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Plant Secondary Metabolite Production During Biotic Stress

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ABSTRACT

Plants produce a wide range of secondary metabolites as part of their adaptive response to biotic stresses such as pathogens, herbivores, and parasites. These compounds, which include alkaloids, phenolics, terpenoids, and flavonoids, serve important roles in defense by repelling invaders, limiting microbial development, and attracting helpful species. Secondary metabolite production is closely controlled and often triggered by hormone-mediated signaling pathways such as jasmonic acid, salicylic acid, and ethylene. Understanding the molecular and physiological processes that drive their synthesis gives insights into plant resilience and the possibility of generating stress-resistant crops using metabolic engineering and biotechnological techniques.

KEYWORDS: Secondary metabolites, Plant, Bacteria, Virus, Fungus, Stress, Hormone

Nature plays a crucial role in promoting physical and emotional well-being, primarily through the resources it offers, such as food, herbs, and medicinal plants. Plants are remarkable chemists, synthesizing many organic compounds from simple inorganic materials. Natural products, typically referring to bioactive compounds derived from living organisms such as plants, animals, and insects, often fall into the category of secondary metabolites. The study of these substances focuses on their biosynthesis, structure, and function, reflecting nature's sophisticated capacity to generate pharmacologically active molecules (Newman and Cragg, 2020).

Natural bioactive compounds are broadly categorized into primary metabolites and secondary metabolites. Primary metabolites, including sugars, proteins, and lipids, are fundamental to plant growth, development, and cellular function. They are typically abundant and serve as essential components in bulk industries, such as those producing oils, cellulose, and sweeteners (Lancini and Lorenzetti, 1993; Kabera et al., 2014; Srivastava et al., 2014; Srivastava et al., 2018). In contrast, plant secondary metabolites (PSMs) are specialized compounds not directly involved in growth or reproduction, but play critical roles in plant survival. Initially considered metabolic byproducts, PSMs are now recognized for their roles in defense against herbivores and pathogens, attraction of pollinators, and stress resilience. These compounds also hold immense value for humans, contributing to the development of pharmaceuticals for conditions like cancer, inflammation, and neurodegenerative diseases, as well as products in the cosmetic, flavor, pigment, and pesticide industries (Lancini and Lorenzetti, 1993; Theis and Lerdau, 2003; Kabera et al., 2014). Despite being produced in limited quantities—often by specific plant species or specialized cells at certain developmental stages—their complex chemical architecture enables potent biological activity, making them key leads in drug discovery (Lancini and Lorenzetti, 1993; Kabera et al., 2014).

An insight into plant secondary metabolites

PSMs diverse bioactive properties contribute to their use in pharmaceuticals, cosmetics, nutrition, dyes, fragrances, flavours, and dietary supplements. Many of these compounds exhibit antioxidant, anti-inflammatory, antimicrobial, anticarcinogenic, and neuroprotective effects, supporting human health by neutralizing free radicals, modulating immune responses, and alleviating allergies and pain. In the context of human disease, especially viral infections, the body relies on innate and adaptive immunity for protection. Innate immunity provides a nonspecific, immediate defense via physical and chemical barriers, phagocytic cells, the inflammatory response, and the complement system. Adaptive immunity, which develops over time, involves lymphocytes, antibodies, antigen presentation via the major histocompatibility complex (MHC), and immunological memory (Smith et al., 2019; Pal and Chakravarty, 2020).

Based on their chemical structure and biosynthetic origin, PSMs are broadly classified into four main groups: Terpenes, phenolics, nitrogen-containing, and sulfur-containing compounds (Figure 1).

Terpenes are derived from the mevalonic acid pathway and are composed almost exclusively of carbon and hydrogen. Terpenes are volatile compounds produced by many plants and some insects. The term "terpene" originates from turpentine, a solvent derived from pine sap. As the largest class of secondary metabolites, terpenes are synthesized from acetyl-CoA or glycolytic intermediates (Grayson, 2000). Plants that produce terpenes often have pleasing smells and flavors,

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earning them the label "aromatic herbs." These compounds are believed to play a role in plant defense, acting as toxins or feeding deterrents against herbivores. Terpenoids are commercially valuable, used in food and cosmetic industries as flavors and fragrances, such as menthol and linalool, and are crucial for the quality of agricultural products. Terpenes are primarily found in plants, especially in essential oils (Gershenzon and Croteau, 1991; Theis and Lerdau, 2003; Saviranta et al., 2010).

