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Synergistic phytochemicals in multi-target drug discovery for complex diseases: A narrative review

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ABSTRACT

Background/problem statement: Single-target pharmaceutical treatments generally fail to address the complex pathophysiology of chronic illnesses such as cancer, cardiovascular disorders, diabetes, and neurodegeneration. These conditions are prone to medication resistance and treatment-related toxicity, underscoring the need for approaches that simultaneously activate multiple biological processes while minimizing undesirable effects.
Aim: This study examines the therapeutic potential of phytochemicals as multi-target drugs, and evaluates current advancements in drug design, delivery methods, and toxicology for clinical use.
Methods: A narrative review methodology was employed. Literature was gathered from PubMed, Scopus, Web of Science, and Google Scholar, emphasizing research published between 2013 and 2024. The Scopus Boolean search syntax was: TITLE-ABS-KEY((“phytochemical*” OR “plant bioactive*” OR “plant-derived compound*” OR “phytomedicine” OR “herbal medicine” OR “natural product*” OR “medicinal plant*”) AND (“multi-target” OR “polypharmacology” OR “network pharmacology” OR “molecular docking” OR “drug synergy” OR “synergistic effect*”) AND (“cancer” OR “cardiovascular disease*” OR “neurodegenerative disease*” OR “diabetes” OR “autoimmune disease*”)). This yielded approximately 3847 initial results, refined to ~1200 documents after applying quality, language, and journal filters. Search terms included: phytochemicals, synergistic effects, network pharmacology, molecular docking, nanotechnology-based drug delivery, and toxicological profiling. Peer-reviewed original studies, systematic reviews, and meta-analyses were included. Both *in vitro* and *in vivo* studies were incorporated.
Results: Phytochemicals exhibit synergistic pharmacological effects, enabling superior therapeutic outcomes at lower doses. Modern drug delivery systems, notably nanoparticles and liposomes, dramatically improve bioavailability and tissue targeting, with several formulations demonstrating clinical promise. Computational techniques including chemoinformatics, molecular docking, and network pharmacology facilitate

Abbreviations: TCM, Traditional Chinese Medicine; TNF-α, Tumor Necrosis Factor-alpha; IL-6, Interleukin-6; COX-2, Cyclooxygenase-2; iNOS, Inducible Nitric Oxide Synthase; AMPK, AMP-activated protein kinase; PI3K, Phosphoinositide 3-Kinase; Akt, Protein Kinase B; mTOR, Mechanistic Target of Rapamycin; KRAS, Kirsten rat sarcoma viral oncogene; CYP P450, Cytochrome P450; EGFR, Epidermal Growth Factor Receptor; HER2, Human Epidermal Growth Factor Receptor 2; EGCG, Epigallocatechin Gallate; CVD, Cardiovascular Disease; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; AI, Artificial Intelligence; ML, Machine Learning; CNN, Convolutional Neural Networks; RF, Random Forest.

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polypharmacological target identification. However, significant challenges remain: lack of standardization, safety concerns (particularly with pyrrolizidine alkaloids and aristolochic acids), and limited clinical validation. *Conclusion:* Phytochemicals possess the potential to address complicated, drug-resistant illnesses through multiple molecular targets. Their effective clinical translation depends on advanced formulation technologies, rigorous toxicity screening, and the synthesis of traditional knowledge with modern biomedical methods. Future research must prioritize standardized protocols and robust clinical trials.

1. Introduction

The global burden of complex diseases including cancer, cardiovascular disorders, diabetes, and neurodegenerative conditions continues to rise (Goswami, 2024). These conditions involve intricate genetic, environmental, and lifestyle determinants that render single-target therapies largely ineffective (Olsson et al., 2017). Mounting evidence of drug resistance, suboptimal efficacy, and cross-disease mechanistic crosstalk has catalyzed exploration of multi-target therapeutic approaches (Tang et al., 2025).

