Table1. The fungal elicitors and their effects on secondary metabolites accumulation in medical plants

Plants	cultured system	secondary metabolites	Types of secondary metabolites	Fungal	Fungal elicitors	Types of fungal elicitors	Folds(Compar ed with the control group)	Reference
Artemisia	hairy root	sesquiterpen	artemisinin	Piriformospora	fungal	fungal	2.44 fold	(Ahlawat et al. 2014)
annua L.	culture	e lactone		indica	extract	extract		
Nicotiana	cell	capsidiol	Sesquiterpene	Trichoderma viride	cellulase	cellulase	23 fold	(Mandujano-Chavez et al.
tabacum	culture							2000)
Artemisia	hairy	artemisinin	sesquiterpene lactone	Penicillium	mycelial	fungal	1.33 fold	(Liu et al. 1999)
annua L.	root			chysogenum 3446	extracts	extract		
	cultures							
Artemisia	hairy	artemisinin	sesquiterpene lactone	Colletotrichum	crude	fungal	1.5 fold	(Wang et al. 2006)
annua L.	root			gloeosporioides	cell-wall	extract		
	cultures				extract			
Artemisia	hairy	artemisinin	sesquiterpene lactone	Colletotrichum sp.	mycelial	fungal	1.44 fold	(Wang et al. 2001)
annua L.	root				extracts	extract		
	cultures							
Atractylodes	plantlet	atractylone		Gilmaniella	fungal	fungal	2 fold	(Wang et al. 2012)
lancea				sp.	extract	extract		
Brugmansia	hairy root	scopolamine	tropane alkaloids	yeast	yeast	fungal	7 fold	(Pitta–Alvarez et al. 2000)
candida	culture				extract:	extract		
Catharanthus	cell	catharanthin	indole alkaloid	Pythium vexans	mycelial	fungal	6.8 fold	(Nef et al. 1991)
roseus	culture	e			extracts	extract		
Catharanthus	cell	ajmalicine	indole alkaloid	Fusarium solani,	mycelial	fungal	2.5-3.3 fold	(Zhao et al. 2001)
roseus	culture				homogena	extract		
					te			
Catharanthus	cell	serpentine	indole alkaloid	Absidia cristata	mycelial	fungal	1.2-1.6 fold	(Zhao et al. 2001)
roseus	culture				homogena	extract		

					te			
Catharanthus roseus	cell culture	ajmalicine	indole alkaloid	Penicillium spimulorum	mycelial homogena te	fungal extract	2.5-3.3 fold	(Zhao et al. 2001)
Catharanthus roseus	cell culture	ajmalicine	indole alkaloid	Verticillium dahliae,	mycelial homogena te	fungal extract	2.5-3.3fold	(Zhao et al. 2001)
Catharanthus roseus	cell culture	ajmalicine	indole alkaloid	Pythium irregulare,	mycelial homogena te	fungal extract	2.5-3.3fold	(Zhao et al. 2001)
Catharanthus roseus	cell culture	ajmalicine	indole alkaloid	Ustilaginodia verens	mycelial homogena te	fungal extract	2.5-3.3 fold	(Zhao et al. 2001)
Catharanthus roseus	cell culture	serpentine	indole alkaloid	Fusarium solani,	mycelial homogena te	fungal extract	1.2-1.6 fold	(Zhao et al. 2001)
Catharanthus roseus	cell culture	serpentine	indole alkaloid	Pythium irregulare,	mycelial homogena te	fungal extract	1.2-1.6 fold	(Zhao et al. 2001)
Catharanthus roseus	cell culture	catharanthin e	indole alkaloid	Fusarium solani,	mycelial homogena te	fungal extract	4-6.6 fold	(Zhao et al. 2001)
Catharanthus roseus	cell culture	catharanthin e	indole alkaloid	Pythium irregulare,	mycelial homogena te	fungal extract	4-6.6 fold	(Zhao et al. 2001)
Catharanthus roseus	cell culture	catharanthin e	indole alkaloid	Absidia cristata	mycelial homogena	fungal extract	4-6.6 fold	(Zhao et al. 2001)

