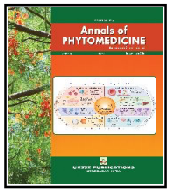
Annals of Phytomedicine 15(1): 1-6, 2026

DOI: http://dx.doi.org/10.54085/ap.2026.15.1.1

Annals of Phytomedicine: An International Journal
http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Invited Commentary

Artificial intelligence-driven molecular target identification for precision phytotherapy

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Article Info

Article history : Received 11 February 2026, Revised 13 March 2026, Accepted 14 March 2026, Published Online 30 June 2026

Abstract

Artificial intelligence (AI) has emerged as a powerful tool in biomedical research, offering new opportunities for molecular target identification and the development of precision phytotherapy. AI enables the systematic identification of bioactive plant compounds by integrating machine learning (ML) and deep learning (DL) approaches with phytochemical and multi-omics datasets, including genomic, transcriptomic, and metabolomic data. It also facilitates the prediction of their pharmacological activities and the elucidation of their molecular mechanisms of action. Advanced computational models such as neural networks, support vector machines, and generative algorithms are increasingly applied in virtual screening, QSAR modeling, and ADMET prediction, accelerating the discovery and optimization of plant-derived therapeutic candidates. Furthermore, AI-driven platforms facilitate the design of novel phytochemical analogues and support drug repurposing strategies, thereby enhancing the efficiency and scalability of natural product-based drug discovery. Despite existing challenges such as data heterogeneity, model interpretability, and the need for clinical validation, the integration of AI with phytochemistry and precision medicine provides a promising framework for translating complex biological data into personalized therapeutic strategies.

1. Introduction

Artificial intelligence (AI) has progressively become an important component of modern drug discovery, evolving alongside advances in computational power and the expansion of biological data. Early computational approaches in pharmaceutical research were largely based on linear regression models and limited chemical descriptors. The introduction of quantitative structure-activity relationship (QSAR) methods marked an important milestone, followed by the development of more sophisticated molecular descriptors such as topological indices and molecular fingerprints (Zefirov and Palyulin, 2002; Hecht, 2011; Zhu *et al.,* 2020). During the 1990s and early 2000s, nonlinear machine learning techniques, including k-nearest neighbors, support vector machines, and random forests, became widely used for predicting biological activity and drug-target interactions. In parallel, greater emphasis was placed on model validation strategies, including cross-validation and external test datasets, which improved the reliability and applicability of computational models. These developments ultimately established QSAR modeling, molecular docking, and other computational tools as fundamental components of computer-aided drug discovery (Sheridan *et al.,* 2000; Willett, 2006; Solimeo *et al.,* 2012; Sprague *et al.,* 2014; Ashiwaju *et al.,* 2023).

The emergence of large-scale biological datasets and improvements in computational infrastructure have significantly increased the importance of deep learning approaches in drug discovery since the 2010s. Advances such as GPU-accelerated computing and cloud-based platforms enabled the training of complex deep neural networks capable of capturing nonlinear relationships between chemical structures and biological activities. These models have demonstrated strong predictive performance in tasks such as toxicity prediction, drug-target interaction analysis, and multi-task learning from large pharmacological datasets (Wen *et al.,* 2017; Workman *et al.,* 2019). At the same time, the growing recognition of variability in individual drug responses has strengthened the concept of precision medicine, which aims to tailor therapeutic strategies according to patient-specific biological characteristics. Medicinal plants and natural products represent valuable resources due to their remarkable structural diversity and multi-target biological activities, making them particularly relevant for the development of precision phytotherapeutic approaches (Zhu *et al.,* 2020; Asharif, 2024; Ajabali *et al.,* 2025). Accordingly, this review provides an overview of current AI-driven strategies for molecular target identification in phytochemical research and discusses their potential to bridge natural product science with precision medicine for the development of next-generation personalized phytotherapeutic interventions.

2. Artificial intelligence for personalized medicine

The development of personalized medicine accelerated in the late 1990s with major advances in biomarker discovery and genomic research. The completion of the Human Genome Project and the emergence of high-throughput sequencing technologies significantly increased the availability of genetic data, enabling researchers to identify individual variations such as single nucleotide polymorphisms, gene expression differences, epigenetic modifications, and metabolic profiles that influence disease susceptibility and drug response. These developments laid the foundation for pharmacogenomics, which examines how genetic variations in drug-metabolizing enzymes, transporters, and receptors affect treatment outcomes (Schrider and Kern, 2018; Sydow *et al.,* 2019). As research progressed, it became evident that molecular heterogeneity plays a critical role in disease progression and therapeutic response. For

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example, tumors within the same cancer type may exhibit distinct genetic and epigenetic characteristics, while autoimmune and metabolic diseases also demonstrate diverse molecular signatures. Consequently, personalized medicine aims to address this biological complexity by aligning therapeutic strategies with the unique molecular and genetic profiles of individual patients, thereby improving treatment efficacy and safety (Schrider and Kern, 2018; Workman *et al.,* 2019; Ajabali *et al.,* 2025).

