International Journal of Scientific Research and Management (IJSRM)
||Volume||5||Issue||07||Pages||6215-6225||2017||
Website: www.ijsrm.in ISSN (e): 2321-3418
Index Copernicus value (2015): 57.47 DOI: 10.18535/ijsrm/v5i7.51

Role of Phytoalexins in Plant-Microbe Interactions and Human Health

Suman Sen.

Assistant Professor of Botany, Department of Botany, A. C. College, Jalpaiguri-735101

Abstract: The biochemical basis of defence mechanisms in plants, conferring disease resistance is under active investigation for years. Plants have evolved a broad array of defense mechanisms involved in disease resistance. Synthesis of Phytoalexins is one such mechanism. Phytoalexins are low molecular weight antimicrobial compounds that are produced by plants as a response to biotic and abiotic stresses. As such they take part in an intricate defense system which enables plants to control invading microorganisms. Most of what is known about phytoalexins derives from extensive work on a limited number of plant families. Various pathways are utilized for producing different phytoalexins. Phytoalexins are considerably less toxic than chemical fungicides. Gain- or loss-of-function genetic approaches addressing phytoalexin production for disease resistance have provided direct and indirect proofs of their implication in plant-microbe interactions. Besides that, Phytoalexins have been reported to display health-promoting effects in humans. A few of them have been reported to exert antioxidant, anti carcinogenic and cardiovascular protective activities.

Keywords: phytoalexins; plants defense mechanisms; biotic stress; antioxidant; fungicides

Introduction:

Plant resistance mechanisms are effective at different levels in host-parasite interactions and include preformed physical and chemical defence barriers as well as defence triggered by the invader. One inducible defence response is the synthesis of phytoalexins at the site of attempted infection. Phytoalexins have been defined as antimicrobial compounds of low molecular weight that are both synthesized as well as accumulated in plants after the exposure of the plant to microorganisms. The concept that resistance is an active process or induced as a result of an interaction between plant and pathogen was clearly formulated in the phytoalexin hypothesis, proposed by Muller and Borger in 1940.As a result of this hypothesis, research initiated in the 1950s led to the isolation and chemical characterization of the first phytoalexin, Pisatin in the early 1960s.Phytoalexin induction is now recognised as an important defence mechanism in plants against microbial infection. Earlier studies of this de novo resistance process suggested that a range of different secondary metabolites were produced, but generally the type of phytoalexin produced was family specific. Recent research corroborated this, although several families have now been recorded as producing more than one class of phytoalexin. The role of these compounds in plant defence has been intensively studied ever since. Resistance appears to depend on the ability of the host to recognize the pathogen rapidly and induce these defence responses in order to limit pathogen spread. Application of molecular technologies has yielded significant new informations on mechanisms involved in pathogen recognition, signal transduction and defence related gene activation, and is leading to novel strategies for engineering enhanced disease resistance.

Characteristics of Phytoalexins: Whitney (1976) summarized some of the very important characteristics of these antimicrobials which are as follows-

i) Phytoalexins are active in a very low concentration and may be fungistatic and bacteriostatic.
ii) They are produced by the host plant in response to infection or in response to the metabolic by-products of microbes and to certain other stimuli.
iii) They are normally absent in healthy cells or present in minute quantities, if at all present.
iv) They usually function close to their site of production.
v) They are produced in quantities proportional to the size of inoculums.
vi) They are produced in larger quantities in response to weak pathogens than to virulent pathogens.
vii) They are produced relatively quickly by the cells, usually within 12-14 hours, reaching the peak around 24 hours after inoculation.
viii) Phytoalexins are host specific rather than pathogen specific.