					te			
Catharanthus roseus	cell culture	catharanthin e	indole alkaloid	Aspergillum niger,	mycelial homogena te	mycelial homogena te	4-6.6 fold	(Zhao et al. 2001)
Catharanthus roseus	cell culture	catharanthin e	indole alkaloid	Ustilaginodia verens	mycelial homogena te	mycelial homogena te	4-6.6 fold	(Zhao et al. 2001)
Catharanthus roseus	cell culture	ajmalicine	indole alkaloid	Aspergillus niger , Fusarium moniliforme and .	cell wall	cell wall	2 fold	(Namdeo et al. 2002)
Catharanthus roseus	cell culture	ajmalicine	indole alkaloid	Trichoderma viride	cell wall	cell wall	3 fold	(Namdeo et al. 2002)
Centella asiatica L.	cell culture	asiaticoside	saponin	yeast	yeast extract	fungal extract	1.4 fold	(Kim et al. 2004)
Cichorium intybus L.	hairy root cultures	coumarin	coumarin	Phyophthora parasitica	media titrate	fungal extract	1.3 fold	(Bais et al. 2000)
Cinchona robusta How.	cell culture	anthraquino ne	anthraquinone	Phytophthora cinnamomi	mycelial homogena te	mycelial homogena te	4 fold	(Ramos-Valdivia <i>et al.</i> 1997)
Coleus blumei	cell culture	rosmarinic acid	alcohol glycoside	Pythium aphanidermatum	glucose equivalent	fungal extract	2 fold	(Szabo <i>et al.</i> 1999)
Cupressus lusitanica	cell culture	β-thujaplicin		fungal elicitor and ferrous ion			3-4 fold	(Zhao et al. 2001)
Daucus carota L.	cell culture	p-hydroxybe nzoic acid		Pythium aphanidermatum (Edson) Fitzp.	mycelial homogena te	mycelial homogena te	2.5 fold	(Schnitzler et al. 1992)
Daucus	callus	anthocyanin	flavonoids	Aspergillus	mycelial	mycelial	1.25 fold	(Rajendran et al. 1994)

carota L.	cultures			flavus	extract	extract		
Dioscorea galeottiana	cell culture	diosgenin	Saponin	Alternaria tenuis	fungal extract	fungal extract	1.2 fold	(Rojas et al. 1999)
Euphorbia pekinensis	cell culture	isoeuphpeki nensin/euph ol	terpenoid	Fusarium sp.	fungal extract	fungal extract	5.81 fold/3.56 fold	(Gao et al. 2011)
Hyoscyamus muticus	root culture	lubimin	sesquiterpene	Rhizoctonia solani	crude cell wall	cell wall	4 fold (compared with MeJa-induced group)	(Singh et al. 1998)
Hypericum perforatum L	shoot organ culture	hypericin	glycoside	yeast	mannan	fungal extract	2 fold	(Kirakosyan et al. 2000)
Hypericum perforatum L	shoot organ culture	pseudohyper icin	anthraquinone	yeast	mannan	fungal extract	4 fold	(Kirakosyan et al. 2000)
Hypericum perforatum L	cell culture	phenolic compounds	flavonoids	Colletotrichum gloeosporioides	fungal extract	fungal extract	2.7 fold	(Conceiçao et al. 2006)
Linum album	root culture	lignan	lignan	Fusarium graminearum	fungal extract	fungal extract	2-3 fold	(Bahabadi et al. 2014)
Linum album	root culture	lignan	lignan	Trichoderma viride	fungal extract	fungal extract	2.4 fold	(Bahabadi et al. 2014)
Linum album	root culture	lignan	lignan	Sclerotinia sclerotiorum	fungal extract	fungal extract	2 fold	(Bahabadi et al. 2014)
Lithospermu m	cell culture	Shikonin	Naphthoquinones	PenicilIium species	cell powder	cell powder	65 fold	(Kim et al. 1990)

