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Research review paper

Natural products from resurrection plants: Potential for medical applications

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ABSTRACT

Resurrection species are a group of land plants that can tolerate extreme desiccation of their vegetative tissues during harsh drought stress, and still quickly – often within hours – regain normal physiological and metabolic functions following rehydration. At the molecular level, this desiccation tolerance is attributed to basal cellular mechanisms including the constitutive expression of stress-associated genes and high levels of protective metabolites present already in the absence of stress, as well as to transcriptome and metabolome reconfigurations rapidly occurring during the initial phases of drought stress. Parts of this response are conferred by unique metabolites, including a diverse array of sugars, phenolic compounds, and polyols, some of which accumulate to high concentrations within the plant cell. In addition to drought stress, these metabolites are proposed to contribute to the protection against other abiotic stresses and to an increased oxidative stress tolerance. Recently, extracts of resurrection species and particular secondary metabolites therein were reported to display biological activities of importance to medicine, with e.g. antibacterial, anticancer, antifungal, and antiviral activities, rendering them possible candidates for the development of novel drug substances as well as for cosmetics. Herein, we provide an overview of the metabolite composition of resurrection species, summarize the latest reports related to the use of natural products from resurrection plants, and outline their potential for medical applications.

Contents

Introduction

Resurrection species are a unique group of land plants that can tolerate desiccation of their vegetative tissues to air-dried state (to just 5%

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relative water content, RWC) and resume normal physiological and metabolic activities after rehydration (Dinakar and Bartels, 2013; Gechev et al., 2012). Resurrection species are more common in bryophytes, relatively rare in pteridophytes and angiosperms, and absent in gymnosperms (Gaff and Oliver, 2013; Porembski, 2011). In total, resurrection plants represent more than 1300 different species, including about 300 angiosperms (Porembski, 2011). They display considerable geographic and habitat diversity. Most of them are herbaceous plants which inhabit deserts or temperate areas with extended periods of drought (Dinakar et al., 2012; Gechev et al., 2012). However, some of them (like the European resurrection plants *Ramonda serbica* and *Haberlea rhodopensis*) can endure freezing winters, and one of them, *Lindernia brevidens*, was recently discovered in the tropical rainforests of Africa, where humidity is constantly high (Phillips et al., 2008). It has to be noted that the number of resurrection plants is likely to grow as more studies discover new desiccation-tolerant species.

To adapt to extreme dehydration, resurrection plants have developed unique molecular mechanisms to protect themselves against desiccation-induced damage. These mechanisms, summarized in the recent review of Dinakar and Bartels (2013), are constitutive (expression of stress-protective genes and high abundance of protective metabolites) as well as inducible (swift transcriptome and metabolome reconfigurations occurring upon the sensing of drought stress). The remarkable geographical and habitat diversity of these species has further contributed to the diverse array of genes and metabolites which they utilize for stress protection and environmental adaptation.

Although the primary interest in resurrection species has been fueled by their ability to withstand desiccation and the potential to use them as a source for gene discovery (Gechev et al., 2013; Rodriguez et al., 2010; Yobi et al., 2012; Yobi et al., 2013), the unique metabolites of several resurrection species have recently attracted much attention with respect to their potential uses in biotechnology and medicine. For example, the predominant polyphenol 3,4,5 tri-*O*-galloylquinic acid in the South African resurrection species *Myrothamnus flabellifolia* has been shown to inhibit M-MLV and HIV-1 reverse transcriptases (Kamng'ona et al., 2011). Myconoside, a glycoside abundantly present in extracts of *H. rhodopensis*, can strongly stimulate antioxidant skin defenses and extracellular matrix protein synthesis (Dell'Acqua and Schweikert, 2012). Amentoflavone, isolated from *Selaginella tamariscina*, has strong anticancer/pro-apoptotic, antibacterial, and antifungal activities (Cheng et al., 2008; Gao et al., 2007; Woo et al., 2005). These and other bioactive features of resurrection plant metabolites are reviewed in this article with a particular focus placed on potential biomedical applications.

Overview of primary and secondary metabolites of resurrection species

The primary metabolites of resurrection species, as in all species, primarily serve to ensure basic physiological functions. However, some of the metabolites are additionally utilized as osmoprotectors against dehydration-induced stress. Comprehensive metabolome profiling has been performed for several resurrection species, including the monocot *Sporobolus stapfianus*, the dicot *H. rhodopensis*, and the spike moss *Selaginella lepidophylla* (Dinakar and Bartels, 2013; Gechev et al., 2013; Oliver et al., 2011a; Yobi et al., 2012; Yobi et al., 2013).

