*	*Rhizopus stolonifer*	PpMYB308 positively modulate the expression of *PpPAL1* and *Pp4CL5* to activate the phenylpropanoid pathway and enhance the accumulation of phenolic compounds, thereby contributing to disease resistance	(Li et al., 2023c)
	CmMYB15	*Chrysanthemum morifolium*	Lignin	*Cm4CL2*	*Macrosiphoniella sanborni*	CmMYB15 directly binds to the promoter region of *Cm4CL2* contributed to lignin deposition and enhanced aphid resistance.	(Li et al., 2023d)
	CaMYB39	*Cicer arietinum*	Kaempferol	*FLAVONOL SYNTHASE2*	*Ascochyta rabiei*	CaMYB39 overexpression increased trichome density and enhanced the accumulation of diverse flavonol derivatives in trichome-rich tissues which aids in partially blocking the penetration efficiency of the fungal pathogen, *Ascochyta rabiei*, resulting in lesser symptoms.	(Saxena et al., 2023)
	CaMYB78	*Cicer arietinum*	Anthocyanin		*Fusarium oxysporum*	Overexpression of CaMYB78 in chickpea improves its tolerance to *F. oxysporum* as well as negatively regulates anthocyanin production.	(Shriti et al., 2023)
	PcMYB44	*Pyrus communis*	Lignin	*PcLAC*	*Alternaria alternata* and *Botryosphaeria dothidea*	PcMYB44 regulates the expression of *PcLAC* which enhanced lignin synthesis and resistance to pathogens.	(Yang et al., 2023)
	SlMYB1	*Solanum lycopersicum*	Lycopene	*SlLCY1* and *SlPSY2*	*Botrytis cinerea*	SlMYB1 directly bind to the promoters of lycopene synthesis-related genes, *SlLCY1* and *SlPSY2*, regulate the fruit lycopene and resistance to *Botrytis cinerea.*	(Yin et al., 2023)
	GhODO1	*Gossypium hirsutum*	Lignin	*Gh4CL1* and *GhCAD3*	*Verticillium dahliae*	GhODO1 interacts with the promoters of lignin biosynthesis-related genes *Gh4CL1* and *GhCAD3*, directly activates their expression, and enhances total lignin accumulation, thereby resistance to *V. dahliae*.	(Zhu et al., 2022)
	VqMYB154	*Vitis quinquangularis*	Resveratrol	*PAL* and *CHS*	*Pseudomonas syringae*	VqMYB154 promotes the expression of *PAL* and inhibits that of *CHS*, further activating the resveratrol pathway. Thus, the accumulation of resveratrol contributes to plant disease resistance.	(Jiang et al., 2021)
	GhMYB4	*Gossypium hirsutum*	Lignin	*GhC4H-1, GhC4H-2, Gh4CL-4,* and *GhCAD-3*	*Verticillium dahlia*	GhMYB4 binds the promoters of several genes involved in lignin synthesis, such as *GhC4H-1, GhC4H-2, Gh4CL-4,* and *GhCAD-3*, and suppressed their expression which reduced lignin	(Xiao et al., 2021)

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Table 3 (*continued*)

Family Name	Transcription Factors	Plant species	Metabolites	Target genes	Resistance against	Effect	References
						deposition and enhanced resistance to *V. dahlia*.	
	PalMYB90	*Populus alba*	Total phenols, proanthocyanidins, anthocyanins, quercetin, and kaempferol	*PalF3H, PalDFR, PalANS*, and *PalANR*	*Botrytis cinerea* and *Dothiorella gregaria*	PalMYB90 function as transcriptional activators of flavonoid pathway genes, *PalF3H, PalDFR, PalANS*, and *PalANR* thereby enhanced total phenols, proanthocyanidins, anthocyanins, quercetin, and kaempferol and increase resistance against pathogens.	(Bai et al., 2020)
	AtMYB15	*Arabidopsis thaliana*	Lignin	*PAL, C4H, 4CL, HCT, C3′H, COMT,* and *CAD*	*Pseudomonas syringae*	MYB15 activated the lignin biosynthesis genes such as *PAL, C4H, 4CL, HCT, C3′H, COMT,* and *CAD*, thereby increased lignin deposition and disease resistance.	(Kim et al., 2020b)
	OsMYB30	*Oryza sativa*	Lignin	*Os4CL3* and *Os4CL5*	*Magnaporthe oryzae*	OsMYB30 activated the promoters of *Os4CL3* and *Os4CL5* resulting in accumulation of lignin which led to obvious thickening of sclerenchyma cells near the epidermis, inhibiting *M. oryzae* penetration.	(Li et al., 2020a)
	CmMYB15	*Chrysanthemum morifolium*	Lignin	*Cm4CL1, CmCCR1, CmF5H1,* and *CmCAD6*	*Macrosiphoniella sanborni*	CmMYB15 directly bind to the promoter regions of some lignin pathway genes, *Cm4CL1, CmCCR1, CmF5H1,* and *CmCAD6* could lead to changes in lignin content, thereby enhancing the aphid resistance.	(An et al., 2019)
	SmMYB44	*Solanum melongena*	Spermidine	*SmSPDS*	*Ralstonia solanacearum*	SmMYB44 directly binding to the *SmSPDS* promoter, activating its expression and increased spermidine content and resistance to *R. solanacearum*.	(Qiu et al., 2019)
	VdMYB1	*V. davidii*	Resveratrol	*VdSTS2*	*Erysiphe necator*	VdMYB1 directly activating the stilbene synthase gene *VdSTS2* therefore increased its expression which increased the accumulation of resveratrol, thereby resistance to pathogen.	(Yu et al., 2019)
	OsMYB30/55/110	*Oryza sativa*	Ferulic acid	*MKK4, MPK3*, and *MPK6*	*Xanthomonas oryzae* pv. *oryzae* (*Xoo*)	The expression of the MYB genes respond to MAMPs, activate most of the cinnamate/monolignol synthesis genes, lead to the accumulation of ferulic acid and enhanced resistance to disease.	(Kishi-Kaboshi et al., 2018)
	CmMYB19	*Chrysanthemum morifolium*	Lignin	*CmPAL1, CmC4H, Cm4CL1, CmHCT, CmC3H1, CmCCoAOMT1,* and *CmCCR1*	*Macrosiphoniella sanborni*	The overexpression of CmMYB19 restricted the multiplication of the aphids on the host, mediated by an enhanced accumulation of lignin through upregulated of lignin synthesis genes.	(Wang et al., 2017a)
	PtMYB115	*Populus tremula*	Proanthocyanin	*ANR1* and *LAR3*	*Dothiorella gregaria*	Overexpression of MYB115 in poplar activated expression of proanthocyanin biosynthetic genes, *ANR1* and *LAR3* resulting in a significant increase in proanthocyanin concentration and disease resistance.	(Wang et al., 2017b)
	oxMYB75	*Arabidopsis thaliana*	Kaempferol-3,7-dirhamnoside		*Pieris brassicae*	Enhancing the activity of the anthocyanin pathway in oxMYB75 plants results in re-channelling of quercetin or kaempferol metabolites which has a negative effect on the accumulation of kaempferol-3,7-dirhamnoside defense against caterpillar.	(Onkokesung et al., 2014)

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Table 3 (*continued*)

Family Name	Transcription Factors	Plant species	Metabolites	Target genes	Resistance against	Effect	References
	AtMYB12	*Arabidopsis thaliana*	Rutin	*NtFLS*	*Spodoptera litura* and *Helicoverpa armigera*	The overexpression of AtMYB12 in transgenic tobacco plants showed resistance against the insect pests due to enhanced accumulation of rutin.	(Misra et al., 2010)
ERF/ AP2	MdERF61	*Malus domestica*	Lignin	*MdLAC7b*	*Fusarium solani*	MdERF61 directly bind to two GCC-boxes of *MdLAC7b* and altered the lignin deposition in apple roots, which led to increased resistance to *F. solani*	Zhou et al. (2024)
	MdERF114	*Malus domestica*	Lignin	*MdPRX63*	*Fusarium solani*	MdERF114 directly binds the GCC-box of the *MdPRX63* promoter and activates its expression, resulting in lignin deposition in apple roots and increased resistance to *F. solani*.	Liu et al. (2023)
	NbERF-IX-16	*Nicotiana benthamiana*	Capsidiol	*NbEAS4*	*Phytophthora infestans*	NbERF-IX-33 bind to the promoter sequence of *NbEAS4*, enhanced the capsidiol production, resulting more resistance to *P. infestans*.	Imano et al. (2022)
	GbERF1	*Gossypium barbadense*	Lignin	*PAL*, *C4H*, *C3H*, *HCT*, *CCoAOMT*, *CCR*, and *F5H*	*Verticillium dahliae*	GbERF1 overexpressed cotton plants showed higher expression of lignin synthesis genes, such as *PAL*, *C4H*, *C3H*, *HCT*, *CCoAOMT*, *CCR*, and *F5H*, resulting in enhanced lignin content and resistance to *V. dahlia*.	Guo et al. (2016)
WRKY	RhWRKY30	*Rosa hybrida*	Lignin	*RhCAD1*	*Botrytis cinerea*	RhWRKY30 required to activate *RhCAD1* expression which increase lignin biosynthesis and improve the resistance of rose petals to *B. cinerea*.	(Li et al., 2024b)
	GhWRKY55	*Gossypium hirsutum*	Lignin	*GhHCT_D10*	*Verticillium dahliae*	GhWRKY55 interacts with the promoters of lignin biosynthesis-related gene *GhHCT_D10* which altered the lignin biosynthesis and negatively regulates cotton resistance to *V. dahliae*.	(Ma et al., 2024b)
	OsWRKY67	*Oryza sativa*	Sakuranetin	*OsNOMT* and *OsMPK6*	*Ustilaginoidea virens*	*OsNOMT*, the key enzyme in sakuranetin biosynthesis and *OsMPK6*, a mitogen-activated protein kinase, are directly regulated by the transcription factor OsWRKY67, thereby modulating sakuranetin biosynthesis and resistance to *U. virens*.	(Ma et al., 2024c)
	PdaWRKY4	*Prunus davidiana*	Botulin	*PdaCYP716A1*	*Myzus persicae*	PdaWRKY4 regulates aphid resistance by promoting *PdaCYP716A1*-mediated anti-aphid metabolite betulin biosynthesis.	(Wang et al., 2024b)
	OsWRKY10	*Oryza sativa*	Diterpenoid	*OsKSL7*, *OsCYP71Z7*, *OsCYP76M7*, *OsKSL4*, *OsCYP99A3*, and *OsKSL10*	*Magnaporthe oryzae*	OsWRKY10 activates the promoter activities of rice diterpenoid phytoalexin biosynthesis genes promotes rice diterpenoid phytoalexin accumulation thereby enhances resistance to rice blast.	(Wang et al., 2023b)
	VqWRKY56	*Vitis quinquangularis*	Proanthocyanidin	*VvCHS3*, *VvLAR1*, and *VvANR*	*Erysiphe necator*	VqWRKY56 significantly increased the transcript level of *VvCHS3*, *VvLAR1*, and *VvANR* genes promoted proanthocyanidin accumulation and improved resistance to powdery mildew.	(Wang et al., 2023c)
	AktWRKY12	*Akebia trifoliata*	Lignin	*4CL*, *C3H*, *C4H*, *CAD14*, *CCR*, and *CCoAOMT6*	*Colletotrichum acutatum*	Overexpression of AktWRKY12 in tobacco suppressed the expression of lignin synthesis key enzyme genes which play a negative role in *A. trifoliata* against pathogen.	(Wen et al., 2023)

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Table 3 (*continued*)

