

The New Era of Natural Drug Discovery is characterized by the Integration of High-Throughput Omics Technologies to Research Medicinal Plants

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The natural sources of innovative bioactive chemicals to meet human pharmacological potentials are medicinal plants. The demand for herbal medicines is rising globally, yet there are currently just a few large-scale producers of medical plants and their derivatives. The rapid development of modern technology has stimulated multi-omics research in medicinal plants, leading to a series of breakthroughs in key genes, metabolites, and enzymes involved in the biosynthesis and regulation of active compounds. Here, we summarise the latest research progress on the molecular intricacy of medicinal plants, including the comparison of genomics to demonstrate variation and evolution among species, the application of transcriptomics, proteomics, and metabolomics to explore dynamic changes of molecular compounds, and the utilisation of potential resources for natural drug discovery. These multi-omics studies enable us to comprehend the chemical variety and composition of bioactive substances as well as the theoretical basis for medicinal plants' environmental adaptability. The phytochemical components and possible health advantages of many therapeutic plants have not been completely investigated. It is important to highlight the research needs of using multi-omics technologies to address basic and applied problems in medicinal plants in order to aid in developing new and improved medicinal plant resources and discovering novel medicinal ingredients. This is due to their large diversity and global distribution as well as the impacts of growth duration and environmental factors on bioactive phytochemicals in medicinal plants.

Keywords: medicinal plant, high-throughput omics, biosynthesis pathways, active ingredients, phytochemicals

Introduction

The pharmaceutical industry has paid growing attention to several therapeutic plant-derived alkaloids, terpenes, polyphenols, coumarins, and saponins as a response to their significant antioxidant, antibacterial, antiphlogistic, anticancer, and antidiabetic activities.[Mumtaz et al., 2017; Pandita et al., 2021] As its genome emerged available, landraces of the Chinese opium poppy was analyzed for the processing, regulation, and transportation of a bioactive substance called benzylisoquinoline alkaloid (BIA) (Hu et al., 2018).

To identify functional genes, essential metabolites, biological components with pharmacological potential and molecular markers connected to phytochemical compounds, medicinal plant research can benefit from incorporating other high-throughput sequencing or analytical techniques from metabolomics, proteomics, and transcriptomics. One significant marker was identified by association analysis of fruit color (anthocyanin intensity) based on the transcriptome data of *A. esculentus*, which may be used for the genetic improvement of *A. esculentus* (An et al., 2022) Crotonylated proteins in the metabolic pathways for the Calvin cycle, photosynthesis, alkaloid, and polysaccharide production was determined by analysing proteome datasets of *Dendrobium huoshanense* (Wu et al., 2022a).

The Global Pharmacopoeia Genome Database (GPGD) is a database that includes 9,682 transcriptome sequences from 350 species and 2,203 organelle genomes from 674 species (Liao et al., 2021). Together, these databases give researchers the ability to perform deep data mining to investigate gene annotation and expression profiles of pharmacological properties, investigate the functions of miRNA in regulating biosynthesis and accumulating secondary metabolites, and gather DNA barcode data to aid in the identification of pharmaceutical materials.

Medicinal plant genome updates

Assembling the genomes of medicinal plants is significant due to various their complex polyploid chromosomes and high genome sizes, however long-read sequencing methods have significantly increased the number of assembled medicinal plant genomes at the chromosomal level. A genome size of less than 2 Gb is present in the majority of

medicinal plants (232 out of 279 known medicinal plant genomes). A few species have short genomes, including the liverwort (*Marchantia polymorpha*, 226 Mb), green chiretta (*Andrographis paniculate*, 284 Mb), and Australian dodder (*Cuscuta australis*, 265 Mb).

However, a few of medicinal plants currently have intact mitochondrial genomes, despite having more than 2,000 chloroplast and mitochondrial genomes available (Wu et al., 2020; Liao et al., 2021). Many medicinal plant molecular markers have been created as a result of the accessibility of mitochondrial and chloroplast genome sequences to help in breeding and assess the reliability and caliber of herbs. The use of these genetic data to demonstrate functional genes in the synthesis of therapeutic plant phytochemicals is seriously lacking, nevertheless.

