Review

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Posted Date: 11 February 2025

doi: 10.20944/preprints202502.0739.v1

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Plant Secondary Metabolites—Central Regulators Against Abiotic and Biotic Stresses

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Abstract: Both biotic and abiotic stresses adversely affect plant growth and development, ultimately reducing agricultural productivity. Secondary metabolites (SMs) are essential compounds that contribute to plant survival by facilitating interactions with the environment. In response to both abiotic and biotic stresses, plants synthesize and accumulate SMs, which in turn trigger signaling pathways that lead to post-transcriptional modifications within plant cells. These changes activate a series of defense mechanisms that enhance the plant's resilience and adaptation to stress. SMs are instrumental in ensuring plant survival under challenging conditions by modulating the plant's defense systems to cope with environmental threats. Beyond their role in stress tolerance, SMs are also bioactive compounds with significant economic and health value. In this review, we explore the functions of various SMs, such as alkaloids, flavonoids, and phenolic acids in defense against abiotic and biotis stresses. Additionally, we discuss the potential of harnessing SMs in the genetic improvement of crop stress tolerance, highlighting their roles in advancing agricultural sustainability.

Keywords: abiotic and biotic stress; defense mechanism; signaling pathway; secondary metabolites; stress tolerance

1. Introduction

Plants are constantly subjected to various abiotic and biotic stresses in their life, , which severely impact their growth, development, and overall productivity (Fahad et al. 2024). Abiotic stresses, such as extreme temperatures, drought, salinity, and pollutants, disrupt critical physiological processes, leading to reduced photosynthesis, impaired water and nutrient absorption, and disordered metabolisms (Al-Khayri et al. 2023a). Biotic stresses, on the other hand, arise from interactions with living organisms, including pathogens and pests. Plant diseases caused by bacteria, viruses, and fungi compromise plant immune defenses, impair nutrient transport, and weaken plant structures (Hou et al. 2022; Khan et al. 2024a). Additionally, insect herbivores, by grazing on plants, cause physical damage and facilitate the transmission of diseases (War et al. 2012).

In response to these abiotic and biotic stresses, plants have evolved a variety of defense mechanisms. Among these, the modulation of metabolites and metabolic pathways has emerged as a crucial strategy for survival and adaptation (Akbar et al. 2024). Metabolites in plants are basically

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categorized into two groups: primary metabolites (PMs) and secondary metabolites (SMs). PMs, such as proteins, carbohydrates, amino acids, vitamins, ethanol, and acetone, are essential for plant growth, respiration, photosynthesis, and reproduction (Ranner et al. 2023; Khan et al. 2024b). In contrast, SMs, which include alkaloids, toxins, essential oils, and pigments, are found in all plant cells (Elshafie et al. 2023). Over recent decades, SMs have been intensively studied in the fields of medicine, nutrition, and cosmetics. Currently, they are also gaining attention in plant sciences for their significant roles in defending against biotic and abiotic stresses.

SMs function as protective molecules, shielding primary metabolites, including nucleic acids and proteins, from stress-induced damage. Upon exposure to stress, plants can initiate or enhance the synthesis of novel or originalSMs through the activation or regulation of specific genes, enabling them to better cope with adverse conditions (Kajla et al. 2023). The role of SMs in stress defense, as well as their genetic regulation, has become a focal point in plant stress physiology and molecular biology, underscoring their importance in adaptive resilience (Haghpanah et al. 2024). However, despite their significance, no comprehensive review has yet addressed this field in its entirety. Accordingly, in this review we aim to consolidate and expand existing knowledge, providing insights into the integral functions of various SMs in supporting plant resilience to abiotic and biotic stresses. Specifically, we explore key groups of protective SMs, including alkaloids, flavonoids, phenolic acids, and anti-reactive oxygen species (ROS) enzymes such as peroxidases, polyphenol oxidases, and chitinases. Additionally, this review highlights knowledge gaps and propose future research directions to better harness plant secondary metabolism for developing stress-resilient crop varieties.

2. Diversity of Secondary Metabolites and their Biosynthesis in Plants

SMs are essential compounds that contribute significantly to plant defense and adaptation against environmental stresses. They are highly diverse and can be classified based on their chemical structures or biosynthetic origins. Structurally, SMs are categorized into four main groups (Tu et al. 2023). The first group, phenolics, includes compounds such as phenolic acids, lignin, lignans, tannins, and coumarins, which are widely recognized for their roles as antioxidants and structural components (Figure 1). The second group, terpenes, comprises sterols, volatile compounds, carotenoids, cardiac glycosides, and flavonoids, all of which are crucial for plant signaling, hormonal regulation, and stress response. Nitrogen-containing compounds, the third group, consist of alkaloids and cyanogenic glycosides that typically serve as chemical deterrents against herbivores and pathogens. Lastly, sulfur-containing compounds such as thionins, lectins, glutathione, defensins, and phytoalexins are particularly vital in counteracting oxidative stress and enhancing pathogen resistance (Al-Khayri et al. 2023b).

From a biosynthetic perspective, SMs are classified into three primary groups: terpenes, phenolics, and nitrogen- and sulfur-containing compounds. Their biosynthesis occurs through three major pathways: the mevalonic acid (MVA) pathway, the malonic acid pathway, and the shikimic acid pathway (Zheng et al. 2022). These pathways are highly responsive to environmental stresses and produce metabolites that equip plants with enhanced tolerance. The shikimic acid pathway generates a variety of metabolites, including flavonoids, anthocyanins, tannins, stilbenes, suberin, and lignin (Marchiosi et al. 2020). These compounds act as both structural barriers to prevent pathogen invasion and signaling molecules that activate plant defense responses (Kaur et al. 2022). The MEP (methylerythritol phosphate) pathway, an alternative to the MVA pathway, produces carotenoids, diterpenes, quinones, tocopherols, and gibberellins, which play critical roles in alleviating oxidative damage and modulating hormonal responses under stress conditions (Khan et al. 2023c). The MVA pathway itself contributes sterols that are pivotal in protecting plants against oxidative stress and physical damage (Perez-Gil et al. 2024).

The biosynthesis of SMs is intricately linked to plant survival under stress conditions, with the resulting metabolites performing multiple roles. These roles include reinforcing plant structures with compounds like lignin and suberin, neutralizing oxidative damage with antioxidants such as tocopherols and flavonoids, and regulating hormonal responses to maintain physiological balance during stress (Khan et al. 2023b). In addition to their defensive functions, these metabolites also participate in complex signaling networks that further enhance plant adaptability. This synergy between biosynthetic pathways and the functional versatility of SMs underscores their central importance in plant stress tolerance and adaptation.

