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Better living through phytochemistry: "Phytoavengins" and reappraising the production-focused dichotomy for defensive phytochemicals

Daniel J. Kliebenstein [a,**], Brian H. Kvitko [b,*]

[a] Department of Plant Sciences, University of California Davis, Davis, CA, USA
[b] Department of Plant Pathology, University of Georgia, Athens, GA, USA

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ABSTRACT

Plant pathologists frequently divide defensive phytochemical specialized metabolites into two functional categories; 1) Phytoalexins that are synthesized *de novo* after pathogen perception, or 2) phytoanticipins that are either constitutively present or synthesized from preformed constituents. This two-category system for defensive phytochemicals based on plant-production has been widely used but reinforces misconceptions about non-phytoalexin phytochemicals. We propose that defensive phytochemicals synthesized from preformed constituents, typically as a consequence of tissue damage, should be classified separately from phytoanticipins as phytoavengins. In addition, we highlight the potential advantages of shifting towards focusing on the diverse modes-of-action and ecological contexts of defensive phytochemicals.

1. Introduction

Plants are marvelous chemists, generating an extensive diversity of phytochemicals across the plant family tree. These compounds aid adaptation to a complex environment by controlling the interaction with biotic and abiotic factors. Regardless of their long history of study and ubiquitous diversity, the roles and contributions of defensive phytochemicals in plant-microbe interactions have been relatively understudied in recent years. It seemed prudent to highlight the need for renewed attention on the roles and mechanisms employed by defensive phytochemical specialized metabolites in plant-microbe interactions.

In the 1940s–1950s defensive phytochemicals (specifically phytoalexins) were proposed by K.O. Müller as mediators of hypersensitivity-based immunity [1–3]. However, as the molecular mechanisms underpinning Nucleotide-binding Leucine rich repeat Receptor (NLR) resistance gene-mediated immunity were uncovered in the 1980s–2000s, it became clear that defensive phytochemicals do not play a broadly generalized role in this form of plant defense. In contrast, defensive phytochemicals contribute to necrotroph resistance where NLR-mediated immunity plays a minor role [4–6]. Defensive phytochemicals mediating disease resistance also have clear roles in non-host resistance systems [7–9]. The presence of a defensive phytochemical in a host forces the pathogen to tolerate this compound to infect the host. If the pathogen cannot tolerate the compound then there is a non-host interaction. Only after this baseline tolerance/resistance requirement for potential pathogenic microbes is achieved can additional layers of genetic and molecular host specificity evolve. This metabolite tolerance/resistance dependency is true both across and within pathogenic species of fungi and bacteria [5–7,10].

Despite this key role, there is a relative dearth of studies into the mechanisms by which defensive metabolites modulate plant-pathogen interactions. This is in contrast to the massive explosion in studies identifying new plant specialized metabolites and their biosynthetic pathways [11–13]. We propose that integrating the identification of new metabolites with assessment of actual mechanisms of action is critical to understanding plant-biotic interactions. This integration is partly hindered by historical concepts structuring our understanding of plant specialized metabolites. The conventional dichotomy for defensive phytochemicals in plant pathology divides phytochemicals based on plant production as either phytoanticipins, (compounds constitutively present in plant cells and tissues or synthesized from preformed constituents) or phytoalexins, (compounds synthesized *de novo* after pathogen perception) [14]. Further distinctions are typically made between defensive phytochemicals with functions against pathogens versus those with functions against plant pests and herbivores. Neither classification system focuses on the actual mechanism or mode-of-action enabling the

* Corresponding author.
** Corresponding author.
E-mail addresses: kliebenstein@ucdavis.edu (D.J. Kliebenstein), bkvitko@uga.edu (B.H. Kvitko).

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compounds to assist the plant.