erythrorhizon								
Nicotiana tabacum	cell culture	capsidiol	sesquiterpene	Trichoderma viride	celluase	celluase	5 fold	(Mandujano-Chavez et al
Panax ginseng	cell culture	saponin	saponin	yeast	yeast extract	fungal extract	28 fold	(Lu et al. 2001)
Panax ginseng C.A. Meyer	hairy root culture	ginseng saponin	saponin	yeast	yeast extracts	fungal extract	1.17 fold	(Jeong et al. 2005)
Meyei Piqueria trinervia	cell culture	antifungal monoterpene	monoterpene	Alternaria alternata, Fusarium poae , Phaecilomyces elegan	fungal strains	fungal strains	/	(Saad et al. 2000)
Polygonum tinctorium	cell culture	indirubin	indole alkaloid	Rhizoctonia solani	cell wall	cell wall	1.43 fold	(Mareroa <i>et al.</i> 1997)
Psoralea corylifolia L.	cell culture	psoralen	furocoumarine	Aspergillus niger	fungal extract	fungal extract	9-fold	(Ahmed et al. 2014)
Psoralea corylifolia L.	cell culture	psoralen	furocoumarine	Penicillium notatum	fungal extract	fungal extract	4-7 fold	(Ahmed et al. 2014)
Rubia tinctorum L.	cell culture	anthraquino ne derivatives	anthraquinone	Botrytis cinerea	fungal polysacch aride	polysacch aride	/	(Orbán <i>et al.</i> 2008)
Scutellaria baicalensis	cell culture	triterpenoids	terpenoids	yeast	yeast extract	fungal extract	2.8 fold	(Yoon et al. 2000)
Solanum tuberosum	hairy root cultures	antimicrobia l	sesquiterpenes	Agrobacterium rhizogenes	mycelial homogena	mycelial homogena	2 fold	(Komaraiah et al. 2003)
		sesquiterpen es			te	te		

Solanum	cell	isoprenoid	sesquiterpenoid	Phytophthora	arachidoni	arachidoni	/	(Choi et al. 1994)
tuberosum L.	culture			infestans	c acid	c acid		
Salvia	hairy root	tanshinone	diterpene	Trichoderma	hyphae	hyphae	21.1 fold	(Ming et al. 2012)
miltiorrhiza	culture			atroviride				
Bge.								
Taverniera	root	saponin	glycyrrhizic acid	Aspergillus niger	hyphae	hyphae	2 fold	(Awad et al. 2014)
cuneifolia	culture							
(Roth) Arn.								
Taverniera	root	saponin	glycyrrhizic acid	Aspergillus tenuis	hyphae	hyphae	1 fold	(Awad et al. 2014)
cuneifolia	culture							
(Roth) Arn.								
Taverniera	root	saponin	glycyrrhizic acid	Penicillium	hyphae	hyphae	2 fold	(Awad et al. 2014)
cuneifolia	culture			fellutanum				
(Roth) Arn.								
Taverniera	root	saponin	glycyrrhizic acid	Fusarium	hyphae	hyphae	2.5 fold	(Awad et al. 2014)
cuneifolia	culture			moniliforme Sheldon				
(Roth) Arn.								
Taverniera	root	saponin	glycyrrhizic acid	Mucor hiemalis	hyphae	hyphae	3 fold	(Awad et al. 2014)
cuneifolia	culture			Wehmer				
(Roth) Arn.								

Table2. The accumulation of secondary metabolites induced by fungal elicitors and their related signaling molecules

Plants	cultured	secondary	Types of	Fungal	Fungal elicitors	Types of	Related signaling	Reference
	system	metabolites	secondary			fungal	molecules	
			metabolites			elicitors		
Artemisia	cell	artemisinin	sesquiterpene	Fusarium	mycelium	myceliu	NO/H ₂ O ₂	(Zheng et al. 2010)s
annua	culture		lactone	oxysporum		m		