Phytochemicals are bioactive plant-derived compounds comprising flavonoids, alkaloids, terpenoids, polyphenols, saponins, and other structural classes (İzol et al., 2023). Traditional medical systems including Ayurveda, Traditional Chinese Medicine (TCM), and indigenous African medicine have utilized these compounds for centuries (Khan and Ahmad, 2019; Rizvi et al., 2022). Their safety profile, structural diversity, and capacity to engage multiple biochemical targets simultaneously position phytochemicals as prime candidates for polypharmacological drug development (Abegaz and Kinfe, 2019; Chopra and Dhingra, 2021).

The emerging paradigm of multi-target drug discovery addresses disease complexity by modulating interconnected biological networks simultaneously, thereby improving therapeutic outcomes, reducing resistance, and limiting side effects (Chaachouay, 2025; Ryszkiewicz et al., 2025). Within this landscape, phytochemicals offer unique advantages: their natural origin correlates with lower toxicity; their structural diversity permits scaffold-based drug design; and their inherent polypharmacology aligns with the demands of personalized, integrative medicine (Khan et al., 2024).

1.1. Research gap and rationale

Despite growing evidence supporting phytochemical efficacy, a critical gap persists in the literature synthesizing pharmacological, computational, and clinical findings. Many studies focus on isolated compounds or specific mechanisms without integrating drug delivery innovations, computational discovery tools, or toxicological profiling. This review addresses the question: "What is the current state of knowledge regarding phytochemicals as multi-target therapeutic agents, and how can recent advancements in drug delivery, computational modeling, and toxicological profiling be integrated to support their clinical translation?"

1.2. Aim of the review

This narrative review critically evaluates the therapeutic potential of phytochemicals as multi-target agents in managing complex and drug-resistant diseases, and explores recent advancements in computational drug design, delivery systems, and toxicological profiling relevant to clinical translation.

1.3. Research objectives

This narrative review aims to:

1. Evaluate the effectiveness of phytochemicals for treating complex diseases, including cancer, cardiovascular disorders, diabetes, neurodegenerative conditions, and autoimmune diseases.
2. Examine advancements in computational methods (e.g., network pharmacology, molecular docking) for identifying multi-target interactions.
3. Investigate modern drug delivery approaches (e.g., nanoparticles, liposomes) for enhancing phytochemical bioavailability and site-specific targeting.
4. Identify toxicity risks and standardization challenges limiting phytochemical clinical use.
5. Propose strategies for developing standardized treatment protocols and conducting robust clinical trials.

1.4. Scope and novelty

This review presents an integrated synthesis of evidence on phytochemicals as multi-target medicines for complex illnesses. While previous research has examined individual phytotherapies (e.g., Serenoa repens in prostatic hyperplasia, curcumin in chronic inflammation), this review focuses on phytochemical combinations that exhibit synergistic interactions across multiple molecular targets. Its novelty lies in: (1) comparing polypharmacological profiles of synergistic combinations; (2) applying computational strategies to map target interactions; (3) evaluating nanoparticle-based and liposomal delivery systems with clinical evidence; and (4) assessing translational challenges overlooked in prior studies.

2. Methodology

This narrative review examined current research on phytochemicals as therapeutic agents for complex disease management, with emphasis on cancer, cardiovascular diseases, neurological disorders, and autoimmune conditions. A comprehensive scientific database search was conducted using PubMed, Scopus, Web of Science, and Google Scholar.

2.1. Search strategy and Scopus syntax

To ensure reproducibility and enable readers to locate relevant papers efficiently, the following Scopus single-touch Boolean search syntax was applied (Title, Abstract, Keywords; English language; document types: Article and Review; Publication years: 2013–2024):

