

Review

Herbal genomics as tools for dissecting new metabolic pathways of unexplored medicinal plants and drug discovery

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Abstract

Herbal drugs, on which 80% of the world's population rely, are relatively safe over conventional drugs. Conventional drugs are costly, have serious side effects and hence over the past few decades researchers have focused on drug discovery from herbal medicines or botanical sources. The majority of new herbal drugs have been generated from secondary metabolites (alkaloids, terpenoids and phenolic compounds) of plant metabolism. Till date, only a small fraction of the vast diversity of plant metabolism has been explored for the production of new medicines and other products. The emergence of new herbal genomics research, medicinal plant genomics consortium, together with advances in other omics information may help for the speedy discovery of previously unknown metabolic pathways and enzymes. This review highlights the importance of genomics research in the discovery of some previously unknown enzymes/pathways which may make significant contributions in plant metabolic biology and may be used for the future discovery of many new pharmaceutical agents.

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1. Introduction (why herbal genomics?)

Traditional herbal medicines, basically plant-based therapies have been used for more than 5000 years [1]. At the time of invention of medicinal properties of herbs, people could not think of scientific evidence, philosophical and experimental basis, molecules responsible for medicinal value and of course the currently emerging herbal genomics. Constant and renewed public interest on alternative and complementary medicine lies mainly due to high cost of new drugs, increased side effects, microbial resistance and lack of curative treatment for several chronic diseases. Countries like India, China, Korea and Japan are now taking lead role and continuously investing in research on evidence-based traditional medicines and scientific validation of fundamental principles. China, the traditional medicine giant has successfully promoted its own

therapies over the globe with a science-based approach and evidenced by the rapid increase in number of licensed Chinese medicine providers in the United states [2]. India is also gearing up, and there has been a steep rise in the global acceptance of Ayurveda, the traditional Indian medicine. The World Health Organization has listed 21,000 medicinal plants, among which 2500 species are in India and now India is known as the largest producer of medicinal herbs [3]. Collectively, global data shows that 80% of world's population, rely primarily on ethnobotanical remedies and plant drugs, e.g. antineoplastic: camptothecin, Taxol, antimalarial: artemisinin, quinine, antigout: colchicine, analgesic: codeine, morphine, cardiac depressant: quinidine, antidiabetic: allicin, and for brain functions: caffeine, nicotine are the well known curative agents (Table 1, Fig. 5, modified from [4,5]).

Although, plant derived natural products remain rich resources for drug development and have had a profound and lasting impact on human health with almost 100 plant-derived compounds in clinical trials as of late 2007, the clinical

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Table 1
Recognized drugs from medicinal plants and their actions against various human diseases.

Drugs	Medicinal plants	Actions against
vinblastine	<i>Catharanthus roseus</i>	Cancer
vincristine	<i>Catharanthus roseus</i>	
camptothecin	<i>Camptotheca acuminata</i>	
taxol	<i>Taxus baccata</i>	
podophyllotoxin	<i>Podophyllum peltatum</i>	
artemisinin	<i>Artemisia annua</i>	Malaria
quinine	<i>Cinchona ledgeriana</i>	
quinoline	<i>Cinchona ledgeriana</i>	
digoxin	<i>Digitalis purpurea</i>	Cardiac disorder
digitoxin	<i>Digitalis purpurea</i>	
quinidine	<i>Cinchona ledgeriana</i>	
codeine	<i>Papaver somniferum</i>	Analgesic
morphine	<i>Papaver somniferum</i>	
allicin	<i>Allium sativum</i>	Diabetes
SMCS (S-methyl cysteine sulfoxide)	<i>Allium cepa</i>	
nicotine	<i>Nicotiana tabacum</i>	Brain disorder
caffeine	<i>Coffea canephora</i>	
diosgenin	<i>Dioscorea Mexicana</i>	sexual problems
stigmasterol	<i>Glycine max</i>	
cannabinoids	<i>Cannabis sativa</i>	psycho-disorder
tubocurarine	<i>Chondodendron tomentosum</i>	muscle disorder
atropine	<i>Atropa belladonna</i>	nervous system
hyoscyamine	<i>Hysocyamus niger</i>	