Chemical Diversity of Phytoalexins: Most of what is known about phytoalexins, derives from extensive work on a limited number of plant families: Fabaceae and Solanaceae [3, 4], on one hand, and investigations on one or a few species within other plant families, namely Amaryllidaceae, Euphorbiaceae, Orchidaceae, Chenopodiaceae, Compositae, Convolvulaceae, Ginkgoaceae, Poaceae, Moraceae,Orchidaceae, Piperaceae, Rosaceae, Rutaceae and Umbelliferae on the other hand [5]. More intensive studies recently focused on phytoalexins from plant families of significant economic importance: Poaceae (maize and rice) [6], Vitaceae [7, 8] and Malvaceae (cotton) [9]. Most phytoalexins produced by the Leguminosae belong to six isoflavonoid classes: isoflavones, isoflavanones, pterocarpans, pterocarpenes, isoflavans and coumestans (Table-1). Some pterocarpan phytoalexins are especially well known: pisatin, phaseollin, glyceollin, medicarpin and maackiain. Pisatin was the first phytoalexin to be isolated and characterized from garden pea, *Pisum sativum* [39]. Besides these compounds, a small number of legumes also produce non-isoflavonoid phytoalexins such as furanoacetylenes and stilbenes (Table- 1).

Table - 1. Phytoalexins from different plant families [38].

Plant Families	Types of Phytoalexins
Amaryllidaceae	Flavans
Brassicaceae	Camalexin(Indole); Brassinin(sulphur containing)
Chenopodiaceae	Betagarin(Flavanones); betavulgarin(Isoflavones)
Compositae	Safynol (Polyacetylenes)

Convolvulaceae	Ipomeamarone (Furanosesquiterpenes)
Euphorbiaceae	Casbene (Diterpenes)
Poaceae	Momilactones(Diterpenoids); Oryzalexins; Zealexins; Phytocassanes; Kauralexins; Apigeninidin; Phenylamides Luteolinidin(Deoxyanthocyanidins);Sakuranetin (Flavanones)
Leguminosae	Isoflavones; Isoflavanones; Coumestans(Isoflavans) Pisatin((Pterocarpans); Phaseollin, Glyceollin and Maiackiain;Wyerone(Furanoacetylenes);Resveratrol (Stilbenes);Pterocarpens
Malvaceae	Terpenoids; gossypol(naphtaldehydes)
Moraceae	Moracins A-H (Furanopterocarpans)
Orchidaceae	Loroglossol(Dihydrophenanthrenes)
Rutaceae	Xanthoxylin (Methylated phenolic compounds)
Apiaceae	Falcarinol(Polyacetylenes) ; Xanthotoxin(Phenolics); 6-methoxymellein
Vitaceae	Resveratrol (Stilbenes)
Rosaceae	Auarperin(Biphenyls) Cotonefurans (Dibenzofurans)
Solanaceae	Phenylpropanoid related compounds; Steroid glycoalkaloids; Norsequi and sesquiterpenoids; Coumarins ;Polyacetylenic derivatives.

Phytoalexin Biosynthetic Pathways: Different phytoalexins utilize different pathways for its synthesis. The three most characteristic ones are outlined below -

1) The phenylpropanoic-polymalonic acid route: All flavonoid phytoalexins (isoflavonoids, isoflavones, pterocarpans, isoflavans, coumestans and arylbenzofurans) as well as stilbene phytoalexins and derivatives (dihydrophenanthrenes) are formed through the universal phenylpropanoic-polymalonic acid pathway. It begins with phenylalanine and the phenylalanine ammonia lyase (PAL) or sometimes with tyrosine and the tyrosine ammonia lyase (TAL). The obtained *para*-coumaric acid is activated to form para-coumaroyl-CoA by ligation to a coenzyme A by 4-coumaroyl: CoA ligase (C4L). Subsequently, chalcone synthase (CHS) on the one hand and stilbene synthase (STS) on the other hand use this same substrate and condense it with three successive units of malonyl-CoA, leading respectively to the

production of naringenin chalcone, the first C15 intermediate in the flavonoid pathway and resveratrol, the precursor of all stilbenes. This pathway is found in Fabaceae for the production of flavonoid and stilbenoid phytoalexins [38].

