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Biological Activity of Defence-Related Plant Secondary Metabolites

Ananth Anbu and Umadevi Ananth

Abstract

The message that everyone needs to know is that secondary metabolites in plants and natural products are involved in various activities. The phenolics, quinones, terpenes, flavonoids, and other thousands of low molecular weight metabolites activity is unknown. Well-understood secondary metabolites have been implicated in the defense against pathogens; the operating system of some of these has been established. In particular, to date, a relatively small number of processes have been shown to be targets of plant metabolism, including electron transport chains, mitochondrial function, and membrane integration. However, it is now emerging that other specific enzymes and processes may also be targets of specific metabolites. There is a general belief that modern genetic approaches will identify new targets and mechanisms of plant metabolism. Molecules that trigger apoptosis or autoimmunity in tumor cells, especially triterpenoids, are of particular interest in this regard. Before proceeding to specific studies in plant or human cells, we discuss whether there is a case for conducting preliminary studies on the mechanism of action in the genetic pathway system, such as yeast *Saccharomyces cerevisiae*, considering the approaches taken so far in botany and strategies that have led to success in the biomedical field.

Keywords: natural products, *Saccharomyces cerevisiae*, Defensins, pathogen

1. Introduction

Secondary metabolites in plants are commonly used to describe metabolic pathways that produce molecules or metabolites that can provide for normal growth or are only needed under certain conditions. In contrast, primary metabolites traditionally describe key household maintenance functions, such as energy production or the production of essential metabolites and macromolecules. These differences may be somewhat misleading; however, as is now known, secondary metabolites compounds plays a very important role in the biology of various organisms. In fact, it is clear that evolution would not selectively maintain the complex pathways that make up secondary metabolites if there were no competing advantages for the developing organism.

This logic, coupled with the fact that the biological function of the majority of plant and microbial secondary metabolites is poorly understood, has led to an

alternative description of plant metabolites as “natural products” [1], though that description also carries some limitations. Nature produces a tremendous array of secondary metabolites or natural products, with the most diversity seen in micro-organisms and plants [2]. It is a great resource for mankind and many examples of microbial or plant metabolisms are exploited by man, for example, antibiotics and pharmaceuticals. However, we have only scratched the surface, especially since there are various natural metabolites that have applications in the field of biomedicine. It is the basis of many natural product discovery projects, for example, attempts to use metagenomics to study marine microbial diversity [3]. In contrast to these attempts to explore metabolic diversity in new key locations, plant metabolic diversity has been exploited by humans throughout history, initially using plant extracts and more recently through scientific activity to identify metabolites with specific functions and then use these products directly or as traces for therapeutic compounds [4].

2. Defense against pathogens with secondary metabolism

Knowledge of how these molecules affect the exploitation of natural materials is often followed by an understanding of the role of metabolism in the producing organism. In plants, well-understood secondary metabolism is involved in pathogen protection or perception and signaling. In terms of pathogen protection, fungal diseases pose a major threat to plant health, with estimates below of 13,000 phytopathogenic fungal species in the United States alone. Therefore, it is not surprising that plants have developed comprehensive protection mechanisms against fungal pathogens, with chemical protection being one of the key weapons in the plant arsenal [5]. Although thousands of different molecular compounds are believed to play a role in plant protection against bacterial and fungal pathogens, the mechanism of action of relatively few has been the subject of extensive research.

Figure 1.
Natural product can be localized into plant tissue or secreted externally.

Plant defense molecules may be pre-formed in plant tissues (**Figure 1**) or synthesized in response to the pathogenic attack, resulting in variations leading to the terms phytoantiseptics and phytoalexins, respectively [6]. This difference does not provide any specific information about the chemical structure or mechanism of metabolism and in some cases, misleading defense molecules are pre-manufactured but concentrated in high concentrations at the site of infection are reasonably considered to be phytoantiseptics or phytoalexins. In practice, when studying the range of possible biological functions involved in metabolism, the chemical structure of natural products is more relevant than the exact time produced at the plant.

