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Review

Mycorrhiza-Mediated Modulation of Plant Coumarins' Immune Regulating Properties

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Abstract

Plant root systems closely collaborate with mycorrhiza as a specialized microbiota that encodes functions in support of the host's nutrition, growth, development, and immunity. Mycorrhizal systems participate in signaling events and modulation of biosynthetic pathways. Mycorrhiza-elicited production of various secondary metabolites plays a vital role in intertissue communication in plants. Mycorrhizal fungi influence the composition, activity, and pharmacological properties of these metabolites. Plant-derived coumarins could be considered novel players in the chemical communication between the mycorrhizal fungi and the plant, unexplored in this respect. Selective antimicrobial properties of coumarins in turn shape the mycorrhiza, resulting in promotion of healthy development in the plant, thereby capable of improved biosynthesis of the pharmaceutically beneficial coumarins. Several studies highlight the role of lactones in the establishment of host–mycorrhiza interactions. The lactonic scaffold of coumarins can serve as one of the underlying mechanisms behind the immunomodulating traits. Upon perception, coumarins induce intensive hyphal branching in the mycorrhizal fungal mycelia, thus increasing the frequency of host plant contact and interaction, and mycorrhiza development. Mycorrhizal fungi upregulate this secondary metabolite's biosynthesis gene expression in the host plant, ultimately leading to the targeted coumarins' enhanced production. Plant-derived coumarins exert selective pressure on the rhizosphere microbiota, and antimicrobial traits of coumarins are inevitably involved; however, the mechanisms underlying these processes remain to be clarified. Immunomodulating properties of the selected phytocoumarins in relation to their antioxidant, metal chelating, anti-inflammatory, and anticancer abilities are considered in this review in terms of the chemical nature of the given derivative compound.

Keywords: immune response; therapeutics; coumarins; lead compounds; plant metabolites; mycorrhizal fungi; plant–fungal communication

1. Introduction

The health and balance within the human immune system are considerably influenced by ingredients of medicinal and nutritional plant resources. Plant secondary metabolite production can be elicited by the associated mycorrhizal fungi as a kind of plant–microbe interaction. Considering mycorrhizal attributes and their relations with host plants is essential for the isolation of bioactive compounds and biotechnological applications. The secondary metabolites, medicinal ingredients exhibiting immune-regulating properties, are produced as a result of various physiological activities [1] coordinated in plants by their communication with microorganisms. Interaction with arbuscular mycorrhizal (AM) fungi is established to be the most widespread plant mutualism, in which about 90% of all land plants participate [2]. AM fungi are therefore the ubiquitous plant symbionts that enhance host growth and yield by facilitating the uptake of nutrients and water, and influence the plant secondary metabolites accumulation in a direct or indirect manner.

Bioactive coumarins occupy an eminent position among plant metabolome constituents. Coumarin derivatives have been identified as important players in the plant–microbiome community only recently. Mycorrhizal fungi-induced signaling compounds, including coumarins, act as mediators in the communication between roots and shoots in plants [3]. Optimized coumarin-based pharmaceuticals have shown improved immunostimulating characteristics [4,5]. Many studies have highlighted the capability of coumarin derivatives to regulate the immune system, evaluated in both *in vitro* and *in vivo* models of disease, such as inflammatory and neurodegenerative disorders, and selected types of cancer. While the literature offers multiple examples of successfully integrated coumarins in plant culture improvements and in drug development, to our best knowledge, there are no works considering both aspects in relation to each other. To address this gap existing in the current knowledge, this review aims to synthesize and critically consider the outcomes from the previously published studies on how the metabolic alterations in mycorrhizal plants could be exploited to obtain secondary coumarin-structured metabolites of pharmaceutical interest. According to this objective, an overview of various phytocoumarins in two interconnected principal aspects, as

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plant health inducers and as potential lead compounds for immunomodulating medications, has been performed. The related limitations, potential applications, and future perspectives have been discussed.

2. Materials and Methods

This review was undertaken by extracting the findings of the relevant works published in international electronic databases, including ScienceDirect, Scopus, Springer, PubMed, Web of Science, and Russian Science Citation Index (RSCI). The databases were thoroughly searched, and the relevant publication records were selected based on the keywords in accordance with the purpose of this study, as follows: natural compounds, coumarins, secondary metabolites, biosynthesis, mycorrhizal fungi, mycorrhizal plants, pathogenic bacteria, antimicrobials, antioxidant activity, and fungal biotechnology. This review follows the framework of collected articles published between 2000 and 2025 in the form of original research articles, articles with their full text and data available, and studies that explore the pharmacological effects of coumarins in various types of diseases. Following a common search strategy, reference lists of included articles and relevant reviews were searched for any additional publications not captured.

3. General Forward to Coumarins and Their Biological Roles

Coumarins belong to a class of compounds with a key bicyclic heterocycle, 2*H*-chromen-2-one (2*H*-1-benzopyran-2-one), and are among the secondary metabolites of plants and several microorganisms. The coumarin backbone is composed of a benzene aromatic ring fused to a condensed six-membered lactone ring. Selected representatives of this class of secondary metabolites promising as candidate drugs display potent pharmacological traits, low toxicity, high bioavailability, and better curative effects. Numerous attempts have been made to develop anticoagulant, antineurodegenerative, antidiabetic, analgesic, antimicrobial, antioxidant, anti-inflammatory, and anticancer drugs based on coumarin derivatives [6].

Coumarins have been considered as promising drug leads, versatile scaffolds for bioactive substances [7], anticancer agents [8,9], innovative agricultural antibacterial ingredients [10,11], combined with the current application prospects for coumarins in immunomodulatory compositions.

Phytochemicals with anti-inflammatory properties have been reported to succeed as novel therapeutics for the treatment of different inflammatory disorders, an increasing global health concern [12]. Coumarins have demonstrated efficacy in complementary therapy by reducing the dose-dependent undesirable effects and minimizing the adverse impact of the synthetic pharmaceuticals. Coumarin and its derivatives possess anti-inflammatory and antioxidant properties, making them applicable to an auxiliary treatment, for instance, of inflammatory bowel illnesses [13], one class of autoimmune disease accompanied by inflammation affecting the digestive and immune systems.

4. Multifaceted Role of Coumarins in Human Health With Specific Impact on the Immune-Mediated Disorder Treatment

Inflammation is a response of the body toward tissue injury, wounds, irritants, infection, and induced oxidative stress. It is mainly triggered by non-specific and specific immune responses to stand in the way of inflammation-causing factors. Oxidative stress seems to be a major contributing factor to the development of inflammatory processes and abnormal immune responses. Coumarins' therapeutic potential in regulating immunological and inflammatory responses is supported greatly by these compounds' antioxidant properties. Owing to their anti-inflammatory and antioxidant abilities, coumarins can modulate the tumor necrosis factor-alpha (TNF-α) and nuclear factor-kappa B (NF-κB) signaling pathways, attenuate excessive immune activation and reduce inflammatory disease-related chronic inflammation [12]. TNF-α is recognized as a major inflammatory cytokine that mediates systemic inflammation and immune responses [14]. The NF-κB pathway inhibition stops the production of cytokines necessary to initiate the inflammatory reaction.

By managing oxidative stress and apparently reducing chronic inflammation, coumarin derivatives can modulate immune responses [15]. Unlike conventional chemically produced drugs frequently targeted to a single pathway and associated with adverse toxicity-related effects, such phytochemicals as plant and fungal coumarins act through a multitarget approach that potentially improves therapeutic outcomes [16].

Psoralens enter the furanocoumarin (or furocoumarin) chemical group, principally taken up by fusion of the benzopyrone nucleus (Fig. 1a) to a furan ring, and detected in different cultured plants [17]. A angular isomer of psoralen (Fig. 1b) is angelicin (Fig. 1c), an angular furanocoumarin, and both isomers are parental compounds of the pharmaceutically valued derivative compound series. Natural coumarins such as bergapten (5-methoxypsoralen) (Fig. 1d) and methoxsalen (8-methoxypsoralen, or xanthotoxin) (Fig. 1e), along with nodakenetin (marmesin) (Fig. 1f) and imperatorin (Fig. 1g), are referred to as the linear furocoumarins according to a linear psoralen skeleton arrangement.

Psoralen derivatives exhibit anti-tumor activity by influencing different intracellular signals [17,18]. Interestingly, the plants studied so far have never been found to produce only angular furanocoumarins [19]. Either both isomer types or the linear one alone have been detected in a given plant species. Psoralens demonstrate various modes of action, including antagonistic effects toward metabolic

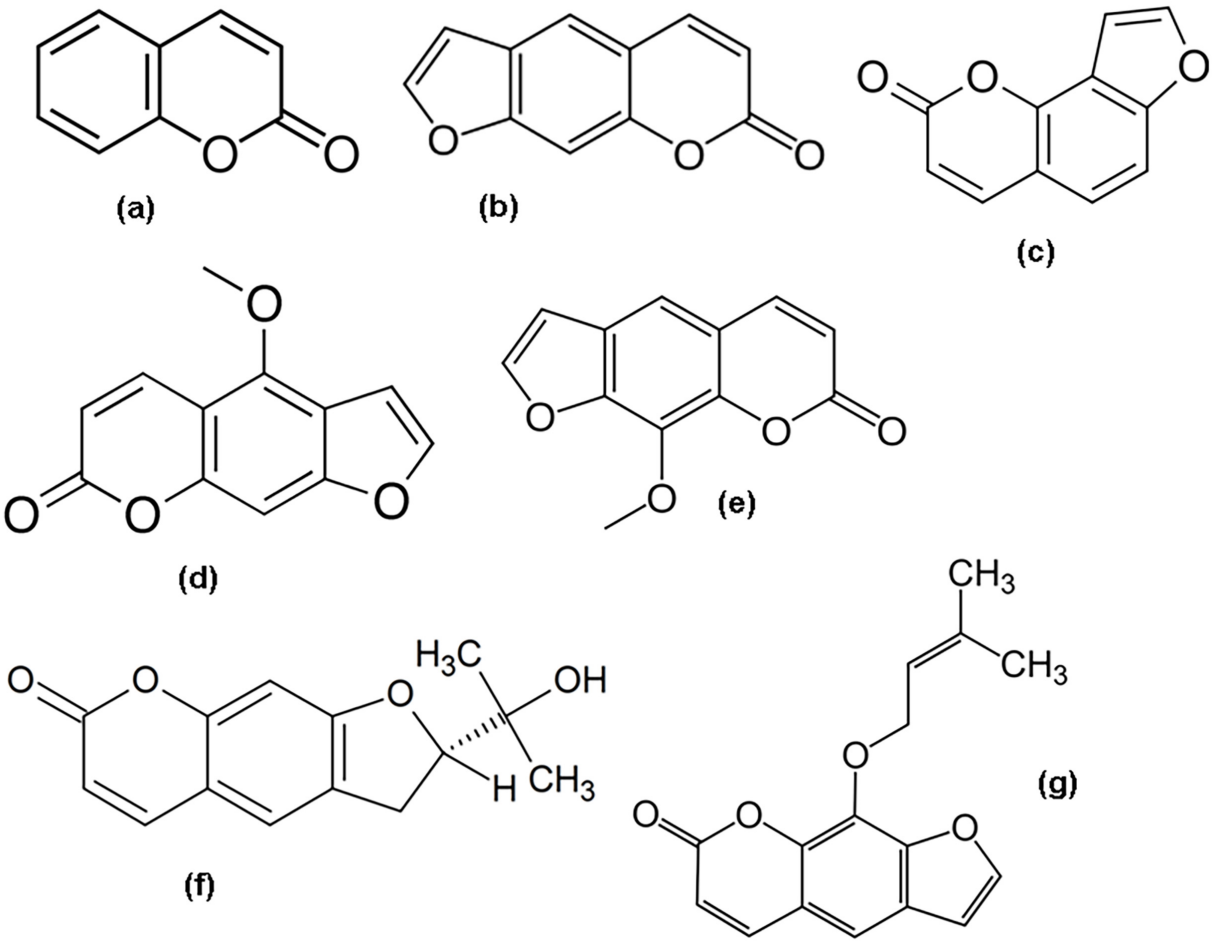


Fig. 1. Structural formulae of coumarins sharing a bicyclic and tricyclic aromatic scaffold. (a) Coumarin; (b) psoralen; (c) angelicin; (d) bergapten; (e) methoxsalen; (f) nodakenetin; (g) imperatorin.

pathways, interference with cell cycle development, and growth factor mitogenic signaling [17].

