Opinion

Plant–Pathogen Interactions: Underestimated Roles of Phyto-oxylipins

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Plant (or phyto-) oxylipins (POs) are produced under a wide range of stress conditions **and although they are well known to activate stress-related signalling pathways, the nonsignalling roles of POs are poorly understo**od. We describe oxylipins as direct biocidal agents and propose that structure–function relationships play here a pivotal role. Based on their chemical configuration, POs, such as reactive oxygen and electrophile species, activate defence-related gene expression. We also propose that their ability to interact with pathogen membranes is important, but still misunderstood, and that they are involved in cross-kingdom communication. Taken as a whole, the current literature suggests that POs have a high potential as biocontrol agents. However, the mechanisms underlying these multifaceted compounds remain largely unknown.

Oxylipin Basics

Almost 30 years ago, the term '**oxylipin**' (see Glossary) appeared in the literature and since then, publications on the topic have increased steadily. Oxylipins are found in almost all organisms and are present in free forms, esterified to phospholipids or galactolipids, or combined with other compounds (e.g., methyl groups, isoleucine) [1–10]. The precursors of oxylipin synthesis vary among organisms, as do the enzymes that will oxidise them. Because aerobic biological systems are continuously subject to autooxidation, oxylipins (e.g., phytoprostanes) are also produced through nonenzymatic routes in the presence of singlet oxygen or reactive oxygen species (ROS) [3,11–15]. Both pathways have been extensively reviewed. Figure 1 summarises the enzymatic production pathways of oxylipins (free forms) in mammals, fungi, and **flowering plants** (for detailed information see [8,13–21]).

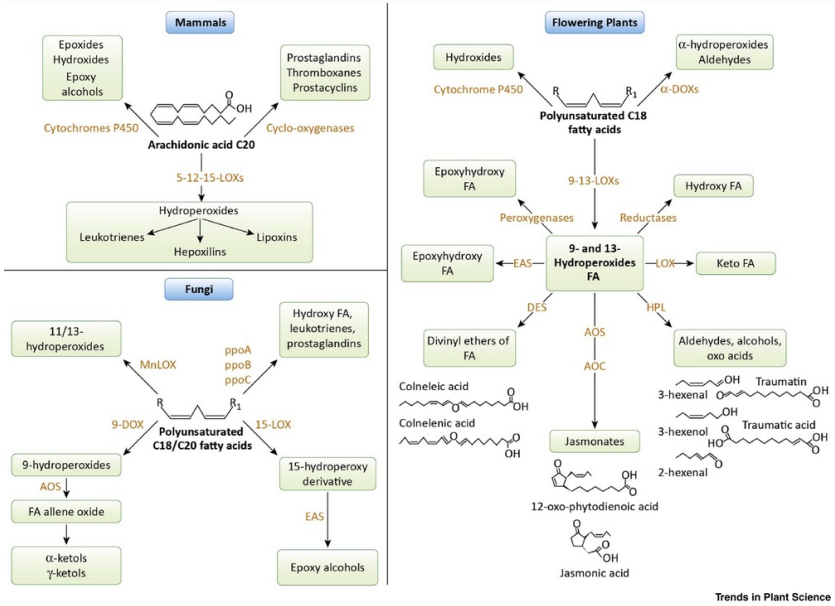

Figure 1 Oxidative Metabolism of Fatty Acids in Mammals, Flowering Plants, and Fungi.

Starting mainly from arachidonic acid in the mammalian system or from C18 polyunsaturated fatty acids (PUFAs) in flowering plants and C18/20 in fungi, both pathways involve oxygenation of fatty acids by one, two, or four oxygen atoms. Moreover, linoleic acid (C18:2) can be a substrate in mammals. 16:3 is also found as a starting substrate in flowering plants. It is important to note that, even if they are not presented in this figure, oxylipin pathways exist in other members of the Plantae reign (mosses algae, etc.) [1,8,9]. FA, fatty acid; LOX, lipoxygenase; α-DOX, α-dioxygenase; AOC, allene oxide cyclase; AOS, allene oxide synthase; DES, divinyl ether synthase; EAS, epoxy alcohol synthase; HPL, hydroperoxide lyase. Adapted from [4,16,17].

PO pathways result in structurally diverse metabolites with key biological activities. POs, especially jasmonic acid (JA), function as vital signalling molecules in plant growth and development (e.g., flower and pollen development, seed maturation) and in plant stress responses [4,7,22–29]. Through its precursor [12-oxo-phytodienoic acid (OPDA)] and its derivatives, JA also plays key roles in plant defences against herbivores and certain pathogens, mainly necrotrophic [25,29,30]. Accordingly, this may be extended to all POs playing crucial roles in early defence reactions against insect or pathogen attacks.

