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Review

Prenylation of aromatic compounds, a key diversification of plant secondary metabolites

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Prenylation plays a major role in the diversification of aromatic natural products, such as phenylpropanoids, flavonoids, and coumarins. This biosynthetic reaction represents the crucial coupling process of the shikimate or polyketide pathway providing an aromatic moiety and the isoprenoid pathway derived from the mevalonate or methyl erythritol phosphate (MEP) pathway, which provides the prenyl (isoprenoid) chain. In particular, prenylation contributes strongly to the diversification of flavonoids, due to differences in the prenylation position on the aromatic rings, various lengths of prenyl chain, and further modifications of the prenyl moiety, e.g., cyclization and hydroxylation, resulting in the occurrence of ca. 1000 prenylated flavonoids in plants. Many prenylated flavonoids have been identified as active components in medicinal plants with biological activities, such as anti-cancer, anti-androgen, anti-leishmania, and anti-nitric oxide production. Due to their beneficial effects on human health, prenylated flavonoids are of particular interest as lead compounds for producing drugs and functional foods. However, the gene coding for prenyltransferases that catalyze the key step of flavonoid prenylation have remained unidentified for more than three decades, because of the membrane-bound nature of these enzymes. Recently, we have succeeded in identifying the first prenyltransferase gene *SfN8DT-1* from *Sophora flavescens*, which is responsible for the prenylation of the flavonoid naringenin at the 8-position, and is specific for flavanones and dimethylallyl diphosphate (DMAPP) as substrates. Phylogenetic analysis showed that *SfN8DT-1* has the same evolutionary origin as prenyltransferases for vitamin E and plastoquinone. A prenyltransferase *GmG4DT* from soybean, which is involved in the formation of glyceollin, was also identified recently. This enzyme was specific for pterocarpan as its aromatic substrate, and (−)-glycinol was the native substrate yielding the direct precursor of glyceollin I. These enzymes are localized to plastids and the prenyl chain is derived from the MEP pathway. Further relevant genes involved in the prenylation of other types of polyphenol are expected to be cloned by utilizing the sequence information provided by the above studies.

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1. Introduction

Polyphenols are common secondary metabolites in all plant species and are widely known as natural anti-oxidants (D'Archivio et al., 2007). Recently, more divergent biological activities, e.g., prevention of high blood pressure and of hardening of veins, anti-aging, anti-bacterial, and anti-tumor activities, have been reported for various polyphenolic compounds as valuable natural products that are beneficial for human health. In the market, many kinds of functional foods and supplements containing these polyphenols are widely sold. Polyphenolic compounds exist in fresh plant cells, in most cases, as derivative forms, such as methyl ethers, glycosides, and other decorations are also often observed. It is worth noting that some of these derivatives exhibit much higher biological activities than their mother compounds without derivatization or decoration, and polyphenol derivatives showing high biological activities have been isolated from various medicinal plants. A large variety of biological activities have been reported particularly in polyphenols having prenyl residues that consists of isoprene units with five carbon atoms, and these plant products provide rich resources for natural medicines (Botta et al., 2005). Thus far, more than 1000 prenylated polyphenols have been isolated from plants, which have drawn substantial attention in the field of applied sciences, such as food industries, breweries, and cosmetic companies. This review provides an overview of prenylated polyphenols showing various biological activities and introduces recent discoveries of plant genes encoding flavonoid-specific prenyltransferases; key enzymes in biosyntheses of those prenylated polyphenols.

2. Structures and biological activities of prenylated polyphenols

Plant polyphenols are classified into several groups according to the basic ring system, e.g., phenylpropanoids, flavonoids, coumarins, phloroglucinols, and xanthones. There seems to be a chemotaxonomical tendency in the occurrence of some polyphenols, e.g., xanthone derivatives mostly occur in Guttiferae (Clusiaceae) (Pinto et al., 2005), and ca. 90% isoflavonoids are derived from Leguminosae (Fabaceae) (Dixon, 1999), but other groups of polyphenols are widely distributed in the plant kingdom. The occurrence of prenylated polyphenols is rather limited in several plant families. Representatives include Leguminosae (Fabaceae), Moraceae, Cannabaceae, Guttiferae (Clusiaceae), Umbelliferae and Rutaceae (Park et al., 2003; Stevens et al., 2000; Wu et al., 1998; Aoki et al., 2008; Ribeiro et al., 2008), whereas some other plant families like Euphorbiaceae and Compositae (Asteraceae) also comprise plant species that contain prenylated polyphenols (Kumazawa et al., 2007, 2003). Plants containing these compounds have often been utilized as medicinal plants in many countries, for example, licorice (Leguminosae) is used as an anti-inflammatory in Chinese traditional medicine (Shin et al., 2008), *Calophyllum inophyllum* (Guttiferae) is used against bronchitis and diarrhea in Latin America (Mesia-Vela et al., 2001), and osage orange (*Maclura pomifera*) is used for cancer treatment (Mahmoud, 1981).

