Pharmacogenomic Mapping of Bioactive Compounds in Ethnomedicinal Plants - A Review

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Abstract

Ethnomedicinal plants are a rich source of structurally diverse bioactive compounds that interact with human drug-metabolizing enzymes, transporters, receptors and signaling networks. Interindividual variation in response to these botanicals is driven partly by human genetic polymorphisms (pharmacogenomics), leading to variable efficacy and risk of herb–drug interactions. Pharmacogenomic mapping combines high-resolution phytochemical profiling, in-vitro functional assays, in-silico prediction and multi-omics integration with population genetic data to identify compounds are most likely to engage clinically relevant human targets and genotypes are at altered risk. Ethnomedicinal plants contain diverse bioactive compounds that show variable therapeutic responses across populations. With advances in genomics, metabolomics, and computational biology, pharmacogenomic mapping offers new approaches to understand how genetic differences influence plant-drug efficacy, metabolism, and toxicity. This review discusses the integration of metabolomics, biological assays, in silico network pharmacology, multi-omics approaches, and population pharmacogenomics in the discovery and validation of plant-derived therapeutics. Evidence shows that phytochemical responses strongly depend on polymorphisms in genes regulating drug metabolism (CYP450), transporters (ABCB1, SLCO1B1),and conjugating enzymes (UGTs).Population-specific pharmacogenomic variations demonstrate that ethnomedicine can complement precision medicine when mapped systematically. This review emphasizes the need to create genomic–phytochemical databases to support personalized herbal therapy and safer drug development.

Keywords; Ethnomedicinal plants, pharmacogenomics, Proteomic technology, databases, Traditional herbal

INTRODUCTION

Ethnomedicinal plants have a substantial impact on global health, particularly in places with traditional medical systems. More than 80% of the global population relies on herbal medicines for primary care (WHO, 2020). The reaction to plant-derived drugs differs among individuals and ethnic groups due to pharmacogenomic variations, especially in metabolizing enzymes and transport proteins (17). Medicinal plants remain an essential source of bioactive chemicals with a wide range of structural diversity and therapeutic potential (21). Traditional herbal medicine systems are the main source of healthcare for almost 80% of the world's population; most of these

treatment approaches have their roots in long-standing medical traditions in China, India, and several African countries. This worldwide reliance on traditional herbal remedies also draws attention to the stark differences in access to contemporary pharmaceutical interventions and conventional medical infrastructure, especially in developing countries where traditional medicine is frequently the most accessible and cost-effective form of healthcare for sizable population segments (9). These natural chemicals' poor absorption and stability issues frequently restrict their medicinal usefulness. By enhancing their distribution and targeting capabilities, advanced nanovesicular delivery methods such as liposomes, niosomes, and solid lipid nanoparticles have shown promise in boosting the therapeutic potential of herbal medicines. Significant obstacles still stand in the way of these innovative herbal-based nanosystems' scalability, safety profiles, and regulatory approval, notwithstanding their medicinal potential (34). Medicinal plants have historically been essential in traditional medicine, providing a variety of therapeutic chemicals.Their research resulted in the creation of contemporary pharmaceuticals such as artemisinin and aspirin. Their potential influence on contemporary therapeutics is still being investigated through ethnopharmacology, substantiating traditional practices for evidence-based treatments (38, 48). Herbal medications have therapeutic potential, but they don't always work as well as they should because of basic pharmacological limitations such low bioavailability, unstable formulations, and poor targeting. To address these issues and improve treatment results, new advanced nanovesicular delivery systems like solid lipid nanoparticles, ethosomes, niosomes, and liposomes have been developed (3). According to recent studies on cancer, successful treatment requires addressing the tumor microenvironment, resistance pathways, and cancer stem cells all at once—domains where phytochemicals show significant promise. Individualized cancer therapy approaches are made possible by the synergistic potential of combining different plant compounds or incorporating them with traditional medications. Enhancing therapeutic applications and developing standardized treatment protocols that maximize efficacy and minimize side effects require an understanding of the molecular mechanisms underlying these actions. Chemicals derived from plants target specific biological processes to demonstrate various cancer-fighting tactics (1).Proteomic technology advancements such as mass spectrometry, MALDI-TOF, NMR, 2D-PAGE, and protein interaction networks can reduce the time needed to develop novel medications and aid in the investigation of drug interactions and biosafety.

Material and tools

2. Phytochemical Profiling of Bioactive Compounds

Pharmacogenomic mapping begins with profiling of chemical constituents through advanced metabolomics. Techniques such as **LC–MS/MS, GC–MS, and NMR spectroscopy** enable quantitative identification of alkaloids, phenolics, terpenoids, and glycosides in extracts (45).High-resolution metabolomics reveals compound diversity and helps correlate phytochemical variability to genetic responses . For instance, LC–MS/MS studies show that curcuminoid composition varies among turmeric cultivars, influencing its absorption and metabolism Thus, metabolite profiling is a crucial foundation for pharmacogenomic mapping High-resolution metabolomics reveals compound diversity and helps correlate phytochemical variability.