Shaping the PO Signature

PO signatures are influenced by the type of stressor, the plant species being stressed, and the affected organ(s), as well as by the pathogen lifestyle (for reviews see [4,18,31–38]). For instance, tobacco (*Nicotiana tabacum*) leaves infected by the hemibiotroph *Pseudomonas syringae* accumulate high levels of α-dioxygenase (α-DOX) and 9-lipoxygenase (LOX) products [39], whereas certain potato cultivars infected by *Phytophthora infestans* and tomato leaves infected by necrotrophic *Botrytis cinerea* accumulate 9(*S*)- and 13(*S*)-polyunsaturated fatty acid (FA) (PUFA) hydroperoxides (HPOs) [40–42].

Considering the context of this review and the extensive diversity among oxylipins and pathogens, we have decided to focus on the role of POs in the interactions between host plants and their pathogens.

Effectiveness of POs as Signalling Molecules in Plant Defence Mechanisms

Like animals, plants have developed a sophisticated ‘immune system’, called innate immunity [43]. The starting phase is the pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) that acts as a basal resistance. Then, pathogens release effectors to thwart PTI. Effectors are recognised and induce a much stronger disease resistance, effector-triggered immunity (ETI). A broad-spectrum resistance called **systemic acquired resistance (SAR)** is finally activated, which will keep the plant alarmed and prepared for other attacks for weeks to months [44]. SAR can also be activated by **elicitors** [45–48].

Literature is replete with publications on oxylipins as signalling molecules in plant defence mechanisms and many studies provide evidence for a strong interplay between phytohormones [3,26,39,49–57]. JA and its derivatives, known as **jasmonates**, are the best-characterised LOX-derived metabolites as they accumulate quickly in damaged plants [2,36,58]. JA has a key role in systemic wound signalling [59]. Methyl-JA can be released as a volatile organic compound for anticipation of mutual danger between plants (i.e., intra- and interspecies communication) [60]. In arabidopsis (*Arabidopsis thaliana*) leaves, the bioactive form of JA, (+)-7-iso-jasmonoyl-L-isoleucine (JA-Ile), accumulates

rapidly (<5 min) in leaves distal to wounding sites [30,50,61]. Interestingly, this long-distance signalling does not seem to involve the direct movement of hormones and could involve much faster systems: electrical coupling or ROS and Ca^2+-mediated waves, 'trio signalling' [62,63]. Also, many studies have reported that JA signalling involves ion channel- or pump-coding genes, such as *GLUTAMATE RECEPTOR-LIKE*, which supports long-distance Ca^2+ signalling [64–66]. Recent studies have also supported the idea that long-distance trafficking of lipid-based signals is involved in the control of SAR [59,63]. Because pest attacks are linked with the release of various PAMPs, herbivore-associated molecular patterns (HAMPs), and/or damage-associated molecular patterns (DAMPs) [44,45], it remains unclear how PAMPs, HAMPs, DAMPs, and, ultimately, POs interconnect leading to JA biosynthesis. Such connections could drastically influence the way plants defend themselves against pathogens. POs may be involved in SAR and act as long-distance signals, like salicylic acid (SA) does on pathogen infection [48]. Usually, this is the role played by elicitors, suggesting that POs may represent a new source of eliciting molecules.

Study of PO: Mind the Gap

Although the roles of POs in plant defence signalling pathways are described extensively in the literature, a direct interaction of POs with pathogens is also possible. Studies regarding the potential antimicrobial activities of POs have focused on the *in vitro* effects of POs against biotrophic, necrotrophic, or hemibiotrophic pathogens. Oxylipins derived from the 9-LOX and α-DOX pathways exhibit strong action against bacterial infections [67]. 9-Keto-10(*E*),12(*Z*),15(*Z*)-octadecatrienoic acid (9-KOT), a 9-LOX major product from linoleic acid (LA), is highly active against *P. syringae* pv. *tomato* (*Pst*) DC3000 [38]. Accordingly, the *in vitro* activity of ~50 POs against 13 agronomically relevant pathogens (bacteria, fungi, and oomycetes) have been examined, as well as their stability [35,68]. As shown in Table 1, all pathogen growth was inhibited by one or more oxylipins. The oxylipins were even more effective on fungal spore germination inhibition, with a very high effectiveness of (ω-5-*Z*)-etherolenic, colneleic, and colnelenic acids [35,68,69]. It is generally accepted that divinyl-, keto-, and hydroxy-FAs and HPOs exhibit strong direct antimicrobial activities while others, JA and some volatile aldehydes, seem to be only implied in signalling.