In this commentary, we highlight some conceptual and biological issues with the production-focused functional dichotomy for defensive phytochemicals, in particular noting that many of the most charismatic examples of phytoanticipins are non-constitutive, (often being produced as a direct consequence of tissue damage), and break the dichotomy. We highlight that shifting towards a focus on mode-of-action for defensive phytochemicals could provide new molecular insights in this growing area of research and match the typical practices used by other fields for classifying fungicides, antibiotics, and the study of plant pathogen toxins. Lastly, we consider the utility of examining microbe-defensive phytochemical secondary metabolite interactions within the infochemical framework of chemical ecology.

2. The diversity of plant specialized metabolites

Antimicrobial plant specialized metabolites have been identified across the plant kingdom and involve compounds from nearly the entire spectrum of phytochemical diversity [15,16]. For this commentary, we will use the typical definition for specialized metabolites as low molecular weight organic compounds that are non-ribosomally synthesized and not essential for core growth and cellular function (although Ribosomally synthesized and Post-translationally modified Peptide a. k. a. RiPP metabolites, such as victorin toxin and plant orbitides, do not fit cleanly into this simple definition [17]). Plant specialized metabolites are chemically diverse and often lineage specific with frequent examples of convergent evolution of specialized metabolites by distant lineages (e. g. caffeine in coffee, tea, cacao [18] and cyanogenic glucosides throughout multiple vascular plant lineages [19]). Some chemical structural classes, like terpenoids (synthesized from isoprene precursors), and phenylpropanoids (synthesized from phenylalanine and/or tyrosine) are broadly distributed among plants. This broader distribution of terpenoids and phenylpropanoids is shaped by their core biochemical pathways contributing to key conserved plant metabolites, e.g. terpenoid metabolism leads to the synthesis of abscisic acid, brassinosteroid, strigolactone, cytokinin, and gibberellin hormones while phenylpropanoid metabolism leads to salicylic acid and monolignol precursors [20,21]. While the core pathway is highly conserved, specialized metabolites arise from these pathways in lineage specific fashion. Alkaloid specialized metabolites (commonly with a nitrogen heterocycle) are also broadly distributed although they are classified by chemical structure and not via a shared common biochemical pathway [22]. Other chemical classes of specialized metabolites have more restricted and lineage-characteristic distributions. For instance, polyynes/polyacetylenes in the carrot family (Apiaceae), glucosinolates in the mustard/crucifer family (Brassicaceae), benzoxazinoids in grasses (Poaceae), and thiosulfinates in the onion and garlic family (Allioideae) [23].

3. A look back at classification shifts for plant specialized metabolites

The broader thinking about specialized metabolites can be constrained by the classification systems used to define them. Currently, phytochemical specialized metabolites potentially active against plant pathogens are typically designated as being either phytoalexins or phytoanticipins. Although the term "phytoalexin" has been in use since 1940, "phytoanticipin" was introduced in 1994 [2,14]. Not surprisingly given the long history of research on antimicrobial specialized metabolites, classification schemes for their diversity have undergone multiple revisions. The portmanteau phytoalexin (plant warding-off substances) was coined by Müller and Bolger in 1940 combining the loan word "alexin" from vertebrate immunity which is a now a dated term for the blood complement system originally applied to antimicrobial protective substances present in serum [2,24]. To be classified as a phytoalexin, Müller proposed that the plant antimicrobial must be absent from non-infected host tissue (or present at concentrations too low to exert an inhibitory effect on the pathogen), must inhibit pathogen growth *in vitro,* and must be present in infected tissue at concentrations sufficient to inhibit pathogen growth [1]. The phytoalexin definition also explicitly excludes preformed antimicrobial compounds found in healthy tissue as well as compounds produced as a result of mechanical tissue damage. In the phytoalexin hypothesis as laid out by Müller, use of the term phytoalexin was restricted to compounds that met the six experimental conditions listed in Box 1. Phytoalexin was proposed as a strictly functional classification without implied association to any particular chemical class, chemical structure, mode of action, or specific pathogen (although obligate biotrophs are effectively excluded due to being non-culturable) [1]. By definition, the phytoalexin assignment should be made in the context of the particular plant-pathogen interaction.

