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Omics-Based Biomarkers for Predicting Chemopreventive Response to Herbal Formulations

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Abstract

Cancer chemoprevention using herbal formulations represents a potentially valuable yet underutilized strategy for reducing cancer incidence and mortality. Despite substantial preclinical and epidemiological evidence supporting the anticancer potential of plant-derived compounds, clinical translation has been limited by pronounced inter-individual variability and the absence of validated biomarkers capable of predicting chemopreventive response. Recent advances in omics technologies, including genomics, transcriptomics, proteomics, metabolomics, epigenomics, and microbiomics, enable systems-level characterization of the complex, multi-target mechanisms that typify herbal agents and provide new opportunities for biomarker discovery.

This review critically evaluates current evidence on omics-based biomarkers relevant to herbal cancer chemoprevention, emphasizing mechanistic insights, analytical approaches, and translational limitations. Molecular signatures associated with representative polyphenolic compounds, including curcumin, epigallocatechin gallate, resveratrol, quercetin, and emodin, are discussed across multiple omics layers. Emerging strategies for multi-omics integration, including network-based and machine-learning approaches, are examined alongside challenges related to reproducibility, standardization, and clinical generalizability. Key barriers to implementation, including formulation heterogeneity, limited prospective human studies, and gaps in regulatory qualification, are highlighted. Integration of omics technologies with evidence-based herbal medicine, often termed herbogenomics, may inform precision prevention strategies, contingent upon rigorous validation and harmonized regulatory frameworks.

Keywords: cancer chemoprevention; herbal medicine; omics-based biomarkers; multi-omics integration; precision prevention

1. Introduction

1.1 Cancer Prevention and the Critical Role of Herbal Formulations

Cancer remains a leading cause of morbidity and mortality worldwide, with global incidence projected to increase by 50% by 2050, reaching approximately 28 million new cases annually (Sung et al., 2021). While substantial therapeutic advances have improved treatment outcomes for diagnosed cancer patients, cancer chemoprevention defined as the use of natural or synthetic compounds to prevent, suppress, or delay the development of invasive carcinoma (Kotecha et al., 2016) remains profoundly underutilized despite compelling epidemiological and experimental evidence supporting its efficacy. This represents a significant missed opportunity, as prevention strategies typically achieve greater population-level impact than treatment of established disease while incurring substantially lower healthcare costs (Ren et al., 2025).

Herbal formulations derived from medicinal plants and traditional medicine systems worldwide represent exceptionally rich sources of bioactive compounds with well-characterized anti-inflammatory, antioxidant, pro-apoptotic, and anti-proliferative properties (Patel et al., 2007). Epidemiological studies consistently demonstrate that populations consuming diets abundant in plant-derived polyphenols and phytochemicals exhibit significantly reduced cancer incidence across multiple cancer types (Dvorska et al., 2025). Specific compounds such as curcumin the active ingredient in turmeric (*Curcuma longa* L.) and epigallocatechin gallate (EGCG), the major bioactive component of green tea (*Camellia sinensis*), have demonstrated substantial inhibitory effects on carcinogen-induced cellular transformation in both *in vitro* and *in vivo* experimental models (Piwowarczyk et al., 2020).

Despite these promising preclinical findings, clinical translation of herbal chemoprevention has been severely hampered by multiple critical factors: (1) limited understanding of inter-individual variability in chemopreventive response, (2) absence of standardized, analytically validated biomarkers to distinguish responders from non-responders, (3) significant chemical heterogeneity in herbal formulations resulting from variation in plant cultivars, geographic origin, environmental conditions, and processing methods, and (4) lack of predictive tools and stratification biomarkers to identify populations most likely to benefit from specific herbal interventions (Swetha et al., 2022; Alum, 2025). These barriers have perpetuated a disconnect between traditional ethnobotanical knowledge and contemporary precision medicine approaches, preventing herbal formulations from achieving their full potential in cancer prevention.

1.2 The Omics Revolution and Systems-Level Biomarker Discovery

The emergence of high-throughput omics technologies has fundamentally transformed biomarker discovery from hypothesis-driven investigation toward comprehensive, unbiased profiling of molecular alterations across multiple biological levels simultaneously (Hristova & Chan, 2018). These revolutionary technologies enable simultaneous quantification of thousands to millions of molecular entities from DNA sequences and structural variants to gene expression patterns, proteins and post-translational modifications, metabolites, and epigenetic marks providing unprecedented systems-level understanding of biological processes and disease mechanisms (Hsu et al., 2025). The multi-layered omics landscape encompasses:

- **Genomics**: Analysis of DNA sequence variations, single nucleotide polymorphisms (SNPs), copy number variations (CNVs), structural variants, and germline polymorphisms influencing drug metabolism and response
- **Transcriptomics**: Quantification of mRNA and microRNA (miRNA) expression patterns via microarray or RNA-sequencing technologies, revealing pathway-level responses
- **Proteomics**: Comprehensive characterization of protein abundance, phosphorylation states, and dynamic protein-protein interactions using mass spectrometry approaches
- **Metabolomics**: Identification and quantification of small-molecule metabolites reflecting functional cellular biochemistry and metabolic remodeling
- **Epigenomics**: Assessment of DNA methylation, histone acetylation and methylation, chromatin accessibility, and three-dimensional chromatin structure
- **Microbiomics**: Characterization of gut microbial community composition and metagenomic/metatranscriptomic signatures reflecting bidirectional host-microbiota interactions

1.3 Rationale for Omics-Based Biomarker Development in Herbal Chemoprevention

The integration of multi-omics technologies directly addresses critical gaps that have hindered herbal chemoprevention development (Carlos-Reyes et al., 2019; Ren et al., 2025). Unlike reductionist single-biomarker approaches, multi-omics strategies capture the characteristic complexity of herbal formulations which typically contain hundreds to thousands of bioactive compounds acting through overlapping and synergistic mechanisms across multiple cellular pathways simultaneously. This multi-targeted nature, traditionally viewed as a liability preventing mechanistic understanding, can be converted to an advantage through omics-based approaches that comprehensively characterize the full spectrum of molecular effects.

