Review Article

ROLE OF SECONDARY METABOLITES IN HOST PLANT RESISTANCE

Abstract: The biosynthesis of phenylpropanoids and flavonoids are a specialized metabolites frequently reported as active in plant defenses against biotic or abiotic stresses. Their accumulation may be intrinsic or induced by external stimuli. Plant signals may stimulate plant defense responses, act as physical or chemical barriers against invasion, or serve as direct toxic weapons against pathogens or insects. It has been suggested that their protective action is the result of their localization during the interaction between the host and aggressors, as well as their sustainability and the predominance of particular compounds or their synergy with each other. Although some of their biosynthesis and regulation have been deciphered, there are still many gaps. The mechanism by which they work on microorganisms and insects likely involve interference with important cellular machinery and structures, but for all types of pests and pathogens, this is not fully understood. Both phenylpropanoids and flavonoids are presented here in an overview of advances in the field.

Keywords: Phenylpropanoids, Flavonoids, Plant defense, Pests and Pathogens

1. Introduction

In plants, secondary metabolites perform many biological functions, plays an important role in biotic and abiotic stress responses and in plant interactions with their environment. As reviewed in [58,2712,5,36,46], some of these metabolites play a fundamental role in the attraction of pollinators mentioned in chemical ecology, while others help the organism cope with stressful stimuli. At the time of discovery, they were considered secondary metabolites, not essential to plant growth and development. However, their definition has changed significantly over the past two decades. Some authors refer to these metabolites as "specialized" metabolites, while others refer to them as "central" metabolites because they play a key role in plant plasticity and response to various environmental factors [37,54,38]. In addition, high-throughput sequencing has allowed the publication of genomes of a number of species, revealing that genes involved in the biosynthesis pathways of these metabolites are present in a large array of genomes [21]. A number of plant specialized metabolites and the enzymes involved in their biosynthesis have been explored large-scale using metabolomics and functional genomics technologies [9,56]. An author in a review clearly mentioned these metabolites as "specialized metabolites" because they fully adhere to the concept that these metabolites are of great importance [27].

PPP leads to the accumulation of many families of compounds, including phenylpropanoids, flavonoids, lignins, monolignols, phenolic acids, stilbenes, and coumarins [59]. Subfamilies of flavonoid molecules are categorized based on their structure, such as flavones, isoflavones, anthocyanidins, flavonols, flavanols, flavanones, aurones and chalcones. In each subfamily, there are a wide variety of molecules resulting from various conjugation processes, such as C- or O-methylation, sulfation, or glycosylation [16,8].

The growth and maturation of pollen tubes, seed maturation, dormancy, and longevity of plant reproductive organs and seeds are affected by flavonoids under stress-free conditions [41,13]. Additionally, they contribute to the attractiveness of plants to pollinators via the color and scent of their flowers. Also they facilitate plant–microorganism communication for the establishment of symbiosis, such as rhizobium interactions during nodulation [13,32].When plants are under adverse abiotic conditions, they can be used to mediate defense responses. For example, in water stress, plants have to deal with oxidative stress caused by reactive oxygen species (ROS). In order to limit lipid peroxidation of cell membranes, high antioxidant activity is necessary [17,39]. The process can be achieved by upregulating the genes involved in the phenolic flavonoid biosynthesis described (Fig. 1). In *Chrysanthemum morifolium* L. cultivars under water stress, genes encoding enzymes such as Phenylalanine ammonia-lyase (PAL), Chalcone isomerase (CHI) and flavanone 3-hydroxylase (F3H) were upregulated, resulting in an increase in flavonoids [19]. Salt and UV stress also resulted in a significant increase in the biosynthesis of flavonoid glycosides and caffeic acid derivatives [1]. Several genes that code for the Myloblastosis (MYB) transcription factor, Chalcone synthase (CHS), and Chalcone isomerases have been mutated to alter *Arabidopsis thaliana* (L.) Heynh's freeze tolerance [43]. *Phillyrea latifolia* L. accumulates strong amounts of flavonoids in its leaves and glandular trichomes when exposed to excessive light [53], leading authors to propose that they play a protective role in *P. latifolia's* integrated mechanisms of acclimation.