Family Name	Transcription Factors	Plant species	Metabolites	Target genes	Resistance against	Effect	References
	GhWRKY41	*Gossypium hirsutum*	Lignin and flavonoids	*GhC4H* and *Gh4CL*	*Verticillium dahliae*	GhWRKY41 directly activates the expression of *GhC4H* and *Gh4CL*, thereby modulating the accumulation of lignin and flavonoids in phenylpropanoid pathway resulting in pathogen resistance.	(Xiao et al., 2023)
	BnWRKY28/ 33	*Brassica napus*	Phytoalexin	*BnPAD3* and *BnCYP71A13*	*Sclerotinia sclerotiorum*	BnWRKY28 and BnWRKY33 regulates the high expression of disease resistance-related genes such as *BnPAD3* and *BnCYP71A13*, which promote phytoalexin biosynthesis and defend against the fungal pathogen invasion.	(Zhang et al., 2022b)
	ZmWRKY83	*Zea mays*	Phenylpropanoid, Flavonoid, and Terpenoid	*POD, PAL,* and *PPO*	*Fusarium graminearum*	ZmWRKY83 improve the resistance to *F. graminearum* via enriched in phenylpropanoid biosynthesis through activating the key enzymes genes *POD*, *PAL*, and *PPO*.	(Bai et al., 2021)
	GhWRKY1	*Gossypium hirsutum*	Lignin	*GhPAL6* and *GhCOMT1*	*Verticillium dahliae*	GhWRKY1 interacts with the promoters of lignin biosynthesis related genes *GhPAL6* and *GhCOMT1*, and activates their expression, which led to enhanced total lignin especially S monomers biosynthesis, thereby enhances *Verticillium* wilt resistance.	(Hu et al., 2021)
	PpWRKY70	*Prunus persica*	Phenylpropanoid	*PpPAL* and *Pp4CL*	*Rhizopus stolonifer*	PpWRKY70 activated *PpPAL* and *Pp4CL* transcription via binding to their promoters and promoted the accumulation of total phenolics, total flavonoids and lignin content, thereby resistance against *Rhizopus stolonifera*.	(Ji et al., 2021)
	VqWRKY53	*Vitis quinquangularis*	Stilbene	*VqSTS32* and *VqSTS41*	*Golovinomyces cichoracearum*	VqWRKY53 positively regulates the accumulation of stilbenes by directly regulating *STS* genes, thereby promotes disease resistance in transgenic Arabidopsis.	Wang et al. (2020)
	StWRKY8	*Solanum tuberosum*	Benzylisoquinoline alkaloids	*TyDC*, *NCS*, and *COR-2*	*Phytophthora infestans*	StWRKY8 have a direct regulatory role on benzylisoquinoline alkaloids biosynthetic genes, *TyDC*, *NCS*, and *COR-2*, which enhanced benzylisoquinoline alkaloids content and disease resistance.	(Yogendra et al., 2017)
	StWRKY1	*Solanum tuberosum*	Hydroxycinnamic acid amide	*4CL* and *THT*	*Phytophthora infestans*	StWRKY1 promoters hydroxycinnamic acid amide biosynthetic genes encoding *4CL* and *THT* which enhanced its accumulation, thereby conferring late blight resistance.	(Yogendra et al., 2015)
bHLH	VabHLH137	*Vitis vinifera*	Proanthocyanidin and anthocyanin	*VaLAR2*	*Colletotrichum gloeosporioides*	VabHLH137 overexpression in transgenic grape calli positively regulated proanthocyanidin and anthocyanin biosynthesis by activating of *VaLAR2* expression, thereby resistance to pathogen.	(Yu et al., 2023c)
	LjbHLH7	*Lotus japonicus*	Cyanogenic glucosides	*CYP79D3*	*Plutella xylostella*	LjbHLH7 directly activated the expression of *CYP79D3* gene through binding to the G-box sequence of its promoter, thereby increased cyanogenic glucosides content and enhanced insect resistance.	(Chen et al., 2022c)
	PalbHLH1	*Populus alba*	Total phenols, proanthocyanidins, anthocyanins, quercetin, and kaempferol	*PalF3H, PalDFR, PalANS*, and *PalANR*	*Botrytis cinerea,* and *Dothiorella gregaria*	PalbHLH1 function as transcriptional activators of flavonoid pathway genes, *PalF3H, PalDFR, PalANS*, and	(Bai et al., 2020)

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Table 3 (*continued*)

Family Name	Transcription Factors	Plant species	Metabolites	Target genes	Resistance against	Effect	References
						PalANR thereby enhanced total phenols, proanthocyanidins, anthocyanins, quercetin, and kaempferol and increase resistance against pathogens.	
bZIP	RhbZIP17	*Rosa hybrida*	Lignin	*RhCAD1*	*Botrytis cinerea*	RhbZIP17 binds to the promoter of the lignin biosynthesis gene *RhCAD1*, activates its expression which increase lignin content and improve the resistance of rose petals to *B. cinerea*.	(Li et al., 2024b)
	VqbZIPC22	*Vitis quinquangularis*	Proanthocyanidin	*VvANR*	*Erysiphe necator*	VqbZIPC22 significantly increased the transcript level of *VvANR* gene promoted proanthocyanidin accumulation and improved resistance to powdery mildew.	(Wang et al., 2023c)
	MdHY5	*Malus domestica*	Anthocyanin	*MdDFR*, *MdDFR*, *MdUF3GT*, *MdF3H*, *MdCHI*, and *MdCHS*	*Venturia inaequalis*	The MdHY5-overexpressing apple produce higher amounts of anthocyanin through upregulated of anthocyanin biosynthesis genes, including *MdDFR*, *MdUF3GT*, *MdF3H*, *MdCHI*, and *MdCHS*, thereby enhanced disease resistance.	(An et al., 2017)
	MebZIP3/5	*Manihot esculenta*	SA		*Xanthomonas axonopodis* pv. *manihotis*	The overexpression MebZIP3 and MebZIP5 conferred improved disease resistance against cassava bacterial blight, with more callose depositions.	(Li et al., 2017a)
	OsTGAP1	*Oryza sativa*	Diterpenoid	*OsDXS3*	*Xanthomonas oryzae* pv. *oryzae*	OsTGAP1 participates in the enhanced accumulation of diterpenoid phytoalexins, through mechanisms other than the direct transcriptional regulation of the genes *OsDXS3* involved in the biosynthetic pathway of diterpenoid phytoalexins, resulting resistance to disease.	(Miyamoto et al., 2014)
NAC	VqNAC44	*Vitis quinquangularis*	Stilbene	*STS*	*Uncinula necator*	Transient overexpression of VqNAC44 in grape leaves resulted in increased expression of the *STS* gene and increased production of stilbene compound, thereby enhancing resistance to disease.	Wang et al. (2024a)
	TaNAC032	*Triticum aestivum*	Lignin	*TaLAC4*	*Fusarium graminearum*	TaNAC032 regulates lignin biosynthetic gene *TaLAC4* increased total lignin content, resulting resistance to disease.	(Soni et al., 2021)
	MdNAC52	*Malus domestica*	Anthocyanin and proanthocyanidin	*MdLAR*	*X. campestris* pv. *vesicatoria*	MdNAC52 directly regulated *LAR* to regulate its expression and promote anthocyanin and proanthocyanidin synthesis, resulting resistance to disease.	(Sun et al., 2019a)
	LrNAC35	*Lilium regale*	lignin	*Ph4CL*	*Cucumber mosaic virus* (CMV) and *tobacco mosaic virus* (TMV)	The overexpression of LrNAC35 regulated the expression of *Ph4CL* resulted in reduced susceptibility to CMV and TMV infections, and enhanced accumulation of lignin in the cell walls.	(Sun et al., 2019b)
	ANAC042	*Arabidopsis thaliana*	Camalexin	*CYP71A12*, *CYP71A13*, and *CYP71B15/PAD3*	*Alternaria brassicicola*	ANAC042 activated camalexin biosynthetic genes *CYP71A12*, *CYP71A13*, and *CYP71B15/PAD3* to accumulate camalexin, and were resistance to pathogen.	(Saga et al., 2012)

5.1. MYB TFs

MYB transcription factors (TFs), also known as myeloblastosis transcription factors, play essential roles in plant biology, including growth, reproduction, and stress management. They are characterized by the MYB domain at their N-terminus, a conserved feature across eukaryotes. The first MYB TF, ZmMYBC1, was discovered in *Zea mays* in 1987. Since then, numerous MYB TFs have been identified and characterized in a

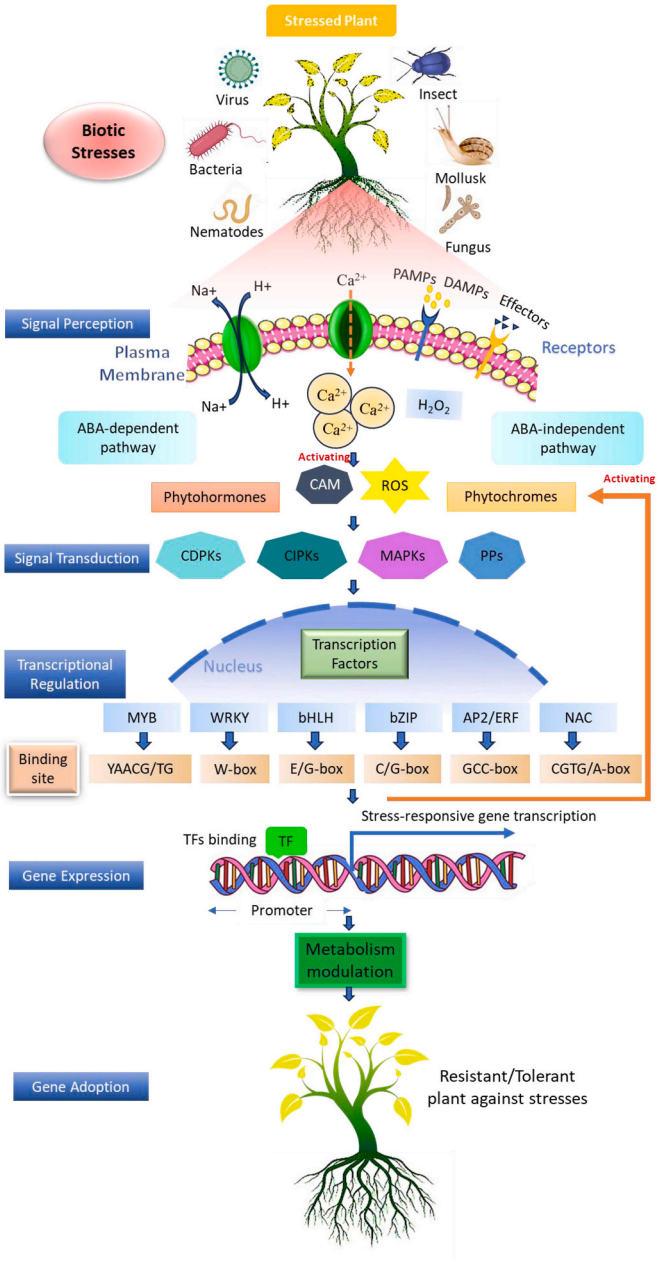

Fig. 4. Schematic representation of the mechanism of transcription factors regulating secondary metabolites signaling under biotic stresses.

wide range of plant species, including *Oryza sativa*, *Triticum aestivum*, *Solanum lycopersicum*, *Glycine* max, *Arabidopsis thaliana*, and *Gossypium hirsutum* (Yu et al., 2023a). MYB TFs are categorized into four subgroups (1R, 2R, 3R, and 4R) based on their DNA-binding domain repeats. These DNA-binding domains consist of 50–53 amino acids, forming α-helices with a helix-turn-helix structure that facilitates DNA binding. Among these, the R2R3 subgroup is particularly notable for regulating secondary metabolite pathways across diverse plant species (Wu et al., 2022). Multi-omics approaches, including genomics, transcriptomics, proteomics, and metabolomics, have provided insights into the functional roles of MYB TFs in orchestrating the biosynthesis of critical secondary metabolites like glucosinolates, flavonoids, hydroxycinnamic acid amides (HCAAs), and proanthocyanidins (Meraj et al., 2020). For instance, transcriptomic data have revealed differential expression patterns of MYB TFs under various biotic stresses, suggesting their involvement in activating specific secondary metabolite pathways. In Arabidopsis, the R2R3 MYB TFs (MYB29 and MYB76) are linked with aliphatic glucosinolate accumulation in aerial parts, while transcriptomic analyses of triple mutants (*myb34*, *myb51*, and *myb122*) have shown reduced expression of genes like *CYP79B2*, *CYP79B3*, and *CYP83B1*, leading to decreased indole glucosinolate levels and increased susceptibility to *Plectosphaerella cucumerina* (Frerigmann and Gigolashvili, 2014; Frerigmann et al., 2016). Integrative multi-omics studies, combining transcriptomics with metabolomics, have further elucidated the functional roles of MYB TFs in stress responses. For instance, the upregulation of lipid transfer protein (LTP) genes in cucumber (*Csa6G410090*) during *Meloidogyne incognita* infection, as observed through proteomic analyses, was correlated with increased expression of CsMYB genes, including *Csa6G538700*, *Csa1G021940*, and *Csa5G641610*, emphasizing their regulatory network in resistance mechanisms (Cheng et al., 2020). Similarly, MYB11, MYB12, and MYB111 are key regulators of flavonoid biosynthesis by activating genes like chalcone synthase (*CHS*), chalcone isomerase (*CHI*), Flavanone 3-hydroxylase (*F3H*), flavonol synthase (*FLS*) (Mehrtens et al., 2005; Stracke et al., 2007), while MYBL2 interacts with PAP1/2 and decreases their transcriptional activation activities through interrupting the expression of key genes required for anthocyanin biosynthesis, such as dihydroflavonol 4-reductase (*DFR*) and Transparent Testa 19 (*TT19*) (Xing et al., 2024). Multiomics analyses have provided deeper insights into the role of these transcription factors, revealing their regulatory networks at multiple levels. Transcriptomic studies have shown differential expression of flavonoid pathway genes under stress conditions, regulated by MYB12 and PAP1. Proteomic approaches identified post-translational modifications of these MYBs, influencing their activity and stability, while metabolomic profiling highlighted changes in flavonoid and anthocyanin levels, correlating with enhanced antioxidant activity, herbivore deterrence, and pathogen inhibition (Winkel-Shirley, 2001).