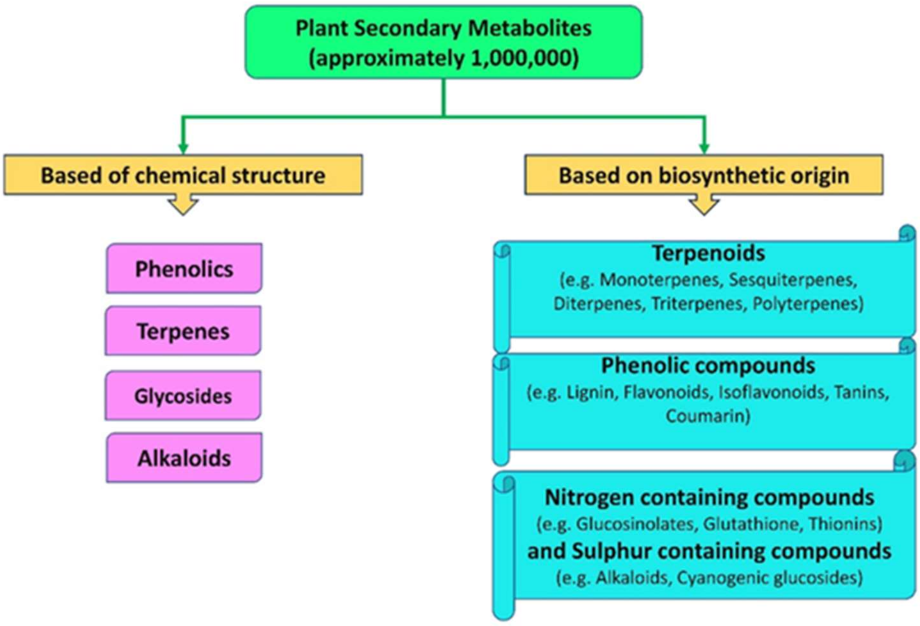

Figure 1. Classification and categories of SMs.

3. The Roles of SMs in Plant Stress Responses

SMs are vital for plants to develop defense mechanisms and their ability to adapt to environmental stresses. These compounds, often produced in response to biotic and abiotic stresses, act as protective agents against pathogens, herbivores, and adverse environmental conditions (Table 1; Figure 2) (Divekar et al. 2022). Each SMs group plays distinct roles in plant stress responses. Here we are focused on terpenes, flavonoids phenolics, tannins, lignans, coumarins, lignin, stilbenes, curcuminoids, chitinases, nitrogen, and sulfur-containing SMs.

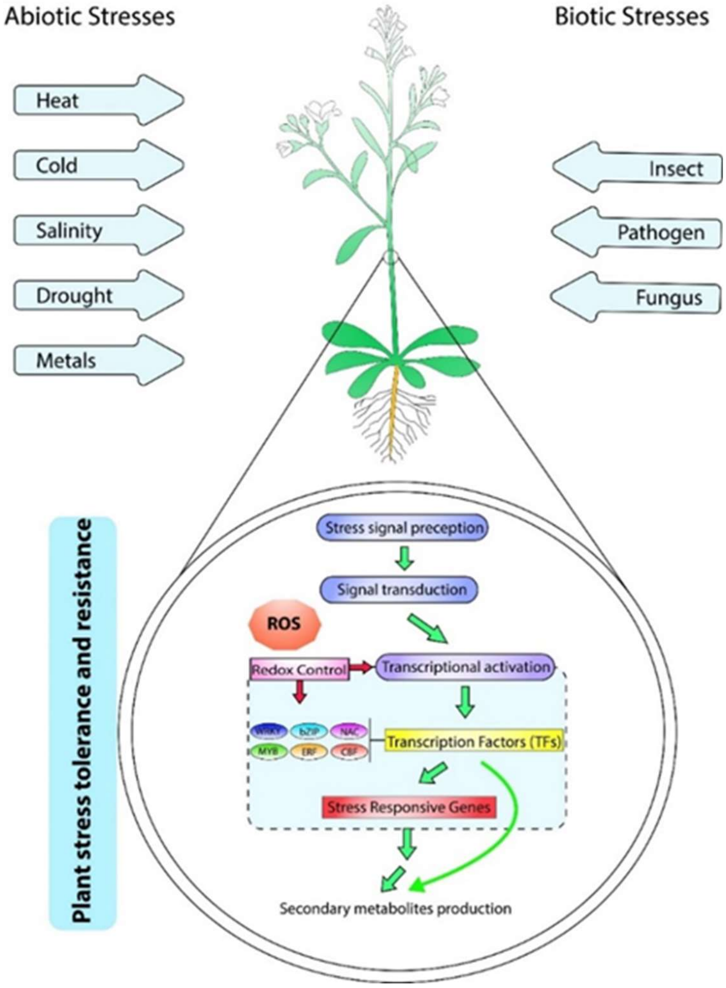

Figure 2. Mechanisms of plant tolerance and resistance to biotic and abiotic stresses. Climate change poses a significant threat to plant survival, particularly in regions vulnerable to extreme conditions. Various ecological stressors, such as insects, pathogens, temperature fluctuations, light intensity, soil salinity, and nutrient availability, significantly impact plant physiological and biochemical responses, including secondary metabolism. Plants produce a range of secondary metabolites as a defense mechanism to mitigate the adverse effects of these stresses.

Table 1. List and role of secondary metabolites (SMs) in plants.

Name	Related functions	Plant specie	Reference
	Terpenes		
Monoterpenes	Chemical products secreted by plants are important against insect toxicity	*Chrysanthemum, Cumin, Pepper, Mint, Eucalyptus*	(Nikolaou et al. 2021)
Diterpenes	Acts as epithelium irritations and inner toxins to pest insects and mammals	*Codiaeum, Hura Phyllanthus*	(Sokan-Adeaga et al. 2023)

Triterpenes	Triterpenes, have some self-protective characters from insects by altering their development	*Higher plants Ferns and marine organisms*	(Chen et al. 2022)
Polyterpenes	it offers defense as a process for infection repair and as a resistance against pests	*Bruce banner*	(Qasim et al. 2024)
	Phenolics		
Phenolics Flavonoids Coumarin Bioflavonoids Others	Flavanol content was significantly lower under the lower temperature treatment in pygmy smartweed.	*Polygonum minus Huds.*	(Jurčević Šangut et al. 2024)
-	HT had little effect on seed phenolics, but did reduce anthocyanins in the skin of grapes	*Vitis vinifera L*	(Ryu et al. 2020)
-	Monoterpenes and Sesquiterpeness were increased in thyme in response to DS.	*Artemisia annua L.*	(Khalid et al. 2020)
-	Monosubstituted flavanols were increased under UVB flavanols were unaffected supplemental UVB also increased tannins in some species	*Tomato,*	(Qaderi et al. 2023)
	Nitrogen containing SMs		
Alkaloids Cyanogenic Glycosides Non protein amino acid	Cause signaling molecule to trigger flavonoid biosynthesis under lower temperatures	*apple (Malus sp)*	(Qaderi et al. 2023)
-	Temperature causes an upregulation of key enzymes in isoprene production	*Carrots (Daucus carota L.)*	(Mukherjee et al. 2019)

-	Increased light may have negative consequences on SM production in sensitive plants. Longer photoperiod increased.	*Ocimum basilicum L*	(Fayezizadeh et al. 2024)
-	Plants have higher cyanogenic glycosides, variability was also observed in alkaloids, which increased under shade in evergreen tropical tree	*Tabernaemontana pachysiphon Stapf*	(Qaderi et al. 2023)
-	Arabidopsis mutants lacking the flavonoid, production Mechanisms are hypersensitive to UVB radiation, flavonoid production are tolerant to typically lethal UVB levels	*Arabidopsis thaliana*	(Peng et al. 2017)
	Sulfur containing SMs		
Glutathione	GSH acts as growth regulator and in stress it acts as an antioxidant strengthening the defense system of the plants	*Spinach* *Avocados* *Okara*	(Zhang et al. 2024)
Glucosinolate GLS	which have a role in defense by poisoning the herbivore insects during damage and as feeding repellents	*mustar Allium allylcysd plant*	(Sun et al. 2020)
Phytoalexins	This shows to be a usual method of defense mechanism against insect's pests in numerous plants	*Grapevine Vitis vinifera*	(Jeandet et al. 2023)

