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Review

Network pharmacology and AI: illuminating the path to precision herbal medicine in *Ganoderma* spp.

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ABSTRACT

Ganoderma species are promising sources of bioactive natural products with substantial pharmacological potential and have long been valued in traditional Chinese medicine (TCM) for their diverse therapeutic properties. However, their complex multi-component, multi-target nature presents significant challenges in elucidating pharmacodynamic mechanisms and optimizing clinical applications. Recent advances in network pharmacology (NP) and artificial intelligence (AI) offer innovative strategies to address these challenges. NP integrates compound-target-pathway-disease networks, while AI enhances predictive modeling, target prioritization, and the analysis of large-scale pharmacological data. Together, these approaches facilitate mechanistic interpretation, rational formulation, and personalized use of *Ganoderma*-derived medicines. This review highlights recent progress in applying NP and AI to identify key bioactive constituents and therapeutic pathways of *Ganoderma* spp., while also addressing limitations related to data quality, standardization, and clinical translation. By emphasizing the synergy between traditional TCM theory and modern computational technologies, this integrative approach advances natural medicine research and holds promise for strengthening the scientific foundation and global acceptance of *Ganoderma*-based therapeutics.

1. Introduction

Network pharmacology (NP) is an effective analytical framework that integrates systems biology and computational modeling [1]. Hopkins first introduced NP in 2008 as an approach that combines systems biology, computational modeling, and large-scale data analysis to explore the complex interactions among bioactive compounds, molecular targets, and disease mechanisms [2]. Unlike traditional pharmacology, which emphasizes single-drug, single-target interactions, NP provides a systems-level perspective on how sets of compounds interact within biological networks. This enables the elucidation of disease-gene-target-drug associations and facilitates drug repurposing [3]. The core concept in NP is that disease arises from disruptions in the equilibrium of biological networks; thus, restoring network protein balance is essential for therapeutic efficacy [4]. This strategy is particularly effective for complex diseases such as cancer, metabolic disorders, and neurodegenerative conditions, which involve multi-pathway and multi-component regulation [5]. Although NP is predominantly used in the development of synthetic drugs, it is equally vital for multi-component herbal medicines containing one or more bioactive molecules that act on multiple pathways [6]. As a multitarget therapeutic system, traditional Chinese medicine (TCM) is highly consistent with the principles of NP. For instance, in the complex mixtures of *Ganoderma* spp., NP facilitates the elucidation of synergistic interactions, the identification of therapeutic targets, and the modernization of TCM [7].

TCM has played a major role in treating numerous diseases in China for millennia, and its therapeutic applications are gaining increasing global recognition [8]. TCM's diagnostic and therapeutic principles are grounded in the concept of Qi (vital energy) and the Yin-Yang theory of balance. TCM encompasses diverse modalities, including massage, dietary therapy, herbal medicine, and acupuncture. These methods, refined over centuries of clinical use, are employed both to treat a wide array of diseases and to promote general health, drawing upon extensive empirical knowledge [9]. TCM also constitutes a significant source of natural products in drug discovery and development. Between 1981 and 2019, more than 60% of small-molecule drugs approved by the FDA were derived directly or indirectly from natural sources [10].

Among the diverse TCM herbs, *Ganoderma* spp. have been used as a medicinal remedy in TCM and across many Asian countries for over two millennia [11]. *Ganoderma* is a genus of polypore macrofungi that grows on decaying logs and tree stumps. Ganodermataceae, one of the largest families of polypores, comprises

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fourteen accepted genera [12, 13]. First described by Karsten in 1881, this genus comprises over 300 species of white-rot, wood-degrading fungi with the capacity to decompose lignocellulose. The medicinal use of *Ganoderma* can be traced back to 100 B.C. [14]. Its fruiting bodies exhibit glossy surfaces due to thick-walled pilocystidia embedded in an extracellular melanin matrix. The colors of *Ganoderma* fruiting bodies-red, black, blue, white, yellow, and purple-are influenced by geographic origin and cultivation conditions [15, 16].

Ganoderma is a well-recognized medicinal genus that has long been valued for enhancing vitality, promoting longevity, and supporting overall health. Modern studies have confirmed its broad therapeutic potential, which is attributed to more than 450 secondary metabolites identified in *Ganoderma* spp. As illustrated in Fig. 1, these bioactive compounds, including polysaccharides, triterpenes, and sterols, are responsible for diverse pharmacological activities, including immunomodulatory, antibacterial, antitumor, anti-inflammatory, lipid-lowering, antiatherogenic, antifungal, and antiviral effects [17–20]. However, significant interspecies variation within the *Ganoderma* genus results in differences in bioactive profiles and therapeutic efficacy, underscoring the necessity of species-specific evaluation for clinical and pharmacological applications [21].

In the 1990s, TCM and NP began to converge, with TCM-NP research formally initiated in 1999 when Li Shao of Tsinghua University proposed linking TCM to biomolecular networks at the annual meeting of the China Association for Science and Technology [22]. Subsequent research has demonstrated that NP shares fundamental characteristics with TCM. The systems-based methodology of NP aligns closely with TCM's holistic philosophy, rendering the two approaches highly complementary [23, 24]. A comprehensive literature review covering the past 20 years was conducted using the keywords "NP", "TCM NP", and "herb NP" in reputable databases including Web of Science, PubMed, and CNKI. The findings indicate that NP has been widely employed to investigate and elucidate the pharmacological mechanisms underlying TCM [25–27]. Among TCM herbs, *Ganoderma* spp. have attracted considerable attention due to their extensive pharmacological properties. NP has provided an effective platform for deciphering the complex mechanisms responsible for their therapeutic potential [28].

Research on *Ganoderma* spp. has evolved from basic phytochemistry to systems-level analyses of intricate networks involving targets, compounds, and pathways [29]. Given the non-linear nature of these interactions, sophisticated computational methods are required to manage high-dimensional omics data and uncover underlying pharmacological mechanisms [30]. Contemporary TCM research increasingly employs artificial intelligence (AI) to address the growing complexity of compound–target–pathway interactions in *Ganoderma* spp. Through large-scale mining of pharmaceutical and biomedical databases, AI facilitates the identification of bioactive compounds and therapeutic targets in *Ganoderma*. Applications of AI in *Ganoderma*-focused TCM research include herbal compound detection [31, 32], novel drug discovery [33], disease diagnosis [34, 35], elucidation of pharmacological mechanisms [36], and NP [37–39]. These advances have been accelerated by recent improvements in AI algorithms and access to large datasets [40–42], leading to enhanced target prediction accuracy, deeper insights into multi-compound interactions, and expanded therapeutic potential of *Ganoderma* spp. in modern TCM research [43, 44]. Concurrently, the integration of AI with multi-omics sequencing technologies offers new support for precision TCM. A primary methodological challenge in NP is the transition from the conventional machine learning (ML) paradigm, which emphasizes object characteristics, to approaches that capture relationships among features, thus expanding the feature space and facilitating feature augmentation [45].

This review proposes that NP provides a systematic approach to understanding the multi-component and multi-target nature of TCM. It emphasizes the use of computational tools and integrated databases to identify bioactive compounds, predict molecular targets, and construct herb-compound-target-disease networks. The review further elaborates on how AI can enhance NP analysis through techniques such as target prioritization, network toxicology, and network relationship mining. The complex pharmacological effects of *Ganoderma* spp. are comprehensively elucidated by integrating NP and AI, highlighting their significance in modern herbal medicine and drug development.

2. Methods and strategies of reviewing

To gather literature on *Ganoderma* spp., a comprehensive search was conducted in PubMed, Web of Science, Scopus, ScienceDirect, and Google Scholar. Eligible sources included original English-language research articles, reviews, books, theses, dissertations, patents, and reports addressing NP, AI, phytochemistry, toxicity, and global dissemination. The most relevant studies were selected for synthesis after records were identified, screened, and assessed for eligibility according to the PRISMA methodology. Reference lists of key articles were also examined to identify additional sources not captured in database searches, ensuring a thorough and rigorous analysis of the available evidence.

2.1. Understanding Databases and Data Analysis Strategies in NP

Large biological databases containing diverse data on drug-gene-disease interactions form the foundation of NP research. Although these databases were developed with distinct yet related objectives, they serve as essential resources for NP-based investigations [46]. Within the TCM framework, the integration of systems biology has become increasingly significant for clarifying pharmacological mechanisms, therapeutic efficacy, and safety profiles. This systems-level approach is pivotal in transitioning TCM from an experience-based practice to an evidence-based medical paradigm. NP, as an interdisciplinary methodology, facilitates comprehensive analysis of complex herbal formulations and their interactions with biological networks [47, 48]. TCM-related resources are accessible *via* the Web [49].

Several specialized databases support drug development research, offering comprehensive coverage from compound identification to clinical interpretation, as summarized in Table 1. For compound and target exploration, TCMSP, ChEMBL, DrugBank, SwissTargetPrediction, and NPASS provide data on bioactive molecules, drug-target interactions, and in silico predictions [49–51]. Additional protein-related information can be extracted from UniProtKB and the Protein Data Bank (PDB), while curated or predicted protein-protein interactions (PPIs), critical for understanding molecular mechanisms, are available through OPHID, STRING, BioGRID, and HPRD. Drug target identification tools such as PDTD, TTD, and PharmGKB enable investigation of therapeutic targets and their associations with drugs and diseases [52, 53]. Pathway analysis databases, including Kyoto Encyclopedia of Genes and Genomes (KEGG), Reactome, and Signalink, supply data on molecular networks and signaling pathways. OMIM, COSMIC, and HPO link genomic, phenotypic, and mutation data to human disorders, providing access to disease-related information [54–56]. Furthermore, SwissADME and pkCSM support ADME profiling and toxicity prediction, aiding pharmacokinetic and safety evaluation [57].

TCM-Mesh, a more recent TCM database, embodies the foundational concept of TCM-NP. By leveraging these biological databases and clinical trial data, researchers can analyze the "herbs-compounds-proteins/genes-diseases" interaction net-

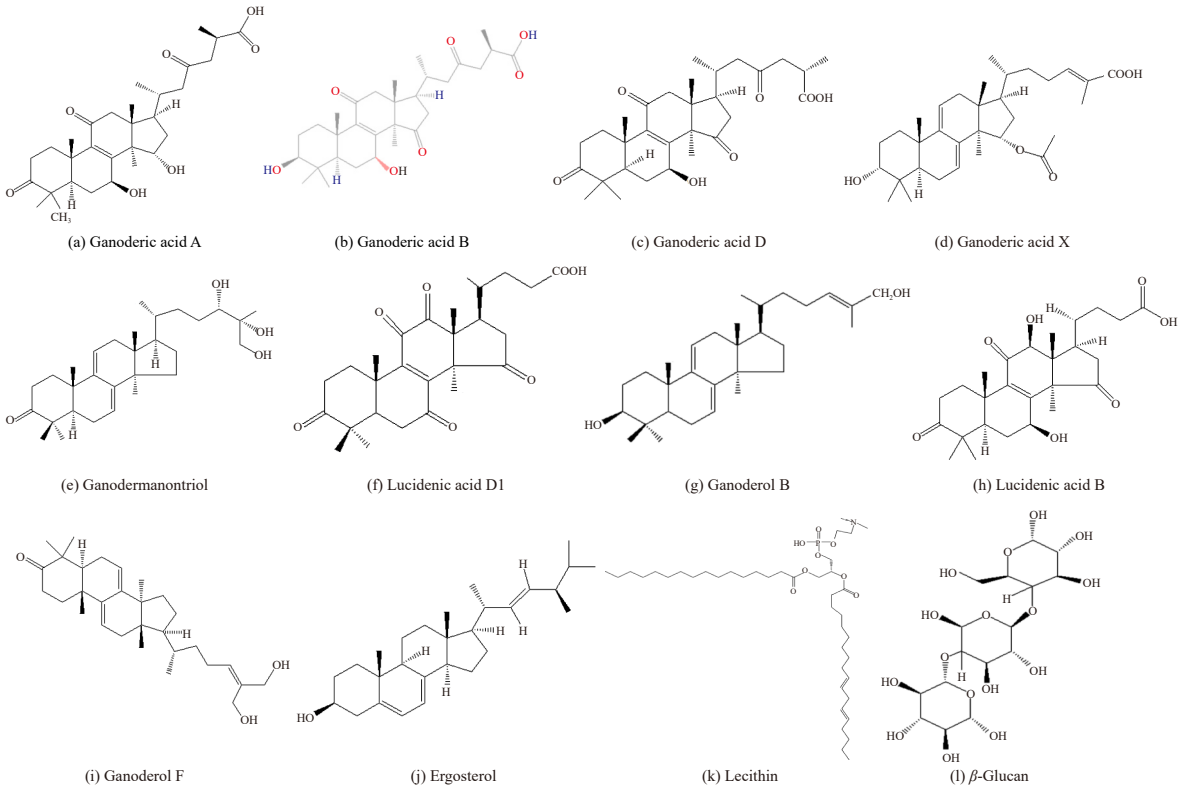

Fig. 1 Functional bioactive compounds derived from *Ganoderma* spp.

work from a systems biology perspective, thereby elucidating how herbs influence disease states [58]. Moreover, NP tools and algorithms are crucial for knowledge mining within these datasets. The Random Walk method, for example, is a widely used network clustering technique that constructs a "drug-target-disease" network by assessing the similarity between a random node (drug, target, or disease) and its neighboring nodes [59]. Additionally, the PRINCE strategy [60] prioritizes disease genes and infers protein complex associations by imposing smoothness constraints on the prioritization function across the network and incorporating prior information. Visualization is a critical component of NP, enhancing the intuitiveness of networks beyond mere data collection and processing. Cytoscape, an open-source tool, enables the display of biological pathways and molecular interaction networks and allows integration with annotations, gene expression profiles, and other state data. Pajek is another advanced network analysis tool suited for examining complex non-linear networks [61].

Within this systems-level, database-driven research framework, TCM continues to draw upon a broad spectrum of botanical and fungal species with centuries of traditional use. Among these, medicinal fungi hold a prominent position, with genera such as *Ganoderma*, *Cordyceps*, *Lentinula*, *Inonotus* and *Phellinus* distinguished by their extensive historical applications and growing relevance in modern NP studies, as illustrated in (Fig. 2). Renowned for their rich pharmacological profiles, including immunomodulatory, antiinflammatory, antioxidant, and anticancer properties, these fungi have played central roles in traditional formulations [76-79].

While *G. lucidum* is the most extensively studied species, researchers are increasingly focusing on *Ganoderma* spp. native to Himalayan tree trunks [80]. The high-altitude environment, characterized by extreme temperature fluctuations and nutrient-poor soils, has driven the evolution of *Ganoderma* spp. with unique metabolic adaptations and potentially enhanced therapeutic properties. By applying NP tools and systems biology approaches, researchers are beginning to decipher the complex molecular mechanisms through which these Himalayan *Ganoderma* species exert their medicinal effects [81]. This integrative approach not only validates the traditional TCM uses of *Ganoderma* but also expands the potential for discovering novel natural therapeutics [82].

Recent NP-based investigations have comprehensively examined various medicinal fungi within the TCM context, identifying their bioactive compounds, molecular targets, disease associations, and the computational tools employed in these analyses, as detailed in Table 2, reflecting the expanding scope of this research field.