Psoralen congener compound, coumarin isopimpinellin (Table 1, Ref. [19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36, 37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55, 56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73]) isolated from the fruits of *Ammi majus* was tested via selected human tumor cells [20] and revealed the ability to display inhibition of cell cycle and to trigger apoptosis. Esculetin (6,7-dihydroxycoumarin) and esculin (esculetin 6-O-glucoside) found in *Fraxinus ornus* leaves present one example of a coumarin aglycone and a coumarin glycoside, respectively (Table 1). Esculetin possesses promising multifaceted therapeutic potential [21]. This dihydroxycoumarin considerably impacts the secretion of inflammatory mediators and oxidative stress. Through esculetin action in rats with streptozotocin-induced Alzheimer's disease, neurotoxicity was mitigated by the inhibited levels of NF-κB, and by the increased cellular resistance to oxidants [22].

Another example is scopoletin (7-hydroxy-6-methoxy-2*H*-1-benzopyran-2-one) and its glucoside scopolin (7-(β-D-glucopyranosyloxy)-6-methoxy-2*H*-1-benzopyran-2-one). Scopoletin (Table 1) is found in many plants, including widely grown crops [23], and exhibits antimicrobial, antioxidant, viricidal, and insecticidal activity [24]. Scopoletin has been explored as a phytoalexin from *Nicotiana tabacum* L. [25]. Numerous *in vivo* studies have evaluated esculetin and scopoletin as coumarins with a broad range of pharmacological effects associated with the regulation of oxidative stress [26,27].

Osthole (Table 1 and Table 2, Ref. [14,39,40,42,50,53,58,67,74,75,76,77,78,79,80,81,82]), a prenylated coumarin found in the mature fruit of *Cnidium monnieri* Cusson, decreases the immunological response of lipopolysaccharide-stimulated macrophages by blocking the formation of reactive oxygen species among other pathways, affecting immune cells' activity and cytokine production via modulating the immune system [28]. Osthole is capable of inhibiting NF-κB-related signaling and reducing pro-inflammatory cytokine production in various *in vitro* models [29,30,31].

Coumarin wedelolactone (Table 1) produced in several plant species (*Blainvillea acmella* (L.) Philipson, (syn. *Eclipta prostrata* Lour.), *Sphagneticola calendulacea* (L.) Pruski (syn. *Wedelia calendulacea* Less)) suppresses NF-κB activity, which leads to diminished lipopolysaccharide (LPS)-caused inflammation in mouse embryonic fibroblasts [32]. Plant *Eclipta alba* leaves also contain wedelolactone, which upregulates estrogen receptor (ER) signaling and heat shock protein Hsp60 expression [33,34], disrupts the mitochondrial membrane potential, leading to downregulation of the anti-apoptotic protein X-linked inhibitor of apoptosis protein (XIAP), and ultimately to apoptosis. On this pathway, a wedelolactone derivative inhibits MCF-7, T47D, and MDA-MB-231 cancer cell lines by stimulating ER signaling [35], thus possessing promising anticancer activity [36].

The angular furocoumarins subgroup includes angelicin (Tables 1,2). This compound stimulates the NF-κB pathway and decreases IL-6 and TNF-α pro-inflammatory cytokine markers, thus revealing anti-inflammatory efficacy in neurological and respiratory diseases [37]. Antioxidant capacity allows angelicin to exhibit a profound protective impact on neural cells by attenuating the neuronal cell damage induced in the course of hydrogen peroxide treatments. Angelicin offers the features of a good candidate for further human-model research into the mechanisms of its action. Angelicin's cardiovascular advantages are also documented. This agent mediates the shifts in expression of various inflammatory genes in rats [19]. Research into the mechanism of angelicin's anti-inflammatory traits has shown that angelicin actively participates in the NF-κB pathway by means of blocking the translocation of NF-κB into the cell nucleus. Similar findings also follow from other works dealing with inflammation in asthmatic mouse models. The researchers underline strong evidence of the NF-κB pathway inhibition involvement in angelicin's anti-inflammatory properties [38].

Xanthotoxin (8-methoxypsoralen) (Tables 1,2) exhibits anti-inflammatory properties by modifying the corresponding pathways and decreasing the yield of inflammatory agents. This coumarin influences the immune cells' activity through modulating the immune system [39,40], and lowers neuroinflammatory cytokine levels in LPS-induced amnesia in mice [41].

Imperatorin (Tables 1,2) significantly reduces nitric oxide (NO) production, displays antioxidative efficiency in animals under the oxidative stress condition activated with 12-O-tetradecanoylphorbol-13-acetate and LPS-inspired macrophages [42], ameliorates the induced colitis NF-κB-mediated pro-inflammatory response, and reveals some neuroprotective benefits [43]. Imperatorin, found in the roots of *Angelica dahurica*, depicts different pharmacological traits, including the anti-tumor activity [42]. It has also been found that this furanocoumarin from the Bael fruit (*Aegle marmelos* L.) exhibits excellent anti-tyrosinase activity [44].

The geometric isomer of imperatorin, isoimperatorin (Tables 1,2), enters the 6,7-furanocoumarin subgroup of coumarin compounds and is abundant in the Umbelliferae family. This furanocoumarin is present in *Citrus limon* (L.) Burm., *Citrus limonia* Osbeck, *Pastinaca sativa* L., *Petroselinum crispum* (Mill.) Nyman, *Foeniculum vulgare* Mill. [83]. Isoimperatorin has been found to possess anti-inflammatory, analgesic [45], anticancer properties [46], and inhibits the TNF-α-stimulated expression of vascular cell adhesion molecule-1 (VCAM-1) in human endothelial cells [14]. Isoimperatorin could be a potential chemopreventive agent [47], as well as a herbal medicine to treat allergic asthma [45]. This substance influences the signaling pathways important in adipogenesis [28] and reveals antihypertensive ability [48]. A linear furanocoumarin core of bergamottin (5-geranoxypsoralen) (Table 1) is functionalized with the geraniol-structured side chains [36]. It reveals antioxidative, anti-inflammatory, and anticancer properties [49].

Decursin (Tables 1,2) is a linear pyranocoumarin-structured compound, prevailing among the coumarins isolated from roots of many *Angelica* species. Decursin displays colon-protective, anti-inflammatory effects [50] and neuroprotective potential [74]. Under exposure to the decursin-enriched solution, the colon tissue affected by dextran sodium sulfate-induced ulcerative colitis in mice relieves weight loss, diminishes disease activity indices, and reduces colon shortening. Decursin identified in *Angelica gigas* Nakai has been shown to diminish the melanin production linked to the reduced intracellular activity of tyrosinase [75].

Isomeranzin (Tables 1,2) from the *Murraya* plant species has been found to inhibit sepsis brought on by LPS. In these *in vivo* experiments, isomeranzin application attenuated tissue damage and lowered the inflammatory cytokine level. This coumarin could be useful for treating experimentally induced colitis [51]. Isomeranzin therapy assists in attenuating many clinical and histological indications of inflammation [52,84]. Isomeranzin isolated from the roots of *Murraya paniculata* (L.) Jack has been explored for its inhibitory effect on LPS-induced nitrogen oxide(II) production in BV-2 microglial cells [76]. Anomalin (Tables 1,2) is an example of an angular pyranocoumarin. It is detected in the plant *Saposhnikovia divaricata* (Turcz.) Schischk, and demonstrates anti-inflammatory, antioxidant, and anticancer properties [53]. In the *in vitro* LPS-induced macrophage model, this coumarin decreases NF-κB binding to DNA and the inflammatory response, and protects against the acute lung damage caused by LPS. Anomalin induces apoptosis and inhibits cell division to cause cytotoxic effects.

Table 1. Coumarins with immune-mediated therapeutic potential produced in plant aerial parts, fruits, and seeds.

