

# The Role of Flavonoids in Plant Terrestrialization

Subjects: Mycology | Ecology | Biochemistry & Molecular Biology

Contributor: Luana Beatriz dos Santos Nascimento, Massimiliano Tattini

Plants evolved an impressive arsenal of specialized metabolites to cope with the novel environmental pressures imposed by the terrestrial habitat when moving from water. Flavonoids are maybe the most important specialized metabolites that show multifarious roles in the success of plant terrestrialization. These compounds modulated auxin transport and signaling and promoted the symbiosis between plants and fungi (e.g., arbuscular mycorrhizal, AM), a central event for the conquest of land by plants. AM improved the ability of early plants to take up nutrients and water from highly impoverished soils. Therefore, flavonoids were essential to plant development in the “new world” scarce of water and nutrients.

Keywords: arbuscular mycorrhizal ; auxin ; drought ; nutrient deficiency ; flavonoids

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## 1. Introduction

Many evolutionary innovations, i.e., the adaptive traits of living organisms <sup>[1]</sup>, occurred over a short time period when plants moved from water to populate land (approx. 460 mya) <sup>[2][3]</sup>. Together with other adaptive features, “molecular” innovations were driven by the novel environmental pressures that the early land plants faced in harsh terrestrial habitats. These included dramatic declines in water and nutrient availabilities, large fluctuations in air temperature, and substantial increases in visible light and UV radiation <sup>[4][5][6]</sup>. However, there is now conclusive evidence that most of the molecular toolkit enabling the conquest of the terrestrial habitat by plants was already present in their ancestors, i.e., members of the Charophyta algae clade (Zygnematophyceae) <sup>[4][7][8][9]</sup>. This molecular tool kit included a set of novel transcription factors, and genes involved in both phytohormone signaling and in the formation of the cell wall, all of them being closely linked to the emergence of land plants <sup>[8]</sup>. Therefore, in other words, plants were apparently “terrestrial from the beginning” <sup>[10]</sup>.

For instance, the two- (2D) to three-dimensional (3D) growth transition was a key innovation increasing the plant complexity <sup>[11][12]</sup> and hence improving their ability to conquest more stressful habitats <sup>[13][14][15][16]</sup>. This is consistent with the notion that 3D plants bodies display higher resistance against desiccation and UV radiation, ultimately providing protection to both vegetative and reproductive tissues <sup>[6][17]</sup>. Interestingly, recent findings show that 2D to 3D growth transition mostly involves the phytohormone auxin and its asymmetrical distribution in different plant tissues, driven by the polar auxin transport (PAT) <sup>[12][18]</sup>. Indeed, PAT was already present in the ancestors of land plants, and it was regulated by a range of transporters, including the PIN-formed (PIN) proteins <sup>[19]</sup>. Nonetheless, PAT in Charophytes is not as tightly regulated as it is in bryophytes and angiosperms <sup>[20][21]</sup>. This only in part is due to the increased numbers of PIN proteins detected in more complex land plants. Instead, the evolution of regulatory mechanisms of both PIN activity and PIN-induced PAT likely represented a major developmental innovation responsible for the increased complexity observed from ancestors of land plants up to angiosperms <sup>[22][23]</sup>. Similar reasoning concerns core components of the ABA signaling pathway, such as SnRK and PP2C proteins, which were already present in land plants' ancestors <sup>[24][25][26]</sup>. The complexity and robustness of the ABA signaling network observed in gymnosperms and angiosperms are due to not only the expansion of core components but also to the evolution of several downstream regulatory network components (MYB transcription factors and MAPKs proteins) <sup>[27][28][29][30]</sup>. The enhanced complexity in this pathway has expanded the function of the ABA signaling up to include the fine tuning of stomata movements, a trait that would allow land plants to later adapt to habitats characterized by severe soil water deficit and excessive sunlight irradiance <sup>[30][31]</sup>.