3. The role of secondary metabolites in plant-microbial signaling

In terms of signal, the most comprehensible metabolites are flavonoids involved in symbiotic lentil-rhizobia interactions that lead to the formation of nitrogen-fixing nodules in root tissues [7]. Collectively, plants produce more than 5000 different flavonoids, with only a small subgroup involved in specific interactions with Rhizobia. This interaction begins with the secretion of signal flavonoids at the root exudates, followed by the bacterial understanding of the signal and direct contact with the bacterial nodule transcriptional activator. This triggers a series of events that create convenient rhizobial infection of the plant root and nitrogen-fixing nodules.

The other major beneficial plant-microbe interaction that occurs in nature is the formation of mycorrhizal roots. Once again, there is a facilitated infection of plant roots, this time by arbuscular mycorrhiza fungi, which develop specialized structures called arbuscles within the root for nutrient exchange between the plant and fungus. Although a role for signaling has long been postulated, it is only in recent years that the first experimental evidence demonstrating a role for a plant chemical has been obtained, showing that a particular class of sesquiterpene, the strigolactones, can induce hyphal branching, an important step in the symbiosis [8].

As an added twist, several studies have shown that certain strigolactones actually play a role in regulating plant hormones and spruce branches in the plant, thus regulating processes above and below the ground [9].

4. Allelopathic reactions

Allelopathy is defined as the inhibition of the growth of one species by chemicals produced by another species, and although this is a matter of controversy in the scientific literature, this concept has been generally accepted in recent years [10]. This definition is significantly shorter than the original use of the word, which may involve both positive and negative interactions, but it is also a reflection of the importance of allelopathy between domestic and introduced plant species, especially when introduced species can invade and displace native plants. Engineering mills, especially those with grains, have a considerable interest in controlling weeds in their own surroundings using allelopathy in agriculture.

The basic premise of allelopathy is that plants secrete phytotoxic metabolites in their surroundings (primarily rhizosphere) and inhibit the growth of plants that are susceptible to these metabolites. This process can be reasonably classified as protective or signal and, in fact, molecules such as strigolactones may have dual roles.

Allelopathy is believed to have an evolutionary dimension, so long-term coexisting plants have developed co-adaptation and tolerance mechanisms, whereas ecologically separated plants may not have these tolerance or resistance mechanisms. The various molecules present in the root glands are known to have phytotoxic properties at biologically related concentrations (**Figure 1**).

The majority are phenolics, including simple phenolics, flavonoids, and quinones; terpenes, monoterpenoids, sesquiterpene lactones, diterpenes and Benzoxazinoids or glucosinolates. An important feature when considering plant protection against microbial or insect pathogens, signaling and allelopathy is that overall classes of molecules are also included in these cases. Our ability to determine whether, specific metabolites may first be lost in evolutionary history as signal molecules, as protection against pathogens, or as phytotoxic agents to enhance competitiveness. With regard to the exploitation of these natural products (lead) as herbicides, plant protection products, or drugs, it is now an important quest to understand their mechanism of action in targeted and non-targeted organisms.

5. Process of plant natural products

5.1 Identifying the targets of plant metabolites

Despite the vast number of biological reactions in biological structures and cells, a relatively small number are exploited by man. For example, 270 herbicides in commercial use target only 17 different processes and medicinal and agricultural fungicides target only six different processes [11]. As the synthesis of natural substances in plants runs into many thousands of different molecules, many new inhibitors of cellular functions can be identified. This belief drives most of the research on plant natural products and their mode of action. Although many plant metabolites have been described chemically and have played many roles in signaling, defense, and allelopathy, the exact action of some has been determined in no detail. In cases where attempts have been made to determine how chemicals cause their effects, the interpretation of the results is often complicated by several goals, including difficulty in separating primary and secondary effects and difficulties in determining whether data obtained from *in-vivo* studies are related to *in-vivo*. To a large extent, these difficulties are indicative of limitations with the test methods used, and there is certainly a case for conducting studies in genetically controllable systems such as yeast. Nevertheless, it was possible to identify key processes that are normally targeted by plant metabolites and specific enzymes that can be inhibited by specific metabolites.