Many antimicrobial specialized metabolites synthesized in response to pathogen (or elicitor/PAMP) exposure fell short of having the experimental evidence necessary to satisfy all qualifications for being classified as phytoalexins leaving their status in limbo. In particular, it was often challenging to demonstrate that putative phytoalexins were responsible for suppressing pathogen growth *in vivo*. In 1981, a new working definition was proposed redefining phytoalexins as low molecular weight, antimicrobial compounds that are both synthesized by and accumulated in plants after exposure to microorganisms [25]. This new definition excluded the previous requirements for the antimicrobial specialized metabolite to have a demonstrated role in disease resistance. Although this change was widely accepted, the same concerns about the role of borderline specialized metabolites remained. Quoted from Ray Hammerschmidt's 1999 review on phytolalexins, "Although this definition is easy to apply to induced secondary metabolites, the definition leaves open the question whether phytoalexins are important in defense, and, if so, to what degree" [26]. Advances in plant and microbial genetics have begun to allow for direct assessment of *in planta* antimicrobial function addressing these concerns albeit largely limited to a few compounds in limited model systems [7,27–30].

In 1972, John L. Ingham, proposed revised definitions for plant antimicrobial specialized metabolites including new categories for non-phytoalexin antimicrobials based on their production relative to pathogen exposure and tissue damage [24]. Interestingly, none of Ingham's categories, (including his revised definition for phytoalexins), included requirements for demonstrated roles in disease resistance. In Ingham's scheme, preformed compounds present in their active forms at concentrations sufficient to inhibit microbial growth were classified as "prohibitins" reviving nomenclature first used by Schmidt in 1933 [31] (of note, the name prohibitin is in current active use for a family of broadly conserved eukaryotic proteins involved in the regulation of cell survival and apoptosis [32]). He classified semi-constitutive compounds present at low concentration in non-infected tissue but induced to high concentrations in response to pathogens as "inhibitins", which partially overlaps with phytoalexins depending on interpretation. Lastly, the category of "post-inhibitins" was proposed for compounds present in tissue in inactive or bound forms that were enzymatically converted into active antimicrobial forms in response to tissue damage either resulting from infection or mechanical means.

In a seminal letter to the editor published in The Plant Cell in 1994, Van Etten et al., proposed the introduction of the new term of "phytoanticipins" coined by John Mansfield with the following definition, "*Phytoanticipins are low molecular weight, antimicrobial compounds that are present in plants before challenge by microorganisms or are produced after infection solely from pre-existing constituents"* [14]. The stated intention for proposing the phytoanticipins category was both to preserve the more limited definition of phytoalexin, and to mirror the working definition of phytoalexin. This definition effectively bundled all non-phytoalexin plant antimicrobials under a single heading based on the model that these defensive specialized metabolites are produced in healthy tissue in anticipation of pathogen attack. Like the new working definition of phytoalexins, phytoanticipins found broad acceptance

Box 1
The six experimental preconditions for phytoalexins as proposed by Müller (reordered from their original presentation) [2].

1. No preformed substances inhibitory to the pathogens used must be present.
2. Mechanical injury which may bring about the formation of other inhibitory factors must not be involved.
3. It must be possible to demonstrate that the antibiotic substance is present *in vivo* at concentrations sufficient to stop the pathogen's growth.
4. The pathogen must be able to be grown on ordinary nutrient media.
5. The interaction between host tissue and pathogen (and so the formation of the antibiotic principle) must take place under conditions. which exclude interference by contaminants.
6. Chemical extraction methods which may affect the active principle must be avoided.

resulting in our current production-focused defensive phytochemical dichotomy; phytoalexin v. phytoanticipin.