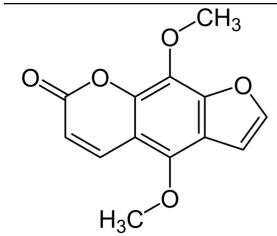
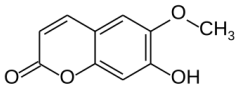
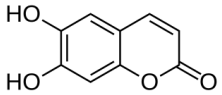
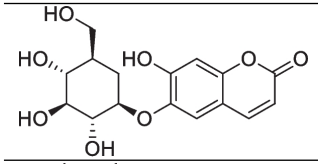
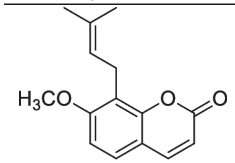
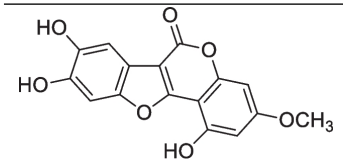
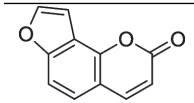
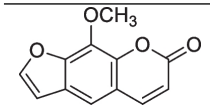
Chemical structure	Trivial and IUPAC name	Plant source	Ascribed medicinal properties	Ref.
	Isopimpinellin (4,9-Dimethoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one) (5,8-methoxypsoralen)	*Ammi majus* L., *Cnidium monnieri* L.	Chemoprevention and treatment of primary osteosarcoma, high activity against human acute promyelocytic leukemia cells (HL-60), modulates melaninogenesis in melanoma cells in mouse model	[20,62,63]
	Scopoletin (7-hydroxy-6-methoxy-2H-1-benzopyran-2-one)	*Angelica dahurica bolting plants*, *Ipomoea batatas* (L.) Lam., *Solanum tuberosum* L., *Melilotus albus*	Antimicrobial, antioxidant, viricidal, and insecticidal activity	[23,24,25,26]
	Esculetin (6,7-dihydroxy-2*H*-1-benzopyran-2-one) (6,7-dihydroxycoumarin)	*Fraxinus ornus, Fraxinus rhynchophylla* Hance, *Citrus limon* (L.) Osbeck, *Euphorbia lathyris* L., *Aesculus hippocastanum* L.	Antioxidant, anti-inflammatory, antiapoptotic activity, and anti-Alzheimer action	[21,22,59]
	Esculin (6-(β-D-glucopyranosyloxy)-7-hydroxy-2*H*-1-benzopyran-2-one)	*Aesculus hippocastanum* L. (tree horse chestnut)	Anti-inflammatory activity	[27,59,64]
	Osthole (7-methoxy-8-(3-methylbut-2-en-1-yl)-2*H*-1-benzopyran-2-one)	*Cnidium monnieri* Cusson (mature fruit)	Influences immune cell activity and cytokine production via modulating the immune system, regulates the expression of inflammatory mediators, reverses oxidative stress	[28,29,30,31]
	Wedelolactone (1,8,9-trihydroxy-3-methoxy-6*H*-[1]benzofuro[3,2-*c*][1]benzopyran-6-one)	*Blainvillea acmella* (L.) Philipson, (syn. *Eclipta prostrate* Lour.); *Eclipta alba*, *Sphagneticola calendulacea* (L.) Pruski (syn. *Wedelia calendulacea* Less)	Suppresses NF-κB activity, diminishes an LPS-caused inflammation in mouse embryo fibroblasts, possesses anti-diabetic and hepatoprotective properties, exhibits antiproliferative and apoptosis-inducing effects in cancer cells	[32,33,34,35,36,50]
	Angelicin (2*H*-furo[2,3-*H*][1]benzopyran-2-one)	*Angelica shikokiana*, *Bituminaria bituminosa*, *Cicuta virosa*, *Ficus carica*, *Heracleum rawianum*, *Psoralea corylifolia*	Anti-inflammatory efficacy in neurological and respiratory diseases, shifts the expression of various inflammatory genes in rats	[19,37,38,65,66,67,68,69]
	Xanthotoxin (methoxsalen, oxsoralen) (9-methoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one)	*Ptilimnium capillaceum* (Michx.) Raf. (syn. *Ammi majus* Walter), *Ficus carica*, *Heracleum platytaenium*	Anti-inflammatory properties, lowers neuroinflammatory cytokine levels on the LPS-induced amnesia in mice	[39,40,41,65,67,70,71]

Table 1. Continued.

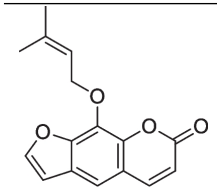
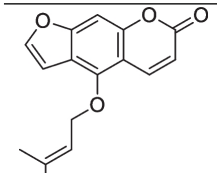
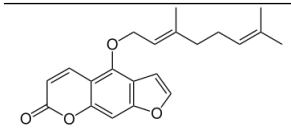
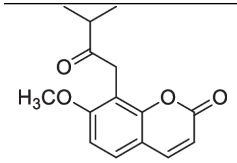
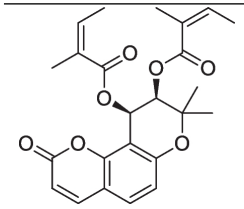
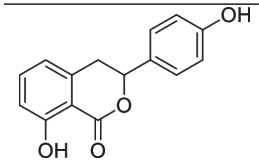
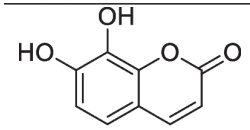
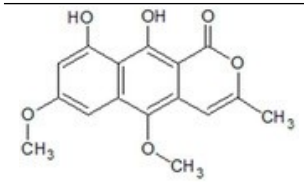
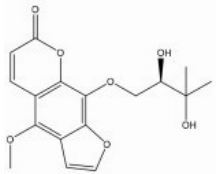
Chemical structure	Trivial and IUPAC name	Plant source	Ascribed medicinal properties	Ref.
	Imperatorin (marmelosin, ammidin, pentosalen) (9-[(3-methylbut-2-en-1-yl)oxy]-7*H*-furo[3,2-*g*][1]benzopyran-7-one)	*Foeniculum vulgare* Mill., *Angelica sylvestris* var. *sylvestris*, *Pastinaca sativa*, *Aegle marmelos* L., *Heracleum sphondylium* subsp. *elegans*	Reduces NO production, displays antioxidative effect in animals under the artificially induced oxidative stress condition, exhibits excellent anti-tyrosinase activity	[42,43,44,58,71,72]
	Isoimperatorin (5-[(3-methylbut- 2-en-1-yl)oxy]-7*H*-furo[3,2-*g*][1]benzopyran-7-one)	*Angelica dahurica bolting plants*, *Citrus limon* (L.) Burm., *Citrus limonia* Osbeck, *Foeniculum vulgare* Mill., *Glehnia littoralis*, *Pastinaca sativa* L., *Petroselinum crispum* (Mill.) Nyman, *Peucedanum ostruthium*, *Poncirus trifoliata* Raf.	Anti-inflammatory, analgesic, anti-hypertension, anti-cancer, chemopreventive properties, potential therapeutic agent for treating allergic asthma and preventing diabetes	[28,45,46,47,48]
	Bergamottin (4-{[(2*E*)-3,7-Dimethylocta-2,6-dien-1-yl]oxy}-7*H*-furo[3,2-*g*][1]benzopyran-7-one)	*Citrus bergamia* Risso & Poiteau, *Citrus paradisi Macf.*, *Citrus limonia Osbeck*, *Citrus limon (L.) Burm.*	Antioxidative, anti-inflammatory, anticancer properties	[36,49]
	Isomeranzin (7-methoxy-8-(3-methyl-2-oxobutyl)chromen-2-one)	*Murraya exotica* L.	Attenuates clinical and histological indications of inflammation, inhibits sepsis brought on by LPS	[51,52]
	Anomalin [8,8-dimethyl-9-[(*Z*)-2-methylbut-2-enoyl]oxy-2-oxo-9,10-dihydropyrano[2,3-f]chromen-10-yl] (*Z*)-2-methylbut-2-enoate	*Angelica* species, *Seseli* species, *Libanotis* species, *Saposhnikovia divaricata* (Turcz.) Schischk, *Selinum cryptotaenium*	Anti-inflammatory, antioxidant, anti-hyperalgesic, and anticancer properties, protects against the acute lung damage caused by LPS, induces apoptosis, inhibits cell division to cause cytotoxic effects	[53,73]
	Hydrangenol (3,4-dihydro-8-hydroxy-3-(4-hydroxyphenyl)-1*H*-2-benzopyran-1-one)	*Hydrangea serrata* (Thunb.) Ser.	Suppresses the LPS-induced nuclear translocation and DNA-binding of NF-κB, ameliorates colitis in a sodium dextran sulfate model in mice	[54]
	Daphnetin (7,8-dihydroxycoumarin)	*Daphne* genus	Modulates signaling pathways, reduces serum levels of proinflammatory cytokines, inhibits ROS production after LPS exposure, reduces experimental colitis, displays neuroprotective properties, including in the mouse model of Alzheimer's disease	[21,28,55,56,57]

Table 1. Continued.

Chemical structure	Trivial and IUPAC name	Plant source	Ascribed medicinal properties	Ref.
	Paepalantine (9,10-dihydroxy-5,7-dimethoxy-1H-naptho(2,3c)pyran-1-one)	*Paepalanthus bromelioides*	Intestinal anti-inflammatory activity	[51]
	Byakangelicin (9-(2,3-dihydroxy-2-methylbutoxy)-4-methoxy-7H-furo[3,2-g][1]benzopyran-7-one)	*Angelica dahurica* bolting plants	Inhibits renal inflammation, shows anti-tumor function, effectively impairs growth and motility in breast cancer cells, and induces breast cancer cell apoptosis	[60,61]

NF-κB, nuclear factor-kappa B; IUPAC, International Union of Pure and Applied Chemistry; LPS, lipopolysaccharide; NO, nitric oxide; ROS, reactive oxygen species.

Table 2. Plant coumarins with immune-mediated therapeutic potential produced in plant roots.

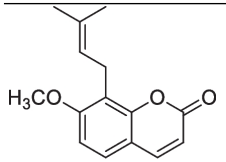
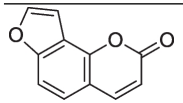
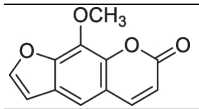
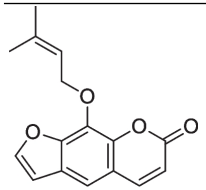
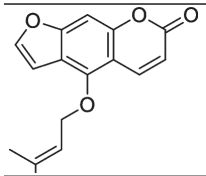
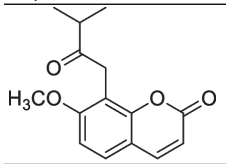
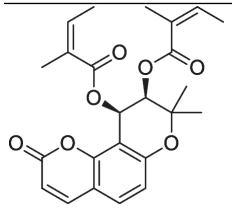
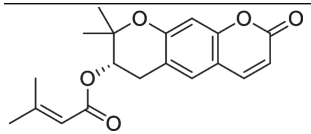
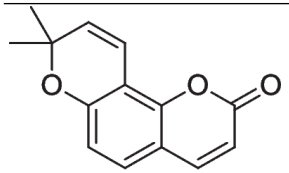
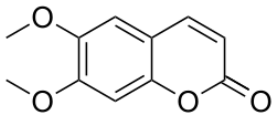
Chemical structure	Trivial and IUPAC name	Plant source	Ascribed medicinal properties	Ref.
	Osthole (7-methoxy-8-(3-methylbut-2-en-1-yl)-2*H*-1-benzopyran-2-one)	*Heracleum sphondylium* subsp. *cyclocarpum*	Anti-inflammatory properties in different inflammation models	[58]
	Angelicin (2*H*-furo[2,3-*H*][1]benzopyran-2-one)	*Heracleum maximum*, *H. meoellendorffi*, *H. persicum*, *H. paphlagonicum*, *H. sphondylium* subsp. *elegans*, *H. sphondylium* subsp. *cyclocarpum*	Anti-inflammatory efficacy in neurological and respiratory diseases, shifts the expression of various inflammatory genes in rats	[58,67,80,81,82]
	Xanthotoxin (methoxsalen, oxsoralen) (9-methoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one)	*Heracleum persicum*, *Heracleum sphondylium* subsp. *ternatum*	Anti-inflammatory properties, lowers neuroinflammatory cytokine levels on the LPS-induced amnesia in mice	[39,40,58,67,81]
	Imperatorin (9-[(3-methylbut-2-en-1-yl)oxy]-7*H*-furo[3,2-*g*][1]benzopyran-7-one)	*Angelica dahurica* (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., *Heracleum sphondylium* subsp. *cyclocarpum*	Anti-tumor, anti-colitis, and anti-arthritis activities, ameliorates the induced colitis NF-κB-mediated pro-inflammatory response, reveals some neuroprotective benefits	[42,58]
	Isoimperatorin (5-[(3-methylbut- 2-en-1-yl)oxy]-7*H*-furo[3,2-*g*][1]benzopyran-7-one)	*Cimicifugae* species (*C. acerina*, *C. dahurica*, *C. foetida*, *C. heracleifolia*, *C. racemosa*, and *C. simplex*)	Inhibits the TNF-α-stimulated expression of vascular cell adhesion molecule-1 (VCAM-1) in human endothelial cells	[14]
	Isomeranzin (7-methoxy-8-(3-methyl-2-oxobutyl)chromen-2-one)	*Murraya paniculata* (L.) Jack	Inhibitory effect on LPS-induced nitric oxide production in BV-2 microglial cells	[76]
	Anomalin [8,8-dimethyl-9-[(*Z*)-2-methylbut-2-enoyl]oxy-2-oxo-9,10-dihydropyrano[2,3-f]chromen-10-yl] (*Z*)-2-methylbut-2-enoate	*Angelica anomala* Avé-Lal., *Arachis hypogaea*, *Seseli hartvigii*, *Seseli incanum*, *Seseli resinosum*	Anti-inflammatory, antioxidant, anti-hyperalgesic, and anticancer properties, protects against the acute lung damage caused by LPS, induces apoptosis, inhibits cell division to cause cytotoxic effects	[53]
	Decursin ([(3*S*)-2,2-dimethyl-8-oxo-3,4-dihydropyrano[3,2-g]chromen-3-yl] 3-methylbut-2-enoate)	*Angelica decursiva* Franch. & Sav., *A. glauca* Edgew., *A. gigas* Nakai	Colon-protective, anti-inflammatory effects, neuroprotective potentialities, reduces the intracellular activity of tyrosinase and melanin production	[50,74,75]

