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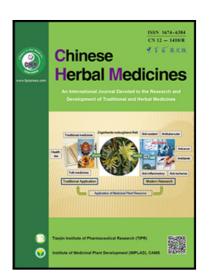
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Deep in shadows: Epigenetic and epigenomic regulations of medicinal plants

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Abstract: Around 60% of the extant plants have medicinal and health-promoting values. genuine medicinal material (geoherb) is produced in particular geographic regions, that is defined ecological environment and cultivation pipeline. The clinical efficacy of a geoherb is superior to that of the same medicinal plant growing in other regions. The special medicinal features of a plant are determined by its genome, while the proper ecological conditions have major effects on the formation of a geoherb, which is at least partially mediated by the epigenetics. By epigenetics/epigenomics, researchers uncover the complexities of the influence of the environment on the expression of genes that control medicinal plant growth, development, stress responses, and medicinal phytometabolite yield, and put the other "omics layers" in a meaningful biological context. The unique phenotypes of geoherb are closely related to the growth, development, and stress responses of medicinal plants. In addition to the commonly known genetic control, epigenetic machineries, active at the population level, play an essential role in the formation of geoherbs. This contribution gives a comprehensive overview of the epigenetic regulation of medicinal plants and the associated microbes, and the role of DNA methylation, small non-coding RNA, transposable elements and histone modifications in the gene expression regulation of geoherbs and relevant microbiota. The epigenetic and epigenomic mechanisms should be highlighted in the study of specific phenotype and indigenousness of geoherbalism. Revealing the correlation between epigenetics and geoherbs could shed light on the quality assessment, authentication, molecular breeding, and sustainable utilization of medicinal plants and the associated microbes. **Key words**: epigenetic regulation; epigenomic; geoherb; medicinal plant; microbe

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1. Introduction

Around 60% of plants have medicinal values. Therapeutic and/or health-promoting substances can be generated in various tissues/organs of medicinal plants. Phytometabolites from secondary/specialized metabolism are highlighted in the blooming R&D initiatives of natural medicine and synthetic biology, as they display myriad polypharmacological activities in disease prevention and treatment. Epigenetic rather than genetic factors may explain phenotypic divergence among populations of medicinal plants (Róis et al, 2013; Wang et al, 2014; Schulz et al, 2014; Sáez-Laguna et al, 2014). Medicinal plants are excellent systems for discovering and studying epigenetic phenomena, such as transposon silencing, RNAi, imprinting, and DNA methylation, and such studies promisingly contribute to basic biology and biotechnological applications.

Medicinal plants have long been utilized since the advent of human civilization. Most Chinese medicinal materials and Ayurveda medicines are of botanical origin. Among the 500 commonly used Chinese medicinal materials, around 200 are recognized as having geoherb (genuine herb) specifications (Zhao et al, 2012). Compared with the non-geoherb of the same botanical origin, geoherb is specific in properties of growth and development, as well as metabolic phenotypes (Hao and Xiao, 2015b). Interestingly, geoherbs are usually restricted in the specific geographic regions (Huang et al, 2004; Zhao et al, 2012), and their unique phenotypic variations are closely related to the growth and development of medicinal plants (Yuan et al, 2015). In addition to the canonical genetic machinery, the epigenetic regulations may play an important role in the formation of geoherbs (Fig. 1) (Li et al, 2015). The concept of epigenetics should be introduced into the geoherb studies, and the role of DNA methylation (Vidalis et al, 2016), histone modifications, chromatin remodeling, small non-coding RNA, and transposable elements (Springer et al, 2016) in the gene expression regulation should be highlighted in the population level enquiries (Taudt et al, 2016; Kawakatsu et al, 2016), might be involved in the evolution of specific phenotype of geoherb, and the regional environmental factors could profoundly influence the epigenomic landscapes. Deeper insights into the relationship of epigenetics and geoherbs would provide a basis for quality assessment and identification of Chinese herbal drugs, as well as enhancing medicinal compound production and advancing medicinal plant breeding.

We here document and capture the global research efforts in the epigenetic and epigenomic regulations of medicinal plants and

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