						extract		
Atractylodes lancea	cell culture	volatile oil	mixture	Cunninghamel la sp AL4	crude extract	fungal extract	NO/H ₂ O ₂	(Fang et al. 2009)
Atractylodes lancea	whole planet	volatile oil	mixture	Gilmaniella sp.	fungal extract	fungal extract	NO mediates the process through SA and H ₂ O ₂ dependent pathways	(Wang et al. 2011)
Catharanthu s roseus	cell culture	terpenoid indole alkaloid	indole alkaloid	Aspergillum niger	fungal extract	fungal extract	Ca ²⁺ /ROS	(Zhao et al. 2001)
Catharanthu s roseus	cell culture	terpenoid indole alkaloid	indole alkaloid	yeast	yeast extract	fungal extract	JA	(Menke FL1 1999)
Catharanthu s roseus	cell culture	catharanthine	indole alkaloid	Penicillium citrinum	cell wall	cell wall	NO(generated by NOS or NOS-like enzymes)	(Xu et al. 2005)
Catharanthu s roseus	cell culture	catharanthine	indole alkaloid	Aspergillus niger	mycelia	mycelia extract	${\rm O}^{2}$ rather than ${\rm H}_2{\rm O}_2$	(Xu et al. 2005)
Catharanthu s roseus	cell culture	catharanthine	indole alkaloid	Aspergillus niger	mycelia	mycelia extract	NO	(Xu et al. 2005)
Camptotheca acuminata	cell culture	camptothecin	indole alkaloid	Phytophthora boehmeriae	protein elicitor PB90	fungal extract	NO(NR-mediated NO generation)	(Lu et al. 2011)
Cupressus lusitanica	Callus culture	β-thujaplicin	tropolone	/	fungal extract	fungal extract	JA	(Zhao et al. 2001)
Cupressus lusitanica	cell culture	β-thujaplicin	tropolone	yeast	oligosaccharide fraction	fungal extract	Ca ²⁺ influx/G-proteins	(Zhao et al. 2003)
Cupressus lusitanica	cell culture	β-thujaplicin	tropolone	yeast	yeast extracts	fungal extract	cAMP/Ca ²⁺ / K ⁺ fluxes	(Zhao et al. 2004)a

Cupressus	cell	β-thujaplicin	tropolone	yeast	yeast extracts	fungal	H ₂ O ₂ /NO	(Zhao et al. 2007)
lusitanica	culture					extract		
Cupressus	cell	β-thujaplicin	tropolone	yeast	yeast extracts	fungal	inositol	(Zhao et al. 2004)b
lusitanica	culture					extract	1,4,5-trisphosphate	
							pathway via a Ca ²⁺	
							signaling pathway	
Cupressus	cell	β-thujaplicin	tropolone	yeast	yeast extracts	fungal	Ca ²⁺ /ETH/JA	(Zhao et al. 2004)
lusitanica	culture					extract		
Euphorbia	cell	isoeuphpekinen	terpenoid	Fusarium sp.	fungal elicitor	fungal	NO/SA	(Gao et al. 2012)
pekinensis	culture	sin				elicitor		
Ginkgo	cell	flavonoid	flavonoid	Sphaeropsis sp	fungal elicitor	fungal	ABA	(Hao et al. 2010)
biloba	culture			B301		elicitor		
Ginkgo	cell	flavonol	flavonol	Phytophthora	protein(90 kD)	fungal	JA/SA	(Xu et al. 2009)
biloba	culture	glycoside	glycoside	boehmeriae		extract		
				PB90				
Hypericum	cell	hypericin	anthrone	Phytophthora	protein(90 kD)	fungal	NADPH	(Qin et al. 2004)
perforatum	culture			boehmeriae		extract	oxidase-mediated	
				PB90			H ₂ O ₂ signaling	
							pathway	
Hypericum	cell	hypericin	anthrone	Phytophthora	cell wall extract	cell wall	JA	(Walker et al. 2002)
perforatum	culture			cinnamoni				
Hypericum	cell	hypericin	anthrone	Aspergillum	fungal extract	fungal	NO mediates it	(Xu 2005)
perforatum	culture			niger		extract	partially via	
							a JA-dependent	
							signaling pathway	
Inonotus	cell	antioxidant	polyphenols	Alternaria	fungal extract	fungal	NO mediates the	(Zheng et al. 2009)
obliquus	culture	polyphenols		alternata		extract	process via a	
							signalling pathway	