Table 2. Continued.

Chemical structure	Trivial and IUPAC name	Plant source	Ascribed medicinal properties	Ref.
	Seselin (8,8-dimethylpyrano[2,3-f]chromen-2-one)	*Angelica gigas*, *Ficus erecta* Thunb., *Citrus sinensis* (L.) Osbeck, *Citrus paradisi* Macf., *Citrus limonia* Osbeck	Anti-inflammatory effects in the LPS-primed macrophage model, shows antioxidant, antibacterial, and cytotoxic activities, suppresses proinflammatory phenotype of macrophages	[77]
	Scoparone (6,7-dimethoxycoumarin; 6,7-dimethylesculetin); (6,7-dimethoxy-2H-1-benzopyran-2-one)	*Anchusa officinalis*	Anti-inflammatory, antioxidant, antibacterial activity	[78,79]

TNF-α, tumor necrosis factor-alpha.

Hydrangenol is an isocoumarin belonging to the phenol class of chemicals, i.e., dihydroisocoumarin (Table 1), broadly revealed in *Hydrangea serrata* (Thunb.) Ser. It suppresses the LPS-induced nuclear translocation and DNA-binding of NF-κB. Hydrangenol prevents structural damage of the colon, ameliorates colitis in a sodium dextran sulfate model in mice [54]. Seselin (Tables 1,2) belongs to a pyranocoumarin subclass of coumarins, an angular-structured compound isolated from the roots of fruit plants *Citrus sinensis* (L.) Osbeck, *Citrus paradisi* Macf., *Citrus limonia* Osbeck. Seselin displays anti-inflammatory effects in the LPS-primed macrophage model, as well as antioxidant, antibacterial, and cytotoxic properties. There is strong evidence of seselin application to treat inflammatory diseases by inhibiting proinflammatory mediator production and suppressing the proinflammatory phenotype of macrophages [77]. Paepalantine (Table 1) is the isocoumarin found in the capitula of *Paepalanthus bromelioides*. The intestinal anti-inflammatory activity was reported for this compound as the first coumarin implemented in an experimental model of intestinal inflammation, in a trinitrobenzene sulphonic acid model of rat colitis [51].

Daphnetin (7,8-dihydroxycoumarin) has a relatively simplified structure (Table 1) comprising two hydroxyl groups in the coumarin backbone. This compound modulates the inflammatory signaling pathways [55]. Through the elevation of Nrf2 expression, daphnetin has the effects of decreased TNF-α and IL-1β production, and inhibited ROS production after LPS exposure. This compound also offers defensive action against oxidative injury and degeneration of neurons [56]. Being endowed with antioxidant and anti-inflammatory properties, daphnetin has been examined in the mouse model of Alzheimer's disease, and has exhibited the capability of improving memory and spatial learning, and improving cognitive deficits [57]. In this way, daphnetin reduced serum levels of proinflammatory cytokines, such as interleukin-1β, interleukin-6, and TNF-α. Therefore, the researchers regard daphnetin as a suitable scaffold potentially contributing to Alzheimer's disease prevention and treatment [21].

Some plant species are commonly recognized for their remarkable anti-inflammatory properties [85,86], accompanied by a relatively high content of coumarins in plants, such as the *Heracleum* genus (hogweed plants) (Tables 1,2). Kurtul et al. (2025) [58] evaluated the extracts from *Heracleum paphlagonicum* and three *H. sphondylium* subspecies for their anti-inflammatory properties in different inflammation models. *Heracleum sphondylium* subsp. *cyclocarpum* was unequivocally estimated as the most efficient species with respect to the observed anti-inflammatory activity attributed to coumarins in *Heracleum*. The specific coumarins responsible for the considerable anti-inflammatory effect of *Heracleum sphondylium* subsp. *cyclocarpum* were detected as angelicin, bergapten, imperatorin, osthole, and xanthotoxin [58].

5. Coumarins in Plant Immunity Networks

Plants secrete increased amounts of specific secondary metabolites into the rhizosphere, including coumarins under stress conditions. These secondary metabolites play an important role in root–microbiome communication, through signaling or selective antimicrobial activity in plant–pathogen interactions [87]. The phyllospheric bacterial community, as an important part of the plant microbiome [88], contributes to plant development, performance, and health not only by increasing nutrient absorption, but also by providing the host with phytohormones, and assisting the plant's tolerance to adverse environmental conditions, including biotic stresses. Coumarins play an appreciable role as a factor in plant antagonism by inducing the plant defense responses to suppress phytopathogen infection. Beneficial bacteria supply a host plant with antimicrobial compounds and induce systemic resistance in plants.

Coumarins may play a substantial role as antioxidants under surrounding stressful conditions, including excess light exposure, owing to these compounds' ability to quench free radicals as ROS [89] at very low coumarin concentrations. A lot of research outcomes suggest that the abiotic stress-inducing agents boost the biosynthesis of very few polyphenol structures, mostly phenylpropanoid pathway metabolites with an ortho-diphenol (catechol) moiety in the benzene ring [59]. Efficient antioxidants—wedelolactone, esculetin, and daphnetin (Table 1)—could be assigned to the catechol coumarins subgroup, whose molecules comprise a catechol fragment possessing diverse biological activities, one of which is relevant to metal chelation processes [90].

Studies on the chemical nature of root exudates through exometabolomics research aimed at elucidating the exudates' inhibiting effect with respect to pathogens or stimulating effect for recruiting beneficial microbes have identified coumarins as a component of root exudates [91]. Plant resistance genes influence the increase in plant resilience to phytopathogenic attack by impacting the assembly of the microbiome beneficial for the plant. A family of transcription factors, WRKY, has been recognized as crucial regulators of plant immune responses to pathogen infection [88]. WRKY transcription factors participate in the regulation of many secondary metabolite biosynthetic pathways, such as phenylpropanoids and flavonoid derivatives, including coumarins [92], capable of regulating plant defense responses to pathogen infection. A common disease of poplar, leaf blight caused by a phytopathogenic fungus, *Alternaria alternata*, can even cause plant death in severe cases. The *PsnWRKY70* gene of *Populus* (*Populus simonii* × *P. nigra*) exhibited, in this gene-overexpressing line, increased coumarin synthesis, accompanied by changes in microbial species, favoring increased resistance to *A. alternata* infection. This phyllospheric microbial network's modulation was to a great extent triggered by the biosynthesis of fraxin and scopolin [88]. The root-specific tran-

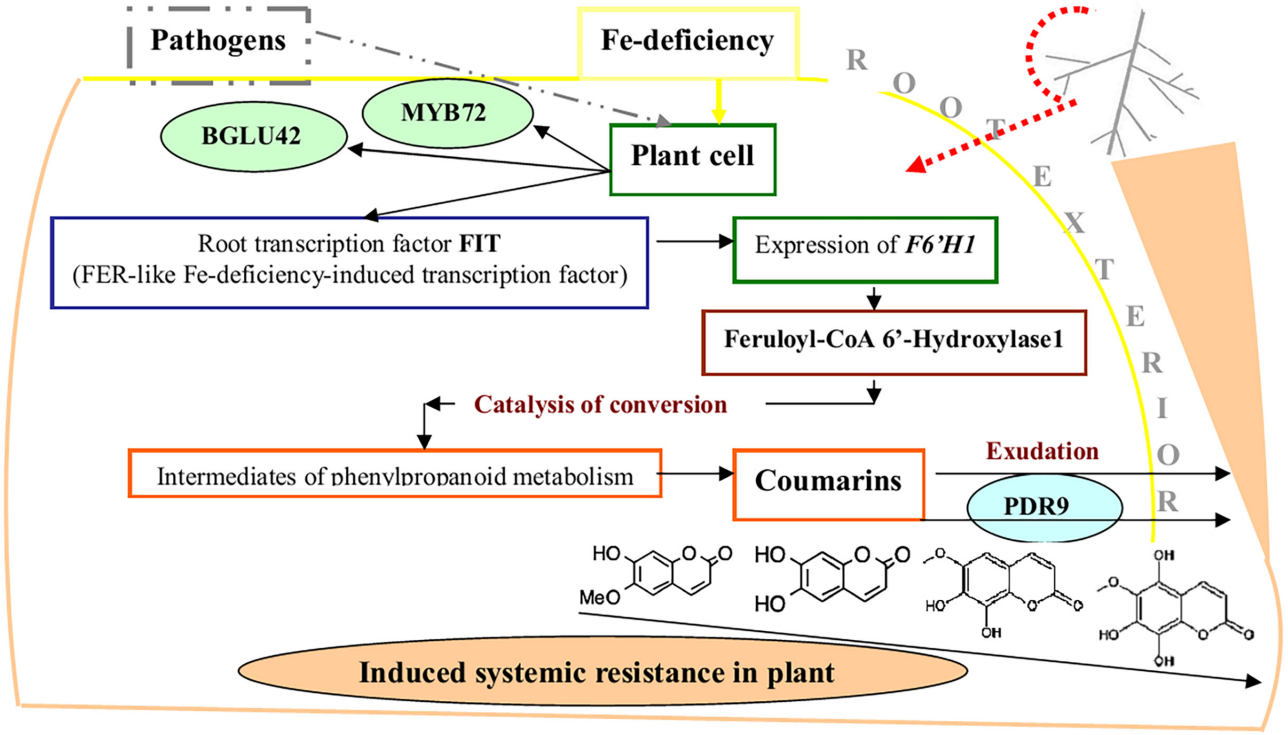


Fig. 2. Schematic representation of links between the plant coumarins, iron deficiency response, and plant immunity. BGLU42, beta-glucosidase 42; MYB72, MYB domain protein 72; PDR9, PLEIOTROPIC DRUG RESISTANCE9; FIT, Fer-like iron deficiency-induced transcription factor.

scription factor myb domain protein 72 (MYB72) and the MYB72-dependent β-glucosidase beta glucosidase 42 (BGLU42) have been identified as key participants during the establishment of induced systemic resistance (ISR) signaling triggered by different microorganisms (Fig. 2).