2.2. NP in *Ganoderma* spp. with experimental approach

The pharmacological effects of *Ganoderma* spp. are largely attributed to the synergistic interactions among their diverse bioactive compounds. In this review, compound synergy was analyzed using the Network Target-Based Identification of Multicomponent Synergy algorithm, which quantifies interactions through a Topology Score and Agent Score to generate a Synergy Score representing the combined therapeutic potential [107]. Molecular structures of these compounds were retrieved from PubChem and Chemical Book and converted to PDB format using Open Babel. Energy minimization of these structures was performed using HyperChem. Potential target proteins were identified *via* TCMSP and DrugBank, with their 3D structures sourced from the PDB [108]. Molecular docking was performed using AutoDock 4.2.6 and AutoDock Tools for protein–ligand preparation and optimization, followed by docking simulations with the Lamarckian genetic algorithm (LGA). The lowest-energy conformation was selected for subsequent analysis. KEGG pathway and Gene Ontology (GO) enrichment analyses were conducted using DAVID with a significance threshold of $P < 0.05$. Additionally, databases including HIT, TCMSP, TCM Database, and TCM-PTD were used to screen active compounds from *Ganoderma* spp. based on drug-likeness (≥ 0.18) and oral bioavailability (OB > 0.3) [109]. Identified-compound-target and predicted-compound-target networks were constructed, as shown in (Fig. 3), and their

Table 1 Integrative computational and database resources for pharmacological and bioinformatics research.

Category	Resource Name	Website/Tool Type	Primary Application	Data Classification	Key Features	Access Link	Reference
Databases	TCMSP	Online Database	Bioactive compounds, ADME properties, and target prediction	Compound-Target Data	Specializing in TCM pharmacology	https://tcmsp-e.com/	62
	DrugBank	Online Database	Drug-target interactions and pharmacokinetics	Drug-Target Data	Includes clinical and experimental drugs	https://go.drugbank.com/	63
	SwissTargetPrediction	Computational Tool	In silico target prediction for small molecules	Target Prediction Models	Ligand-based target prediction	http://www.swisstargetprediction.ch/	64
	STRING	Online Database	Protein-protein interaction networks	Protein-Protein Interaction	Experimental and predicted PPI data	https://string-db.org/	65
Pathway analysis	KEGG	Online Database	Functional pathway mapping and enrichment analysis	Pathway & Network Data	Metabolic and disease pathways	https://www.kegg.jp/	66
	Reactome	Online Database	Biological pathway and molecular interaction analysis	Pathway & Network Data	Human-focused pathway database	https://reactome.org/	67
Molecular docking	AutoDock	Software	Structure-based molecular docking simulations	Molecular Docking Models	Open-source docking tool	https://autodock.scripps.edu/download-autodock4/	68
Pharmacokinetics & ADME	SwissADME	Computational Tool	ADME profiling and bioavailability prediction	Pharmacokinetics & Toxicity	Includes BBB permeability predictions	http://www.swissadme.ch/	69
Gene & protein data	UniProt	Online Database	Protein sequence, structure, and function annotations	Protein Function & Annotation	Comprehensive protein knowledge base	https://www.uniprot.org/	70
	GeneCards	Online Database	Gene-specific biomedical and genomic data	Gene Function & Annotation	Integrates multi-omics datasets	https://www.genecards.org/	71
Nutraceutical databases	NPASS (Natural Product Activity & Species Source Database)	Online Database	Bioactive natural products and species sources	Natural Products Database	Integrates chemical and biological activity data	https://bidd.group/NPASS/	72
	SuperNatural II	Online Database	Comprehensive collection of natural compounds	Natural Products Database	Focuses on bioactive natural molecules	https://bioinf-applied.charite.de/supernatural_new/index.php	73
Disease-target associations	DisGeNET	Online Database	Disease-associated gene and target information	Disease-Target Data	Integrates various human disease datasets	https://www.disgenet.org/	74
Toxicity prediction	ToxCast	Online Database	Predictive toxicity data for chemical compounds	Toxicity Screening Data	High-throughput toxicity screening	https://comptox.epa.gov/dashboard	75

topological properties were evaluated using betweenness centrality (BC), closeness centrality (CC), and degree (De). Hub nodes were determined using threshold values of Avg (BC), Avg (CC), and Avg (De). Overlapping nodes between the two networks were proposed as potential biomarkers for evaluating the efficacy of *Ganoderma* extract [110, 111]. This integrated approach provides a comprehensive understanding of bioactive compounds, their molecular targets, and the synergistic mechanisms underlying *Ganoderma* spp. pharmacology.

To experimentally validate key components predicted by NP tools, Hepa1-6 cells were cultured in DMEM supplemented with 10% FBS and penicillin-streptomycin, and tumor-bearing C57BL/6 mice were used to model the effects of *Ganoderma* spp. [112]. Mice were randomly assigned to three groups: control, model, and *G. lucidum* extract (GLE). Tumor volumes were measured every three days, and mice received oral administration of sodium chloride solution for 28 days, with dosing adjusted using a human-to-mouse conversion factor. Tumor formation was confirmed by histopathological examination using H&E staining, and tissue sections were analyzed with a pathological image analysis system. Quantitative real-time polymerase chain reaction (qRT-PCR) was performed to quantify mRNA expression, with ACTB serving as the housekeeping gene. Western blotting was used to assess protein expression of key biomarkers, including NR3C1, NR3C2, AR, PGR, ESR1, and CHRM2, in tumor tissues. Proteins were separated by SDS-PAGE and detected *via* immunoblotting using primary and secondary antibodies. Protein concentrations were determined using the BCA assay. This multidisciplinary computational and experimental approach has yielded a detailed understanding of the bioactive compounds in *Ganoderma* spp. and their therapeutic effects on tumor growth and molecular targets [112].

2.3. Multi-target mechanisms and disease-associated gene prediction of Ganoderma spp.

To systematically evaluate the pharmacological potential of *Ganoderma* spp., we employed an integrated "effect-compound-target-biomarker" model inspired by the Q-marker approach [113–114]. This framework emphasizes the identification of quality markers that reflect both therapeutic efficacy and safety [115]. Rooted in Q-marker theory, the approach advances toward the discovery of functional biomarkers by considering their pharmacological relevance and disease-specific targeting [116].

According to TCM theory, biomarkers are measurable indicators that reflect therapeutic efficacy and safety through the interaction between active ingredients and biological responses. Their definition adheres to five core principles: (1) they must be present in herbs, extracts, or formulations; (2) they must be de-

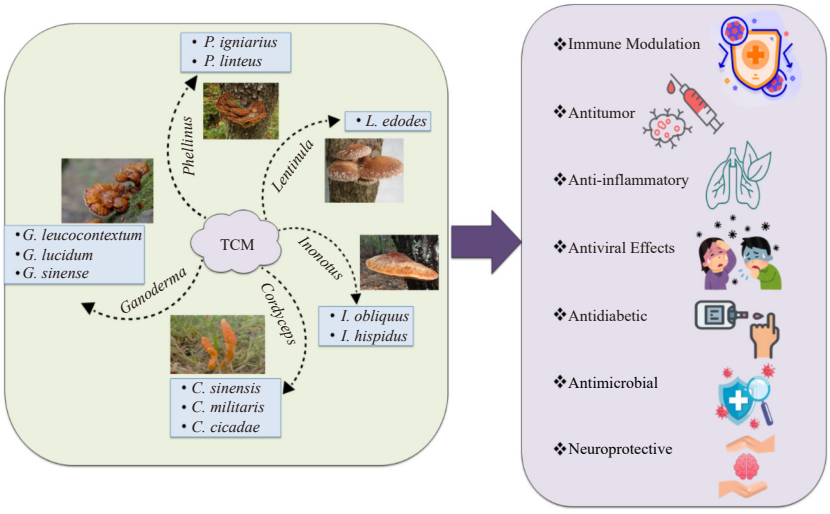

Fig. 2 Overview of major medicinal fungi used in TCM and their principal therapeutic activities.

Table 2 Cases integrating NP with its associated disease.

Ganoderma spp.	NP tool used	Extract type	Protein/ target gene	Diseases association	References
G. lucidum	DisGeNET	Ethanolic extract	(HSPB1, PDGFRB, PRKCB, PRKCA, MAPK14, RELA, and PLA2G4A	Atherosclerosis	83
G. lucidum	Gene Cards, OMIM, PharmGkb	Ethyl acetate	AR, CHRM2, ESR1, NR3C1, NR3C2 and PGR	Anticancer	84
G. lucidum	GeneCards and OMIM databases	Ethanolic extract	Caspase-3 (CASP3), caspase-8 (CASP8), caspase-9 (CASP9) and B-cell lymphoma-2 (BCL2)	Gastric cancer	85
G. lucidum	DisGeNET and GeneCards	Ethanolic extract	SRC, MAPK1, MAPK3, HSP90AA1, TP53, PIK3CA, and AKT1	Chronic metabolic disease	86
G. lucidum, sanghuangporus vaninii	SwissTargetPrediction, DisGeNET, and GeneCards	Ethanol extract, ethyl acetate extract	CYP24A1 and TERT	Anticolorectal cancer	87
G. lucidum	Gene Cards, OMIM, PharmGkb, TDD, and Drugbank	-	ADRB2, OPRM1, SLC6A4, and JUN	Lung cancer and the immune infiltrating cells.	88
G. lucidum	TTD, BATMAN-TCM, and Uniprot	Ethanolic extract	CASP3, PRKACA, CYP19A1, NR3C1, JUN	Diabetes mellitus	89
G. lucidum	Swiss Target Prediction and TCMSP databases	-	TNF, CASP3, JUN, and HSP90αA1	Anti-insomnia effect	90
G. lucidum	Swiss Target Prediction and TCMSP databases	-	P53, TNF, CASP3, and IL6.	Optic atrophy	91
G. lucidum	GeneCards, DisGeNET	Ethanolic extract	INS, TP53, AKT1, SRC, MAPK3, MAPK1, ESR1, IL6, HRAS, and CASP3	Endometrial Cancer	92
G. leucocontextum	SwissTargetPrediction, PharmMapper, STITCH	Ethanolic extract	TNF, IL6, B-cell lymphoma 2, cellular tumor antigen p53, Caspase-3 subunit p12, JUN, IL1B	Lung inflammation	93
Cordyceps sinensis	SwissTargetPrediction, STRING, KEGG	Aqueous extract	AKT1, TNF, IL6, TP53, VEGFA	Diabetic Nephropathy	94
Cordyceps cicadae	SwissTargetPrediction, STRING, GeneCards	-	ALB, GAPDH, CASP3, MAPK1, FN1, and IL-10	Renal Ischemia/Reperfusion Injury	95
Grifola frondosa	Metascape, Cytoscape, GeneMANIA	Aqueous extract	Gck, Scd, Abcb4, and Cyp3a9	Antidiabetic	96
Lentinula edodes	SEA, STP, OMIM, and DisGeNET	Ethanolic extract	FAAH, TNF, PPARG, PPARD, and PPARA	Obesity	97
Phellinus igniarius	STITCH and TCMSP	Ethanolic extract	Bax, Bad, PARP, Caspase-3, Bcl-2	Antitumor	98
Inonotus hispidus	TCMSP, SwissTargetPrediction, STITCH, UniProt	Aqueous ethanol extract	HSP90AA1, AKT1, STAT3, EGFR, ESR1, PIK3CA, HIF1A, ERBB2, TERT, EP300 and HSP90AB1	Antitumor	99
Armillaria ostoyae mycelia	GeneCards, DrugBank, DisGeNET, PharmGKB	Ethanolic extract	EGFR, SCR, and IL6	Gastric cancer	100
Ophiocordyceps sinensis	Metscape, STRING	Methanolic, aqueous extract	SRC, RHOA, HSP90AA1, VEGFA, ITGB1, PRKCA, and ITGA1	Antiinfluenza properties	101
Antrodia camphorata	KEGG	-	Tnfα, Il6, and Ppary	Antidiabetic activity	102
Morchella esculenta	NPASS, GeneCards, DisGeNET	Ethanolic extract	NR1I2, PTGS1, PTGS2, PLA2G4A, MAPK1, CYP3A4, and TLR4	Anti-inflammatory	103
Cordyceps militaris	TCMSP database	Aqueous extract	TNF, MAPK3, CASP3, VEGFA, and STAT3	Immunomodulatory Activity	104
Pleurotus osteratus	KEGG	Ethanolic extract	NR1H2, MMP13, CHRNB4, CA2, CSF1R, HMGCR, COMT, ROS1, FABP3, SHBG, TKT	Anticancer activity	105
Chroogomphus rutilus	SuperPred, PharmMapper, SwissTargetPrediction, and Target Net	Ethanolic extract	AKT1, ESR1, SRC, ERBB2, EGFR, CCND1, KDR, PTGS2, MET, and AR.	Liver cancer	106

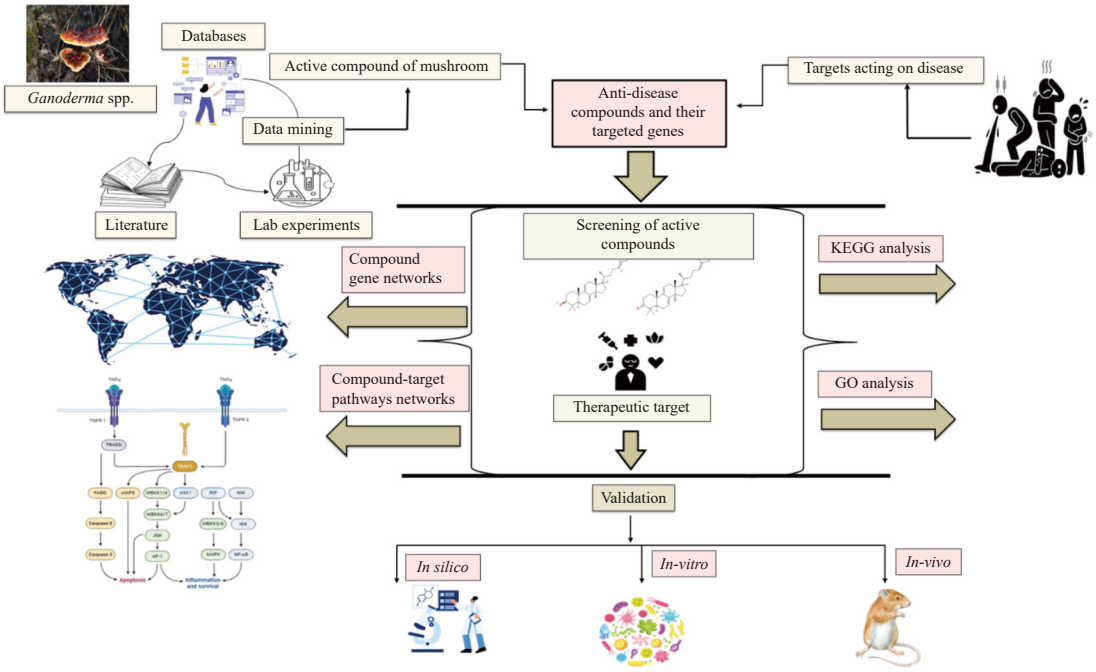

Fig. 3 Flowchart illustrating the network pharmacology analysis of *Ganoderma* spp. bioactive compounds, including target prediction, molecular docking, and pathway enrichment ($P < 0.05$).

tectable *via* qualitative or quantitative methods; (3) they must correlate with biological effects relevant to safety and efficacy; (4) they must align with TCM principles, such as compatibility theory and syndrome differentiation; and (5) they must be traceable throughout production and preparation. These criteria enable the integration of traditional knowledge with modern pharmacological validation and quality control [117-119]. When combined with advanced technologies, this scientific quality assurance system is particularly effective in ensuring the efficacy and safety of TCM products [120].