Metabolomic profiling has also highlighted MYB TFs' role in regulating flavonoid biosynthesis pathways, with altered metabolite accumulation observed in MYB-regulated mutants. In cotton, GhMYB33's interaction with *cis*-elements in the promoters of GhSPL9 and GhDFR1 was confirmed through chromatin immunoprecipitation (ChIP)-seq data, indicating a transcriptional regulation mechanism that enhances resistance to *Verticillium dahliae* (Guang et al., 2023). Similarly, the *Brassica juncea* gene *BjMYB1* has been implicated in activating *BjCHI1*, encoding a chalcone isomerase enzyme, leading to flavonoid accumulation and enhanced defense against *Botrytis cinerea*. By integrating ChIP-seq to map BjMYB1 binding sites and RNA-seq to quantify downstream gene activation, researchers confirmed the role of BjMYB1 in binding the W-box-like-4 (Wbl-4) element, a key regulatory site (Gao et al., 2016). Metabolomics data further supported flavonoid accumulation, corroborating its role in cell wall reinforcement and antifungal activity. Proteomics and metabolomics analyses of transgenic plants overexpressing *SpMYB* from *Solanum pimpinellifolium* have shown increased activities of defense-related enzymes (NtPAL, NtSOD, and NtPOD), correlating with enhanced resistance to *Botrytis cinerea* and *Fusarium oxysporum*. In these transgenic plants, the expression of *SpMYB* led to a decrease in malonaldehyde content, indicating reduced lipid peroxidation and oxidative damage. Moreover, increased activity of key antioxidant enzymes such as POD, SOD, and PAL suggests that SpMYB promotes the synthesis of secondary metabolites (e.g., phenolics), enhancing cell wall defenses and reducing pathogen invasion. Thus, SpMYB serves as a critical regulatory factor linking secondary metabolite biosynthesis and the JA signaling pathway to strengthen plant defenses against biotic stresses (Liu et al., 2015). Furthermore, the integration of transcriptomic and metabolomic datasets has allowed researchers to identify key regulatory nodes controlled by MYB TFs. In apple, *MdMYB30* was shown to bind to the promoter of *MdKCS1*, as evidenced by combined transcriptomic and metabolomic data, activating wax biosynthesis pathways that improve resistance against *Botryosphaeria dothidea* (Zhang et al., 2019). Moreover, the cotton gene GhMYB36 not only confers resistance to *Verticillium* wilt but also

enhances drought tolerance. By employing proteogenomic approaches, researchers identified the interaction of GhMYB36 with *PR1*, a salicylic acid pathway marker. Metabolomic profiling revealed an accumulation of defense-related secondary metabolites, confirming its dual role in biotic and abiotic stress tolerance (Liu et al., 2022b). Furthermore, overexpression of MYB58 and MYB63 specifically triggered the activation of lignin biosynthetic genes, which were validated through integrated transcriptome and metabolome analyses. For instance, transcriptomic data confirmed the upregulation of lignin biosynthetic genes and the secondary wall-associated laccase gene *LAC4*, while metabolomic profiling revealed increased lignin deposition, fortifying cell walls to create a physical barrier against pathogens (Riseh et al., 2024; Zhou et al., 2009). Multiomics approaches have also highlighted the interaction of MYB transcription factors with other TF families (e.g., bHLH and WRKY) and co-factors like the DELLA protein GhGAI1, which suppresses gibberellin signaling. For example, *GhMYB33* collaborates with GhGAI1 to enhance disease resistance, as revealed by interactome analyses and transcriptome studies (Guang et al., 2023). Multiomics approaches further elucidated the regulatory pathway and epigenomic studies demonstrated chromatin remodeling at loci regulated by SND1, NST1, NST2, VND6, and VND7, upstream activators of MYB58 and MYB63 (Zhou et al., 2009). Additionally, the pepper MYB TF CaPHL8 enhances resistance against *Ralstonia solanacearum* by activating and positively regulating defense-related genes and promoting the accumulation of reactive oxygen species (ROS) to limit pathogen spread. Multiomics analyses revealed the activation of specific ROS-associated proteins and accumulation of ROS metabolites, further linking MYB TF activity to oxidative stress management (Noman et al., 2019). Similarly, in wheat, *TaRIM1* boosts resistance to *Rhizoctonia cerealis*, with multiomics studies showing coordinated regulation at the transcriptional level, protein level, and downstream metabolite changes of defense-related genes, including *chitinase1*, *PR10*, *nsLTP1*, and *PR17c* that are involved in strengthening the plant cell walls and enhancing antifungal activity, thereby improving the plant's defense response (Shan et al., 2016). These specific regulatory mechanisms highlight how MYB TFs control secondary metabolite pathways like flavonoids and glucosinolates, contributing directly to enhanced plant defense and adaptation to various biotic stresses. These findings demonstrate the utility of multi-omics approaches in uncovering the complex regulatory roles of MYB TFs in secondary metabolite biosynthesis and plant defense.

However, not all MYB TFs act as positive regulators of plant defense. For example, SlMYB28 in tomato downregulates antiviral genes, reducing resistance to *Tomato yellow leaf curl virus* (TYLCV). By employing epigenomic analyses, researchers identified methylation changes at key antiviral loci under SlMYB28 regulation (Li et al., 2018). Additionally, AtMYB75 negatively regulates flavonoid synthesis, leading to reduced kaempferol-3,7-dirhamnoside levels and increased susceptibility to insect attack, as confirmed by CRISPR-Cas9 functional genomics and metabolomics (Onkokesung et al., 2014).

Overall, the application of multi-omics technologies has provided a deeper understanding of the versatile roles of MYB transcription factors in regulating secondary metabolite pathways. This holistic view has revealed novel regulatory mechanisms and interactions, offering valuable insights into enhancing crop resilience through targeted manipulation of MYB TFs in metabolic engineering and breeding programs.

5.2. AP2/ERF TFs

The APETALA2/ETHYLENE RESPONSE FACTOR (AP2/ERF) transcription factor (TF) family is recognized for its conserved DNA-binding domain of approximately 60 amino acids, playing a pivotal role in secondary metabolite biosynthesis and modulating plant responses to biotic and abiotic stresses (Feng et al., 2020). Initially identified in the flower homeotic gene APETALA2 (AP2) of *Arabidopsis thaliana*, it has become a focal point for understanding the multifaceted roles of this TF family. Structurally, AP2/ERF proteins are distinguished by three β-sheets preceding an α-helix motif, a configuration that facilitates precise DNA binding (Chen et al., 2020b). The family is further classified into subgroups, including AP2 (two AP2 domains), ERF (one AP2 domain and a B-subfamily), RAV (one AP2 domain and a B3 domain), and DREB (one AP2 domain and an A-subfamily), based on the number and combination of domains, has been further refined using genomic and proteomic data to reveal their diverse contributions to biotic stress responses and secondary metabolite biosynthesis (Zhu et al., 2021; Ma et al., 2024a). Recent multiomics approaches, such as transcriptomics, metabolomics, and ChIP-seq, have unveiled complex regulatory mechanisms by which AP2/ERF TFs interact with signaling pathways and downstream targets, emphasizing their dual roles as activators and repressors in plant defense (Anjali et al., 2023).

AP2/ERFs are critical in activating secondary metabolite pathways that bolster plant defense. Integrating transcriptomics with metabolomics, studies have revealed that AP2/ERF TFs such as ORCA1 and ORCA2 in *Catharanthus roseus* bind to promoters of terpenoid indole alkaloid (TIA) biosynthetic genes, such as *TDC* and *STR*, leading to the accumulation of TIAs like catharanthine. These metabolites, known for their roles in deterring insects and fungi by disrupting cellular functions, demonstrate how AP2/ERFs contribute directly to plant defense by regulating stress-responsive secondary metabolism (Kajla et al., 2023). Multiomics analyses, combining phosphoproteomics and signalome mapping, have shown that ORCA3, ORCA4, and ORCA5 function downstream of MAPK signaling pathways, further establishing the intricate cross-talk between TFs and defense-related signaling cascades (Singh et al., 2020). Similarly, members of the AP2/ERF family, such as GAME9, regulate steroidal glycoalkaloid (SGA) biosynthesis, enhancing resistance to pathogens like *Verticillium dahliae* and herbivores such as *Spodoptera litura*. Integrating ChIP-seq with targeted metabolomics, researchers have shown that GAME9 binds to promoters of SGA biosynthetic genes such as *HMGR* and *CAS*, leading to the accumulation of SGAs with cytotoxic properties that disrupt pathogen and herbivore cell membranes (Thagun et al., 2016; Nakayasu et al., 2017). Similarly, ERF114 and ERF11 activated *PAL1* transcription by binding to its promoter site to initiate salicylic acid biosynthesis and confer disease resistance against *Pseudomonas syringae* (Li et al., 2022b). Recently, resveratrol in grapes acts as an antibacterial agent against *B. cinerea*, with stilbene synthase (*STS*) being the main enzyme responsible for the biosynthesis of resveratrol (Meraj et al., 2020).

In the tobacco plant, jasmonic acid (JA)-responsive AP2/ERFs, including NtMYC2, NtORC1/ERF221, and NtERF189, upregulate nicotine biosynthetic genes like *PMT* and *QPT*. Transcriptomic profiling combined with metabolomics has revealed that overexpression of these TFs leads to enhanced nicotine and alkaloid levels, which act as potent herbivore deterrents (Jan et al., 2021). Furthermore, multiomics studies have shown that these TFs interact with bHLH TFs, suggesting a coordinated activation of nicotine biosynthetic pathways. Similarly, in *Artemisia annua*, the JA-responsive AP2/ERFs AaERF1 and AaERF2 bind to regulatory regions of the *CYP71AV1* and *ADS* genes, activating artemisinin biosynthesis. By integrating RNA-seq, metabolite profiling, and protein-DNA interaction assays, researchers have confirmed the regulatory role of these TFs in boosting artemisinin acid levels, a key secondary metabolite with antifungal and insecticidal properties (Yu et al., 2012). On the contrary, AP2/ERF TFs also participate in the downregulation of specific metabolic pathways. For instance, NtERF32 represses the expression of *NtPMT1a*, which encodes putrescine *N*-methyltransferase, thereby limiting nicotine biosynthesis. Combining epigenomics with transcriptional analyses, researchers have identified chromatin modifications associated with NtERF32-mediated suppression (Meraj et al., 2020). In another example, PnERF1 in *Panax notoginseng* upregulates triterpenoid saponin biosynthesis, a process confirmed using integrative metabolomics and genomics approaches that link PnERF1 to binding sites of genes such as *HMGR*, *FPS*, and *DS*, thereby enhancing saponin accumulation (Deng et al., 2017). Similarly,

lignin biosynthesis, crucial for cell wall reinforcement, is activated by GbERF1 in *Gossypium barbadense* through regulation of genes like *PAL*, *C3H*, *C4H*, *CCR*, *CoMT*, *F5H*, and *HCT*. This regulatory mechanism has been demonstrated using co-expression networks generated from transcriptomics and metabolomics data (Guo et al., 2016). Moreover, AP2/ERFs such as EREB58 in *Zea mays* regulate sesquiterpene biosynthesis, attracting natural predators of lepidopteran larvae. Virus-induced gene silencing (VIGS) and targeted proteomics have confirmed that EREB58 directly activates TPS10, linking transcriptional regulation to enhanced predator attraction as part of an indirect defense strategy (Li et al., 2015b). In the rose, RcERF099 and jasmonic acid-mediated TFs like RhCCCH12 and RhEFR005 regulate the expression of *PR10.1*, conferring resistance to *Botrytis cinerea*. Multiomics approaches, including ChIP-seq and metabolomic flux analyses, have further highlighted the role of these TFs in boosting pathogenesis-related protein production and secondary metabolite synthesis (Li et al., 2020b). Integrating multiomics approaches has deepened our understanding of the multifaceted roles of AP2/ERF transcription factors in regulating secondary metabolite biosynthesis and plant defense, highlighting their potential for enhancing crop resilience through targeted biotechnological strategies.

5.3. *WRKY TFs*

The WRKY gene family represents a vital group of transcription factors in higher plants, playing a key role in mediating biotic stress responses through the regulation of genes involved in secondary metabolite biosynthesis, including alkaloids, terpenoids, and their subclasses. These proteins are characterized by a conserved 60-amino-acid domain containing a WRKYGQK motif and a zinc finger region, which enables them to bind specifically to W-box elements in promoter regions of target genes, influencing diverse biochemical pathways (Phukan et al., 2016). This domain is distinguished by two highly preserved structural domains, i.e., the WRKYGQK sequence located at the N-terminus and the C-terminus at C-X7-C-X23-H-X-C, and a zinc finger region. WRKY proteins are grouped into three different groups depending on the variations in structural domain number, arrangement, and zinc-finger motif composition. Group I WRKY proteins feature two WRKY domains along with a C2H2-type zinc finger motif (C-X4–5-C-X22–23-H-X-H), while Group II and Group III proteins each comprise one WRKY domain (Xiong et al., 2024). Furthermore, Group II has a C2H2 zinc finger, while Group III has a C2HC zinc finger. Structural classification into three groups based on domain number and zinc-finger motifs (C2H2 in Group I and II, C2HC in Group III) underscores their functional diversity.