Panax ginseng C. A. Meyer	cell culture	saponin	saponin	Colletotrichu m lagenarium	Cle	cell wall	independent of oxylipins or JA singlet oxygen /ethylene(ETH)	(Xu et al. 2005)
Meyer Panax ginseng C. A. Meyer	adventiti ous root	saponin	saponin	yeast	yeast extract	fungal extract	JA/H ₂ O ₂	(Rahimi et al. 2014)
Petroselinum crispum	cell culture	phytoalexin	mixture	Phytophthora sojae	crude cell wall	cell wall	Ca ²⁺ /O ₂ -	(Jabs <i>et al.</i> 1997)
Pueraria thomsonii Benth.		puerarin	flavonoid	Penicillium citrinum	fungal extract	fungal extract	NO might mediate it through SA- and JA-dependent signal pathways	(Xu et al. 2006)
Sanguinaria canadensis L.	cell culture	benzophenanthr idine alkaloid	alkaloid	Penicillium expansum	fungal extract	fungal extract	G proteins	(Mahady <i>et al.</i> 1998)
Solenostemo n scutellarioid es	whole plant	rosmarinic acid		Aternaria alternate/Aspe rgillus niger/ Fusarium solani	fungal extract	fungal extract	JA/H ₂ O ₂	(Dewanjee et al. 2014)
Sorbus aucuparia	cell culture	aucuparin	biphenyl	yeast	yeast extract	yeast extract	H_2O_2 rather than that of O_2	(Qiu et al. 2012)
Taxus yunnanensis	cell culture	taxol	diterpene	Fusarium sp.	cerebroside	fungal extract	NO	(Wang et al. 2004)
Taxus chinensis	cell culture	taxol	diterpene	/	mycelial wall	mycelial wall	SA	(Yu et al. 2001)

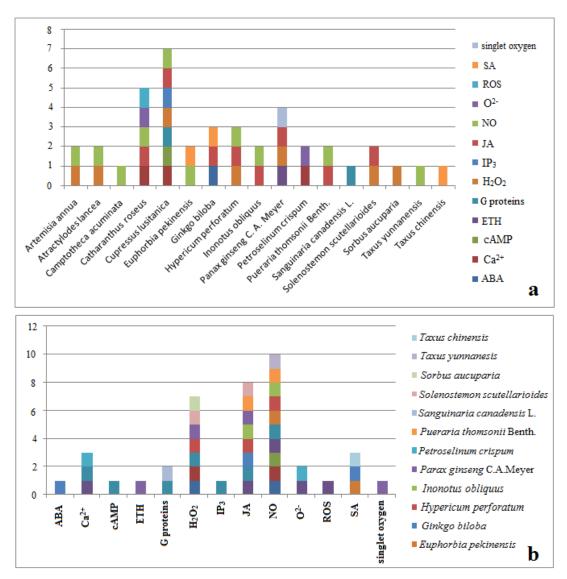


Figure 1. a. The signal molecules which have ben investigated in medicinal plants induced by fungal elicitors. b.The frequecy of each signaling molecules having been studied in the process of secondary metabolites accumulation induced by fungal elicitors in medicinal plants.