2) The methylerythritol phosphate and geranyl-geranyl diphosphate pathway: These phytoalexins are represented by members of the monoterpene, sesquiterpene, carboxylic sesquiterpene and diterpene families. Specific attention will be given to the diterpene phytoalexin class [6]. Diterpenoids result from the subsequent action of diverse enzymes using GGDP as the starting block. Class II diterpene cyclases named copalyldiphosphate synthases (CPS) are the first to act on GGDP catalyzing the initial cyclization of the latter to copalyldiphosphate (CDP). CDP is the required substrate for class I diterpene synthases named kaurene synthase like (KSL). Sequential action of CPS and KSL produces the olefin precursors of the main diterpene phytoalexin families [6].
3) The indole phytoalexin pathway: An indole phytoalexin is camalexin, the major phytoalexin of *Arabidopsis.* The indolic ring of camalexin is derived from tryptophan (Trp) which in turn arises from chorismate. The first step in the route from Trp to camalexin is under the control of two cytochrome P450 homologues, leading to indole-3-acetaldoxime. The latter is then transformed into indole-3-acetonitrile (IAN) via the cytochrome P450. Subsequently conjugation of IAN with glutathione takes place by the combined action of a glutathione-S-transferase and most likely a cytochrome P450. The IAN glutathionyl derivative is then converted into IAN cysteinyl-glycine via a phytochelatin synthase or into γ-glutamyl-cysteine IAN through the action of two γ-glutamyl transpeptidases 1 and 3. Both intermediates lead to the IAN cysteine conjugate. In the last step of this biosynthesis pathway camalexin is formed via dihydrocamalexic acid by a multifunctional enzyme.[38]

Biosynthesis of phytoalexin is up- or down regulated by expression of many endogenous molecules such as phytohormones (jasmonic acid, salicylic acid, ethylene, auxins, abscisic acid, cytokinins and to a lesser extent gibberellins), transcriptional regulators, defense-related genes, phosphorylation relays and cascades [1, 2].Regulatory mechanisms of phytoalexin biosynthesis also depend on the nature of the infecting pathogen as well as the nature of the induced phytoalexin itself. Other phytohormones have been involved in the regulatory mechanisms of phytoalexin biosynthesis. Auxins and abscisic acid (ABA) generally appear to negatively regulate phytoalexin production [1].

Mechanism of action: Fungitoxicity due to phytoalexin is clearly evidenced by the inhibition of germ-tube elongation, radial mycelial growth and/or mycelia dry weight increase. Phytoalexin antifungal activity can considerably vary from one compound to another. For example, Hasegawa *et al*. showed that the rice phytoalexin sakuranetin displays a higher activity against the blast fungus than does another rice phytoalexin, momilactone A, both *in vivo* and *in vitro* [15]. Phytoalexins may also exert some effects on the

