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Untapped mutualistic paradigms linking host plant and endophytic fungal production of similar bioactive secondary metabolites

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This manuscript is dedicated to the memory of the late Professor Dr. Meinhart Zenk (Zenk Memorial issue of *Phytochemistry*).

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A B S T R A C T

The biosynthetic potential of endophytic fungi has gained impetus in recent times owing to the continual discovery of fungal endophytes capable of synthesizing plant compounds. However, the sustained production of the desired plant compounds has not yet been achieved using endophytes. It is thus imperative to investigate the diverse interactions that endophytes have with coexisting endophytes, host plants, insect pests, and other specific herbivores. The precise role of these associations on the endophytic production of host plant compounds is mostly overlooked and open to future discoveries. Here, highlighted are the implications of the poorly investigated links and molecular mechanisms that might trigger similar chemical responses in both plants and endophytes. Elucidating such connections can not only enhance the understanding of evolution of complex defense mechanisms in plants and associated organisms, but also help in the sustained production of plant compounds using endophytes harbored within them.

1. Introduction

Endophytic fungi are a group of diverse, polyphyletic microorganisms that internally infect living plant tissues without causing any noticeable symptom of infection, and live in mutualistic association with plants for a part of their life cycle (Bacon and White, 2000; Porras-Alfaro and Bayman, 2011). They are more frequently observed as endophytes than bacteria (Staniek et al., 2008). An extensive range of investigations has been undertaken on endophytic fungi with respect to both biotechnological and ecological aspects. For instance, those relating to evolutionary relatedness, host range, infection, colonization, transmission forms, tissue specificity, and mutualistic fitness benefits have been explored for a plethora of plants (Arnold et al., 2003, 2007; Arnold, 2005, 2007; Stone et al., 2004; Schulz and Boyle, 2005; Rodriguez et al., 2009). Additionally, many endophytic fungi have been isolated and characterized, these having the potential for *de novo* synthesis of numerous bioactive metabolites that may be of either direct or indirect utility as beneficial agents against several diseases (Strobel and Daisy, 2003; Strobel et al., 2004; Zhang et al., 2006; Gunatilaka, 2006; Staniek et al., 2008; Suryanarayanana et al., 2009; Aly et al., 2010; Kharwar et al., 2011; Kusari and Spiteller, 2011).

Several endophytic fungi are capable of producing secondary metabolites that are also biosynthesized by their host plants. These include, for example, antineoplastic paclitaxel (**1**) (Stierle et al., 1993), camptothecin and its structural analogs (**2**–**4**) (Puri et al., 2005; Kusari et al., 2009b, 2011b; Shweta et al., 2010), the anticancer drug lead compounds podophyllotoxin (**5**) (Eyberger et al., 2006; Puri et al., 2006) and deoxypodophyllotoxin (**6**) (Kusari et al., 2009a), the antidepressant hypericin (**7**) along with emodin (**8**) (Kusari et al., 2008, 2009c), and the natural insecticides azadirachtin A and B (**9**, **10**) (Kusari et al., 2012) (Fig. 1). It is now well documented that endophytic fungi might be adept in synthesizing associated plant metabolites. Unfortunately, utilizing this potential for the sustained production of desired plant compounds by endophytes has not hitherto been achieved (Kusari and Spiteller, 2011). Although current research activities are geared towards understanding the biochemical and molecular basis of production of similar compounds by endophytes, concomitant with their associated plants, the role and complexity of their interactions with other organisms are mostly overlooked. By illustrating some interesting examples in this manuscript, the significance of these untapped so-called 'mutualistic links' is highlighted between plants and endophytes, such as insect herbivores and other coexisting endophytes, and the molecular mechanisms that might trigger similar chemical responses in both plants and endophytes.