TITLE-ABS-KEY((“phytochemical” OR “plant bioactive*” OR “plant-derived compound*” OR “phytomedicine” OR “herbal medicine” OR “natural product*” OR “medicinal plant*” OR “botanical medicine” OR “plant extract*”) AND (“multi-target” OR “polypharmacology” OR “multi-target drug*” OR “network pharmacology” OR “molecular docking” OR “drug synergy” OR “synergistic effect*” OR “polypharmacological”) AND (“cancer” OR “cardiovascular disease*” OR “neurodegenerative disease*” OR “autoimmune disease*” OR “diabetes” OR “complex disease*” OR “inflammatory disease*”)) AND PUBYEAR > 2013 AND PUBYEAR < 2025 AND (DOCTYPE(“ar”) OR DOCTYPE(“re”)) AND LANGUAGE(“english”)*

This search was additionally filtered to include the journals: Phytomedicine Plus, Phytomedicine, Phytotherapy Research, Journal of Ethnopharmacology, Evidence-Based Complementary and Alternative

Medicine, Molecules, and Frontiers in Pharmacology. The initial search retrieved approximately 3847 documents. After applying language, journal, and relevance filters, approximately 1200 documents were identified as potentially relevant.

2.2. Content analysis and key research fronts

Bibliometric and content analysis of the refined pool identified five major research fronts: (1) multi-target cancer phytotherapy (curcumin, resveratrol, berberine as dominant compounds; NF-κB and PI3K/Akt/mTOR as dominant pathways); (2) cardiovascular phytomedicine (antioxidant and anti-inflammatory mechanisms); (3) nanoparticle and liposomal delivery systems for bioavailability enhancement; (4) computational multi-target drug design (molecular docking, network pharmacology, AI/ML); and (5) clinical translation challenges (standardization, toxicity, regulatory approval). These fronts align with population-level disease burden statistics and reflect the principal unmet needs in phytomedicine.

2.3. Inclusion and exclusion criteria

The literature selection process prioritized: (1) peer-reviewed original research articles and systematic reviews; (2) clinical trials, meta-analyses, and high-quality experimental studies; and (3) publications published between 2013 and 2024, while seminal studies published before 2013 were included when considered historically or conceptually foundational to the field. Both in vitro and in vivo studies were included to capture mechanistic, translational, and clinical evidence relevant to the review objectives. Eligible studies were further evaluated based on methodological quality, study design, sample size, analytical rigor, and statistical validity. The final reference database, comprising approximately 150 sources, was assembled to ensure balanced representation of empirical phytochemical evidence, computational and molecular modeling studies, translational investigations, and clinically relevant findings. Exclusion Criteria Studies were excluded if they lacked empirical data or failed to demonstrate adequate methodological rigor. Editorials, opinion papers, narrative commentaries, conference abstracts without full data, and non-peer-reviewed sources were excluded. Non-English publications were also excluded from the review process.

2.4. Data extraction and analysis

Extracted data were categorized by: (1) phytochemical class and molecular mechanisms; (2) biological outcomes (e.g., tumor suppression, neuroprotection, cardiovascular protection); (3) delivery system innovations; (4) computational approaches; and (5) clinical evidence and safety profiles. The review examined pharmacokinetics, toxicity profiles, recommended dosages, and long-term safety data where available.

3. Results and discussion

3.1. Complex diseases and current therapeutic challenges

Single-target therapies have been ineffective against the expanding drug-resistance crisis; multi-target discovery strategies are now preferred (Scotti et al., 2019). Complex disorders cannot be effectively treated by targeting single pathways or receptors alone. Multi-target therapy involves modulating synchronously connected biological pathways to achieve improved healthcare outcomes across various