cytological, morphological and physiological characteristics of fungal cells. The activity of four phytoalexins from the Solanaceae family (rishitin, phytuberin, anhydro-β-rotunol and solavetivone) on three *Phytophthora* species resulted in loss of motility of the zoospores, rounding-up of the cells associated with some level of swelling, cytoplasmic granulation and bursting of the cell membrane [16]. The two latter are very similar features of the action of phytoalexins on fungal cells ([13, 14, 17] and references therein). The extensive membrane damage occurring after fungal exposure to phytoalexins is reflected in substantial leakage of electrolytes and metabolites [18]. Asymetric growth of the germ tube resulting in the production of "curved-germ tubes" has also been observed in *B. cinerea* conidia treated with sub-lethal doses of resveratrol [13]. This cytological abnormality suggests that stilbenic compounds may interact with tubulin polymerization, the mode of action of many synthetic fungicides and anticancer agents [19]. Moreover, phytoalexins may affect glucose uptake by fungal cells as reported in the interactions between phaseollin or kievitone and *Rhizoctonia solani* [18]. Observations of *B. cinerea* conidia showed a complete disorganization of mitochondria and disruption of the plasma membrane upon treatment with the stilbene phytoalexins, resveratrol and pterostilbene [13, 14, 17]. Pterostilbene especially led to a rapid and complete cessation of respiration in *B. cinerea* conidia which can be explained by its activity as an uncoupling agent of electron transport and phosphorylation [17]. Camalexin has recently been involved in the induction of fungal apoptotic programmed cell death in *B. cinerea* [20]. The efficaciousness *in vivo* of some phytoalexins, namely the coumarin phytoalexin, scopoletin on the reduction of green mold symptoms caused by *Penicillium digitatum* on oranges was shown [21]. In the same way, phenolic phytoalexins (resveratrol, scopoletin, scoparone and umbelliferone) were shown to significantly inhibit the growth of *Penicillium expansum* and patulin accumulation in apples [22]. To increase the fungitoxicity of phytoalexins, design and synthesis of more active phytoalexin derivatives is needed [23, 24].Beside their antifungal activity, phytoalexins possess some antibacterial activity. Rishitin for instance decreased the viability of cells of *Erwinia atroseptica* by around 100% at a dose of 360 µg/L [25]. Resveratrol also exerts some activity against numerous bacteria affecting humans like *Chlamydia*, *Helicobacter*, *Staphylococcus, Enterococcus*, *Pseudomonas* and *Neisseria* [10] .It is thus clear that phytoalexins exhibit toxicity across much of the biological spectrum, prokaryotic and eukaryotic.

Role of Elicitors in triggering phytoalexins: Phytoalexins are considerably less toxic than chemical fungicides. Effective doses of phytoalexins generally fall within orders of magnitude 10^{-5} to 10^{-4} M [12, 13]. Phytoalexin antifungal activity can considerably vary from one compound to another. In *Pisum sativum* cv.*Alcan* endocarp tissue when infected with incompatible fungal pathogen *Fusarium solani* f.asp. *phaseoli* or fungal elicitors induce accumulation of pisatin, a phytoalexin. Kessmann et.al. (1987) showed that cell suspension culture of *Cicer arietinum* from cultivars ILC 3279 and ILC 1929 were found to be resistant and susceptible to *Ascochyta rabiei*, the chickpea pathogenic fungus. The cultures of the two cultivars

significantly differ in accumulation of phytoalexin medicarpin and maackiain, elicited on the use of yeast extract as an inducing agent. Treatment of tubers of *Solanum tuberosum* or cell cultures with fungal culture of *Phytophthora infestans* or arachidonic acid elicited accumulation of sesquiterpenoid phytoalexins.(Rohwer *et. al.*,1987).The callus of *Trifolium repens* when treated with 1 millimolar p-chloromercuribenzoic acid(PCMBA) stimulates the biosynthesis of medicarpin phytoalexin as demonstrated by Gustine *et.al*.(1987). Biosynthetic activity of carrot phytoalexin 6-methoxymellen was induced in cell suspension culture by treatment with oligogalacturonide elicitor. Elicitors from plant pathogen *Erwinia carotovora* trigger coordinate induction of the tryptophan biosynthesis pathway and trp oxidizing genes in *Arabidopsis thaliana*. Brader *et.al*. (2001) characterized the production of secondary defence metabolites such as camalexin and indole glucosinolates derived from precursors of this pathway. Inspite of evidences pouring in from across the globe, still the mechanisms involved in the elicitation process of phytoalexins, by both biotic and abiotic elicitors, is not yet clearly understood.

Phytoalexin engineering and its role in plant defence: Incase of grapevine phytoalexin resveratrol relatively simple gene construct with the introduction of single gene is done which is controlled by stilbene synthase (STS).Increased disease resistance due to introduction of foreign phytoalexin gene into a novel plant was first reported by Kindl and group with the transfer of Vst1 and Vst2 (grapevine STS genes) into tobacco.Introduction of these two genes confer higher resistance to *B. Cinerea*.Since then, number of transformations were done in alfalfa, rice, barley, wheat, tomato, papaya and Arabidopsis using the same STS genes or STS genes from other plant origins, conferring resistance to various pathogens [1].