Defensins, Thionins, and Lectins	Defensins, Thionine, lectins are stimulated by numerous stresses and show resistance against them	Circulatory white blood cells and tissue cell, Wheat, Corn, Tomato	(Roy-Barman et al. 2017)
	Stilbenes		
Resveratrol and pterostilbene)	Increased stilbene accumulation, greater with UV-C compared to fungal inoculum and show resistance.	*Vitis vinifera cvs. Alphonse Lavallée, Dan Ben-Hanna,*	(Valletta et al. 2021)
anthocyanins; flavonoids; hydroxycinnamic acids Napoleon	Increased stilbene accumulation, greater with UV-C compared to UV-B (3 and 2-fold, respectively) and show resistance.	*V. vinifera cv. Sangiovese*	(Valletta et al. 2021)
Stilbenes	Downregulation of STS expression under both low and high temperature and upregulation of STS expression in response to CuSO4, and show resistance	*V. vinifera cv. Cabernet Sauvignon*	(Valletta et al. 2021)
Mono-glucosylated derivatives resveratrol (trans- and cis-piceid and trans- and cis-resveratroloside)	Increased in trans-resveratrol endogenous accumulation and decreased release into the culture medium. Glucosides show response to stress.	*V. vinifera cv. Barbera*	(Valletta et al. 2021)
	Curcuminoids		
Curcumin	It shows physically and chemically defense system against pathogens and as well as other stresses.	*Curcuma longa.L*	(Fuloria et al. 2022)

Curcumin/bisdemethoxycurcumin	Volatile compound shows antibacterial mechanism against a wide distribution of Gram-positive bacteria.	*Curcuma longa.L*	(Jyotirmayee and Mahalik 2022)
Demethoxycurcumin	which show antipathogenic action against fungi, bacteria and other pathogen agents	*Turmeric*	(Kępińska-Pacelik and Biel 2023)
	Chitinases		
Maize chitinase 2 gene	Secondary metabolites considered as molecular targets of selection in plant–pathogen.	*Transgenic maize plant*	(El-Sayed et al. 2024)
Chitinase I gene	Inhibits phytopathogenic fungi *A. solani, R. solani, F. spp., V. dahliae*	*Hordeum vulgare cultivar, Haider-93*	(Vaghela et al. 2022)
Rice class I chitinase gene (Rchit)	Resistance against late leaf spot, rust disease, and *A. flavus* infection	*Oryza sativa (Rice)*	(Kumar et al. 2018)
Tobacco osmotin (ap24) and rice chitinase (chi 11) gene	Reduce sheath blight disease caused by *R. solani*	*Nicotiana sp. (Tobacco) and Oryza sativa (Rice)*	(Manghwar and Hussain 2022)
Rice chitinase-3 gene	Resistance against leaf spot in peanut by *Cercospora arachidicola*	*Oryza sativa (Rice)*	(Vaghela et al. 2022)
	Peroxidase		
Glutathione peroxidase	Glutathione causing of reduction of substrate to convert H_2O_2 hydroperoxides into water or oxygen and show resistances	*Nicotiana sp. (Tobacco)*	(Gullner et al. 2018)

Horseradish peroxidase	Plants have adopted peroxidase systems to show resistance against numerous stresses	*Armoracia rusticana*	(Gleń-Karolczyk et al. 2021)
Cytochrome c peroxidase	These enzymes used peroxides as an electron acceptor for reduction of oxidative damage against stress in plants	*yeast*	(Kaya et al. 2017)
myeloperoxidase	It includes plant immune responses to biotic stresses	*spinach*	(Szechyńska-Hebda et al. 2022)

3.1. Terpenes

Terpenes, a diverse class of SMs, have been shown to play pivotal roles in plant defense and adaptation to both biotic and abiotic stresses. These compounds are synthesized from C5 units, such as dimethylallyl diphosphate (DMAPP) or isopentenyl diphosphate (IPP), and are categorized based on the number of these units they contain (Ma et al. 2024). Categories include hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterpenes (C25), triterpenes (C30), polyterpenes (C40) (Maurya et al. 2021). However, substantial research has been made in understanding their biochemical pathways and ecological functions, numerous critical gaps remain in elucidating their exact mechanisms and roles across different plant species and environmental contexts (Chiquito-Contreras et al. 2024). Despite extensive studies on individual terpenes, there is still a lack of comprehensive data on how terpenes interact with other plant metabolites and environmental factors to provide holistic protection against stressor. Moreover, the variability of terpene production in response to stressors like heat, drought, and pathogens remains poorly understood, particularly in the species with underexplored terpene profiles.

3.1.1. Biotic Stress Responses

Terpenes are actively produced by plants in response to biotic stressors such as herbivore attacks. For example, *Pinus sylvestris* produces increased amounts of terpenes when subjected to caterpillar feeding, with more terpenes emitted from branches under heavy caterpillar attack compared to less affected branches (Rivas-Ubach et al. 2018). These volatile compounds serve as a deterrent to herbivores and act as repellents. In addition, transgenic tobacco plants have been shown to release isoprene when attacked by caterpillars, a response not observed in wild-type plants (Qian et al. 2024). Terpenes also attract pollinators in certain plants, facilitating ecological interactions (Akbar et al. 2024).

Furthermore, sesquiterpenes, lactones, and other compounds like taraxinic acid beta-D-glucopyranosyl ester, are known to protect plants from root-feeding pests. For example, dandelions release latex that is rich in these terpenes, offering protection from both above-ground and root-feeding stressors (Bont et al. 2020). The latex serves a dual purpose, it provides a defense mechanism against pathogens while also protecting the plant from underground pests (Merchán-Gaitán et al. 2023). This highlights the need for a deeper understanding of how terpenes interact with multiple layers of plant defense systems.

3.1.2. Abiotic Stress Responses

Terpenes also play an essential role in protecting plants from abiotic stressors such as drought, salinity, and oxidative stress. For instance, the production of oleuropein in the leaves and roots of olive trees is a response to salinity stress (Palm et al. 2024). This compound helps the plant manage oxidative stress resulting from high salt concentrations, demonstrating the protective function of terpenes in saline environments (Ahmad et al. 2022). Oleuropein serves as a glucose reservoir, which aids in osmoregulation and contributes to the plant's adaptation to harsh saline conditions (El Yamani and Cordovilla 2024).

Non-volatile antioxidants, including those within the terpene family, have been identified as vital for enhancing stress tolerance in plants. Specific terpenes such as isoprene help mitigate the effects of photooxidative stress, ozone stress, and heat stress (Shahrajabian et al. 2023). While some plants like grapevines do not emit isoprene, they still produce other terpenoid compounds such as monoterpenes that confer heat stress tolerance (Bertamini et al. 2021). Moreover, terpenes are essential for stabilizing plant cell membranes, reducing oxidative stress, and enhancing abiotic stress resilience. Compounds like monoterpene hydrocarbons and isoprene have been shown to provide antioxidant properties, crucial for mitigating oxidative damage in response to heat, UV radiation, and other environmental stresses (Tang et al. 2024), but how these compounds interact with other cellular protective mechanisms like the ROS scavenging system remains crucial for future investigation.