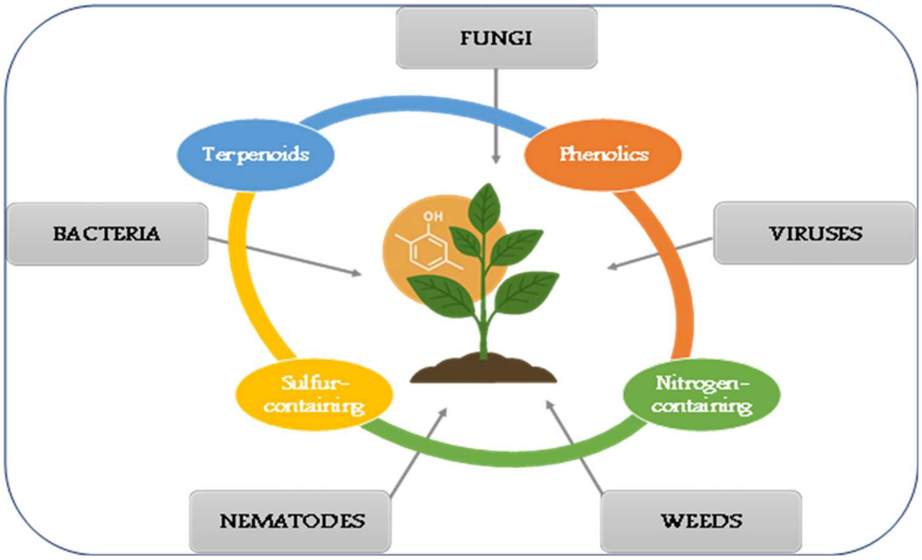

Figure 1. Plants produce four major classes of secondary metabolites, each contributing to defense against various biotic components present in the environment.

Phenolic compounds are a diverse group of secondary metabolites synthesized from simple sugars via the shikimate and phenylpropanoid pathways. They are characterized by the presence of one or more hydroxyl groups attached to aromatic benzene rings, forming structures derived from phenol (Nicholson and Hammerschmidt, 1992; Vogt, 2010). Phenolics play crucial roles in plant defense against a wide range of biotic stressors, including herbivorous pests, pathogenic microbes, and root parasitic nematodes. Beyond their ecological functions, these compounds are widely recognized for their antioxidant properties, which contribute to the scavenging of free radicals and the mitigation of oxidative stress-related diseases (Nicholson and Hammerschmidt, 1992). Dietary phenolics are primarily categorized into flavonoids, phenolic acids, and polyphenols. Among these, flavonoids represent the most extensively studied class and are associated with numerous health benefits. Phenolic acids, including hydroxybenzoic and hydroxycinnamic acids, are ubiquitous in plants, while tannins, high-molecular-weight phenolic polymers, are subdivided into hydrolyzable and condensed forms based on their chemical structure (Dai and Mumper, 2010; Goleniowski et al., 2013).

Nitrogen-containing metabolites – a diverse group known for their potent biological activity. he nitrogen-containing secondary metabolites in plants are broadly classified into three major groups: alkaloids, cyanogenic glucosides, and nonprotein amino acids, mostly derived from amino acids. They are well known for their roles in deterring herbivores and their toxicity to humans. These compounds often exhibit strong bioactivity and can serve as potent defenses against herbivores and pathogens due to their toxicity. Alkaloids are widely distributed in angiosperms and are particularly abundant in plants with medicinal properties, such as morphine and quinine (Ziegler and Facchini, 2008; Mithöfer and Boland, 2012; Schläger and Dräger, 2016).