Table 1 Summary of the Most Effective Antimicrobial Free POs (Based on [35,67], *In Vitro* Assays)[a,b]

PO	Strain												
	Bacteria				Fungi							Oomycetes	
	Pc	Ps	Xc	Ab	Bc	Ch	Fo	Lm	Rsp	Ss	Vl	Pi	Pp
ω-5(*Z*)-Etherolenic acid	−	++++	−	+++	−	+	−	++	−	−	−	+	−
(±)-*cis*-12,13-Epoxy-9(*Z*)-octadecenoic acid	−	−	−	++	−	+++	−	−	+	++	−	−	+++
(±)-*cis*-9,10-Epoxy-12(*Z*)-octadecenoic acid	−	++	−	−	−	+++	−	++	+	−	−	−	++
(±)-*threo*-12,13-Dihydroxy-9(*Z*)-octadecenoic acid	−	−	−	++	−	+++	−	+++	−	+	−	−	−
(±)-*threo*-9,10-Dihydroxy-12(*Z*)-octadecenoic acid	−	−	+	++	−	−	−	−	−	+	−	−	−
10(*S*),11(*S*)-Epoxy-9(*S*)-hydroxy-12(*Z*),15(*Z*)-octadecadienoate	−	−	−	x	−	−	−	x	−	x	x	−	−
11(*S*),12(*S*)-Epoxy-13(*S*)-hydroxy-9(*Z*),15(*Z*)-octadecadienoate	−	++	−	x	+	−	−	x	−	x	x	+	−
13(*S*)-Hydroperoxy-9(*Z*),11(*E*),15(*Z*)-octadecatrienoic acid (13-HPOT)	−	−	−	++	++++	++++	+	++	−	−	−	−	++++
13(*S*)-Hydroperoxy-9(*Z*),11(*E*)-octadecadienoic acid (13-HPOD)	−	+	−	−	−	++++	−	−	−	−	−	−	++++
13(*S*)-Hydroxy-9(*Z*),11(*E*),15(*Z*)-octadecatrienoic acid (13-HOT)	−	−	−	+	++++	++++	−	+++	−	−	−	−	++++
13(*S*)-Hydroxy-9(*Z*),11(*E*)-octadecadienoic acid (13-HOD)	−	+	−	−	+	++++	+	−	−	−	−	+	++++

13-Keto-9(*Z*),11(*E*)-octadecadienoic acid (13-KOD)	−	−	−	−	−	−	−	x	−	x	x	−	+
13-Keto-9(*Z*),11(*E*),15(*Z*)-octadecatrienoic acid (13-KOT)	−	+	−	−	++	+++	−	x	+	x	x	+	++++
9(*S*)-Hydroperoxy-10(*E*),12(*Z*),15(*Z*)-octadecatrienoic acid (9-HPOT)	−	−	−	−	+++	++++	−	−	−	−	−	−	++++
9(*S*)-Hydroperoxy-10(*E*),12(*Z*)-octadecadienoic acid (9-HPOD)	−	+	−	−	++	++++	−	x	−	x	x	−	++++
9(*S*)-Hydroxy-10(*E*),12(*Z*),15(*Z*)-octadecatrienoic acid (9-HOT)	−	−	−	−	++	+++	++	x	+	x	x	−	++++
9(*S*)-Hydroxy-10(*E*),12(*Z*)-octadecadienoic acid (9-HOD)	−	−	−	−	−	++++	+	x	−	x	x	−	++++
9-Keto-10(*E*),12(*Z*)-octadecadienoic acid (9-KOD)	−	++	+++	−	−	+++	−	x	−	x	x	−	+++
9-Keto-10(*E*),12(*Z*),15(*Z*)-octadecatrienoic acid (9-KOT)	−	+	−	−	−	++++	−	x	−	x	x	−	++++
Colneleic acid	−	++++	−	−	−	++++	+	x	−	x	x	−	−
Colnelenic acid	−	++	−	−	+	++++	−	x	−	x	x	+	+
Anacardic acid	−	−	++++	−	−	−	+	x	−	x	x	+++	−
12-Oxo-10,15(*Z*)-phytodienoic acid (OPDA)	–	+	–	+	+++	++++	+	x	+	x	x	+	++++
2(*E*)-Nonenal	−	++	−	−	−	−	−	x	−	x	x	+	−
3(*Z*)-Nonenal	−	++	−	−	−	−	+	x	++	x	x	−	−
2(*E*)-Hexenal	x	++++	++++	++++	++++	++++	++++	x	++++	x	x	++++	++++
3(*Z*)-Hexenal	−	++	−	−	−	−	−	x	−	x	x	−	−

[a] The oxylipins were tested at concentrations of around 100 µM and measurements were taken after 24-h incubation.

[b] The bacteria tested were Pectobacterium carotovorum (Pc), Pseudomonas syringae (Ps), and Xanthomonas campestris (Xc). The fungi tested were Alternaria brassicae (Ab), Botrytis cinerea (Bc), Cladosporium herbarum (Ch), Fusarium oxysporum (Fo), Leptosphaeria maculans (Lm), Rhizopus sp. (Rsp), Sclerotinia sclerotiorum (Ss), and Verticillium longisporum (Vl). The oomycetes tested were Phytophthora infestans (Pi) and Phytophthora parasitica (Pp). ++++, very highly effective; +++, highly effective; ++, moderately effective; +, effective; −, not effective; x, not tested.