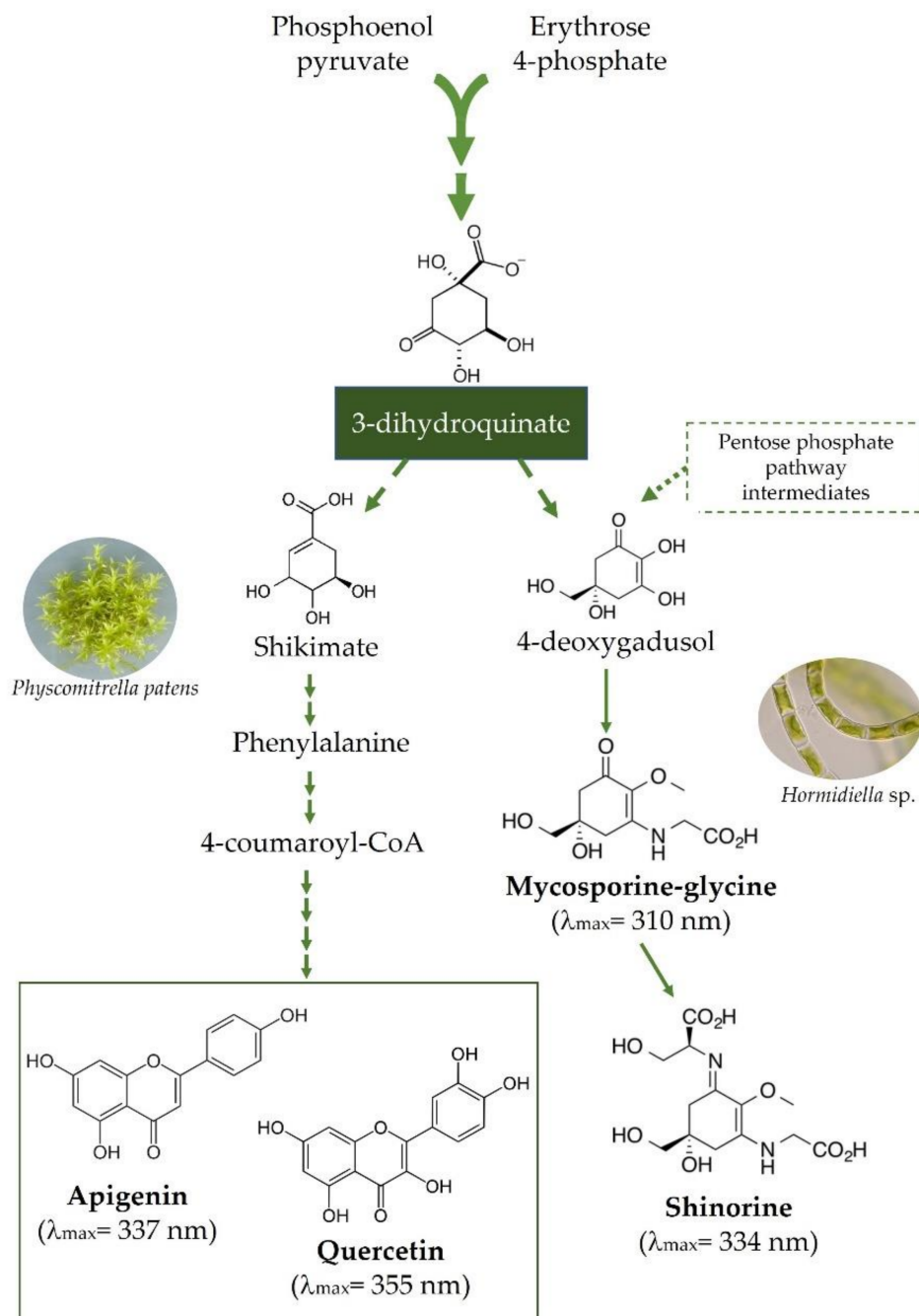
The outstanding ability of terrestrial plants to adapt to this “ever-changing” new environment has depended not only on the evolution of a pre-existing molecular toolkit but largely on the impressive chemical diversity originated by the rise of a huge number of specialized metabolic pathways <sup>[32][33][34]</sup>. The pivotal role of specialized metabolism in the successful responses of plants to environmental stressors also depends on the huge numbers of metabolites synthesized by different taxa. It is long known that each specialized metabolite class serves a multiplicity of functions in plant-environment interaction <sup>[35]</sup>, changing with the plant developmental stage and the type and intensity of environmental injuries <sup>[36][37][38]</sup>. Indeed, these metabolic networks enable plants' diversification, biotic interactions, and, to a greater extent, the occupation