Sulfur-containing secondary metabolites represent a diverse group of defense-related compounds in plants, often characterized by their volatility, reactivity, and broad-spectrum bioactivity. These metabolites include glucosinolates, glutathione, phytoalexins, thionins, defensins, and alliin, many of which also contain nitrogen, placing them at the intersection of nitrogen- and sulfur-based defense pathways (Hell, 1997; Halkier and Gershenzon, 2006; Burow et al., 2008). These compounds play pivotal roles in plant defense against a range of biotic stressors, including bacteria, fungi, and herbivorous insects. For example, glucosinolates and their hydrolysis products (e.g., isothiocyanates) exhibit strong antimicrobial and insecticidal activity, while defensins and thionins function as antimicrobial peptides that disrupt microbial membranes. Similarly, glutathione acts both as a redox buffer and as a precursor in detoxification and defense signaling. The biosynthesis and accumulation of sulfur-containing metabolites are tightly regulated by environmental conditions such as light, temperature, and sulfur/nitrogen nutrient availability. Their production is frequently induced upon herbivore attack or pathogen infection, forming part of the plant's inducible immune responses (Halkier and Gershenzon, 2006; Burow et al., 2008).

With the growing demand for safe, natural products, PSMs have attracted significant interest due to the limitations of synthetic production and challenges associated with traditional cultivation. Plant cell and tissue culture offer a sustainable, year-round alternative for large-scale metabolite production under controlled, sterile conditions. These techniques not only simplify extraction and enable the production of compounds not typically found in intact plants but also aid in conserving rare and slow-growing species. Biotechnology further enhances these systems by applying traditional and metabolic engineering strategies to increase yields. In vitro cultures can also model whole plants and be radiolabeled to trace biosynthetic pathways, making them valuable tools for both research and commercial applications (Romano and Gonçalves, 2018).

To enhance the production of secondary metabolites in plant cell cultures, various strategies are employed, combining traditional methods with modern metabolic engineering. Since metabolite synthesis is genotype-dependent, selecting high-yielding parent plants and productive cell or organ lines is crucial. Traditional approaches focus on optimizing culture conditions such as medium composition, pH, temperature, light, and aeration to improve biomass and metabolite output. Elicitation, using agents like methyl jasmonate, salicylic acid, microbial extracts, or heavy metals, mimics stress and triggers plant defense mechanisms, significantly boosting metabolite synthesis (Pandey et al., 2016; Romano and Gonçalves, 2018; Srivastava et al., 2018). These effects can be amplified when combined with physical factors like UV light and heat. Other strategies include nutrient and precursor feeding, where added substrates are converted into metabolites, and cell immobilization, which enhances viability and simplifies downstream processing. Physical techniques like membrane permeabilization, electric fields, and ultrasound also facilitate metabolite release. Metabolic engineering, on the other hand, involves modifying biosynthetic pathways by overexpressing or silencing specific genes to redirect metabolic flux towards desired compounds (Romano and Gonçalves, 2018). Though promising, this approach requires a deeper understanding of pathway regulation and rate-limiting steps, as gene overexpression alone may not always lead to increased yields. Together, these methods aim to ensure consistent and high-level production of valuable secondary metabolites for commercial applications.

Plant secondary metabolites against biotic stress

As agriculture faces growing pressures from biotic stresses, such as pathogens, pests, and weeds, sustainable and eco-friendly crop protection strategies are urgently needed. Biotic stressors significantly reduce crop yields and quality, causing global losses of billions. Although chemical pesticides have been effective, their overuse raises environmental and health concerns, prompting interest in plant-derived natural products as an alternative defense. Plants combat biotic threats through complex defense systems centred on PSMs, such as alkaloids, terpenoids, phenolics, flavonoids, and glucosinolates. These compounds, often induced during stress, function as antimicrobial agents, herbivore deterrents, or signaling molecules. Beyond direct defense, PSMs mediate ecological interactions, including pest repulsion and microbiome modulation.

Biotic stress alters hormone and PSM biosynthesis via intricate signaling pathways. Transcription factors regulate these responses by modulating gene expression related to secondary metabolism (Singh et al., 2014; Srivastava et al., 2014; Srivastava et al., 2015; Srivastava et al., 2016; Kharayat et al., 2017; Srivastava et al., 2018; Agarwal et al., 2020). Advances in omics, genome editing (e.g., CRISPR/Cas9), and metabolic engineering have deepened our understanding of PSM biosynthesis and enabled the enhancement of plant defense through precise genetic modifications (Pandey et al., 2016; Pandey et al., 2019; Rai et al., 2019).