WRKY proteins play a pivotal role in plant stress responses by binding to promoter elements of key enzymatic genes, as initially evidenced by the cloning of the sweet potato gene *SPF1*, with subsequent discoveries in crops like *Oryza sativa*, *Zea mays*, *Solanum lycopersicum*, and *Arabidopsis thaliana*. Their functional diversity is exemplified by Group I WRKY transcription factors, which are heavily involved in regulating terpenoid biosynthesis, a crucial metabolic pathway for plant defense (Gao et al., 2023b). For example, *GmWRKY31* has been shown to regulate *GmSAGT1* gene expression during *Peronospora manshurica* infection in soybean, highlighting its role in modulating specific stress-related pathways (Dong et al., 2019). Similarly, in cotton, GhWRKY33 reduces whitefly egg and nymph counts, while GhWRKY25 exhibits moderate involvement in mitigating both whitefly and drought stresses, demonstrating a broader defensive spectrum (Ehsan et al., 2023). In barley, WRKY proteins also engage in post-translational modifications, as seen with SnRK1-mediated phosphorylation, which destabilizes the WRKY3 repressor to enhance protection against powdery mildew caused by *Blumeria graminis f.* sp. *hordei* (Han et al., 2020).

Advances in multiomics approaches, particularly integrating genomics, transcriptomics, and metabolomics, have deepened the understanding of their roles in modulating stress-responsive pathways. For instance, the involvement of NaWRKY3 in *Nicotiana attenuata* in regulating phytoalexins like scopoletin and scopolin against *Alternaria alternata* has been confirmed through RNA-seq and metabolite profiling, highlighting the linkage between transcriptional regulation and metabolite production (Xu et al., 2023c). Similarly, WRKY1 in *Artemisia annua* has been shown to control artemisinin biosynthesis, and multiomics analyses have further identified its interactions with sesquiterpene synthesis genes, revealing its critical role in plant defense (Jan et al., 2021). Integrative proteomics and functional genomics approaches have also shed light on the role of WsWRKY1 in *Withania somnifera*, which not only enhances phytosterol and withanolide biosynthesis but also confers resistance against *Pseudomonas syringae* and *Spodoptera litura* (Singh et al., 2017). In *Salvia sclarea*, SsWRKY18, SsWRKY40, and SsMYC2 regulate abietane-type diterpenes, whose antifungal and antibacterial properties have been confirmed through transcriptomic analysis and targeted metabolomics, underscoring the synergetic action of WRKY TFs in metabolic pathway regulation (Alfieri et al., 2018). Multiomics investigations have also shown that WRKY TFs contribute to resistance against fungal, bacterial, and viral pathogens, as well as herbivores (Xiong et al., 2024). For instance, VvWRKY1 in grapevine modulates jasmonic acid pathways during *Plasmopara viticola* infection, enhancing tolerance to downy mildew, a mechanism confirmed through expression profiling and hormonal assays (Marchive et al., 2013). In rice, OsWRKY31 boosts resistance against *Magnaporthe oryzae* by promoting the accumulation of jasmonic and salicylic acids, and integration of metabolomics with transcriptional data has elucidated its role in hormone-regulated defense (Wang et al., 2023a). Furthermore, WRKY proteins interact with other signaling pathways, as seen with AtWRKY52, equipped with TIR-NBS-LRR domains, which collaborates with *RPS4* to enhance resistance against *Colletotrichum higginsianum* and *Pseudomonas syringae*, a process linked to specific co-expression networks identified through multiomics datasets (Phukan et al., 2016). Similarly, CsWRKY25 in citrus directly binds to W-box elements of the CsRBOH2 promoter to confer resistance against *Xanthomonas citri*, an interaction validated by ChIP-seq and functional genomics (Li et al., 2024a). During fungal infection in wheat and barley, TaWRKY70 activates genes related to hydroxycinnamic acid amide (HCAA) biosynthesis, including *ACT*, *DGK*, and *GL1* (Kage et al., 2017), while HvWRKY23 enhances the *PAL*, *CHS*, and *HCT* genes expression, which are involved in HCAA biosynthesis during *Fusarium* head blight infection as shown by metabolomic flux analysis and gene regulatory network studies (Karre et al., 2019). HvWRKY2 suppresses the immunity of *Blumeria graminis* f. sp. *hordei* in barley through direct binding to a W-box-containing sequence in the *Hv*CEBiP promoter (Yu et al., 2023b).

However, not all WRKY proteins confer resistance; for instance, in sweet orange, CsWRKY22 activation of *CsLOB1* expression has been linked to increased susceptibility to canker, illustrating the nuanced roles these transcription factors play in plant-pathogen interactions (Long et al., 2021). Likewise, AtWRKY18 and AtWRKY40 in *Arabidopsis* negatively regulate defense pathways against powdery mildew (*Golovinomyces orontii*), whereas AtWRKY48 reduces resistance to *Pseudomonas syringae*, highlighting their dual roles in plant immunity (Pandey et al., 2010; Pandey and Somssich, 2009). Similarly, OsWRKY6 increases rice plant resistance against bacterial leaf blight caused by *Xanthomonas oryzae* pv. *oryzae* by directly regulating the expression of *OsICS1* (Im et al., 2024), while SbWRKY86 TF acts as a candidate gene that underlies sorghum's resistance to *Melanaphis sacchari* (Poosapati et al., 2022). However, certain WRKY TFs can also promote susceptibility, as seen with MdWRKY71 in apple, which increases susceptibility to *Colletotrichum fructicola* by binding to salicylic acid degradation genes *MdDLO1*, an interaction identified using functional assays and chromatin accessibility studies (Pei et al., 2024). These findings underscore the complex and often dual regulatory functions of WRKY proteins in modulating plant defense and susceptibility pathways. Thus, multiomics approaches provide a comprehensive framework to elucidate the regulatory mechanisms of WRKY transcription factors in plant defense, linking their structural properties, binding specificity, and target gene

networks to metabolic and physiological outcomes in response to biotic stress.

5.4. bHLH TFs

The basic helix-loop-helix (bHLH) family of transcription factors is defined by a conserved 60-amino-acid bipartite domain, where the N-terminal basic residues facilitate DNA binding, and the alpha-helices in the helix-loop-helix motif mediate homo- or heterodimeric protein-protein interactions. These transcription factors play pivotal roles in modulating stress responses by regulating the biosynthesis of a diverse array of secondary metabolites, including alkaloids, anthocyanins, diterpenoid phytoalexins, glucosinolates (GLs), and saponins (Zuo et al., 2023). Their regulatory functions extend to the phenylpropanoid pathway, particularly anthocyanin and flavonoid biosynthesis, through the formation of intricate protein complexes. For instance, specific bHLH proteins like GL3, eGL3, and TT8 interact with MYB in the presence of TTG1 to orchestrate the transcriptional regulation of anthocyanin biosynthesis (Dubos et al., 2010). Furthermore, MYB51 collaborates with bHLH proteins such as bHLH04, bHLH05, and bHLH06 to regulate GL biosynthesis in *Arabidopsis* (Frerigmann and Gigolashvili, 2014). The bHLH family also integrates hormonal signaling pathways, such as jasmonic acid (JA) and gibberellic acid (GA), with MYC2 serving as a key regulator in JA-mediated secondary metabolism. MYC2 binds to jasmonic acid-responsive elements in promoters like ORCA-3 to activate alkaloid biosynthesis (Jan et al., 2021), while interactions with DELLA proteins further link bHLH-mediated transcription to sesquiterpene gene expression in *Arabidopsis* flowers (Nemesio-Gorriz et al., 2017). In grapes, the overexpression of VvbHLH1 significantly enhances flavonoid biosynthesis by upregulating genes such as *CHS*, *DFR*, *F3H*, and *PAL* and increases flavonoid accumulation in transgenic *Arabidopsis* (Wang et al., 2016).

However, there have been reports of regulator complexes involving bHLH TFs controlling anthocyanin accumulation. For instance, bHLH proteins function in synergistic regulatory complexes, as seen with the bipartite interaction between Delila (bHLH) and Rosea1 (MYB) that controls anthocyanin accumulation in tomato and tobacco (Outchkourov et al., 2014). In other cases, a tripartite MYB-bHLH-WDR (MBW) complex orchestrates anthocyanin and proanthocyanidin biosynthesis in *Arabidopsis* (Nemesio-Gorriz et al., 2017). Beyond flavonoids, bHLH transcription factors independently or collaboratively modulate the biosynthesis of other defensive metabolites, such as glucosinolates, diterpenoid phytoalexins, and saponins. For example, ILR3 (IAA-Leucine Resistant 3) has been shown to play a role in these processes (Samira et al., 2018). Integrating multiomics approaches to study the bHLH family offers insights into the complex regulatory networks underlying secondary metabolite biosynthesis and stress responses in plants.

5.5. bZIP TFs

Basic leucine zipper (bZIP) transcription factors (TFs) are homodimeric proteins characterized by conserved leucine zipper dimerization domains and positively charged DNA-binding regions, indicating their importance in transcriptional regulation. The bZIP TFs are broadly distributed in plants and contribute to a variety of processes, such as plant growth and development, secondary metabolism, biotic and abiotic stresses, photomorphogenesis, resistance against pathogenic microorganisms, and signal transduction (Han et al., 2023). Their involvement in stress resistance is well-documented, as demonstrated by GmbZIP15 in soybeans, which modulates defense-related gene expression to confer resistance against *Phytophthora sojae* and *Sclerotinia sclerotiorum* (Zhang et al., 2021). Similarly, LrbZIP1 from *Lilium regale* enhances resistance to *Fusarium oxysporum* f. sp. *lilii* (Zhang et al., 2014), and FabZIP46 bolsters strawberry defenses against gray mold caused by *Botrytis cinerea* (Lu et al., 2020). bZIP TFs also regulate secondary metabolism, such as VvibZIPC22 in *Vitis vinifera*, which induces flavonoid biosynthesis (Malacarne et al., 2016), and GmbZIP5 in soybean, which increases isoflavone content in hairy roots (Anguraj Vadivel et al., 2021). Conversely, BcbZIP134 negatively regulates triterpenoid saponin metabolism in *Bupleurum chinense* (Xu et al., 2019a).

Notably, OsTGAP1 in rice enhances terpenoid phytoalexin biosynthesis by activating promoters of terpene synthase genes such as *OsKSL4* and *OsCPS4* while modulating the MEP pathway to supply isoprenoid precursors (Meraj et al., 2020). Beyond plants, Yap-like bZIP TFs in fungi, such as *Yap1*, play critical roles in stress responses, secondary metabolism regulation, and fungal adaptation across species like *Aspergillus*, *Magnaporthe oryzae*, *Botrytis cinerea*, and *Fusarium graminearum* (Jan et al., 2021). *Yap1*'s regulation of oxidative stress tolerance and secondary metabolite biosynthesis underscores its functional versatility in fungal physiology (Simaan et al., 2019). Similarly, anthocyanin accumulation in tomatoes is regulated by SlHY5, which is attached to the G-box and ACGT elements in promoters of anthocyanin biosynthetic genes such as chalcone synthase (*CHS*) and dihydroflavonol 4-reductase (*DFR*). Reduced anthocyanin accumulation is the result of silencing SlHY5, underscoring the crucial regulatory function of SlHY5 (Liu et al., 2018). Additionally, HY5 influences monoterpene biosynthesis by binding to the promoter region of the monoterpene synthase gene *QH6*, further highlighting the broad regulatory roles of bZIP TFs (Zhou et al., 2015). Integrating multiomics approaches enables comprehensive insights into the multifaceted roles of bZIP TFs in stress tolerance and metabolic regulation across biological systems.

5.6. NAC TFs

The NAC transcription factor (TF) family is a plant-specific group with crucial roles in regulating physiological processes and providing defense against biotic and abiotic stresses, with over 100 members identified in both rice and *Arabidopsis* (Yuan et al., 2019). These proteins are characterized by a conserved N-terminal NAC domain involved in regulatory binding and a diverse C-terminal region that acts as a transcriptional regulator. This structural diversity allows NAC TFs to control the expression of genes linked to stress responses and secondary metabolite biosynthesis (Kumar et al., 2021). For instance, ANAC042 enhances resistance to *Alternaria brassicicola* by binding to the promoters of camalexin-biosynthesis genes such as *CYP71A12*, *CYP71A13*, and *CYP71B15* (Saga et al., 2012). Similarly, PtrNAC72 in *Poncirus trifoliata* and MfNAC in *Medicago falcata* regulate ROS homeostasis through the modulation of putrescine and glutathione biosynthesis via the *ADC* and *GLO1* genes, respectively (Duan et al., 2017; Wu et al., 2016). In *Hevea brasiliensis*, HbNAC1 facilitates latex biosynthesis by binding to the CACG motif in the promoter region of the *SRPP* (small rubber particle protein) gene (Cao et al., 2017).