Table1. Phytochemical profiling techniques used to identify bioactive compounds in ethnomedicinal plants

Technique	Type of Bioactive Compounds Identified	Application / Purpose in Pharmacogenomic Mapping	Plant Examples	Reference
LC–MS/MS (Liquid Chromatography–Tandem Mass Spectrometry)	Alkaloids, polyphenols, terpenoids, glycosides	High-resolution quantification and structural elucidation of metabolic variants influencing drug interaction	*Curcuma longa* (curcuminoids), *Rauwolfia serpentina* (reserpine)	(8), (19)
GC–MS (Gas Chromatography–Mass Spectrometry)	Volatile oils, fatty acids, aromatic compounds	Profiling of thermally stable metabolites affecting drug metabolism-related enzymes	*Zingiber officinale* (gingerols), *Ocimum sanctum* (eugenol)	(36),(35)
NMR Spectroscopy (1H/13C NMR)	Structural identification of secondary metabolites (terpenes, flavonoids, alkaloids)	Non-targeted metabolomics to detect structural differences relevant to population-specific drug responses	*Camellia sinensis* (catechins), *Panax ginseng* (ginsenosides)	(29,) (43)
UPLC–QTOF–MS	Trace-level phytochemicals including saponins and phenolics	Accurate mass detection and biomarker discovery for pharmacogenomic screening	*Withania somnifera* (withanolides), *Tinospora cordifolia* (berberine)	(24),(27)
HPTLC (High-Performance Thin Layer Chromatography)	Alkaloids, steroids, phenolics	Rapid fingerprinting for quality control and variability studies	*Azadirachta indica* (limonoids), *Aloe vera* (anthraquinones)	(2) (30)
FT–IR (Fourier Transform Infrared Spectroscopy)	Functional group characterization (phenolics, flavonoids, tannins)	Chemometric profiling for standardization of medicinal plant extracts	*Terminalia chebula*, *Emblica officinalis*	(12),

2.1Biological Assays and Target Identification

Pharmacogenomic mapping requires establishing **human targets of bioactive compounds** using in-vitro biological assays. CYP450 enzyme inhibition/induction assays,transporter assays (P-gp,BCRP), and receptor-binding studies identify metabolic interactions (Guengerich, 2008).Many ethnomedicinal extracts significantly modulate CYP activity. For example, **berberine inhibits CYP2D6, CYP1A2, and CYP3A4**, altering the metabolism of co-administered drugs (Pan et al., 2013). Similarly, flavonoids such as quercetin influence P-gp and ABC transporter activity, affecting oral bioavailability (Xu et al., 2015). These interactions underscore the need to assess ethnomedicines in relation to genetic variability in drug targets.

Table of Biological assays used for target identification and pharmacogenomic mapping of ethnomedicinal plant compounds

Assay type	Pharmacogenomic relevance	Bioactive compound (Plant Source)	Human molecular target / Pathway	Reference
CYP450 Enzyme Inhibition/Induction Assay	Identifies effects on drug-metabolizing enzymes affected by genetic polymorphisms (CYP2D6, CYP2C19)	Berberine (*Tinospora cordifolia*, *Berberis aristata*)	CYP3A4, CYP1A2, CYP2D6	(46)
P-gp Transporter (MDR1/ABCB1) Assay	Determines interaction with efflux transporters affected by ABCB1 gene variants	Quercetin (*Camellia sinensis*), Resveratrol (*Vitis vinifera*)	P-glycoprotein (ABCB1/MDR1)	(39)
BCRP (Breast Cancer Resistance Protein) Transport Assay	Examines absorption changes of polyphenols influenced by transporter polymorphisms	Curcumin (*Curcuma longa*)	BCRP/ABCG2	(22)
Receptor Binding / Ligand Assay	Verifies binding affinity and dose-response changes due to receptor-genetic variations	Withanolides (*Withania somnifera*)	GABAergic / HSP90 receptors	(15)
Enzyme Activity Assay (Anti-inflammatory / Metabolic)	Confirms molecular pathway activity influenced by inflammatory gene polymorphisms	Curcumin (*Curcuma longa*), Boswellic acids (*Boswellia serrata*)	COX-2, NF-κB pathway	(40)

Kinase Assay (Cell Signaling)	Determines effects on kinases altered by gene mutations affecting drug activity	Epigallocatechin gallate (EGCG) (*Camellia sinensis*)	PI3K/Akt/mTOR pathway	(41)
Reporter Gene Assay	Studies gene expression modulation by phytochemicals affected by SNPs	Gingerol (*Zingiber officinale*)	TNF-α / IL-6 signaling	(23)

3 In Silico Mapping and Network Pharmacology

Computational methods facilitate mapping of phytochemical–gene interactions using network pharmacology, molecular docking, and databases such as TCMSP, STRING, CHEMBL, and STITCH. These tools predict bioactive compounds, their protein targets, and possible gene polymorphism influences (16).Network pharmacology studies show that resveratrol interacts with genes regulating metabolic syndrome, including SIRT1, PPARG, and CYP3A4, whose variant alleles alter therapeutic effectiveness (Szklarczyk et al., 2015). Bioinformatic pharmacogenomic mapping thus enhances target validation and predicts population-specific responses.