Figure 1.a. summarizesthe signal molecules which are involved in different kinds of medicinal plants in fungal elicitor- inducing process. The figure displays several signaling molecules been studied in Artemisia annua, Atractylodes lancea, Camptotheca acuminata, Catharanthus roseus, Cupressus lusitanica, Euphorbia pekinensis, Ginkgo biloba, Hypericum perforatu, Inonotus obliquus, Panax ginseng C. A. Meyer, Petroselinum crispum, Pueraria thomsonii Benth., Sanguinaria canadensis L., Solenostemon scutellarioides, Sorbus aucuparia, Taxus yunnanensis and Taxus chinensis. We can see that the fungal elicitor-inducing secondary metabolites accumulation in *Cupressus lusitanica* are studied most frequently, involving Ca²⁺, cAMP, G protein, H₂O₂, IP₃, JA, NO. That is to say that Cupressus lusitanica are the most commonly researched medicinal plant about signal transduction so far. The nextin rank is Catharanthus roseus and Panax ginseng. We can study the signal transduction of secondary metabolites accumulation in other medicinal plants induced by fungal elicitor according to the mature approach applied in the research of Cupressus Iusitanica, Catharanthus roseus and Panax ginseng. With the further study in other medical plants, we cantry to find the similarities and differences in different medicinal plants and summarize the rule of signal transduction of secondary metabolites accumulation induced by fungal elicitor in medical plants.b. shows the frequency of the signal molecule having been studied in fungal- inducing process in medicinal plants so far. We can see that NO, ABA, Ca²⁺, cAMP, ETH, G protein, IP₃, O₂-, ROS, H₂O₂ and JA are related to the secondary metabolism induced by fungal elicitors in medical plants. Among these signaling molecules, NO is the signaling molecule which is studied most frequently and followed by H₂O₂ and JA. This illustrates that these three signaling molecules may be relevant widely to the signal transduction of secondary metabolisminduced by fungal elicitors in medical plants. That is to say NO, JA, H₂O₂ may be the essential signaling molecules in the process of fungalinduced secondary metabolism though more research isneeded to support this argument. On the other hand, ABA, Ca²⁺, cAMP, ETH, G protein, IP₃, O₂, ROS and singlet oxygen are less studied in fungal- induced secondary metabolism. Therefore, we can pay more attention to the study of these signal molecules for improving the whole lines of signal transduction.

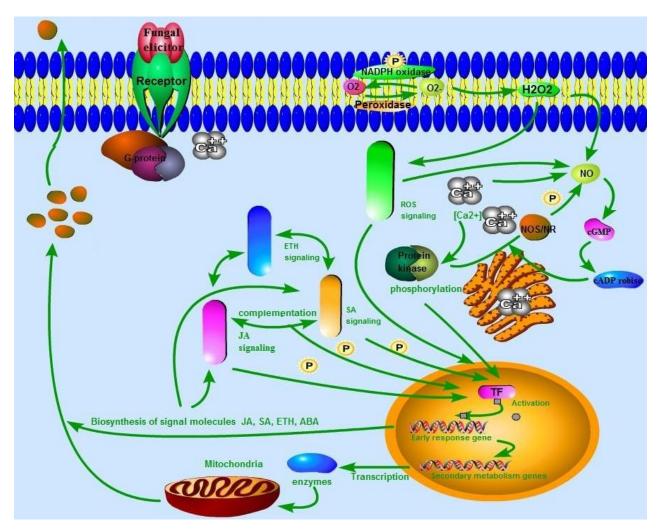
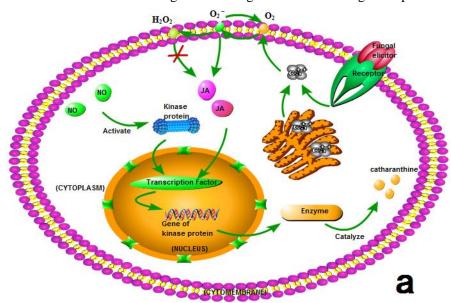


Figure 2. The signaling pathway of fungal elicitor inducing secondary metabolites synthesis in plant cell

Fungal elicitors are identified and combined by receptors selectively on cell membrane, next the expression of related genes is regulated in the nucleus through complicated signal transduction pathways, and ultimately this activates the defensive secondary metabolism system to accumulate specific secondary metabolites. There are many signal molecules involved in the fungal elicitors-induced secondary metabolites in medical plants, such as Ca²⁺,

cAMP, inositol phosphate, G protein, salicylic acid, jasmonic acid, NO, ETH and so on. The signal transduction is intricacy and several signal molecules interact and talk with one another under different circumstances. In general, fungal elicitors cause the ion channels to open and G protein coupling through IP₃ as intracellular second messengers. The production of ROS through oxidative burst is common and universal. O₂ and H₂O₂ are transformed mutually and mediate different signal pathway in various medical plantsand NO can respectively delivery the signaling through dependent- or independent- oxidative burst signaling pathway. NO can promote the accumulation of SA which can hold up the synthesis of JA in plant cells There is a relationship of mutual inhibition but also special coordination complementary between SA and JA signaling pathways. All those signal molecules are involved in the accumulation of secondary metabolites in fungal-induced medical plants however, the mechanism is clearly defined, but they eventually gather into the response of transduction factors which is a bridge between signal molecules and gene expression.



