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Medicinal plants: physiology and secondary metabolism

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Physiology and Secondary Metabolism of Medicinal Plants

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INTRODUCTION

The past decade has witnessed a tremendous resurgence in the interest and use of medicinal plant products, Surveys indicated that plant medicinal usage by the people have shown an increase with climb in sales of plant medicinals. Phytomedicines have clearly re-emerged into the mainstream as evidenced by their availability for sale at a wide range of retail outlets, the extent of their advertisement in the popular media, and the recent entrance of several major pharmaceutical companies into the business of producing phytomedicinal products (Brevoort, 1998; Glaser, 1999).

For many of the medicinal plants of current interest, a primary focus of research to date has been in the areas of phytochemistry, pharmacognosy, and horticulture. In the area of phytochemistry, medicinal plants have been characterized for their possible bioactive compounds, which have been separated and subjected to detailed structural analysis. Research in the pharmacognosy of medicinal plants has also involved assays of bio-activity, identification of potential modes of action, and target sites for active phytomedicinal compounds. Horticultural research on medicinal plants has focused on developing the capacity for optimal growth in cultivation. This has been especially pertinent as many medicinal plants are still harvested in the wild, and conditions for growth in cultivation have not been optimized. Wild harvesting of medicinal plants can be problematic in terms of biodiversity loss, potential variation in medicinal plant quality, and occasionally, improper plant identification with potential tragic consequences. From the perspective of plant physiology, extensive opportunities exist for basic research on medicinal plants and the study of their phytomedicinal chemical production. Therefore, a discussion on some fundamental aspects of phytomedicinal chemical production by plant cells is must with an emphasis on several medicinal plants that have received considerable use and attention over the past decade.

PHYTOMEDICINAL ACTIONS AND SECONDARY PRODUCTS

The beneficial medicinal effects of plant materials typically result from the combinations of secondary products present in the plant. That the medicinal actions of plants are unique to particular plant species or groups is consistent with this concept as the combinations of secondary products in a particular plant are often taxonomically distinct (Wink, 1999). This is in contrast to primary products, such as carbohydrates, lipids, proteins, heme, chlorophyll, and nucleic acids, which are common to all plants and are involved in the primary metabolic processes of building and maintaining plant cells (Kaufman *et al*., 1999; Wink, 1999). Although plant secondary products have historically been defined as chemicals that do not appear to have a vital biochemical role in the process of building and maintaining plant cells, recent research has shown a pivotal role of these chemicals in the ecophysiology of plants (Briskin, 2000). Accordingly, secondary products have both a defensive role against herbivory, pathogen attack, and inter-plant competition and an attractant role toward

beneficial organisms such as pollinators or symbionts (Kaufman *et al*., 1999; Wink and Schimmer, 1999). Plant secondary products also have protective actions in relation to abiotic stresses such as those associated with changes in temperature, water status, light levels, UV exposure, and mineral nutrients. Furthermore, recent work has indicated potential roles of secondary products at the cellular level as plant growth regulators, modulators of gene expression, and in signal transduction (Kaufman *et al*., 1999).

Although secondary products can have a variety of functions in plants, it is likely that their ecological function may have some bearing on potential medicinal effects for humans. For example, secondary products involved in plant defense through cytotoxicity toward microbial pathogens could prove useful as antimicrobial medicines in humans, if not too toxic (Briskin, 2000). Likewise, secondary products involved in defense against herbivores through neurotoxin activity could have beneficial effects in humans (i.e. as antidepressants, sedatives, muscle relaxants, or anesthetics) through their action on the central nervous system (Wink and Schimmer, 1999). To promote the ecological survival of plants, structures of secondary products have evolved to interact with molecular targets affecting the cells, tissues, and physiological functions in competing microorganisms, plants, and animals (Wink and Schimmer, 1999). In this respect, some plant secondary products may exert their action by resembling endogenous metabolites, ligands, hormones, signal transduction molecules, or neurotransmitters and thus have beneficial medicinal effects on humans due to similarities in their potential target sites (e.g. central nervous system, endocrine system, etc.) (Kaufman *et al.*, 1999). As noted by Wink (1999), the development of structural similarity between plant secondary products and the endogenous substances of other organisms could be termed "evolutionary molecular modeling."

ROLE OF SPECIALIZED SUBJECTS

Once an area of research reserved for organic chemists, the study of plant secondary metabolism has expanded from the isolation of natural products and the elucidation of their structures to an analysis of enzymes, genes, regulation and genetic engineering (Toni Kutchan and Richard A Dixon, 2005). The role of specialized subjects in the secondary metabolism of medicinal plants is as follows:

I. Plant Physiology

For the plant physiologist, work on medicinal plants opens up a wide range of research possibilities, and plant physiological studies would indeed have a major role to play in this burgeoning field. With only a few exceptions, many widely used medicinal plants have not received the extensive plant physiological characterization received by food crops or model plant systems. Although active phytochemicals may have been identified, in general, many pathways for the biosynthesis of specific medicinal compounds and the factors (biotic and abiotic) regulating their production remain unclear. At present, a major concern with the use of phytomedicines regards the maintenance of consistent medicinal quality in botanical medicines (Matthews *et al*., 1999). Whereas the focus has tended to be on quality control in herbal manufacturing practices, variation in phytomedicinal content due to environmental effects upon secondary plant metabolism in the plant material could represent a significant factor. It is clear that understanding how environmental factors affect phytomedicinal production will be of great importance toward optimizing field growth conditions for maximal recovery of phytomedicinal chemicals.