Pathway for the synthesis of phenolic acid

Phenolic acids, which are monophenols' representative molecules, have received a considerable amount of attention due to their anti-inflammatory, antibacterial, and antioxidant properties. According to the official Chinese Pharmacopoeia, phenolic acids, particularly salvianolic acid, are the main marker component utilised for quality assessment in commercial Danshen (*Salvia*) decoctions. Based on comprehensive transcriptome and metabolomic profiling, a putative biosynthesis route for phenolic acids in *Salvia apiana* has been developed (Shi et al., 2021; Hu et al., 2022). Moreover, functional genes and transcription variables that regulate the biosynthesis of phenolic compounds in *Salvia miltiorrhiza* have been discovered (Yu et al., 2018; Deng et al., 2020; Zhou et al., 2021c).

Lignin biosynthetic pathway

Lignin from medicinal plants has been described as an antioxidant (Karmanov et al., 2021; Lu et al., 2022). Lignin has exhibited high anti-UVC (ultraviolet C) properties, as have several of its breakdown products, such as *phenylpropanoids* (Sakagami et al., 2022). *Achyranthes bidentate* root transcriptomes for NG (normal growth for a year) and CM (consecutive monoculture) revealed that genes expressing POD were predominantly active in the CM condition, suggesting that POD participates to the pathway for lignin biosynthesis. (Yang et al., 2018). Comparing to the number of research in the area of phenolic acids in medicinal plants, research that focus on exploring lignin synthetic pathway from medicinal plants are limited.

Proteomic dissection of medicinal plants in different ways for potential drug development

Most medicinal plants have been established throughout the years to have powerful effects on a variety of human diseases based on their unique medicinal properties. Figure 1 Identifies the primary study areas of medicinal plant proteomics that, in recent years, have resulted in the identification of proteinaceous compounds involved in the conversion of active bioactive metabolites. These four foci's contents frequently overlap and aren't researched individually. For instance, global proteome and phosphoproteome profilings of *Dendrobium huoshanense* grown under greenhouse planting (GP) and grown under forest conditions (SPUF) showed that SPUF was more favorable for the accumulation of polysaccharides and alkaloids as well as the possibility of a connection between the phosphorylation levels of different enzyme sites and the polysaccharide/alkaloid content (Wu et al., 2022b).

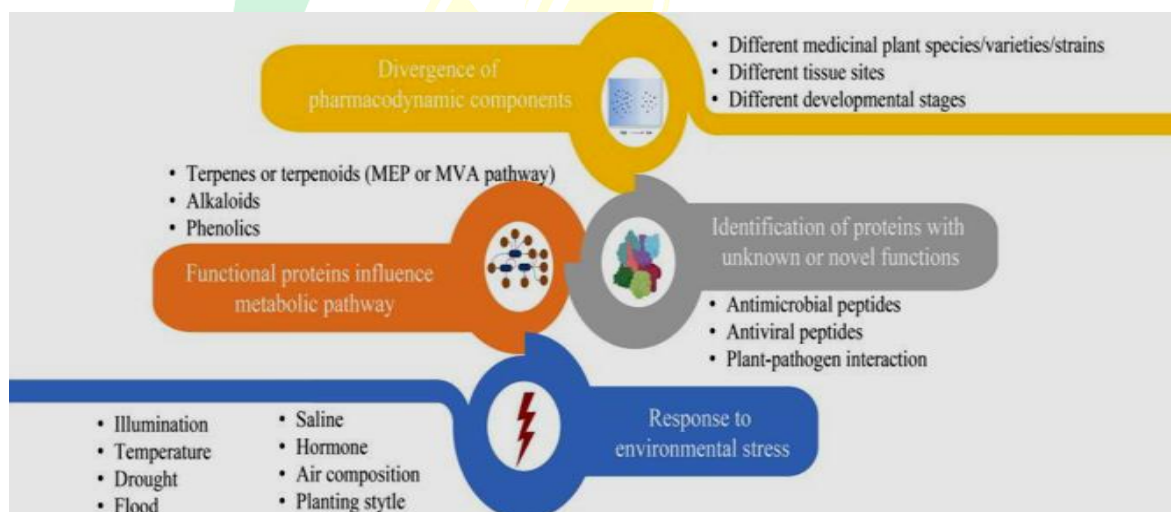


Figure 1 The main contents of proteome research related to biosynthesis or accumulation of metabolites in medicinal plant.