Moreover, some acidic terpenoids, including zealexins and kauralexins, also act as phytoalexins that protect plants from pathogens and environmental stressors, including drought and salinity (Kumar et al. 2023b). These terpenoids help to maintain biomass production in crops like maize, though their effectiveness is reduced under severe water deficiency (Rezaei-Chiyaneh et al. 2023). Similarly, terpenoids like sabinene, myrcene, and limonene, produced in response to UV-B radiation and hydrogen peroxide, stimulate rice seedling growth and enhance stress resistance (Mohammadi et al. 2024). Additionally, certain terpenes, such as carnosic acid, a diterpene, protect plants in the Labiatae family from water stress and other environmental challenges. These findings collectively demonstrate the multifaceted role of terpenes in promoting plant resilience under both biotic and abiotic stress conditions. Filling these knowledge gaps is key to advancing our understanding of terpene-mediated plant resilience and improving agricultural practices focused on stress tolerance.

3.2. Phenolics

Phenolic compounds, which encompass a wide range of biologically active molecules such as flavonoids, lignin, coumarins, tannins, and bioflavonoids, play essential roles in plant defense against both biotic and abiotic stresses (Zagoskina et al. 2023). These metabolites, characterized by their aromatic ring structure and hydroxyl groups, are synthesized primarily in the sub-epidermal layers of plant tissues, forming a critical part of the plant's defense against environmental extremes, pathogens, and herbivores (Figure 3) (Ali et al. 2022). Despite their broad protective functions, which include antioxidant, anti-inflammatory, and anti-carcinogenic activities, several critical gaps in our understanding of their synthesis, regulation, and interaction with other plant metabolites remain unknown.

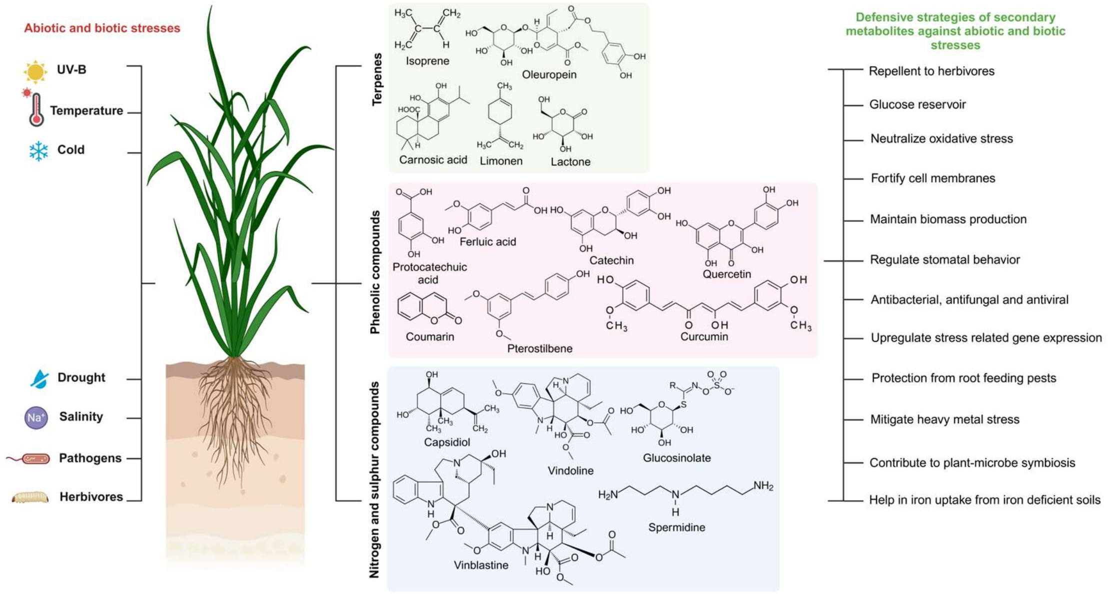

Figure 3. The main pathways producing end products associated with stress tolerance or resistance in plants.

3.2.1. Biotic Stress Responses

Phenolic compounds are vital for defending plants against biotic stress, including attacks by pests, pathogens, and herbivores (Ahlawat et al., 2023). These compounds help maintain the structural integrity of the plant by acting as a defense mechanism against harmful agents such as bacteria, fungi, viruses, and nematodes (Kaur et al., 2023). One prominent group of phenolics, coumarins, is found in plant membranes and plays a key role in plant defense (Ortiz & Sansinenea, 2023). The accumulation of coumarins has been shown to enhance tolerance to fungal, bacterial, and viral infections, which is particularly evident in the defense against pathogens like oomycetes (Al-Khayri et al., 2023). Furthermore, other phenolic compounds such as ferulic acid and protocatechuic acid accumulate in rice plants during fungal attacks, reducing the impact of mycotoxins (Kaur et al., 2022). These findings emphasize the protective roles of phenolic compounds in the face of biotic stress but highlight a gap in understanding the precise molecular pathways through which phenolics interact with other defense mechanisms.

3.2.2. Abiotic Stress Responses

Phenolic accumulation plays a crucial role in protecting plants from abiotic stresses, such as cold, drought, and heavy metal toxicity (Kumar et al. 2020). In response to environmental stressors, phenolics contribute to cell wall fortification and antioxidant defense, which stabilize plant structure and protect against oxidative damage (Madany et al. 2020). For example, in *Secale cereale* (winter rye), cold stress triggers an increase in phenolic production, specifically the deposition of lignin and suberin, which enhance cell wall stability and cold tolerance (Ali et al. 2022). Similarly, phenolic compounds like catechin and quercetin accumulate in corn plants under aluminum toxicity, helping mitigate oxidative stress (Zhang et al. 2023a). Despite these well-established roles, the exact biochemical signaling pathways that regulate phenolic biosynthesis in response to abiotic stresses remain inadequately understood (Qaderi et al. 2023). In addition, the production and accumulation of phenolic compounds fluctuate according to environmental conditions, seasonal changes, and plant growth stages (Saqib et al. 2023). These compounds vary in concentration, increasing or decreasing depending on developmental stage, environmental stress, or pathogen attacks (Rizaludin et al. 2021). However, there is limited research on how these fluctuations are regulated at the molecular level. The varying phenolic concentrations observed during different growth stages or seasonal changes suggest that these compounds play a dynamic role in plant adaptation (Gashu et al. 2023).

Understanding how phenolic synthesis interacts with plant development and environmental condition will help identify how these compounds can be harnessed to improve plant resilience.

3.3. Flavonoids

Flavonoids are a distinct class of SMs that differ structurally from other plant compounds. These polyphenolic compounds are synthesized in plants from phenylalanine, which serves as a key precursor in the biosynthetic pathway (Qiu et al. 2024). The majority of flavonoids contain aromatic rings with two to six carbon atoms and a heterocyclic compound ring with one oxygen atom, forming the characteristic C6-C3-C6 skeleton system (Shamsudin et al. 2022). This structure allows flavonoids to serve a wide range of functions in plants, including coloration, UV protection, and regulation of cell physiology (Figure 3). These functions are crucial for the plant's developmental processes, resistance mechanisms, and signaling pathways (Zhou et al. 2024b). Flavonoids, including flavones, are known to act as feeding deterrents for herbivores like *Spodoptera exempta*, thereby providing a first line of defense against insect damage. These compounds also serve as biochemical signals, attracting beneficial microorganisms or pollinators and contributing to plant-microbe symbiosis (Wei et al. 2024). Moreover, flavonoids act as phytochemical alexins, helping plants combat pathogenic microbes, including bacteria, fungi, and viruses. Their role in pathogen resistance extends to regulating the formation of reactive oxygen species (ROS) (Mansoor et al. 2023). During photosynthetic electron transport, flavonoids detoxify ROS to prevent oxygen-mediated toxicity, which is particularly important under stress conditions (Kuljarusnont et al. 2024). Recent research highlights the antifungal properties of flavonoids, including isoflavones and flavanones, which offer protection against a variety of phytopathogens (Kumar et al. 2024). These SMs, containing a phenol and a hydroxyl functional group, are crucial in defending plants against parasites and diseases (Kajla et al. 2023). Their antimicrobial activity is particularly effective in combating viral infections, contributing to plant immunity (Chen et al. 2023). In short, flavonoids are vital in maintaining plant health by enhancing pathogen-triggered immunity and protecting against a broad range of microbial threats.