The role of MYB72-dependent metabolites in root microbiome assembly has been discussed in many studies [24]. It was revealed that both MYB72 and BGLU42 participate in the biosynthetic pathway of coumarins, which are dominantly present in the root exudates under iron deficiency [93]. Arabidopsis knockout mutants *myb72* and *bglu42* were unable not only to excrete Fe-mobilizing coumarins, but also to develop the rhizobacteria-mediated ISR [94]. These coumarins, vital for Fe mobilization and uptake from the soil, are synthesized via FERULOYL-COA 6′-HYDROXYLASE1 (F6′H1) through the phenylpropanoid pathway and secreted by the Fe-deficit-regulated ABC transporter PLEIOTROPIC DRUG RESISTANCE9 (PDR9) [95] into the rhizosphere [96]. Importantly, it was found that the coumarin-deficient *f6′h*1 mutant plants assembled a distinct root microbiome, indicating once again that coumarins can shape the root microbiome assembly. Comparative analysis of microbiota associated with roots of wild-type plants and roots of the mutant *f6′h*1 impaired in scopoletin biosynthesis has demonstrated that the antimicrobial and Fe-mobilizing properties of coumarins impact the assembly of the root-associated microbiome [97].

Even though plant coumarins are not directly involved in core metabolism, they share overlapping functions in microbial recruitment, signaling, and defense. Fungal signaling pathways are very similar to the route that coordinates the well-known symbiosis between the rhizobial bacteria and leguminous plants [98]. In rhizobia-leguminous plant symbiosis, the symbiotic association begins with the perception of specific root-exuded isoflavonoid compounds by the microbes, which stimulates root nodule formation [99]. The perception of specific root-exuded coumarins by soil fungi stimulates the formation of a plant host–fungal association. Plant growth-promoting rhizobacteria (PGPR) can promote plant growth by affecting the hormonal balance of plants. Among plant-associated fungi, numerous species, too, can produce indole-3-acetic acid or auxin-mimicking molecules, which play a direct role in plant growth and development. This beneficial effect can be induced by the secretion of microbial secondary metabolites that can act as hormone-like plant growth regulators. Moreover, coumarins exhibit selective antimicrobial activity, contributing to the assembly of beneficial rhizosphere microbiomes [24]. E.g., scopoletin inhibits the growth of soilborne pathogens, whereas rhizobacteria that induce systemic resistance were insensitive to its antimicrobial activity.

Induced systemic resistance is a mechanism of elevated plant defense potential, which is triggered by bene-

ficial members of the root microbiome in a wide range of plant hosts, making them resistant to various pathogenic threats. This mechanism modulates plant defense-related hormonal signaling, including salicylic acid, jasmonic acid, and ethylene [100]. Systemic activation of plant defenses is ensured by a complex network of defense-related hormone signaling pathways, which brings the message of a beneficial interaction in different plant organs, and is determined by the perception of microbial-secreted secondary metabolites, including coumarins. Induced systemic resistance has been described for many PGPR of the genera *Bacillus*, *Serratia*, as well as for plant growth-promoting fungi of the genera *Trichoderma*, *Fusarium*, *Serendipita*, and others [101].

6. Regulation of Coumarin Metabolism in Mycorrhizal Plants

6.1 Coumarins Role in Mycorrhization

Several series of bioactive substances valuable for biotechnology are typically acquired from fungi. These eukaryotes include an extremely diverse kingdom of microorganisms capable of synthesizing a lot of secondary metabolites [102], such as anticancer, antitumor, antioxidative, antibacterial, and antifungal compounds, as well as those with yet unpredicted novel traits and molecular architectures. Mycorrhiza has been designated as a mutual symbiotic association of plant roots and fungi [103]. The majority of researchers distinguish two principal types of mycorrhizae, namely endomycorrhiza and ectomycorrhiza (which does not exceed 5%), depending on the internal or external location of the mycorrhizal structures established in regard to root cells. Other distinctions and revisions have led to a detailed classification of the mycorrhizae into seven types: ectomycorrhiza, endomycorrhiza (of which 72% are arbuscular mycorrhiza), ect-endomycorrhiza, arbutoid mycorrhiza, ericoid mycorrhiza, monotropoid mycorrhiza, and orchidoid mycorrhiza [104], among which two dominant types are arbuscular mycorrhizae (AM) and ectomycorrhizae (EM). Orchidoid mycorrhizal fungi and ericoid mycorrhizal fungi form simpler (than arbuscules) intracellular structures, and their symbiotic relationships are restricted to the Orchidaceae or Ericaceae family, respectively. Therefore, the AM fungi and EM fungi are the most widespread.

AM fungi are obligate biotrophs, key taxa of belowground microbiomes [105]. With the assistance of mycorrhizal hyphae, fungi are capable of providing micronutrients for effective host plant growth, development, productivity, and yield quality. AM fungi produce arbuscules, which aid in the interchange of vitally important organic compounds and minerals. Moreover, AM fungi have been commonly reported to assist in shielding symbiont plants from adverse environments, providing nutritional support to root cells even under harsh conditions [106]. By now, mycorrhizal biotechnology has already been applied to resolve a variety of environmental and agricultural challenges. Simultaneously, the mycorrhiza-linked research focus shifts progressively to the role of AM fungi metabolites as lead compounds for different drugs [107].

Mycorrhizal fungi have the distinctive potential to convert nutritionally vital components from unavailable to available form through biochemical processes. Plant root-exuded substances could be immobilized within the fungal hyphae cell wall and stored, or modified with other substances within the cytoplasm. Alternatively, fungi could act as an elicitor, thus influencing the selected metabolic changes to biosynthesize a targeted product, even promoting the increment of its production [108]. As for the ectomycorrhizal fungi's communication with plant roots, lateral root production is stimulated even before fungal colonization or without direct fungus–plant contact, owing to diffusible fungal signals, involving different signal molecules [109]. On the one hand, such signaling leads to the enhanced root surface area beneficial for plant nutrient uptake, and on the other hand, leads to the improved fungal access to the root-exuded carbon sources. Furthermore, the production of metabolites with antimicrobial properties has been demonstrated for mycorrhizal fungi by many researchers [110,111]. The studies discussed have highlighted the biotechnological potential of mycorrhizal fungi as producers of metabolites, in which both plants and pharmaceuticals are concerned. Reportedly, there are a lot of fungal elicitors for the pharmaceutically valuable compounds derived from plants.

Plant bioprospecting studies have identified coumarins among the bioactive compounds with extensive therapeutic potentialities [34], including antitumor activity [112]. These secondary metabolites implemented in plant-based diets stimulate regulatory T cells and initiate anti-inflammatory reactions [113]. A huge amount of the data on plant endophytic fungi relates these fungal antioxidant, anti-inflammatory, anticancer activity, and other medicinal attributes to their biochemical constituents of coumarin nature [114]. As for the mycorrhizal community fungal representatives, the relevant works are very limited (Table 3, Ref. [115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131]).

The mycorrhiza-forming basidiomycetous fungi are famous for their bioactive compounds, and some of those exhibit promising immunomodulating activity. *Hericium erinaceus* is an ectomycorrhizal basidiomycete associated with Pinaceae and Fagaceae trees in the Northern Hemisphere [132]. *Hericium erinaceus* also possesses a wound-healing ability [133]. Ectomycorrhizal edible basidiomycete *Lyophyllum decastes* is known for its delectable flavor and abundant nutrients [115,116] along with a wide range of health benefits, including antioxidant [117], immunomodulating, and antitumor properties. *Lyophyllum decastes* synthesizes several coumarins at its different de-

Table 3. Biological activities ascribed to a selection of mycorrhizal fungi.

Fungus	Type	Ascribed bioactivity	Chemical evidence	Ref.
Floccularia luteovirens	EM	Antitumor activity; low-molecular-weight components inhibit lung cancer by inducing apoptosis through activating caspase-3	EM-produced small molecules, incl. coumarins, esculentoside A, 6-hydroxy-4-methylcoumarin	[127,128]
Funneliformis mosseae	AM	Different levels of bioprotection against *Phytophthora* root rot in tomato, and *Fusarium* wilt in melon	Coumarin derivative 2*H*,8*H*-Benzo[1,2-b:3,4-b']dipyran-2-one,8,8-dimethyl in root exudates of AM-inoculated *Poncirus trifoliata*	[123]
Gigaspora gigantea	AM	Antifungal activity against cosmopolitan pathogen *Puccinia striiformis*, causative agent of stripe rust	Cinnamic acid, coumarin, and esculetin in response to AM fungal inoculum	[126]
Glomus intraradices	AM	Displays allelopathic activity in *Nicotiana glauca*, *Nicotiana tabacum*	Coumarins scopoletin, its glucoside scopolin in response to mycorrhization	[129]
Lyophyllum decastes	EM	Antioxidant, immunomodulating, and antitumor properties	EM-produced abundant nutrients, polysaccharides, coumarins (scopoletin, isoscopoletin, sideretin, esculetin)	[115,116,117,118]
Morchella esculenta	EM	Antitumor potential against breast cancer	EM-produced coumarin derivative acenocoumarol	[119]
Rhizoglomus clarum	AM	Antifungal activity against cosmopolitan pathogen *Puccinia striiformis*, causative agent of stripe rust	Cinnamic acid, coumarin, and esculetin in response to AM fungal inoculum	[126]
Rhizophagus irregularis	AM	Increased resistance of the tomato shoots to necrotrophic foliar pathogen *Botrytis cinerea*	Ferulic acid, chlorogenic acid, coumarin in tomato mycorrhizal plants	[124]
Rhizophagus irregularis	AM	Antifungal activity against cosmopolitan pathogen *Puccinia striiformis*, causative agent of stripe rust	Cinnamic acid, coumarin, and esculetin in response to AM fungal inoculum	[126]
Rhizophagus irregularis	AM	Displays allelopathic activity in *Nicotiana attenuata*	Coumarins scopoletin and scopolin increased foliar levels in AM-inoculated plants	[125]
Tuber aestivum	EM	Displays allelopathic activity	EM-produced coumarins scopoletin, angelicin, and bergapten	[120,121]
Tuber borchii	EM	Displays allelopathic activity	EM-produced coumarins scopoletin, angelicin, and bergapten	[120,130,131]
Tuber melanosporum	EM	Displays allelopathic activity	EM-produced coumarins scopoletin, angelicin, and bergapten	[120,121,122]

EM, ectomycorrhizae; AM, arbuscular mycorrhizal.

velopmental steps, from vegetative mycelium toward the mature fruit bodies, among other fungal secondary metabolites [118].