NP analyses reveal that *Ganoderma* spp. constituents simultaneously engage multiple targets and signaling pathways, underpinning their broad pharmacological effects. Recurrently predicted protein targets include kinases, transcription factors, receptors, and cytokines. For example, studies have identified kinases such as SRC, mitogen-activated protein kinase 1/3 (MAPK1/3), protein kinase B 1 (AKT1), and PIK3CA (phosphatidylinositol 3-kinase, PI3K) as key nodes in signaling cascades modulated by *Ganoderma* triterpenes, particularly within the PI3K-AKT pathway, which plays a pivotal role in metabolic regulation and cancer progression. In the context of type 2 diabetes (T2DM), triterpenes were predicted to modulate SRC, AKT1, MAPK1/3, insulin secretion pathways, and endocrine resistance mechanisms [121].

Additionally, Zhao et al. [112] screened 122 effective active compounds of *G. lucidum* and predicted 116 targets from public databases. An identified-compound-target network was constructed (Fig. 4A), followed by a predicted-compound-target network using the screened compounds (Fig. 4B). Network parameters, BC, CC, and De, were calculated, yielding 18 hub targets, including ABCB1, ACHE, AR, CHRM1, CHRM2, CHRM3, CHRNA2, ESR1, F2R, GABRA1, GABRA2, HTR2A, NR3C, OPRK1, OPRM1, PGR, and PRSS1 (Fig. 4C). These hub targets may be critical for evaluating *G. lucidum* properties. Based on overlapping nodes between the identified and predicted compound-target networks, six hub targets, NR3C, AR, PGR, ESR1, and CHRM2, were identified (Fig. 4D) and proposed as potential indicators for assessing the efficacy of GLE in tumor therapy. Collectively, these findings provide an initial mechanistic understanding of GLE pharmacology, suggesting its potential as a therapeutic and chemopreventive agent against cancer, as illustrated in Fig. 4.

Furthermore, in models of neurodegenerative and cognitive disorders, *Ganoderma* extracts demonstrated cognitive-enhancing effects. Network analysis of a learning/memory impairment (LMI) model identified 21 active compounds, notably β-sitosterol, lucidenic acids, and lucidumol A, targeting 59 genes involved in synaptic signaling, with Alzheimer's disease and tumor necrosis factor (TNF)/nuclear factor κB (NF-κB) inflammatory pathways prominently enriched. TNF emerged as the most significant protein associated with cognitive effects. A visual network linking *Ganoderma* compounds (yellow) to LMI-related targets (green) highlights the multi-target action [122].

Key inflammatory mediators, including TNF, interleukin-6 (IL-6), caspase-3 (CASP3), and PTGS2 (COX-2), are consistently implicated across inflammatory, metabolic, and neurodegenerative models. In an optic nerve atrophy network analysis, TNF, CASP3, IL-6, and p53 (TP53) ranked as top nodes, while a diabetes-related study identified overlapping roles for CASP3/9, BCL2, and JUN [123–124]. Pathway enrichment analyses frequently converge on several core signaling systems, including PI3K-AKT, MAPK/ERK, apoptosis, and inflammatory pathways. For instance, 53 *G. lucidum* triterpenoids were linked to PI3K-AKT, Rap1, and lipid/atherosclerosis pathways in a T2DM network. Similarly, insulin secretion, AGE-RAGE (diabetic complications), and adrenergic signaling were significant in one diabetes study. Immune-related pathways (NF-κB, cytokine signaling) and neurodegenerative pathways (Alzheimer's disease signaling) also emerged in CNS-focused investigations [121–122, 124].

Therapeutically, *Ganoderma* spp. have been associated with multiple disease areas. Their antitumor potential remains the most prominent, with network studies in hepatocellular carcinoma (HCC) and colorectal cancer (CRC) implicating steroid hormone receptors (AR, ESR1, PGR) and apoptosis regulators as key targets (Fig. 5). In HCC, *Ganoderma* extract modulated tumor growth by targeting AR, ESR1, NR3C, and PGR, with enriched pathways including "Pathways in cancer" and "apoptosis" [113]. Integration with transcriptomic analysis further revealed the regulation of lncRNAs and cell cycle pathways. In CRC, NP combined with multi-herb formulations implicated immune-cell regulation and oncogenes such as CCND1 [125].

To enhance the clinical relevance of NP-AI predictions, several case studies have been critically evaluated. Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by joint inflammation and destruction, and resveratrol exhibits anti-inflammatory and immunomodulatory potential as a therapeutic agent. In a recent study, NP and AI platforms were integrated to elucidate resveratrol's mechanisms in RA. Using the GSE205962 dataset, 2202 differentially expressed genes (DEGs) were identified, and 47 putative therapeutic genes (PT-genes) were determined by intersecting DEGs with resveratrol pharmacophore targets predicted by PharmMapper and visualized in Cytoscape. Functional annotation (GO and KEGG) revealed PT-gene involvement in metabolic pathways, insulin signaling, chemokine signaling, and cancer pathways, with 36% overlap between resveratrol targets and DEGs. A PPI network and cytoHubba MCC algorithm identified nine key therapeutic genes (ABL1, ANXA5, CASP3, HSP90AA1, LCK, MAP2K1, MAPK1, PIK3R1, RAC1). AlphaFold-based AI-assisted protein structure prediction and molecular docking further confirmed strong resveratrol binding to these targets (binding energies: −6.4 to −8.4 kcal·mol^{-1}), demonstrating an integrated NP-AI approach to uncover resveratrol's mechanisms and therapeutic targets in RA [126].

Likewise, T2DM is a serious condition with severe complications, and celastrol shows promise in reversing insulin resistance. In a recent study, combined with AI was used to explore the mechanisms of celastrol. Analysis of 618 DEGs from blood samples of patients with type 2 diabetes mellitus (T2DM) identified nine hub genes, including *HBB*. Pharmacophore-based NP screening identified 228 potential celastrol targets, which were overlapped with the DEGs to reveal key therapeutic genes, such as *S100A11*, *HBB*, and *BMP7*, and nine signaling pathways, including TGF-β. AlphaFold2-assisted structure prediction and molecular docking further supported the binding of celastrol to these targets. This NP–AI approach suggests that celastrol acts through hub genes and signaling pathways, providing mechanistic insights and supporting its potential clinical application [127].

Similarly, Xiaokewan, a TCM used for diabetes treatment, contains multiple natural compounds and glibenclamide. Using an AI-supported NP strategy, five major hypoglycemic constituents, puerarin, daidzein, formononetin, deoxyschizandrin, and glibenclamide, were identified *in vivo*. NP analysis indicated these compounds act on PI3K, PTP1B, MAPK, AKT, TNF, and NF-κB targets, modulating β-cell function and inflammation. Hypoglycemic activity was confirmed in a zebrafish diabetic model, with deoxyschizandrin exhibiting the strongest effect. This work demonstrates that integrating intelligent mass spectrometry recognition, NP, and computer-aided target prediction is effective for elucidating TCM mechanisms and identifying lead compounds [128].

When combined with clinical or experimental validation, these findings show how the AI-NP When combined with clinical or experimental validation, these findings illustrate how the AI-NP approach can reliably predict therapeutic targets and pathways, thereby strengthening the foundation for clinical translation. Discrepancies in hub gene identification, pathway enrichment, and compound efficacy across studies highlight the need for rigorous dataset selection, appropriate algorithmic choices, and experimental verification to maximize the translational applicability of NP-AI predictions [129–130]. Concurrently, applying NP-AI outcomes to clinical practice requires overcoming regulatory and practical challenges. Regulatory approval pathways demand stringent safety assessments, reproducibility, and standardization of NP formulations, particularly for multi-component natural products or TCM-derived molecules. Practical implementation also entails coordination with conventional therapies, optimization of dosing and delivery, and ensuring pharmacokinetic consistency across diverse patient populations.

2.4. Exploring the clinical studies based on Ganoderma spp.

Unlike the traditional reductionist one-drug-one-target paradigm, NP facilitates the mapping of diverse phytochemicals to multiple biological targets and disease pathways. TCM fungi rich in polysaccharides, triterpenoids, and sterols are particularly amenable to NP-guided research due to their pleiotropic pharmacological actions. Recent studies have shown that NP not only predicts the therapeutic potential of these fungi but also informs clinical validation strategies, thereby bridging traditional wisdom with modern biomedical science. For example, a study conducted by Zhao et al. [112] identified compounds from GLE, including ganoderic acids (A, B, D, H, Y), genistein, and ergosterol. Molecular docking revealed direct compound-target interactions, while database-driven analyses predicted 122 effective compounds and 116 targets. By integrating the identified and predicted compound-target networks, six hub targets were highlighted: AR, CHRM2, ESR1, NR3C1, and PGR. Among these, ESR1 and PGR were significantly upregulated, and AR was significantly downregulated in GLE-treated Hepa1-6-bearing C57BL/6 mice, as validated by qRT-PCR and Western blotting. Additionally, GLE treatment effectively suppressed tumor growth *in vivo*, supporting its anticancer potential.

Similarly, recent studies have applied this framework to evaluate the pharmacodynamics of various *Ganoderma* spp. Qian et al. [131] investigated the therapeutic effects of GLE against silicosis using NP, molecular docking, and animal experiments. A total of 76 compounds were identified by UPLC-QE-MS, with 36 meeting drug-likeness criteria and 67 potential targets linked to anti-inflammatory activity. Network analysis emphasized interleukin and cytokine signaling pathways, particularly involving TNF, IL-6, IL-1β, and Caspase-3. Glycyrrhetinic acid and ganoderic acid DM showed strong binding affinity in molecular docking. *In vivo*, an experiment in silica-exposed mice demonstrated that GLE reduced lung inflammation, fibrosis, and significantly suppressed IL-6 expression, although TNF-α and IL-1β remained unchanged. These findings suggest that GLE acts through multi-component, multi-target immunoregulatory mechanisms, particularly *via* IL-6 suppression. These case examples indicate the translational applicability of NP-based predictions and underline TCM fungi's growing clinical credibility, as seen in Table 3. Although it provides an overview of clinical investigations involving TCM medicinal fungi, the translational bridge between in silico prediction and clinical validation remains insufficiently addressed. Most mechanistic insights, such as PI3K/AKT, VEGF, or SIRT1/AMPK modulation, are inferred from computational or preclinical models, while outcomes largely emphasize symptomatic or biomarker improvements rather than mechanistic confirmation. Moreover, inconsistencies in formulation standardization and trial design limit reproducibility and translational reliability. Future studies integrating pharmacokinetic modeling, biomarker-guided validation, and multi-omics correlation are essential to strengthen mechanistic insights and clinical continuums for TCM fungal therapies.

2.5. Challenges and development in TCM-Based NP

TCM NP holds great promise for understanding the complex, multi-target action of herbal medicines, but it is currently affected by several major obstacles. The multifaceted and complex chemical composition of TCM formulations, which typically contain hundreds of bioactive molecules, makes it impossible to identify, characterize, and model one or more synergistic effects using traditional pharmacological procedures [150]. Furthermore, the discipline lacks standardized, integrated, and regularly updated databases. Available resources, such as TCMSP, TCMID, and HERB, while beneficial, exhibit scarce compound-target

Table 3 Summary of clinical investigations involving TCM medicinal fungi.

Fungal spp.	Bioactive compound	Mechanism insight	Clinical outcomes	Therapeutic focus	References
G. lucidum	Ganoderic acids, polysaccharides	Predicted modulation of PI3K/Akt and immune signaling;	Clinical trials showed improved immunity and quality of life in cancer patients	Immunomodulation, adjunct cancer therapy	132, 133
G. lucidum	*β*-glucans, sterols	Induction of apoptosis *via* caspase-3 and Bax/Bcl-2 signaling	Enhanced response to chemotherapy and improved immune indices in lung cancer patients	Apoptosis induction, lung cancer	134, 135
G. lucidum	Ganoderic acids, triterpenoids	Inhibition of VEGF, COX-2, and EGFR signaling	Tumor size reduction and improved survival as complementary therapy in hepatocellular carcinoma (HCC)	Anti-angiogenesis, hepatocellular carcinoma	136, 137
cordyceps sinensis	Cordycepin, adenosine, and polysaccharides	Regulation of oxidative stress and mitochondrial function (e.g., SIRT1, AMPK)	Improved renal biomarkers and stamina in CKD and aging patients	Antioxidant, renal protection, antidiabetic	138, 139
Lentinula edodes	Lentinan (*β*-glucan)	TLR2/4 and IL-10 pathway modulation, enhancing host immune response	Enhanced survival as an immunoadjuvant in gastric and colorectal cancer patients	Immune support in cancer therapy	140, 141
Grifola frondosa	*β*-glucans (D-fraction)	Predicted immune checkpoint regulation and glucose metabolism enhancement	Increased NK cell activity and lowered blood glucose in cancer and diabetic patients	Immunostimulant, antidiabetic	142, 143
Hericium erinaceus	Erinacines, hericenones	NGF pathway stimulation, neuroprotective and neurodegenerative activity	Improved cognitive performance in mild cognitive impairment patients	Cognitive enhancement, neuroprotection	144, 145
Antrodia camphorata	Anthraquinone, triterpenoids	Anti-inflammatory and hepatoprotective signaling modulation	Reduced liver enzyme levels in hepatitis B patients	Hepatoprotection	146, 147
Inonotus obliquus	Betulinic acid, polysaccharides	Suppression of inflammation and tumor proliferation pathways	Reported reduction in inflammatory markers and enhanced antioxidant capacity in patients	Anti-inflammatory, antioxidant support	148, 149

mappings, limited clinical data, and conflicting ontological models [151–152]. Another key hurdle is the lack of credible absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles for the majority of TCM substances, which hampers accurate drug-likeness prediction and safety assessment [153].

Furthermore, many computational predictions in NP remain theoretical and lack experimental confirmation, reducing translational significance. Additionally, most NP research relies on static, linear models that fail to capture the dynamic, individualized, and holistic perspectives inherent in TCM theory. TCM clinical practice is heterogeneous, with prescriptions typically individualized and context-dependent, which further limits reproducibility and model standardization.

Although classical NP focuses on the identification of bioactive compounds, targets, and pathways through experimental and computational methods, its integration with AI provides enhanced predictive capability, efficiency, and scalability [154–155]. To address this gap, a comparative framework is presented in Table 4.