A wide range of biological activities has been reported for prenylated polyphenols, e.g., anti-tumor, anti-bacterial, anti-virus, anti-oxidant, anti-tyrosinase, estrogenic, inhibition of sulfotransferase, anti-nitric oxide production, and inhibition of phospholipase (Miranda et al., 2000; Appendino et al., 2008; Lee et al., 2009; Kapche et al., 2009; Kim et al., 2003; Son et al., 2003; Dong et al., 2007; Mesia-Vela et al., 2001; Lee et al., 2005; Oh et al., 2005). A representative of the prenylated flavonoids, 8-dimethylallylnaringenin, has been identified in some leguminosaeous plants and is recognized as a strong phytoestrogen leading to its potential usage for the prevention of osteoporosis and for the enhancement of collagen synthesis in the skin (Tielens et al., 2008). Xanthohumol is another example of important prenylated flavonoids for its divergent biological activities, such as estrogenic, anti-oxidant, and anti-tumor. This compound is the main component (80–90% of total flavonoids) in hops (*Humulus lupulus* L., Cannabaceae), which are used to add bitterness and flavor to beer (Stevens and Page, 2004). Also found in hops, humulone and lupulone, phloroglucinol derivatives known as the bitter principle of beer, exhibit anti-tumor activity via the inhibition of cyclooxygenase-2 expression, which is mediated by a signal transduction pathway with transcriptional regulators NF-κB and AP-1 (Lee et al., 2007). As an example of a xanthone derivative, prenylated xanthone (rubraxanthone) identified in *Garcinia dioica* (Guttiferae) shows antithrombotic, anti-allergic, and anti-inflammatory activities via suppression of the binding of platelet activation factor to its receptor (Iinuma et al., 1996; Jantan et al., 2002). The enhancement of drug effects has been reported in prenylated furanocoumarin of grapefruit, which is caused by the inhibition of enzymes of drug metabolism in the human intestine (Row et al., 2006).

Even a single prenylated compound may show multiple effects, e.g., kurarinone (a prenylated flavanone) isolated from *Sophora flavescens* (Leguminosae) exhibits estrogenic, anti-tyrosinase, anti-glycosidase, and anti-lipoxygenase activities (De Naeyer et al., 2004; Kim et al., 2003, 2006; Son et al., 2003; Chi et al., 2001; Yamahara et al., 1990) (Fig. 1). It is noteworthy that the prenyl moiety often plays a crucial role in these divergent biological activities in many of these compounds (Row et al., 2006). This suggests, in turn, the addition of a prenyl residue to polyphenol skeletons may contribute to the enhancement of the biological activities of polyphenolic compounds.

For plants, prenylated polyphenols function as protectants against pathogenic microorganisms and herbivores (Moesta et al., 1983; Robbins et al., 1985), or they may act against abiotic environmental stresses like oxidative stress as they show strong anti-oxidant activity (Kumazawa et al., 2007). Humans utilize these active compounds for multiple purposes in different fields, such as

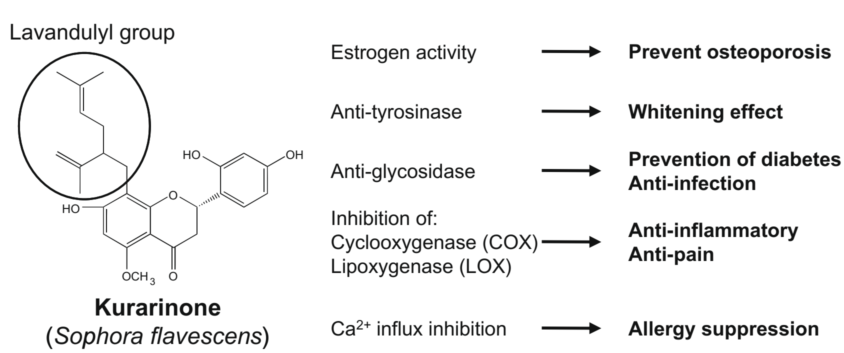

Fig. 1. Types of biological activities of a prenylated flavonoid. Kurarione is a flavanone with a lavandulyl group at the 8-position.

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