4. The limitations of the production-focused dichotomy and three classes of plant defensive specialized metabolites, phytoalexins, phytoanticipins, and "phytoavengins"

A long-standing challenge with categorizing defensive phytochemical specialized metabolites is that a specialized metabolite's status as a phytoalexin or phytoanticipin is not an intrinsic quality of the metabolite but instead dependent on regulation by host that produces them. As a consequence, phytochemicals that are pathogen-inducible in one plant species may constitutively accumulate in another plant species, or even accumulate constitutively in one organ and inducibly in a different organ of the same plant [14,33]. Van Etten et al. proposed that phytoalexin and phytoanticipin classifications should not be considered as mutually exclusive and that it is appropriate to classify a single compound, as both a phytoalexin and as a phytoanticipin even within a single plant species [14]. This taxonomic compromise eliminates the need for the separate "inhibitin" category proposed by Ingham for compounds and is particularly useful given the inherent challenges and ambiguity for determining *in vivo* concentration efficacy thresholds for specialized metabolites that are pre-formed in tissues but still display microbe-responsive synthesis.

The deeper conceptual issue of the phytoalexin and phytoanticipin dichotomy is the loss of resolution that comes from grouping all non-phytoalexin defensive phytochemicals under a single classification heading. An unfortunately common misconception is that all phytoanticipins are suffused into plant tissues in a manner similar to how antibiotics are added to selective media acting as passive antimicrobial selective barriers. In truth, some of the most charismatic and well-studied phytochemicals that currently fall under the phytoanticipin heading, namely glucosinolates, benzoxazinoids, cyanogenic glycosides, and thiosulfinates, require activation by the plant to be converted into active antimicrobials [34–38] (Fig. 1). As such, they are represented by Ingham's post-inhibitin category and the sub-definition of phytoanticipins *i.e. they are produced after infection primarily from pre-existing constituents*. That is to say, they are largely stored in what is considered an inactive form and the active form only becomes present upon biotic or physical attack. For example, in the glucosinolates, myrosinase (thioglucosidase) enzymes and the glucosinolates are stored separately and stably in plant tissues. Tissue damage and the associated cellular disruption or active vesicular transport bring the myrosinase enzyme and glucosinolate substrates together resulting in the production of the "mustard oil bomb (used by Matile in 1980) of reactive isothiocyanates, thiocyanates, nitriles or epithionitriles [35,39,40]. Similarly, in onion, garlic, and other *Allium* spp., the cysteine sulfoxide thiosulfinate precursors (e.g. alliin) and alliinase (cysteine sulfoxide lyase) enzymes are localized in distinct cellular compartments until cellular disruption allows them to interact resulting in the production of the volatile and reactive thiosulfinate antimicrobials (e.g. allicin) that contribute to their characteristic odors and flavors [34,41]. Likewise, benzoxazinoids (e.g. DIMBOA) and cyanogenic glycosides are stored as non-active glucones until they are enzymatically deglycosylated resulting in the accumulation of their active forms [36,37]. These systems had largely been placed in the phytoanticipin class because it was considered that activation was a passive response to tissue damage mixing cellular components but recent work is showing that active vesicular transport is key to their antimicrobial function [40]. This would seem to place them in a different category than constitutively active phyoanticipins that