While conventional NP has its uses, its effectiveness and scalability are limited by several inherent constraints [171]. The time-consuming and manual nature of typical NP techniques hinders the discovery process. However, AI accelerates data management and reduces human error by enabling the automated integration of diverse datasets, including multi-omics, clinical, and literary sources [172]. While AI employs ML and deep learning (DL) algorithms to uncover hidden patterns, enhance predictive reliability, and rank drug-target interactions with improved specificity, conventional NP approaches frequently suffer from poor prediction accuracy due to their reliance on static network inferences [173–174]. By efficiently constructing and evaluating large-scale dynamic biological networks, AI overcomes the significant complexity of representing multi-target and multi-disease interactions in traditional NP systems, leading to more comprehensive insights into disease systems and polypharmacology. This transformation is further illustrated in Fig. 4, which depicts the workflow of AI integration into the NP pipeline.

2.6. AI interpretability and clinical Trust

Interpretability of AI systems is a critical issue in natural product research, particularly when integrating prediction with TCM and clinical application [175]. DL models, and most AI approaches generally, are "black boxes," producing outputs without transparent explanations of their decision-making processes [176]. Such opacity can hinder clinician confidence, regulatory approval, and the real-world deployment of healthcare interventions. In NP-AI case studies such as resveratrol in RA, celastrol in T2DM, and Xiaokewan, interpretability methods can provide confidence in predicted targets, pathways, and compound efficacy [126-128]. To address this issue, various strategies have been developed. Model-agnostic techniques such as Shapley Additive Explanations (SHAP) and Local Interpretable Model-Agnostic Explanations (LIME) can identify which features, such as specific compounds, targets, or pathways, most heavily contribute to predictions [177]. In addition, visual representation of network-based compound-target-pathway interactions enables intuitive understanding of mechanistic relationships [178]. By integrating such interpretability tools, NP-AI research can provide more transparent and explainable predictions, facilitating clinical decision-making, regulatory approval, and, most importantly, the safe and effective translation of AI-augmented natural product science to patient care [179].

2.7. Emergence of AI solutions

Over the last decade or two, AI has emerged as a solution to many of the challenges listed above. AI, particularly ML and DL, excels at extracting, integrating, and interpreting large amounts of diverse data from chemical, biological, clinical, and text sources. Random forests, support vector machines, and graph neural networks (GNNs) are examples of ML algorithms that significantly enhance compound-target-disease prediction accuracy

Table 4 Advancing NP through AI: comparative insights.

Feature	Traditional NP	AI-enhanced NP	Key advantages of AI	References
Data sources	Restricted to known databases, literary curation, and experimental bioassays	Real-world datasets, literature, high-throughput screening, and multi-omics (genomics, proteomics, and metabolomics)	Integrates complex datasets for more comprehensive analysis	156-158
Compound target prediction	Docking, either semi-automated or manual, and *in-vitro* assays	Deep learning and machine learning models	Higher accuracy and identifies novel targets	159-161
Network construction	Utilising known interactions between proteins or compounds and their targets	AI-assisted network modeling, dynamic simulations, predictive network inferences	Identifies hidden links and ranks important nodes and routes	162-164
Pathway analysis	Static pathways enrichment using curated databases	AI-guided pathways prioritization, multi-pathway integration, system-level modeling	Identifies novel mechanisms and synergistic interactions	165, 166
Compound prioritization	Based on bioactivity, literature support	AI-driven models, predictive efficacy, and toxicity evaluation	More efficient and predictive for lead compound selection	167, 168
Validation	Experimental testing *In vivo* and *in-vitro*	*In silico* validation (docking, simulation) followed by targeted experimental validation)	Reduces time and experimental workload	169, 170

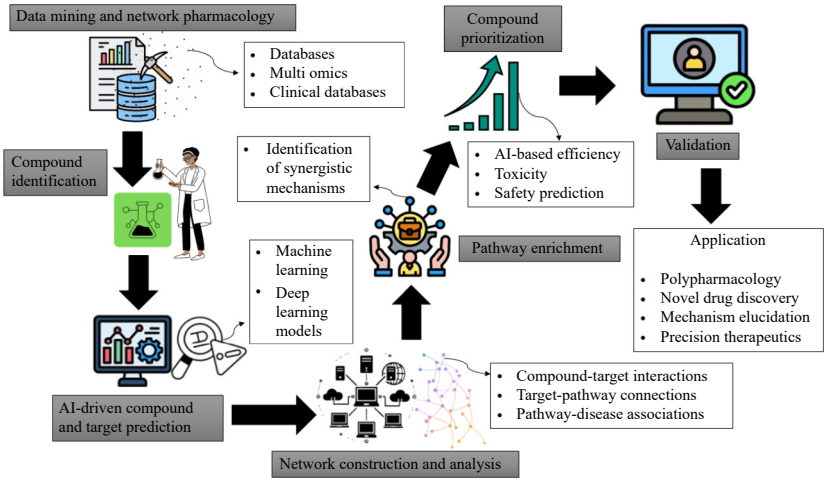

Fig. 4 Workflow diagram for the integration of AI in NP.

compared to traditional similarity-based or statistical inference methods [180]. AI also enables in silico prediction of pharmacokinetic and toxicological properties for understudied herbal substances, expediting early-phase screening and reducing reliance on costly wet-lab trials [181]. Finally, AI-based decision support systems are gradually evolving to offer precision medicine techniques that distinguish between an individual's constitution and syndrome, aligning with TCM's individualized treatment philosophy. Overall, by overcoming structural, computational, and epistemological barriers, AI integration is revolutionizing TCM NP and producing more reliable and translational research.

2.8. AI and bioinformatics in advancing TCM and Ganoderma-based therapies

Researchers studying herbal medicine can uncover profound relationships between chemical components, diseases, and targets using AI tools [182]. By illustrating the complex relationships and efficacious pathways of TCM components through pattern recognition and predictive models, AI facilitates the development of innovative therapeutic approaches and personalized medical treatments [183]. AI-driven deep analysis accelerates the discovery of new compounds and formulations while improving the precision and effectiveness of TCM treatments [184].

In addition to enhancing drug discovery, AI integration has significantly improved the search capabilities of *Ganoderma*-related TCM databases. ML algorithms enable intelligent semantic searches that can rapidly retrieve pertinent chemical, pharmacological, and clinical information, interpret user intent, and produce context-aware recommendations [185]. These enhanced tools support researchers in navigating large datasets, expediting the exploration of *Ganoderma*'s medicinal potential.

Applications of AI are also found in analytical chemistry, where liquid chromatography and mass spectrometry are coupled with AI-driven data analysis to screen TCM preparations. The synergy between these sophisticated techniques and AI-driven data enhances the efficiency and precision of identifying herbal constituents and their interactions, which is critical for formulation fine-tuning, quality control, and mechanism elucidation [186]. The combination of chemical profiling and AI not only strengthens characterization but also enables predictive modeling of herb-compound-target interactions [187]

Bioinformatics and AI are also essential in the functional evaluation and screening of *Ganoderma* spp. [188]. Grienke et al. [189] applied computational methods to predict which bioactive components of *G. lucidum* could be applied in nutraceuticals and functional foods. The authors built a database of biological activities and chemical structures from 279 *Ganoderma* constituents and employed in silico screening to simulate interactions of these compounds with biological targets related to viral infection and metabolic syndrome. Using 3D pharmacophore modeling, they elucidated how these compounds interact with specific targets and identified key molecular interaction properties. The researchers also used 3D molecular docking to predict the binding affinity of bioactive compounds to their targets, a widely used method for predicting molecular interactions in bioinformatics. Additionally, genome mining methods, such as screening fungal genomes for biosynthetic gene clusters (BGCs), are employed to identify those responsible for producing bioactive secondary metabolites [190]. Another study by Cao et al. [191] employed bioinformatic modeling of enzymes to predict g-cadinene-producing enzymes, a terpene molecule. The investigation aimed to identify and model the terpene synthases of *G. lucidum* and *G. sinensis*, including g-cadinene synthases. The researchers predicted and confirmed three g-cadinene synthases using bioinformatics tools. Using conserved amino acid patterns, they developed an initial enzyme model (model 1), which was refined into model 2 after screening 67 corresponding sequences from the NCBI database. Five sequences were empirically confirmed as g-cadinene synthases, and bioinformatics analysis showed that the conserved regions of both models were highly similar. This approach was also applied to other enzymes, such as (−)-*α*-bisabolol synthases from green plants and Δ6-protoilludene synthases from fungi [191].

In addition, molecular docking coupled with AI and ML has been effective in identifying bioactive molecules from *Ganoderma* spp. that exhibit therapeutic potential. Yang et al. used molecular docking and ML to predict the antitumor activity of compounds derived from *G. lucidum*. Molecular docking predicts binding affinity and activity by simulating the interaction between drug candidates and target biological proteins. The analysis achieved 86% accuracy; the combination of ML and molecular docking accelerates antitumor drug development and prioritizes candidates for experimental validation. Riahi et al. [192] improved the hot water extraction of *G. lucidum* polysaccharides using supervised machine-learning methods. To enhance the yield and bioactivity of the extracted polysaccharides by 10% and 20%, respectively, this study utilized supervised learning to optimize extraction parameters. This illustrates how ML can augment traditional bioprocessing.

Altogether, the integration of AI and bioinformatics with conventional medicine and *Ganoderma* research has transformed the discovery, assessment, and manufacture of therapeutic molecules. These technologies enable rapid data analysis, compound screening, mechanistic discovery, and bioprocess optimization. Together, they constitute a critical step toward accelerating fungal pharmacology and modernizing natural product drug

discovery, making AI a prime driver of precision *Ganoderma*-based phytotherapy and evidence-based innovation.

2.9. Technologies in the analysis of TCM-derived compounds

Research on natural products and drug development is being revolutionized by advanced AI technologies in TCM [193]. Complex herbal formulations with diverse therapeutic properties, such as *Ganoderma* spp., are a key component of TCM. However, traditional analysis is hampered by the structural complexity and chemical diversity of these compounds [194].

AI tools such as ML and neural networks provide strong capabilities for feature extraction, complexity reduction, and the modeling of chemical structures, bioactivities, and therapeutic effects. This strategy integrates TCM databases, spectral information, and predictive models, including ANN, SVM, and RF, to improve compound identification and evaluate pharmacological potential [195-196]. More advanced techniques, such as GNNs, DL, and multi-modal AI, are improving the understanding of complex herbal preparations by enabling analysis of the intricate interactions among chemical constituents, biological targets, and patient-specific factors [197]. GNNs are particularly adept at learning non-Euclidean structural data, such as biological interaction networks and molecular graphs, to naturally represent complex compound-target-pathway relationships inherent in TCM formulas [198]. A notable example is the application of such AI methods to *Ganoderma* spp., a hallmark medicinal fungus in TCM known for its rich triterpenoid content (e.g., ganoderic acid A, lucidenic acid), polysaccharide content (e.g., ganoderan A/B), and sterols with intricate structures and multi-target pharmacological profiles [199-201].

AI-based cheminformatics methods, including QSAR modeling and GNNs, employ chemical fingerprints and SMILES strings to perform structural classification, compound grouping, and biological activity prediction. DL tools such as DeepChem and ChemBERTa enhance initial screening by forecasting the drug-likeness, bioavailability, and ADMET properties of *Ganoderma* compounds [202, 203]. Compound-target interaction prediction platforms like DeepTarget, DeepDTI, and Mol2Vec have revealed multi-target regulatory activities of major compounds such as ganoderic acid A, which modulates the PI3K/AKT and MAPK pathways implicated in inflammation, cancer, and metabolic disorders [204-206].

AI-enhanced NP systems and knowledge graph frameworks enhance our capacity to model and analyze the intricate pharmacological networks of *Ganoderma*-based products. Kaliaperumal et al. [207] employed HPLC and NMR spectroscopy to identify and characterize secondary metabolites produced by Penicillium verruculosum. Molecular docking was used to predict metabolite interactions with biological targets, supported by precise chemical structure characterization. The authors demonstrated that the anticancer activity of these metabolites opens new prospects for functional food applications. Collectively, these studies reflect the broad potential of bioinformatics-based methods in the food sector, particularly in quality control. For screening and characterizing bioactive peptides in fungal extracts, mass spectrometry coupled with bioinformatics spectrum library searches was employed. High-resolution mass spectrometry enables comprehensive structural analysis of peptides. Concurrently, bioinformatics tools can predict potential biological activities such as antimicrobial effects, making them widely applicable in food preservation. Beyond food preservation, these methods also support taste enhancement and functional food development, with bioactive compounds discoverable through genome mining, molecular docking, and ML technologies [208]. The identification of natural antimicrobials, antioxidants, preservatives, and other bioactive compounds that enhance food quality, safety, and nutritional value similarly relies on these approaches.

Dong et al. [209] used NIR spectroscopy and DL to predict the polysaccharide content of Lentinula edodes. The study demonstrated, with 95.5% accuracy, that 1D-CNN models outperformed alternatives such as siPLS. This work offers new options for the food industry, particularly in quality control and nutrient profiling of edible mushrooms, ensuring products consistently meet consumer expectations. To differentiate bolete mushroom species, FT-NIR spectroscopy and DL, specifically residual neural networks (ResNets), were employed. ResNets utilize residual connections to optimize deep network training, enabling more efficient and rapid learning. The approach achieved 100% accuracy, highlighting the potential of DL for enhanced species identification. Additionally, Wang et al. [210] utilized Fourier Transform Near-Infrared (FT-NIR) spectroscopy to develop a DL approach for predicting the shelf life of Phlebopus portentosus. Coupled with two-dimensional correlation spectroscopy (2DCOS) and ML, the methodology provided rapid, non-destructive, and highly precise as-

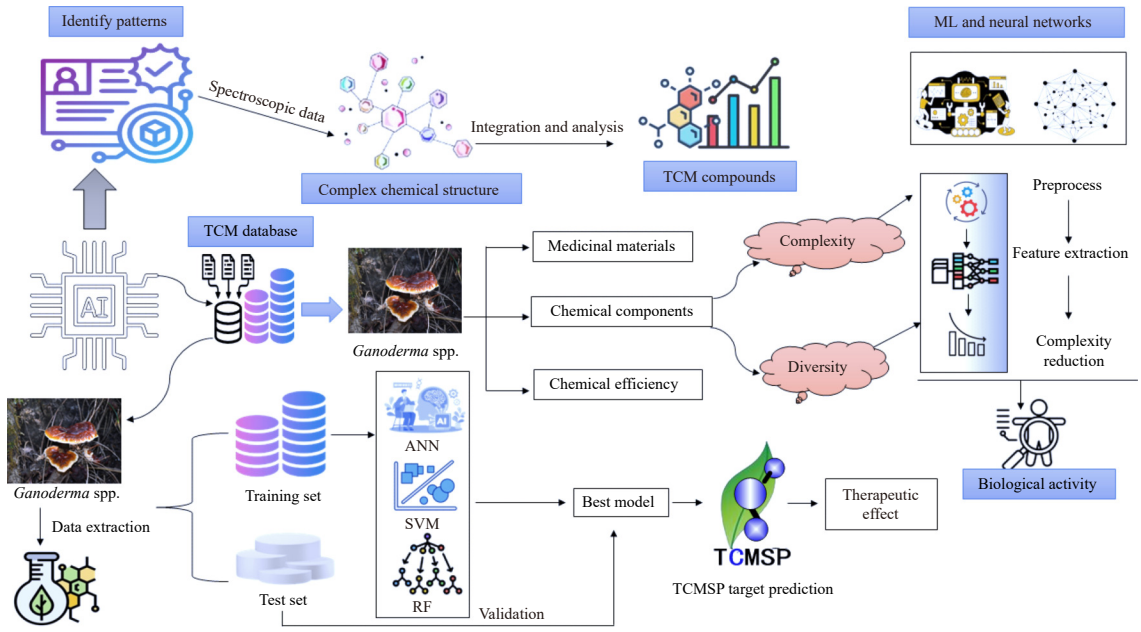

Fig. 5 AI-driven workflow for chemical component identification and therapeutic effect prediction in *Ganoderma* spp.

sessments of freshness. With its potential for prompt and accurate mushroom freshness analysis, this technology holds significant promise for improving food safety and minimizing waste. The integration of AI with conventional quantitative methods would further enhance the precision of detecting key chemicals in *Ganoderma* spp. samples, thereby improving in-depth profiling and quality control.