However, because the studies above were conducted *in vitro*, it remains unclear whether oxylipins can induce such defence mechanisms under field conditions. In nature, plants never face an isolated stress and responses are controlled by various pathways that may interact and inhibit each other [52]. To partially explore this issue, arabidopsis plants grown in a conditioned culture chamber were pretreated with 9-LOX-derived oxylipins and then challenged using *P. syringae* DC3000. A maximal effect was observed in local tissues and a significant reduction of bacterial growth occurred in distal leaves, mostly with 9-KOT as predicted by *in vitro* assays. Further genetic evaluations have also determined that 9-LOX affects *Pseudomonas*-responsive genes that are linked to oxidative stress and hormonal responses [38]. Therefore, 9-LOX and other active PO compounds may help to establish plant innate immunity, as elicitors and/or direct biocides. Since only 50 POs have been tested *in vitro*, the ability of the others as direct biocides or elicitors can be questioned. Concomitantly, the molecular mechanisms of this biocidal effect must be elucidated. Multidisciplinary and complementary approaches (e.g., transcriptomics, proteomics, metabolomics) will lead to a better understanding of the action modes of oxylipins in plant stress responses. Also, the subcellular localisation of oxylipins during pathogen attack must be elucidated because this is the key element in the development of new biocontrol agents. Moreover, an integrated biological approach should be adopted whereby researchers aim to mimic real field stresses (culture substrate, choice of strain, mode of application, duration and timing of stress, growing conditions, etc.).

The Road to the Next Level

The Link Between Structure and Biocidal Activity

The biocidal properties of POs could be linked to various lethal mechanisms such as membrane pore formation, membrane destabilisation, protein or nucleic acid denaturation, or oxidative bursts. *In vitro* assays notably showed that 2(*E*)-hexenal exhibits the highest efficacy among POs (Table 1), with detergent-like action that severely damages membranes and cell walls [70]. Such behaviour is typically observed with reactive electrophiles species (RES). By analogy with ROS, the term RES was given to molecules containing an α,β-unsaturated carbonyl moiety that accumulate in diseased and wounded plant tissues. Nowadays, this term is also used for molecules like FA ketodienes, ketotrienes, and OPDA, as other chemical configurations can confer electrophilic properties on molecules [13,71]. In pathogen-infected plants, RES have been reported to stimulate the expression of defensive genes and to directly modify proteins [71]. For example, OPDA has been reported to bind cyclophilin 20-3 (CYP20-3), a binding protein that regulates stress-responsive cellular redox homeostasis [72,73]. Regardless of the defence route, it is well known that the excessive production of electrophilic molecules can disrupt natural cellular functions and, eventually, cause cell collapse [74].

Perhaps less well-known is the role that chemical structure might play in this biological machinery. PUFAs, starting points of oxylipin synthesis pathways, owe their antibacterial properties to their structure and shape (i.e., carbon or chain length and the presence, number, position, and orientation of double bonds) [75]. FAs with *cis* double bonds are stronger antibacterial agents than FAs with *trans* double bonds [75,76], owing to the lower thermodynamic stability of *cis* double bonds compared with *trans* double bonds. Also, *cis* forms may induce greater membrane deformation than *trans* forms. In addition, conjugated *cis* bonds activation energy is lower and, apparently, more active against pathogens than monounsaturated FA [77].

The PO family is versatile in terms of chemical structure, with many geometric isomers. Regioisomers of the same oxylipin structure can have different biological effects [35]. Modifications in the hydroxy or epoxy groups change drastically the biological activity of the corresponding oxylipins. Even HPOD and HPOT, which differ structurally by only a simple double bond, exhibit different antimicrobial efficacies. Conversely, the difference between 9- and 13-forms was unclear for the inhibition of pathogen growth, whereas linolenic acid (LnA) products seem more effective than LA products [68]. In addition, epimerisation is a simple mechanism that regulates hormone activity by converting bioactive (+)-7-iso-jasmonoyl-L-isoleucine into the inactive form, JA-Ile [30].

Further investigations are needed to determine whether all isomers exhibit growth-inhibitory activity against various pathogens, ultimately to elucidate potential structure–activity relationships, and to determine how much those mechanisms, or still-unknown mechanisms, contribute to the biocidal effect of POs. As they might still cause detergent-like disruption of membranes, the effects of selected oxylipins on membrane permeability should be investigated in the future. Nevertheless, they presumably depend on the chemical nature of the oxylipin, the damage exerted, and the molecular mechanisms involved.

Are Membranes Active Actors or Passive Filters in PO Biocidal Activity?