3. Computational modeling and artificial intelligence

As the scale of genomic and molecular datasets expanded, computational approaches became indispensable for interpreting biological heterogeneity. Contemporary personalized medicine increasingly depends on integrative computational modeling frameworks capable of predicting drug-target interactions, reconstructing metabolic networks, and uncovering population-specific genetic patterns. Multidimensional datasets and these data-driven strategies reveal latent hierarchical relationships within biological systems, thereby enabling researchers and clinicians to identify individuals who are most likely to benefit from a given therapeutic intervention (Sydow *et al.,* 2019; Zhu, 2020).

This transition has been strongly supported by large-scale international initiatives. The NIH precision medicine initiative, for example, stimulated extensive data generation and sharing efforts, leading to the expansion of genomic repositories and the development of advanced bioinformatics infrastructures. Among these resources, the National Cancer Institute's Genomic Data Commons stands out as a comprehensive platform that integrates cancer-related genomic information and currently encompasses data from tens of thousands of patient cases. Such repositories allow systematic comparison of genetic, transcriptomic, and proteomic variation across populations, facilitate more refined disease stratification, and help uncover previously unrecognized therapeutic vulnerabilities (Collins and Varmus, 2015; Grossman *et al.,* 2016). Although, whole-genome sequencing falls outside the primary scope of this review, it is important to acknowledge the growing role of AI-driven analytical methods in this context. Techniques such as automated variant calling, unsupervised clustering, and deep learning-based annotation have become integral to precision oncology, the diagnosis of rare diseases, and individualized treatment planning. As data integration strategies continue to mature, computational medicine is increasingly positioned as a foundational component of personalized healthcare (Lippmann *et al.,* 2018; Workman *et al.,* 2019).

4. Phytochemicals as multi-target therapeutic agents in precision phytotherapy

Unlike many synthetic drugs that typically act on a single molecular target, phytochemicals often exert their therapeutic effects through multiple biological pathways simultaneously, reflecting a systems-level mode of action. Plant-derived compounds such as polyphenols, flavonoids, alkaloids, terpenoids, and fatty acids interact with diverse molecular targets including transcription factors, signaling pathways, metabolic enzymes, inflammatory mediators, and epigenetic regulators. This multi-target activity allows phytochemicals to modulate complex biological networks associated with chronic diseases such as cancer, metabolic disorders, and neurodegenerative conditions. Well-known phytochemicals including curcumin, berberine, resveratrol, quercetin, EGCG, sulforaphane, ginsenosides, and lignans demonstrate broad pharmacological effects through pathways related to inflammation, oxidative stress, mitochondrial function, and metabolic regulation (Dlamini *et al.,* 2020; Alsharif, 2024; Ajabali *et al.,* 2025).

Inter-individual genetic variability further influences responses to plant-derived compounds. Polymorphisms in drug-metabolizing enzymes, transporters, and regulatory proteins can significantly affect the bioavailability and pharmacological effects of phytochemicals. Consequently, the integration of pharmacogenomics with phytotherapy is increasingly recognized as an important step toward personalized herbal medicine. In this context, systems biology and network pharmacology approaches enable the analysis of complex phytochemical-target interactions within biological networks, facilitating the identification of disease-specific molecular pathways and the development of individualized plant-based therapeutic strategies (Gezici, 2019; Chihomvu *et al.,* 2024; Varghese *et al.,* 2025).

5. Phytochemicals in systems pharmacology: Multi-target interactions and pharmacogenomic perspectives

In contrast to many synthetic drugs that are typically designed to act on a single molecular target, phytochemicals often exert their therapeutic effects through multiple biological pathways simultaneously. This characteristic reflects a systems-level mode of action in which plant-derived compounds interact with diverse molecular targets across complex biological networks. Phytochemicals such as polyphenols, flavonoids, alkaloids, terpenoids, lignans, carotenoids, phytosterols, and plant-derived fatty acids exhibit broad pharmacological activities by modulating transcription factors, signaling pathways, inflammatory mediators, metabolic enzymes, mitochondrial processes, and redox-regulating systems. Through these multi-target interactions, phytochemicals can influence interconnected cellular processes associated with chronic diseases including cancer, metabolic disorders, neurodegenerative diseases, and inflammatory conditions (Khedkar *et al.,* 2007; Gezici, 2023; Alsharif, 2024).