2.10. Challenges and future perspectives

The integration of NP and AI into TCM research, particularly concerning *Ganoderma* spp., offers both substantial opportunities and significant challenges. Notably, various constraints, including database reliability and algorithm selection, affect NP predictions, which depend on the quality and completeness of underlying databases; different algorithms can yield divergent results. For example, the common use of oral bioavailability and drug-likeness as criteria for selecting active ingredients may overlook important compounds, potentially leading to incomplete and biased mechanistic insights [211, 212].

Data quality and standardization: The primary challenge in integrating AI into TCM is data quality and standardization. TCM treatments encompass a broad range of medicines, treatment protocols, and individualized therapies, which can result in non-uniform data. AI models trained on such inconsistent datasets may produce unreliable predictions, limiting their applicability in research and practice. Xu et al. [213] and Zhou et al. [214] emphasize the need for standardized data collection methods to improve the accuracy of AI applications in TCM.

The complexity and subtlety of TCM further complicate AI and NP integration. Herbal interactions are context-dependent, with effects on the human body arising from multi-component synergies that are difficult to model. Without accounting for these non-linear, system-level interactions, AI predictions may misrepresent true pharmacological effects [215, 216]. Finally, clinical integration remains a practical limitation. Even accurate AI outputs require interpretability and usability for practitioners to incorporate them into patient care. Lack of transparency or a user-friendly interface can hinder adoption in routine TCM practice.

Despite these challenges, the future is highly promising. With the advancement of multi-omics technologies, dynamic quantitative NP models, and deep learning algorithms, researchers will be better equipped to unravel the pharmacological complexity of *Ganoderma* spp. Integration of AI with ADMET modeling, gut microbiome interactions, and real-time simulation tools can help optimize compound screening, improve druggability predictions, and enhance personalized therapy. Furthermore, AI-guided syndrome differentiation and patient-specific prescription modeling in TCM can enable precise, individualized treatments. The continued development of robust, unified databases and the standardization of analytical methods will ensure more reliable outcomes. In the context of chronic disease management, neurodegeneration, metabolic disorders, and cancer, *Ganoderma* spp., supported by AI and NP tools, hold great promise as scientifically validated, multi-target therapeutic agents aligned with the future of personalized and integrative medicine.

3. Conclusion

The integration of NP and AI in the study of *Ganoderma* spp. marks a transformative advancement in the fields of TCM and herbal pharmacology. This synergistic approach enables a holistic understanding of the intricate interactions between bioactive compounds, molecular targets, and disease pathways, thereby unraveling the multi-target and multi-component nature of *Ganoderma's* therapeutic effects. By leveraging advanced computational tools and high-quality biological databases, researchers can efficiently identify active constituents, predict their pharmacological targets, and construct complex herb-compound-target-disease networks. The incorporation of AI further enhances data mining, refines target prediction, and facilitates the discovery of synergistic relationships, accelerating drug discovery and supporting the scientific validation and modernization of TCM.

While challenges such as data inconsistency, model interpretability, and limited experimental validation remain, ongoing advances in dynamic modeling, omics integration, and machine learning offer promising solutions. Future research should focus on developing standardized, high-quality databases, improving AI model transparency, validating computational predictions experimentally, and integrating patient-specific data to enable precision herbal medicine. Investigating *Ganoderma* effects in complex disease contexts, such as neurodegeneration, metabolic disorders, and cancer, while incorporating real-time pharmacokinetic and gut microbiome interactions, will further enhance translational potential.

Ultimately, the fusion of NP and AI in *Ganoderma* research not only bridges traditional knowledge with modern biomedical science but also paves the way for precision herbal medicine. It holds great potential for treating complex diseases and for enhancing the global credibility, standardization, and clinical integration of TCM in contemporary healthcare systems.

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Declaration of Competing Interests

These authors have no conflict of interest to declare.

References

1 Joshi CP, Baldi A, Kumar N, et al. Harnessing network pharmacology in drug discovery: an integrated approach. *Naunyn Schmiedebergs Arch Pharmacol*. 2024;398(5):4689-4703. https://doi.org/10.1007/s00210-024-03625-3.
2 Pei L, Bao Y, Liu S, et al. Material basis of Chinese herbal formulas explored by combining pharmacokinetics with network pharmacology. *PLoS One*. 2013;8(1):e57414. https://doi.org/10.1371/journal.pone.0057414.
3 Li S, Zhang B, Zhang N. Network target for screening synergistic drug combinations with application to traditional Chinese medicine. *BMC Syst Biol*. 2011;5(Suppl 1):S10. doi:10.1186/1752-0509-5-S1-S10
4 Assenov Y, Ramírez F, Schelhorn SE, et al. Computing topological parameters of biological networks. *Bioinformatics*. 2008;24(2):282-284. https://doi.org/10.1093/bioinformatics/btm554.
5 Meng W, Chao W, Kaiwei Z, et al. Bioactive compounds from Chinese herbal plants for neurological health: mechanisms, pathways, and functional food applications. *Front Nutr*. 2025;12:1537363. https://doi.org/10.3389/fnut.2025.1537363.
6 Chen Y, Tang Y, Li Y, et al. Enhancing the efficacy of active pharmaceutical ingredients in medicinal plants through nanoformulations: a promising field. *Nanomaterials*. 2024;14(19):1598. https://doi.org/10.3390/nano14191598.
7 Wang C, Ren K, Yang M, et al. How Traditional Chinese Medicine can play a role in nanomedicine? A comprehensive review of the literature. *Int J Nanomed*. 2025;20:6289-315. https://doi.org/10.2147/IJN.S518610.
8 Du HZ, Hou XY, Miao YH, et al. Traditional Chinese medicine: an effective treatment for 2019 novel coronavirus pneumonia (NCP). *Chin J Nat Med*. 2020;18(3):206-210. https://doi.org/10.1016/S1875-5364(20)30022-4.
9 Song Z, Chen G, Chen CYC. AI empowering traditional Chinese medicine? *Chem Sci*. 2024;15(46):16844-16886. https://doi.org/10.1039/d4sc04107k.
10 Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *J Nat Prod*. 2020;83(3):770-803. https://doi.org/10.1021/acs.jnatprod.9b01285.
11 Sliva D. Cellular and physiological effects of *Ganoderma lucidum* (Reishi). *Mini Rev Med Chem*. 2004;4(8):873-879. https://doi.org/10.2174/1389557043403323.
12 Khanal S, Thakur P, Sharma A, et al. Unlocking the therapeutic potential of bioactive compounds in *Ganoderma lucidum*: a new frontier in natural medicine. *3 Biotech*. 2025;15(7):21. https://doi.org/10.1007/s13205-025-

04353-y.
13 Kumar HMA, Sarkar M, Darshan K, et al. The *Ganoderma*: biodiversity and significance. In: Mushrooms: Biodiversity, Nutritional and Medicinal Value. Springer; 2022:255-291. https://doi.org/10.1007/978-981-16-8877-5_12.
14 Li JF, Guo HL, Dong Y, et al. Polysaccharides from Chinese herbal medicine: a review on the hepatoprotective and molecular mechanism. *Chin J Nat Med*. 2024;22(1):4-14. https://doi.org/10.1016/S1875-5364(24)60558-3.
15 Varghese R, Dalvi YB, Lamrood PY, et al. Historical and current perspectives on the therapeutic potential of higher basidiomycetes: an overview. *3 Biotech*. 2019;9(1):1-15. https://doi.org/10.1007/s13205-019-1886-2.
16 Pascale C, Sirbu R, Cadar E. Importance of bioactive compounds of extract in medical field. *Eur J Nat Sci Med*. 2022;5(1):40-48. https://doi.org/10.26417/ejnmed.v5i1p40-48.
17 Xiong C, Chen C, Chen ZQ, et al. Potentiation of neuritogenic activity of *Ganoderma leucocontextum* on rat pheochromocytoma cells. *Nat Prod Res Dev*. 2016;28(7):1135-1139. https://doi.org/10.16333/j.1001-6880.2016.7.025.
18 Li X, Xie Y, Peng J, et al. Ganoderiol F purified from *Ganoderma leucocontextum* retards cell cycle progression *via* inhibiting CDK4/CDK6. *Cell Cycle*. 2019;18(21):3030-3043. doi:10.1080/15384101.2019.1667705
19 Zhao ZZ, Chen HP, Li ZH, et al. Leucocontextins A–R, lanostane-type triterpenoids from *Ganoderma leucocontextum*. *Fitoterapia*. 2016;109:91-98. https://doi.org/10.1016/j.fitote.2015.12.004.
20 Wang K, Bao L, Xiong W, et al. Lanostane triterpenes from the Tibetan medicinal mushroom *Ganoderma leucocontextum* and their inhibitory effects on HMG-CoA reductase and α-glucosidase. *J Nat Prod*. 2015;78(9):1977-1989. https://doi.org/10.1021/acs.jnatprod.5b00331.
21 Peng G, Xiong C, Zeng X, et al. Exploring nutrient profiles, phytochemical composition, and the antiproliferative activity of *Ganoderma lucidum* and *Ganoderma leucocontextum*: a comprehensive comparative study. *Foods*. 2024;13(5):775. https://doi.org/10.3390/foods13050775.
22 Zhai Y, Liu L, Zhang F, et al. Network pharmacology: a crucial approach in traditional Chinese medicine research. *Chin Med*. 2025;20(1):1-20. https://doi.org/10.1186/s13020-024-01056-z.
23 Wu J, Zhang F, Li Z, et al. Integration strategy of network pharmacology in traditional Chinese medicine: a narrative review. *J Tradit Chin Med*. 2022;42(3):479-484. https://doi.org/10.19852/j.cnki.jtcm.20220328.001.
24 Xu F, Cai W, Ma T, et al. Traditional uses, phytochemistry, pharmacology, quality control, industrial application, pharmacokinetics and network pharmacology of *Pogostemon cablin*: a comprehensive review. *Am J Chin Med*. 2022;50(3):691-721. https://doi.org/10.1142/S0192415X22500288.
25 Li N, Gu X, Liu F, et al. Network pharmacology-based analysis of potential mechanisms of myocardial ischemia-reperfusion injury by total salvianolic acid injection. *Front Pharmacol*. 2023;14:1202718. https://doi.org/10.3389/fphar.2023.1202718.
26 Dai Y, Chen X, Yang H, et al. Evidence construction of Huangkui Capsule against chronic glomerulonephritis: a systematic review and network pharmacology. *Phytomedicine*. 2022;102:154189. https://doi.org/10.1016/j.phymed.2022.154189.
27 Zhai Y, Zhang F, Zhou J, et al. Mechanism of norcantharidin intervention in gastric cancer: analysis based on antitumor proprietary Chinese medicine database, network pharmacology, and transcriptomics. *Chin Med*. 2024;19(1):1-21. https://doi.org/10.1186/s13020-024-01000-1.
28 Qiu Y, Mao ZJ, Ruan YP, et al. Exploration of the anti-insomnia mechanism of *Ganoderma via* central-peripheral multi-level interaction network analysis. *BMC Microbiol*. 2021;21(1):1-16. https://doi.org/10.1186/s12866-021-02361-5.
29 Zhang H, Xu Z, Gao H, et al. Systematic analysis on the mechanism of Zhizi-Bopi Decoction against hepatitis B *via* network pharmacology and molecular docking. *Biotechnol Lett*. 2023;45(4):463-478. https://doi.org/10.1007/s10529-023-03359-x.
30 Agamah FE, Bayjanov JR, Niehues A, et al. Computational approaches for network-based integrative multi-omics analysis. *Front Mol Biosci*. 2022;9:967205. https://doi.org/10.3389/fmolb.2022.967205.
31 Chen Z, Zhao M, You L, et al. Developing an artificial intelligence method for screening hepatotoxic compounds in traditional Chinese medicine and western medicine combination. *Chin Med*. 2022;17(1):1-7. https://doi.org/10.1186/s13020-022-00617-4.
32 Jia S, Lai H, Bai H, et al. Harnessing the application of artificial intelligence in identification of traditional Chinese medicines. *J Ethnopharmacol*. 2026;355(Pt B):120704. https://doi.org/10.1186/1752-0509-5-S1-S10.
33 Saldívar-González FI, Aldas-Bulos VD, Medina-Franco JL, et al. Natural product drug discovery in the artificial intelligence era. *Chem Sci*. 2022;13(6):1526-1546. https://doi.org/10.1039/d1sc04471k.
34 Wang J, Liu YM, Li J, et al. Artificial intelligence in Traditional Chinese Medicine: multimodal fusion and machine learning for enhanced diagnosis and treatment efficacy. *Current Medical Science*. 2025;45:1013–1022. https://doi.org/10.1007/s11596-025-00103-6
35 Zhang H, Ni W, Li J, et al. Artificial intelligence-based traditional Chinese medicine assistive diagnostic system: validation study. *JMIR Med Inform*. 2020;8(6):e17608. https://doi.org/10.2196/17608.
36 Guo F, Tang X, Zhang W, et al. Exploration of the mechanism of traditional Chinese medicine by AI approach using unsupervised machine learning for cellular functional similarity of compounds in heterogeneous networks, XiaoErFuPi Granules as an example. *Pharmacol Res*. 2020;160:105077. https://doi.org/10.1016/j.phrs.2020.105077.
37 Zhou W, Yang K, Zeng J, et al. FordNet: recommending traditional Chinese medicine formula *via* deep neural network integrating phenotype and molecule. *Pharmacol Res*. 2021;173:105752. https://doi.org/10.1016/j.phrs.2021.105752.
38 Zhu C, Cai T, Jin Y, et al. Artificial intelligence and network pharmacology based investigation of pharmacological mechanism and substance basis of Xiaokewan in treating diabetes. *Pharmacol Res*. 2020;159:104935. https://doi.org/10.1016/j.phrs.2020.104935.
39 Gan X, Shu Z, Wang X, et al. Network medicine framework reveals generic herb-symptom effectiveness of traditional Chinese medicine. *Sci Adv*. 2023;9(28):eadh0215. https://doi.org/10.1126/sciadv.adh0215.
40 Zhang S, Wang W, Pi X, et al. Advances in the application of traditional Chinese medicine using artificial intelligence: a review. *Am J Chin Med*. 2023;51(6):1067-1083. https://doi.org/10.1142/S0192415X23500490.
41 Tian Z, Wang D, Sun X, et al. Current status and trends of artificial intelligence research on the four traditional Chinese medicine diagnostic methods: a scientometric study. *Ann Transl Med*. 2023;11(2):145. https://doi.org/10.21037/atm-22-5905.
42 Ma S, Liu J, Li W, et al. Machine learning in TCM with natural products and molecules: current status and future perspectives. *Chin Med*. 2023;18(1):1-17. https://doi.org/10.1186/s13020-023-00741-9.
43 Zhou E, Shen Q, Hou Y. Integrating artificial intelligence into the modernization of traditional Chinese medicine industry: a review. *Front Pharmacol*. 2024;15:1181183. https://doi.org/10.3389/fphar.2024.1181183.
44 Li W, Ge X, Liu S, et al. Opportunities and challenges of traditional Chinese medicine doctors in the era of artificial intelligence. *Front Med (Lausanne)*. 2023;10:1336175. https://doi.org/10.3389/fmed.2023.1336175.
45 Zhang P, Wang B, Li S. Network-based cancer precision prevention with artificial intelligence and multi-omics. *Sci Bull*. 2023;68(13):1219-1222. https://doi.org/10.1016/j.scib.2023.05.021.
46 Li S, Ding Q, Wang X. "Network target" theory and network pharmacology. In: Network Pharmacology. Springer; 2021:1-34. https://doi.org/10.1007/978-981-16-0753-0_1.
47 Li X, Wu L, Liu W, et al. A network pharmacology study of Chinese medicine QiShenYiQi to reveal its underlying multi-compound, multi-target, multi-pathway mode of action. *PLoS One*. 2014;9(5):e95004. https://doi.org/10.1371/journal.pone.0095004.
48 Liang X, Li H, Li S. A novel network pharmacology approach to analyse traditional herbal formulae: the Liu-Wei-Di-Huang Pill as a case study. *Mol Biosyst*. 2014;11(2):535-543. https://doi.org/10.1039/c3mb70507b.
49 Zhang RZ, Yu SJ, Bai H, et al. TCM-Mesh: the database and analytical system for network pharmacology analysis for TCM preparations. *Sci Rep*. 2017;7:2821. https://doi.org/10.1038/s41598-017-03039-7.
50 Prasad TS, Goel R, Kandasamy K, et al. Human protein reference database—2009 update. *Nucleic Acids Res*. 2009;37:D767-D772. doi:10.1093/nar/gkn892
51 Brown KR, Jurisica I. Online predicted human interaction database. *Bioinformatics*. 2005;21(9):2076-2082. https://doi.org/10.1093/bioinformatics/bth315.
52 Gao Z, Li H, Zhang H, et al. PDTD: a web-accessible protein database for drug target identification. *BMC Bioinformatics*. 2008;9:104. https://doi.org/10.1186/1471-2105-9-104.
53 Whirl-Carrillo M, McDonagh EM, Hebert JM, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther*. 2012;92(4):414-417. https://doi.org/10.1038/clpt.2012.96.
54 Klimov KY. Analysis of retinoblastoma-associated genes using bioinformatic methods. *Digit Diagn*. 2023;4(1):66-69. https://doi.org/10.17816/DD430347.
55 Vastrik I, D'Eustachio P, Schmidt E, et al. Reactome: a knowledge base of biologic pathways and processes. *Genome Biol*. 2007;8(3):R39. https://doi.org/10.1186/gb-2007-8-3-r39.
56 Fazekas D, Koltai M, Türei D, et al. SignaLink 2—a signaling pathway resource with multi-layered regulatory networks. *BMC Syst Biol*. 2013;7(1):7. https://doi.org/10.1186/1752-0509-7-7.
57 Durán-Iturbide NA, Díaz-Eufracio BI, Medina-Franco JL. *In silico* ADME/Tox profiling of natural products: a focus on BIOFACQUIM. *ACS Omega*. 2020;5(26):16076-16084. https://doi.org/10.1021/acsomega.0c01581.
58 Li X, Ren J, Zhang W, et al. LTM-TCM: a comprehensive database for the linking of traditional Chinese medicine with modern medicine at molecular and phenotypic levels. *Pharmacol Res*. 2022;178:106185. https://doi.org/10.1016/j.phrs.2022.106185.
59 Chen X, Liu MX, Yan GY. Drug–target interaction prediction by random walk on the heterogeneous network. *Mol Biosyst*. 2012;8(7):1970-1978. https://doi.org/10.1039/c2mb00002d.
60 Vanunu O, Magger O, Ruppin E, et al. Associating genes and protein complexes with disease *via* network propagation. *PLoS Comput Biol*. 2010;6(1):e1000641. https://doi.org/10.1371/journal.pcbi.1000641.
61 Zhang R, Zhu X, Bai H, et al. Network pharmacology databases for traditional Chinese medicine: review and assessment. *Front Pharmacol*. 2019;10:123. https://doi.org/10.3389/fphar.2019.00123.
62 Fan M, Jin C, Li D, et al. Multi-level advances in databases related to systems pharmacology in traditional Chinese medicine: a 60-year review. *Front Pharmacol*. 2023;14:1289901. https://doi.org/10.3389/fphar.2023.1289901.
63 Huang Y, Dong D, Zhang W, et al. DrugRepoBank: a comprehensive database and discovery platform for accelerating drug repositioning. *Database*. 2024;2024:baae051. https://doi.org/10.1093/database/baae051.
64 Daina A, Michielin O, Zoete V. SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. *Nucleic Acids Res*. 2019;47(W1):W357-W364. https://doi.org/10.1093/nar/gkz382.
65 Keskin O, Tuncbag N, Gursoy A. Predicting protein-protein interactions from the molecular to the proteome level. *Chem Rev*. 2016;116(8):4884-4909. https://doi.org/10.1021/acs.chemrev.5b00683.
66 Zhou T, Yao J, Liu Z. Gene ontology, enrichment analysis, and pathway analysis. In: Bioinformatics in Aquaculture. Wiley; 2017:150-168. https://

