Signaling Molecules in Endophytic Bacteria and Medicinal Plants

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Signaling molecules act as the links and bridges between endophytes and host plants. The recognition of endophytes and host plants, the regulation of host plant growth and development, and the synthesis of secondary metabolites are not separated by the participation of signaling molecules.

Keywords: endophyte ; medicinal plants ; interaction relationship

1. Introduction

Secondary metabolites of higher plants are the main source of many natural medicines, and the plant origins of which are gradually occupying a dominant position in the field of medicine and healthcare on a global scale. Among these chemicals are ginsenosides [1], tanshinones [2], vinblastine [3], camptothecin [4], paclitaxel [5], and others with anti-fatigue, anti-blood pressure, anti-thrombotic, and anti-tumor properties, which serve as a foundation for novel medications development. However, the majority of these natural active components have distinct chemical structures, which means artificial synthesis to directly replace natural plant resources is difficult. The existing single extraction and separation method is far from satisfying the complex and diversified extraction of natural active compounds in medicinal plants, resulting in resource waste. In addition, the wave of economic development has also brought about the destruction of wild medicinal resources and unplanned and unregulated exploitation. This has accelerated the formation of the global shortage of herbal resources.

However, after medicinal plants are invaded by specific environmental microorganisms, they establish symbiotic relationships including partial symbiosis and mutualistic symbiosis, which was been accompanied by in-depth understanding and exploration of medicinal plant microbiota in recent years. Symbiosis includes offset symbiosis and mutualism. Endophytic bacteria and host plants have evolved a comparatively robust equilibrium maintenance symbiosis mechanism through ongoing synergistic evolution and balanced confrontation [6]. In the symbiotic system involving endophytic bacteria, the convenient generation of secondary metabolites of medicinal plants fully reflects the characteristics of high yield, rapid generation, high plasticity, convenient operation, and mild reaction. Therefore, endophytic bacteria act as a special "inducer" signal to regulate plant growth and metabolism [7] and biotic and abiotic resistance [8] and to induce specific secondary metabolites [9] in a mutualistic system with plants. The signaling molecules such as organic molecules and signaling hormones in the symbiotic system are also key to the processes of endophytic bacteria recruitment, infestation, colonization [10], signal integration [11], and regulation of plant secondary metabolite synthesis.

2. Signaling Molecules Involved in the Interactions between Endophytic Bacteria and Medicinal Plants

Endophytes and host plants have formed a unique symbiotic system under long-term symbiotic synergy, becoming a functional symbiosis with diverse structures, complex composition, and dynamic change. The orderly operation of various signaling molecules and symbiotic systems provides a basis for subsequent research on the synthesis pathways of secondary metabolites in medicinal plants. Plants recognize endophytes through selective metabolic signals to restrict other microorganisms from entering the plant. After initiation of intracellular symbiotic signaling pathways, endophytes successfully colonize host plants.