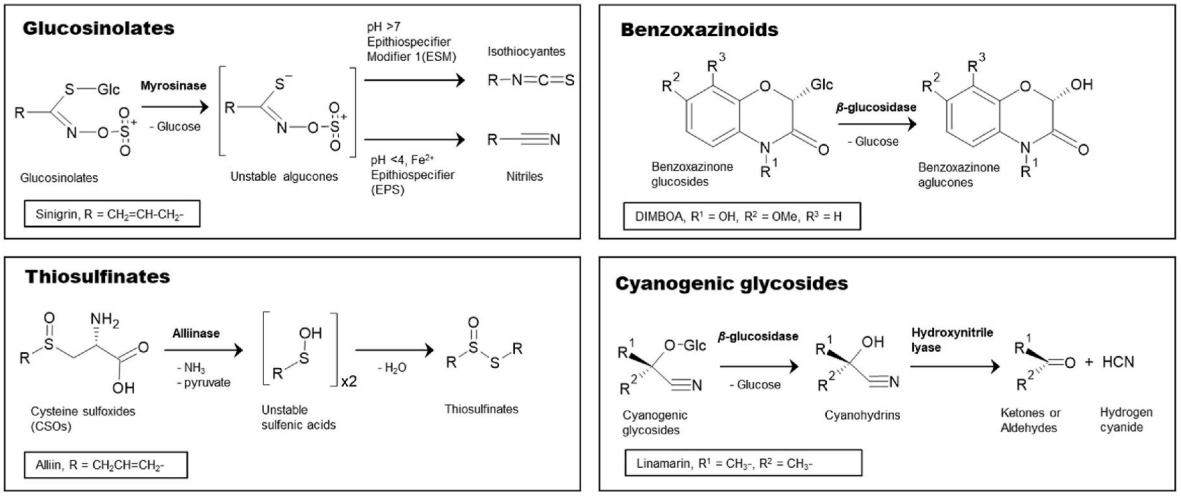

Fig. 1. Example phytoavengins and their enzymatic activation pathways. Only a subset of activation forms are shown. Adapted from Konno et al., 2010 [17], Wouters et al., 2016 [38], and Stice et al., 2021 [6].

accumulate in healthy plant tissue. In addition, there are far fewer ambiguities about when, where, and how these activatable defensive phytochemicals are produced and accumulated in their active forms than for phytoalexin compounds that may accumulate differentially based on species-variable transcriptional regulation of their biosynthetic pathways.

Thus, we support the broader use of the new functional category of phytoavengins (coined by Jovana Mijatović) as a counterpart to phytoalexins and phytoanticipins with the following definition drawing aspects from Ingham's post-inhibitin and the phytoanticipin definition of Van Etten et al. "*Phytoavengins are low molecular weight, antimicrobial compounds that are enzymatically converted from inactive pre-existing constituents after plant tissue damage*". In addition, we suggest that phytoanticipin be retained with the following more limited definition. "*Phytoanticipins are low molecular weight, antimicrobial compounds that are present in their active forms in plants before challenge by microorganisms*". The term phytoavengin was selected to partner well with the phytoalexin and phytoanticipin taxonomy and is conceptually appropriate for this production strategy for defensive phytochemicals based on the Oxford English dictionary definition of avenge, "*inflicting harm in return for an injury or wrong done to oneself or another*".

We recognize that broadly accepted taxonomies often have their own momentum and can require substantial effort and time to be shifted or replaced. However, the value of any taxonomy or categorization scheme is based on its utility for effective communication and making useful and accurate predictions. Taxonomy can influence thinking and this is particularly problematic when category definitions substitute for biological nuance resulting in broad misconceptions. This is exacerbated by the somewhat limited attention given to defensive phytochemicals in modern molecular phytopathology. We hope that the phytoavengin functional category may facilitate easier communication across the field without the continual need to caveat that multiple groups of pre-formed defensive phytochemicals are inactive as antimicrobials without enzymatic activation typically associated with tissue damage.

5. The potential advantages for classifying defensive phytochemicals based on mode of action

An appealing aspect of a production-focused taxonomy for defensive phytochemicals is that it roughly maps with predictions about how these chemicals might interact with pathogens of different lifestyles. Especially in the context of understanding how the plant is controlling these compounds and possibly allowing for translation of underlying mechanisms across lineages when the compounds are not conserved. For instance, phytoalexins by definition cannot be produced by dead cells so pathogens that kill cells rapidly, like soft rot necrotrophs, may avoid phytoalexin exposure. Conversely an obligate biotroph that does not cause cellular decompartmentalization would presumably not be exposed to active phytoavengin compounds. However, this very simplified model is easily challenged by specific microbe-defensive metabolite interactions. For instance, glucosinolates contribute to Arabidopsis non-host resistance to biotrophic powdery mildew [42]. While it is tempting to think of these classifications as having a microbial-centric focus, it is also possible that these variations in production scheme are shaped by the plant. For example, one hypothesis is that the different production schemes for defensive phytochemicals could have arisen to manage risks of self-intoxication based on the compound's modes of action. As has been noted previously by Wittstock and Gershenzon, 2002, plants must live with their own defensive phytochemicals [43,44]. If a defensive specialized metabolite acts on a target that is present in the host and exerts a negative effect, then the plant must use some strategy to limit or balance its own exposure risks. One option is to limit production to after pathogen exposure (e.g. phytoalexin) or produce the compound in an inactive form that requires a last activation step that occurs upon attack or after tissue damage (e.g. phytoavengin). Conversely, if the target of the defensive specialized metabolite is absent in plants, for instance specifically acting on a key component of the nervous system, then the plant would be free to accumulate that phytochemical constitutively without risking self-intoxication (e.g. phytoanticipin).