5.2 Inhibition of specific enzymes

Plant secondary metabolites can inhibit specific enzymes in plants or other organisms, such as fungi or animals. In some cases, it appears to be the only function of the metabolism, while in others, it forms part of a set of enzyme inhibitory effects. It should be noted, however, that the uniqueness of some of the findings and the biological relevance of *in-vivo* are questionable. An example of this is the inhibition of various enzyme reactions, including the plant hormone biosynthetic enzymes, catalase, maltase, and phosphatase by phenolics and phenolic acids [12].

Sesquiterpenes are one of the largest families of plant natural products and have many common effects associated with this type of molecule. It is believed that some

sesquiterpenes inhibit the activity of enzymes containing sulfhydryl-containing enzymes (e.g., phosphor-fructokinase) and that this may be due to the general apoptotic effects of plant sesquiterpenes on animal cells, but more detailed investigations are needed in this area. In contrast to those common effects, quinone sorgoleone (**Figure 1**) inhibits the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD) [11]. Plastoquinone and ultimately chloroplast synthesis require HPPD activity and are targeted to sulcotrione and other herbicides [13]. Other quinones, such as juglone made from the walnut tree, can also inhibit HPPD activity.

Another example is the steroidal alkaloid tomatidine, which in particular inhibits the C24 sterol methyltransferase reaction, which is essential for the synthesis of the essential fungal membrane sterol, ergosterol. This anti-fungal metabolism is

Figure 2.
 Structures of some plant secondary metabolites.

synthesized in tomatoes in a glycosylated form called α -tomatine and is closed to the steroidal alkaloid tomatidine by fungal enzymes during plant infection (**Figure 2**). Studies with yeast *Saccharomyces cerevisiae* have unique modes of action with tomatidine, which is 50 times more potent than α -tomatine and tomatitin action α -tomatine.

Interestingly, the importance of C24 sterol methyltransferase for ergosterol biosynthesis has already been recognized and commercial fungicides such as fenpropimorph target the same enzyme. The fact that the enzymes in question have already been identified, and used as pharmacological targets in both sorgoleone/HPPT and tomatidine/C24 sterol methyltransferase confirms the technique of identifying new enzyme targets of plant natural products as intervention drugs or chemicals. Some new natural ingredients or enzymes are under investigation in this regard. For example, 1,4-cineole (monoterpene) inhibits the synthesis of asparagine and quassinoids (diterpenes) are believed to inhibit membrane NADH oxidase [14].

6. Inhibition of electron transport systems

6.1 Target of photosynthesis and respiration

Photosynthesis is centrally important for plant health; It is, therefore, a clear target for natural and synthetic inhibitory molecules. At least 59 different herbicides target Photo System II (PSII), primarily by interfering with electron transport [13]. PS-II quinone was found to be the main target of sorgoleone, the same metabolite that inhibits the enzyme HPPD (above). Sorgoleone is believed to compete with plastoquinone for binding to D1 proteins in PS-II [15] and is secreted in droplets from the root hairs, which accumulate in the soil around the plant roots at 10–100 μ M.

The imbalance between the number of herbicides and natural metabolites that inhibit photosynthesis is surprising and suggests that there may be many more natural inhibitors of photosynthesis yet to be identified. Respiration is another important function of the cell based on electron transport chains and also is the target of inhibitory molecules. The clearest example is probably the cyanogenic glycosides that are produced by more than 200 different types of plants. These are synthesized by converting amino acid precursors to oximes, which are then glycosylated. The hydrolysis of cyanogenic glycosides in response to tissue damage produces hydrogen cyanide (HCN), a potent respiratory toxin [6]. Glucosinolates are molecules associated with the evolution that is synthesized only by a subgroup of organisms, mainly within the order capparalase, including the agriculturally important Brassicaceae family [16].

The hydrolysis of glucosinolates yields isothiocyanates, thiocyanates, and nitriles and although the fungal pattern of these metabolites has not been demonstrated, cyanide moiety is said to be the target of some of these metabolites. Other low molecular weight natural products are also believed to target respiration, but in many cases, it is difficult to establish definitively and studies with isolated mitochondria have sometimes produced conflicting results. Therefore, although some phenolic acids inhibit the absorption of iodine by the mitochondria, the concentrations of phenolics appear to be unreliable, while there are suggestions that phenolics may inhibit electron transport in the b/c1 cytochrome complex and those phenolics actually induce respiration in some cases [17].