Following the works on stilbene phytoalexins, other genetic transformations were achieved with other phytoalexin genes. Surprisingly, engineering phytoalexins seems to have been limited to exploiting only a few phytoalexin biosynthetic genes. Overexpression of the isoflavonoid-7-*O-methyltransferase* in alfalfa, an enzyme with a crucial role in the biosynthesis of the phytoalexin maiackiain, was also linked to an increased resistance of that plant to *Phoma medicaginis* [26]. Transformation of soybean hairy roots with both the peanut resveratrol synthase 3 *gene* and resveratrol-*O-methyltransferase* gene catalyzing the transformation of resveratrol to pterostilbene [27] resulted in the resistance of that plant to *Rhizoctonia solani* [28]. In many cases, engineering the entire phytoalexin biosynthetic pathway is not feasible and the problem researchers are facing is to choose the right enzyme catalyzing the limitant step of this pathway. Finally loss-of-function genetic approaches have underlined the role of phytoalexin glycosylation in plant-pathogen interactions. Transgenic tobacco leaves downregulated for a tobacco specific phenylpropanoid glucosyltransferase saw their scopolin content decreased by 70% to 75% associated with a 63% increase in TMV lesion surfaces [29]. Indirect modulation of phytoalexin levels through manipulation of hormone signaling, phosphorylation cascades or defense-related marker genes also demonstrated the role of phytoalexins in plant defense mechanisms. For instance cytokinin overexpression in tobacco led to increased

resistance to *P. syringae* which strongly correlated with up-regulated synthesis of two phytoalexins, capsidiol and scopoletin [11]. Though phytoalexin engineering seems to have been limited to exploiting only a few genes mainly

stilbene and isoflavonoid ones, indirect modulation of phytoalexin accumulation employing transcriptional regulators or components of upstream regulatory pathways becomes a useful approach to improve plant disease resistance.

Impact of Phytoalexins in Human Health: Phytoalexins may show health-promoting effects in humans. A few of them have been reported to have antioxidant, anticarcinogenic and cardiovascular protective activities. Maslinic acid, a natural phytoalexin-type triterpene from olives exerts a wide range of biological activities as an antitumor, antidiabetic, neuroprotective, cardioprotective, antiparasitic and growth-stimulating agent, providing

evidence of the potential of this molecule as a nutraceutical [30]. Camalexin from Brassicaceae is able to induce apoptosis in prostate cancer cells [32].3-deoxyanthocyanidins, flavonoid phytoalexins produced by members of the Poaceae family, are helpful in reducing the incidence of gastro-intestinal cancer [33]. Moreover, other indolic phytoalexins such as brassinin and its derivative, homobrassinin, show marked antiproliferative activities in human colorectal cancer cells *in vitro* [34]. Resveratrol, the phytoalexin from grapevine showed remarkable results in this area by acting as antiproliferative agent exerting antitumor activity either as a cytostatic or a cytotoxic agent in various cancers [9]. The first report of the cancer chemoprotective activity of a phytoalexin is the study of the group of Pezzuto [35]. The most frequently described mode of antitumor action for phytoalexins concerns apoptosis which may be via the inhibition of antiapoptotic molecules such as survivin [36] or by alterations of expression and activity of lysosomal protease cathepsin D [32]. Resveratrol show antitumour activities in vivo in skin cancer by topical application. But it does not seem to be effective against leukemia. However, it seems to have some anticancer activities in hepatoma, lung carcinoma and intestinal tumors [10].Several studies provide evidence of the cardioprotective activity of phytoalexins such as indoles and stilbenes [10, 31]. Some other phytoalexins like the steroid glycoalkaloids from potato or the dimeric sesquiterpene gossypol from cotton display a certain level of toxicity for humans. So such plants should be genetically modified to get rid of these undesirable compounds [9, 37].