The majority of proteomic research on medicinal plants analyses variations in protein abundance under various environmental circumstances. The well-known saline-alkali- and drought-tolerant medicinal plant *Sophora alopecuroides*. Salt stress affected many transporter proteins involved in the process for the biosynthesis of the secondary metabolite in *S. alopecuroides* leaves, according to tandem mass tag (TMT) based proteomic profiling of *S. alopecuroides* leaves (Ma et al., 2022). Many functional enzymes are involved in the regulation of secondary metabolite production, which offers direction for pharmaceutical

discovery based on protein expression. The common precursor isopentenyl diphosphate (IPP), from which the terpenoid metabolites are derived, can be produced by two distinct pathways: the methylerythritol phosphate (MEP) pathway in plastids and the mevalonate (MVA) pathway in the cytoplasm. Terpenoids found in medicinal plants can be categorised as monoterpenes, sesquiterpenes, meroterpenes, triterpenes, diterpenoids, and other terpenoids (Awouafack et al., 2013; Sandjo and Kuete, 2013b; Sandjo and Kuete, 2013a; Tchimene et al., 2013; Nazir et al., 2021)

Label-free quantitative proteomics was applied to evaluate the proteomes of Korean ginseng's leaves, roots, shoots, and fruits. Out of 1,179 differentially regulated proteins, 67 were discovered to be linked to the pathways that generate ginsenosides, including the MEP pathway, MVA pathway, UDP-glycosyltransferase, and oxidoreductase (Van Nguyen et al., 2021).