2.1. Interaction of Metabolic Signaling Molecules in Endophytic Bacteria and Medicinal Plants

Symbiosis is a complex nutrient environment. In a symbiotic system, many chemicals can be used as signals to recruit and identify endophytic bacteria. These metabolites generally include (i) nutrients available only to specific microorganisms, (ii) antibacterial substances toxic to some microorganisms, and (iii) a metabolite that attracts specific microorganisms. For example, organic acids such as citric acid, malic acid, fumaric acid, and salicylic acid have been shown to play important roles as nutrients in the recruitment of endophytic bacteria [12]. Triterpenoids are another large and diverse group of plant metabolic nutrients that mediate the establishment of symbiotic systems by promoting and limiting the growth of endophytic bacteria [13]. Similarly, plants may produce a wide range of antimicrobial substances, but the regulatory mechanisms of how these molecules allow endophytic bacteria to proliferate while resisting pathogenic bacteria have not been fully described in studies. Plant-derived coumarins have antimicrobial activity against some pathogenic bacteria, but not against endophytic bacteria [14]. Similarly, rhizobacteria have evolved resistance to the toxic structural mimic of arginine (cotinine) produced by legumes, thus allowing proliferation in the inter-rhizosphere of legumes [15]. These examples show that plants can use antimicrobial products to select specific endophytes while excluding other microorganisms. Plant-secreted metabolites can also serve as signals used by hosts in symbiotic systems to attract specific endophytic bacteria. Nitrogen-fixing rhizobacteria can sense the presence of plant flavonoids through bacterial regulators that biosynthesize in conjunction with Nod factors [16]; the phytohormone strigolactone can trigger the germination of mycorrhizal (AM) fungal spores, thus signaling the presence of a potential plant host [17][18]. Symbionts can also use the presence of plant metabolites, including polyamines [19], amino acids, organic acids, or sugars [20], to indicate the presence of a plant host. Thus, the secretion of induced signals such as nutrients, antimicrobial substances, and metabolites provides the basis for plants to invoke only beneficial endophytes in a complex microbiota.The release of plant metabolic signals may be a major determinant of the formation of specific symbiotic systems between host plants and endophytes.

2.2. Receptor Signaling Molecules in the Interactions between Endophytic Bacteria and Medicinal Plants

Endophytic bacteria form a symbiosis with the host plant after successfully competing for nutrients in the host and surviving the attack of host antimicrobial metabolites. Plant receptors need to sense and integrate multiple signaling cues to successfully recognize the symbiont and determine the pathway to initiate symbiosis. Plant genomes encode hundreds of structure-specific membrane-associated pattern recognition receptors (PRRs) [21] to specifically recognize microbial-associated molecular patterns (MAMP). MAMPs that play a role in symbiotic pathways include chitosan, bacterial extracellular polysaccharides (EPS) [22], lipopolysaccharides (LPS) [23], and various protein components. In addition to this, endophytic bacteria have evolved effectors that can also act as receptor signaling molecules involved in the symbiotic pathway between endophytes and plants. The symbiosis between rhizobia and legumes begins when rhizobia secrete lipid chitooligosaccharides (LCO) and release Nod factors [24]. Both the effector and the host plant have multiple LysM structural domains, and the LysM structural domain receptors of the host plant need to recognize the correct Nod factor separately, regulating parallel signaling pathways [25]. For example, *Tribulus Terrestris* NFP and LYK3 recognize the non-reducing and reducing ends of Nod factors, respectively [26], and initiate the signaling pathways of NFP and LYK2 [27]. In summary, the symbiont signal can be selectively, and with high affinity, delivered to downstream intracellular signaling molecules through successful recognition of multiple receptors' signaling molecules by host plants for MAMP signaling and effector signaling of endophytes, and transduction of invasion colonization signals by endophytes (schematized in **Table 1**).

Table 1. Signal molecules and their sources in the interaction between endophytes and medicinal plants.

Source	Action Category	Signal Molecule	Strain (Genus)	Reference
Metabolic signal molecules	Nutrients	Citric acid	*Rhizoctonia*	[28]
		Malic acid	*Bacillus subtilis FB17*	[29]
		Fumaric acid	*Pseudomonas fluorescens*	[30]
		Succinic acid	*Bacillus amylolyticus*	[31]
	Antibacterial substances	Coumarin	*Pseudomonas*	[32]
		Concanavaline	*Nitrogenous Rhizobium*	[33]
	Specific products	Triterpene	*Endophytic flora*	[34]
		Salicylic acid	*Endophytic flora*	[35]
		Flavonoid	*Nitrogenous Rhizobium*	[36]
	Metabolites	Unicornolactone	*Arbuscular mycorrhiza*	[37]
		Polyamine	*Pseudomonas*	[38]
		Amino acid	*Nitrogenous Rhizobium*	[39]
		Organic acid	*Nitrogenous Rhizobium*	[39]
		Sugar	*Nitrogenous Rhizobium*	[39]
Receptor Signal Molecules	Conservative MAMP	Extracellular polysaccharide	*Nitrogenous Rhizobium*	[40]
		Lipopolysaccharide	*Nitrogenous Rhizobium*	[41]
		Cell wall polysaccharide	*Verticillium dahuricum*	[42]
		Phospholipid protein	*Phytophthora camphora*	[43]
		Ribosomal protein	*Phytophthora cryptogea*	[44]
	Nod factor	LCO	*Laccaria bicolor*	[45]
Intracellular signal molecule	Second Messenger	Ca^{2+}	*Nitrogenous Rhizobium*	[46]
		NO	*Soybean Stalk Rot Pathogen*	[47]
		ROS	*E.festucae*	[48]
	Hormone molecule	JA	*Epichloë gansuensis*	[49]
		SA	*Penicillium citri*	[50]