7. Biological activity of the antimalarial drug artemisinin

The use of sesquiterpene lactone artemisinin has been reported to have a variety of physiological effects on target cells, including disruption of mitochondrial function [18]. Artemisinin is a natural product synthesized by the Chinese plant *Artemisia annua* (sweet wormwood), which means that this molecule and its derivatives are now part of the front-line anti-malarial treatment. The effect of artemisinin on plant cells is unknown, but several studies have attempted to determine why this metabolism is toxic to the malaria parasite *Plasmodium falciparum* and other protozoa. Artemisinin is abnormal in possessing an endoperoxide moiety essential for cell function (Figure 2).

Artemisinin *Plasmodium falciparum* inhibits the absorption of oxygen, indicating that it may be the target respiratory chain [19]. In a new strategy, Li and colleagues explored the mechanism of action of artemisinin using a yeast sample and using yeast genetics to disrupt the mitochondrial membrane capacity of artemisinin [20]. Their work pointed out that the electron transport chain actually activates the mitochondrial depolarizing function of artemisinin. In contrast, Nagamun and colleagues found that artemisinin could not affect the mitochondrial membrane ability of another protozoan parasite *Toxoplasma gondii*, suggesting that mitochondria were not a primary target in the *T. gondii* [21]. In fact, there is now strong evidence that calcium affects homeostasis in the target species of artemisinin.

Eukaryotic cells use Ca^{2+} as a second messenger and generally maintain very low cytoplasmic concentrations of Ca^{2+} by dividing Ca^{2+} into segments, such as the endoplasmic reticulum. One of the key enzymes in this process is the sarcoplasmic/endoplasmic reticulum Ca^{2+} -ATPase (SERCA). Heterologous host, *Xenopus lewis* using early work, demonstrated that artemisinin inhibits *P. falciparum* function [22] and recent experiments revealing the *T. gondii* in *S.cerevisiae* demonstrated that the *T. gondii* enzyme was inhibited by artemisinin. Physiological tests in many protozoa are consistent with the effects of artemisinin on calcium homeostasis, suggesting that it may account for a significant portion of the biological activity of this metabolite [23]. There are conflicting opinions on the biological functions of artemisinin with further studies to determine whether the malaria parasite *P. falciparum* and in fact plant organisms affect the mitochondria as the primary or secondary target of artemisinin. Artemisinin appears to cause specific nonspecific effects such as the production of free radicals and immune stimulation, and it is absolutely plausible that, like sorgoleone, artemisinin has more than one target or effect. The interactions between mitochondrial function, calcium signaling, and apoptosis should go unnoticed, and the effects that appear pleiotropic may actually become part of the same process.

8. Disruption of plasma membrane integrity

8.1 Importance of the fungal membrane as a target

As previously highlighted, secondary metabolites play an important role in protection of plants against fungal pathogens. This is an important area of interest in modern agriculture and medicine with the fungal cell membrane for clinical medicine and agro-fungal drugs. The fungal membrane has unique features, especially sterol ergosterol other than cholesterol or stigmasterol, which is present in animal and plant membranes, respectively. Other differences include the presence of specific lipids on

the outer leaf of the membrane. Common antifungal compounds include amphotericin B, which binds to ergosterol, which leads to pore formation, azoles, and morpholine, which inhibit ergosterol biosynthesis. Evolution has failed to observe this effect on fungi and plants but develops different types of antifungal defense metabolites that target the membranes of phytopathogenic fungi. The well-understood of these are defensins and saponins.