doi.org/10.1002/9781118782392.ch10.
67 Rothfels K, Milacic M, Matthews L, et al. Using the Reactome database. *Curr Protoc*. 2023;3(6):e722. https://doi.org/10.1002/cpz1.722.
68 Valdés-Tresanco MS, Valdés-Tresanco ME, Valiente PA, et al. AMDock: a versatile graphical tool for assisting molecular docking with Autodock Vina and Autodock4. *Biol Direct*. 2020;15(1):1-12. https://doi.org/10.1186/s13062-020-00267-2.
69 Ecker GF. *In silico* ADME modeling. In: Drug Discovery and Evaluation: Safety and Pharmacokinetic Assays. Springer; 2024:1901-1927. https://doi.org/10.1007/978-3-031-35529-5_108.
70 Soudy M, Anwar AM, Ahmed EA, et al. UniprotR: retrieving and visualizing protein sequence and functional information from Universal Protein Resource (UniProt knowledgebase). *J Proteomics*. 2020;213:103613. https://doi.org/10.1016/j.jprot.2019.103613.
71 Iden M, Tsaih SW, Huang YW, et al. Multi-omics mapping of human papillomavirus integration sites illuminates novel cervical cancer target genes. *Br J Cancer*. 2021;125(10):1408-1419. https://doi.org/10.1038/s41416-021-01545-0.
72 Bhattarai P, Rai S, Koirala P, et al. Computational approach and its application in the nutraceutical industry. In:Bioactive Extraction and Application in Food and Nutraceutical Industries. Springer; 2024:449-468. https://doi.org/10.1007/978-1-0716-3601-5_18.
73 Kumar G, Barman P, Konwar R, et al. Natural product databases: discovering nature's riches. In: Natural Products in Drug Discovery. Taylor Francis. 2026:555–84. https://doi.org/10.1201/9781998511297-22.
74 Ahmed Z, Zeeshan S, Mendhe D, et al. Human gene and disease associations for clinical-genomics and precision medicine research. *Clin Transl Med*. 2020;10(2):297-318. https://doi.org/10.1002/ctm2.28.
75 Zhu H, Zhang J, Kim MT, et al. Big data in chemical toxicity research: the use of high-throughput screening assays to identify potential toxicants. *Chem Res Toxicol*. 2014;27(9):1643-1651. https://doi.org/10.1021/tx500145h.
76 Cör Andrejč D, Knez Ž, Knez Marevci M. Antioxidant, antibacterial, antitumor, antifungal, antiviral, anti-inflammatory, and nevro-protective activity of *Ganoderma lucidum*: an overview. *Front Pharmacol*. 2022;13:934982. https://doi.org/10.3389/fphar.2022.934982.
77 Michalska A, Sierocka M, Drzewiecka B, et al. Antioxidant and anti-inflammatory properties of mushroom-based food additives and food fortified with them—current status and future perspectives. *Antioxidants (Basel)*. 2025;14:519. https://doi.org/10.3390/antiox14050519.
78 He P, Zhang Y, Li N. The phytochemistry and pharmacology of medicinal fungi of the genus *Phellinus*: a review. *Food Funct*. 2021;12(2):1856-1881. https://doi.org/10.1039/d0fo02342f.
79 Agnihotri C, Aarzoo, Agnihotri S, et al. Mushroom bioactives: traditional resources with nutraceutical importance. In: Traditional Resources and Tools for Modern Drug Discovery. Springer; 2024:617-639. https://doi.org/10.1007/978-981-97-4600-2_24.
80 Gafforov Y, Rašeta M, Rapior S, et al. Macrofungi as medicinal resources in Uzbekistan: biodiversity, ethnomycology, and ethnomedicinal practices. *J Fungi*. 2023;9(9):922. https://doi.org/10.3390/jof9090922.
81 Dhar GA, Karmakar R, Mukhopadhyay S, et al. Insights into natural product–based drug discovery using a systems biology approach. In: Bioactive Ingredients for Healthcare Industry Volume 1. Springer; 2025:159-180. https://doi.org/10.1007/978-981-96-3663-1_7.
82 Eira A, Gonçalves MBS, Fongang YSF, et al. Unlocking the potential of *Ganoderma lucidum* (Curtis): botanical overview, therapeutic applications, and nanotechnological advances. *Pharmaceutics*. 2025;17(4):422. https://doi.org/10.3390/pharmaceutics17040422.
83 Oh KK, Adnan M, Cho DH. A network pharmacology analysis on drug-like compounds from *Ganoderma lucidum* for alleviation of atherosclerosis. *J Food Biochem*. 2021;45(6):e13906. https://doi.org/10.1111/jfbc.13906.
84 Zhao RL, He YM. Network pharmacology analysis of the anti-cancer pharmacological mechanisms of *Ganoderma lucidum* extract with experimental support using Hepa1-6-bearing C57BL/6 mice. *J Ethnopharmacol*. 2018;210:287-295. https://doi.org/10.1016/j.jep.2017.08.041.
85 Zhong JY, Chen HB, Ye DZ, et al. Molecular mechanism of *Ganoderma* against gastric cancer based on network pharmacology and experimental test. *Chin J Chin Mater Med*. 2022;47(1):203-214. https://doi.org/10.19540/j.cnki.cjcmm.20211115.601.
86 Shi J, Chen J, Cheng C, et al. Systems pharmacology-based drug discovery and active mechanism of *Ganoderma lucidum* triterpenoids for type 2 diabetes mellitus *via* integrating network pharmacology and molecular docking. *Curr Pharm Des*. 2025;31(4):1-13. https://doi.org/10.2174/0113816128365423250126035306.
87 Huo J, Nie K, Yang T, et al. Network pharmacology combined with transcriptomics reveals that *Ganoderma lucidum* spore and *Sanghuangporus vaninii* compound extract exerts anti-colorectal cancer effects *via* CYP24A1-mediated VDR pathway and TERT-mediated Wnt signaling pathway. *J Ethnopharmacol*. 2025;348:119820. https://doi.org/10.1016/j.jep.2025.119820.
88 Luo Y, Luo X, Xue Z, et al. Exploring the anti-lung cancer mechanism of *Ganoderma lucidum* and its relationship with the level of immune cell infiltration based on network pharmacology and molecular docking. *Oncologie*. 2024;26(4):831-843. https://doi.org/10.1515/oncologie-2024-0194.
89 Guo S, Yang L, Zhou J, et al. Mechanistic insights into *Ganoderma lucidum* for diabetes treatment *via* network pharmacology and validation. *Diabetes Metab Syndr Obes*. 2025;18:1263-1284. https://doi.org/10.2147/DMSO.S500955.
90 Mei X, Zhang J, Chen L, et al. Systematic network pharmacology and experimental validation reveal anti-glioma mechanisms of *Ganoderma lucidum via* multi-target regulation. *Discov Oncol*. 2025;16:1467. https://doi.org/10.1007/s12672-025-03280-x.
91 Zhilin L, Haobo F, Juan W, et al. Investigating the therapeutic potential of *Ganoderma lucidum* in treating optic nerve atrophy through network pharmacology and experimental validation. *Biochem Biophys Res Commun*. 2025;760:151702. https://doi.org/10.1016/j.bbrc.2025.151702.
92 Shi M. The efficacy of *Ganoderma lucidum* extracts on treating endometrial cancer: a network pharmacology approach. *Reprod Sci*. 2024;31(6):1881-1894. https://doi.org/10.1007/s43032-024-01500-3.
93 Qian R, Zhang L, Xu Y, et al. Network pharmacology reveals the effect and mechanism of *Ganoderma leucocontextum* ethanol extract on improving inflammatory response in silicosis lungs. *China Occup Med*. 2024;51(1):6-15. https://doi.org/10.20001/j.issn.2095-2619.20240202.
94 Li Y, Wang L, Xu B, et al. Based on network pharmacology tools to investigate the molecular mechanism of *Cordyceps sinensis* on the treatment of diabetic nephropathy. *J Diabetes Res*. 2021;2021:8891093. https://doi.org/10.1155/2021/8891093.
95 Dong J, Cao M, Yu H, et al. Network pharmacology-based exploration of the therapeutic mechanisms of *Cordyceps cicadae* in renal ischemia/reperfusion. *Ann Transplant*. 2022;27:e937469. https://doi.org/10.12659/AOT.937469.
96 Xiao C, Jiao C, Huang L, et al. Network pharmacology-based elucidation of the hypoglycemic mechanism of *Grifola frondosa* GF5000 polysaccharides *via* GCK modulation in diabetic rats. *Nutrients*. 2025;17(6):964. https://doi.org/10.3390/nu17060964.
97 Kaur J, Farooqi H, Chandra K, et al. Predicting the bioactive compounds of *Lentinula edodes* and elucidating its interaction with genes associated to obesity through network pharmacology and *in vitro* cell-based assay. *Heliyon*. 2024;10(5):e27363. https://doi.org/10.1016/j.heliyon.2024.e27363.
98 Dong Y, Qiu P, Zhu R, et al. A combined phytochemistry and network pharmacology approach to reveal the potential antitumor effective substances and mechanism of *Phellinus igniarius*. *Front Pharmacol*. 2019;10:266. https://doi.org/10.3389/fphar.2019.00266.
99 Zan LF, Xin JC, Guo HY, et al. Systematic characterization of active antitumor constituents from the shaggy bracket medicinal mushroom *Inonotus hispidus* (Agaricomycetes) by UPLC-Q-TOF/MS and network pharmacology. *Int J Med Mushrooms*. 2023;25(1):47-62. https://doi.org/10.1615/IntJMedMushrooms.2022044406.
100 Wang Z, Wang R, Na Z, et al. Network pharmacology analysis of liquid-cultured *Armillaria ostoyae* mycelial metabolites and their molecular mechanism of action against gastric cancer. *Molecules*. 2024;29(7):1668. https://doi.org/10.3390/molecules29071668.
101 Zhou J, Wang M, Sun T, et al. Uncovering anti-influenza mechanism of *Ophiocordyceps sinensis* using network pharmacology, molecular pharmacology, and metabolomics. *Medicine*. 2023;102(9):E34843. https://doi.org/10.1097/MD.0000000000034843.
102 Kuang Y, Chai Y, Su H, et al. A network pharmacology-based strategy to explore the pharmacological mechanisms of *Antrodia camphorata* and antcin K for treating type II diabetes mellitus. *Phytomedicine*. 2022;96:153851. https://doi.org/10.1016/j.phymed.2021.153851.
103 Xiaoying M, Zhiming H, Tao Y, et al. Elucidating the molecular mechanisms underlying anti-inflammatory effects of *Morchella esculenta* in the arachidonic acid metabolic pathway by network pharmacology and molecular docking. *Sci Rep*. 2023;13(1):1-23. https://doi.org/10.1038/s41598-023-42658-1.
104 Pei H, He Z, Chen W, et al. Network pharmacology and molecular docking analysis on the mechanism of *Cordyceps militaris* polysaccharide regulating immunity through TLR4/TNF-α pathways. *J Biochem Mol Toxicol*. 2023;37(4):e23345. https://doi.org/10.1002/jbt.23345.
105 Shreya S, Kumar DN, Mohapatra D, et al. Tracing the anti-cancer mechanism of *Pleurotus ostreatus* by the integrative approach of network pharmacology and experimental studies. *Appl Biochem Biotechnol*. 2023;195(1):152-171. https://doi.org/10.1007/s12010-022-04111-3.
106 Jiang S, Bao H. Exploring the mechanism of esculetin extracted from *Chroogomphus rutilus* in treating liver cancer based on network pharmacology, molecular docking, and *in vivo* experimental validation. *J Ethnopharmacol*. 2025;348:119837. https://doi.org/10.1016/j.jep.2025.119837.
107 Li S, Zhang B, Jiang D, et al. Herb network construction and co-module analysis for uncovering the combination rule of traditional Chinese herbal formulae. *BMC Bioinformatics*. 2010;11(Suppl 11):S6. doi:10.1186/1471-2105-11-S11-S6
108 Morris GM, Ruth H, Lindstrom W, et al. AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility. *J Comput Chem*. 2009;30(15):2785-2791. https://doi.org/10.1002/jcc.21256.
109 Huang DW, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nat Protoc*. 2009;4(1):44-57. https://doi.org/10.1038/nprot.2008.211.
110 Ye H, Ye L, Kang H, et al. HIT: linking herbal active ingredients to targets. *Nucleic Acids Res*. 2011;39:D1055-D1059. https://doi.org/10.1093/nar/gkq1165.
111 Chen CYC. TCM Database@Taiwan: the world's largest traditional Chinese medicine database for drug screening *in silico*. *PLoS One*. 2011;6(1):e15939. https://doi.org/10.1371/journal.pone.0015939.
112 Zhao R, Chen Q, He YM, et al. The effect of *Ganoderma lucidum* extract on immunological function and identification of its anti-tumor immunostimulatory activity based on the biological network. *Sci Rep*. 2018;8:1-14. https://doi.org/10.1038/s41598-018-30881-0.
113 Liu C, Cheng Y, Guo D, et al. A new concept on quality marker for quality assessment and process control of Chinese medicines. *Chin Herb Med*. 2017;9(1):3-13. https://doi.org/10.1016/S1674-6384(17)60070-4.
114 Liu Z, Guo F, Wang Y, et al. BATMAN-TCM: a bioinformatics analysis tool for molecular mechANism of traditional Chinese medicine. *Sci Rep*. 2016;6:

21146. https://doi.org/10.1038/srep21146.
115 Li Y, Zhang Y, Wang Y, et al. A strategy for the discovery and validation of toxicity quality marker of Chinese medicine based on network toxicology. *Phytomedicine*. 2019;54:365-370. https://doi.org/10.1016/j.phymed.2018.10.003.
116 Wang M, Lamers RJAN, Korthout HAAJ, et al. Metabolomics in the context of systems biology: bridging traditional Chinese medicine and molecular pharmacology. *Phytother Res*. 2005;19(3):173-182. https://doi.org/10.1002/ptr.1624.
117 Wang H, Chen Y, Wang L, et al. Advancing herbal medicine: enhancing product quality and safety through robust quality control practices. *Front Pharmacol*. 2023;14:1265178. https://doi.org/10.3389/fphar.2023.1265178.
118 Wang M, Yin F, Kong L, et al. Chinmedomics: a potent tool for the evaluation of traditional Chinese medicine efficacy and identification of its active components. *Chin Med*. 2024;19:47. https://doi.org/10.1186/s13020-024-00917-x.
119 Ahmad A, Imran M, Ahsan H. Biomarkers as biomedical bioindicators: approaches and techniques for the detection, analysis, and validation of novel biomarkers of diseases. *Pharmaceutics*. 2023;15(6):1630. https://doi.org/10.3390/pharmaceutics15061630.
120 Wang Y, Cui T, Li Y, et al. Prediction of quality markers of traditional Chinese medicines based on network pharmacology. *Chin Herb Med*. 2019;11(4):349-356. https://doi.org/10.1016/j.chmed.2019.08.004.
121 Kapoor G, Prakash S, Jaiswal V, et al. Chronic inflammation and cancer: key pathways and targeted therapies. *Cancer Invest*. 2025;43:1. https://doi.org/10.1080/07357907.2024.2437614.
122 Zhang XT, Ji CL, Fu YJ, et al. Screening of active components of *Ganoderma lucidum* and decipher its molecular mechanism to improve learning and memory disorders. *Biosci Rep*. 2024;44(5):1-15. https://doi.org/10.1042/BSR20240127.
123 Kumar A, Behl T, Jamwal S, et al. Exploring the molecular approach of COX and LOX in Alzheimer's and Parkinson's disorder. *Mol Biol Rep*. 2020;47:9895-9912. https://doi.org/10.1007/s11033-020-06033-x.
124 Cheng KC, Huang HC, Chen JH et al. *Ganoderma lucidum* polysaccharides in human monocytic leukemia cells: from gene expression to network construction. *BMC Genomics*. 2007;8:411. https://doi.org/10.1186/1471-2164-8-411.
125 Zhao X, Xiu J, Yang H, et al. Network pharmacology and bioinformatics study of six medicinal food homologous plants against colorectal cancer. *Int J Mol Sci*. 2025;26(3):1-18. https://doi.org/10.3390/ijms26030930.
126 Swallah MS, Bondzie-Quaye P, Wu Y, et al. Therapeutic potential and nutritional significance of *Ganoderma lucidum*–a comprehensive review from 2010 to 2022. *Food Funct*. 2023;14:1812-38. https://doi.org/10.1039/d2fo01683d.
127 Wu M, Zhang Y. Combining bioinformatics, network pharmacology and artificial intelligence to predict the mechanism of celastrol in the treatment of type 2 diabetes. *Front Endocrinol*. 2022;13:1030278. https://doi.org/10.3389/fendo.2022.1030278.
128 Xu P, Lin B, Deng X, et al. Anti-osteoporosis effects of Anemarrhenae Rhizoma/Phellodendri Chinensis Cortex herb pair and its major active components in diabetic rats and zebrafish. *J Ethnopharmacol*. 2022;293:115269. https://doi.org/10.1016/j.jep.2022.115269.
129 Mukherjee A, Abraham S, Singh A, et al. From data to cure: a comprehensive exploration of multi-omics data analysis for targeted therapies. *Mol Biotechnol*. 2024;67(4):1269-1289. https://doi.org/10.1007/s12033-024-01133-6.
130 Cui G, Li M, Guo W, et al. AI-driven network pharmacology: multi-scale mechanisms of traditional Chinese medicine from molecular to patient analysis. *Comput Struct Biotechnol J*. 2025;27:5087. https://doi.org/10.1016/j.csbj.2025.11.016.
131 Qian R, Xu Y, Zhang L, et al. *Ganoderma leucocontextum* ethanol extract alleviates silica-induced pulmonary injury *via* TGF-β1/RUNX3/SMADs pathway. *J Ethnopharmacol*. 2026;355:120757. https://doi.org/10.1016/j.jep.2025.120757.
132 Zhong L, Yan P, Lam WC, et al. *Coriolus versicolor* and *Ganoderma lucidum* related natural products as an adjunct therapy for cancers: a systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol*. 2019;10:1222. https://doi.org/10.3389/fphar.2019.01222.
133 Zhao H, Shao Y, Mao C, et al. Research progress on antitumor effects of active proteins, polysaccharides, and triterpenoids in *Ganoderma lucidum*. *J Biotech Res*. 2023;14:171-184.
134 Chaitanya MVNL, Pereira G, Ali HS. Alternative remedies and natural products for cancer therapy: an integrative approach. In: Alternative Remedies and Natural Products for Cancer Therapy: an Integrative Approach. Springer; 2023:1-309. https://doi.org/10.1007/978-981-19-9109-0.
135 Jakopovic B, Oršolić N, Jakopovich I. Proteomic research on the antitumor properties of medicinal mushrooms. *Molecules*. 2021;26(21):6708. https://doi.org/10.3390/molecules26216708.
136 Sevindik M, Eraslan EC, Krupodorova T, et al. The role of medicinal mushrooms in cancer treatment: bioactive compounds and therapeutic potential. *Int J Med Mushrooms*. 2025;27(1):1-25. https://doi.org/10.1615/IntJMedMushrooms.2024051758.
137 Gao X, Homayoonfal M. Exploring the anti-cancer potential of *Ganoderma lucidum* polysaccharides (GLPs) and their versatile role in enhancing drug delivery systems: a multifaceted approach to combat cancer. *Cancer Cell Int*. 2023;23(1):1-29. https://doi.org/10.1186/s12935-023-03146-8.
138 Thongsawang S. Effects of *Cordyceps sinensis* supplementation combined with repeated sprint training in hypoxia on markers of oxidative stress and physical performance in female soccer. Chulalongkorn University Theses and Dissertations (Chula ETD). 2023.
139 Liu W, Gao Y, Zhou Y, et al. Mechanism of *Cordyceps sinensis* and its extracts in the treatment of diabetic kidney disease: a review. *Front Pharmacol*. 2022;13:881835. https://doi.org/10.3389/fphar.2022.881835.
140 Varnosfaderani SMN, Ebrahimzadeh F, Oryani MA, et al. Potential promising anticancer applications of β-glucans: a review. *Biosci Rep*. 2024;44(1):BSR20231686. https://doi.org/10.1042/BSR20231686.
141 Dai X. The mechanism by which Lentinula edodes modulates cytokine production of innate immune cells. West Virginia University. 2015.
142 Masuda Y, Nawa D, Nakayama Y, et al. Soluble β-glucan from *Grifola frondosa* induces tumor regression in synergy with TLR9 agonist *via* dendritic cell-mediated immunity. *J Leukoc Biol*. 2015;98(5):1015-1025. https://doi.org/10.1189/jlb.1A0814-415RR.
143 Garcia J, Rodrigues F, Saavedra MJ, et al. Bioactive polysaccharides from medicinal mushrooms: a review on their isolation, structural characteristics and antitumor activity. *Food Biosci*. 2022;49:101955. https://doi.org/10.1016/j.fbio.2022.101955.
144 Roda E, Priori EC, Ratto D, et al. Neuroprotective metabolites of *Hericium erinaceus* promote neuro-healthy aging. *Int J Mol Sci*. 2021;22(12):6379. https://doi.org/10.3390/ijms22126379.
145 Szućko-Kociuba I, Trzeciak-Ryczek A, Kupnicka P, et al. Neurotrophic and neuroprotective effects of *Hericium erinaceus*. *Int J Mol Sci*. 2023;24(21):15960. https://doi.org/10.3390/ijms242115960.
146 Yen YT, Park JH, Kang SH, et al. Clinical benefits of golden-*Antrodia camphorata* containing antroquinonol in liver protection and liver fat reduction after alcoholic hepatitis. *Front Pharmacol*. 2022;13:757494. https://doi.org/10.3389/fphar.2022.757494.
147 Li ZW, Kuang Y, Tang SN, et al. Hepatoprotective activities of *Antrodia camphorata* and its triterpenoid compounds against CCl4-induced liver injury *in vivo*. *J Ethnopharmacol*. 2017;206:31-39. https://doi.org/10.1016/j.jep.2017.04.015.
148 Wang Y, Gu J, Wu J, et al. Natural products and health care functions of *Inonotus obliquus*. *Curr Issues Mol Biol*. 2025;47(4):269. https://doi.org/10.3390/cimb47040269.
149 Ingo C. A comparative study between the medicinal mushrooms *Inonotus obliquus* and *Ganoderma lucidum*—an analysis between polysaccharides, triterpenes and their functions. Alato University. 2013.
150 Li Y, Liu X, Zhou J, et al. Artificial intelligence in traditional Chinese medicine: advances in multi-metabolite multi-target interaction modeling. *Front Pharmacol*. 2025;16:1541509. https://doi.org/10.3389/fphar.2025.1541509.
151 Ru J, Li P, Wang J, et al. TCMSP: a database of systems pharmacology for drug discovery from herbal medicines. *J Cheminform*. 2014;6(1):1-6. https://doi.org/10.1186/1758-2946-6-13.
152 Xue R, Fang Z, Zhang M, et al. TCMID: traditional Chinese medicine integrative database for herb molecular mechanism analysis. *Nucleic Acids Res*. 2013;41(D1):D1089-D1095. https://doi.org/10.1093/nar/gks1100.
153 Wang Y, Liu M, Jafari M, Tang J. A critical assessment of Traditional Chinese Medicine databases as a source for drug discovery. *Front Pharmacol*. 2024;15:1303693. https://doi.org/10.3389/fphar.2024.1303693.
154 Li XL, Zhang JQ, Shen XJ, et al. Overview and limitations of database in global traditional medicines: A narrative review. *Acta Pharmacol Sin*. 2025;46:235-63. https://doi.org/10.1038/s41401-024-01353-1.
155 Akhtar M, Nehal N, Gull A, et al. Explicating the transformative role of artificial intelligence in designing targeted nanomedicine. *Expert Opin Drug Deliv*. 2025;22(10):971-991. https://doi.org/10.1080/17425247.2025.2502022.
156 Vitorino R. Transforming clinical research: the power of high-throughput omics integration. *Proteomes*. 2024;12(3):25. https://doi.org/10.3390/proteomes12030025.
157 Cho MH, Jin H, Ha J, et al. An integrated systems pharmacology approach combining bioinformatics, untargeted metabolomics and molecular dynamics to unveil the anti-aging mechanisms of *Tephroseris flammea*. *Biomolecules*. 2025;15(12):1740. https://doi.org/10.3390/biom15121740.
158 Yang L, Wang H, Zhu Z, et al. Network pharmacology-driven sustainability: AI and multi-omics synergy for drug discovery in traditional Chinese medicine. *Pharmaceuticals*. 2025;18(7):1074. https://doi.org/10.3390/ph18071074.
159 Moreira-Filho JT, Silva AC, Dantas RF, et al. Schistosomiasis drug discovery in the era of automation and artificial intelligence. *Front Immunol*. 2021;12:642383. https://doi.org/10.3389/fimmu.2021.642383.
160 Chaudhari R, Tan Z, Huang B, et al. Computational polypharmacology: a new paradigm for drug discovery. *Expert Opin Drug Discov*. 2017;12(3):279-291. https://doi.org/10.1080/17460441.2017.1280024.
161 Creanza TM, Lamanna G, Delre P, et al. DeLA-Drug: a deep learning algorithm for automated design of druglike analogues. *J Chem Inf Model*. 2022;62(6):1411-1424. https://doi.org/10.1021/acs.jcim.2c00205.
162 Niazi SK. Artificial intelligence in small-molecule drug discovery: a critical review of methods, applications, and real-world outcomes. *Pharmaceuticals*. 2025;18(9):1271. https://doi.org/10.3390/ph18091271.
163 Russell R, Aloy P, et al. Targeting and tinkering with interaction networks. *Nat Chem Biol*. 2008;4:666. https://doi.org/10.1038/nchembio.119.
164 Xu J, Bai L, Yang M, et al. Advances in the application of artificial intelligence in mass spectrometry-based analysis of traditional Chinese medicine: compound identification and metabolic pathway elucidation. *Anal Bioanal Chem*. 2025;2025:1-16. https://doi.org/10.1007/s00216-025-06260-w.
165 Fontanella F, D'Alessandro T, Nardone E, et al. Artificial intelligence for natural products drug discovery in neurodegeneration therapies: a review. *Biomolecules*. 2026;16:129. https://doi.org/10.3390/biom16010129.
166 Patil VS, Deshpande SH, Harish DR, et al. Gene set enrichment analysis, network pharmacology and *in silico* docking approach to understand the molecular mechanism of traditional medicines for the treatment of diabetes