References

1. Zhou, L.; Li, Z.-K.; Li, C.-Y.; Liang, Y.-Q.; Yang, F. Anticancer properties and pharmaceutical applications of ginsenoside compound K: A review. Chem. Biol. Drug Des. 2022, 99, 286–300.
2. Chen, H.; Wu, H.; Yan, B.; Zhao, H.; Liu, F.; Zhang, H.; Sheng, Q.; Miao, F.; Liang, Z. Core Microbiome of Medicinal Plant Salvia miltiorrhiza Seed: A Rich Reservoir of Beneficial Microbes for Secondary Metabolism? Int. J. Mol. Sci. 2018, 19, 672.
3. Neha, D.; Shikha, S. Cancer chemotherapy with novel bioactive natural products. J. Chin. Pharm. Sci. 2022, 31, 589–607.
4. Ran, X.; Zhang, G.; Li, S.; Wang, J. Characterization and antitumor activity of camptothecin from endophytic fungus Fusarium solani isolated from Camptotheca acuminate. Afr. Health Sci. 2017, 17, 566–574.
5. Kumaran, R.S.; Kim, H.J.; Hur, B.K. Taxol-producing fungal endophyte, Pestalotiopsis species isolated from Taxus cuspidata. J. Biosci. Bioeng. 2010, 110, 541–546.
6. Gao, Y.-G.; Mo, Q.-Q.; Zhao, Y.; Zang, P. Microbial mediated accumulation of plant secondary metabolites and its action mechanism in medicinal plants: A review. Guangxi Agric Sci. 2019, 50, 2234–2240.