of several niches <sup>[34]</sup>. Therefore, the multi-functionality represents an effective way to reduce the metabolic cost of specialized metabolite biosynthesis <sup>[39]</sup>, being, indeed, a widespread property of most secondary metabolites <sup>[40]</sup>.

Researchers examine here the multi-functionality of flavonoids, the ancient class of secondary metabolites synthesized through a branch-pathway of the general phenylpropanoid metabolism, which is unique to land plants <sup>[41][42]</sup>, in the “plant terrestrialization”. The primary functions of flavonoids during the water-to-land transition are still uncertain <sup>[41][42]</sup>. This originates from (1) the inherent ability of flavonoids to serve multiple functions in the response of plants to environmental stimuli and (2) the contemporary action of novel environmental stressors plants faced in the terrestrial habitat <sup>[37][43][44][45][46][47]</sup>. Researchers reason on the environmental drivers that were mostly responsible for the rise of the flavonoid metabolism, a pre-requisite to unveil their primary roles during the early steps of plant terrestrialization.

## **2. A “Revolutionary” Molecular Innovation: The Rise of Flavonoid Metabolism during Water-to-Land Transition of Plants**

One of the most intriguing molecular innovations that accompanied the water-to-land transition of plants was the replacement of the mycosporine-like amino acids (MAAs) metabolism, typical of streptophytic algae, by the flavonoid biosynthetic pathway (**Figure 1**), a common feature of all extant land plant taxa . Actually, there is evidence of the occurrence of early genes of the phenylpropanoid pathway, such as those involved in lignin and coumarin biosynthesis, in algal relatives closest to land plants <sup>[41][41]</sup>. This was of pivotal value for cell wall reinforcement and for the initial steps of both plant vascularization and defense, allowing their successful growth and development on land <sup>[48]</sup>. Indeed, the localization of phenolic compounds in different cell organelles in comparison to the predominantly cytoplasmatic position of MAAs <sup>[49][50]</sup> supports the importance of phenolics in the early steps of land conquest. Researchers suggest that the presence of both MAA <sup>[51]</sup> and phenylpropanoid metabolism <sup>[41]</sup> in clades sisters of the early land plants was an expensive adaptation strategy, and it is likely due to reminiscence of the evolution of both basal and highly branched streptophytic algae in nutrient-rich habitats. Indeed, it is speculated that early land plants were firstly dependent on MAAs instead of flavonoids as UV protectants <sup>[52]</sup>. Researchers observe that while flavonoids are merely carbon-based compounds, MAAs have nitrogen atoms in an amino-cyclohexanone or amino-cyclohexenimine core skeleton <sup>[50]</sup> (**Figure 1**). Therefore, it is conceivable that when plant ancestors moved to land, the MAA metabolism was unfavored and further definitively lost because of the large deprivation of nitrogen (as well as phosphorous) and water in land soils <sup>[2][53]</sup>. This “saving strategy” <sup>[54][55]</sup> allowed the nitrogen to be fully available for sustaining the growth of early plants in nutrient-poor terrestrial habitats. Indeed, several studies have shown a positive correlation between flavonoids’ biosynthesis and nitrogen depletion <sup>[56][57]</sup>, and a high C/N ratio has been reported to promote the accumulation of flavonols <sup>[58]</sup>. It is suggested that, despite the biosynthesis of flavonoids requiring high-energy consumption, their preferential accumulation might represent a “power drain valve” in a scenario of higher solar irradiation <sup>[59][60]</sup>, such as that faced by early plants. However, the matter is much more complex than researchers discuss here. As speculated by Harholt et al. <sup>[10]</sup>, the Streptophyta algae were “terrestrial from the beginning”, which is consistent with the rise of phenylpropanoid metabolism in several of these lineages. Nonetheless, researchers note that Charophyceae ancestors of land plants first colonized moderately moist habitats near freshwater, then gradually moved into drier lands <sup>[54][61]</sup>.