Although hundreds of studies have investigated PO biosynthesis, to the best of our knowledge no studies have investigated the trafficking of POs at the subcellular level during pathogen attack, and it remains unclear how POs contact and interact with plant cells or pathogens after being released into cellular compartments. Recently, a study reported that HPOs can interact with biomimetic plant plasma membranes (PM) by modifying domains' lateral organisation, in a lipid-dependent manner [78]. The chemical structure and subsequent conformation of HPOs seems to be involved, thereby implicating a structure–activity relationship. These results raise the question of the origin of PO antimicrobial activities and whether/how POs interact with the pathogen PM (Figure 2).

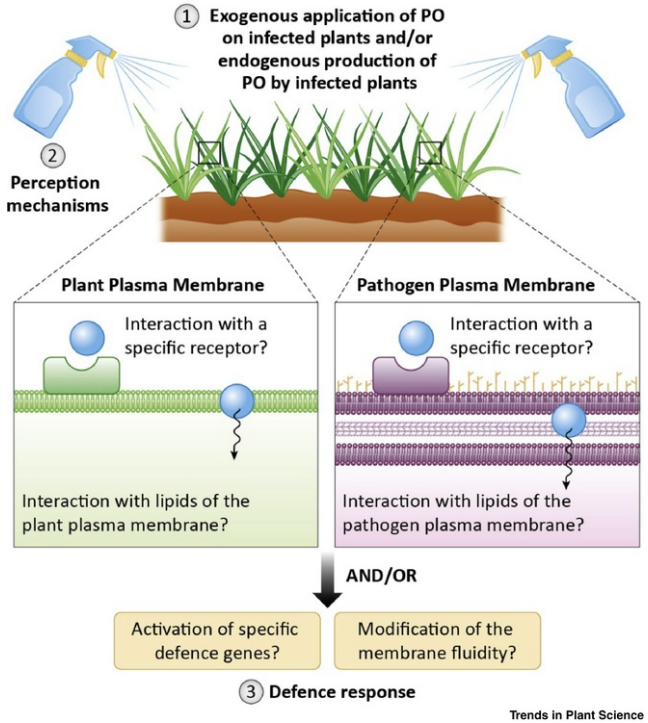

Figure 2 Hypothetical Schematic Diagram Showing the Roles of the Plasma Membrane (PM) in Plant Oxylipin (PO)–Pathogen Interactions.

After being sprayed on infected plants, POs meet the PM of plants and pathogens. Also, POs may be produced by infected plants and encounter the PM of the cell or a neighbour. They can interact directly with the lipid part of the membranes or with specific receptors present at the surface. This may lead to a series of membrane modifications (stiffening, thinning, pore formation, etc.). POs exogenously applied or endogenously produced by infected plants can result in the activation of various cascades and lead to different responses.

The **amphiphilic** nature of HPOs may also explain their central role in plant defence, allowing them to interact with PM lipids. Other amphiphilic molecules, such as lipopeptides, exhibit direct biocidal activity, which seems directly linked to their ability to interact with the lipid part of biological membranes and, therefore, to modify membrane properties [79,80]. **Biomimetic membranes** are reportedly sensitive to lipopeptides in a lipid composition- and organisation-dependent manner, confirming the essential role of lipids in these interactions [81]. By analogy with chemical structure and amphiphilic properties, we can assume the same behaviour for HPOs along with other POs that interact with bacterial or fungal membranes.

The composition and organisation of the PM are remarkably complex, with strong asymmetrical distribution, and it is evident that its organisation and dynamics ensure good communication that regulates key physiological processes. However, although the role of lipids as important regulators remains indisputable, the mechanisms by which lipids are assembled in the PM remain under investigation [82]. Lipids have frequently been implicated as signals regulating reproductive development, secondary metabolism, and pathogen growth [83,84] or the mitigation of stress responses, immune signalling, and inflammatory processes [75,85–88] in plants and mammals. Emerging evidence showed that FA functions were related to membrane lipid composition changes and adjustment of fluidity [89]. By analogy, it can be assumed that HPOs exhibit similar behaviours, since they are differentiated only by an additional highly reactive hydroperoxide function. Further studies are required to identify additional lipids involved in those interactions and to reveal lipid patterns that are common or distinct among infections with pathogens. Membrane interactions are also suspected to differ between monocotyledons and dicotyledons, since the lipid compositions are extremely variable from one plant species to another. Furthermore, the involvement of membrane receptors, proteic or not, has not been ruled out. Recent reports revealed oxylipin plant transporters such as the AtJAT1/AtABCG16 transporter in arabidopsis, which exhibits an unexpected dual localisation in both the nuclear envelope and the PM [6]. It controls the cytoplasmic and nuclear partitioning of jasmonate phytohormones by mediating both cellular efflux of JA and nuclear influx of JA-Ile. It is thus essential for the maintenance of a critical nuclear JA-Ile concentration to activate JA signalling. Meanwhile, additional studies have reported that GLUCOSINOLATE TRANSPORTER-1 (GTR1) is another JA and JA-Ile transporter in arabidopsis [90,91]. Those studies highlight new mechanisms of signalling hormone regulation, and many other transporters may be described in coming years.