The regulatory influence of NAC TFs is also evident in pathogen defense, as observed in PaNAC03, which modulates flavonoid biosynthesis genes in response to *Heterobasidion annosum*, and in NAC028, which, along with bZIP23, activates *CAD8B* expression to enhance rice resistance against sheath blight disease (Dalman et al., 2017; Yuan et al., 2023). In wheat, TaNACL-D1 interacts with the orphan protein TaFROG to confer resistance against *Fusarium graminearum*, whereas TaNAC30 negatively regulates immunity against stripe rust caused by *Puccinia striiformis* (Perochon et al., 2019; Wang et al., 2018a). In rice, NAC TFs display contrasting roles, with OsNAC60 suppressing immunity to blast disease caused by *Magnaporthe oryzae*, while OsNAC096 and OsNAC58 enhance immunity against *Xanthomonas oryzae pv. oryzae* and blast disease through regulation of downstream targets such as *OsWRKY62*, *OsPAL1*, and *OsRap2.6* (Wang et al., 2018b; Wang et al., 2021; Park et al., 2017). Likewise, OsNAC111 positively regulates resistance of rice against blast disease caused by *Magnaporthe oryzae* (Yokotani et al., 2014).

Integrating multiomics approaches can reveal the complex regulatory networks mediated by NAC TFs, their interactions with other

molecular players, and their roles in linking transcriptional responses to metabolomic and proteomic changes, offering deeper insights into plant stress resistance and secondary metabolism.

Taken together, although significant progress has been made in identifying TFs involved in secondary metabolite pathways, comprehension of the specific mechanisms by which these transcription factors integrate biotic stress responses with secondary metabolite synthesis is still incomplete. Further research should focus on dissecting these regulatory networks using sophisticated tools such as CRISPR-Cas9 and multi-omics approaches, including transcriptomics and metabolomics, for a comprehensive understanding of TF roles in plant stress response.

6. Metabolic engineering of plant secondary metabolites accelerates breeding for biotic stress tolerance

Metabolic engineering of plant secondary metabolism is a transformative approach that modifies endogenous pathways to redirect enzymatic reactions, aiming to enhance or suppress the production of specific secondary metabolites or generate novel compounds utilizing genetic engineering (Mipeshwaree Devi et al., 2023; Razzaq et al., 2023). A thorough understanding of metabolic pathways and their regulatory networks underpins successful metabolite engineering, enabling the development of pathogen- and pest-resistant plants, fostering sustainable agricultural practices (Zhou and Jander, 2021; Mahmood et al., 2022; Ren et al., 2024). This holistic technique facilitates researchers to discover genomic variations, candidate resistance or susceptible genes, and evolutionary signatures linked with biotic stresses like pathogens, pests, and herbivores and uncover the molecular basis of these stresses in plants.

Recent advancements in genomic approaches, such as genome-wide association studies (GWAS), have facilitated the identification of natural genetic diversity within plant populations to discover genomic regions and candidate genes associated with pests and diseases (Qi et al., 2024). Advances in genomic, transcriptomic, proteomic, and metabolomic approaches have revolutionized the study of plant secondary metabolites, facilitating the discovery of genes, enzymes, and regulatory elements that underpin these pathways (Aggarwal et al., 2024). For example, genome-wide association analyses and functional studies in *Brassica napus* have identified *CYP90A1*, *ALDH3F1*, *BnLegLus-16*, and *BnaA07.MKK9* as key genes conferring resistance to *Sclerotinia sclerotiorum* through mechanisms involving ethylene, camalexin, and indole glucosinolates biosynthesis (Gan et al., 2022; Zuo et al., 2022; Lin et al., 2024). Studies in cotton have demonstrated that *GHHIT4_4* indirectly regulates the *PAL*, *4CL*, and *CHI* genes and enhances resistance to *Verticillium* wilt (Zhang et al., 2024). Additionally, mGWAS has identified genes like *OsLSC6* linked to Cyanidin-3-Galc of anthocyanin biosynthesis, which is responsible for the color of the rice leaf sheath and its resistance to cold (Lv et al., 2024). Similarly, *GBSOT4* enhances resistance in *Gossypium barbadense* to *Fusarium oxysporum* by regulating flavonoid content, which was revealed by different bioinformatics tools (Su et al., 2023).

Transcriptomic studies have emerged as a valuable tool over the past decade for studying gene expression patterns of secondary metabolites, providing insights into plant defense activation against diseases and herbivores with the ability to detect increases in plant secondary metabolites (Vishwanath et al., 2024). For instance, in soybeans, the flavonoid biosynthesis genes *GmF3'H* and *GmDFR* have been identified as critical regulators of isoflavonoid production, enhancing resistance to pathogens (Dastmalchi et al., 2017). Similarly, transcriptomic analyses in *Arabidopsis thaliana* revealed the role of *SAD2* in flavonoid biosynthesis and resistance to *Pseudomonas syringae* pv. Tomato DC3000 via interactions with ERF/AP2, MYB, and bHLH transcription factors (Li et al., 2023e). Genome-wide transcriptome analysis in ramie identified 777 differentially expressed genes (DEGs), with 12 confirmed by qRT-PCR as being involved in carotenoid, phenylalanine, and phenylpropanoid biosynthesis pathways, affected by *Pratylenchus coffeae* infection (Zhu et al., 2014). In black pepper, genes involved in phenylpropanoid metabolism were identified in response to *Phytophthora capsici* through *de novo* transcriptome sequencing (Hao et al., 2016). Single-cell transcriptomics has emerged as a potent tool in recent years, exposing high-resolution gene expression patterns at the cellular level. Advances in this technique facilitated an opportunity to achieve a complete understanding of how plants respond to biotic stresses as well as the functional annotation of novel candidate genes (Ali et al., 2024; Shaw et al., 2021). However, single-cell transcriptomics offers unprecedented resolution, identifying five candidate genes, i.e., *ZmWOX5b*, *ZmCOMT*, *ZmCCoAOMT2*, *ZmPAL6*, and *ZmPIN1a*, in maize that regulate flavonoid, phenylpropanoid, and phenylalanine biosynthetic pathways, conferring resistance to stalk rot caused by *Fusarium verticillioides* (Cao et al., 2023). Two salicylic acid-responsive proteins, ALD1 and FMO1, crucial for resistance against *Pseudomonas syringae*, were expressed in numerous vascular cells identified through single-cell transcriptomics (Tenorio Berrío and Dubois, 2024). Transcriptomic studies enable the characterization of dynamic changes in gene expression patterns upon pathogen challenge, revealing signaling pathways and regulatory networks involved in defense responses (Manzano et al., 2022).

Metabolomics complements genomic and transcriptomic approaches, providing a snapshot of plant metabolic profiles under stress. By revealing changes in metabolite levels, it helps uncover compounds essential for defense (Divekar et al., 2022; Roessner et al., 2001; Shen et al., 2023; Wu et al., 2023). As the current knowledge of the pathways' regulation, transport, and accumulation of the novel compounds makes accurate change prediction in metabolically engineered plants challenging, metabolite analysis has become an indispensable tool in this field. Unpredictable changes and other overall effects can be detected through non-targeted metabolite profiling, which can also help interpret the effects of gene transfer and provide insight into the unknown steps and regulation in the engineered pathway (Selma et al., 2023; Tan et al., 2023). For instance, a metabolomics study conducted on Sorghum stressed by *Colletotrichum sublineolum* showed changes in their metabolomes that were caused by modifications in the flavonoid and phenylpropanoid pathways and led to the excessive accumulation of phenolic compounds, such as phytoalexins, apigeninidin, luteolinidin, and other related molecules (Tugizimana et al., 2019). Similarly, metabolomics studies in *Medicago truncatula* have identified defense-related metabolites, including malic acid, phosphoric acid, tetrahydroxychalcone, and soluble carbohydrate alterations that were used as metabolic markers for breeding *Fusarium*-tolerant varieties (Dickinson et al., 2018). According to Aliferis et al. (2014), there was also an increase in the synthesis of flavonoids, coumarins, and phytoalexins against *R. solani* infestation in soybeans. Betulin, a defensive metabolite in peaches, exhibits potent aphidicidal activity by regulating the cytochrome P450 gene *PpCYP716A1*, which is responsible for its synthesis (Wang et al., 2022). However, proteomic approaches complement transcriptomics by identifying and quantifying the abundance of proteins involved in defense-related processes, including pathogen identification, signal transduction, and antimicrobial compound biosynthesis (Pandey et al., 2019). Recently, it was found that rice's resistance to *Rhizoctonia solani* is mediated by a novel protein called 14–3-3GF14f (Karmakar et al., 2019). Additionally, *Agrobacterium*-mediated transformation provides a versatile platform for overexpressing key genes, suppressing competing pathways, or introducing foreign genes to optimize metabolite production, further advancing targeted metabolic engineering (Bomzan et al., 2022; Mora-Vásquez et al., 2022). These combined strategies underscore the transformative potential of integrating genomic tools with metabolic engineering to improve the synthesis of valuable secondary metabolites in plants.

Following advancements in next-generation sequencing (NGS), targeted genome-editing technologies such as CRISPR/Cas9, zinc-finger nucleases (ZFNs), and transcription activator-like endonucleases (TALENs) are increasingly being integrated into synthetic biology, genetic engineering, and metabolic engineering of different plants (Mitra et al.,

2022a). While multi-omics approaches have identified key enzymes involved in secondary metabolite biosynthesis, many pathways remain unexplored. Once the critical genes in these pathways are identified, they can be manipulated through techniques such as transgenic methods, accelerated mutagenesis, RNA interference (RNAi)-mediated gene silencing, CRISPR/Cas9-mediated genome editing, and so on to enhance or suppress the production of targeted secondary metabolites, thereby strengthening plant resistance to biotic stresses (Fig. 5) (Das et al., 2024; Mipeshwaree Devi et al., 2023; Mitra et al., 2022b).

6.1. Transgenic breeding

Transgenic crop cultivars are developed through a series of precise genetic engineering steps, including the cloning of desirable genes, construction of expression vectors, genetic transformation of recipient crops, and rigorous screening and identification of transformed lines, with the aim of enhancing undesirable traits or introducing new, beneficial characteristics (Raymond Park et al., 2011; Kamthan et al., 2016). This technology also facilitates the modification or knockout of undesirable genes to alter genetic characteristics and achieve favorable phenotypes (Georges and Ray, 2017). Following comprehensive safety assessments, transgenic cultivars demonstrating significant improvements in yield, quality, or environmental adaptability are approved for commercial deployment. Transgenic manipulation strategies encompass heterologous expression of exogenous genes, overexpression of endogenous genes, and suppression of undesirable gene expression, offering versatile approaches to revolutionize crop improvement (Yu et al., 2022).