Plant defense often relies on secondary metabolites like camalexin to inhibit pathogens, but their transport requires specific exporters. A screen of Arabidopsis ABCG transporter mutants identified *AtABCG34* as critical for resistance: *atabcg34* mutants were hypersensitive to the antifungal sclareol and pathogens *Alternaria brassicicola* and *Botrytis cinerea*. *AtABCG34* expression was induced by infection and jasmonate treatment, and the protein localized to the outer plasma membrane of epidermal cells. Mutants secreted less camalexin and were more susceptible, while overexpression enhanced secretion and resistance. Thus, *AtABCG34* plays a key role in camalexin-mediated defense by transporting it to the leaf surface (Khare et al., 2017). Camalexin plays a defensive role in Arabidopsis against *Plasmodiophora brassicae*, with the partially resistant Bur-0 genotype showing 4–7 times higher camalexin accumulation than the susceptible Col-0 during infection. This increase is linked to stronger induction of biosynthetic genes (*CYP71A13, CYP71A12*, and *CYP79B2*) and slower pathogen development in Bur-0. Disruption of camalexin biosynthesis in Col-0 (*pad3* mutant) led to more severe symptoms, supporting its role in basal defense. Moreover, allele substitution at the *PbAt5.2* QTL (Chr5) in HIF lines linked enhanced camalexin production to reduced clubroot symptoms, indicating that camalexin contributes to partial resistance in a genotype-dependent manner (Lemarié et al., 2015).

A study examined defense-related enzymes in groundnut (*Arachis hypogaea*) varieties infected with *Cercosporidium personatum*. Tolerant varieties (ICGV 86590, ICG FDRS 10) showed increased activity of peroxidase, phenylalanine ammonia-lyase (PAL), and lipoxygenase after infection, unlike the susceptible ICG 221, which showed little change. Glucanase activity increased in ICG 221 and ICG FDRS 10 but decreased in ICGV 86590. Phenolic content rose in all varieties, while catalase activity declined. These enzyme responses highlight their role in defense against leaf spot disease (Rani and Yasur, 2009). Another study investigated the chemical basis of resistance in California oak trees to *Phytophthora ramorum*, responsible for widespread tanoak and oak mortality. Nine phenolic compounds were quantified in phloem samples from trees either inoculated or naturally infected with the pathogen. Significant differences in phenolic profiles were observed between healthy and infected phloem tissues. Gallic acid, tyrosol, and ellagic acid showed the most notable differences and exhibited strong inhibitory effects against *Phytophthora* species in vitro. These findings suggest that changes in phloem chemistry, especially phenolic compounds, may contribute to resistance in oak trees (Ockels et al., 2007). BTH and BABA, two systemic resistance elicitors, reduce *Uromyces pisi* infection in pea by boosting phytoalexin production. BTH triggered scopoletin, pisatin, and medicarpin accumulation, especially in resistant genotypes, while BABA primed responses in all genotypes. These phytoalexins directly inhibited fungal growth, confirming their role in rust resistance (Barilli et al., 2015).

A study identified seven phenolic compounds in olive leaves, including caffeic acid, oleuropein, and luteolin, using HPLC/DAD. The antimicrobial activity of these compounds was evaluated against several pathogens, such as Gram-positive bacteria (e.g., *Bacillus cereus*, *Staphylococcus aureus*), Gram-negative bacteria (e.g., *Escherichia coli*, *Pseudomonas aeruginosa*), and fungi (e.g., *Candida albicans*). At low concentrations, olive leaf extracts exhibited combined antibacterial and antifungal effects, highlighting their potential as nutraceuticals, especially as a source of bioactive phenolic compounds (Pereira et al., 2007). Glutathione (GSH) and indole glucosinolates (IGs) are crucial for Arabidopsis immunity, with GSH supporting disease resistance and the PEN2 pathway enabling pre-invasion defense. This study identifies Glutathione-S-Transferase class-tau member 13 (GSTU13) as essential for the PEN2 pathway, mediating GSH's role in IG metabolism. *GSTU13* mutants are more susceptible to fungal pathogens and fail to deposit callose after bacterial recognition, highlighting its role in Arabidopsis' immune response (Piślewska-Bednarek et al., 2017)