Conclusion: This review has focussed on both fundamental and applied aspects of phytoalexin study. A large number of phytoalexins have been isolated from variety of plants, identified and their role in plant disease resistance has been emphasized. There is no doubt that much has been achieved by phytoalexin research, but still more remains to be done in this exciting and dynamic area of plants defence study. Many mysteries are yet to be solved. Mechanisms involved in elicitation of phytoalexin by biotic and abiotic

elicitors are not yet clearly understood. Why some pathogens degrade phytoalexins both *in vivo* and *in vitro*, while others degrade it *in vivo* or *in vitro* remains a question. Whether the activity of PAL increases long before phytoalexin production is still unknown. Do lower plants behave like higher plants with regard to phytoalexin reaction needs to be looked into. These are some of the interesting but intricate problems that awaits investigation. In future, with more improved technology and further advancement of knowledge, there is greater promise in the field of phytoalexin research.

References

[1] Jeandet, P.; Clément, C.; Courot, E.; Cordelier, S. Modulation of phytoalexin biosynthesis in engineered plants for disease resistance. *Int. J. Mol. Sci.* **2013**, *14*, 14136–14170.

[2] Ahuja, I.; Kissen, R.; Bones, A.M. Phytoalexins in defense against pathogens. *Trends Plant Sci*. **2012**, *17*, 73–90.

[3] Ingham, J.L. Phytoalexins from the Leguminosae. In *Phytoalexins*; Bailey, J.A., Mansfield, J.W., Eds.; Blackie: Glasgow/London, UK, 1982; pp. 21–80.

[4] Kuc, J. Phytoalexins from the Solanaceae. In *Phytoalexins*; Bailey, J.A., Mansfield, J.W., Eds.;Blackie: Glasgow/London, UK, 1982; pp. 81–105.

[5] Coxon, D.T. Phytoalexins from other plant families. In *Phytoalexins*; Bailey, J.A., Mansfield, J.W., Eds.; Blackie: Glasgow/London, UK, 1982; pp. 106–132.

[6] Schmelz, E.A.; Huffaker, A.; Sims, J.W.; Christensen, S.A.; Lu, X.; *et al*.Biosynthesis, elicitation and roles of monocot terpenoid phytoalexins. *Plant J.* **2014**, *79*, 659–678.

[7] Langcake, P.; Pryce, R.J. The production of resveratrol by *Vitis vinifera* and other members of the *Vitaceae* as a response to infection or injury. *Physiol. Plant Pathol*. **1976**, *9*, 77–86.

[8] Jeandet, P.; Delaunois, B.; Conreux, A.; Donnez, D.; Nuzzo, V.; Cordelier, S.; *et al.* Biosynthesis, metabolism, molecular engineering and biological functions of stilbene phytoalexins in plants. *BioFactors* **2010**, *36*, 331–341.

[9] Sunilkumar, G.; Campbell, L.M.; Pukhaber, L.; Stipanovic, R.D.; Rathore, K.S. Engineering cottonseed for use in human nutrition by tissue-specific reduction of toxic gossypol. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 18054–18059.

[10] Jeandet, P.; Delaunois, B.; Aziz, A.; Donnez, D.; Vasserot, Y.; Cordelier, S.; *et al* . Metabolic engineering of yeast and plants for the production of the biologically active hydroxystilbene, resveratrol. *J. Biomed. Biotechnol.* **2012**, doi:10.1155/2012/579089.

[11] Grosskinsky, D.K.; Naseem, M.; Abdelmoshem, U.A.; Plickert, N.; Engelke, T.; Griebel, T.; *et al*. Cytokinins mediate resistance against *Pseudomonas syringae* in tobacco through increased antimicrobial phytoalexin synthesis independent of salicylic acid signaling. *Plant Physiol.* **2011**, *157*, 815–830.