A rare natural resource, the edible ectomycorrhizal fungus *Morchella esculenta* is one of the most economically beneficial, precious, nutritional, and medicinal ascomyceteous mushrooms widely harvested for consumption [119]. Fruit bodies of *M. esculenta* highly valued for their properties, as well as vegetative mycelia, show rather high antioxidant, anti-inflammatory, antitumor, and anticancer activities [119,134,135] owing to the presence of polysaccharides [136,137] and the coumarin derivative acenocoumarol [119]. These mushroom extracts have been reported to display antagonistic activity against such pathogenic bacteria as *Escherichia coli*, *Enterobacter cloacae*, *Listeria monocytogenes*, *Salmonella typhimurium* and *Staphylococcus aureus* [138].

The most widely known species of truffle-like fungi belong to the genus *Tuber*, whose representatives serve as a useful source of antitumor agents. For instance, *T. aestivum*, *T. himalayense*, *T. indicum*, *T. melanosporum*, and *T. sinense* constituents (mainly polysaccharides) have demonstrated a considerable potential to promote antitumor activity [139]. Truffles are known as the most relevant examples of allelopathic effects induced by the edible ectomycorrhizal fungi [140]. Different coumarins secreted by the ectomycorrhizal mycelium, including scopoletin, angelicin, and bergapten, are reportedly responsible for the allelopathic activity found in *Tuber aestivum*, *Tuber borchii*, and *Tuber melanosporum* [120,121,122].

The strong metabolic rearrangement in arbuscular mycorrhizal plant roots was accompanied by higher levels of phenolic compounds and coumarins. Colonization of plant roots by the AM fungus *Funneliformis mosseae* resulted in different levels of bioprotection against *Phytophthora* root rot in tomato (*Solanum lycopersicum*) or *Fusarium* wilt in melon. *Funneliformis mosseae* inoculation dramatically increased the relative abundance of coumarin derivative 2*H*,8*H*-Benzo[1,2-b:3,4-b']dipyran-2-one,8,8-dimethyl [123,141]. *Rhizophagus irregularis* colonization of tomato roots resulted in increased resistance of the shoots to the necrotrophic foliar pathogen *Botrytis cinerea*, likely through defense priming involving the induction of a set of secondary metabolites, including coumarin. Coumarin levels were increased in the tomato mycorrhizal plants as compared to non-colonized plants with *Rhizophagus irregularis* [124]. *Rhizophagus irregularis* colonization of *Nicotiana attenuata* plants impaired in their interactions with AM fungi led to an increase in foliar levels of the coumarins scopoletin and scopolin [125].

Cosmopolitan pathogenic fungus *Puccinia striiformis* f. sp. *tritici*, the causal agent of stripe rust, represents one of the most devastating pathogens that threatens wheat (*Triticum aestivum* L.). Mycorrhization of wheat roots by the complex AM inoculum (*Rhizoglomus clarum*, *Gigaspora gigantea*, and *Rhizophagus irregularis*), and the subsequent colonization of plant roots by *Puccinia striiformis* resulted in the accumulation of different flavonoids, phenolic acids, and coumarins [126]. In particular, cinnamic acid, coumarin, and esculetin were detected in response to colonization with AM fungal inoculum, followed by a reduction in the disease severity of stripe rust in wheat leaves.

Arbuscular mycorrhizal fungi form obligate symbiotic associations with most plant families. For research into these symbiotic relationships and for the mass production of AM-fungal inoculants, *in vitro* root organ culture is very useful. Abd Ellatif et al. [142] studied the effect of different low-molecular-mass compounds, including two coumarins, on the growth of AM fungus *Gigaspora gigantea* using *in vitro* tomato root organ culture. When comparing the intensity of external appearance of root hair growth in liquid media, the number of spores (spore density per mL of culture) in liquid media, mycorrhizal colonization in liquid media, and the abundance of arbuscules in liquid media, the authors revealed that coumarin was the most effective compound used at pH 6.5 to activate root hair growth. Abundant arbuscules were achieved by using esculetin at pH 5.7. The highest significant values of the varieties of the mycorrhizal frequency and the relative mycorrhizal intensity were observed for esculetin. Coumarin showed the highest significant values of absolute abundance of arbuscules, and esculetin displayed the highest significant values of the relative abundance of arbuscules. In general, it was observed that the values of the parameters of mycorrhizal colonization and the abundance of arbuscules in tomato roots grown on solid media at pH 6.5 were always better for esculetin than for coumarin.

6.2 Iron Chelation and Antioxidation Involvement of Coumarins From Mycorrhizal Plants

An important role of coumarins in bidirectional chemical communication along the microbiome–root–shoot axis [3] allows one to establish a complicated picture within the plant–mycorrhiza community implementing coumarins, partially reflected by the following scheme (Fig. 3).

Coumarin production and secretion are induced upon colonization of roots via several routes, including those emerging in response to soil depletion of mineral nutrients [122], and coumarins alleviate the nutrient stress by functioning in favor of iron or phosphate mobilization and uptake. Thus, AM fungi supply plants with up to 80% of their phosphorus requirements [143]. Consistently, mycorrhizal fungi stimulate coumarin biosynthesis in roots and the excretion of these substances into the rhizosphere. Root-exuded coumarins can be further converted by fungi to produce modified structures with biological activities that are even more applicable to plant life and as lead compounds for medicines. Data presented in Table 1 and Table 2 unequivocally testify to the coumarins' coexistence in both

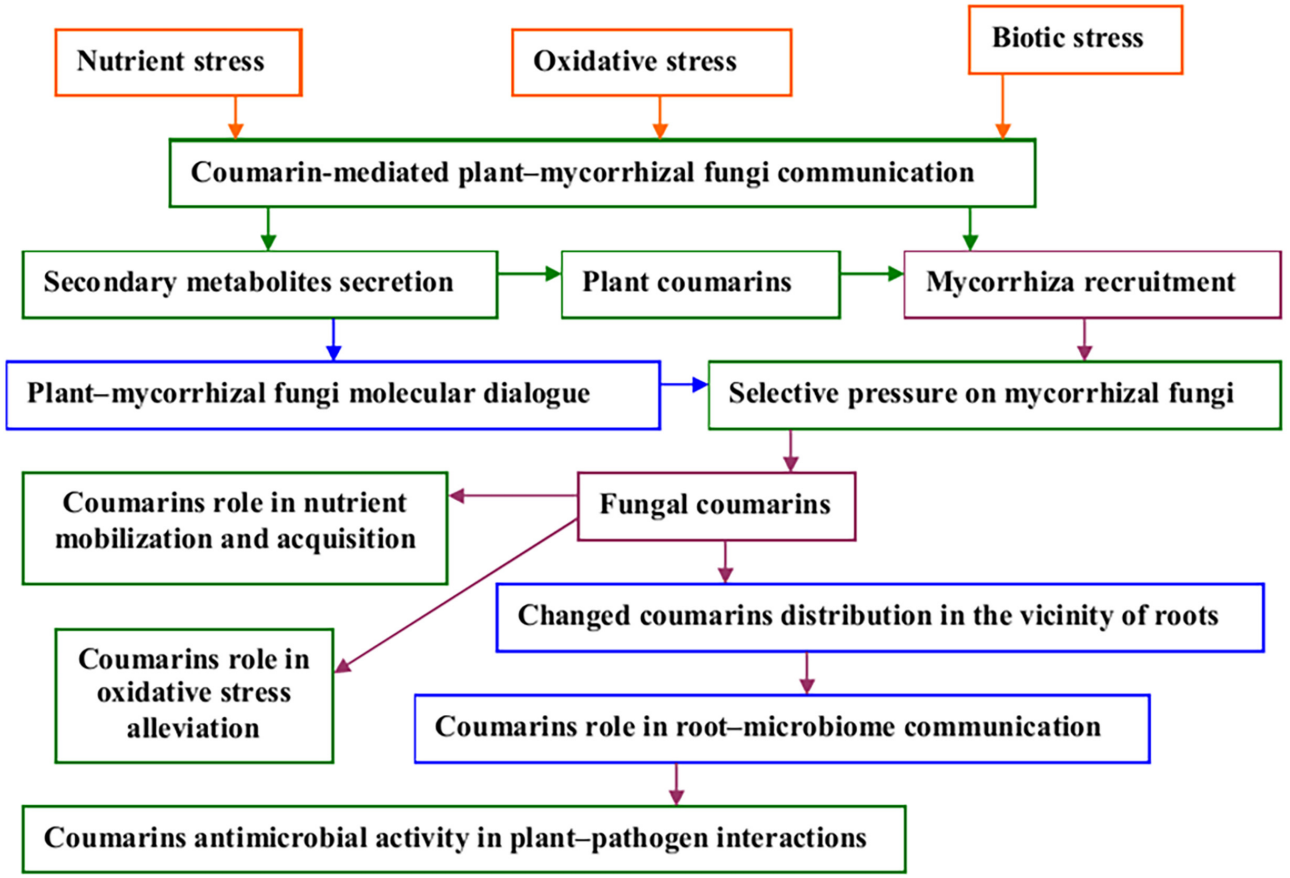


Fig. 3. Scheme outlining the coumarin-mediated plant–mycorrhiza interactions.

plant aerial parts and roots involved in the plant–fungal mycorrhizal associations.

Diverse secondary metabolites of coumarin nature detected in the mycorrhizal fungi-colonized plants compared to non-colonized infer the fungi's potential to influence the coumarin-relevant biosynthetic pathways in plants. To give one example, *Anchusa officinalis* is recognized for its therapeutic properties, including anti-inflammatory, antioxidant, and antibacterial activity [78]. The experiments on associating this plant with the AM fungus *Rhizophagus irregularis* under a semi-hydroponic cultivation system [79] were intended to reveal the differentially accumulated plant metabolites. Two compounds were observed in the mycorrhized plants in contrast to the non-mycorrhized ones, namely scoparone (coumarin) and byakangelicin (furanocoumarin) (Table 1). Byakangelicin is mostly detected and obtained from the root of *Angelica dahurica*. Byakangelicin reportedly reduces renal inflammation and apoptosis of renal epithelial cells [60]. This furanocoumarin has been recently described as displaying anticancer effects by suppressing breast tumor cell proliferation, and inducing cancer cell apoptosis [61].

In the Arabidopsis root, coumarin scopoletin (Table 1) is constitutively present and further induced and secreted into the rhizosphere during iron deficiency [96]. While earlier studies have documented the Fe-mobilizing activity of coumarins facilitating iron uptake from the soil [3], very recent studies highlight the central role of coumarins for the microbiome-assisted improvement of plant Fe nutrition. To resolve the iron-mobility bottleneck, mycorrhiza-mediated phytocoumarin transformation into coumarins more efficient in iron-chelating processes, seems to be of extreme importance for iron acquisition by plants. In this way, an *Arabidopsis* root fungal endophyte *Macrophomina phaseolina* (F80) enhances plant Fe nutrition [144]. This fungal strain is capable of transforming the host-derived coumarin scopoletin into the iron-chelating coumarin esculetin. Owing to its catechol fragment-containing structure, esculetin chelates and subsequently releases iron available for plant nutrition. Ultimately, *M. phaseolina* mediates *Arabidopsis* iron nutrition and rescues plants exposed to iron-limiting conditions.