As a keynote, plant defense can be mediated indirectly by flavonoids and phenylpropanoid compounds acting as signaling molecules in biotic stress situations or directly by phytoanticipins (active compounds accumulating in plant tissues) and phytoalexins (newly synthesized active compounds that reduce pathogen detection) [33,34,20]. It has been shown that genes involved in their biosynthesis increase resistance to biotic stress [13,27]. This has been described in the literature from two perspectives. The study of basal defense has addressed a variety of constitutive defense mechanisms, including physical barriers and chemical barriers [52,49,15]. Among these are phenylpropanoid derivatives for cell wall reinforcement. The abundance of phenylpropanoids in Maize (*Zea mays* L.) grain pericarps has been shown to reduce disease symptoms in genotypes resistant to *Fusarium graminearum*, *Fusarium verticillioides*, and Maize weevil (*Sitophilus zeamais* Motsch.) [15,42,6]. As an alternative, research focused on induced investigated how these metabolites may suppress or limit invader pathogenicity through their potential resistance toxicity. A growing interest in decoding the molecular dialogue between the host and the pathogen has stimulated the study of this direct effect of bioactive compounds against pathogens, however these mechanisms are still unknown. Contrary to this, plant-derived compounds-especially flavonoids-have been extensively studied in drug research [35,40]. As a result of searching for natural anti-inflammatory compounds, some flavones have been found to have intracellular targets [10].

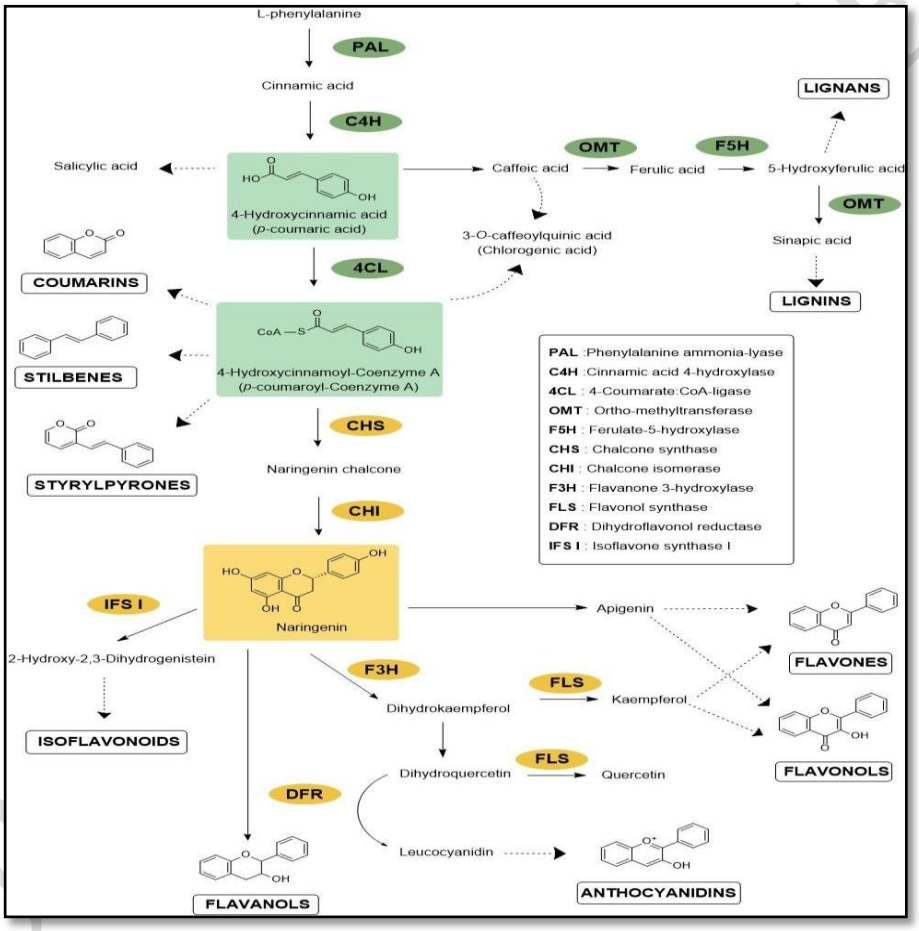

Figure 1. Main steps of the phenylpropanoid and flavonoid pathways. Enzymes mentioned in this paper are shown in green and yellow for central phenylpropanoid pathways and flavonoid biosynthesis, respectively. Complete arrows refer to one step in the biosynthetic pathway, whereas dashed arrows represent undetailed pathways leading to one molecule or molecule subfamilies [27].