Flavonoids also play a key role in plant responses to abiotic stresses, such as drought and high salinity. Their antioxidant capacity helps mitigate oxidative stress (Singh et al. 2024). Additionally, flavonoids are involved in pigmentation and defense mechanisms, helping plants to better withstand environmental challenges (Shoaib et al. 2024). Flavonoids have also been shown to regulate stomatal behavior, modulating stomatal opening and closing to optimize water use under drought conditions, thereby improving water-use efficiency (Zhou et al. 2024a). This ability to influence stomatal function underscores their crucial role in maintaining plant growth and development during stress. One of the major functions of flavonoids, especially flavones and flavonols, is their ability to protect plants from harmful UV-B radiation. These compounds are primarily found in the epidermal layers of plant stems and leaves, where they serve as a protective barrier against UV-B light (Singh et al. 2023). By modulating photoprotective mechanisms, flavonoids help maintain cellular integrity under high solar exposure, shielding plants from oxidative damage caused by UV rays (Mahdavian 2024). This UV protection is particularly important for plants growing in areas with high solar radiation, where exposure to UV-B can otherwise cause significant cellular harm.

3.4. Tannins

Tannins, a group of phenolic compounds, play an essential role in plant defense systems. They act as repellents to pests and parasites, inhibiting their growth and reducing feeding activities (Singh et al. 2021). Moreover, tannins are actively involved in regulating defense pathways, particularly the jasmonic acid and salicylic acid signaling pathways, which are crucial for plant immune responses (Naz et al. 2024). These compounds have an unpleasant taste, making them unpalatable to herbivores.

Tannins' antifungal properties are well-documented. For instance, the *PtMYB123* gene plays a crucial role in regulating tannin formation in plants, and its expression is linked to systemic acquired resistance (Iqbal and Poór 2024). Moreover, tannin-rich extracts from *Acacia mearnsii* have demonstrated fungicidal properties, effectively inhibiting fungi like *Aspergillus niger* (Iqbal and Poór 2024). Also, tannic acid and related phenolic compounds are known to inhibit the activity of extracellular enzymes produced by pathogens, preventing the degradation of plant cell walls and protecting plant nutrients from depletion (Zhang et al. 2023b). Thus, these studies suggest that tannins are not only key deterrents against pests and pathogens but also actively modulate plant defense mechanisms through biochemical pathways such as jasmonic acid and salicylic acid signaling. Environmental factors like soil pH and metal ion availability influence tannin production, suggesting that these compounds are dynamic components in plant defense that can be enhanced under certain conditions.

3.5. Lignans

Lignans are polyphenolic compounds that are integral to plant defense mechanisms, particularly under environmental stress conditions. They are predominantly found in seeds, such as flaxseeds, and in other fibrous, phenolic-rich plant tissues (Plamada and Vodnar 2021). Lignans are structurally distinct from other SMs, featuring specific bonds between carbon atoms and differing in carbon frame, oxygen positioning, and functional arrangements (Ruan et al. 2023).

Lignans are part of the phytoestrogen family, which includes biologically active compounds such as isoflavones, coumestans, and flavonoids. Their diverse structures contribute to a wide range of biological activities, including antioxidant properties that help plants manage oxidative stress during growth and development (Gill and Tuteja 2010). In addition, lignans are also known for their ability to inhibit pathogen-derived degradative enzymes such as cellulase, glucosidase, and laccase, thus maintaining the integrity of plant cell walls and preventing microbial invasion (Jha and Mohamed 2022). Lignans also serve as deterrents to herbivores, contributing to plant resistance by deterring feeding and protecting plants from further damage. Recent studies have suggested that lignans modulate stress-related gene expression, further enhancing the plant’s ability to cope with adverse environmental conditions (Sharma et al. 2019). Additionally, lignans' ability to scavenge free radicals plays a crucial role in safeguarding plants from oxidative stress.

Importantly, lignans also help to regulate plant-pathogen interactions. Their presence in plants is associated with a reduction in the activity of microbial enzymes, which protects the plant from pathogen-related damage (Kaur et al. 2022). Furthermore, the diverse biological activities of lignans highlight their importance in both biotic and abiotic stress responses, contributing significantly to plant resilience and adaptation (Riaz et al. 2023). Together, lignans not only play a crucial role in protecting plants from oxidative stress but also serve as effective inhibitors of microbial enzymes, ensuring the integrity of plant tissues under pathogen attack. As both herbivore deterrents and regulators of stress-related genes, lignans contribute to the broader plant defense network, enhancing plant resilience to various biotic and abiotic stresses.

3.6. Lignin

Lignin, the second most abundant natural polymer after cellulose, plays a vital role in plant defense by enhancing cell wall strength and contributing to structural integrity. Lignin is synthesized through the combination of three phenolic compounds: coniferyl alcohol, sinapyl alcohol, and p-coumaryl alcohol (Al-Khayri et al. 2023b). As a complex and branched polymer, lignin serves as a physical barrier in the plant cell wall, blocking the invasion of pathogens and preventing damage from herbivores (Riseh et al. 2024). Its chemical and physical properties contribute to making plant tissues tough and resistant to external damage, thus strengthening the plant’s defense against pests and pathogens (Wang et al. 2022; Al-Khayri et al. 2023b).

Lignin's defensive function is particularly evident in its ability to resist phytopathogenic fungi. The polymer forms a protective barrier around plant tissues, which prevents fungal hyphae from penetrating the cell walls and spreading further. Studies have demonstrated that lignin accumulation increases during pathogen attacks, indicating a protective response through a process known as lignification (Kumar et al. 2023a). Furthermore, lignin is highly effective against fungal pathogens such as *Diplodia pinea*, highlighting its antifungal potential compared to other phenolic compounds (Ghosh et al. 2024).

Beyond its physical barrier properties, lignin also contributes to other aspects of plant growth, such as plant cell wall rigidity, water transport, and overall plant hydrophobicity (Jędrzejczak et al. 2021). Lignin's ability to resist herbivores, microbial pathogens, and environmental stresses showcases its multifunctionality in plant defense systems. Moreover, lignification acts as an adaptive response, making plant tissues more indigestible to herbivores and limiting pathogen growth during infection. Thus, lignin is crucial for plant defense, providing a robust physical barrier against pathogens and herbivores while strengthening plant tissues through lignification. Its antifungal properties and its role in the overall growth of plants highlight its multifunctionality. Lignin's ability to enhance cell wall strength and resist various environmental stresses underscores its significance in plant defense strategies.