The pharmacological versatility of phytochemicals becomes particularly relevant when considering the genetic and molecular diversity among individuals. Variations in genetic background, epigenetic regulation, metabolic status, and environmental exposures contribute to substantial heterogeneity in disease progression and therapeutic responses. Within this context, the pleiotropic nature of phytochemicals may offer advantages over conventional single-target drugs by enabling more adaptable and individualized therapeutic effects. Several well-studied phytochemicals exemplify these multi-target mechanisms. For example, curcumin modulates inflammatory and oxidative stress-related pathways such as NF-κB, STAT3, AP-1, and Nrf2; berberine regulates metabolic signaling networks including AMPK and insulin receptor pathways; while resveratrol influences mitochondrial function and energy homeostasis through SIRT1, AMPK, and PGC-1α signaling. Similarly, quercetin affects PI3K/Akt and MAPK pathways involved in cell survival and oxidative stress, whereas epigallocatechin gallate (EGCG) regulates epigenetic mechanisms and oncogenic signaling pathways. Other compounds such as sulforaphane activate cellular detoxification responses via the Nrf2 pathway, ginsenosides modulate neuroendocrine and immune signaling, and lignans interact with estrogen receptors, illustrating their relevance in hormone-related disorders (Wiens and Shenov, 2018; Chihomvu *et al.,* 2024; Aljabali *et al.,* 2025).

Genetic polymorphisms in drug-metabolizing enzymes and transport systems further influence individual responses to phytochemicals. Variations in enzymes such as cytochrome P450 isoforms, UDP-glucuronosyltransferases, and transporters including P-glycoprotein can significantly affect the metabolism, bioavailability, and systemic exposure of plant-derived compounds. Consequently, integrating pharmacogenomic insights into phytotherapy represents a critical step toward the development of personalized herbal medicine, where specific phytochemicals or plant extracts are selected based on an individual's genetic and metabolic characteristics (Tahara *et al.,* 2023; Varghese *et al.,* 2025).

In recent years, systems biology and network pharmacology approaches have significantly advanced the understanding of phytochemical actions within complex biological systems. These computational frameworks enable the modeling of interactions between multiple phytochemicals and their molecular targets across multilayered biological networks. By integrating patient-specific omics data with phytochemical interaction networks, researchers can identify disease subtypes that may respond preferentially to certain plant-derived compounds, design synergistic phytochemical combinations, and discover predictive biomarkers for treatment responsiveness. The convergence of phytochemistry, omics technologies, and systems pharmacology therefore provides a powerful framework for developing individualized plant-based therapeutic strategies and advancing precision phytotherapy (Adir *et al.,* 2020; Gezici, 2025; Gokcen *et al.,* 2026; Turkmen *et al.,* 2026).

6. Conclusion and future directions

Artificial intelligence has become a key driver in accelerating drug discovery by enabling the analysis of large and complex biomedical datasets and significantly reducing research time and costs. Advances in machine learning and deep learning have enhanced the ability to identify molecular targets, predict drug-target interactions, and prioritize therapeutic candidates. Although, standardized frameworks for AI-based drug discovery are still evolving, the integration of artificial intelligence with big data, omics technologies, and high-performance computational infrastructures is rapidly transforming pharmaceutical research. In the future, closer integration of AI with ethnopharmacological knowledge and phytochemical databases is expected to expand the role of medicinal plants in personalized medicine. The integration of omics-based diagnostics with bioactive compounds derived from traditional medical systems such as Ayurveda, Traditional Chinese Medicine, and Anatolian ethnobotany may evolve toward more holistic and individualized therapeutic strategies, thereby enhancing both treatment diversity and accessibility.

In the emerging scientific landscape of the 21st century, phytomedicine is gaining wider acceptance and increasing importance. Phytomedical research is truly a multidisciplinary activity, involving botany, pharmacognosy, natural product chemistry, biochemistry, medicinal chemistry, pharmacology, pharmaceutical sciences, molecular genetics, and other related disciplines. In the proper dissemination of emerging scientific knowledge, scientific journals play a key role by publishing carefully scrutinized, peer-reviewed, high-quality research papers and review articles. Although, the literature includes a large number of journals, devoted to the above-mentioned branches of science, only a few publish articles covering multidisciplinary areas. It is gratifying to see that **"Annals of Phytomedicine: An International Journal"** is catering to the needs of scientists from different but closely related disciplines across the globe. I am confident that researchers in phytomedicine will find this journal to be an appropriate and valuable forum for the publication of their work.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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Biography

Dr. Sevgi Gezici is a Professor in the Department of Medical Biology and Genetics, Faculty of Medicine, Gaziantep University, Turkiye. She also serves as the Head of the Molecular and Biological Activities of Natural Products Research Group. She is an interdisciplinary scientist whose research bridges molecular oncology, bioinformatics, artificial intelligence, and natural product sciences, with a particular focus on translational biomedical applications.