Mycorrhiza-induced coumarins functioning as plant signaling compounds serve as mediators in the communication between roots and shoots. The established bidirectional biochemical communication [3] may shape mycorrhizal composition to enhance the fungal community functions useful in supporting the host plant. The molecular signals implemented by plants and AM fungi to detect and assess a degree of plant–fungal incompatibility were largely

unknown until recently [145]. Coumarin was proven to be one of these molecular signals. Cosme et al. (2021) [146] found that the plant-derived coumarins can mitigate symbiotic incompatibility in nonhost *Arabidopsis thaliana* species caused by defense activation and plant growth antagonism. For that, the pre-established mycelium of the AM fungus *Rhizophagus irregularis* was examined with 18 Arabidopsis genotypes. Outcomes showed that the plant-derived coumarin scopoletin could serve as a novel signal capable of stimulating AM fungal metabolism and promoting initial steps of the plant–AM fungus interactions. The possible implication of coumarin in chemical communication before AM colonization of the plant was uncovered.

Chemical composition of root exudates markedly influences the plant–microbiome interactions in the rhizosphere and the efficiency of nutrient mobilization/acquisition (Fig. 3). Coumarin exudation is strongly inducible by plant response to iron deficit [95]. ATP-binding cassette (ABC) transporters manage in part the exudation of metabolites. Metabolite profiling of the root exudates of *Arabidopsis thaliana* plants and mutants deficient in the expression of two ABC transporters has allowed the compromised coumarin accumulation to be detected in *abcg37* mutants only, i.e., in one transporter ABCG37-deficient plant, as compared to other certain metabolites under study. The mentioned Arabidopsis genotypes feature an allocation of separate coumarins between roots and exudates in such a manner that is supportive of the exudation specifically of polyhydroxylated coumarins rather than monohydroxylated ones [93]. Under the Fe-scarcity growth conditions, the accumulation of primarily highly oxygenated coumarins was strongly promoted [95,147,148].

Recent data obtained in the research [93] are also indicative of more intense accumulation of the catechol fragment-containing coumarins in root exudates, and of substantial contribution from catechol coumarins to iron acquisition. The research output testifies to the exudation of coumarins structurally featured by a catechol moiety (esculin, fraxetin, and dihydroxyscopoletin) rather than the release of monohydroxylated coumarins (scopoletin, isofraxidin) aimed at improved Fe acquisition [93,95]. This is additionally evidenced by the research [149], according to which the coumarins or coumarinolignols comprising a catechol fragment are heavily accumulated under iron-scarcity conditions. In line with earlier results [147,148], the authors of [149] also prove that the coumarin-structured compounds comprising a catechol fragment (catechol coumarins mentioned above) render more efficient iron chelation.

A lot of pathophysiological states proceed through the participation of iron, a dyshomeostasis of which may contribute to the onset of neurodegenerative disorders, including Alzheimer's disease. Therefore, iron chelation could present a therapeutic strategy to target the "metal hypothesis" of this disease [150]. The ability of coumarin-core structured compounds to capture and displace Fe cations, thereby interfering with iron participation in redox pathological processes, and additionally to function as potent antioxidants and anti-inflammatory agents, makes coumarins an appropriate chemical group of anti-Alzheimer therapeutics. Overall, chemical interactions available to a given coumarin compound include those established via the bonds by substituent groups on the coumarin skeleton, eventually constructing their bioactivity profile [7].

Oxidative stress is likewise associated with the principal reasons for neurodegenerative processes and disorders progression [151]. Reactive oxygen and nitrogen species are normally a component of metabolic pathways, being neutralized in a timely manner by the intrinsic cellular antioxidants [152]. This redox balance is disturbed under definite neuropathophysiological conditions [21], accompanied by a further deepened stressful state and a self-propagating inflammatory event. For regaining the redox balance, exogenous antioxidant agents may be acceptable to overcome undesirable biochemical alterations assigned to neurodegenerative processes. Natural coumarin derivative profiles have been screened accordingly under neurodegeneration-related pathological conditions.

Neuroinflammation is also closely related to the progression of Alzheimer's disease. Previously unexplored aspects have been assessed in natural products bearing the coumarin core, which could be potentially useful for the antioxidant therapy to alleviate oxidative stress boosted through imbalanced redox homeostasis [153]. Scopoletin, this simple naturally occurring coumarin, shows promising antioxidant ability, and has appeared to be endowed with neuroprotective properties realized through the antioxidant enzyme activity enhancement to reduce neurodegeneration [154].

However, non-derivatized natural coumarins fit rather poorly the demands placed on the anti-neurodegenerative treatment procedures. Novel combined synthetic scaffolds endowed with a coumarin counterpart promote antioxidative response, neuroprotection, restore redox homeostasis, and enhance cell viability [155,156]. These complex molecular structures present a current challenge to meet the above requirements, and to succeed in therapy, owing to the synergistic neuroprotection provided by the hybrid molecules of pharmaceuticals.

Several coumarins arouse great interest owing to their antitumor activities toward various cancer types, among which skin cancer stands out. Melanoma, the most aggressive form of this disease, is the third most common type of skin cancer [157]. Excess melanin, resulting from abnormal overexpression of the enzyme tyrosinase, is associated with hyperpigmentation and melanoma [158]. Tyrosinase is a copper-containing metalloenzyme belonging to the oxidoreductase class, to which an important if not central role in melanogenesis is commonly assigned [159]. Tyrosinase-inhibiting traits should therefore be inherent in the design of anti-melanoma remedies. A series of plant

secondary metabolites with a phenolic function in their molecular structure attached to a coumarin backbone are among the tyrosinase inhibitors. Pynam and Dharmesh [44] have reported on a remarkable anti-tyrosinase activity of the furanocoumarin imperatorin (Table 1). The coumarin decursin (Table 1) lowers both melanin production and intracellular tyrosinase activity [75]. An important contribution from the phenolic moiety on the coumarin ring has been validated through a dramatically improved anti-tyrosinase activity as a result of methyl substituent replacement by a hydroxyl group. Imperatorin has demonstrated impressive inhibitory activity with respect to tyrosinase, and thereafter low IC_{50} values of about 87 μM, compared to the reference compound kojic acid (72 μM), and especially ascorbic acid (387 μM). Multiple studies offer evidence of a considerable role in tyrosinase inhibition played by different hydroxycoumarins [159,160]. This is related in great part to their metal-complexation ability, exemplified by not only iron chelation as discussed above, but also copper chelation critical for inhibiting tyrosinase because of the decisive involvement of copper ions in catalytic reactions of tyrosinase.

Although the potent radical scavenging traits are frequently ascribed to coumarins, the role of plant coumarins as antioxidants seems controversial. Some studies revealed the unusual mechanism exerted by furanocoumarins in realizing their antioxidant abilities [161]. At least, this mechanism remains undisclosed for natural coumarins. Furanocoumarins are highly photoactive compounds. Being photoactivated, they can yield adducts with DNA pyrimidine bases and induce cross-linking. Due to steric factors, the psoralen-type coumarins' action can result in covalent cross-linkages between DNA strands, whereas the angelicin-type coumarins can only lead to the formation of quickly repaired monoadducts [19]. As stronger photosensitizers than the angelicin-type counterparts, psoralen and congener compounds have been preferred in phototherapy to treat autoimmune disorders [162].

Many findings suggest a link between coumarins as iron mobilizers and phytoalexins. Phytoalexins are antimicrobial chemicals of low molecular weight biosynthesized by host plants after pathogen attack. Biosynthesis of coumarins is induced by various biotic and abiotic elicitors, as well as by stress factors [163]. Scopoletin is considered a phytoalexin because it has antifungal activity and its biosynthesis is elicited by pathogen attack in many species [164]. Coumarins have been extensively studied for their involvement in responses of dicotyledonous plants to iron deficiency [96]. When Fe is unavailable in the soil around the roots, Fe-deficiency responses activate MYB72 and β-glucosidase BGLU42, which act in the biosynthesis and secretion of coumarins. Such coumarins as scopolin, scopoletin, esculin, esculetin, fraxetin, and sideretin are produced, and their exudation increases with time in response to iron deficiency [100]. Therefore, plant coumarins could be considered as phytoalexins with iron-binding and pathogen-inhibiting functions, which improve plant defense against phytopathogens by modulating Fe homeostasis. Plants can withhold iron from pathogens using Fe sequestration and low Fe availability in the rhizosphere. Iron-chelating coumarins likely evolved to "starve" pathogens of essential iron.

6.3 Glycosylation of Coumarins From Mycorrhizal Plants

Evidence has accumulated that the secondary metabolites of fungal symbionts are involved in the biochemical defense mechanisms against pathogens of the mycorrhiza. In general, by modifying the core structure of coumarin and its derivatives, substances exhibiting diverse bioactivities can be potentially obtained. These modification reactions *in planta* are catalyzed by enzymes such as plant uridine glycosyltransferases [165], or UDP-Glc: phenylpropanoid glucosyltransferases (UGTs) [166,167]. Glycosylation processing supplies the plant with an efficient opportunity to modify molecular structure, thus bioactivity. Besides, the glycoside form of a given phenylpropanoid substance is easier to store and transfer compared to the aglycone owing to such variables as solubility in aqueous media, and reactivity related to the timely hindered hydroxyl group(s). The resulting plant coumarins occur in glycosylated (glycoside) or deglycosylated (aglycone) forms; therewith, the aglycone–glycoside couple of scopoletin–scopolin is reportedly a remarkable participant of the plant defense events under the biotic stress exposure.

A crucial role of UGPs in plant defense responses seems to be undisputed [25]. Under plant exposure to adverse environments, coumarin glycosides retained in vacuoles can be deglycosylated to yield the corresponding aglycones [168], which are more biochemically reactive and subsequently released to the rhizosphere [24,93,169]. In *Arabidopsis thaliana*, the major coumarin, scopolin, is concomitantly deglycosylated to be converted into its aglycone-structured compound, scopoletin, and subsequently secreted to the rhizosphere [24]. Subsequently, the scopoletin-containing root exudates could modify root microbiome composition through a selective inhibitory effect on soil-borne fungal pathogens, while boosting induced systemic resistance in the plant [23], taking into account the scopoletin specificity in suppressing phytopathogens rather than beneficial organisms [24].