potential of these compounds is often curtailed due to low production levels in plant species or due to loss of source for extinction [6]. For example, use of the blockbuster drug Taxol almost stopped in the early 1990's because the primary source, yew tree bark, could not be used as a sustainable source of the drug. A taxol precursor and a semi-synthetic protocol could have been the ideal way to convert it into the active drug. More generalized solutions, such as metabolic engineering of effective plant and microbial production platforms, are urgently needed to ensure that the plant-derived compounds having enormous structural diversity and biological activities enter the clinical pipeline and find widespread use in medicine.

Considering the vast chemical biodiversity of the plant world, and widespread medicinal values of plant derived natural products, researchers are now focusing on the poorly understood areas of herbs such as genetic background, the agricultural traits, and the medicinal quality. With rapid advances in high throughput sequencing technologies and greatly reduced costs, a new discipline called “herbal genomics” is now emerging. Systematic analysis of medicinal herbs genes' functions are necessary and achievable through sequencing, assembling and annotating their genomes. There have been only a few well assembled herbal genomes released to date, partly because of their complexity. Genomic information, together with transcriptomic, proteomic and metabolomic data, can therefore be used to predict the secondary metabolic pathways of herbs. Moreover, functional herbal genomics can contribute to model herb research platforms, geoherb

research, and herbal synthetic biology, all of which are important for securing the sourcing of the medicinal plants and their active compounds in the future.

2. Genomes and metabolic activities/pathways of herbs

Plants synthesize an abundance of metabolites that can be exploited for pharmacological purposes. Till today, only a small fraction of the immense diversity of plant metabolism has been explored for the production of new medicines and other products important to human well-being. All plants synthesize basic metabolites through primary metabolism needed for their survival but different taxa produce distinct metabolites through secondary or specialized metabolism that are specialized for some specific reactions. As stationary autotrophs, plants have to cope with a number of challenges such as local fluctuations of the simple nutrients they require to synthesize their foods, coexistence of herbivores and pathogens in their immediate environment. Plants have therefore evolved secondary biochemical pathways that allow them to synthesize a diverse array of organic compounds to counter-attack to specific environmental stimuli [7,8]. The palette of secondary metabolites are subdivided into a number of distinct groups, on the basis of their chemical structure and synthetic pathways and those groups are the alkaloids, terpenoids and the phenolic compounds. With a view to understand the full metabolic potential/pathways of the plant/herbs, the whole nuclear and chloroplast genomes needed to be sequenced. In this regard, Chen et al. [44,45] initiated a project, “Herb Genome Programme” for the genome sequencing of various medicinal plants and post genomic functional analysis of various secondary metabolite biosynthetic pathways. Unfortunately, there have been only a few well assembled herbal genomes released to date, partly because of their complexity. The genomes of some commonly used herbs such as *Ganoderma lucidum*, *Salvia miltiorrhiza* and *Catharanthus roseus* have already been sequenced and they emerged as valuable models for studying the genetics and metabolic activities of herbs [1,9,10,50]. These species have been shown to synthesize active pharmaceutical components, including triterpenes, diterpene quinone and indole alkaloids. Analysis of a draft genome sequence of *C. roseus* provided evidence for partial clustering of genes for the biosynthesis of the monoterpene indole alkaloids vinblastine and vincristine. With the help of bacterial artificial chromosome (BAC) sequencing, Kellner et al. [50] showed seven small clusters each of two to three genes that contained genes encoding enzymes for vinblastine/vincristine biosynthesis pathway and other genes for other pathway. In addition to those, the whole genome of medicinal plant, *Z. jujuba* [46,51], *A. Indica*(Neem) [47], and chloroplast genomes of *P. cablin* [48] and *S. miltiorrhiza* [49] have been sequenced successfully. *Z. jujuba* has got significant medicinal value and its fruits are rich in vitamin C and sugar, and the plant contains various therapeutically important alkaloids, flavonoids and phenolics. De novo assembly of its complex genome and transcriptomics data established that L-galactose pathway is the major synthesis pathway for vitamin C and

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