2. Host plant resistance against different microbes

2.1 Fungal pathogens

Metabolomics has contributed greatly to the identification of specialized PPP metabolites correlated with plant resistance to fungi and oomycetes [7,22,45,67]. O-glycosylated flavonoids are the most frequently reported hosts-pathogen interactions. In most mechanistic studies published so far, phenolic derivative accumulation in plant tissues associated with fungi resistance has been emphasized in terms of quantitative or spatiotemporal aspects.

In order to illustrate quantitative aspects, Carrot leaves (*Daucus carota* L.) will be used. A comparison with susceptible genotypes revealed significantly higher levels of feruloylquinic acid, apigenin (4′-O- and 7-O-glycosides), luteolin, and chrysoeriol in genotypes more resistant to *Alternaria dauci* [22]. There are similar differences in PPP metabolites between resistant and susceptible genotypes in numerous other ecosystems, supporting plant breeders. In spite of the same combination of factors, disease resistance and metabolite contents can be correlated in opposite directions depending on the pathogen. A specific example was observed in Potato tubers enriched in rutin and nicotiflorin that were resistant to *Pectobacterium atrosepticum*, but susceptible to *Phytophthora infestans* [24], a biotrophic fungal pathogen. Thus, a systemic approach is required to achieve increased resistance to a specific pathogen without decreasing resistance to another.

An example of a spatial aspect is the Maize-*Fusarium graminearum* patho system and Maize-*Fusarium verticillioides* patho system, where ferulic acid levels in grain tissues was found to correlate with a lesser extent of disease in resistant genotypes [42,6]. To prevent pathogen invasion, this strategy of localizing the defense metabolite seems very strategic. For example, in Cotton (*Gossypium hirsutum* L. and *Gossypium barbadense* L.), catechin and gallocatechin were dominant near the *Verticillium dahliae* infection site in the vessels, creating a toxic environment that confined the pathogen to the vessel lumens [28]. By preventing the spread of vascular disease through the formation of tyloses, this local accumulation contributed to preventing its systemic spread. It has also been observed in Grapevines (*Vitis vinifera* L.) defense against *Phaeomoniella chlamydospora* and *Phaeoacremonium* species [11]. Barley (*Hordeum vulgare* L.) is resistant to mildew (*Blumeria graminis*) as a result of the accumulation of light-absorbing compounds in its coleoptiles [2], thought to be phenylpropanoids.

As an example of temporality, the Date palm tree (*Phoenix dactylifera* L.) is resistant to *Fusarium oxysporum* fungal diseases. This resistance has been attributed to a quantitative differential in the concentration of 5-O-caffeoyl-shikimic acid at physiological stage 3 (ripening of dates) [71]. Often, the difference in phenotypic characteristics between resistant and susceptible cultivars of fungal diseases is explained by the early or constitutive availability of the compound of interest in the tissues, which results in an efficient defense response, as demonstrated by preformed chlorogenic acid in Tobacco plants resistant to *Cercospora nicotianae* [29]. It has also been found that 194 metabolites have been identified in the Barley (*Gibberella zeae*) patho system and that they accumulate significantly more in a resistant genotype than in a susceptible genotype [7]. The active compounds included kaempferol-3-O-rhamnopyranoside, naringenin-7-O-glucopyranoside, kaempferol-3-O-glucopyranoside, and kaempferol-3-O-glucopyranoside-7-O-rhamnopyranoside-7-O-sophoroside. It is becoming increasingly apparent that constitutive accumulation of flavonoids occurs in various plants–fungus pathosystems as a result of disease resistance [7,4,62]. Besides an early or constitutive synthesis of the defense compounds, the maintenance of their concentration over time *i.e.*, when disease pressures are high [31]. As a result, plant resistance to fungal diseases is more complicated than a simple quantitative difference between resistant and susceptible genotypes during infection. Also, the durability of the system is determined by the stability of the metabolite contents in the tissues over time. It is thus necessary to maintain an efficient metabolic ratio according to the disease and plant development cycles.