Cinnamoyl-CoA reductase (CCR) catalyzes the first committed step in monolignol biosynthesis. In *Arabidopsis thaliana*, two CCR genes—*AtCCR1* and *AtCCR2*—have distinct roles. *AtCCR1* is more efficient with feruloyl- and sinapoyl-CoA and is mainly expressed in lignifying tissues, supporting its role in constitutive lignification. *AtCCR2* is less efficient enzymatically but is strongly induced during pathogen attack, particularly in response to *Xanthomonas campestris*, suggesting its role in defense-related phenolic production (Lauvergeat et al., 2001). *X.campestris* pv. *campestris* (Xcc) causes major losses in *Brassica* crops. This study used mass spectrometry to analyze metabolic changes in *Brassica oleracea* over five days of Xcc infection. Results showed dynamic, time-dependent shifts in metabolites, with alkaloids, coumarins, and sphingolipids playing key roles in defense. These insights may help develop more resistant *Brassica* varieties (Tortosa et al., 2018). Myrosinase enzymes and their substrate glucosinolates play a key role in plant defense within the Brassicaceae family. Overexpressing the myrosinase enzyme *TGG1* in Arabidopsis improved resistance to *Pseudomonas syringae* by enhancing stomatal defense. The transgenic plants showed faster stomatal closure upon infection and increased sensitivity to ABA and salicylic acid, while being less responsive to IAA. *TGG1* overexpression also delayed flowering by promoting the *Flowering Locus C* gene. These findings suggest TGG1 plays a role in both plant defense and flowering regulation (Zhang et al., 2019). A study examines the transient accumulation of phenolics in the extracellular environment of *Nicotiana tabacum* suspension cells during early interactions with bacterial pathogens. Four acetophenones and four hydroxycinnamic acid amides were identified. Treatment with *Pseudomonas syringae* or heat-killed bacteria triggered increased phenolic production and altered their composition. These phenolics were sensitive to oxidative stress, with oxidation and depletion occurring during an oxidative burst. The phenolic makeup was also influenced by cell age and density. This study suggests the kinetics of extracellular phenolic compounds and oxidative stress in the initial hours of plant–bacterial interactions (Baker et al., 2005).

Two pesticidal naphthoquinones from *Calceolaria andina* inhibit mitochondrial complex III in insects. Their activity depends on structural features like the acylation of the 2-hydroxy group. Despite strong bioactivity, poor field performance was linked to volatilization and degradation, which improved with better formulation (Khambay and Jewess, 2000). A study investigated the defense responses of *Gossypium hirsutum* (cotton) to *Spodoptera litura* herbivory. Insect feeding increased phenol and protein levels while reducing carbohydrates and amino acids. Antioxidant enzymes such as peroxidase, catalase, and superoxide dismutase were elevated, while polyphenol oxidase and PAL were suppressed. HPLC analysis revealed increases in gallic acid, catechin, and caffeic acid in infested plants. Feeding assays showed these phenolics induced detoxifying enzymes in *S. litura*, indicating their toxicity and potential for pest management (Usha Rani and Pratyusha, 2013). A study investigated the role of phenolic acids in wheat's resistance to *Sitodiplosis mosellana* larvae. Resistant wheat varieties showed higher and faster increases in ferulic acid levels, which suppressed larval growth, with concentrations above 0.35 µg/g fresh weight linked to higher larval mortality. Resistance also correlated with the induction of p-coumaric acid in some varieties. Although mature seeds of resistant and susceptible wheats had similar phenolic acid levels, ferulic acid induction varied across wheat lines and growing conditions (Ding et al., 2000). Herbivore attacks trigger systemic defense that can affect other herbivores, but how different feeding guilds coexist on the same plant is unclear. In experiments with *Nicotiana attenuata*, no negative interactions were found between a leaf chewer (*Manduca sexta*) and a stem borer (*Trichobaris mucorea*). *T. mucorea* increased chlorogenic acid levels in the stem pith, a response requiring jasmonic acid signaling. Silencing chlorogenic acid biosynthesis reduced defense against *T. mucorea*. *T. mucorea* did not activate jasmonic acid signaling in leaves, while *M. sexta* induced minor pith jasmonic acid responses. These results suggest that tissue-specific defense allows herbivores to coexist by occupying different chemical niches (Lee et al., 2017).