The Parallelism with Eicosanoids

Plants and mammals are not so different, especially when considering their analogous signalling systems. In both groups of organisms, PUFA oxidation products (e.g., oxylipins in plants, eicosanoids in mammals) are crucial stress signalling mediators. Eicosanoids are frequently cited for their multiple biological roles (i.e., in regulating wound responses, inflammation, and cancer and immune responses) and are involved in many enzymatic pathways (Figure 1).

Interplay between eicosanoids is well known, although incompletely understood [92]. For example, transcellular leukotriene (LT) biosynthesis is frequently observed and changes in levels of eicosanoids regulate each other [17,20,87,93]. In mammals, eicosanoids are recognised by various **G protein-coupled receptors (GPCRs)** at the cell membrane [94]. LA-derived oxylipins, including 9(*S*)- and 13(*S*)-HOD, are also produced by mammalian cells and the human GPCR G2A functions as their specific receptor [17,95–97]. This suggests a possible involvement of GPCRs in HPO recognition in plant cells.

Based on their biosynthesis pathways, jasmonates exhibit many similarities to eicosanoids, particularly LTs. Their functional similarities and capacity for being synthesised and released for immediate, local, and systemic responses to stress reinforce this parallelism [3,98,99]. Furthermore, the use of JA as an anticancer agent has been investigated by several *in vitro* and *in vivo* experimental systems [98]. This supports the potential for interkingdom communication and applications.

Oxylipin Interkingdom ‘Communication’: An Even More Complicated Interplay?

Given that oxylipins are involved in plant–plant, plant–pathogen, and plant–insect interactions, research on lipid-mediated cross-kingdom communication between hosts and pathogens has emerged in the past years [100]. It is becoming increasingly clear that organisms commonly use oxylipin pathways as a means of communication to elicit biological responses.

During the past decade, studies on fungi and their ability to produce oxylipins for their own development have exploded. Fungal oxylipins (FOs) have appeared to modify plant and mammalian host responses [17,37]. The possibility of **crosstalk** has also been proposed, given the discovery that many microbes, including fungi, produce eicosanoids. Fungal eicosanoids may mediate host–pathogen crosstalk by downregulating host local defence responses and increase their virulence [95]. In general, oxylipins could also have this potential. It is suggested that plants and fungi communicate through an oxylipin ‘language’, mostly mechanisms that resemble **quorum sensing** [96]. Thus, a clear response to exogenous application of PUFAs derivates purified from the interacting partners should be observed. Previous studies have shown that C18:2 products like 9(*S*)- and 13(*S*)-HPOD, and even compounds like green leaf volatiles, regulate fungal growth, spore development, and mycotoxin production in *Aspergillus* sp. grown on diverse plant species [84,101,102]. This supports the hypothesis that FOs and POs could be involved in quorum sensing. Because precocious sexual inducer (*psi*) factors are similar to POs, especially 9(*S*)- and 13(*S*)-HPOD, they may affect physiological processes in fungi by mimicking the action of FOs [37,84,101], thus facilitating the reciprocal cross-kingdom perception of these molecules [100,101]. Several genome analyses have shown the presence of fungal GPCRs. Affeldt reported that GPCRs were responsible for HPO perception and thus should be recognised as oxylipin receptors [96,97]. This reinforces the hypothesis that POs, along with all forms of stimuli, might be perceived by fungi through a GPCR-mediated cascade (Figure 3).

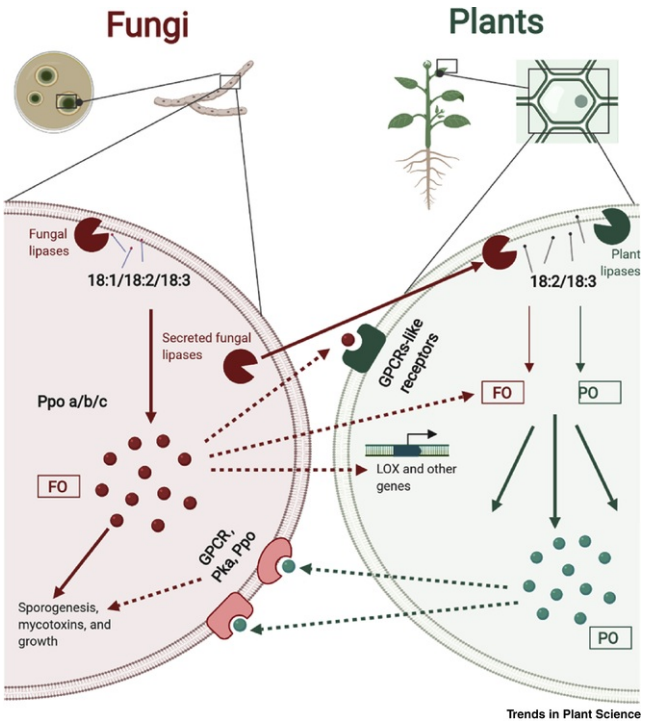

Figure 3 Hypothetical Model of Fungal Oxylipin (FO) and Plant Oxylipin (PO) Crosstalk (Based on [16,37,99]).

