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Review

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Recent advances in biosynthesis of bioactive compounds in traditional Chinese medicinal plants

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Abstract Plants synthesize and accumulate large amount of specialized (or secondary) metabolites also known as natural products, which provide a rich source for modern pharmacy. In China, plants have been used in traditional medicine for thousands of years. Recent development of molecular biology, genomics and functional genomics as well as high-throughput analytical chemical technologies has greatly promoted the research on medicinal plants. In this article, we review recent advances in the elucidation of biosynthesis of specialized metabolites in medicinal plants, including phenylpropanoids, terpenoids and alkaloids. These natural products may share a common upstream pathway to form a limited numbers of common precursors, but are characteristic in distinct modifications leading to highly variable structures. Although this review is focused on traditional Chinese medicine, other plants with a great medicinal interest or potential are also discussed. Understanding of their biosynthesis processes is critical for producing these highly value molecules at large scale and low cost in microbes and will benefit to not only human health but also plant resource conservation.

Keywords Medicinal plant · Biosynthesis · Phenylpropanoid · Terpenoid · Alkaloid

SPECIAL TOPIC: Advances in Artemisinin Study

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1 Introduction

China is rich in plant resources. Of the ~300,000 species of higher plants on the earth, around 10 % can be found in China. As in many other countries, people in China have used plants for treatment of diseases for thousands of years. *Compendium of Materia Medica* has been held in high esteem since it was first published in 1593, and this ancient encyclopedia of traditional Chinese medicine (TCM) described more than 1,000 species of plants. Plants produce a wealth of specialized (or secondary) metabolites also known as natural products, which are small molecular weight compounds with enormous structural diversity and show various biological activities. It is estimated that there are approximately 200,000 secondary metabolites in plant kingdom [1], which, based on biosynthetic origins, can be classified into three major categories: phenylpropanoids, terpenoids and alkaloids, plus a few other less abundant groups. The usage records of China's ancient medical books, such as *Sheng Nong's Herbal Classic*, *Huang Di's Canon of Medicine* and *Compendium of Materia Medica*, already recognized that plant extracts contain active principles in treating illness and classified them into assumptive, intuitive or largely philosophic categories, such as cold, neutral or hot, toxic or nourishing. Over the past century, hunting the active ingredients has led to important findings, such as artemisinin for malaria, huperzine A for Alzheimer's disease, ephedrine for cold and camptothecin

for cancer, which were isolated from *Artemisia annua*, *Huperzia serrata*, *Ephedra sinica*, *Camptotheca acuminate*, respectively [2]. Very recently, tetrandrine, an alkaloid isolated from the TCM plant *Stephania tetrandra* previously used for reducing blood pressure, were reported to have the therapeutic efficacy against Ebola [3], and celastrol, a triterpene extracted from *Tripterygium Wilfordi*, has the potential as an anti-obesity agent [4]. These findings strongly support that TCMs are the reliable source for new therapies in treatment of lethally epidemic disease and long unsolved disease.

However, multi-classes of natural products are generated by each plant species. In addition, geographic distributions, growth conditions and harvesting seasons could significantly affect chemical compositions of the plant. Whereas one component may act as the active ingredient, the effects of a mixture of many ingredients are often uncertain and this has caused increasing concerns [5]; thus, the traditional practice of herbology has to face the challenges from modern medicine and the manufactures' requirement.

While plant natural products continue to be a prime source for drug discovery and development, supply of these compounds is often curtailed due to limitation of natural resources and/or low contents in plant. The biotechnological platforms, such as metabolic engineering of effective plant and microbial production, are urgently needed to ensure that the supply of bioactive natural products is sustainable and environmentally friendly, rather than at the expense of resource exhaustion [6–9]. A prerequisite to these solutions is the understanding of the biosynthetic pathways of these specialized metabolites, in particular the cloning and identification of enzymes and the regulatory factors.

In the past two decades, the rapid development in genomics and high-throughput technologies of chemical analysis, in combination with molecular biology tools, has accelerated the research of medicinal plants. In this review, we summarize the recent advances in the elucidation of biosynthetic pathways of secondary metabolites in, not exclusively, TCM plants. Although alkaloids are probably the most important resource for drug discovery and biosynthesis of these amino acid-derived compounds has been investigated intensively, there are, surprisingly to some extent, relatively few studies of alkaloids from TCM plant; thus, this review is emphasized on phenylpropanoids and terpenoids. In addition to enzymes, transcription factors characterized from medicinal plants are also discussed.

2 Phenylpropanoids

Phenylpropanoids, commonly found in plants, are derived from the six-carbon aromatic phenyl group and the three-carbon propene tail [10], and form a large group of specialized metabolites including monolignols, lignans, flavonoids, phenolic acids and stilbenes [11]. They serve as basic components of a number of structural polymers, as well as floral pigments, scent compounds or signaling molecules to mediate bio-interactions, phytoalexins against herbivores and pathogens, and protective components against ultraviolet light radiation and other abiotic stresses [12]. In many TCM plants, such as the plants of Lamiaceae, Fabaceae (Leguminasae) and Asteraceae, phenylpropanoids are also the bioactive principles (Table 1), which have been shown to act as anti-oxidants, free radical scavengers, anti-inflammatories and anticancer compounds [13].

The majority of phenylpropanoids are derived from phenylalanine. The first three steps are catalyzed by phenylalanine ammonia lyase (PAL), cinnamate

Table 1 List of examples of TCM plants rich in phenylpropanoids

Plant species	Chinese name in Pin-yin	Family	Representative compounds
Salvia miltiorrhiza	Danshen	Lamiaceae	Salvianolic acid A, B and C
Scutellaria baicalensis	Huangqin	Lamiaceae	Baicalin, wogonin, scutellarin
Glycyrrhiza uralensis	Gancao	Leguminosae	Liquiritin, isoliquiritin, 7,4′-dihydroxyflavone
Astragalus membranaceus	Huangqi	Leguminosae	Calycosin-7-glucoside, ononin
Sophora flavescens	Kushen	Leguminosae	Sophoraflavecromane A, B, C
Sophora tonkinensis	Shandougen	Leguminosae	Sophoranone, sophoradin
Pueraria lobata	Ge	Leguminosae	Puerarin, daidzin, genistein
Lonicera japonica	Jinyinhua	Caprifoliaceae	Chlorogenic acid, luteolin
Dendranthema morifolium	Juhua	Asteraceae	Chlorogenic acid, acacetin-7-*O*-β-D-glucoside, apigenin-7-*O*-β-D-glucoside, and luteolin-7-*O*-β-D-glucoside
Ginkgo biloba	Yinxing	Ginkgoaceae	Ginkgetin, isoginkgetin
Epimedium brevicornu	Yinyanghuo	Berberidaceae	Icariine, icarisid
Isatis indigotica	Songlan	Brassicaceae	Lariciresinol