Omics-based biomarkers can enable the following critical advances: (1) predictive stratification of individuals likely to respond favorably to specific herbal interventions based on baseline molecular profiles; (2) optimization of therapeutic doses tailored to individual metabolic capacity and genetic polymorphisms; (3) elucidation of molecular mechanisms underlying chemopreventive effects; (4) early identification of individuals at elevated risk for unintended adverse effects; (5) standardization and authentication of complex herbal preparations ensuring formulation reproducibility and quality; and (6) acceleration of clinical translation by bridging gaps between preclinical promise and clinical efficacy (Hristova & Chan, 2018; Sánchez-Vidaña et al., 2017). Furthermore, multi-omics approaches uniquely enable integration with artificial intelligence and machine learning algorithms, generating predictive models of superior performance compared to single-omics biomarkers (Hsu et al., 2025; Hernández-Lemus et al., 2024).

This comprehensive review examines the state-of-the-art in omics-based biomarker discovery for herbal chemoprevention, emphasizing both methodological advances and practical clinical applications, with particular focus on mechanistic understanding, standardization frameworks, and translation pathways.

2. Omics Technologies and Analytical Approaches for Herbal Biomarker Discovery

2.1 Genomics and DNA-Level Biomarkers for Herbal Response

Genomic approaches identify germline genetic variants particularly single nucleotide polymorphisms (SNPs) in genes encoding drug-metabolizing enzymes, xenobiotic transporters, and pathway-specific proteins that substantially influence individual chemopreventive responses to herbal compounds (Braytee et al., 2024). These polymorphisms predict altered drug bioavailability, metabolic clearance rates, and consequently variable biological effects among treated individuals.

Cytochrome P450 Variants and Herbal Metabolism: Metabolism of many herbal compounds depends critically on cytochrome P450 (CYP) enzymes, particularly CYP3A4 and CYP2C8. Functional variants in the *CYP3A4* gene including loss-of-function alleles *CYP3A4**3 and *CYP3A4**4 significantly predict altered curcumin bioavailability and systemic exposure levels (Kotecha et al., 2016). Individuals carrying reduced-function variants exhibit elevated systemic curcumin concentrations and potentially enhanced intracellular chemopreventive activity, though this relationship requires careful dose-response studies to establish clinical relevance.

Aryl Hydrocarbon Receptor Polymorphisms: Multiple herbal polyphenols, including quercetin, kaempferol glycosides, and EGCG, function as ligands for the aryl hydrocarbon receptor (AhR) a critical environmental sensor of carcinogens (Ren et al., 2025). Functional SNPs in the *AhR* gene promoter region (particularly -2234G>T) significantly influence basal AhR expression levels and predict responsiveness to polyphenol-mediated inhibition of carcinogen-induced xenobiotic gene expression.

Glutathione S-Transferase Variants: GSTP1 variants encoding functionally distinct isoforms (Ile105Val, Ala114Val) demonstrate different substrate specificities and catalytic efficiencies. The GSTP1 105 Val variant exhibits lower enzymatic activity toward carcinogenic metabolites such as benzo(a)pyrene-7,8-diol-9,10-epoxide (BPDE), predicting enhanced chemopreventive benefit from compounds including curcumin and EGCG that increase GST activity (Swetha et al., 2022).

Tumor Suppressor Gene Variants: TP53 germline variants (Arg72Pro polymorphism, intron 3 16 bp duplication) demonstrate differential capacity to induce apoptosis in response to herbal compounds. Individuals carrying the Pro72 allele exhibit enhanced p53-mediated apoptotic response following EGCG treatment of pre-malignant cells, suggesting potential biomarker utility for stratification (Kotecha et al., 2016).

2.2 Transcriptomics: Gene Expression and miRNA Biomarkers

Transcriptomic profiling quantifies mRNA and microRNA levels genome-wide, revealing biological pathways and cellular processes affected by herbal interventions. This approach proves particularly valuable for identifying multi-target effects characteristic of complex herbal formulations containing hundreds of bioactive compounds (Ren et al., 2025).

RNA-Sequencing and Microarray Technologies: High-density microarrays and next-generation RNA-sequencing enable simultaneous quantification of mRNA expression levels for thousands of genes in response to herbal compounds. Studies across multiple cancer models demonstrate that curcumin treatment produces characteristic transcriptional signatures with coordinated upregulation of apoptotic genes (BAX, BAK, PUMA, NOXA, BAD, caspase-3, caspase-9) and simultaneous downregulation of anti-apoptotic genes (BCL-2, BCL-XL, MCL-1) and cell-cycle regulators (Cyclin E2, Cyclin A, CDC25A, CDC25B, CDK2, CDK4) (Kotecha et al., 2016). These coordinated transcriptional changes reflect engagement of multiple apoptotic pathways and cell-cycle checkpoint activation.

MicroRNA Biomarkers: MicroRNAs are non-coding RNA molecules regulating gene expression post-transcriptionally through mRNA silencing and translational repression. EGCG treatment of breast cancer cells produces characteristic alterations in miRNA expression, with significant changes in miR-16, miR-21, miR-222, miR-29 family members, and miR-145 (Piwowarczyk et al., 2020). These miRNA expression changes correlate directly with reduced cell proliferation, enhanced apoptosis, and diminished angiogenic potential. Importantly, circulating miRNA profiles in serum and plasma can serve as non-invasive biomarkers of chemopreventive response, detectable without tissue biopsy.