7. Ding, C.; Wang, S.; Li, J.; Wang, Z. Transcriptomic analysis reveals the mechanism of host growth promotion by endophytic fungus of Rumex gmelinii Turcz. Arch. Microbiol. 2022, 204, 443.
8. Yipare, P.; Zulihumaer, R.; Tian, Y.-Z.; Zhu, Y.-L.; Li, Y.-T.; Ma, X.-L. Research Progress in Diversity of Endophytic Microbial Communities Isolated from Desert Plants and Their Strengthening Effect on Drought and Salt Tolerance in Crops. Biotechnol. Bull. 2022, 38, 88.
9. Li, Z.; Wen, W.; Qin, M.; He, Y.; Xu, D.; Li, L. Biosynthetic Mechanisms of Secondary Metabolites Promoted by the Interaction Between Endophytes and Plant Hosts. Front. Microbiol. 2022, 13, 928967.
10. Mengistu, A.A. Endophytes: Colonization, Behaviour, and Their Role in Defense Mechanism. Int. J. Microbiol. 2020, 2020, 6927219.
11. Lu, X.; Wang, Y.-Y.; Zhang, F.-Y.; Lin, X.-Y.; Tang, K.-X. Advances in studies on transcriptional regulatory factor in secondary metabolites regulation of Chinese materia medica. Chin. Tradit. Herb. Drugs 2010, 41, 159–162.
12. Dubey, A.; Malla, M.A.; Kumar, A.; Dayanandan, S.; Khan, M.L. Plants endophytes: Unveiling hidden agenda for bioprospecting toward sustainable agriculture. Crit. Rev. Biotechnol. 2020, 40, 1210–1231.
13. You, C.; Qin, D.; Wang, Y.; Lan, W.; Li, Y.; Yu, B.; Peng, Y.; Xu, J.; Dong, J. Plant Triterpenoids Regulate Endophyte Community to Promote Medicinal Plant Schisandra sphenanthera Growth and Metabolites Accumulation. J. Fungi 2021, 7, 788.
14. Harbort, C.J.; Hashimoto, M.; Inoue, H.; Niu, Y.; Guan, R.; Rombolà, A.D.; Kopriva, S.; Voges, M.J.E.E.E.; Sattely, E.S.; Garrido-Oter, R.; et al. Root-Secreted Coumarins and the Microbiota Interact to Improve Iron Nutrition in Arabidopsis. Cell Host Microbe. 2020, 28, 825–837.
15. Hauth, F.; Buck, H.; Stanoppi, M.; Hartig, J.S. Canavanine utilization via homoserine and hydroxyguanidine by a PLP-dependent γ-lyase in Pseudomonadaceae and Rhizobiales. RSC Chem. Biol. 2022, 3, 1240–1250.
16. Ghantasala, S.; Roy Choudhury, S. Nod factor perception: An integrative view of molecular communication during legume symbiosis. Plant Mol. Biol. 2022, 110, 485–509.
17. Akiyama, K.; Hayashi, H. Strigolactones: Chemical signals for fungal symbionts and parasitic weeds in plant roots. Ann. Bot. 2006, 97, 925–931.
18. Besserer, A.; Puech-Pagès, V.; Kiefer, P.; Gomez-Roldan, V.; Jauneau, A.; Roy, S.; Portais, J.C.; Roux, C.; Bécard, G.; Séjalon-Delmas, N. Strigolactones stimulate arbuscular mycorrhizal fungi by activating mitochondria. PLoS Biol. 2006, 4, e226.
19. Liang, S.-M.; Zheng, F.-L.; Wu, Q.-S. Elucidating the dialogue between arbuscular mycorrhizal fungi and polyamines in plants. World J. Microbiol. Biotechnol. 2022, 38, 159.
20. Qu, Z.; Zhang, H.; Wang, Q.; Zhao, H.; Liu, X.; Fu, Y.; Lin, Y.; Xie, J.; Cheng, J.; Li, B.; et al. Exploring the Symbiotic Mechanism of a Virus-Mediated Endophytic Fungus in Its Host by Dual Unique Molecular Identifier-RNA Sequencing. mSystems 2021, 6, e0081421.
21. Snoeck, S.; Abramson, B.W.; Garcia, A.G.K.; Egan, A.N.; Michael, T.P.; Steinbrenner, A.D. Evolutionary gain and loss of a plant pattern-recognition receptor for HAMP recognition. Elife 2022, 11, e81050.
22. Kawaharada, Y.; Kelly, S.; Nielsen, M.W.; Hjuler, C.T.; Gysel, K.; Muszyński, A.; Carlson, R.W.; Thygesen, M.B.; Sandal, N.; Asmussen, M.H.; et al. Receptor-mediated exopolysaccharide perception controls bacterial infection. Nature 2015, 523, 308–312.
23. Bourassa, D.V.; Kannenberg, E.L.; Sherrier, D.J.; Buhr, R.J.; Carlson, R.W. The Lipopolysaccharide Lipid A Long-Chain Fatty Acid Is Important for Rhizobium leguminosarum Growth and Stress Adaptation in Free-Living and Nodule Environments. Mol. Plant Microbe Interact. 2017, 30, 161–175.
24. Gough, C.; Cullimore, J. Lipo-chitooligosaccharide signaling in endosymbiotic plant-microbe interactions. Mol. Plant Microbe Interact. 2011, 24, 867–878.
25. Miyata, K.; Hayafune, M.; Kobae, Y.; Kaku, H.; Nishizawa, Y.; Masuda, Y.; Shibuya, N.; Nakagawa, T. Evaluation of the Role of the LysM Receptor-Like Kinase, OsNFR5/OsRLK2 for AM Symbiosis in Rice. Plant Cell Physiol. 2016, 57, 2283–2290.
26. Smit, P.; Limpens, E.; Geurts, R.; Fedorova, E.; Dolgikh, E.; Gough, C.; Bisseling, T. Medicago LYK3, an entry receptor in rhizobial nodulation factor signaling. Plant Physiol. 2007, 145, 183–191.
27. Jones, K.M.; Kobayashi, H.; Davies, B.W.; Taga, M.E.; Walker, G.C. How rhizobial symbionts invade plants: The Sinorhizobium-Medicago model. Nat. Rev. Microbiol. 2007, 5, 619–633.
28. Tao, J.-H.; Wang, D.-G.; Pu, X.-L.; Huang, J.-H.; Zhao, X.; Qiu, W.-Q.; Jiang, S. Signal transduction of atractylodin biosynthesis in Atractylodes lancea cell induced by endophytic fungal elicitor mediated with nitric oxide followed by