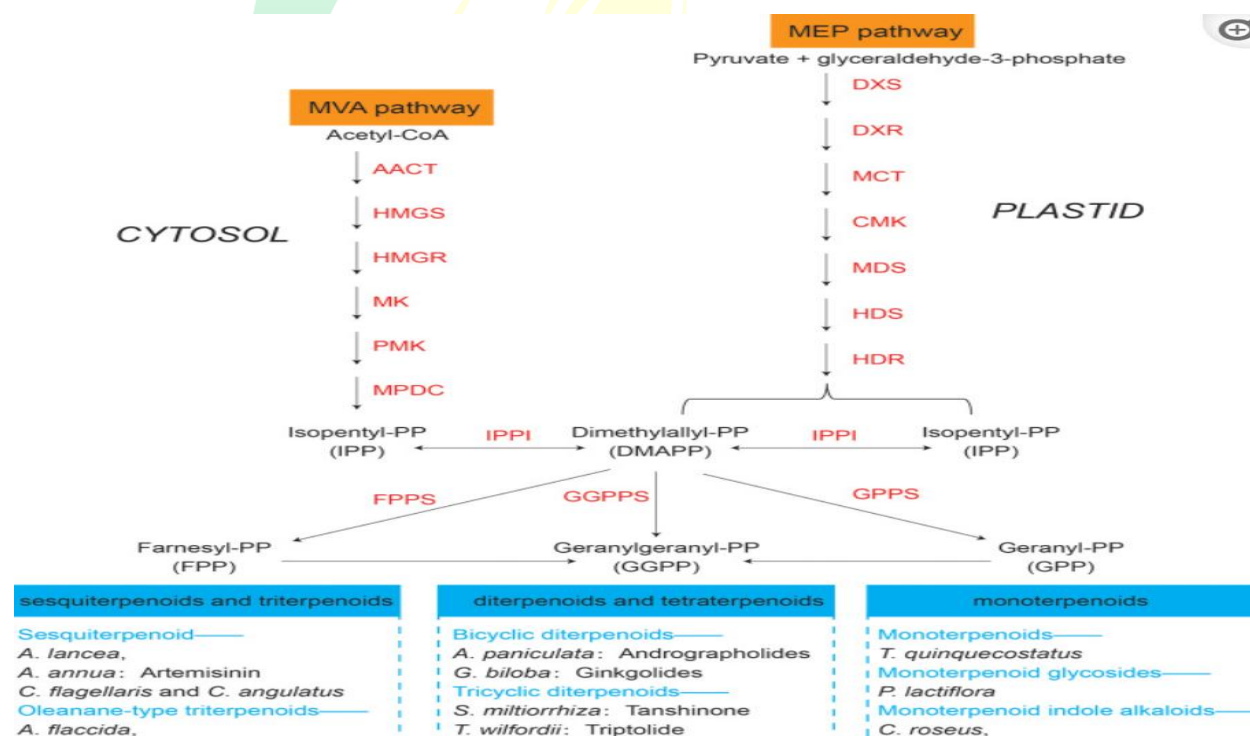


Figure 2

Terpenoids synthesized by representative medicinal plants through mevalonate (MVA) and methylerythritol phosphate (MEP) pathways. The key proteins involved in the two pathways are in orange. AACT, acetoacetyl-CoA thiolase; HMGS, 3-hydroxy-3-methylglutaryl-CoA synthase; HMGR, 3-hydroxy-3-methylglutaryl-CoA reductase; MK,

mevalonate kinase; PMK, phosphomevalonate kinase; MPDC, mevalonate diphosphate decarboxylase; DXS, 1-deoxy-d-xylulose 5-phosphate synthase; DXR, 1-deoxy-d-xylulose 5-phosphate reductoisomerase; MCT, 2C-methyl-d-erythritol 4-phosphate cytidyl transferase; CMK, 4-diphosphocytidyl-2C-methyl-d-erythritol kinase; MDS, 2C-methyl-d-erythritol 2,4-cyclodiphosphate synthase; HDS, 1-hydroxy-2-methyl-2- ϵ -butenyl 4-diphosphate synthase; HDR, 1-hydroxy-2-methyl-2-(E)-butenyl 4-diphosphate reductase; IPPI, Isopentenyl diphosphate-isomerase; FPPS, farnesyl diphosphate (FPP) synthase; GGPPS, geranylgeranyl diphosphate (GGPP) synthase; GPPS, geranyl diphosphate (GPP) synthase. Representative medicinal plants containing various terpenoids are listed in the blue dashed box.

Primary and Secondary metabolites have pharmacological potential, according to metabolomics profiles of medicinal plants

A complete analysis of metabolite profiles and an estimate of the efficacy of medicinal plants are the goals of metabolomics research on plants. Roots, leaves, flowers, fruits, seeds, rhizomes, bark, or whole plants of many natural plants can contain a variety of active ingredients with nutritional or therapeutic functions, and although the extraction method may impact the effective acquisition of metabolites, the difference in medicinal material quality is primarily attributed to metabolite diversity and composition among different tissues or species. (Rai et al., 2021) Nuclear magnetic resonance (NMR) and/or gas/liquid chromatography-mass spectrometry (GC-MS or LC-MS/MS) are two technological platforms that we frequently modify in order to thoroughly analyse metabolites and low-molecular-weight compounds with therapeutic relevance. For instance, GC-MS and LC-MS/MS metabolic profiles of *Panax notoginseng* roots, stems, and leaves from various geographical regions discovered that the saponin composition was similar between root and stem but different from plant leaves. These results indicate that additional portions of *P. notoginseng*, such as their stems, could be used in practice in addition to their roots. (Gao et al., 2022).

Prospects

The pharmacological effects of medicinal plants have a significant positive impact on society and the economy (Wang et al., 2020). Medicinal plants are increasingly at risk of going extinct due to habitat degradation on a larger scale and human usage. Discovering the

chemical variety, regulatory mechanisms, and development of pharmacological qualities of medicinal plants requires a comprehensive approach, which includes multi-omics study in conjunction with bioinformatics and statistical analysis. Through genome engineering or synthetic biology, active medicinal plant bio-compounds can be produced efficiently and sustainably after the genes, metabolites, peptides, or proteins involved in their biosynthetic pathways have been identified. Therefore, organizations and research institutions around the world should promote the incorporation of multi-omics technologies into medicinal plant research to encourage their cultivation in order to satisfy the requirements of synthesising bioactive components of medicinal plants for pharmaceutical applications.

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