mellitus. *J Proteins Proteomics*. 2020;11(4):297-310. https://doi.org/10.1007/s42485-020-00049-4.
167 Zhang R, Wen H, Lin Z, et al. Artificial intelligence-driven drug toxicity prediction: advances, challenges, and future directions. *Toxics*. 2025;13(7):525. https://doi.org/10.3390/toxics13070525.
168 Xia Q, Herath Mudiyanselage SHB, Lafond S, et al. *In Silico* modeling of nanoparticles transport across the blood–brain barrier: a systematic review. *Comput Struct Biotechnol J*. 2026;35(3):0020. https://doi.org/10.34133/csbj.0020.
169 Huang YX, Zhao J, Song QH, et al. Virtual screening and experimental validation of novel histone deacetylase inhibitors. *BMC Pharmacol Toxicol*. 2016;17(1):1-14. https://doi.org/10.1186/s40360-016-0075-8.
170 Zhou S, Zhang H, Li J, et al. Potential anti-liver cancer targets and mechanisms of kaempferitrin based on network pharmacology, molecular docking and experimental verification. *Comput Biol Med*. 2024;178:108693. https://doi.org/10.1016/j.compbiomed.2024.108693.
171 Noor F, Qamar MTU, Ashfaq UA, et al. Network pharmacology approach for medicinal plants: review and assessment. *Pharmaceuticals*. 2022;15(5):572. https://doi.org/10.3390/ph15050572.
172 Yang X, Huang K, Yang D, et al. Biomedical big data technologies, applications, and challenges for precision medicine: a review. *Glob Chall*. 2024;8(3):2300163. https://doi.org/10.1002/gch2.202300163.
173 Brugere I, Gallagher B, Berger-Wolf TY. Network structure inference, a survey. *ACM Comput Surv*. 2018;51(2):1-37. https://doi.org/10.1145/3154524.
174 Wang B, Zhang T, Liu Q, et al. Elucidating the role of artificial intelligence in drug development from the perspective of drug-target interactions. *J Pharm Anal*. 2025;15(1):101144. https://doi.org/10.1016/j.jpha.2024.101144.
175 Ke Z, Liu M, Liu J, et al. The application of artificial intelligence in the research and development of traditional Chinese medicine. *Int J Drug Discov Pharmacol*. 2024;3(1):100001. https://doi.org/10.53941/ijddp.2024.100001.
176 Hassija V, Chamola V, Mahapatra A, et al. Interpreting black-box models: a review on explainable artificial intelligence. *Cogn Comput*. 2024;16(1):45-74. https://doi.org/10.1007/s12559-023-10179-8.
177 Wang A, Luo Q, Tan X, et al. Development and application of artificial intelligence in traditional Chinese medicine research and development. *Chin Med*. 2026;21:17. https://doi.org/10.1186/s13020-025-01288-7.
178 Eicher T, Kinnebrew G, Patt A, et al. Metabolomics and multi-omics integration: a survey of computational methods and resources. *Metabolites*. 2020;10(5):202. https://doi.org/10.3390/metabo10050202.
179 Taha HA, Zeilani RS, Haddad RH, et al. Artificial intelligence and machine learning techniques for predicting neuropathic pain in patients with cancer: a systematic review. *Digit Health*. 2025;11:1-15. https://doi.org/10.1177/20552076251358315.
180 Ou H, Ye X, Huang H, et al. Constructing a screening model to obtain the functional herbs for the treatment of active ulcerative colitis based on herb-compound-target network and immuno-infiltration analysis. *Naunyn Schmiedebergs Arch Pharmacol*. 2024;397(5):4693-4711. https://doi.org/10.1007/s00210-023-02900-z.
181 Venkataraman M, Gopi C, Rao JK, et al. Leveraging machine learning models in evaluating ADMET properties for drug discovery and development. *ADMET DMPK*. 2025;13(1):2772. https://doi.org/10.5599/admet.2772.
182 Khan SR, Al Rijjal D, Piro A, et al. Integration of AI and traditional medicine in drug discovery. *Drug Discov Today*. 2021;26(5):982-992. https://doi.org/10.1016/j.drudis.2021.02.019.
183 Gupta U, Pranav A, Kohli A, et al. The contribution of artificial intelligence to drug discovery: current progress and prospects for the future. In: *Microorganisms for Sustainability*. Springer; 2024:1-23. https://doi.org/10.1007/978-981-99-9621-6_1.
184 Zheng X, Cai Z. Privacy-preserved data sharing towards multiple parties in industrial IoTs. *IEEE J Sel Areas Commun*. 2020;38(5):968-979. https://doi.org/10.1109/JSAC.2020.2980802.
185 Lim J, Li J, Zhou M, et al. Machine learning research trends in traditional Chinese medicine: a bibliometric review. *Int J Gen Med*. 2024;17:5397-5414. https://doi.org/10.2147/IJGM.S500001.
186 Yu Y, Yao C, Guo DA. Insight into chemical basis of traditional Chinese medicine based on the state-of-the-art techniques of liquid chromatography–mass spectrometry. *Acta Pharm Sin B*. 2021;11(4):1469-1492. https://doi.org/10.1016/j.apsb.2021.03.002.
187 Huang R, Ma S, Dai S, et al. Application of data fusion in traditional Chinese medicine: a review. *Sensors*. 2024;24(1):106. https://doi.org/10.3390/s24010106.
188 Khanal S, Sharma A, Pillai M, et al. Artificial intelligence-driven innovation in *Ganoderma* spp.: potentialities of their bioactive compounds as functional foods. *Sustain Food Technol*. 2025;3(4):759-775. https://doi.org/10.1039/d4fb00357h.
189 Grienke U, Kaserer T, Pfluger F, et al. Accessing biological actions of *Ganoderma* secondary metabolites by *in silico* profiling. *Phytochemistry*. 2015;114:114-124. https://doi.org/10.1016/j.phytochem.2014.10.013.
190 Vassaux A, Meunier L, Vandenbol M, et al. Nonribosomal peptides in fungal cell factories: from genome mining to optimized heterologous production. *Biotechnol Adv*. 2019;37(6):107449. https://doi.org/10.1016/j.biotechadv.2019.107449.
191 Cao R, Wu X, Wang Q, et al. Characterization of γ-Cadinene enzymes in *Ganoderma lucidum* and *Ganoderma sinensis* from Basidiomycetes provides insight into the identification of terpenoid synthases. *ACS Omega*. 2022;7(8):7229-7239. https://doi.org/10.1021/acsomega.1c06792.
192 Tran PN, Yen MR, Chiang CY, et al. Detecting and prioritizing biosynthetic gene clusters for bioactive compounds in bacteria and fungi. *Appl Microbiol Biotechnol*. 2019;103:3277-3287. https://doi.org/10.1007/s00253-019-09708-z.
193 Yang JS, Tsai SC, Hsu YM, et al. Integrating natural product research laboratory with artificial intelligence: advancements and breakthroughs in traditional medicine. *Biomedicine (Taipei)*. 2024;14(1):1. https://doi.org/10.3772/tw.2024.001.
194 Latif R, Nawaz T. Medicinal plants and human health: a comprehensive review of bioactive compounds, therapeutic effects, and applications. *Phytochem Rev*. 2026;25:2299. https://doi.org/10.1007/s11101-025-10194-7.
195 Tripathi MK, Nath A, Singh TP, et al. Evolving scenario of big data and artificial intelligence (AI) in drug discovery. *Mol Diversity*. 2021;25(3):1439-1460. https://doi.org/10.1007/s11030-021-10256-w.
196 Zuo R, Xiong Y, Wang J, et al. Deep learning and its application in geochemical mapping. *Earth Sci Rev*. 2019;192:1-14. https://doi.org/10.1016/j.earscirev.2019.03.003.
197 Spanakis M, Tzamali E, Tzedakis G, et al. Artificial intelligence models and tools for the assessment of drug–herb interactions. *Pharmaceuticals*. 2025;18(3):282. https://doi.org/10.3390/ph18030282.
198 Zhou J, Cui G, Hu S, et al. Graph neural networks: a review of methods and applications. *AI Open*. 2020;1:57-81. https://doi.org/10.1016/j.aiopen.2021.01.001.
199 Sanodiya BS, Thakur GS, Baghel RK, et al. *Ganoderma lucidum*: a potent pharmacological macrofungus. *Curr Pharm Biotechnol*. 2009;10(5):717-742. https://doi.org/10.2174/138920109789978757.
200 Boh B, Berovic M, Zhang J, et al. *Ganoderma lucidum* and its pharmaceutically active compounds. *Biotechnol Annu Rev*. 2007;13:265-301. https://doi.org/10.1016/S1387-2656(07)13010-6.
201 alappaththi MCA, Patabendige NM, Premarathne BM, et al. A review of Ganoderma triterpenoids and their bioactivities. *Biomolecules*. 2023;13(1):24. https://doi.org/10.3390/biom13010024.
202 Gangwal A, Lavecchia A. Artificial intelligence in natural product drug discovery: current applications and future perspectives. *J Med Chem*. 2025;68(5):3948-3969. https://doi.org/10.1021/acs.jmedchem.4c01257.
203 Gurung M, Shrestha S, Professor A. Machine learning in modern drug discovery: applications, advances, and future horizons. *KEC J Sci Eng*. 2025;9:116-126.
204 Chen M, Ji G, Fu H, et al. A survey on identification and quantification of alternative polyadenylation sites from RNA-seq data. *Brief Bioinform*. 2020;21(4):1261-1276. https://doi.org/10.1093/bib/bbz068.
205 Li X, Zhang W. Expression of PD-L1 in EBV-associated malignancies. *Int Immunopharmacol*. 2021;95:107553. https://doi.org/10.1016/j.intimp.2021.107553.
206 Cheng M, Pan H, Zhao X, et al. Integrative network pharmacology and molecular docking elucidate the multi-target mechanisms of the artist's conk medicinal mushroom *Ganoderma applanatum* (Agaricomycetes) triterpenoids against hepatocellular carcinoma. *Int J Med Mushrooms*. 2026;28(4):71. https://doi.org/10.1615/INTJMEDMUSHROOMS.2025062402.
207 Kaliaperumal K, Salendra L, Liu Y, et al. Isolation of anticancer bioactive secondary metabolites from the sponge-derived endophytic fungi *Penicillium* sp. *and in-silico computational docking approach. Front Microbiol*. 2023;14:1216928. https://doi.org/10.3389/fmicb.2023.1216928.
208 Ahmed T, Juhász A, Bose U, et al. Research trends in production, separation, and identification of bioactive peptides from fungi: a critical review. *J Funct Foods*. 2024;119:106343. https://doi.org/10.1016/j.jff.2024.106343.
209 Dong X, Gao X, Wang R, et al. Evaluation of polysaccharide content in shiitake culinary-medicinal mushroom, *Lentinula edodes* (Agaricomycetes), *via* near-infrared spectroscopy integrated with deep learning. *Int J Med Mushrooms*. 2023;25(1):13-28. https://doi.org/10.1615/IntJMedMushrooms.2022044622.
210 Wang L, Li J, Li T, et al. Method superior to traditional spectral identification: FT-NIR two-dimensional correlation spectroscopy combined with deep learning to identify the shelf life of fresh *Phlebopus portentosus*. *ACS Omega*. 2021;6(31):19665-19674. https://doi.org/10.1021/acsomega.1c02317.
211 Li J, Long Q, Ding H, et al. Progress in the Treatment of Central Nervous System Diseases Based on Nanosized Traditional Chinese Medicine. *Adv Sci*. 2024;11(16):e2308677. https://doi.org/10.1002/advs.202308677.
212 Adipo M, Mudalungu CM, Santos CBR, et al. Insect-derived compounds as novel source for drug discovery: a systematic review and critical in silico analysis. *Chem Biodivers*. 2025;23:e02495. https://doi.org/10.1002/cbdv.202502495.
213 Xu Q, Guo Q, Wang CX, et al. Network differentiation: a computational method of pathogenesis diagnosis in traditional Chinese medicine based on systems science. *Artif Intell Med*. 2021;118:102134. https://doi.org/10.1016/j.artmed.2021.102134.
214 Hou GL, Dong BQ, Yu BX, et al. Artificial intelligence in acupuncture: bridging traditional knowledge and precision integrative medicine. *Front Med*. 2025;12:1633416. https://doi.org/10.3389/fmed.2025.1633416.
215 Zhao Z, Ren X, Song K, et al. PreGenerator: TCM prescription recommendation model based on retrieval and generation method. *IEEE Access*. 2023;11:103679-103692. https://doi.org/10.1109/ACCESS.2023.3316219.
216 Wang X, Wang ZY, Zheng JH, et al. TCM network pharmacology: a new trend towards combining computational, experimental and clinical approaches. *Chin J Nat Med*. 2021;19(1):1-11. https://doi.org/10.1016/S1875-5364(21)60001-8.