Pathway-Level Transcriptional Biomarkers: Rather than examining individual gene expression changes, pathway-level approaches integrate expression measurements for gene sets participating in specific biological processes. Genes participating in programmed cell death, cell-cycle control, DNA damage response, and oxidative stress responses demonstrate consistent modulation across diverse herbal compounds. Systematic assessment of coordinated transcriptional changes in these functionally-related gene sets provides robust, reproducible biomarkers of herbal efficacy more resistant to biological noise than single-gene measurements (Swetha et al., 2022).

Xenobiotic Response Element Activation: Transcription of genes regulated by xenobiotic response elements (XRE) indicates activation of cellular detoxification and xenobiotic-responsive pathways. EGCG, curcumin, and other herbal polyphenols activate the aryl hydrocarbon receptor and upregulate expression of CYP1A1, CYP1B1, and NAD(P)H quinone oxidoreductase 1 (NQO1) genes critical for detoxification of environmental carcinogens and management of reactive oxygen species (Ren et al., 2025).

2.3 Proteomics: Protein-Level Biomarkers and Signaling Analysis

Proteomics technologies measure protein abundance, post-translational modification states, and dynamic protein-protein interactions, offering superior insights into immediate functional consequences of herbal treatments compared to transcriptomics alone (Hristova & Chan, 2018).

Mass Spectrometry-Based Quantitative Proteomics: Liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) enables unbiased, genome-scale protein quantification across thousands of proteins simultaneously. Isobaric labeling methods (tandem mass tags [TMT], isotope tags for relative and absolute quantitation [iTRAQ]) allow multiplexing of samples, substantially increasing analytical throughput and statistical power. Proteomic studies of curcumin-treated colorectal cancer cells identified coordinated downregulation of 20S proteasome catalytic subunits (PSMB5, PSMB6, PSMB7, PSMA4), α-synuclein, and associated proteasome machinery, providing mechanistic explanation for curcumin-induced G1-phase cell-cycle arrest and cellular senescence (Valdés et al., 2017).

Phosphoproteomic Biomarkers: Post-translational phosphorylation regulates signaling pathway activation and cellular responses. Phosphoproteomic profiling reveals that EGCG suppresses phosphorylation of receptor tyrosine kinases (EGFR, HER2, MET) and downstream effectors including extracellular signal-regulated kinase (ERK1/2), protein kinase B (AKT), and mammalian target of rapamycin (mTOR), providing detailed mechanistic biomarkers of anti-proliferative activity (Kwon et al., 2021).

Protein-Protein Interaction Networks: Advanced proteomics approaches capture physical interactions between proteins at systems level, revealing network-level responses to herbal treatment. These interactome studies identify hub proteins and network bottlenecks whose altered expression or modification triggers cascading changes affecting multiple downstream cellular pathways and phenotypes (Hristova & Chan, 2018).

Extracellular Vesicle Proteomes: Cancer cells and stromal cells release extracellular vesicles including exosomes (50-150 nm) and microvesicles (100-1000 nm) containing proteins reflecting their cellular origin and physiological state. These EV proteomes serve as liquid biopsy biomarkers, enabling detection of chemopreventive effects at systemic level without tissue sampling (Kwon et al., 2021).

2.4 Metabolomics: Metabolic Biomarkers and Functional Readouts

Metabolomics quantifies small-molecule metabolites (molecular weight < 1,500 Da), providing unique functional readout of cellular metabolism and immediate biochemical consequences of herbal exposure (Ahmad et al., 2022). This approach captures downstream metabolic remodeling preceding gene expression and protein changes.

Targeted Metabolomics: Quantification of pre-defined metabolite sets using authenticated standard compounds and precise chromatographic/spectrometric methods. Serum amino acid profiles demonstrate characteristic changes following herbal intervention, with selective depletion of glutamine, branched-chain amino acids (leucine, isoleucine, valine), and elevated aromatic amino acids (tyrosine, phenylalanine). These metabolic signatures correlate with activated anti-cancer immunity and reduced tumor cell proliferative capacity (Alum, 2025).

Untargeted Metabolomics: Comprehensive profiling of metabolite diversity without *a priori* hypotheses enables discovery of unexpected biomarkers and characterization of metabolite diversity in herbal formulations. Untargeted analysis identifies hundreds of bioactive compounds and their metabolic derivatives. Distinct metabolomic signatures emerge for specific herbal interventions: curcumin-treated cells exhibit characteristic lipid metabolic remodeling with increased diacylglycerols, increased monoacylglycerols, and dramatically decreased lysophosphatidylcholine species (Zeng et al., 2023).

Lipidomics: Specialized metabolomic analysis focusing on lipid diversity (sterols, phospholipids, glycerolipids, sphingolipids, oxidized lipids). Herbal polyphenols significantly remodel cellular lipidomes via modulation of lipase activities, fatty acid desaturase expression, and lipogenic enzyme activities. LPC-O 22:0 (lysophosphatidylcholine with odd-chain fatty acid) emerged as a sensitive biomarker of curcumin and EGCG intervention in mast cell degranulation and allergy models (Zeng et al., 2023).

Pathway-Level Metabolic Integration: Metabolomic data integrated with transcriptomic and proteomic findings reveal coordinated metabolic remodeling underlying chemopreventive effects. Systems metabolomics approaches using flux balance analysis and kinetic modeling elucidate how herbal compounds reprogram central carbon metabolism, one-carbon metabolism, energy metabolism, and biosynthetic pathways (Ahmad et al., 2022; Ren et al., 2025).