salicylic acid. Chin. Tradit. Herb. Drugs 2014, 45, 701–708.

29. Rudrappa, T.; Czymmek, K.J.; Paré, P.W.; Bais, H.P. Root-secreted malic acid recruits beneficial soil bacteria. Plant Physiol. 2008, 148, 1547–1556.
30. Liu, C. Research progress on biological control mechanism of Pseudomonas fluorescens. Sci. Technol. Res. 2014, 23, 683.
31. Fang, Z.Y. The Effects and Mechanisms of Bacillus amyloliquefaciens SQY162 on Biological Control of Bacterial Wilt of Tomato. Nanjing Agric. Univ. 2016, 4, 82.
32. Voges, M.J.E.E.E.; Bai, Y.; Schulze-Lefert, P.; Sattely, E.S. Plant-derived coumarins shape the composition of an Arabidopsis synthetic root microbiome. Proc. Natl. Acad. Sci. USA 2019, 116, 12558–12565.
33. Cai, T.; Cai, W.; Zhang, J.; Zheng, H.; Tsou, A.M.; Xiao, L.; Zhong, Z.; Zhu, J. Host legume-exuded antimetabolites optimize the symbiotic rhizosphere. Mol. Microbiol. 2009, 73, 507–517.
34. Huang, A.-C.; Jiang, T.; Liu, Y.-X.; Bai, Y.-C.; Reed, J.; Qu, B.; Goossens, A.; Nützmann, H.-W.; Bai, Y.; Osbourn, A. A specialized metabolic network selectively modulates Arabidopsis root microbiota. Science 2019, 364, eaau6389.
35. Lebeis, S.L.; Paredes, S.H.; Lundberg, D.S.; Breakfield, N.; Gehring, J.; McDonald, M.; Malfatti, S.; Del Rio, T.G.; Jones, C.D.; Tringe, S.G.; et al. Salicylic acid modulates colonization of the root microbiome by specific bacterial taxa. Science 2015, 349, 860–864.
36. Yang, C.-Q.; Yang, W.-Y.; Liu, J. Advances on Chemical Ecology of Plant Flavonoids. Nat. Prod. Res. Dev. 2018, 30, 2009–2016.
37. Yoneyama, K.; Xie, X.; Nomura, T.; Yoneyama, K.; Bennett, T. Supra-organismal regulation of strigolactone exudation and plant development in response to rhizospheric cues in rice. Curr. Biol. 2022, 32, 3601–3608.e3.
38. Liu, Z.; Beskrovnaya, P.; Melnyk, R.A.; Hossain, S.S.; Khorasani, S.; O'Sullivan, L.R.; Wiesmann, C.L.; Bush, J.; Richard, J.D.; Haney, C.H. A Genome-Wide Screen Identifies Genes in Rhizosphere-Associated Pseudomonas Required to Evade Plant Defenses. mBio 2018, 9, e00433-18.
39. Sasse, J.; Martinoia, E.; Northen, T. Feed Your Friends: Do Plant Exudates Shape the Root Microbiome? Trends Plant Sci. 2018, 23, 25–41.
40. Wang, G.; Kong, J.; Cui, D.; Zhao, H.; Niu, Y.; Xu, M.; Jiang, G.; Zhao, Y.; Wang, W. Resistance against Ralstonia solanacearum in tomato depends on the methionine cycle and the γ-aminobutyric acid metabolic pathway. Plant J. 2019, 97, 1032–1047.