II. Biochemistry

Novel enzymes involved in the biosynthesis of plant secondary metabolites have been discovered by De-Eknamkul (1998) from both differentiated plants and *in vitro* cultures of Thai medicinal plants. The discovered enzymes included (1) geranylgeraniol-18-hydroxylase from *Croton sublyratus* containing plaunotol, an anti-peptic ulcer diterpenoid, (2) dopamine-secologanin condensing enzymes from *Alangium lamarckii* containing emetine, an amoebicidal tetrahydroisoquinoline monoterpene alkaloid, (3) lawsone-forming multienzyme complex from *Impatiens balsamina* root cultures containing lawsone, an antimicrobial naphthoquinone, and (4) 1,2-dehydroreticuline reductase from *Papaver somniferum* seedlings containing morphinan alkaloids. Each of these enzymes was isolated, partially purified, characterized and evaluated for its role involved in the biosynthetic pathway of each secondary metabolite accumulated in its producing plant. These four examples of research works demonstrated the usefulness of enzymological techniques in elucidating the biosynthetic enzymes of secondary metabolites found in medicinal plants (De-Eknamkul, 1998). It is believed that the complete understanding of secondary metabolism at the enzyme level is a prerequisite for metabolic engineering of medicinal plants, which potentially leads to yield improvement of pharmaceutically important secondary products.

III. Molecular Biology

In most cases, it is also unknown as to the extent to which levels of phytomedicinal chemical production by medicinal plants are determined by genetic potential versus environmental modulation. Here, the use of molecular markers (i.e. RFLP, randomamplified polymorphic DNA, and amplified fragment length polymorphism) in the characterization of medicinal plant populations for levels of phytomedicinal chemical production could prove useful for the analysis of traits and in selective breeding (Matthews *et al*., 1999). The use of molecular approaches and biotechnology could also have wide application and promise especially with regard to such topics as the modification of phytomedicinal chemical pathways. Production of medicinal chemicals in plants may be modified by overexpression, antisense expression, or cosupression of biosynthetic genes. Transgenic genes could also be introduced to modify existing pathways. Mutational alterations and analysis could also be performed to dissect out basic components of metabolic pathways (Briskin, 2000). The application of molecular approaches with medicinal plants would also benefit from the development of cell, tissue, and organ culture systems for in vitro growth and regeneration of medicinal plants. In addition, such tissue culture systems could also prove useful for large-scale biotechnological production of medicinal plant phytochemicals (Korver, 1998).

Overall, metabolic engineering could be useful for modifying or enhancing synthesis of valuable therapeutic agents present in medicinal plants (Matthews *et al*., 1999). However, as the beneficial actions of medicinal plants can be related to combinations of phytochemicals acting collectively or synergistically, alteration of single phytochemical components could potentially affect the efficacy of a phytomedicine (Briskin, 2000). In this respect, any work on modification of the phytomedicinal chemical composition of a medicinal plant through molecular methods would need to be conducted in conjunction with pharmacological studies on drug effectiveness.

a. ***Combinatorial biosynthesis of secondary metabolites***: Combinatorial biosynthesis is a new tool in the generation of novel natural products with the basic concept of combining metabolic pathways in different organisms on a genetic level. As a

consequence heterologous organisms provide precursors from their own primary and secondary metabolism that are metabolised to the desired secondary product due to the expression of foreign genes (Julsing, 2006)

b. Genetic manipulation: Advances in the cloning of genes involved in relevant pathways, the development of high throughput screening systems for chemical and biological activity, genomics tools and resources, and the recognition of a higher order of regulation of secondary plant metabolism operating at the whole plant level facilitate strategies for the effective manipulation of secondary products in plants (Gómez et al., 2007).

c. Application of metabolomics in research of plant metabolites: Metabolomics, a branch of systems biology, has gained extensive attention and profound achievements in the plant. It has been one of the most effective methods to study the physiological and biochemical process and gene modification in pattern plants. Metabolomics provides methodology to elucidate the whole biological process, identify and quantify the complex components in the plant (Dan et. al., 2007)

d. Functional genomic approaches to explore secondary metabolites in medicinal plants: Extensive genomic data concerning medicinal plants are rather scarce and insights of the secondary metabolic pathways and their regulatory mechanism are insufficient, hampering the broad application of cell or tissue cultivation and metabolic engineering to producing high-value secondary metabolites. The integration of cDNA-AFLP based transcript profiling and metabolomics, could establish correlations between the changes of secondary metabolites and expressions of related genes. Functional genomic approaches are promising trends in the field of medicinal plants secondary metabolites research and will lead to better utilization of natural medicinal resources (Wang et al., 2009).

CONCLUSION

Traditional systems of medicine in most developing countries depend primarily on the use of plant products either directly or indirectly. Besides serving the healthcare needs of a large number of people, medicinal plants are the exclusive source of some drugs even for modern medical treatment. The use of plant products as nutrition supplements and in the cosmetic and perfume industry has increased the value of medicinal and aromatic plants in recent years. The over dependence on forests, natural woodlands and long-term fallows for extraction of MAPs is threatening the survival of many valuable plant species. It is imperative therefore that such endangered species are cultivated outside their natural habitats to ensure their regular supply for human needs as well as to preserve the genetic diversity. Cultivation is an important strategy for conservation and sustainable maintenance of natural stocks, but, few MAPs are actually cultivated. Lack of basic knowledge on biology, ecology, propagation methods and cultural practices for the concerned species is an important constraint. Agroforestry offers a convenient way of producing many MAPs without displacing the traditional crops (Rao et al, 2004). Research is needed in each country, however, on germplasm improvement for priority species, appropriate systems in which they can be grown, input management, and value-adding processes. Existing government policies may not be conducive to promotion of MAPs in many places. The potential of MAPs can be realized when policy constraints are removed and efforts are made simultaneously to

commercialize the products and explore markets for less known species. Research on the line of basic science is required elucidating potential areas of medicinal plants by which an insight could be targeted for sustainable exploitation of its use for end users.

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