2.5 Epigenomics: Epigenetic Biomarkers and Chromatin Remodeling

Epigenetic modifications regulate gene expression without altering DNA sequences, and emerging evidence demonstrates that herbal compounds exert chemopreventive effects substantially through epigenetic mechanisms (Carlos-Reyes et al., 2019). These modifications are potentially reversible, enabling therapeutic opportunities for epigenetic re-sensitization of resistant populations.

DNA Methylation Biomarkers: DNA methylation at cytosine-guanine dinucleotides (CpG sites) controls gene expression; hypermethylation of tumor suppressor gene promoters represents a hallmark epigenetic alteration in cancer. Herbal compounds, particularly EGCG and quercetin, effectively reverse aberrant DNA hypermethylation. Quercetin reduces DNA methylation levels at tumor suppressor gene promoters (DAPK1, RASSF1A, VHL, PTEN) by 50-85%, with methylation reversal correlating strongly with restoration of gene expression and tumor-suppressive function (Farheen, 2024). Single-base-resolution DNA methylation sequencing (whole-genome bisulfite sequencing) identifies specific CpG sites whose methylation status predicts chemopreventive response with high sensitivity.

Histone Modification Biomarkers: Acetylation of histone lysine residues (H3K9ac, H3K27ac, H4K16ac) and methylation of histone lysines and arginines (H3K4me3, H3K27me3) regulate chromatin accessibility and gene expression. Herbal compounds that inhibit histone deacetylases (particularly sirtuins and class I/II HDACs) increase histone acetylation at tumor suppressor gene promoters, shifting chromatin from repressive heterochromatin toward permissive euchromatin and reactivating tumor-suppressive gene expression. Curcumin-induced HDAC inhibition increases H3K9 acetylation and H3K27 acetylation at apoptotic gene promoters (BAX, BAK, BIM) and senescence-related genes (CDKN1A/p21, CDKN2A/p16), demonstrating epigenetic reactivation of growth-suppressive pathways (Carlos-Reyes et al., 2019).

Chromatin Accessibility Biomarkers: ATAC-seq (Assay for Transposase-Accessible Chromatin using sequencing) quantifies chromatin accessibility genome-wide at single-nucleotide resolution, revealing sites of transcriptionally active chromatin. Herbal treatment produces characteristic alterations in chromatin accessibility at inflammatory response genes, proliferation-related genes, and apoptotic genes, providing functional chromatin-level biomarkers (Kwon et al., 2021).

Non-Coding RNA Epigenetics: Herbal compounds regulate expression of epigenetically-active non-coding RNAs including long non-coding RNAs (lncRNAs, >200 nt) and circular RNAs (circRNAs) that modulate chromatin state, transcription factor activity, and gene expression (Wu et al., 2023). lncRNAs such as HOTAIR and XIST demonstrate altered expression in response to herbal compounds, reflecting and potentially mediating epigenetic remodeling.

2.6 Microbiomics: Gut Microbiota as Mediators and Biomarkers of Chemopreventive Response

The gut microbiota represents an increasingly recognized contributor to herbal compound bioavailability, metabolism, and chemopreventive efficacy (Ren et al., 2025). Microbiomics encompassing 16S rRNA gene sequencing, metagenomic sequencing, metatranscriptomics, and metabolomic analysis of microbial metabolites provides insights into microbiota-mediated mechanisms of herbal chemoprevention.

Microbiota Composition and Diversity: Herbal compounds including curcumin and EGCG significantly alter gut microbiota composition, increasing abundance of beneficial taxa (Faecalibacterium prausnitzii, Akkermansia muciniphila, Roseburia spp.) while reducing pathogenic populations (Enterobacteriaceae, Clostridium difficile) (Ahmad et al., 2022). Changes in microbial alpha-diversity and beta-diversity predict chemopreventive response and correlate with improved intestinal barrier function and reduced systemic lipopolysaccharide (LPS) translocation.

Microbial Metabolite Production: Gut bacteria metabolize herbal compounds and dietary fiber to generate bioactive short-chain fatty acids (SCFA) principally butyrate, propionate, and acetate which serve as histone deacetylase inhibitors and G-protein coupled receptor ligands. Fecal butyrate concentrations and the ratio of butyrate-producing bacteria emerge as sensitive biomarkers of herbal chemoprevention efficacy, particularly for gastrointestinal cancers (Ahmad et al., 2022). Secondary bile acid metabolism by the microbiota generates farnesoid X receptor (FXR) and G-protein coupled bile acid receptor 1 (TGR5) ligands with anti-inflammatory properties.

3. Multi-Omics Integration, Data Analysis, and Predictive Modeling

3.1 Multi-Omics Integration Strategies

The transformative power of omics-based biomarker discovery emerges through systematic integration of multiple omics datasets, revealing systems-level understanding invisible to single-omics analyses (Hernández-Lemus et al., 2024; Hsu et al., 2025).

Concatenated Multi-Omics Analyses: Direct combination of standardized, normalized omics datasets into unified computational pipelines. For example, integration of proteomic and transcriptomic data with metabolomic measurements generates comprehensive molecular signatures. Studies analyzing herbal interventions in cancer models have successfully integrated serum and fecal metabolomics data with proteomic identification of tight-junction protein alterations and immune-regulatory protein changes, revealing gut barrier-protective mechanisms (Ahmad et al., 2022).

Network Pharmacology Integration: Integration of molecular interaction data with transcriptomic/proteomic findings constructs drug-target networks revealing multi-target mechanisms of herbal compounds. Network analysis identifies hub proteins and master regulatory nodes whose alteration triggers cascading changes across multiple pathways. Analysis of *Marsdenia tenacissima* identified tenacisosides as active components selectively inhibiting anti-apoptotic proteins (BCL-2 family) and promoting pro-apoptotic signaling through convergence of multiple pathway alterations (Zhang et al., 2023).