Fungal lipases are secreted in the plant cells where fatty acids (FAs) are cleaved and processed by a lipoxygenase (LOX) (fungal and/or plant based) for oxylipin production. POs are perceived by G protein-coupled receptors (GPCRs), protein kinase (Pka), and psi-producing oxygenase (Ppo) and exploited by fungi for growth, sporogenesis, and mycotoxin production. Also, the host is manipulated through oxylipin mimicry (FO binding GPCR-like receptors). All fungal properties are in orange and all plant properties are in green. Broken arrows indicate hypothetical interactions and unbroken arrows established interactions.

By contrast, the production of such FOs should have an impact on PO content. Studies on wild-type and oxylipin-reduced fungal mutant strains showed a decrease in PO content in the latter [27,84,101]. *Aspergillus* infection has been reported to increase the levels of 9- and 13-LOX metabolites in maize lines and peanut seeds and to induce specific oxylipin signature profiles [37,101–103]. Lately, Battilani have confirmed that FOs strongly regulate PO gene expression [22], possibly owing to the direct sensing of FOs by plant tissues or to the perception of intact fungal *psi*-producing oxygenase (*ppo*) enzymes. In *A. nidulans*, the three *ppo* genes are not expressed simultaneously in plant cultures, which suggests that oxylipin production is triggered by a complex but organised network of signalling cascades in a variety of tissues. Although plants seem to lack GPCRs or GPCR homologs, a mode for FO recognition was proposed in 2009, when two arabidopsis GPCR proteins (GTG1 and GTG2) were finally identified and characterised as an abscisic acid (ABA) ligand involved in plant signalling [37,104]. GTG1 and GTG2 seem to be ABA receptors, since arabidopsis mutants that lack GTG1 and GTG2 exhibit ABA hyposensitivity [104]. In addition, the GPCR GCR2 has recently been discovered, resembling GTG1 and GTG2 without being able to bind ABA [105]. Therefore, further detailed analyses are needed to identify their roles and, potentially, new receptor pathways for oxylipins. So far, plants possess many transmembrane proteins and receptor-like kinases that might also function as oxylipin receptors [100].

Finally, based on the similarities of FOs and POs, it appears that FOs may be able to hijack the host oxylipin pathway to facilitate disease development and the production of mycotoxin and spores [88,101]. Such properties have already been reported for the phytotoxin coronatine, which is a JA-Ile mimic and virulence determinant that is produced by various *P. syringae* pathovars and activates the JA pathway and suppresses the SA pathway when applied to arabidopsis plants [49,89]. Recent studies have also shown the production of hydroxylated JA (11-OH-JA, 12-OH-JA), *N*-[(-)-jasmonoyl-(*S*)]-isoleucine, and other forms by different strains of fungi [106–108].

Regardless the mechanisms, these studies provide the first evidence of the apparent impact of fungi on PO content. Unfortunately, to date, information on the impact of POs or FOs in mediating host responses is scarce. However, it remains unclear whether POs are recognised by tissues or cell-surface receptors or at what biological concentrations such POs are effective. Furthermore, a specific oxylipin could have different effects in different species. Currently, nothing is known about bacterial crosstalk and everything remains to be discovered in other pathosystems.

Concluding Remarks and Future Perspectives

As suggested above, the molecular crosstalk between different kingdoms persists in a shadow, in terms of both biological significance and its governing mechanisms. We are at the dawn of deciphering the key elements of this interkingdom communication. Recent studies using molecular genetics and biochemical approaches in both pathogens and their host plants have enhanced our understanding in this area. It has been proposed that certain HPOs can exert antimicrobial effects by interacting with pathogen membranes [68]. 13(*S*)-HPOD, in particular, appears to increase yeast membrane fluidity in a concentration-dependent manner, likely at the membrane lipid level [109]. This raises the idea that oxylipins might sometimes be incorporated into membrane bilayers, thereby progressively increasing membrane disorder, modifying their function and, thus, affecting microorganism–plant crosstalk. Given the recent discovery of RNAi and small RNA exchange between *A. thaliana* and *B. cinerea*, bidirectional cross-kingdom trafficking could also be suspected for oxylipins [110,111]. Despite these important findings, oxylipin-mediated crosstalk between pathogens and host plants is a complex system that needs further study. Many questions remain to be answered, some of which have been neglected for years (see Outstanding Questions).