An integrated approach of reverse genetics and biochemical analysis of the resulting proteins has helped explain how phenylpropanoid derivatives mediate fungal disease resistance. First of all, since the PAL gene is located upstream in the PPP pathway, modifications would prevent the plant from synthesizing many compounds driven by downstream genes. Tobacco PAL mutants (PAL-suppressed YE-6-16 transformants) exhibited rapid growth of lesions after infection by *Cercospora nicotianae*, while PAL gene overexpression reduced symptoms [29,44]. The inactivation of the gene encoding a CHS in *Arabidopsis thaliana* decreased anthocyanin content and *Verticillium dahliae* resistance. However, overexpression of genes encoding CHS, CHI, and dihydroflavonol reductase (DFR) in flax (*Linum usitatissimum* L.) has been linked to increased resistance to *Fusarium* species. Poplar (*Populus tomentosa* Carr.) resistance to *Dothiorella gregaria* was clearly impacted by overexpression and mutation of an R2R3 MYB transcription factor, respectively [60]. Additional evidence shows that chemical inhibition of a CHS enzyme and down regulation of its corresponding gene suppressed *Podosphaera xanthii* induced resistance in cucumber (*Cucumis sativus* L.).

Antifungal activity of phenylpropanoids and flavonoids is supported by metabolomic and functional genomic data. Flavonoids extracted from the needles of *Picea neoveitchii* Mast., used at 1 mg.mL−1, exhibited very interesting antifungal activities: kaempferol-7-*O*- (2″-*E*-*p*-coumaroyl)-*α*-L-arabinofuranoside exhibited strong activity against *Fusarium ox- ysporum* with a relative inhibitory percentage of 108.1%, while 5,7,4′-trihydroxy-3,8,-di- methoxy-6-*C*-methylflavone, 5,8,4′-trihydroxy-3,7-dimethoxy-6-*C*-methylflavone, 7-methoxy-6-*C*-methylkaempferol and kaempferol-7-*O*-(2″-*E*-*p*-coumaroyl)-*α*-L-arabino- furanoside were active against *Rhizoctonia solani*, with 49.5%, 53.3%, 95.3% and 49.5% rel- ative inhibitory percentages, respectively [45]. Compared to Carbendazim, a synthetic chemical fungicide used to treat these two pathogens, these compounds showed to be as active as Carbendazim. In addition, other flavonoids, such as eriodictyol, homoeriodictyol, dihydroquercetin, and luteolin, were isolated from *Ficus sarmentosa*. It was found that Henryi (King) Corner was highly effective against pathogenic fungi, including *Fusarium graminearum* and *Septoria zeicola*. Luteolin showed the strongest antagonistic activity among these flavonoids, with half-maximal inhibitory concentrations (IC50) of 56.38 and 81.48 mg·L−1 to each fungus, respectively [61]. In an in vivo assay, Cherry tomatoes sprayed with Laurel (*Laurus nobilis* L.) oil containing 44% eugenol and 30% cinnamaldehyde were less infected by *Alternaria alternata* after 5 days of storage. In particular, decayed tomatoes treated with laurel oil were reduced by 86.4% [64]. A few studies have assessed the integrity of plant fungal pathogens by phenylpropanoid derivatives. One of them is the study shown above on essential oil from laurel leaves: fungicidal activity was demonstrated by invaginations and folds in the fungus cell walls.

2.2 Bacterial pathogens

There have been many studies investigating how PPP affects bacterial resistance. It has been shown that infection increases the content of flavonoids and other phenylpropanoid derivatives, especially coumaric acid, in Tobacco (*Nicotiana tabacum* L.)-*Pseudomonas syringae* pathosystems [49]. Orange leaves (*Citrus sinensis* L.) infected with *Candidatus liberibacter asiaticus* produced significantly more flavonoid glycosides and hydroxycinnamic acids [18]. A necrotrophic bacterial pathogen, *Pectobacterium atrosepticum*, was shown to be resistant to rutin (quercetin-3-O-rutinoside) and nicotiflorin (kaempferol-3-O-rutinoside) in Potato tubers [24]. A higher concentration of pelargonidin-3-O-rutinoside-5-O-glucopyranoside and peonidin-3-O-rutinoside, both acylated with p-coumaric acid, was found in the *E. carotovora* of transgenic potato tubers [26].