Machine Learning and Deep Learning Integration: Advanced machine learning algorithms including random forest, support vector machines, gradient boosting machines, and deep neural networks learn complex non-linear patterns from multi-omics data, generating predictive models. These approaches substantially outperform single-variable statistical tests, achieving classification accuracy exceeding 85-90% in benchmark datasets (Hsu et al., 2025). Cross-validation and independent test set validation ensure model generalizability to new populations.

Tensor Decomposition and High-Order Integration: Tensor decomposition methods including Tucker decomposition and parallel factor analysis handle inherently multi-way omics data (samples × molecular features × omics modalities), capturing higher-order relationships invisible to pairwise correlation methods (Braytee et al., 2024). These methods efficiently integrate genomics, transcriptomics, proteomics, and metabolomics into unified predictive models.

3.2 Quality Control, Standardization, and Analytical Validation

Robust biomarker discovery requires stringent quality control and standardization at every analytical stage:

Pre-Analytical Standardization: Herbal compound bioavailability and metabolism vary substantially with food intake, gut microbiota composition, individual metabolic capacity, circadian rhythm, and medication use. Standardized sampling protocols must specify: fasting versus fed state, time-of-day consistency, sample collection volume, anticoagulant type, and precise processing timelines. These variables dramatically influence omics data quality and biomarker reproducibility (Lee et al., 2017).

Metabolomics Standardization for Herbal Preparations: Integration of complementary metabolomics platforms NMR (quantitative, non-destructive), LC-MS (high selectivity and sensitivity), and GC-MS (volatiles and small hydrophobic molecules) captures comprehensive herbal metabolite diversity. HPTLC-MS (High-Performance Thin-Layer Chromatography–Mass Spectrometry) coupled with HPLC serves essential quality control functions, ensuring formulation reproducibility and authenticating plant materials (Alum, 2025). These standardized approaches are increasingly adopted by international herbal medicine regulatory bodies.

Biomarker Analytical Validation: Omics biomarkers require rigorous analytical validation demonstrating: (1) **accuracy** (unbiased measurement of true analyte concentration), (2) **precision** (inter- and intra-assay reproducibility with coefficient of variation < 15%), (3) **analytical sensitivity and specificity** (detection of true signals while rejecting noise and interference), (4) **robustness** (resistance to variations in pre-analytical and analytical procedures), and (5) **stability** (preservation of biomarker levels under storage conditions) (Lee et al., 2017). Metabolomic biomarkers specifically require recovery of spiked standards (85-115%), inter-laboratory agreement, and inter-platform concordance.

4. Key Herbal Compounds and Their Omics-Derived Biomarker Signatures

4.1 Curcumin: The Turmeric Paradigm

Curcumin the yellow pigment of turmeric (*Curcuma longa* L.) represents the most extensively studied herbal compound with established chemopreventive activity in multiple cancer models (Piwowarczyk et al., 2020). Its complex multi-omics biomarker signature illustrates the multi-targeted nature of herbal chemoprevention.

Transcriptomic Signatures: Curcumin induces characteristic transcriptional reprogramming involving upregulation of apoptotic genes (BAX, BAK, BAD, PUMA, NOXA, caspase-3, caspase-9) and downregulation of anti-apoptotic genes (BCL-2, BCL-XL, MCL-1) and proliferation-related genes (Cyclin E, CDK2, CDK4, CDK6) (Kotecha et al., 2016). In hepatocellular carcinoma and colorectal cancer models, curcumin upregulates expression of tumor suppressor genes whose promoters have undergone aberrant DNA hypermethylation, indicating functional epigenetic reactivation. Gene expression profiling reveals activation of p53-dependent stress response pathways and suppression of Wnt/β-catenin signaling in multiple cancer contexts.

Proteomic and Phosphoproteomic Biomarkers: LC-MS/MS proteomics identified that curcumin-induced G1-phase cell-cycle arrest in colorectal cancer cells correlates with coordinated downregulation of 20S proteasome catalytic subunits (PSMB5, PSMB6, PSMB7, PSMA3, PSMA4) and complete inhibition of ubiquitin-proteasome-dependent protein degradation (Valdés et al., 2017). This proteasomal inhibition causes accumulation of CDK inhibitor p21^(CDKN1A), enforcing cell-cycle arrest. Phosphoproteomic analysis reveals suppression of receptor tyrosine kinase signaling (EGFR, HER2, c-Met) and MAPK/ERK pathway deactivation via reduced ERK1/2 and p38 MAPK phosphorylation.

Metabolomic Biomarkers: Curcumin profoundly remodels cellular lipidomes through altered lipase and lipogenic enzyme activities. Characteristic changes include increased diacylglycerols, increased monoacylglycerols, increased unsaturated fatty acids (oleic acid, linoleic acid), and dramatically decreased lysophosphatidylcholine abundance (Zeng et al., 2023). These lipid metabolic changes correlate directly with anti-inflammatory effects and reduced mast cell degranulation. Amino acid metabolism shifts toward increased proline and hydroxyproline, reflecting altered collagen metabolism and reduced epithelial-mesenchymal transition.

Epigenomic Biomarkers: Single-base-resolution DNA methylation sequencing demonstrated that curcumin reverses colitis-associated carcinogenesis-induced downregulation of DNA methylation in mouse models of colorectal cancer (Farheen, 2024). Additionally, curcumin increases histone H3K9 acetylation and H3K4 methylation at apoptotic gene promoters (BAX, BAK, BIM, caspases), shifting chromatin from repressive heterochromatin toward permissive euchromatin states.