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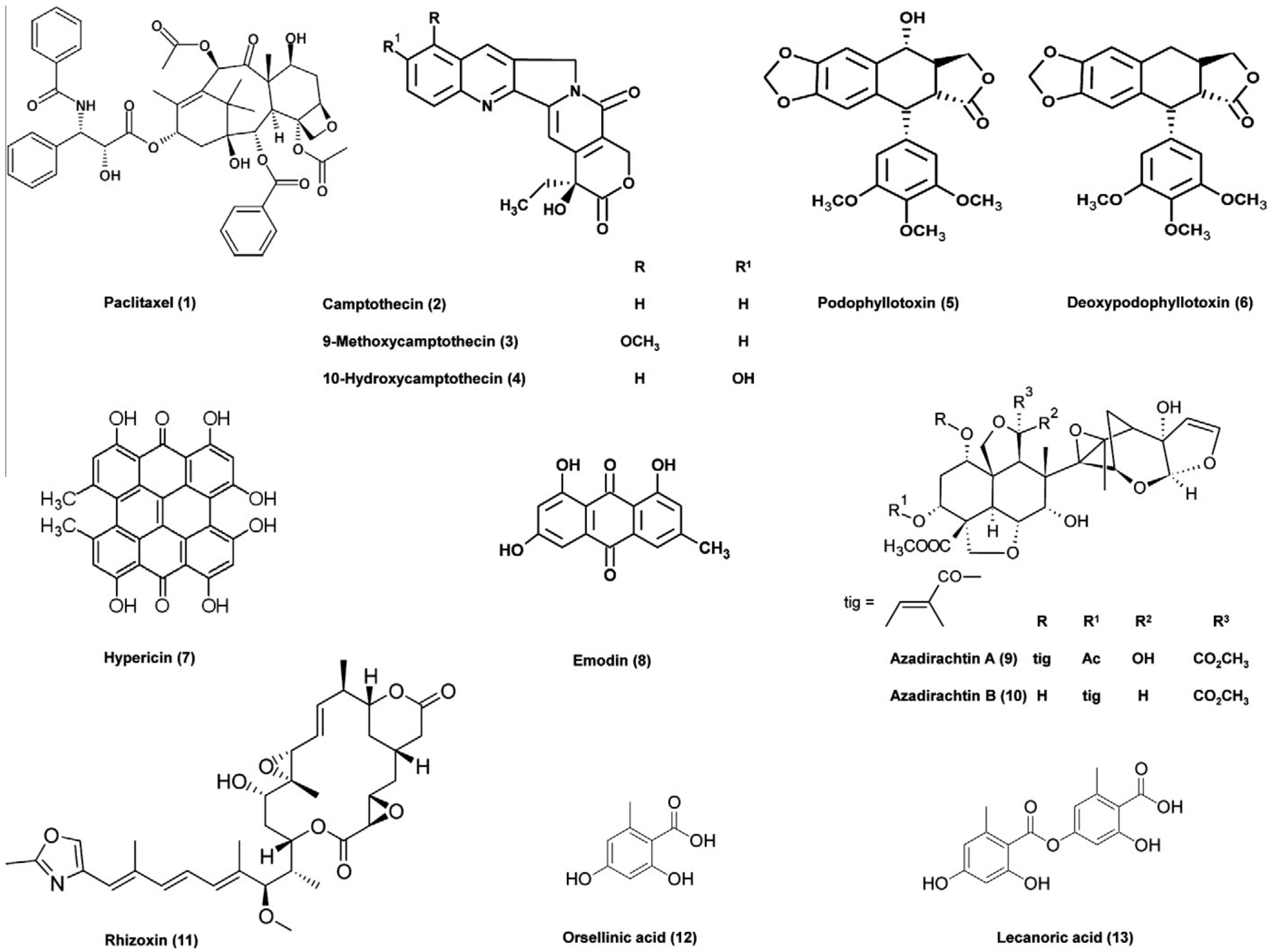

Fig. 1. Structures of compounds produced by endophytes (**1**–**13**).

2. Insects as 'links' between endophytic fungi producing associated plant bioactive compounds and the host plants

A major emphasis has been bestowed on the effects of endophytes on insects. One of the initial reports demonstrating that host plants could indeed be protected by endophytic fungi was that of endophytic *Phomopsis oblonga* protecting elm trees against the beetle *Physocnemum brevilineum* (Webber, 1981). This research proposed that the endophytic fungus, *P. oblonga*, could reduce the spread of the causal agent of Dutch elm disease (*Ceratocystis ulmi*) by producing toxic repellants against *P. brevilineum*. Claydon et al. (1985) later proved that endophytic fungi belonging to the genus *Xylariacea* could indeed synthesize toxic secondary metabolites in hosts of the genus *Fagus* that affected the beetle larvae. Following these discoveries, a plethora of investigations on the positive and negative roles of endophytes against insects (herbivores, pests, and opportunists) were reported (for example, see Azevedo et al., 2000; Arnold and Lewis, 2005). However, there is a dearth of information on the role of endophytes producing associated plant compounds against insects and the corresponding effect of the insects on the *in planta* metabolic processes of these endophytes.

A generalized understanding of the paradigm 'attack-defense-counterdefense strategies' linking insects with plants and endophytes that produce either similar or the same compounds might be useful (Fig. 2). Plants, being sessile organisms, are equipped with a wide range of defense mechanisms to counter attacks from insects. The direct mechanisms encompass a constitutive defense (which is available permanently), the induced defense (which is an up-regulated form of constitutive defense upon recognizing an attack), and the activated defense (in which the non-toxic plant metabolites are instantly converted to the toxic forms upon identifying an attack) (Spiteller, 2008). When a plant is attacked by an insect (Fig. 2a), it can mount one of the above defense reactions. For example, in *Hypericum* species, it has been demonstrated that the photodynamic compound, hypericin (**7**), is produced by the plant as a mode of chemical defense against a number of insect pests (constitutive defense) (Guillet et al., 2000). It has been proposed that hypericin (**7**) is synthesized in specialized glandular structures called 'dark glands' (Cellarova et al., 1994; Onelli et al., 2002), which are dispersed over all above-ground parts of the plant (flowers, capsules, leaves), and is also localized to these tissues (Briskin et al., 2000). Furthermore, the role of hypericin (**7**) in induced *Hypericum* plant defense has been directly demonstrated by an increase in its production in the plant tissues in response to constant attack by insect pests (Sirvent et al., 2003). Recently, an endophytic fungus *Thielavia subthermophila*, from the stem of *H. perforatum*, was isolated which is capable of producing hypericin (**7**) and emodin (**8**) under *in vitro* axenic conditions (Kusari et al., 2008, 2009c). Therefore, it is compelling to infer that this endophytic fungus might aid in the chemical defense of its host. Since this endophyte has been isolated from the stem and was not found