Sugar metabolism plays a paramount role in stress protection in plants. In desiccation-tolerant *S. lepidophylla*, some sugars such as sucrose, trehalose, and several monosaccharides are highly abundant, in contrast to its desiccation-sensitive sister species *Selaginella moellendorffii* (Yobi et al., 2012; Yobi et al., 2013). The basic levels of several sugars, including sucrose, raffinose, melibiose, and trehalose, are also very high in *H. rhodopensis* in comparison with other species like *Arabidopsis thaliana* or *Thellungiella halophila* (Benina et al., 2013). Sucrose accumulation is observed in most resurrection species during dehydration (Benina et al., 2013; Djilianov et al., 2011; Gechev et al., 2013; Peters et al., 2007; Rakić et al., 2014; Yobi et al., 2012). Raffinose is another abundant sugar in most of the resurrection species and, like sucrose, can act as an osmoprotector (Peters et al., 2007). Additionally, raffinose and galactinol were suggested to protect against cellular damage caused by oxidative stress (Nishizawa et al., 2008). Some resurrection species contain less studied or even unique sugars. *Craterostigma plantagineum*, for example, accumulates large amounts of the 8-carbon sugar octulose, which is used as a carbohydrate reserve during dehydration (Bianchi et al., 1991; Norwood et al., 2000), while *H. rhodopensis* can accumulate verbascose, a constituent together with stachyose of the raffinose family of oligosaccharides (Gechev et al., 2013).

Resurrection species have abundant amounts of different sugar alcohols and sugar acids, which together with the sugars may collectively alleviate the consequences of dehydration by stabilizing proteins and other macromolecules, and protecting them from reactive oxygen species (ROS)-induced damage (Gechev et al., 2013; Oliver et al., 2011a; Yobi et al., 2012; Yobi et al., 2013). The basal levels of threonate, erythronate, and glycerate are much higher in *H. rhodopensis* than in *A. thaliana* or *T. halophila* (Benina et al., 2013). Resurrection species may also utilize di-carboxylic acids and various amino acids as an additional tool to alleviate dehydration. Nitrogen-rich and γ-glutamyl amino acids, citrulline, and nucleotide catabolism products increase in desiccated *S. lepidophylla* (Yobi et al., 2013).

Lipid metabolism can also change during dehydration and subsequent rehydration. While most lipids were produced constitutively in *S. lepidophylla*, choline phosphate accumulated during dehydration, suggesting a role in membrane hydration and stabilization (Yobi et al., 2013). On the other hand, several polyunsaturated fatty acids were found at higher levels in unstressed plants (Yobi et al., 2013). Like sugars, lipids may play multiple roles: as signaling molecules, as an energy source (especially after sugars are consumed), and as protectors against desiccation-induced damage (Beckett et al., 2012; Gasulla et al., 2013).

In contrast to primary metabolites, much less is known about secondary metabolites present in resurrection plants. Secondary metabolites are chemically very diverse in exhibiting many different biological functions. Although much progress has been made on elucidating their structure, function, and biosynthesis in the past decade, still many questions related to the biosynthetic pathways and their regulation remain to be explored. Furthermore, it is believed that we currently know only a small fraction of the rich diversity of secondary metabolites in the plant kingdom which has been estimated at about 200,000 compounds (Dixon and Sumner, 2003; Yonekura-Sakakibara and Saito, 2009). Resurrection plants contribute to this diversity, as evidenced by the presence of a wide range of unique compounds. So far, the structures of only a fraction of these metabolites have been resolved, a fact that is greatly complicated by the lack of commercially available reference compounds for secondary metabolism (Fernie, 2007); and we know even less about their biological functions in plants. In general, resurrection species utilize their secondary metabolites not only for protection against dehydration but also against other stresses such as UV-light and herbivore attack, thus gaining advantage over competitor species within particular ecological niches.

In several studies, many secondary metabolites that belong to different classes were identified in *Anastatica hierochuntica*. Among others, these included anastatins A and B, apigenin, luteolin, caffeoyl- and dicaffeoylquinic acids, (+)-dehydrodiconiferyl alcohol,3,4-dihydroxybenzoic acid, eriodictyol, hierochins A and B, kaempferol, luteolin, quercetin, and silybins A and B (Al Gamdi et al., 2011; Nakashima et al., 2010; Yoshikawa et al., 2003).

Boea hygrometrica (Bunge) R. Br. (Gesneriaceae) is a resurrection plant distributed widely from the tropics to the northern temperate regions of East Asia (Mitra et al., 2013). It contains *C*-glycosylflavones and phenolic acids (5,7,3′4′-tetrahydroxy-6-methoxy-8-C-[β-D-xylopyranosyl-(1 → 2)]-β-D-glucopyranosyl flavone, *p*-hydroxy phenethyl alcohol, 3,4-dihydroxy phenethyl

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