4.2 Epigallocatechin Gallate: The Green Tea Catechin

EGCG the most abundant catechin in green tea (*Camellia sinensis*) demonstrates exceptionally broad chemopreventive activity against multiple cancer types (Piwowarczyk et al., 2020). Its biomarker profile shows both overlapping and distinctive features compared to curcumin.

Transcriptomic Biomarkers: EGCG treatment downregulates expression of growth-promoting genes (c-myc, growth factor receptors including EGFR and HER2) and upregulates pro-apoptotic genes (BAX, BAK, PUMA, NOXA). Gene expression microarray studies identified that EGCG treatment results in coordinated downregulation of 30+ genes involved in cell-cycle progression, DNA replication, and oxidative phosphorylation, reflecting reduced energetic capacity for proliferation. Circulating miRNA analysis reveals that EGCG treatment alters miR-16, miR-21, miR-222, and let-7 family expression patterns, with these alterations correlating with reduced proliferation and enhanced apoptosis (Piwowarczyk et al., 2020).

Proteomic and Phosphoproteomic Biomarkers: EGCG suppresses phosphorylation of EGFR, HER2, and downstream effectors (ERK1/2, AKT, p70S6K), constituting a characteristic phosphoproteomic signature distinct from curcumin (Kwon et al., 2021). Proteomic analysis reveals increased expression of detoxification proteins including glutathione S-transferase (GST), NAD(P)H quinone oxidoreductase (NQO1), and UDP-glucuronosyltransferase (UGT) enzymes, suggesting enhanced xenobiotic processing capacity.

Metabolomic Biomarkers: Like curcumin, EGCG remodels cellular lipidomes but with partially overlapping, partially distinctive signatures. EGCG preferentially increases abundance of specific lipid subclasses including bismonoacylglycerols and cardiolipins cardiolipins are particularly enriched in mitochondrial membranes and their increased abundance suggests altered mitochondrial function, enhanced autophagy, and apoptotic pathway activation (Zeng et al., 2023).

Epigenomic Biomarkers: EGCG reverses DNA hypermethylation in tumor suppressor genes through multiple mechanisms: inhibition of DNA methyltransferase (DNMT) activity and increased ten-eleven translocation (TET) dioxygenase activity, promoting active DNA demethylation (Farheen, 2024). Histone acetylation profiling shows increased H3K9ac and H3K27ac at regulatory regions of apoptotic genes.

4.3 Additional Polyphenolic Compounds: Resveratrol, Quercetin, and Emodin

Resveratrol (from grapes and berries) exhibits distinct mechanisms including sirtuin (SIRT1/SIRT3) activation and estrogen receptor modulation. Transcriptomic profiling reveals coordinated upregulation of sirtuins, AMP-activated protein kinase (AMPK) pathway components, and metabolic regulators, distinguishing its biomarker signature from other polyphenols. This metabolic remodeling reflects enhanced oxidative metabolism and mitochondrial biogenesis.

Quercetin (ubiquitously present in plant foods) demonstrates particularly potent epigenetic effects exceeding many synthetic histone deacetylase inhibitors. DNA methylation analysis shows that quercetin achieves near-complete reversal of aberrant tumor suppressor gene hypermethylation (methylation reduced to 7-60% of control levels) within 24-48 hours (Farheen, 2024). This rapid epigenetic effect distinguishes quercetin from slower-acting HDAC inhibitors and natural HDAC inhibitors such as butyrate. The speed of epigenetic reactivation suggests quercetin-mediated DNMT inhibition or enhanced TET activity.

Emodin (from rhubarb and other plants) exhibits distinctive proteomic and transcriptomic signatures characterized by potent STAT3 pathway inhibition and increased expression of pro-death signaling proteins (TRAIL receptors, FAS) in multiple cancer cell types. Metabolomic analysis reveals preferential effects on sphingolipid metabolism and amino acid metabolism distinct from other polyphenols (Zhang et al., 2023).

5. Clinical Translation: From Discovery to Clinical Application

5.1 Biomarker Validation Framework and Regulatory Pathways

Translating omics biomarkers from research discovery to clinical implementation requires rigorous, phase-based validation following FDA guidance on biomarker qualification (Kotecha et al., 2016):

Analytical Validity Phase: Biomarkers must be accurately and reproducibly measured across multiple laboratory platforms, demonstrating: (1) **inter-platform concordance** (microarray versus RNA-seq for transcriptomics, HPLC versus LC-MS for metabolomics, concordance correlation coefficients > 0.85), (2) **inter-laboratory reproducibility** across multiple independent sites, and (3) **stability** under different sample storage and processing conditions (Lee et al., 2017). For omics biomarkers, this includes ensuring that batch effects and technical variation do not exceed biological signal.

Clinical Validity Phase: Biomarkers must demonstrate statistically significant and clinically meaningful association with herbal chemopreventive efficacy in well-powered, prospective clinical studies. Phase II prevention trials incorporating comprehensive omics assessment should compare detailed biomarker profiles between responders (defined as significant reduction in cancer incidence, pre-malignant lesion regression, or validated biomarker endpoint improvement) and non-responders. Effect sizes must exceed 0.8 standard deviations to ensure practical utility (Swetha et al., 2022).

Clinical Utility Phase: Beyond demonstrating statistical association, biomarkers must improve patient outcomes beyond current clinical practice and standard of care. This requires: (1) **prospective randomized controlled trials** stratifying patients based on baseline omics profiles, comparing outcomes between biomarker-guided and standard prevention approaches; (2) **comparison of outcome rates** including cancer incidence reduction, adverse event rates, quality-of-life measures; and (3) **rigorous cost-effectiveness**

analysis demonstrating acceptable incremental cost-effectiveness ratios relative to willing-to-pay thresholds (Kotecha et al., 2016).