The secondary metabolites of phenolic nature, and also coumarins with phenolic functional groups in their structure, reportedly play an indispensable role in plant–environment interaction [170]. A large amount of polyphenols found in leaves are glycosylated [171], thus possess higher solubility in aqueous media. Glycosylation facilitates the transport of phenylpropanoid-nature metabolites from the endoplasmic reticulum to different cellular compartments, as well as the glycosides secretion out of the cell [172,173,174]. Fini et al. [175] have found that dur-

ing the *Fraxinus ornus* response to the concomitant impact of severe drought and excessive light stress, the biosynthesis of esculetin (6,7-dihydroxycoumarin, potent antioxidant) was more intense compared to esculin (esculetin 6-O-glucoside, poor antioxidant) [89,176]. Further research has provided evidence that the coumarin glycosides exhibit substantially lower antioxidant activity compared to the coumarin aglycones, since the reactive phenolic groups appear to be blocked by the carbohydrate moiety in the glycoside [177]. The latter study underlines a noticeable interplay between the increased esculetin concentration, activity of vacuolar peroxidases, and gradually decreased enzymatic activity of catalase and ascorbate peroxidase. Consequently, in cooperation with a set of peroxidases, the aglycone esculetin may present a secondary antioxidant system [175] capable of interfering with the hydrogen peroxide entrance to the vacuole in adverse environments, thus compensating for the primary antioxidant defense system malfunction under this condition.

The fact that the individual coumarins have distinct subcellular distribution has been corroborated for the first time by Şen et al. [177], who compared the presence of esculetin (6,7-dihydroxy-substituted coumarin) and two of its glucosides, esculin and chicorin, with glucosylation at the 6- or 7-position on the coumarin ring, respectively. UV–VIS spectral features of these coumarin solutions were visualized by adding 2-aminoethyl ester of diphenylborinic acid (Naturstoff reagent, NR). The observations correlated with the formation of a coumarin-NR adduct through the catechol group (i.e., dihydroxylic moiety at 6 and 7 carbon atoms on the coumarin core). NR-staining allowed the selective excitation of the esculetin complex formed, whereas the monohydroxylated coumarins escaped the formation of NR-adducts. As a result, a 37% increment in the esculetin level compared to its glycosides, esculin or chicorin was observed [177]. The detected differential vacuolar distribution of esculin and esculetin in mesophyll cells of *Fraxinus ornus*, complemented by the esculin absence in the vacuole of epidermal cells, may be indicative of diverse functions performed by coumarin aglycones and glycosides in the plant response to environmental challenge. Besides, these stress-related functions could rely upon the outstanding antioxidative properties of the ortho-dihydroxylated aglycone esculetin.

Another extensively explored natural coumarin aglycone–glycoside couple is scopoletin and scopolin. There are several studies that confirm an important role of the phenylpropanoid pathway, including scopoletin and its β-glucoside form, scopolin, in eliciting plant responses to infections. Exclusive distribution of scopoletin in the infected tissues of *Arabidopsis* leaves reacting hypersensitively to *Pseudomonas syringae* pv. tomato, or scopolin in tissue cells surrounding the infected ones [178], may be explained in terms of these coumarins' diverse ROS-scavenging capacities. Antifungal phytoalexins that suppress phytopathogen propagation include coumarins.

The late blight of potato causative agent is the oomycete *Phytophthora infestans*. Metabolic profiling of the stems of infected plants of the late blight-susceptible Russet Burbank potato genotype has allowed scopoletin to be identified among the potato resistance-related metabolites [179]. Beyer et al. [23] have found that scopoletin protects soybeans from Asian soybean rust. Soybean, the most important legume crop, suffers from the attack of the phytopathogenic fungus *Phakopsora pachyrhizi*, a causative agent of Asian soybean rust disease. In the shoots of the nonhost plant Arabidopsis, scopoletin accumulates after microbial attack. The expression of a set of genes is specifically linked to post-invasion nonhost resistance of Arabidopsis to *Phakopsora pachyrhizi*. This set, being transferred from Arabidopsis to the soybean host plant, reduced the soybean susceptibility to the Asian soybean rust disease [180]. Therefore, the antifungal metabolites antagonizing *Phakopsora pachyrhizi* have been identified in the nonhost plant Arabidopsis, offering an opportunity for efficient soybean defense. As a result, foliar application of scopoletin has provided protection from this fungal pathogen acting via the development of *Phakopsora pachyrhizi* infection structures [23].

Cucumber plant response to early stages of disease caused by the green mottle mosaic virus [181], as well as the salicylic acid-induced *Nicotiana tabacum* L. response to the tobacco mosaic virus infection [166], appeared to be mediated by the coumarins and their glucoside form biosynthesis, regulation of scopoletin glucosylation, ultimately implemented in the mitigation of virus systemic infection through oxidative stress alleviation and decreased viral replication.

This hydroxycoumarin glucosylation *in planta* is efficiently catalyzed by UGTs via a mechanism of the sugar moieties conjugation to secondary metabolites of the phenylpropanoid nature serving as substrates [182], including a glucose transfer to coumarins. In this way, the reactivity of molecules performing a substantial part of the plant defense response is modulated. The observed glucosylation is critical for scopoletin accumulation in cells adjacent to infection lesions of plant leaves. That is consistent with the proposed role of scopoletin as the compound exerting a direct antiviral effect [166], a potent ROS scavenger [182], and the agent with strong antifungal activity [183].

The multifunctional role of UGTs in the production of pathogen-responsive metabolites, catalyzed by these multisubstrate enzymes [164], is broadly discussed. Phytoalexins' glycosylation can manage the level of such metabolites. In *Nicotiana tabacum*, pathogen-induced tobacco UGTs (scopoletin UGTs TOGT1 and TOGT2) catalyze the scopoletin glucosylation after treatment with salicylate, fungal elicitors (e.g., an elicitin-like glycoprotein from *Phytophthora megasperma*), and the tobacco mosaic virus [184].

Similarly, a phytoalexin, N-feruloyl tyramine glucosylation modulates the level of pathogen-responsive metabolites in *Nicotiana benthamiana* [164].

Wild tobacco *Nicotiana attenuata* accumulates high amounts of scopoletin to withstand the necrotic pathogen *Alternaria alternata*. Glucosylated scopoletin was also elicited, thereby, to a great extent, even exceeding the scopoletin level under this fungal infection condition in the plant. But scopolin may serve merely as a storage form of scopoletin without functioning as a phytoalexin. To resolve this challenge, the assays on scopolin antagonistic traits with respect to *A. alternata* were conducted [170] to disclose the phytoalexin-like traits of scopolin in plant resilience. Scopolin activity against *A. alternata* appeared to be moderate but slightly weaker than the antifungal effect of scopoletin. Therefore, not only scopoletin, but also its β-glucoside form scopolin were found to be two jasmonate-signaling-dependent phytoalexins involved in *Nicotiana attenuata* resistance against the ubiquitous fungal pathogen *Alternaria alternata* [170]. In general, mycorrhizal fungi contribute to plant support by mitigating specific nutrient uptake, resistance against soil-borne pathogens, playing a key role in plant growth promotion, antistress protection, soil structure improvement, and ultimately strengthening the quality and production of plant-derived medicines.

Coumarin glucosides are almost exclusively found inside roots and most likely represent the major storage form before being cleaved and exuded [185]. Coumarin glucoside profiles obtained from root tissue are qualitatively and quantitatively correlated to coumarin aglycone profiles in exudates [93]. Coumarins, like other secondary metabolites, are often converted to their glycoconjugates. Several roles have been postulated for glucosylation, as follows: it allows these compounds' solubilization in aqueous solvents and water; it regulates the action of functional compounds; in the case of coumarins, it acts to detoxify more harmful aglycones to form less active glucosides.

Upon their production, coumarins are found in their aglycone form. However, highly reactive aglycones could damage host cells if not stored as glucosides, and a self-detoxification mechanism should work. Consequently, the coumarins modified by UGT activity into the corresponding glycoconjugates appear to be accumulated in vacuoles. In response to various stresses, disruption of the cells can bring the glucosylated forms into contact with beta-glucosidases in the cytosol. These enzymes catalyze the hydrolysis of the glucosidic bond to yield the bioactive coumarin aglycone forms predominantly detected in root exudates, whereas their respective monoglucosides, such as scopolin, esculin, fraxin, and siderin, are almost exclusively found in root extracts [186].

7. Limitations, Potential Applications, and Future Perspectives

Possible limitations of the review are the exclusion of grey literature sources [187] in the form of dissertations/theses, book chapters, conference proceedings, posters, or abstracts. Descriptive works and studies conducted with secondary data were also excluded from the search. The fact that scientific journal papers published in the English language were considered eligible for inclusion could have the potential to miss relevant studies. The work did not perform a formal quality assessment of the selected papers.

Several plant metabolites, including coumarin derivatives, could be effective in treating diverse parasitic diseases. However, these compounds are present in small amounts in plants [188], and therefore research into cultivation in order to enhance the quantity and quality of the active coumarins is of high interest. A plethora of metabolic changes take place in the mycorrhizal fungi-colonized plants upon infection. Certain changes located in the phenylpropanoid pathway indicate that several intermediaries are over-accumulated in the arbuscular mycorrhizae [124]. A strong metabolic rearrangement in mycorrhizal roots may lead to a negative impact of mycorrhizal symbiosis on amino acid content, mainly on those involved in the biosynthesis of phenylpropanoids [141]. The challenge is to reveal how mycorrhizal plants respond to adverse environments with respect to the changed levels of coumarins. Of importance is the selectivity of the given fungal partner in mycorrhizal association, its capability of producing coumarins at a level compatible with normal plant growth and development, in view of the known inhibiting properties of coumarins towards plants' symbionts, including beneficial bacteria. Promising are further studies of conditions and products of the natural coumarins' biotransformation, aimed at solving the urgent problem of searching for materials for agricultural and biomedical engineering.

On the basis of this information, the main directions of future studies could be the following. Biological roles of coumarins related to their functions in human health (immunoregulation, antioxidant activity). Functions of coumarins in plants in the facets of iron chelation and defense against pathogens. Regulation of coumarin metabolism in mycorrhizal plants, including their role in mycorrhization itself. Specifically, mycorrhizal-derived coumarins are involved in the functions described above, and the immunoregulatory and therapeutic properties of coumarins for human health. These studies can pave the way to improving the biotechnological applications of mycorrhizal fungi in agricultural settings and in the production of plant secondary metabolites with medicinal or nutritional properties.

8. Conclusions

As a concluding remark, it could be noted that both components of mycorrhizae, plants and fungi, are famous

for their proven therapeutic capacity and harbor an important spectrum of pharmaceutically interesting chemical compounds still to be identified. Coumarin-structured metabolites provided by mycorrhizae can serve as novel immunomodulatory and antioxidant natural-derived agents, play a relevant role in the bioinspired lead scaffolds implemented in drug design, and be applied as promising adjuvants to conventional drugs. That is why the exploration of their regulatory mechanisms over the mycorrhizal phyto-constituents may present a current challenge and substantial contribution to the phyto-pharmaceutical development.

Author Contributions

Conceptualization, formal analysis, funding acquisition, visualization, writing—original draft, review and editing, OT. All work was conceived and completed by OT. The author has read and approved the final manuscript and agrees to the published version of the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The author declares no conflicts of interest.

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