She received her B.Sc. degree in Biology from Gaziantep University and subsequently completed her M.Sc. and Ph.D. degrees in Molecular Biology and Genetics at Gaziantep University. During her doctoral training, she was selected as a visiting researcher at Texas A&M University, Faculty of Life Sciences (USA), where she conducted part of her Ph.D. research focusing on molecular and cellular biology approaches. Following her doctoral studies, she carried out postdoctoral research at Kumamoto University, Department of Life Sciences, Japan, further strengthening her expertise in molecular biology and international collaborative research. Throughout her graduate studies, she was awarded competitive fellowships from the Scientific and Technological Research Council of Turkiye (TUBITAK) for both her M.Sc. and Ph.D. programs.

Professor Gezici has established an active and internationally recognized research profile in molecular cancer biology, translational oncology, and computational biomedical sciences. Her research focuses on the molecular mechanisms underlying cancer development and progression, including apoptosis, cell signaling pathways, cancer genetics, and clinical proteomics. In recent years, she has expanded her research toward artificial intelligence-supported biomedical studies, integrating machine learning, transformer-based diagnostic models, bioinformatics, and multi-omics data analysis for early cancer detection, biomarker discovery, and precision medicine applications. Another important dimension of her research involves the phytochemistry and pharmacological activities of medicinal and aromatic plants. Her work investigates secondary metabolites, nutraceutical compounds, and plant-derived bioactive molecules, particularly their anticancer, antioxidant, neuroprotective, and anti-inflammatory properties. She employs a multidisciplinary approach that combines experimental molecular techniques with computational biology, network pharmacology, and artificial intelligence-driven data analytics to identify novel therapeutic targets and develop innovative strategies for drug discovery and precision phytotherapy.

Professor Gezici has authored and co-authored more than 250 scientific contributions, including peer-reviewed journal articles, book chapters, conference proceedings, and presentations delivered at national and international scientific meetings and congresses. She has actively participated in numerous international conferences, scientific workshops, and collaborative academic activities held in various countries across Europe, Asia, and North America, contributing to global scientific dialogue in molecular biology, phytotherapy, oncology, and pharmaceutical sciences.

In addition to her research activities, Professor Gezici plays an active role in the international academic publishing community. She serves on the Editorial Advisory Boards of several international journals in the fields of molecular biology, pharmacognosy, and pharmaceutical sciences. She is Co-Editor of Current Perspectives on Medicinal and Aromatic Plants (CUPMAP) and serves as Assistant Editor for the Journal of Pharmaceutical Research (JPR) and Current Research in Pharmaceutical Sciences (CRPS). She is also a member of the Editorial Board of the International Journal Annals of Phytomedicine (AP) and contributes to peer-review and editorial activities in multiple SCI-indexed journals. Moreover, she has undertaken editorial responsibilities in academic publications and thematic sections of journals such as Medicine Research, The Natural Products Journal, and the Journal of Phytonanotechnology and Pharmaceutical Sciences (JPPS), particularly in areas related to natural metabolites, drug discovery, and pharmaceutical biotechnology.

Professor Gezici is actively involved in international scientific networks and academic organizations. She serves as the Scientific Secretary of the International Mediterranean Symposium on Medicinal and Aromatic Plants (MESMAP) and as the Chair of the

International Symposium on Pharmaceutical and Biomedical Sciences (ISPBS). She is also the General Secretary and a Board Member of the Global Federation of Medicinal and Aromatic Plants (GOFMAP). Prof. Dr. Gezici is a member of several international and national scientific organizations, including the European Association for Cancer Research (EACR), the European Proteomics Association (EuPA), and the Basic Oncology Association (TEOD). In addition, she serves as a Board Member of the Molecular Biology Association of Turkey and the Association of Medicinal and Aromatic Plants of the Mediterranean (AMAPMED). She also holds the title of Honorary Faculty Member of the Novel Global Community Educational Foundation (NGCEF).

Through her interdisciplinary research and international collaborations, Professor Gezici continues to contribute to advances in molecular medicine, precision oncology, and phytotherapeutic drug discovery, particularly through the integration of artificial intelligence, bioinformatics, and natural product-based biomedical research.