The literature also lacks information about the involvement of PO esterified forms; since they accumulate in large amounts in the PM on infection, they may act as a reservoir for the rapid synthesis/release of other oxylipins (or directly interact with the PM). Several modes of recognition have been proposed for plant–pathogen crosstalk. The obvious chemical resemblance of POs and lipopeptides, which are strongly involved in **induced systemic resistance (ISR)**, highlights their potential as elicitors [112]. One and/or the other process can fundamentally change the way in which POs could be used as biocontrol agents. These findings add relevance to a deeper understanding of how plant innate immunity and defence mechanisms work. In the current context of finding alternatives to intensive agriculture, this is a challenging research area. Increasing our knowledge of plant response to stresses at the molecular, physiological, and metabolic levels will be vital for the development of new plant varieties and even more in developing new biopesticides.

Outstanding Questions

What are the nonsignalling roles of phyto-oxylipins?

Do oxylipins studied *in vitro* retain interesting antimicrobial properties *in planta*? What are their spectrum and mechanisms of action? Why do POs cause damage to the pathogen and not to the plant?

Are POs involved in innate immunity as elicitors or are they only direct biocides – or maybe both? Can POs be potential biocontrol agents?

Do plants use proteic receptors or equivalents for perception of oxylipins (POs or other oxylipins) or is it a mechanism independent of receptors (e.g., interaction with the lipidic fraction of the plant plasma membrane)?

How are POs, and more generally oxylipins, involved in interkingdom communication?

Uncited references

[113], [114]

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Glossary

Amphiphilic: adjective given to molecules containing a nonpolar hydrophobic region and a polar hydrophilic region assembling automatically in aqueous solution to form distinct structures such as micelles, vesicles, and tubules.

Biomimetic membranes: model membranes in which the lipid composition is representative of the main lipids found in natural biological membranes and the lipid organisation best mimics the natural lipid arrangement. These systems are helpful in dissecting the molecular mechanisms acting at the level of the biological membranes. Three systems are widely used in biophysics; namely, lipid monolayers, supported lipid bilayers, and liposomes.

Crosstalk: a term used when a common cellular component is engaged in more than one signal transduction chain and allows information exchange between different signalling pathways.

Elicitors: natural or synthetic compounds that are exogenously applied and induce defence responses in plants similar to those induced by pathogen infections.

Flowering plants: also known as angiosperms or magnoliophytes. They are a division of vascular plants that produce seeds (spermatophytes). These plants, which bear flowers then fruits, are commonly called flowering plants. They include dicotyledons and monocotyledons.

G protein-coupled receptors (GPCRs): cell type-specific transmembrane proteic receptors detecting external signals and transmitting them into the cell to induce various responses.

Induced systemic resistance (ISR): strengthening of the defence capacity of the entire plant against a broad spectrum of pathogens; acquired during local induction by beneficial microbes.

Jasmonates: oxylipin family comprising JA and its derivatives, which are lipid-based plant hormones that regulate plant defence mechanisms and a wide range of processes in plants (growth, photosynthesis, reproduction, etc.).

Oxylipin: large class of lipid metabolites derived from the oxidation of PUFAs.

Quorum sensing: cell-to-cell communication process that permits microorganisms to share information about cell density and adjust gene expression accordingly. This communication is provided by the production (depending on cell density) and release of chemical signal molecules.

Systemic acquired resistance (SAR): strengthening of the defence capacity of the entire plant against a broad spectrum of pathogens; acquired after a primary local pathogen infection.

Keywords: oxylipins; lipoxygenase pathway; plant–pathogen interactions; membrane interactions; interkingdom communication

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Highlights

Many studies have shown that specific oxylipin signatures are shaped during (a)biotic stresses.

It is generally accepted that divinyl-, keto-, and hydroxy-fatty acids and fatty acid hydroperoxides exhibit strong direct antimicrobial activities, whereas the roles of jasmonic acid and some volatile aldehydes seem to be related to signalling activities only.

Oxylipins' chemical structures are related to their biological activities.

Current studies show that the lipid composition of the plasma membrane has important roles in the interaction of plant oxylipins with plant cells.

It is becoming clear that many organisms use the oxylipin pathways as a common process for interkingdom communication

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Queries and Answers

Query: Refs [24–94,22,95–106,23] were cited out of sequence in the manuscript and have been numbered as [22–92,93,94–105,106]. Please check carefully. Also, please cite refs [113,114] at the appropriate places in the text. (They were not cited in the manuscript.)

Answer: Indeed, ref 113 and 114 can be removed from the list as they are not used in the manuscript at the end. Sorry for the mistake.