3.7. Stilbenes

Stilbenes, a subclass of SMs derived from the phenylpropanoid pathway, are composed of a 14-carbon scaffold with two benzene rings connected by an ethylene bridge (Jan et al. 2021; Kumar et al. 2023b). They exist in two stereoisomeric forms, with the transform being the naturally occurring one in plants. These compounds play a crucial role in plant defense, protecting against both biotic and abiotic stresses (Kumar et al. 2023b).

Stilbenes are known to have direct toxic effects on bacteria and act as antioxidants, protecting plants from oxidative damage. They also influence fungal development and exhibit strong antifungal activity, likely due to their hydrophobic nature. For example, pterostilbene, a more mobile stilbene, spreads more effectively across the cytoplasmic membrane compared to the less hydrophobic resveratrol, showing enhanced antifungal properties (Kunova et al. 2023; Lin et al. 2024). Stilbene glucosides, produced in large quantities in the roots of *P. cuspidatum*, increase plant defense during pathogen stress (Lin et al. 2024). Furthermore, stilbenes are elicited not only by pathogens but also by herbivores and other stressors, such as in the sapwood of plants (Gao et al. 2024). Together, stilbenes are vital for plant defense, acting as antioxidants and antifungal agents that are synthesized in response to biotic and abiotic stressors, including pathogens and herbivores.

3.8. Curcuminoids

Curcuminoids are polyphenolic compounds synthesized by plants, known for their potent antioxidant properties and significant role in plant defense. These SMs are produced in plants through type III polyketide synthases (PKS) and contain two phenylpropanoid components linked to a central moiety derived from malonyl-CoA (Uka et al. 2020; Vicidomini et al. 2024). Curcuminoids, particularly curcumin, are found in several plants and exhibit strong antioxidant and anti-inflammatory effects, not only protecting plants from oxidative stress but also defending against microbial and fungal threats (Qin et al. 2024; Vicidomini et al. 2024).

Curcumin, a well-known curcuminoid, has been shown to reduce cytokine levels such as IL-1β and IL-6 and protect against liver apoptosis by inhibiting certain cellular signaling pathways (Qin et al. 2024). The biosynthesis of curcumin is influenced by plant genotype, developmental stage, and exposure to stressors like pathogen attacks, which stimulate the production of curcuminoids to strengthen plant defenses (Jha and Mohamed 2022; Nicoliche et al. 2024). Additionally, curcuminoids have antiviral effects, including reducing viral RNA expression and virus titer, and their anti-inflammatory properties are mediated by their antioxidant activity (Nicoliche et al. 2024). These studies suggest that curcuminoids provide antioxidant and anti-inflammatory protection to plants, enhancing their defense against microbial, fungal, and viral stress, particularly when produced in response to pathogen exposure.

3.9. Chitinases

Chitinases are enzymes that play a key role in plant defense against phytopathogens, particularly fungi. These enzymes hydrolyze the β-1,4 linkages in the chitin of fungal cell walls, inhibiting fungal growth by breaking down hyphal tips (Plaza et al. 2020; Chouhan et al. 2023). Plants produce different types of chitinases, including secretory, cellular, and vacuolar chitinases, each serving specific functions in the defense process (Vaghela et al. 2022). Secretory chitinases are involved in pathogenesis-related reactions and contribute to plant defense by interacting with fungal hyphae (Chouhan et al. 2023).

Genetic modifications have shown that enhancing chitinase expression can increase resistance to fungal diseases in plants. For example, transgenic plants expressing chitinase DNA have shown improved resistance against fungal blight (Singh et al. 2015; Vaghela et al. 2022). Moreover, chitinase activity is regulated by plant hormones such as ethylene and jasmonate, which play a significant role in modulating local defense responses against pathogens (Vaghela et al. 2022; Fahad et al. 2023). Chitinases are vital enzymes in plant defense, breaking down fungal cell walls and providing resistance to fungal pathogens. They play an essential role in strengthening plant defenses, with their activity regulated by plant hormones in response to pathogen attacks.

3.10. Nitrogen and Sulfur-Containing SMs

Approximately 20% of vascular plants produce nitrogen and sulfur containing SMs. These compounds, including alkaloids, cyanogenic glucosides, phytoalexins, non-protein amino acids, defensins, and lanine, are found across various plant groups such as gymnosperms, monocots, and herbaceous plants (Wu 2009; Ali et al. 2022). Most of these metabolites are derived from simple amino acids, which serve as their precursors (Wu 2009). These nitrogen- and sulfur-containing metabolites are essential for plants to defend themselves against various biotic and abiotic stresses (Figure 3).

Alkaloids, which are nitrogen-containing SMs, are known for their antimicrobial properties. Specifically, polyamine alkaloids have been shown to target gram-negative bacteria by disrupting their external membrane and depolarizing the membranes of gram-positive bacteria (Basagni et al. 2023). Phytoalexins, sulfur-containing metabolites, play a critical role in plant defense against fungal and bacterial pathogens (Künstler et al. 2020; Gogoi et al. 2024). These compounds also function in response to mechanical stress by reducing pathogen proliferation and inducing a hypersensitive response (HR), a form of programmed cell death (Gogoi et al. 2024). Other sulfur-containing metabolites, such as lectins, defensins, and thionins, further bolster the plant's immune system, providing resistance against microbial invaders (Gogoi et al. 2024).

Glucosinolates, found primarily in the mustard family (Brassicaceae), are activated when plant tissue is damaged, releasing toxic isothiocyanates through enzymatic breakdown by myrosinase (Divekar et al. 2022; Lv et al. 2022). These compounds serve as a defense against herbivores, such as the diamondback moth in cabbage plants (Divekar et al. 2022; Nabaei et al. 2024). Moreover, alkaloids like vinblastine and vindoline show increased levels in response to salinity and stress, which contribute to plant adaptation and resilience (Nabaei et al. 2024). Overall, nitrogen- and sulfur-containing metabolites play a significant role in plant adaptation, protecting them against environmental challenges.

4. Roles of Secondary Metabolites in Plant-Microbiome Interactions

Secondary metabolites are not directly involved in growth or reproduction, but play crucial roles in ecological interactions, particularly in plant-microbiome dynamics (Mathur and Ulanova 2023; Kumar et al. 2024). These compounds include phenolics, alkaloids, terpenoids, and flavonoids, which possess bioactive properties that can modulate microbial populations, facilitate plant defense, and support environmental adaptation (Saini et al. 2024). For instance, flavonoids play a key role in promoting nitrogen fixation in legumes, while terpenoids and alkaloids exhibit antimicrobial properties, suppressing harmful pathogens while encouraging beneficial microbes (Kumar et al.

2024). In this context, secondary metabolites are not only pivotal in defending plants but also in shaping the composition of plant-associated microbial communities, helping plants thrive in diverse environments.

4.1. Mechanisms of Interaction

Secondary metabolites mediate plant-microbe interactions through attraction, defense, and signaling mechanisms. Secondary metabolites act as chemo attractants for beneficial microbes. Phenolic acids, for instance, create environments that promote the growth of beneficial microbes while inhibiting pathogens (Shah and Smith 2020; Kumar et al. 2024). Flavonoids also promote the colonization of beneficial bacteria, improving the overall composition of the plant microbiome (Kumar et al. 2024). These metabolites defend plants by inhibiting pathogen growth and biofilm formation. For example, certain metabolites disrupt pathogen signaling pathways, preventing the establishment of harmful microbes (Kaur et al. 2022; Pandey et al. 2023). Coumarins and glucosinolates, in particular, exhibit potent antimicrobial properties (Plaszkó et al. 2022). Secondary metabolites, such as flavonoids, activate specific genes in microbes, fostering beneficial symbiotic relationships (Pandey et al. 2023). Flavonoids, for example, activate nod genes in nitrogen-fixing bacteria, which is crucial for successful symbiosis. This signaling promotes nutrient exchange between the plant and microbes, enhancing plant health and growth. While these interactions generally benefit plant health, some secondary metabolites may attract harmful microorganisms, underscoring the complexity of these relationships.