Regulatory Harmonization: Different regulatory jurisdictions (FDA, EMA, PMDA) maintain varying expectations for biomarker evidence. International efforts through organizations such as Global Alliance for Genomics and Health (GA4GH) seek to harmonize biomarker standards, enabling multi-center collaborative trials and biomarker implementation (Hristova & Chan, 2018).

5.2 Liquid Biopsy Applications and Non-Invasive Monitoring

Detection of chemopreventive effects in readily accessible biofluids is critical for clinical translation and long-term monitoring. Liquid biopsy approaches offer substantial advantages over tissue biopsy (invasiveness, sampling bias, cost):

Circulating Cell-Free DNA (cfDNA): Fragmented DNA released from apoptotic cancer cells and healthy cells circulates in blood at low concentrations in healthy individuals and elevated concentrations in cancer patients. Changes in cfDNA methylation patterns particularly at tumor-suppressor gene promoters and oncogenic regions predict chemopreventive response with high sensitivity, potentially preceding morphologic evidence of tumor regression by months (Hristova & Chan, 2018).

Circulating microRNAs: Serum and plasma miRNAs reflect the physiologic state of multiple tissues. miRNA profiles demonstrate remarkable sensitivity to herbal compound treatment, with single-sample collection providing whole-body information on chemopreventive response. Circulating miR-21 and miR-92a levels predict response to EGCG chemoprevention and correlate with reduced circulating endothelial cells (a marker of angiogenic burden) (Kwon et al., 2021).

Extracellular Vesicles and Exosomes: Extracellular vesicles including exosomes (50-150 nm) and microvesicles (100-1000 nm) are released by cancer cells, immune cells, and stromal cells, carrying proteins, lipids, and nucleic acids reflecting cellular origin and physiological state. EV surface markers (CD44, CD147, EpCAM) and cargo proteins (pro-invasive metalloproteinases, hypoxia-inducible factor) predict responsiveness to herbal immunomodulatory compounds (Kwon et al., 2021).

Fecal Metabolites: For gastrointestinal and systemic cancers, fecal metabolomic analysis reveals effects of herbal compounds on gut microbiota metabolism and intestinal barrier function. Short-chain fatty acids (butyrate, propionate, acetate) and secondary bile acids produced by transformed microbiota correlate strongly with herbal chemopreventive efficacy (Ahmad et al., 2022). These non-invasive biomarkers enable frequent monitoring without blood sampling.

5.3 Companion Diagnostics and Precision Prevention Medicine

Companion diagnostics tests performed in parallel with therapeutic agents enhance clinical utility and enable precision prevention strategies:

Pre-Treatment Biomarker Profiling and Stratification: Baseline omics assessment (genomic, transcriptomic, proteomic, metabolomic profiles) identifies individuals likely to respond to specific herbal formulations or combinations. Polymorphisms in CYP3A4, CYP2C8, GST, AhR, and TP53 genes could guide initial herbal formulation selection, dose adjustment, and predicted response magnitude (Kotecha et al., 2016). Integration of baseline omics profiles with lifestyle factors (diet quality, physical activity, sleep, stress) and microbiota composition enables comprehensive individual risk stratification.

On-Treatment Biomarker Monitoring: Serial omics measurements (every 3-6 months) during herbal chemoprevention assess achievement of pre-specified molecular endpoints reversal of epigenetic abnormalities, normalization of circulating miRNA profiles, improvement of metabolite biomarkers without requiring cancer incidence endpoints, which may require decades of follow-up (Swetha et al., 2022). This enables early identification of non-responders for formulation adjustment or escalation to other prevention strategies.

Dose Adjustment and Optimization: Machine learning models integrating baseline omics profiles, genetic variants, dietary intake, and on-treatment biomarker responses could enable real-time dose optimization, potentially increasing efficacy while minimizing adverse effects (Hsu et al., 2025). Pharmacogenetic algorithms could predict individual optimal doses based on metabolizer phenotypes and pathway engagement.

6. Challenges, Limitations, and Future Directions

6.1 Current Limitations and Barriers to Clinical Translation

Herbal Formulation Standardization: Complex herbal preparations contain hundreds to thousands of compounds in varying proportions influenced by plant cultivar, geographic origin, growing conditions, and processing methods. This chemical complexity creates profound challenges for metabolomic standardization, compound identification, and linking specific compounds to biomarker responses (Alum, 2025). While metabolomics has revolutionized herbal characterization, establishing definitive relationships between individual compounds and specific biomarker responses requires carefully designed dose-response and combination studies with reductionist compound isolates.

Individual Heterogeneity and Personalization: Chemopreventive response varies profoundly across individuals due to genetic polymorphisms, baseline metabolic capacity, lifestyle factors (diet, physical activity, sleep, stress), medication use, and microbiota composition. The omics approaches to date have primarily focused on cancer cell lines and rodent models; large, diverse human prospective studies remain limited. Substantially larger and more diverse human cohorts including geographic diversity, ethnic diversity, age ranges, and socioeconomic diversity are necessary to establish robust biomarker performance across populations and contexts (Swetha et al., 2022).

Biological Complexity and Multi-Target Effects: The multi-targeted nature of herbal formulations acting on numerous pathways simultaneously complicates biomarker interpretation and effect attribution. A single biomarker typically cannot capture the full spectrum of chemopreventive mechanisms; panel-based approaches are more appropriate but introduce statistical challenges of multiple comparisons, requiring careful correction and independent validation (Kotecha et al., 2016). Determining which biomarker changes are causally related to chemopreventive efficacy versus epiphenomenal remains challenging.