8.2 Plant defenses have specific binding sites in fungal membranes

Defensins are the most basic, cysteine-rich peptides, typically 40–45 amino acids in length, produced by plants, insects and other animals as antimicrobial defensins molecules [24]. Molecular phylogenetic analysis while the evolutionary roots of these molecules were probably in plants, there was a significant functional difference in the family of cationic antimicrobial peptides (cAMPs) defensins by evolution [25]. A variety of defensins has been reported to have antiviral, antibacterial, and antifungal activity. The prevailing opinion is that the positive charge of peptides mediates specific non-binding with phospholipids, which leads to pore formation and loss of membrane integrity. Although this is a common feature of cAMPs, in recent years it has emerged that specific interactions play a role in the functioning of some cAMPs. For example, human α -defensins have been shown to inactivate adenovirus by binding directly to the viral protein, and endogenous targets for cAMPs have been identified in some bacteria. It is already known that plant defensins and some insect defensins have a specific binding target and mode of action. This discovery initially came from work using *S. cerevisiae* as a model to study the antifungal activity of plant defensins. Yeast strain DmAMP1, a mutation in a gene required for the synthesis of sphingolipids, altered sensitivity to plant defensins [26]. Sphingolipids are commonly found on the outer leaf of eukaryotic membranes and resemble phospholipids, except that the vertebrae are not made of diacylglyceride.

Many variants of Sphingolipids have some unique structures in different fungi in eukaryotic membranes. In a series of studies, some plant and insect defensins bind to different fungal sphingolipids or different nuclei in the same sphingolipids. Following binding, membrane infiltration occurs, but it is not yet known whether this is the result of the signal layer or the biophysical effect. However, it is clear that plant defensins do not particularly penetrate fungal membranes, creating pores and destroying membrane integrity. Interestingly, in *Candida albicans*, the anti-fungal activity of a plant called RsAFP2, which binds to glucosylceramide, was found to

Figure 3. The antifungal activity of plant defensins is specific and involves receptors and signal transduction pathways.

involve the production of reactive oxygen species (ROS) suggesting that binding to the membrane ligand initiated a signal transduction cascade that culminated in the production of ROS and membrane infiltration (**Figure 3**).

Despite advances in the study of plant defensins, some serious questions and challenges remain to be resolved. First, most extensive work has been done with a limited number of specific defensins, and it remains to be determined whether this is the only procedure. Second, it is not known what signal transmission paths are activated in response to defensins. Third, it is not yet clear whether defensins are internalized after binding to or with sphingolipids. Working with human cAMPs is said to be at least absorbed by some bacteria and reported to be absorbed by the fungal cells of pea defensins [27].

8.3 Lysis of fungal membranes by saponins

Saponins are a structurally different class of secondary metabolites found in different plants. For example, a survey lists more than 200 plants that isolated saponins between 1998 and 2003. The basic structure of all saponins consists of the polar core and the polar glycosyl group or groups, which give the molecules ambiguous properties. Typically, saponins are classified as triterpenoid or steroidal, with a subset of steroidal alkaloids (steroidal glycoalkaloids) depending on the structure of the hydrophobic center. However, some authors consider steroidal glycolic colloids to be a unique natural product, and recently, a new saponin classification has been proposed into 11 different families depending on the structure of the spine. Saponins are present in significant concentrations in many traditional herbal medicines and a variety of beneficial functions, including common ingredients such as ginseng, are often attributed to the components of saponin.

Within plants, saponins are believed to provide protection against phytopathogenic fungi because they have powerful antifungal activity, are usually accommodated in the epidermal layers of plant tissues and have been shown to play a protective role in many pathogenic interactions. The amphibian nature of saponins represents a mechanism of action and it has been demonstrated that saponins penetrate fungal membranes. The proposed mechanism is that the hydrophobic core enters the outer membrane, forming a compound with ergosterol. Subsequent interaction between polar glycosyl sidechains leads to aggregation, pore formation, and loss of membrane integrity [28]. The ability to penetrate membranes has been demonstrated *in vitro* and *in vivo* in sample membranes of *S.cerevisiae* to explore the anti-fungal activity of the steroidal glycoalkaloid saponin. However, the study also showed that the alkaloid α -tomatine did not penetrate the membranes of the α -tomatine, which is more potent than the α -tomatine, in fact inhibiting ergosterol biosynthesis.