The function of phenolic-based defenses in wheat against the root-lesion nematode *Pratylenchus thornei* was investigated. Resistant genotypes showed higher levels of total phenols and greater induction of oxidative enzymes, such as PPO and POD, compared to susceptible lines. The resistant genotypes CPI133872 and CPI133859 had notably higher phenol content. PPO activity peaked at 4 weeks, while POD activity peaked at 6 weeks post-inoculation in the resistant genotypes, highlighting time-dependent defense mechanisms. These findings suggest that phenols and related enzymes are crucial for wheat's resistance to *P. thornei* (Rahaman et al., 2020).

A study evaluated the biocontrol activity of arbuscular mycorrhizal fungi (AMF) against Tomato Mosaic Virus (ToMV) in tomato plants. AMF colonization reduced disease severity, viral accumulation, and improved plant growth. The study also assessed the impact of AMF on gene expression related to phenylpropanoid, flavonoid, and chlorogenic acid biosynthesis. Several genes, particularly *PAL1* and *HQT*, were up-regulated in response to mycorrhizal colonization under ToMV infection. AMF enhanced growth parameters, photosynthetic pigments, and flavonoid content. These findings demonstrate AMF's protective and growth-promoting effects, supporting their potential use as an eco-friendly, cost-effective solution for controlling tomato mosaic disease (Aseel et al., 2019). To understand resistance to Tomato yellow leaf curl virus (TYLCV), researchers analyzed the metabolome and transcriptome of resistant (R) and susceptible (S) tomato plants before and after infection. The results revealed that resistant (R) plants had a more coordinated metabolic response, especially in amino acids, polyamines, and phenolic compounds. Key pathways, including phenylpropanoid, tryptophan/nicotinate, and salicylic acid biosynthesis, were activated in R plants. Gene expression analysis showed that the resistance in R tomatoes is intermediate between susceptible cultivars and the wild relative, *Solanum habrochaites* (Sade et al., 2015). The effects of Grapevine Leafroll-associated Virus 3 (GLRaV-3) on grapevine physiology were investigated. Infected plants exhibited a decrease in photorespiratory intermediates, such as glycine and serine, and a reduction in malate content, indicating a defense response. Additionally, the virus led to an increase in flavonols (myricetin, kaempferol, quercetin derivatives) and hydroxycinnamic acids, including caffeic acid derivatives (Montero et al., 2016). Cucumber mosaic virus (CMV) affects *Passiflora edulis*, but its interactions were poorly understood. Using small RNA sequencing, electron microscopy, and PCR, we identified CMV infection and found that it reduced phytochemical content and plant development. In response, *P. edulis* increased secondary metabolites and antioxidant enzyme activities to combat the virus (Lan et al., 2020). Telosma mosaic virus (TeMV) infection in *P. edulis* increases total phenols and boosts antioxidant enzyme activities (SOD and CAT), enhancing the plant's defense. This study highlights how TeMV alters the biochemical profile of *P. edulis*, triggering a defensive response through elevated secondary metabolites and antioxidant activity (Chen et al., 2018).

A study explored the effects of abiotic (salicylic acid, jasmonic acid, methyl jasmonate) and biotic (chitosan, yeast extract) elicitors on xanthone production in *Gentiana dinarica* hairy root clones. Hairy root clone 3 showed the highest responsiveness, with chitosan significantly enhancing norswertianin levels. Higher elicitor concentrations increased the aglycone form of norswertianin while decreasing its glycosylated form. Treatments with salicylic acid and chitosan resulted in up to a 24-fold rise in norswertianin and triggered the formation of new xanthone compounds (Krstić-Milošević et al., 2017).

Conclusion

In conclusion, PSMs play vital roles in plant defense, contributing significantly to human health, agriculture, and the environment. Their diverse biological activities, including antimicrobial, anti-inflammatory, and antioxidant effects, are central to their value in pharmaceuticals, cosmetics, and crop protection. The intricate biosynthesis of PSMs, influenced by various genetic and environmental factors, allows plants to respond dynamically to biotic stressors. Advancements in biotechnology, including metabolic engineering and plant cell culture, offer promising strategies for enhancing the sustainable production of these bioactive compounds. As natural alternatives to synthetic chemicals, PSMs hold immense potential for combating global challenges in health and agriculture.

Conflicts of Interest: The author declares no conflicts of interest.

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