We could potentially improve our understanding of how plant specialized metabolites influence biotic interactions by categorizing them based on shared mode of action (MOA) instead of biochemical (phenylpropanoid, terpenoid, etc) or production (phytoavengin, phytoanticipin, phytoalexin) frameworks. A MOA classification system, based on the cellular targets and biochemical mechanisms by which compounds mediate their effects, is at the core of our developing knowledge about both commercial biocides (fungicides, antibiotics, antivirals) and drugs where compounds are typically classified by their target/mechanism of action. This has allowed for the application of genomics pipelines such as yeast toxicity screens allowing rapid classification of compounds based on their biological activities. Interestingly, there is a long history of mode-of-action research on plant specialized metabolites in the study of human physiology which is largely disconnected from the functions of these compounds in the plant's environment. There is also an asymmetry between the study of plant and pathogen secondary metabolites and pathogen toxins where the target and mode of action of pathogen toxins are more frequently studied [45–47]. Recent observations on the MOA of specialized metabolites in plant/biotic interactions suggests that focusing on the compound's mode-of-action may be a useful approach to understand the biological function of plant specialized metabolites and the processes driving diversity.

Commonality in biochemical classification systems and MOA are often assumed to be shared. For example, cyanogenic glucosides, while being independently evolved, share a common biosynthetic route based on enzyme activity. This leads to the production of a cyanogen that during tissue disruption is catabolized leading to the accumulation of cyanide [36]. The released cyanide targets the heme within the cytochrome C oxidase leading to a block in respiratory electron flow and resulting toxicity [48]. Likewise, while thiosulfinates have variable side-chains, they all carry the same functional group and can participate in similar chemical reactions allowing them to react with cellular thiols [38,49].

In contrast, the literature on other specialized metabolite groups does not equally support the assumption of shared biochemistry and MOA. Glucosinolates are a class of compounds often assumed to have a common MOA that is due to the formation of isothiocyanates that have a generic ability to react with proteins. However, work in humans, insects and bacteria shows that structurally different glucosinolates can have different modes of action even when made into isothiocyanates not supporting the generic MOA assumption. In humans, sulforophane (4-methylsulfinylbutyl isothiocyanate) and allyl isothiocyanate have specific and distinct biological properties mediated by specific protein interactions. Sulforophane alters human gene expression by interacting with a cysteine in the keap1 (Kelch-like ECH-associated protein1). In contrast, allyl isothiocyanate stimulates a bitter taste by reversibly reacting with a cysteine on TRPA1 [50]. In contrast to the assumption of shared isothiocyanate reactivity, sulforophane does not appear to interact with TRPA1 and allyl isothiocyanate has little interaction with keap1 [51] Their likely difference in target mechanisms is supported by observations of synergistic activity in human systems [52]. Further work in humans is beginning to illustrate the potential that these plant specialized metabolites may not be limited to single protein targets but have a small but defined set of targets [53]. This suggests that while sulforophane and allyl isothiocyanate are separated by a single plant enzyme, they likely have different MOAs.