Terpene synthases (TPSs) are critical enzymes in the biosynthesis of terpenes (Dudareva et al., 2013; Tholl, 2015). The strategic metabolic engineering of TPS pathways offers significant potential for enhancing terpene production and improving crop resilience. For instance, overexpression of the rice TPS gene *OsTPS19* boosts (*S*)-limonene levels, conferring enhanced resistance to the blast fungus *Magnaporthe oryzae* (Chen et al., 2018). Similarly, cassava lines engineered to overexpress tannin biosynthesis genes such as leucoanthocyanidin reductase (*LAR*) and anthocyanidin reductase (*ANR*) show elevated tannin concentrations, providing resistance to the two-spotted spider mite (Chen et al., 2022d). In conifers, terpene biosynthesis genes like *PmTPS4* and *PmTPS21* contribute to defense against pine wood nematodes by producing α-pinene and longifolene, which serve as chemical deterrents (Liu et al., 2021). Additionally, overexpression of *PmGPPS1* in pine boosts monoterpene and diterpene production, enhancing resistance by upregulating key genes in the mevalonic acid (MVA) and methylerythritol phosphate (MEP) pathways (Liu et al., 2022c). Solanaceous crops demonstrate the power of interspecies pathway transfers. For example, *Solanum habrochaites* sesquiterpene synthase genes introduced into cultivated tomatoes (*S. lycopersicum*) result in the production of novel insecticidal compounds, providing effective resistance to pests like whiteflies and spider mites (Bleeker et al., 2012). Another notable advancement is the introduction of the biosynthetic pathway for 7-epizingiberene from wild tomatoes into cultivated varieties. This sesquiterpene, produced by glandular trichomes expressing *ShZIS* and Z-FPP synthase, confers herbivore resistance while maintaining agronomic traits (Bleeker et al., 2011). Furthermore, tobacco plants overexpressing cytokinin exhibit resistance to *Phytophthora syringae* by regulating capsidiol and scopoletin levels (Grosskinsky et al., 2011). Advances in gene manipulation, such as silencing or overexpressing terpenoid-related genes like 5-epi-aristolochene synthase, have demonstrated increased terpene production and improved defense mechanisms against pests

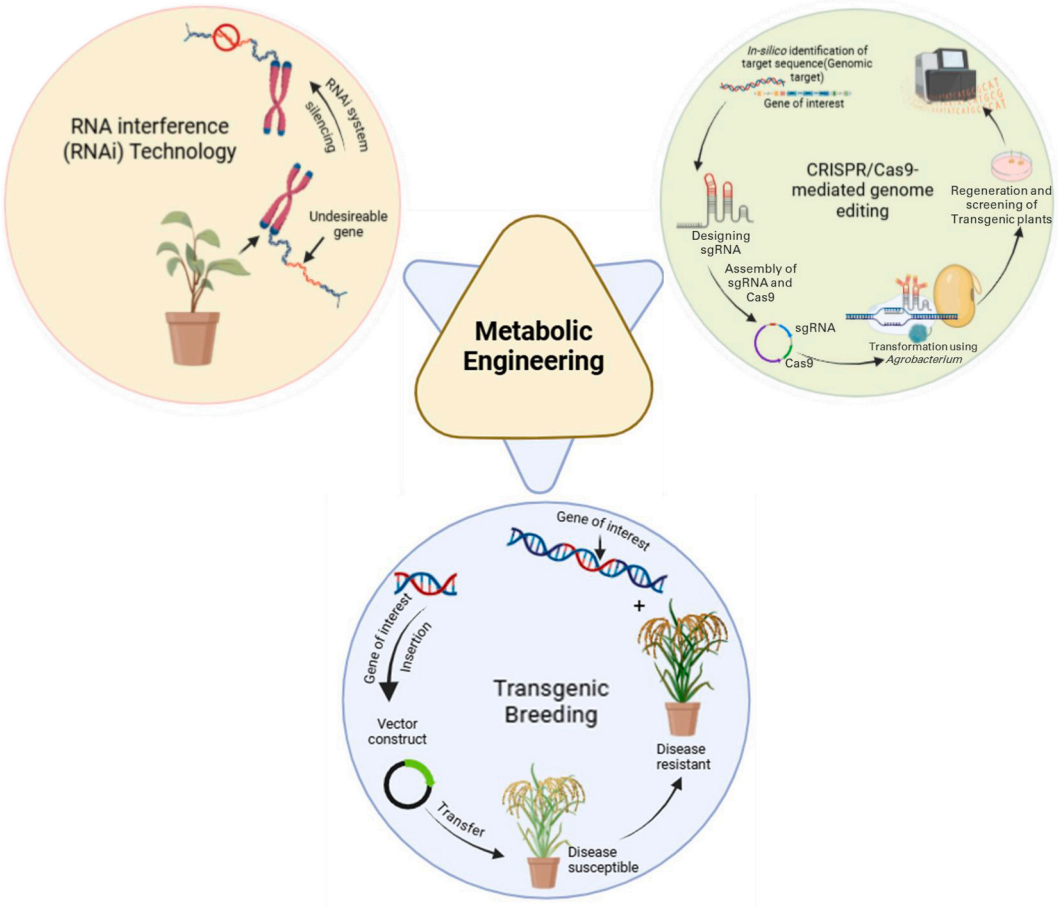

Fig. 5. Metabolic engineering through Transgenic breeding, RNA interference (RNAi)-mediated gene silencing, and CRISPR/Cas9-mediated genome editing.

such as whiteflies (Luan et al., 2013). These findings illustrate the versatility of terpene pathways as targets for metabolic engineering, offering exciting opportunities to enhance crop defense systems against a wide range of biotic threats. By leveraging advances in synthetic biology and genetic engineering, researchers can develop sustainable solutions for global agricultural challenges.

Isoflavone reductase (IFR) plays a pivotal role in the biosynthetic pathway of isoflavonoid phytoalexins, essential for plant defense mechanisms. This enzyme, critical for isoflavone synthesis, is activated in response to a range of biotic stresses, highlighting its significance in plant resilience (Cheng et al., 2015; Gui et al., 2023). Alongside IFR, enzymes like phenylalanine ammonia-lyase (*PAL*), 4-coumarate-CoA ligase (*4CL*), and chalcone synthase (*CHS*) serve as crucial mediators within the phenylpropanoid pathway, directing metabolic flux toward isoflavonoid biosynthesis (Vogt, 2010; Yi et al., 2010). In soybean, genetic modifications have showcased the potential to enhance isoflavonoid content substantially. For instance, the overexpression of a fusion gene, maize C1 and R (*CRC*), alongside flavanone 3-hydroxylase (*F3H*), amplifies isoflavone production in transgenic soybean seeds up to fourfold (Yu et al., 2003). Additionally, the co-overexpression of transcription factors like GmMYB176 and GmbZIP5 in soybean hairy roots results in a 1.4-fold increase in total isoflavonoid content (Anguraj Vadivel et al., 2021). Pathogen-triggered gene expression further underscores the interplay between these enzymes and stress responses. The upregulation of *GmPAL*, *GmCHS*, and *Gm4CL* genes during *Phytophthora sojae* infection suggests a synergistic role in glyceollin biosynthesis, bolstering resistance in soybean (Cheng et al., 2015). Similarly, overexpression of *GmIFR* enhances glyceollin accumulation and acts as an antioxidant, mitigating oxidative stress and improving pathogen resistance. In alfalfa, genetic interventions have yielded promising results; overexpression of isoflavone *O*-methyltransferase (IOMT) leads to increased levels of formononetin and medicarpin, conferring enhanced resistance to *Phoma medicaginis* (He and Dixon, 2000). Likewise, the heterologous expression of *MtIFS1* in alfalfa facilitates the accumulation of medicarpin in response to pathogen infection, demonstrating the potential of targeted metabolic engineering for improved disease resilience (Deavours and Dixon, 2005). These findings collectively underscore the critical roles of isoflavonoid biosynthesis and its regulation in plant defense, presenting valuable targets for enhancing crop resistance through genetic engineering.

Lignin accumulation is a pivotal defense mechanism in plants, contributing significantly to resistance against various biotic stresses, including insect pests and pathogens. Functioning as a physical and chemical barrier, lignin fortifies cell walls, hindering pathogen invasion and reducing the effectiveness of fungal enzymes and toxins (Ma et al., 2017; Miedes et al., 2014). Advances in genetic engineering have enabled researchers to manipulate lignin biosynthesis, modifying its structure, content, and composition to enhance plant resilience (Vanholme et al., 2012). For instance, overexpressing the *4CL* gene *OsAAE3* in rice resulted in reduced lignin content and increased susceptibility to rice blast disease due to decreased peroxidase and pathogen-related 1a (PRI) activity (Liu et al., 2017). Similarly, fungal pathogens such as *Macrophomina phaseolina*, responsible for chickpea dry root rot, induce localized lignin deposition alongside elevated *LAC* gene expression (Sharma et al., 2023). In cotton, transgenic overexpression of the laccase gene *GhLac1* enhanced lignin accumulation, bolstering defenses against *Verticillium dahliae* and insect pests like cotton bollworm (*Helicoverpa armigera*) and cotton aphid (*Aphis gossypii*) (Hu et al., 2018a). In flax (*Linum usitatissimum*), responses to fungal pathogens such as *Botrytis cinerea* and *Fusarium oxysporum* revealed increased expression of lignin-associated genes (*PAL*, *CCR*, and *CAD*) and heightened lignin accumulation, emphasizing its defensive role (Hano et al., 2006). Overexpressing *ZmCCoAOMT2*, encoding a key enzyme in lignin biosynthesis, conferred resistance to southern leaf blight and gray leaf spot diseases in maize (Yang et al., 2017). Further innovations include modifying lignin biosynthesis to redirect metabolic fluxes under stress. For example, downregulating *CCoAOMT* in alfalfa enhanced medicarpin production upon fungal infection, improving both cell wall polysaccharide availability and pathogen resistance (Gill et al., 2018). Similarly, overexpressing *GbRLK* in *Arabidopsis thaliana* promoted lignin synthesis and enhanced resistance against *Verticillium dahliae* (Jun et al., 2015). OsRac1, a regulatory protein, has been shown to influence lignin biosynthesis by modulating *OsCCR1* activity during defense responses (Kawasaki et al., 2006). Collectively, these findings underscore lignin's multifaceted role in plant defense and highlight the potential of lignin engineering to enhance crop resilience.

Glucosinolates, a significant class of secondary metabolites in cruciferous plants, have been linked to pest resistance, including against whitefly. Elevated glucosinolate levels achieved through genetic engineering substantially reduced whitefly oviposition and nymphal development. For example, Markovich et al. (2013) overexpressed aliphatic and indolyl-glucosinolate biosynthetic genes under the constitutive CaMV35S and phloem-specific AtSUC2 promoters in *Arabidopsis thaliana*. This strategy resulted in higher aliphatic and total glucosinolate accumulation, significantly impairing the reproductive and survival success of *Bemisia tabaci*. Similarly, dhurrin, a tyrosine-derived cyanogenic glucoside, has been shown to enhance plant resistance. The complete biosynthetic pathway of dhurrin, derived from *Sorghum bicolor*, was successfully transferred to *Arabidopsis thaliana*. This genetic modification conferred protection against herbivorous pests such as the flea beetle *Phyllotreta nemorum*, with dhurrin increasing larval mortality and reducing plant damage (Tattersall et al., 2001; Razzaq et al., 2023). Additionally, the production of farnesene by Brassicaceae plants plays a dual defensive role by deterring aphids and attracting the parasitic wasp *Diaeretiella rapae*, which preys on aphids, offering a natural pest control mechanism.

Beyond Brassicaceae, advances in metabolic engineering are revealing novel avenues for crop protection. Leptines, potent steroidal glycoalkaloids that deter *Leptinotarsa decemlineata* (Colorado potato beetle), are present in *Solanum chacoense* but absent in cultivated *Solanum tuberosum*. Recent cloning of a 2-oxoglutarate-dependent dioxygenase, the first enzyme needed for leptine biosynthesis in *Solanum tuberosum*, offers promise for engineering beetle-resistant potatoes if the second enzyme is identified (Cárdenas et al., 2019b). Similarly, while acylsugars confer effective insect resistance in wild relatives of tomatoes, introgressing acylsugar-related traits into cultivated varieties has faced challenges due to conflicts with fruit quality (Smeda et al., 2018). However, Vendemiatti et al. (2022) demonstrated progress by engineering type-IV trichomes in transgenic tomatoes to produce higher acylsugar levels, potentially providing resistance to whiteflies. With the near-complete identification of enzymes involved in tomato acylsugar biosynthesis, targeted overexpression of this pathway in cultivated varieties could reconcile pest resistance with fruit quality traits, representing a significant breakthrough in sustainable agriculture. These examples illustrate the transformative potential of metabolic engineering to enhance crop resilience through precise manipulation of secondary metabolite pathways.

Scopoletin, a prominent member of the coumarin class of secondary metabolites, is recognized for its potent antioxidant properties and broad-spectrum biological activities, including antifungal, antibacterial, antiviral, and insect deterrent effects (Beesley et al., 2023). This versatility positions coumarins as promising candidates for engineering pest- and disease-resistant crops. Beesley et al. (2023) demonstrated this potential by overexpressing the *Arabidopsis thaliana* feruloyl-CoA 6-hydroxylase 1 (*AtF6'H1*) gene, the key enzyme in scopoletin biosynthesis, in transgenic *Nicotiana benthamiana*, *Glycine max*, and *A. thaliana*. The resulting elevated scopolin levels in *A. thaliana* roots were associated with enhanced resistance to the root-parasitic nematode *Heterodera schachtii*. Similarly, transgenic soybean plants displayed increased tolerance to the soil-borne pathogenic fungus *Fusarium virguliforme*, underscoring the potential of engineered coumarin accumulation for crop resilience. Additionally, Hu et al. (2018b) highlighted a

dual defense strategy in *Chrysanthemum morifolium* through the overexpression of the chrysanthemol synthase (*TcCHS*) gene. This manipulation led to the emission of volatile chrysanthemol and the accumulation of a glycoside derivative, effectively reducing aphid reproduction. The dual mechanism combined the repellence conferred by chrysanthemol's odor with the deterrent effects of its nonvolatile glycoside. Together, these findings underscore the transformative potential of targeted metabolic engineering to enhance plant defense systems through natural secondary metabolites.