41. Becker, A.; Fraysse, N.; Sharypova, L. Recent advances in studies on structure and symbiosis-related function of rhizobial K-antigens and lipopolysaccharides. Mol. Plant Microbe Interact. 2005, 18, 899–905.
42. Jiang, D.-H.; Kong, S.H.; Guo, Z.-J. Cloning of cryptogein gene and construction of its plant expression vector. J. Zhejiang Univ. 2002, 6, 62–67.
43. Gui, X.; Zhang, P.; Wang, D.; Ding, Z.; Wu, X.; Shi, J.; Shen, Q.-H.; Xu, Y.Z.; Ma, W.; Qiao, Y. Phytophthora effector PSR1 hijacks the host pre-mRNA splicing machinery to modulate small RNA biogenesis and plant immunity. Plant Cell 2022, 34, 3443–3459.
44. Rush, T.A.; Puech-Pages, V.; Bascaules, A.; Jargeat, P.; Maillet, F.; Haouy, A.; Maes, A.Q.; Carriel, C.C.; Khokhani, D.; Keller-Pearson, M.; et al. Lipo-Chitooligosaccharides: From Plant Symbiosis to Conserved Fungal Signals. 2020. Available online: https://www.researchgate.net/publication/342819957_Lipo-chitooligosaccharides_from_plant_symbiosis_to_conserved_fungal_signals (accessed on 10 March 2023).
45. Cope, K.R.; Bascaules, A.; Irving, T.B.; Venkateshwaran, M.; Maeda, J.; Garcia, K.; Rush, T.A.; Ma, C.; Labbé, J.; Jawdy, S.; et al. The Ectomycorrhizal Fungus Laccaria bicolor Produces Lipochitooligosaccharides and Uses the Common Symbiosis Pathway to Colonize Populus Roots. Plant Cell 2019, 31, 2386–2410.
46. Gong, X.-F.; Song, Z.-F.; Ming, M.-G.; Li, Y.-J. Regulation Molecular Mechnisms or Ca2+ Singaling on Plant-Environmental Microorgainsm Interactions. Acta Bot. Boreali-Occident. Sin. 2016, 36, 2128–2136.
47. Modolo, L.V.; Cunha, F.Q.; Braga, M.R.; Salgado, I. Nitric oxide synthase-mediated phytoalexin accumulation in soybean cotyledons in response to the Diaporthe phaseolorumf. sp. meridionalis elicitor. Plant Physiol. 2002, 130, 1288–1297.
48. Yuan, Z.-L.; Zhang, C.-L.; Lin, F.-C. Recent advances on physiological and molecular basis of fungal endophyteplant interactions. Acta Ecol. Sin. 2008, 28, 4430–4439.
49. Lan, W.-Z.; Yu, L.-J.; Li, W.; Cai, H.-X. Selecting Preparation Methods and Isoating Components of Fungal Elicitor to Enhance Taxol Biosyn thesis. Wuhan Bot. Res. 2002, 1, 66–70.

50. Xu, M.-J.; Long, J.F.; Zhu, M.-Y. NO promotes the biosynthesis of puerarin in Pueraria lobata suspension cells through salicylic acid or jasmonic acid signaling pathway mediated by fungal elicitors. Sci. Sin. 2006, 36, 10.