**Figure 1.** A synthetic diagram showing the metabolic pathways of mycosporine-like amino acids (MAAs, here exemplified as the mycosporine glycine and shinorine) and flavonoids (here represented by the flavone apigenin and the flavonol quercetin). The two pathways diverge early in the shikimate pathway. Mycosporine glycine and shinorine have, on average, molar extinction coefficients 80% higher than those of apigenin and quercetin over the UV-B portion of the solar spectrum (280–315 nm, G. Agati personal communication).

The replacement of nitrogen-containing MAAs with carbon-based products synthesized by the “late” flavonoid pathway, particularly the flavonol branch, was, therefore, a molecular event of outstanding significance during plant terrestrialization [30][62], although this matter has not received the deserved attention in the pertinent literature yet. The nutrient-centered hypothesis for the rise of flavonoid metabolism outlined above is reasonable but also raises a series of concerns that needs deep analysis. For instance: (i) it is necessary to determine which are the benefits associated with flavonoid metabolism in primitive terrestrial plants that were facing nutrient and water-deficient soils; (ii) it moves to the background of the UV-B centered hypothesis, i.e., the increase in UV-B irradiance was the evolutionary environmental driver responsible for the rise of the flavonoid metabolism.

### 3. Arbuscular Mycorrhizal Associations: A Central Event in Plant Terrestrialization Aided by Flavonoids

As outlined above, one of the most severe challenges faced by early land plants was the drastic reduction in the availability of water and nutrients [63][64]. Once again, land plant ancestors were already equipped with a toolkit potentially enabling their adaptations to land, which includes their ability to form symbiotic associations with fungi and bacteria [65].

This is intriguingly in line with the findings that nutrient-impovertished-ancient soils are indeed hotspots of plant biodiversity [66][67]. It is also consistent with the recent suggestion that ancestral and modern streptophyte algae could recognize fungi since they have homologous genes of LysM-RLK receptors, through which land plants recognize fungi [65][68][69]. However, even the most branched/complex algae miss other genes required for mycorrhizal association (MA), including those involved in the formation of arbuscules [70]. In fact, mycorrhizal symbiosis is a shared derived character, unique to land plants [65], playing a key role in the terrestrialization 450 million years ago [71][72][73]. The current paradigm is that the earliest rootless terrestrial plants coevolved with Glomeromycota arbuscular mycorrhiza fungi that, in exchange for plant photosynthates, enhanced their access to mineral nutrients and water [74][75][76][77]. There are few examples of AM or similar associations in streptophytic algae [69], whereas liverworts, hornworts, and lycophytes have recently been shown to form symbioses with members of two ancient fungal lineages: arbuscular mycorrhizal fungi of the Glomeromycotina and the symbiotic fungi of the Mucoromycotina [72][78]. Even if recent reports have revealed that fungi associations between liverworts and members of the Glomeromycotina are particularly few [79], a limited number of species have been studied so far [80]. The outstanding significance of arbuscular mycorrhiza fungi in assisting not only the water-to-land transition [81] but mainly in the expansive conquest of land by plants is also well exemplified by the observation that more than 80% of plant species form AM [82][83]. Notably, a study conducted with members of the different plant groups revealed that all the gymnosperms surveyed were mycorrhizal, most of them obligate [84], which was attributed to their evolution in nutrient-poor habitats. Moreover, there is compelling evidence that even symbioses between “modern” flowering plants and nitrogen-fixing bacteria (e.g., *Rhizobium*) must probably have evolved from the ancient AM symbiosis since several of the pathway signals are common between both biological interactions [75][85].