[12] Ingham, J.L.; Deverall, B.J.; Kuc, J.; Coxon, D.T.; Stoessl, A.; VanEtten, H.D.;

et al .Toxicity of phytoalexins. In *Phytoalexins*; Bailey, J.A., Mansfield, J.W., Eds.; Blackie: Glasgow/London, UK, 1982; pp. 218–252.

[13] Adrian, M.; Jeandet, P.; Veneau, J.; Weston, L.A.; Bessis, R. Biological activity of resveratrol, a stilbenic compound from grapevines, against *Botrytis cinerea*, the causal agent for gray mold. *J. Chem. Ecol*. **1997**, *23*, 1689–1702.

[14] Adrian, M.; Jeandet, P. Effects of resveratrol on the ultrastructure of *Botrytis cinerea* conidia and biological significance in plant/pathogen interactions. *Fitoterapia* **2012**, *83*, 1345–1350. *Molecules* **2014**, *19* **18052**

[15] Hasegawa, M.; Mitsuhara, I.; Seo, S.; Okada, K.; Yamane, H.; Iwai, T.; *et al*. Analysis on blast fungus-responsive characters of a flavonoid phytoalexin sakuranetin; Accumulation in infected rice leaves, antifungal activity and detoxification by fungus. *Molecules* **2014**, *19*, 11404–11418.

[16] Harris, J.E.; Dennis, C. The effect of post-infectional potato tuber metabolites and surfactants on zoospores of Oomycetes. *Physiol. Plant Pathol.* **1977**, *11*, 163–169.

[17] Pezet, R.; Pont, V. Ultrastructural observations of pterostilbene fungitoxicity in dormant conidia of *Botrytis cinerea* Pers. *J. Phytopathol.* **1990**, *129*, 29–30.

[18] VanEtten, H.D.; Bateman, D.F. Studies on the mode of action of the phytoalexin phaseollin. *Phytopathology* **1971**, *61*, 1363–1372.

[19] Woods, J.A.; Hafield, J.A.; Pettit, G.R.; Fox, B.W.; McGown, A.T. The interaction with tubulin of a series of stilbenes based on combretastatin A-4. *Br. J. Cancer* **1995**, *71*, 705–711.

[20] Shlezinger, N.; Minz, A.; Gur, Y.; Hatam, I.; Dagdas, Y.F.; Talbot, N.J.; *et al*. Anti-apoptotic machinery protects the necrotrophic fungus *Botrytis cinerea* from host-induced apoptotic-like cell death during plant infection. *PLoS Pathog.* **2011**, *7*, e1002185.

[21] Sanzani, S.; Schena, L.; Ippolito, A. Effectiveness of phenolic compounds against citrus green mould. *Molecules* **2014**, *19*, 12500–12508.

[22] Sanzani, S.M.; de Girolamo, A.; Schena, L.; Solfrizzo, M.; Ippolito, A. Visconti, A. Control of *Penicillium expansum* and patulin accumulation on apples by quercetin and umbelliferone. *Eur. Food Res. Technol.* **2009**, *228*, 381–389.

[23] Pont, V.; Pezet, R. Relation between the chemical structure and biological activity of hydroxystilbenes against *Botrytis cinerea*. *J. Phytopathol.* **1990**, *130*, 1–8.

[24] Chalal, M.; Klinguer, A.; Echairi, A.; Meunier, P.; Vervandier-Fasseur, D.; Adrian, M. Antimicrobial activity of resveratrol analogues. *Molecules* **2014**, *19*, 7679–7688.

[25] Lyon, G.D.; Bayliss, C.E. The effect of rishitin on *Erwinia carotovora* var. *atroseptica* and other bacteria. *Physiol. Plant Pathol.* **1975**, *6*, 177–186.