Data Integration and Computational Complexity: Combining high-dimensional omics datasets presents substantial computational and interpretative challenges. Consensus on standardized analysis pipelines, effect size thresholds, statistical adjustment methods, and biomarker classification remains elusive, impeding multi-center collaborative studies (Hernández-Lemus et al., 2024). Batch effects, platform biases, and normalization strategies can substantially impact integrated analyses.

Extended Timeline for Validation: Chemoprevention trials frequently extend over years or decades, with cancer incidence as the ultimate endpoint. Long-term follow-up required to validate omics biomarkers as surrogate markers of chemopreventive efficacy represents substantial time and financial investment, potentially delaying implementation even after strong mechanistic data accumulate (Patel, 2007).

6.2 Emerging Technologies and Analytical Approaches

Single-Cell and Spatial Omics: Single-cell RNA-sequencing, single-cell proteomics, and spatial transcriptomics reveal cellular heterogeneity and tissue-level context invisible to bulk omics approaches. These technologies enable identification of rare cell populations responsive or resistant to herbal compounds, providing cellular-resolution understanding of chemopreventive mechanisms (Kwon et al., 2021). Spatial proteomics approaches including multiplex imaging preserve spatial organization of tissues while measuring dozens to hundreds of proteins simultaneously.

Artificial Intelligence and Deep Learning: Advanced machine learning architectures, particularly deep neural networks, convolutional neural networks, and transformer-based models, can extract complex non-linear patterns from multi-omics datasets that conventional statistics cannot detect (Hsu et al., 2025). Graph neural networks represent biological systems as molecular interaction networks, enabling more biologically realistic pattern recognition. Autonomous AI systems integrating multi-omics data with clinical variables achieve diagnostic accuracy exceeding 90% in benchmark datasets.

Real-Time Wearable Monitoring and Continuous Biomarkers: Wearable biosensors and smartphone-based diagnostic devices enable continuous or frequent omics monitoring outside clinical settings. Microfluidic devices measuring circulating cell-free DNA, miRNAs, and proteins from capillary blood samples provide real-time biomarker assessment. Integration of sensor data with omics measurements could provide unprecedented insights into how behaviors, diet, and environmental factors dynamically influence herbal chemopreventive responses (Kwon et al., 2021).

Organoid and Organ-on-Chip Models: Three-dimensional organoid cultures and microfluidic organ-on-chip systems recapitulate tissue architecture and cellular interactions substantially better than traditional 2D monolayer culture. Combined with high-throughput omics profiling, these models enable patient-derived personalized assessment of herbal chemopreventive responses using primary patient cells, moving beyond cancer cell line models (Kwon et al., 2021).

Multi-Omics Standardization and Data Harmonization Initiatives: International consortia (GA4GH, Human Cell Atlas, NIH Common Fund initiatives) are actively developing standardized data formats (GA4GH Schemas), analysis pipelines (Nextflow, Snakemake), and quality metrics for omics data. Implementation of these standards across research centers will facilitate multi-center collaborative studies and enable biomarker harmonization and meta-analysis (Hristova & Chan, 2018).

6.3 Regulatory Pathways and Future Clinical Implementation Strategies

Biomarker Co-Development with Drug Development: Future herbal chemoprevention development should integrate biomarker discovery and validation from early phases, following FDA guidance on biomarker qualification. This process requires: (1) biochemical assay development and analytical validation, (2) biological plausibility and mechanistic characterization in disease models, (3) demonstration of analytical validity across platforms, (4) prospective clinical validity in relevant populations, and (5) prospective demonstration of clinical utility (Kotecha et al., 2016).

Adaptive and Bayesian Clinical Trial Designs: Adaptive clinical trial designs incorporating biomarker-driven treatment stratification or dose adjustment enable more efficient chemoprevention trials compared to traditional fixed-design approaches. Bayesian adaptive designs with pre-specified biomarker decision rules can reduce overall trial duration while maintaining statistical rigor and family-wise error control (Swetha et al., 2022).

Integration with Electronic Health Records and Real-World Evidence: Linking omics biomarker data with electronic health records (EHRs) and claims databases enables large-scale observational studies validating biomarker performance in diverse real-world populations. EHR integration also facilitates longitudinal tracking of cancer incidence and causes of death over extended follow-up periods (Hristova & Chan, 2018).

Precision Prevention and Personalized Herbal Medicine: The convergence of omics-based biomarkers, pharmacogenetic data, lifestyle assessments, and machine learning creates the opportunity for truly personalized prevention medicine tailoring herbal formulations, doses, combinations, and administration schedules to individual risk profiles and molecular characteristics. This "herbogenomics" approach synthesizes traditional ethnobotanical wisdom with cutting-edge precision medicine (Sánchez-Vidaña et al., 2017).

Conclusion

Omics-based biomarkers provide an important framework for advancing herbal cancer chemoprevention from predominantly empirical practice toward evidence-based precision prevention. Current evidence indicates that polyphenolic compounds such as curcumin, epigallocatechin gallate, resveratrol, quercetin, and emodin induce reproducible molecular alterations across genomic, transcriptomic, proteomic, metabolomic, epigenomic, and microbiotic levels, offering mechanistic insight into their chemopreventive activity. Multi-omics integration has enabled more comprehensive characterization of the multi-target actions of herbal agents and has improved understanding of inter-individual variability in response.

Despite substantial mechanistic progress, translation into clinical practice remains limited, reflecting challenges related to biomarker validation, formulation heterogeneity, and the complexity of long-term prevention endpoints. The concept of integrating omics technologies with traditional herbal medicine, often described as herbogenomics, highlights the potential for aligning ethnobotanical knowledge with modern systems biology. Continued refinement of omics methodologies and careful interpretation of existing evidence are essential to realizing the potential of herbal chemoprevention within precision cancer prevention paradigms.

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