In addition to studies of how plant specialized metabolites affect humans, the observation of potentially different MOAs for highly similar chemicals is also supported more directly by studies in plant interacting organisms. Arabidopsis produced sulforophane has been linked to the suppression of type III secretion in Pseudomonads by targeting a

cysteine in HrpS [54]. Unfortunately, this study did not compare the activity of other compounds like allyl isothiocyanate. In contrast, sulforophane was not highly active against *Sclerotinia sclerotorium*. Instead, it was longer chain aliphatic isothiocyanates that had the strongest activity hinting at distinct targets and MOAs [55]. Like the differential TRPA1 reactivity, allyl isothiocyanate and sulforophane differ as oviposition attractants in insects further suggesting the possibility for differential targets [56]. Similarly, the structurally similar glycoalkaloids have a broad range of biological activities from the cardiac glycosides that directly target a Na+-K+-ATPase to tomatine and solanine (solanaceous glycoalkaloids) that may target acetylcholinesterase or other as yet unidentified components [57,58]. Unfortunately, in most specialized metabolite studies, the specific target or MOA is not pursued. So, it is presently unclear how MOA maps to any classification scheme for plant specialized metabolism.

Studies of the mechanisms by which plant specialized metabolites interact with humans has raised an intriguing possibility that diverse unrelated chemicals can actually target the same protein. The best example of this is TRPA1. In addition to interacting with allyl isothiocyanate, TRPA1 also interacts with the structurally similar but biosynthetically independent sulfinates [59]. TRPA1 also interacts with the phenylpropanoids cinnamaldehyde, cuminaldehyde and capsaicin that are structurally unrelated to the sulfur containing allyl isothiocyanate or sulfinates [60]. Even further, diverse terpenes can interact with TRPA1 [61]. These compounds are all sufficiently different that they can't have the same precise chemical MOA with TRPA1. It is presently unclear if TRPA1 evolved to perceive diverse compounds or if diverse compounds may coalesce on common targets in other systems. Understanding the mechanisms by which plant specialized metabolites influence plant-bacterial systems will require more in-depth analysis of the specific MOAs for a diversity of plant specialized metabolites. Simply relying on assumptions about general chemical properties, e.g. all isothiocyanates are reactive, is not sufficient to develop the models necessary to understand these compounds.

6. Defensive plant specialized metabolites in the infochemicals framework

Often defensive specialized metabolites are generically classified as antimicrobial with an assumption of an activity focused on killing or suppressing microbial growth. Querying the literature on the mode of action for defensive phytochemical also highlights how the microbe-phytochemical interactions are far more nuanced than solely growth suppression. Phytochemical defense, mirroring the diversity pathogen toxins, could potentially involve manipulation of any stage of disease or the pathogen lifecycle from attachment/invasion through dissemination. A growing number of plant defensive specialized metabolites have been identified with the capacity to suppress pathogen virulence in the absence of overt suppression of microbial growth. Specialized metabolites extracted from the wild potato species *Solanum chacoense* with high degrees of tolerance to bacterial soft rot were able to interfere with *Pectobacterium brasiliense* quorum signaling and expression of soft rot virulence factors without impacting bacterial growth [62]. The above mentioned sulforaphane, suppresses growth at high concentrations, but was shown to suppress the expression of the *P. syringae* pv. *tomato* DC3000 (*Pto*) type three secretion system (T3SS) virulence regulon via reaction with a conserved cysteine residue of the HrpS transcription factor at physiological concentrations that were sub-inhibitory for growth suppression [54]. Expression of the *Pto* motility and expression of the T3SS were suppressed by the tomato flavonoids morin, naringenin and phloretin at sub-inhibitory concentrations [63]. Of note *Pto*, a compatible pathogen of both Arabidopsis and tomato, encodes detoxification and/or efflux systems for both sulforaphane and flavonoid plant defensive specialized metabolites [7,63]. It has been proposed that targeting virulence may result in reduced selective pressure on microbes to evade or detoxify these compounds than those that directly suppress microbial replication [64,65]. In addition to encompassing wider range microbe-specialized metabolite interactions, a broader appreciation of these diverse functions could enhance the use of this extended definition would facilitate more ready inclusion of defensive specialized metabolite in interactions with obligate biotrophs that cannot be readily assessed *in vitro* for growth suppression.