[26] He, X.Z.; Dixon, R.A. Genetic manipulation of isoflavone 7-*O-methyltransferase* enhances biosynthesis of 4'-*O*-methylated isoflavonoid phytoalexins and disease resistance in alfalfa. *Plant Cell* **2000**, *12*, 1689–1702.

[27] Schmidlin, L.; Poutaraud, A.; Claudel, P.; Mestre, P.; Prado, E.; Santos-Rosa, M.; *et al.* A stress-inducible resveratrol *O-methyltransferase* involved in the biosynthesis of pterostilbene in grapevine. *Plant Physiol*. **2008**, *148*, 1630–1639. *Molecules* **2014**, *19* **18053**

[28] Zernova, O.V.; Lygin, A.V.; Pawlowski, M.L.; Hill, C.B.; Hartman, G.L.; Widholm, J.M.; Lozovaya, V.V. Regulation of plant immunity through modulation of phytoalexin synthesis. *Molecules* **2014**, *19*, 7480–7496.

[29] Chong, J.; Baltz, R.; Schmitt, C.; Beffa, R.; Fritig, B.; Saindrenan, P. Downregulation of a pathogen-responsive tobacco UDP-Glc:phenylpropanoid glucosyltransferase reduces scopoletin glucoside accumulation, enhances oxidative stress, and weakens virus resistance. *Plant Cell* **2002**, *14*, 1093–1107.

[30] Lozano-Mena, G.; Sanchez-Gonzalez, M.; Juan, M.E.; Planas, J.M. Maslinic acid, a natural phytoalexin-type triterpene from olives—A promising nutraceutical? *Molecules* **2014**, *19*, 11538–11559.

[31] Jahangir, M.; Kim, H.K.; Choi, Y.H.; Verpoorte, R. Health-affecting compounds in Brassicaceae. *Compr. Rev. Food Sci. Food Saf.* **2009**, *8*, 31–43.

[32] Smith, B.; Randle, D.; Mezencev, R.; Thomas, L.; Hinton, C.; Odero-Marah, V. Camalexin-induced apoptosis in prostate cancer cells involves alterations of expression and activity of lysosomal protease cathepsin D. *Molecules* **2014**, *19*, 3988–4005.

[33] Yang, L.; Browning, J.D.; Awika, J.M. Sorghum 3-deoxyanthocyanidins possess strong phase II enzyme inducer activity and cancer cell growth inhibition properties. *J. Agric. Food Chem.* **2009**, *57*, 1797–1804.

[34] Kello, M.; Drutovic, D.; Chripkova, M.; Pilatova, M.; Budovska, L.; Kulikova, L.; *et al.* ROS-dependent antiproliferative effect of brassinin derivative homobrassinin in human colorectal cancer Caco2 cells. *Molecules* **2014**, *19*, 10877–10897.

[35] Jang, M.; Cai, L.; Udeani, G.O.; Slowing, K.V.; Thomas, C.F.; Beecher, C.W.; *et al* . Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science* **1997**, *275*, 218–220.

[36] Fuda, S.; Debatin, K.M. Sensitization for tumor necrosis factor-related apotosis-inducing ligand-induced apoptosis by the chemopreventive agent resveratrol. *Cancer Res.* **2004**, *64*, 337–346.

[37] Matthews, D.; Jones, H.; Gans, P.; Coates, S.; Smith, L.M.J. Toxic secondary metabolite production in genetically modified potatoes in response to stress. *J. Agric. Food Chem.* **2005**, *53*, 7766–7776.

[38] Jeandet, P.; Hebrard, C.; Deville,M.A.; Cordelier,S.; Dorey,S.; Aziz, A.; *et al.* Deciphering the Role of Phytoalexins in Plant-Microorganism Interactions and Human Health. *Molecules* **2014**, *19*, 18033–18056; doi: 10.3390.

[39] Cruickshank, I.A.M.; Perrin, D.R. Isolation of a phytoalexin from *Pisum sativum* L. *Nature* **1960**, *187*, 799–800.