4.2. Bi-Directional Influence of Secondary Metabolites and Microbial Activity

The interaction between microbes and secondary metabolites is bi-directional. Microbial activity can enhance the production of secondary metabolites, bolstering plant defense mechanisms. For instance, the presence of arbuscular mycorrhizal fungi induces the production of terpenoids, which enhance the plant’s resistance to pathogens (Amani Machiani et al. 2022; Kumar et al. 2023b). Similarly, microbial elicitors such as beneficial bacteria can trigger stress responses in plants, leading to the biosynthesis of alkaloids and other secondary metabolites that improve plant resilience (Rani et al. 2023). In increasing biomass, the presence of beneficial microorganisms is the key for the evaluation of the terpenoid biosynthesis which is an important factor in the plant's ability to survive biotic and abiotic stresses (Kumar et al. 2023b). While the influence of microbes on the biosynthesis of secondary metabolites is mainly positive, it must be mentioned that the project fulfilling the maximum cycle of production may not always be the one that provides the output of bio-improving some novel products.

4.3. Role of Secondary Metabolites in Sustainable Agriculture

The relationship between secondary metabolites and plant-microbe interactions has significant implications for agricultural productivity and sustainability. Flavonoids, produced by legumes like *Medicago truncatula*, play a pivotal role in the nitrogen fixation process by signaling rhizobial bacteria to initiate root nodulation (Shumilina et al. 2023; Raza et al. 2024). This interaction enhances soil productivity by reducing the need for synthetic fertilizers, supporting sustainable agricultural practices (Wei et al. 2024). Additionally, phenolic compounds such as ferulic acid, secreted by wheat, promote the growth of beneficial rhizobacteria like *Pseudomonas* and *Bacillus*, which produce antimicrobial substances to suppress soil-borne pathogens (Raza et al. 2024).

Phenolic compounds are also linked to improved disease resistance in wheat. Varieties with higher total phenolic content (TPC), including flavonoid glycosides, exhibit enhanced resistance to diseases like stripe rust, contributing to higher yields (Maserumule et al. 2023). Moreover, wheat cultivars with elevated polyphenol levels, such as Lincang Hulled Wheat (LHW), show improved resistance to pre-harvest sprouting, further supporting agricultural resilience (Kiani et al. 2021). These findings suggest that breeding crops with higher phenolic profiles can lead to more robust and productive agricultural systems. Furthermore, secondary metabolites are integral to sustainable agriculture by enhancing plant resilience to stress and improving soil health, offering a pathway for reducing reliance on synthetic fertilizers and pesticides. As research progresses, the potential of secondary metabolites in promoting agricultural sustainability becomes increasingly clear, highlighting the need for further exploration of these complex biochemical processes.

5. Expression Strategies and Manipulation of Gene Clusters for SMs Biosynthesis

The biosynthesis of SMs in plants involves complex pathways regulated by multiple genes, often organized in biosynthetic gene clusters (BGCs). These pathways are difficult to study due to redundancy, regulatory complexity, and the intricate networks involved (Ji et al. 2024). To overcome these challenges, advanced expression strategies and genetic manipulation techniques are employed to enable the study and optimization of SM biosynthesis (Figure 4).

Heterologous expression, where plant genes are expressed in microbial hosts like *Escherichia coli*, *Saccharomyces cerevisiae*, and *Streptomyces* species, has become a key method for studying SM biosynthesis. This approach bypasses the complexity of native plant systems, allowing researchers to better understand metabolic pathways (Cravens et al. 2019; Ji et al. 2024). Using these hosts, which offer rapid growth rates and genetic tractability, the plant genes are cloned and expressed in microbial systems. Researchers then study the resulting metabolites and elucidate biosynthetic pathways (Cravens et al. 2019; Scherlach and Hertweck 2021). Bioinformatics tools and genome sequencing help identify BGCs, and subsequent experiments, such as precursor feeding, enable the validation of complete biosynthetic pathways (Scherlach & Hertweck 2021). Synthetic biology has further advanced heterologous expression by facilitating the modular design of biosynthetic pathways, improving metabolite yields, and enabling the discovery of novel SMs with potential applications in agriculture and medicine (Li et al. 2024b).

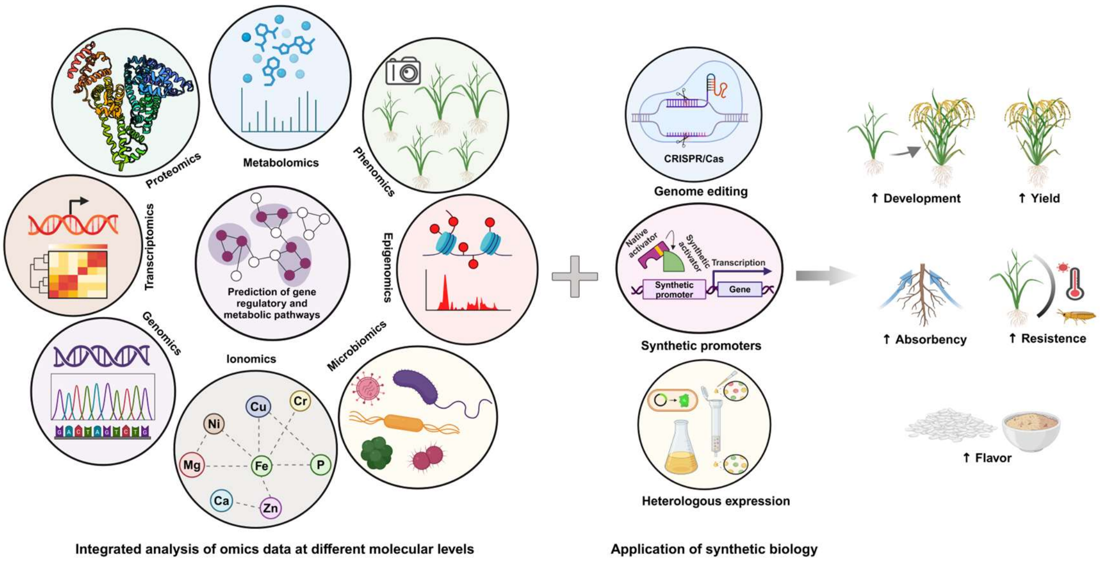

Figure 4. Strategies for studying the biosynthetic pathways of secondary metabolites. The intensification of climate change exacerbates the impact of environmental stress on crop productivity. Understanding the roles of primary and secondary metabolites in stress resistance mechanisms is crucial for developing crop varieties with improved stress tolerance, ensuring food security for an expanding global population. Advanced "omics" technologies, bioinformatics, and integrated molecular data analysis will provide deeper insights into secondary metabolite (SM) biosynthesis. Additionally, identifying the genetic basis of metabolite diversity in plants will enhance efforts to improve stress resilience. Genetic manipulation and overexpression of key genes in secondary metabolite biosynthetic pathways offer promising solutions to enhance plant tolerance to environmental stresses.