The ability of plant specialized metabolites to have a diversity of nuanced functions has been long recognized in the chemical ecology field with the concept of "infochemicals" [66,67]. This chemical ecology classification scheme is commonly used in entomology to help contextualize the specialized metabolites mediated molecular and ecological interactions between plants and arthropods. The infochemical framework (See Fig. 2) classifies specialized metabolites based on whether they mediate interactions within the individual that produces them (hormones), between individuals of the same species (pheromones), or between individuals of different species (allelomones/allelochemicals). Allelochemicals are further divided based on whether the producer individual or receiver individual derives benefits. Using this framework generically, plant specialized metabolites that modify the growth or behavior of another species, be it microbe, animal, or plant, would be classified as allelomones, while defensive phytochemical specialized metabolites (phytoalexins, phytoanticipins, phytoavengins) that benefit the plant producer by restricting the proliferation or virulence of a pathogen would be considered specifically allomones. Although distinctions are routinely made between phytochemical defenses against pathogens and pests or herbivores, in a chemical ecology framework, those distinctions are unnecessary. However, it may be challenging to definitively assess whether specific plant specialized metabolites confer benefits to one or the other partner. Of course, these classifications are always contextual and defensive phytochemicals in different contexts can result in other ecological outcomes. For instance, defensive phytochemicals may be exploited by adapted or specialist pests and pathogens and serve as kairomones providing benefits to the pathogen or pest as specific chemical cues of their preferred hosts. For instance, as noted previously, glucosinolate profiles influence egg laying preferences of the diamondback moth *Plutella xylostella*, and the sclerotia of *Stromatinia cepivora,* causative agent of *Allium* white rot, germinate in response to thiosulfinate derivatives [56,68].

7. Conclusion

In this commentary we suggest that our current production-focused dichotomy, born out of the long history of classification schemes to organize the complexity and diversity of plant defensive specialized metabolites, may be engendering biological misconceptions within the field. We propose that adopting the phytoavengin category for defensive antimicrobials that are enzymatically converted from inactive pre-existing constituents after plant tissue damage will provide an additional biologically-relevant level of resolution. However, as is typically the case in biology, it is likely that no single classification scheme, be it biochemically focused, plant-production focused, mode-of-action focused, or ecologically focused, will be singularly sufficient to help derive the necessary insights to understand and utilize plant specialized metabolism in plant-microbe interactions. Instead, it is likely that we as a community will need accommodate terminology/schema that are less prescriptive and presumptive and more nuanced and appropriate to the questions being asked. For example, the chemical ecology scheme may be more useful and relevant to microbiome-specialized metabolites interaction studies studying impacts on the structure of the community as a whole. In contrast, a mode-of-action framework may provide more insight when focusing on how specific genes shift within the community's metagenome. We hope that expanding the frameworks in which we consider microbe-specialized metabolite interactions will facilitate improved understanding and integration of phytochemical defenses into the larger modern molecular conversation of plant immune mechanisms.

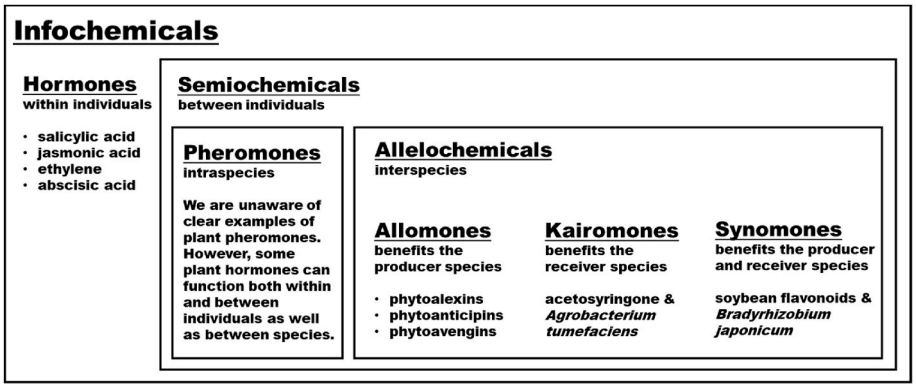

Fig. 2. Taxonomic structure of the infochemicals classification scheme with examples from plant-microbe interactions. Adapted from Dicke and Sabelis, 1988 [67] and Hansson and Wicher, 2016 [68].

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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