Resveratrol synthase and stilbene synthase (STS) have been extensively studied and employed for metabolic engineering in plants (Dasgupta et al., 2020). Resveratrol, a phytoalexin achieved by stilbene synthase synthesized de novo in response to pathogen attack, demonstrates a broad spectrum of antimicrobial properties and significant roles in plant defense (Xu et al., 2019b). Initially isolated from *Veratrum grandiflorum* (Takaoka, 1939), resveratrol was later identified in grapevine (*Vitis vinifera*) leaves, berries, and wine (Langcake and Pryce, 1976; Jeandet et al., 1991; Siemann and Creasy, 1992). Its biosynthesis, catalyzed by stilbene synthase, utilizes hydroxycinnamoyl-CoA and malonyl-CoA as substrates, and the STS gene family in grapevine comprises 48 members, of which 33 are potentially functional (Chong et al., 2009; Parage et al., 2012; Vannozzi et al., 2012; Wang et al., 2024c). Meanwhile, the functional versatility of STS has made it a prime candidate for genetic transformation aimed at enhancing plant defense. In tobacco, overexpression of grapevine STS genes (*Vst1* and *Vst2*) under stress-responsive promoters increased phytoalexin accumulation, conferring resistance to *Botrytis cinerea* and *Phytophthora infestans* (Hain et al., 1993; Thomzik et al., 1997). Similarly, transformation of alfalfa with *Arachis hypogea* STS (*AhRS*) driven by an enhanced CaMV35S promoter conferred resistance to *Phoma medicaginis* (Hipskind and Paiva, 2000). Moreover, the PEG-mediated direct gene transfer has improved the resistance of rice to *Piricularia orizae* (grapevine STS gene *Vst1* with the stress-responsive promoter pVst1) (Stark-Lorenzen et al., 1997). Grapevine rootstocks overexpressing *Vst1* under a fungus-inducible promoter demonstrated higher stilbene production and resistance to *B. cinerea* (Coutos-Thévenot et al., 2001). In *Rehmannia glutinosa*, the introduction of *AhRS3* from peanut enhanced resveratrol production and resistance to *Fusarium oxysporum* (Lim et al., 2005). Transgenic strawberries expressing *NS-Vitis3*, a stilbene synthase from *Vitis riparia*, exhibited enhanced resistance to gray mold caused by *B. cinerea* through alterations in phenylpropanoid metabolism (Hanhineva et al., 2009). In grapevines, overexpression of *Vst1* under the CaMV35S promoter elevated resveratrol levels by 7.5-fold, significantly enhancing resistance to *B. cinerea* (Dabauza et al., 2015). Fusion of *4CL* and *STS* genes under a CaMV35S promoter in tobacco improved tolerance to peach brown rot caused by *Monilinia fructicola* (He et al., 2018). Likewise, bread wheat transformed with *Vst1* and *Vst2* under combined stress-responsive promoters displayed resistance to *Septoria nodorum* and *Puccinia recondita* (Serazetdinova et al., 2005). Further applications of resveratrol engineering highlight its versatility in enhancing crop resilience. In papaya, the grapevine *Vst1* gene conferred resistance to fruit rot caused by *Phytophthora palmivora* (Zhu et al., 2004). In transgenic Arabidopsis, overexpression of *PcRS* from *Polygonum cuspidatum* resulted in higher trans-piceid accumulation and resistance to *Colletotrichum higginsianum* (Liu et al., 2011). Transformation of wild Chinese grapevine *VqSTS6* into grapevine roots significantly improved resistance to powdery mildew (*Uncinula necator*) (Liu et al., 2019). In hybrid grapevines, expression of *VlvSTS* under a double CaMV35S promoter enhanced resveratrol levels and resistance to *Erwinia carotovora* in tobacco (Rukavtsova et al., 2022). Barley and wheat transformed with *Vst1* through biolistic methods demonstrated increased resistance to *B. cinerea* (Leckband and Lörz, 1998). Similarly, resveratrol synthase gene introduction into spring wheat enhanced resistance to powdery mildew (Liang et al., 2000).

While resveratrol and its derivatives have been recognized as key contributors to plant defense, their effectiveness in conferring resistance to pathogens is not universal. Certain cases demonstrate the limitations of stilbene synthase (STS) gene transformations in enhancing resistance, underscoring the complexity of plant-pathogen interactions. For instance, Giorcelli et al. (2004) successfully introduced the STS gene (*StSy*) from grapevine into transgenic white poplar (*Populus alba*), leading to the production of resveratrol-3-glucoside in both cis- and trans-isomer forms. However, despite these biochemical changes, the transformed poplars did not exhibit enhanced resistance to leaf rust caused by *Melampsora pulcherrima*. This suggests that while stilbene production was induced, it alone was insufficient to counteract this particular pathogen. Similarly, Kobayashi et al. (2000) isolated the stilbene synthase gene *pSV25* from grapevine and transferred it into kiwi (*Actinidia deliciosa*) under the control of the CaMV35S promoter. Although transformed plants showed increased piceid (resveratrol-glucoside) content, they did not exhibit resistance to gray mold disease caused by *Botrytis cinerea*. This highlights potential challenges in translating resveratrol's antimicrobial properties to functional resistance across plant species. Another example comes from *Populus tremula* × *tremuloides* hybrids, where *Pinosylvin synthase* from *Pinus sylvestris* was introduced via *Agrobacterium tumefaciens*-mediated transformation. Transgenic aspen clones accumulated specific mRNA and showed stilbene synthase enzyme activity in vitro but failed to display increased resistance to *Phellinus tremulae* (Seppänen et al., 2004). These results point to the possibility that stilbene accumulation might not sufficiently disrupt the life cycle of certain pathogens or that other resistance mechanisms are required to complement stilbene action. These findings also emphasize that while stilbene synthases such as STS hold promise for engineering plant resistance, their effectiveness depends on the pathogen species, host plant context, and the biochemical environment. Further research is essential to fully exploit the potential of stilbene synthase (STS)-based engineering for plant resistance. A deeper understanding of the mechanisms by which stilbenes interact with pathogen-specific defense pathways is crucial for elucidating their roles in the broader resistance network. Optimizing gene integration through combinatorial approaches such as co-expressing STS genes with other resistance-related genes could significantly enhance the efficacy of these metabolic pathways. Additionally, conducting pathogen-specific studies will help clarify why certain pathogens remain unaffected by stilbene induction, providing insights for more targeted interventions. Advanced genetic engineering technologies, such as CRISPR/Cas9, offer promising avenues for precise regulation of STS gene expression under specific stress conditions, potentially maximizing their effectiveness against diverse pathogens. By addressing these challenges, researchers can unlock the full potential of stilbenes, paving the way for robust, disease-resistant crops and contributing significantly to the field of plant metabolic engineering.

These findings underscore the potential of metabolic engineering to boost plant defenses. Overexpressing biosynthetic genes, such as those for glucosinolate or dhurrin production, can optimize pest resistance and enhance the yield of defense metabolites. Future advancements should focus on integrating gene overexpression techniques with cutting-edge tools like CRISPR/Cas9 to fine-tune pathway regulation and meet agricultural challenges.

6.2. RNAi and target-specific gene silencing: transformative applications in plant metabolic engineering

Target-specific gene silencing has gained significant traction in plant science, with RNA interference (RNAi) emerging as a powerful tool for sequence-specific suppression of gene expression at the post-transcriptional stage (Agrawal et al., 2003; Halder et al., 2022). RNA silencing operates through two mechanisms: transcriptional gene silencing (TGS) and post-transcriptional gene silencing (PTGS), with the latter involving double-stranded RNA (dsRNA) to induce sequence-specific RNA degradation (Agrawal et al., 2003; Halder et al., 2022). In plants, RNAi facilitates PTGS to develop resistance against pests and

pathogens by targeting specific genes with dsRNA. RNAi has demonstrated practical applications in agriculture, such as spraying dsRNA on maize to trigger gene knockdown in piercing, sucking, and stem-boring insects, resulting in increased insect mortality (Li et al., 2015c; Mamta and Rajam, 2017). Beyond pest resistance, RNAi has revolutionized secondary metabolite research, enabling both the discovery of gene functions and the development of plants with novel chemical phenotypes (Mitra et al., 2022b). For instance, silencing flavone synthase (*FNS*) genes in soybeans reduced apigenin and anthocyanin synthesis, promoting isoflavone accumulation. Dual silencing of *FNSII* and *F3H* leads to the increase of isoflavone content by approximately 2.2-fold in transgenic hairy roots (Jiang et al., 2010, 2014). RNAi has also been instrumental in enhancing genistein yield in tobacco and Arabidopsis by co-silencing key flavonoid biosynthetic genes and overexpressing soybean isoflavone synthase (*IFS*). In Arabidopsis *F3H* and *DFR* double mutants *tt3/tt6*, *IFS* overexpression increased genistein production 5- to 30-fold (Liu et al., 2002, 2007). Similarly, co-expression of *AtMYB12* and *LjIFS* in tomato *F3H* mutants boosted isoflavone biosynthesis (Zhang et al., 2015). These findings highlight RNAi's potential for engineering secondary metabolite pathways.

RNAi also enables precise targeting of pathogen-related gene functions. In cotton, *GhBGLU46*, a β-glucosidase targeted by the fungal effector protein *VdSP8*, is crucial for lignin biosynthesis and plant immunity. Silencing *GhBGLU46* reduced the expression of lignin-related genes (*GhCCR4*, *GhCCoAOMT2*, *GhCAD3*, and *GhCAD6*), lowering lignin deposition and increasing susceptibility to *Verticillium dahliae*. This underscores the indispensable role of *GhBGLU46* in activating systemic acquired resistance (SAR) and hypersensitive response (HR) pathways, reinforcing its significance in plant defense (Wang et al., 2024c). A similar result was observed for *GhBsr-k1* in cotton. Silencing *GhBsr-k1* enhanced resistance to both *Verticillium dahliae* and *Fusarium oxysporum*. This resistance was associated with the upregulation of phenylpropanoid metabolism-related genes, leading to increased lignin deposition. Notably, *GhPAL2* and *GhPAL5*, encoding phenylalanine ammonia-lyases, exhibited a strong negative correlation with *GhBsr-k1*, suggesting that *GhBsr-k1* acts as a negative regulator of resistance to these pathogens (Li et al., 2021). These results provide strong proof that gene silencing and overexpression studies have provided significant insights into plant defense mechanisms against pathogens and pests. In tobacco, whitefly feeding elevated the levels of terpenoids, including cedinene. Manipulation of cedinene content through silencing or overexpression of *5-epi-aristolochene synthase* revealed that cedinene positively regulates whitefly resistance (Luan et al., 2013). Similarly, potato sesquiterpenoid phytoalexins, such as lubimin and rishitin, have been implicated in defense against *Phytophthora infestans* and *Alternaria solani*. RNA interference targeting sesquiterpene cyclase, a key enzyme in phytoalexin production, demonstrated that these compounds contribute to preinvasive resistance to necrotrophic pathogens like *A. solani* and postinvasive resistance to hemibiotrophic pathogens like *P. infestans* (Yoshioka et al., 2019). In grapevines, overexpression of the stilbene synthase gene *VqNSTS4* in the susceptible cultivar Thompson Seedless increased stilbene accumulation and enhanced resistance to *Uncinula necator* by activating salicylic acid (SA) signaling. Conversely, RNAi-mediated silencing of *VqNSTS4* and its regulator *VqAL4* heightened susceptibility to *U. necator*, underscoring the importance of *VqNSTS4* in grapevine resistance to powdery mildew (Yan et al., 2023). In rice, overexpression of *OsTPS19*, which encodes an (*S*)-limonene synthase, conferred enhanced resistance to rice blast disease caused by *Magnaporthe oryzae*. This resistance correlated with increased production of (*S*)-limonene, a monoterpene that inhibits *M. oryzae* spore germination in vitro. In contrast, RNAi lines of *OsTPS19* exhibited reduced (*S*)-limonene levels and greater susceptibility to the pathogen, highlighting the critical role of this gene in rice defense (Chen et al., 2018). These findings highlight that gene silencing and overexpression studies have provided significant insights into plant defense mechanisms against pathogens and pests.

Isoflavonoids represent a well-studied class of phenylpropanoid-derived specialized metabolites predominantly found in leguminous plants. These compounds often serve as phytoalexins, providing critical protection against pathogenic microbes in their natural environments (Yang and Wang, 2024). For instance, in soybeans, isoflavonoids play a pivotal role in resistance to *Phytophthora sojae* (Graham et al., 2007). The enzyme isoflavone synthase (IFS), a cytochrome P450 hydroxylase, is indispensable for isoflavone biosynthesis. As the first and key enzyme in this pathway, IFS catalyzes a critical step, particularly in leguminous plants (Jung et al., 2000). RNA interference (RNAi)-mediated suppression of IFS pathway genes, including flavanone 3-hydroxylase (*F3H*) and flavone synthase II (*GmFNSII*), has demonstrated significant potential in enhancing isoflavone production in soybeans. For example, RNAi silencing of *GmFNSII* effectively regulated flavone and isoflavone production in soybean hairy roots transformed with *Agrobacterium rhizogenes* (Jiang et al., 2010, 2014). These findings position IFS pathway genes as promising targets for metabolic engineering.