However, the study also showed that the aglycone of α -tomatine did not penetrate the membranes of the α -tomatine, was more potent than the α -tomatine, and actually inhibited ergosterol biosynthesis. Furthermore, several studies have proposed additional functions for α -tomatine and its derivatives. β 2-tomatine (created by removing sugar from sugar α -tomatine) has been found to be capable of suppressing plant defense response, and α -tomatine has been reported to induce projected cell death in fungi called *Fusarium oxysporum*, lack of membrane penetration. Finally, studies with potato steroidal glycoalkaloids (saponins), α -chaconine and α -solanine, have identified various toxic effects on animal systems that differ from membrane penetrating activity. In conclusion, although membrane penetration activity contributes

to the antifungal activity of saponins, saponins may have other biological properties, including beneficial roles in human health [29].

9. Anti-tumor activity of plant natural products

Among the various properties associated with saponins, the ability of some saponin products to inhibit the growth of tumor cells *in vitro* attracts much attention. In fact, many saponins have been reported to have such activity, increasing the likelihood of developing novel saponin-based anti-cancer drugs [30]. Some commentators have questioned the relevance of these *in vitro* data and want to prove that their validity covers specific endogenous targets and is not related to membrane penetration. Significant progress in this direction is due to the synthesis of two different groups of legume triterpenoid saponins, avicins, *Acacia victoria* (**Figure 2**), and soyasaponin from soybean plants. This work was triggered by reports that Avicenna had apoptotic activity against human tumor cells. Several studies have established that it is mediated by mitochondrial dysfunction, indicating that the effects are twofold—disruption of the outer membrane energy and closure of the voltage-dependent ion channel (VDAC) in the mitochondrial membrane. The link between saponin-induced mitochondrial dysfunction and apoptosis was further supported by a recent report showing that treatment of HeLa cells with soyasaponin products led to apoptosis via the mitochondrial pathway [31].

Other endogenous targets for specific avicin have also been reported; however, pro-apoptotic effects may involve multiple targets or indicate that different avicins have specific target processes. In the East model, evidence was obtained for the modulation or inhibition of RO-based signaling and CAMP/PKA signal transmission pathways. A more direct link to apoptosis or automation was obtained from studies with avicin D, where avicin D activates AMP-activated kinase (AMPK), thereby inhibiting mTORC1 and downstream targets. Although many studies of plant natural products have reported a “pro-apoptotic” function, it is worth noting here that there is not much difference between apoptosis and autoimmunity in the plant literature in general. In fact, although the end result is the same, the paths and processes involved are completely different and this is a topic that will require closer attention in the future. Autophagy is given more importance by discovering that the production of β -group soysasaponins reduces mTORC activity, this time apparently by activating another kinase, Akt. The general significance of apoptotic pathways as a target for plant natural metabolism is that other saponin non-metabolites, such as sesquiterpenoid helenalin, which inhibits telomerase, have proliferative effects on mammalian cells [32]. Some of the more than 5000 different flavonoids that occur naturally in plants have effects associated with apoptosis in the future. Nutmeg flavonoid, (–) catechins, for example, inhibit seed germination and cause cell death in sensitive species. This effect appears to involve the generation of reactive oxygen species and may also be linked to calcium signaling or homeostasis. Again, the relationship between ROS, calcium homeostasis, mitochondrial function, autoimmunity, and apoptosis [33] should be kept in mind.

10. Conclusion

Plant natural products, especially those involved in the protection against pathogens, can lead to biotechnological applications. However, beyond the phytochemical list and general studies, there is a need to go for experiments to identify specific screens and

functional patterns. It should take two forms, identifying the biological role of metabolism in the plant and determining the effects of metabolism on other organisms. The latter is a compelling argument for the use of unbiased genetic or proteomic methods and cell-based assessments to avoid confusion with specific nontargets. Finally, once the candidate goals have been identified, it is necessary to carry out detailed structural and functional studies of the interaction in the actual hosts. However, for preliminary screens and analyzes, plant natural product scientists must follow their biomedical counterparts in eukaryotes and *S. cerevisiae* using chemical genetics and molecular techniques.

Conflicts of interest

The author declares no conflict of interest.

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