In the context of plant protection, phenylpropanoids have been heavily studied in vitro to develop biological alternatives to synthetic phytoprotectants. Nevertheless, [65] claims that efficient protection is not the result of significant toxicity, but rather from the host's defense system. Therefore, it is important to explore both the direct and indirect modes of action of these compounds for effective pest management. Consequently, it is imperative to explore their biosynthesis and targets.

Post-inoculation transcriptomic shifts revealed that some genes encoding enzymes in the PPP are rapidly activated. However, others are induced much later in the infection response [69,49]. Among the earliest genes activated were CHS, F3H and isoflavone synthase I (IFS I) in soybeans infected by *Pseudomonas syringae* [69]. A number of PAL genes were found in tobacco infected by the same bacterium, including cinnamic acid 4-hydroxylase (C4H), 4-coumarate: CoA-ligase (4CL), Ortho-methyltransferases (OMT) and ferulate-5-hydroxylase (F5H). Although this discovery may pave the way for the development of new plant varieties resistant to bacteria, little is known about how these enzymes work biologically. PPP compounds have been reported to disrupt vital cellular functions and jeopardize bacterial survival without detailing the mechanisms. In *Clavibacter michiganensis*, fragarin from strawberry leaves disrupted cell membrane integrity [27].

The electron transport pathway and cell survival, in particular, can be significantly affected by compounds with better penetrability. A case study on *Micrococcus luteus* demonstrated that two retrochalcones isolated from Chinese licorice (*Glycyrrhiza inflata* L.) roots compromised the enzymatic activity of the NADH-cytochrome C reductase with licochalcones A and C. A compound's antibacterial activity may also be attributed to preventing cell proliferation through direct interference with cell division. Chlorogenic acid inhibited cell division by inhibiting the polymerization of the cytoskeletal protein FtsZ [27], which is essential for cytokinesis. It has been suggested that chlorogenic acid makes hydrogen bonds and hydrophobic interactions with various residues of this protein, altering its conformation and inhibiting GTPase activity [27].

2.3 Viruses

In response to viral agents, plants produced salicylic acid (SA) and other defense metabolites from the PPP to initiate systemic acquired resistance (SAR). Viruses such as Sugarcane mosaic and Dwarf mosaic virus have been shown to cause Dwarf mosaic diseases in Maize [68]. Tobacco mosaic virus (TMV) has been investigated in the exploration of the antiviral activity of candidate specialized metabolites owing to its host diversity, which includes several economically important plant species, including Tobacco and Tomato (*Solanum lycopersicum* L.). Although 5-O-caffeoylquinic acid and quercetin were abundant at the TMV infection site in Tobacco leaves, kaempferol was predominant in a distant part of the plant with SAR [27].

In most of publications, quercetin and kaempferol are cited as triggers of the plant's defense response rather than a direct action on viral particles. Such as *Datura stramonium* L.-TMV and *Chenopodium amaranticolor* -TMV pathosystems [23]. Several studies suggest that metabolite levels are associated with plant resistance to viruses, but do not assess whether they are potentially harmful to viruses.

2.4 Insects

The insects are the most problematic macroscopic pests on cultivated plants, not just because of their direct damage caused by their herbivorous larvae, but also because of their indirect damages caused by their ability to spread microbial pathogens. A number of studies have been conducted to identify plants' natural defense mechanisms against herbivores. Defensive compounds are produced constitutively or in response to plant damage and affect herbivore feeding, growth, and survival. Aside from releasing volatile organic compounds, plants also attract herbivores' natural enemies. Phenylpropanoids and flavonoids are defensive compounds against insects. It has been shown that chlorogenic acid and feruloylquinic acid distinguish between resistant and susceptible chrysanthemum genotypes [25] and Thrips (*Frankliniella occidentalis*). Both molecules have higher amounts in thrip-resistant genotypes. The wild-cultivated crosses of Groundnut plants (*Arachis hypogaea* L. X *Arachis kempff-mercadoi* Krapov.) contain similar amounts of quercetin, chlorogenic acid and rutin .