Conversely, silencing IFS genes has also provided insights into plant susceptibility to pathogens. Ralston et al. (2005) reported that RNAi-mediated silencing of *F3H* and *GmFNSII* genes in soybean enhanced susceptibility to *P. sojae*, highlighting their defensive roles. Similarly, silencing *IFS1* and *IFS2* led to reduced isoflavone accumulation and increased susceptibility to *P. sojae* in soybean cotyledons (Subramanian et al., 2005). Additionally, RNAi-mediated silencing of *IFS* or chalcone reductase (*CHR*) disrupted Rps-mediated resistance to race 1 of *P. sojae* in resistant soybean cultivars, suppressing hypersensitive response (HR) cell death, hydrogen peroxide activation, and peroxidase activity. This underscores the critical role of 5-deoxyisoflavonoids in establishing cell death and race-specific resistance, as well as the ability of *P. sojae* cell wall glucan elicitors to trigger this response, which was suppressed by silencing *CHR* or *IFS* (Graham et al., 2007).

RNAi has emerged as an indispensable tool in genetic engineering, enabling precise modulation of gene expression for enhanced secondary metabolite production and plant resilience. By combining RNAi with advanced biotechnologies like CRISPR/Cas9 and multi-omics approaches, researchers can unlock new possibilities for sustainable crop improvement, addressing pressing agricultural and environmental challenges.

6.3. CRISPR/Cas9: a breakthrough in plant metabolic engineering

The Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein9 (CRISPR/Cas9) genome editing technology has emerged as a transformative tool for precise genetic modifications, enabling targeted manipulation of metabolic pathways to enhance secondary metabolite production. It allows scientists to target specific genes and make precise changes, such as deleting, inserting, or modifying DNA sequences. This versatile technology allows for the development of crop plants with improved resistance to biotic stresses while serving as a sophisticated metabolomic engineering technique (Alamillo et al., 2023; Das et al., 2024). CRISPR-mediated gene editing has revolutionized genetic studies by enabling precise and efficient genome modifications across various organisms. The system employs guide RNAs to direct the Cas9 nuclease to specific DNA target sites, where Cas9 creates double-stranded breaks. These breaks are typically repaired via non-homologous end-joining (NHEJ), a repair mechanism prone to introducing small insertions or deletions (indels). Indels that disrupt the reading frame can lead to premature termination codons (PTCs), triggering nonsense-mediated decay (NMD) and resulting in loss-of-function (LOF) mutations. Over the years, this straightforward and versatile CRISPR/Cas9 approach has been widely used to induce LOF mutations in a range of organisms, including mammals, for functional genomics and therapeutic research (Tang et al., 2018). Compared to earlier tools such as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs), CRISPR/Cas9 offers higher precision, faster implementation, lower cost, and scalability for multiplex genome

editing. Its user-friendly design has accelerated the development of non-transgenic genome-edited crops, crucial for combating climate change and ensuring food security in tropical regions (Kafle, 2023; Haque et al., 2018; Kaur et al., 2022a, 2022b; Sedeek et al., 2019; Wang et al., 2019; Wada et al., 2022).

CRISPR/Cas9 has been widely utilized to edit genes involved in biosynthetic pathways critical for secondary metabolite production. For instance, the shikimate pathway is a pivotal metabolic route for secondary metabolite biosynthesis. *3-Dehydroquinate dehydratase/shikimate dehydrogenase* (*DQD/SDH*) catalyzes a critical step in this pathway, influencing gallic acid and flavonoid production (Maeda and Dudareva, 2012). Similarly, this technology also enables precise modifications in lignin biosynthesis. Knockout of *BnF5H*, a key enzyme converting guaiacyl to syringyl monolignols, reduced the S/G lignin ratio and increased resistance to *Sclerotinia sclerotiorum* in *Brassica napus* (Cao et al., 2022). Such studies underscore the potential of targeting lignin pathway genes to enhance structural defense mechanisms. In tomatoes, overexpression of *SlDQD/SDH2* increased shikimate and flavonoid content, enhancing resistance to *Botrytis cinerea*, whereas its knockout reduced metabolite accumulation (Wang et al., 2023d). These findings highlight the pathway's potential for metabolic engineering to improve plant resilience. Furthermore, the 4′-*O*-methyltransferase (*OMT2*) gene in opium poppy was targeted to reduce the accumulation of benzylisoquinoline alkaloids, including morphine and thebaine (Alagoz et al., 2016). Similarly, the diterpene synthase gene (*SmCPS1*) in *Salvia miltiorrhiza* was edited to modify tanshinone biosynthesis (Li et al., 2017b). In rice, the carotenoid cleavage dioxygenase 7 (*CCD7*) gene, which controls strigolactone biosynthesis, and the *CCD4* gene in banana, which regulates β-carotene degradation, have also been successfully edited using CRISPR/Cas9 (Butt et al., 2018). Further research should be carried out to explore the potential of CRISPR/Cas9-mediated metabolic engineering to enhance plant stress tolerance. By manipulating the biosynthesis of secondary metabolites, which often play a role in plant defense mechanisms, it may be possible to develop crop varieties that are more resilient to biotic and abiotic stresses.

Recent advances highlight the transformative potential of this technology to alter the biosynthesis pathway of secondary metabolites. Isoflavonoids, a significant class of secondary metabolites derived from the phenylpropanoid pathway, are predominantly found in leguminous plants and play crucial roles in plant defense and ecological interactions. These compounds function as phytoalexins, combating a wide range of pathogens, including nematodes, oomycetes, fungi, bacteria, and viruses (Yang and Wang, 2024). CRISPR/Cas9-directed mutagenesis has been instrumental in enhancing the biosynthesis of isoflavonoids, key secondary metabolites involved in plant defense. By precisely editing enzymes such as *GmF3H1*, *GmF3H2*, *GmFNS-1*, and *GmIFS*, researchers achieved a two-fold increase in isoflavone content in soybeans, significantly improving leaf resistance to soybean mosaic virus (SMV) (Zhang et al., 2020). This work underscores the critical role of isoflavonoid biosynthesis genes in conferring resistance to pathogens and their interactions with secondary metabolites influencing plant growth (Mipeshwaree Devi et al., 2023; Wang et al., 2024b). The enzyme isoforms flavonoid-3-hydroxylase (*F3H*), flavonoid synthase II (*FNS II*), and isoflavone synthase (*IFS*) share common substrates, emphasizing the competitive dynamics within the phenylpropanoid pathway. Manipulating these enzymes provides a powerful strategy for targeted enhancement of metabolite accumulation and associated stress resistance. Similarly, *GmUGT*, a key gene regulating flavonoid biosynthesis, was edited via CRISPR/Cas9 to improve resistance to leaf-chewing insects, including *Helicoverpa armigera* and *Spodoptera litura*, through modifications in flavonoid content and gene expression patterns (Zhang et al., 2022c). CRISPR/Cas9 has also been applied in horticulture to elucidate genes involved in pigmentation and metabolic processes. For instance, knockout of *lnCCD4* in *Ipomoea nil* increased carotenoid content by 20-fold, altering flower pigmentation, whereas mutagenesis of the *DFR-B* gene, responsible for anthocyanin biosynthesis, produced several white flower mutants in *Ipomoea nil*, demonstrating the utility of genome editing in studying traits like flower color (Watanabe et al., 2017). This approach provides valuable insights into gene function and opens avenues for breeding ornamental and functional traits in horticultural plants.

A "knockdown" in CRISPR technology reduces gene expression by introducing changes at the RNA level without altering its DNA, typically by using a catalytically dead Cas9 enzyme (dCas9) to bind to the target gene's DNA to block transcription (Tang et al., 2018). In contrast, a "knockout" permanently disrupts a gene's function by creating DNA mutations using functional Cas9 to create a double-stranded break in the DNA, leading to complete disruption of gene expression (Ishibashi et al., 2020). These techniques have proven instrumental in unraveling gene functions and engineering plant resistance mechanisms against biotic stresses. In cotton, knockdown studies revealed critical roles for genes involved in flavonoid and lignin biosynthesis. The knockdown of *GhCH3*, encoding chalcone synthase (CHS), heightened susceptibility to *Verticillium dahliae* due to reduced anthocyanin accumulation (Lei et al., 2018). Similarly, *GhUMC1*, a blue copper-binding protein regulating lignin synthesis, was shown to modulate the expression of lignin biosynthetic genes (*C4H*, *HCT*, *CCoAOMT*, and *CAD*), with knockdown increasing susceptibility to *Verticillium wilt* (Zhu et al., 2018). These findings underscore the importance of *GhCH3* and *GhUMC1* in plant defense.

CRISPR-mediated knockouts have demonstrated significant success in metabolic engineering. In tomato (*Solanum lycopersicum*), knockout of the *CCD8* gene reduced orobanchol content, increased carotenoid levels, and enhanced resistance to the parasitic weed *Phelipanche aegyptiaca* (Bari et al., 2019). Furthermore, *SlSGR1* knockouts in tomato elevated chlorophyll and lycopene levels, with transcriptomic analyses identifying nine differentially expressed genes (DEGs) influencing carotenoid and chlorophyll biosynthesis. The study could further help in elucidating the role of the *SRG1* gene involved in the chlorophyll and carotenoid biosynthesis pathway (Kim et al., 2023). Similarly, in *Fagopyrum tataricum*, the knockout of the transcription factor FtMYB45 using CRISPR/Cas9 led to a significant reduction in flavonoid accumulation, highlighting the role of transcription factors in regulating metabolite biosynthesis (Wen et al., 2022). Ferulate-5-hydroxylase (*F5H*) plays a critical role in lignin biosynthesis, catalyzing the conversion of guaiacyl (G) monolignols to syringyl (S) monolignols, which are key components of plant cell walls. Using CRISPR/Cas9, the knockout of the *BnF5H* gene in *Brassica napus* reduced the S/G lignin compositional ratio, enhancing resistance to *Sclerotinia sclerotiorum*, a fungal pathogen causing stem rot (Cao et al., 2022). This study highlights the potential of targeted gene editing to modify lignin composition for improved structural defenses against biotic stresses.

Taken together, CRISPR/Cas9 has revolutionized plant metabolic engineering by enabling precise gene edits, significantly enhancing secondary metabolite production, and increasing resistance to biotic stresses. This transformative technology has reshaped our ability to manipulate metabolic pathways, creating resilient crops better equipped to combat biotic and abiotic challenges. Integrating genome editing with multi-omics and synthetic biology is the next frontier, offering insights into regulatory networks and optimizing biosynthetic pathways to develop high-yield, sustainable crops tailored to address global agricultural challenges. As our understanding of plant metabolic pathways deepens, CRISPR/Cas9-based engineering offers unprecedented opportunities to develop crop varieties with enhanced nutritional profiles, stress tolerance, and novel traits. Leveraging multi-omics approaches and synthetic biology will allow researchers to fine-tune metabolic processes, fostering the creation of plants with customized phenotypes suited for specific environmental and agricultural needs. This powerful technology is poised to address critical global issues, including food security, climate resilience, and sustainable agriculture, marking a new era in crop improvement and resource management.

7. Conclusions and future prospects

The field of secondary metabolite research has expanded significantly, driven by advancements in multi-omics, genetic engineering, and synthetic biology. The integration of omics technologies and the study of transcription factors have revolutionized our understanding of plant secondary metabolites, offering novel strategies for sustainable crop improvement. Multiomics approaches, combining genomics, transcriptomics, proteomics, and metabolomics, enable the comprehensive elucidation of biosynthetic pathways, regulatory networks, and environmental interactions of secondary metabolites. Meanwhile, transcription factors, as master regulators, facilitate precise control over these biosynthetic pathways, linking external stimuli with internal metabolic reprogramming. This progress underscores the immense potential of metabolic engineering in tailoring plants to withstand biotic stresses, enhance nutritional profiles, and produce valuable compounds for industrial and medicinal use. However, challenges persist, including limited knowledge of biosynthetic pathways, regulatory networks, and interactions among metabolites. Additionally, the translation of laboratory findings into field applications remains a significant bottleneck, compounded by ecological concerns such as the stability and persistence of engineered traits in natural environments.

Future prospects include leveraging CRISPR/Cas9, RNAi, and other precise genome-editing tools to address gaps in pathway elucidation and regulatory mechanisms. Integrating multiomics approaches can uncover novel gene functions and complex regulatory networks. Moreover, combining computational modeling and advanced synthetic biology, researchers can decode intricate regulatory hierarchies and design novel pathways to enhance plant resilience and metabolite production. While these tools promise transformative changes, their success depends on collaborative efforts to address ethical considerations, regulatory barriers, and the scalability of technologies. By bridging fundamental science with applied research, we can unlock the full potential of secondary metabolites to address pressing agricultural and environmental challenges. The future lies in developing tailored, high-yield crops with optimized metabolite profiles that can withstand biotic and abiotic stresses while addressing the demands of sustainable agriculture. This comprehensive approach offers a promising roadmap for achieving food security and ecological balance in the face of global challenges.

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Declaration of competing interest

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

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