Auxin is a major regulator of plant growth and developmental processes, and it is a central modulator/regulator in AM symbiosis [86]. Increased auxin level in colonized cells has promoting effects on hyphal branching (possibly by weakening the cell wall) and, consequently, on arbuscule incidence [87][88]. There is also evidence of auxin involvement in the early stages of AM formation, e.g., during pre-symbiotic signal exchange [89], in part through the control of the strigolactone levels [90]. The feedback regulation of the host IAA biosynthesis offers strong support to the tight auxin-AM relationship. This mechanism avoids the excessive auxin accumulation in colonized cells and modulates the subsequent auxin-induced gene expression, both contributing to the phenotypical changes during mycorrhizal colonization [88][91].

The strong dependence of AM on the auxin perception and signaling highlights the importance of endogenous regulators of this hormone, such as the flavonoids [92][93]. Actually, several secondary metabolic pathways are interconnected with phytohormone networks, making most specialized metabolites active in plant growth and development regulation, besides their general metabolic function [34]. Flavonoids have long been reported to be involved in AM formation [94][95][96][97], being active in root colonization, spore germination, hyphal growth, and branching [98][99][47]. Nonetheless, the molecular mechanisms that drive the effects of flavonoids in AM are largely unexplored. It is conceivable that the flavonoid-induction of AM partially involves the regulation of local auxin levels (by acting on its transport and catabolism) [100] and of the level of downstream components of the auxin signaling pathway, as well known to occur in flavonoid-induced nodulation [101][102]. As outlined above, some features of root nodule endosymbiosis have been likely recruited from the more ancient AM symbiosis [103][104], and there is compelling evidence that flavonoids act as both essential signals for the establishment of legume nodulation and prime candidates in AM symbiosis [105]. The observation that flavonoid aglycones are much more active than flavonoid glycosides in the promotion of AM, likely through the inhibition of auxin transport, similarly to what is observed during nodulation [106], further corroborates the idea of a strong relationship between flavonoids, auxins and AM [98].

Overall, this is consistent with the relatively old suggestions that flavonoids play a crucial role as developmental regulators [107][108], which is closely linked to their ability to modulate phytohormone signaling pathways, as also recently shown for the ABA signaling network [109][110]. As already reported, this signaling ability is deeply dependent on the capacity of flavonoids to regulate “key downstream” components of phytohormone signaling, such as H<sub>2</sub>O<sub>2</sub> and a range of protein kinases, including PID and mitogen-activated protein kinases (MAPKs) [30][108]. In general, this supports the idea of a primary function of flavonoids as developmental regulators in both the process of plant terrestrialization and the subsequent steps toward drier habitats.

## 4. Conclusions

Plants were challenged against a wide range of novel environmental pressures when moving to land. The excellent capacity of plants to adapt to the harsh terrestrial habitat has depended on both the evolution of a pre-existing molecular toolkit and the rise of a huge number of specialized metabolites. Among the latter, the replacement of MAAs with flavonoids was an extraordinary molecular innovation, producing more than 9000 different flavonoid structures known to date. Modern land plants are capable of finely modulating flavonoid biosynthesis depending on the type and intensity of

environmental stressors. In addition, the occurrence of flavonoids in different tissues and subcellular compartments well explains their ability to play multiple functions in response to environmental stimuli. The multiple roles served by a nascent flavonoid metabolism during the “early steps” of plants in a land environment were crucial. Although these molecules undoubtedly allowed primitive plants to effectively deal with the most damaging solar wavelengths by acting as both UV filters and ROS scavengers, it is unlikely that these were their most prominent function in the process of terrestrialization. Indeed, the benefits associated with the replacement of MAAs (excellent UV filters) with flavonoids mostly have involved the ability of these last to modulate phytohormone signaling and to assist the plant-fungus symbiosis, which is essential to plant development in the “new world” scarce of water and nutrients.

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