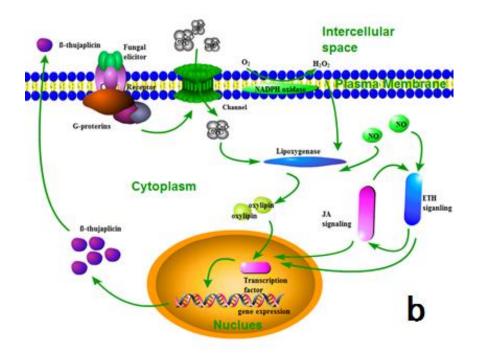


Figure 3 a. Fungal elicitor signaling pathway leading to catharanthine biosynthesis in *Catharanthus roseus*cell cultures.b. Fungal elicitor signaling pathway leading to β -thujaplicin biosynthesis in the cell of *Cupressus lusitanica*.

a. Ca^{2+} influx is a prerequisite for an elicitor-triggered oxidative burst as the first message transducer. Due to the oxidative burst, a substantial lipid peroxidation is related to indole alkaloid production. Thus fungal elicitor-induced indole alkaloid accumulation in *Catharanthus roseus* cell cultures is mediated at least partially by ROS or lipid peroxidation via the jasmonate signaling pathway. O_2^- rather than H_2O_2 from oxidative burst was demonstrated to be necessary for mediating fungal elicitor-induced catharanthine biosynthesis. NO released from SNP triggeresfungal elicitor- induced terpenoid indole alkaloid biosynthesis of *C. roseus* cells through a protein kinase-dependent signal pathway. b. Fungal elicitor signaling pathway leading to β -thujaplicin biosynthesis in *Cupressus lusitanica* cell cultures. The ethylene and jasmonate signaling pathways can be regulated upstream by Ca^{2+} whose influx negatively regulates ethylene production, and differentially regulates fungal elicitor- or methyl jasmonate-stimulated ethylene productionand G-proteins may mediate elicitor signals to the jasmonate pathway. The ethylene and jasmonate pathways interact in mediating β -thujaplicin production, with the jasmonate pathway controlling the production and the ethylene pathway acting as as a fine modulator for accumulation of β -thujaplicin (Zhao *et al.* 2004). Reactive oxygen species (ROS) and nitric oxide (NO) signaling interact in cell death induction and β -thujaplicin production in Cupressus lusitanica cell cultures. Yeast elicitor

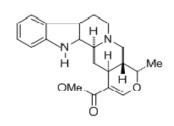
activates multiple signal components such as GTP-binding proteins, Ca^{2+} influx, and protein kinases. Following O_2^- , H_2O_2 and NO generation in elicited *C. lusitanica* cell cultures, jamonate and ethylene accumulate to induce β -thujaplicin production. NO at low concentration induces cell death while high NO concentrations may inhibit ascorbate peroxidase (APX) activity and lipid peroxidation, probably through peroxynitrite. H_2O_2 and NO enhance each other's production and H_2O_2 is a positive inducer for β -thujaplicin production, most probably through hydroxyl radical-dependent lipid peroxidation-derived oxylipin signaling(Zhao *et al.* 2007).

Shikonin, the only secondary metabolite that is successfully produced by large-scale plant cell culture

Psoralea, furocoumarine from Psoralea corylifolia L. cell induced by fungal elicitor

Tanshinone IIA, a diterpene which make big breakthrough in fungal elicitor-inducing process

Hypericin, the secondary metabolite produced by Hypericum perf oratum cell



Ajmalicine, an extensively studied teepenoid indole from *Catharanthus roseus* cell

Aucuparin, the biphenyl compounds produced in *Sorbus* aucuparia cell

Catharanthine, a widely researched indole alkaloid from Catharanthus roseus

HO HO OH H

Puerarin, the flavonoid produced by *Pueraria* thomsontt Benth.,which are used to study the signal transduction of secondary metabolism

Figure 4. Several secondary metabolites tightly related to fungal elicitor-inducing effects.