Table of in silico tools and network pharmacology strategies for mapping phytochemical–gene interactions

In Silico / Network Tool	**Purpose in Pharmacogenomic Mapping**	**Phytochemical / Plant Source**	**Predicted / Validated Target Genes & Pathways**	**Reference**
TCMSP (Traditional Chinese Medicine Systems Pharmacology Database)	Predicts ADME, target genes, and bioavailability related to genetic variation	Resveratrol (*Vitis vinifera*)	SIRT1, PPARG, CYP3A4	Ru et al., 2014
STRING Database	Protein–protein interaction (PPI) mapping for drug response pathways	Curcumin (*Curcuma longa*)	NF-κB, TNF-α, COX-2 pathways	Szklarczyk et al., 2015

STITCH (Chemical–Gene Interaction Database)	Maps compound–gene interactions and metabolic polymorphisms	Quercetin (*Camellia sinensis*)	ABCB1, CYP1A1, CYP2C9	20
Molecular Docking (AutoDock, Schrödinger)	Predicts ligand binding affinity influenced by SNPs in targets	Berberine (*Berberis aristata*)	CYP2D6, CYP3A4 variants affecting metabolism	31
SwissTargetPrediction	Predicts target specificity based on structural similarity	Withanolides (*Withania somnifera*)	HSP90, GABA receptors	10

2.4 Multi-Omics and Systems Approaches

Integration of genomics, proteomics, transcriptomics, and metabolomics helps uncover complex plant–gene interactions. Systems biology reveals how genetic variants influence metabolic pathways triggered by phytochemicals (Misra, 2021). For example, transcriptomics shows that curcumin modulates inflammatory responses differently depending on NF-κB pathway polymorphisms (Wilkinson et al., 2016). Such multi-omics integration supports precision herbal medicine.

2.5 Population Pharmacogenomics in Ethnomedicinal Plants

Drug metabolism varies significantly among populations with distinct genetic backgrounds. Variations in CYP2D6, CYP2C19, UGT1A1, ABCB1, and SLCO1B1 affect metabolism of alkaloids, flavonoids, phenolics, and terpenoids commonly found in herbal medicines (46).Curcumin biotransformation is affected by UGT1A1*28 polymorphism predominant in South Asians (Prasad et al., 2020).Rauwolfia alkaloids show reduced metabolism in CYP2D6 poor metabolizers, common in Europeans (17).Berberine metabolism differs in East Asians due to CYP2C19 polymorphism (47).These findings demonstrate that ethnomedicines may be scientifically tailored to population genetics, reinforcing their relevance to precision medicine.

Table of population pharmacogenomics key Genes, Variation and relevance to ethnomedicinal uses

Gene / Pharmacogene	Function / Relevance (Metabolism / Transport / Detox)	Known Population / Ethnic Variation	Implication for Ethnomedicinal Bioactives & Herbal-Drug Interactions	Reference
CYP3A5 (and by extension CYP3A subfamily)	Major drug-metabolizing enzyme in liver/intestine; metabolizes many xenobiotics including plant compounds	The functional allele *CYP3A5*1 frequency varies strongly — high in some African populations, low (mostly nonfunctional *CYP3A5*3)	Phytochemicals (or drugs co-administered with herbs) processed by CYP3A5 may have different metabolic rates	**32**

CYP2C19	Drug-metabolizing enzyme, relevant for metabolism of many xenobiotics including possibly plant-derived compounds	Loss-of-function alleles	When herbs or plant compounds are metabolized via CYP2C19, individuals with poor-metabolizer genotypes	**37**
Multiple pharmacogenes (e.g. CYP, transporters, detox enzymes)	Determines overall metabolism, transport, conjugation, clearance of xenobiotics	Large ethnogeographic differences in allele frequencies across many pharmacogenes, affecting many drugs and xenobiotics.	Use of ethnomedicinal plants (or plant + drug combinations) should consider population-level genotype distributions.	**4**

Conclusion

Pharmacogenomic mapping is a promising pathway to translate ethnomedicinal knowledge into precision-safe therapeutics and to reduce herb–drug interaction risk. Success depends on rigorous phytochemical characterization, multi-omics and systems biology, population genetic data, and targeted clinical validation. Building interoperable databases that connect phytochemical, pharmacologic and genomic evidence will accelerate both discovery and safer clinical use of plant-derived medicines.Pharmacogenomic mapping bridges traditional herbal medicine and precision therapeutics. Establishing population-specific herb–gene interaction databases, implementing genotype-based clinical trials, and integrating pharmacogenomics into herbal regulatory frameworks will optimize global healthcare outcomes. Future research must emphasize.Pharmacogenomic mapping offers a promising approach for validating ethnopharmacology, guiding personalized herbal therapies, and enhancing drug discovery. Establishing genomic–phytochemical interaction databases, community genetic biobanking, and global standards for herbal pharmacogenomics will accelerate the integration of traditional medicine with precision health care.

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