In addition to heterologous expression, manipulating BGCs and cryptic genes has proven to be a powerful strategy for optimizing SM production (Wang et al. 2025). Tools like CRISPR-Cas9 allow precise gene editing, which can induce targeted knockouts or modifications in plant DNA (Wang et al. 2025). For example, CRISPR-Cas9 was used to mutate the HOS1 gene in *Arabidopsis thaliana*, impacting SMs levels by altering gene expression and leading to changes in glucosinolate and flavonoid glycoside production (Ali et al. 2022). Other transcription factors like MYB and bHLH can be targeted to fine-tune SM biosynthesis under various stress conditions. RNA-based tools such as RNA interference (RNAi) and transcription activator-like effector nucleases (TALENs) complement CRISPR by providing additional methods for regulating gene expression (Bhuyan et al. 2023).

The integration of heterologous expression and advanced genetic tools, like CRISPR-Cas9 and RNAi, has revolutionized the study of SM biosynthesis. Genome sequencing has revealed numerous BGCs (Wang et al. 2025), encoding compounds such as terpenoids, phenolics, and non-ribosomal peptide synthetase (NRPS) products, opening new avenues for exploration (Wang et al. 2025). Synthetic biology approaches further enhance the discovery and production of these metabolites, which can be used in stress tolerance and industrial applications. Together, these innovations have not only enhanced the understanding of plant stress responses but also allowed the discovery and optimization of novel compounds for various applications.

6. Biotechnological Advances in Engineering SMs Pathways

Advances in biotechnology, particularly in molecular biology, metabolic engineering, and synthetic biology (Patra et al. 2023; Liu et al. 2024a), have enhanced our ability to manipulate SM pathways (Figure 4). Abiotic stresses like drought, salinity, and temperature extremes often induce SM production, which helps organisms adapt to challenging environments (Liu et al. 2024a). Engineering SM pathways under abiotic stress conditions is now a major focus, offering opportunities to boost metabolite production and uncover stress-response mechanisms (Zhang et al. 2023c).

For instance, CRISPR/Cas9 technology enables the precise regulation of SM production by enhancing or reducing the activity of specific genes. This has been demonstrated in plants like *Salvia miltiorrhiza* and *Medicago truncatula*, where gene modifications led to alterations in metabolite levels (Li et al. 2024a). CRISPR-based approaches help modulate various SMs, including flavonoids, alkaloids, and terpenoids, critical for stress adaptation. Recent advancements in systems biology allow researchers to exploit abiotic stress to stimulate SM biosynthesis (Singh and Ramakrishna 2021). Technologies such as transcriptomics, proteomics, and metabolomics provide insights into the cellular response to stress and guide the identification of key genes and proteins involved in SM pathways (Mashabela et al. 2023). Omics technologies enable the optimization of SMs production, particularly by analyzing how stress-induced signaling pathways activate biosynthetic gene clusters (Lu et al. 2022; Ali et al. 2024). Furthermore, transcription factors (TFs) are key to regulating SM biosynthesis. For example, overexpression of transcription factors like MYB and WRKY can enhance the production of metabolites under stress conditions (Lu et al. 2022). These TFs coordinate multiple biosynthetic genes and help optimize SMs pathways, improving stress resistance in plants.

Omics technologies are pivotal in understanding how abiotic stress influences SM biosynthesis. By integrating transcriptomic, proteomic, and metabolomic data, researchers can identify bottlenecks in metabolic pathways and design strategies to overcome them (Roychowdhury et al. 2023). This approach has been applied to enhance antioxidant production by targeting the phenylpropanoid pathway under stress conditions. Moreover, synthetic biology has enabled the transfer of stress-responsive SM pathways into microbial hosts like *E. coli* and *Saccharomyces cerevisiae* (Roychowdhury et al. 2023; Xu et al. 2024). CRISPR-based tools, including CRISPR activation (CRISPRa) and interference (CRISPRi), allow fine-tuned control of gene expression to optimize SM production (Bhojiya and Joshi 2024). Additionally, microbial consortia, where different strains cooperate to enhance SM synthesis, offer an innovative approach to improving production efficiency (Liu et al. 2024b).

In summary, biotechnological advances in engineering SM pathways have unlocked new possibilities for sustainable metabolite production. By utilizing tools like CRISPR, synthetic biology, and omics technologies, researchers can harness stress responses to boost SM biosynthesis and discover novel metabolites. These innovations hold promise for addressing challenges in medicine, agriculture, and environmental sustainability.

7. Conclusions and Perspectives

Plants, as sessile organisms, face a variety of biotic and abiotic stresses, including pathogen attacks, herbivore feeding, environmental changes, and resource scarcity. To overcome these challenges, plants have developed complex biochemical pathways leading to the production of a diverse range of SMs, each playing distinct roles in stress tolerance and adaptation. While primary metabolites are vital for maintaining cellular function, SMs serve as the frontline defense mechanisms that help mitigate the impacts of these stresses. One significant observation is that secondary metabolites like stilbenes, curcuminoids, and chitinases help plants not only resist oxidative damage and microbial infections but also respond to environmental stressors such as drought, salinity, and temperature extremes (Santos-Beneit 2024). These metabolites contribute to plant resilience by modulating key physiological processes such as stomatal regulation, ion balance, and antioxidant activation, thus improving overall stress tolerance.

Despite the growing body of research highlighting the importance of SMs, several questions remain unanswered regarding the precise mechanisms by which plants produce these metabolites under stress. For instance, how are specific genes regulating the biosynthesis of these compounds activated during stress? What are the genetic and transcriptional networks that control the expression of these defense-related metabolites, and how can they be harnessed to develop stress-resistant crops? Additionally, while studies have shown the positive effects of natural SMs, their application in field conditions especially the external supplementation of SMs remains underexplored. Future research should focus on elucidating the regulatory pathways and gene networks involved in secondary metabolite biosynthesis, with particular attention to how stress-related genes and transcription factors are activated. It is also essential to investigate how the external application of SMs can enhance plant resilience to biotic and abiotic stresses.

Another promising avenue for future research is the use of synthetic biology to produce bioactive SMs *in vitro*, a technique that could be employed to improve the stress tolerance of plants in a controlled environment. Furthermore, understanding how SMs accumulate under different stress conditions will be vital for manipulating their biosynthesis in crops to achieve higher resilience in the face of climate change and other environmental challenges. With the development of advanced molecular tools and systems biology approaches, it is now possible to investigate not only the biosynthetic pathways of SMs but also their interactions with each other and with the plant's overall stress response network (Selwal et al. 2023).

Collectively, while significant progress has been made in understanding the role of SMs in plant stress tolerance, the field still holds significant potential for discovery. Future research must address key questions about gene regulation, the effect of external metabolites, and the application of synthetic biology in improving plant resilience. The integration of these findings could lead to the development of crops that are more resistant to environmental stress, ensuring food security in an era of rapid climate change.

Acknowledgments: This study was supported by the Key Research Foundation of the Science and Technology Department of Zhejiang Province of China (2021C02064-3) and the Jiangsu Collaborative Innovation Center for Modern Crop Production (JCIC-MCP).

Author Contributions: GZ Conceptualization, Supervision. AK Writing original draft. FK writing, review & editing. MF review & editing. L.T, M.T figure preparation and tables. Asad Riaz: Formal analysis. G Z review & editing, and funding acquisition. All authors read and approved the final manuscript.

Conflicts of Interest: The authors declare no competing interests.

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