In carrot leaves, the flavone luteolin and the phenylpropanoid sinapic acid significantly distinguished thrip-resistant cultivars from susceptible ones. The ratio of specific metabolites played a preponderant role in plant resistance to insects, as in Carrot, which showed resistance to the fly *Psila rosae* F. is positively correlated with high luteolin-7-*O*-glucopyranoside/kaempferol-3-*O*-glucopyranoside and methyluteolin-7-*O*-glucopyranoside/kaempferol-3-*O*-glucopyranoside ratios [27]. *F. occidentalis* thrips were shown to be significantly harmed by chlorogenic acid when they were fed artificial diets containing 5% chlorogenic acid [25]. Castor bean leaf extracts (*Ricinus communis* L.) contain quercetin that can kill adults and also prevent oviposition and ovipos from developing. One of the most common Bean weevils, *Callosobruchus chinensis* L., known as a pest to many stored legumes [57]. While some molecules do not directly have insecticidal activity, their physical and chemical properties can enhance other compounds solubility, improving their penetration and effectiveness. This kind of synergy was illustrated with non-PPP metabolites in an in vitro analysis that revealed an up to 19-fold increase in penetration of camphor in a binary mixture with 1,8-cineole through the larval integument of the Cabbage looper (*Trichoplusia ni*) compared to Camphor alone. As shown by the LD50 for 1,8-cineole: camphor of 60:40 (186.9 g/insect) [51,50], such a synergy was found in PPP metabolites. One metabolite may act in opposing ways against different targets, as we have discussed previously for fungal targets. For instance, chlorogenic acid may function as an auxiliary to control thrips but on the other hand promote oviposition by the Black swallow tail (*Papilio polyxenes* Fabr.) [14]. It is therefore necessary to adopt an integrative approach to protect against one target without increasing the severity caused by another.

Insects can cause direct damage to plants, as well as be vectors of economically threatening diseases, including Pierce's disease caused by *Xyllella fastidiosa* [3], Grapevine yellow disease caused by phytoplasmas [47] or other major crop viruses. A major concern in crop management is preventing host contact with disease-carrying vectors in order to limit epidemics. As a result, Su and collaborators [48] linked metabolic changes in Tomato leaves with vector behaviour to address this dimension. The whiteflies (*Bemisia tabaci*) recognized plants that had previously been attacked by conspecifics due to decreased terpenoid and flavonoid contents. By treating Tomato plants infested by *B. tabaci* with naringenin they increased their content of rutin, kaempferol-rhamnopyranoside, quercetin-trisaccharide, 3- *O*-methylmyricetin and anthocyanin up to the same level as those measured in non-infested plants. Later showed that the preference of *B. tabaci* for oviposition on previously infested plants was reversed. As a consequence of reduced *B. tabaci* population, both the pest and the vectored virus *eg.*, the Tomato yellow leaf curl virus (TYLCV)- that causes damage to the plant can be decreased. Moreover, whiteflies fed less on flavonoid-rich Tomato leaves, and TYLCV spread was reduced [66]. Their findings suggest that flavonoids are more likely to inhibit host–vector interaction than to have antiviral activity,

since only disease expression was delayed. Flavonoids were also accumulated in Grapevine after *phytoplasma* infection. Flavonoids were thought to repel insects [30].

3.Conclusion

A complex plant-environment interaction mediated in part by secondary metabolites, including phenylpropanoids, flavonoids result in diversity within the structural and regulatory genes of several super families involved in secondary metabolism. Ultimately, the desired systems biology approach will be realized through rapid progress in sequencing, structural elucidation, and analytical tools. Several model plants and crops, like Arabidopsis, alfalfa, poplar, and rice, could be used at the beginning. A comprehensive understanding of the pathway leading to phenylpropanoids and flavonoids formation and function should continue to be explored.

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