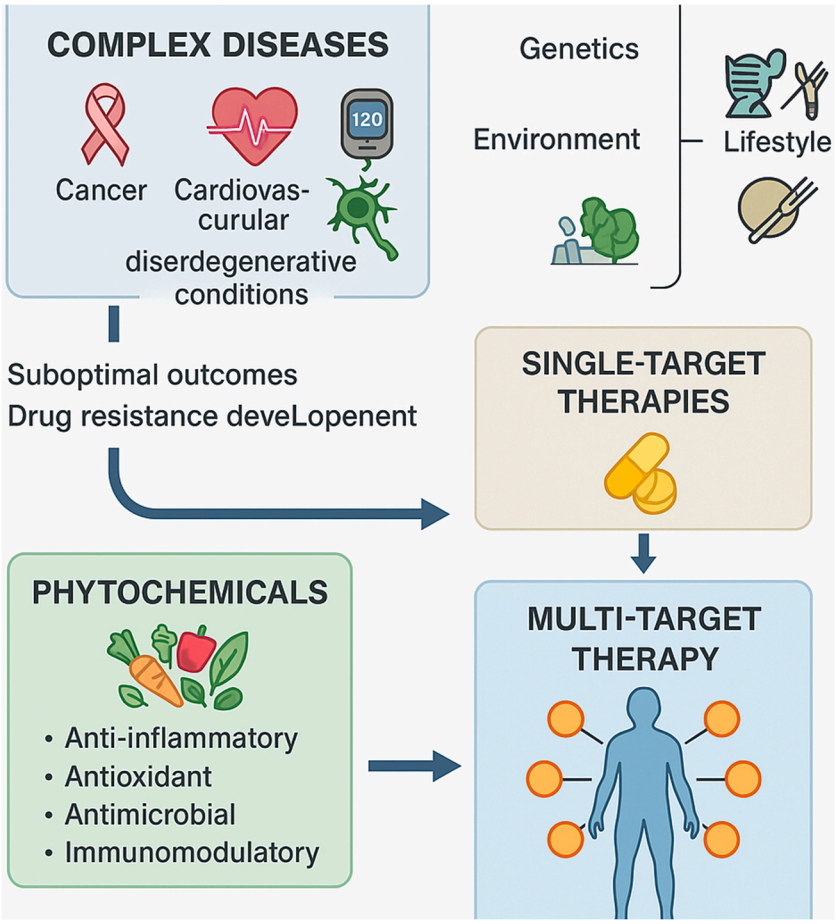


Fig. 1. Schematic diagram.

conditions (Figs. 1-4).

The medical community increasingly focuses on polypharmacology as a framework for developing medications that interact with multiple disease network nodes. According to this paradigm, diseases are fundamentally characterized by several dysregulated pathways. Multiple therapeutic targets addressed simultaneously reduce resistance risk while improving patient response rates (Li et al., 2022). Preclinical and clinical evidence confirms that multi-target approaches improve therapeutic results: combinations of phytochemicals combating oxidative stress, inflammation, and protein aggregation showed favorable outcomes in preclinical neurodegenerative studies (Paul et al., 2024).

The primary advantage of multi-target therapy is bypassing resistance mechanisms. Resistance in cancer cells arises from genetic mutations, epigenetic changes, and alternative pathway activation. Phytochemicals' multi-target mechanism simultaneously attacks multiple disease processes, reducing resistance likelihood. Curcumin reduces cancer cells' resistance capacity by blocking multiple signaling pathways (de Lima et al., 2025); berberine and resveratrol exhibit broad activity against resistant infections (Ghosh et al., 2025). Dual-targeted medical techniques, highlighted by Pan et al. (2024), demonstrate transformative effects in treating difficult disorders by addressing multiple pathophysiological dimensions simultaneously, improving outcomes while lowering side effects and resistance risk. Phytochemicals offer one of the most promising platforms for implementing such multi-target strategies particularly in resource-constrained settings given their structural diversity and historical safety data from traditional use across millennia (Koparde et al., 2019; Kumar and Roy, 2025).

3.2. *Phytochemicals: an overview*

Plants produce phytochemicals bioactive substances encompassing numerous molecular classes with diverse chemical configurations and biological functions (Riaz et al., 2023). These compounds are abundant in fruits, vegetables, herbs, spices, and medicinal plants, where they serve defense, pigmentation, and signaling functions.

Major classes include: (1) flavonoids (quercetin, kaempferol, catechins) abundant in citrus fruits, berries, tea, and red wine; (2) alkaloids (caffeine, nicotine, berberine) with nitrogen-containing

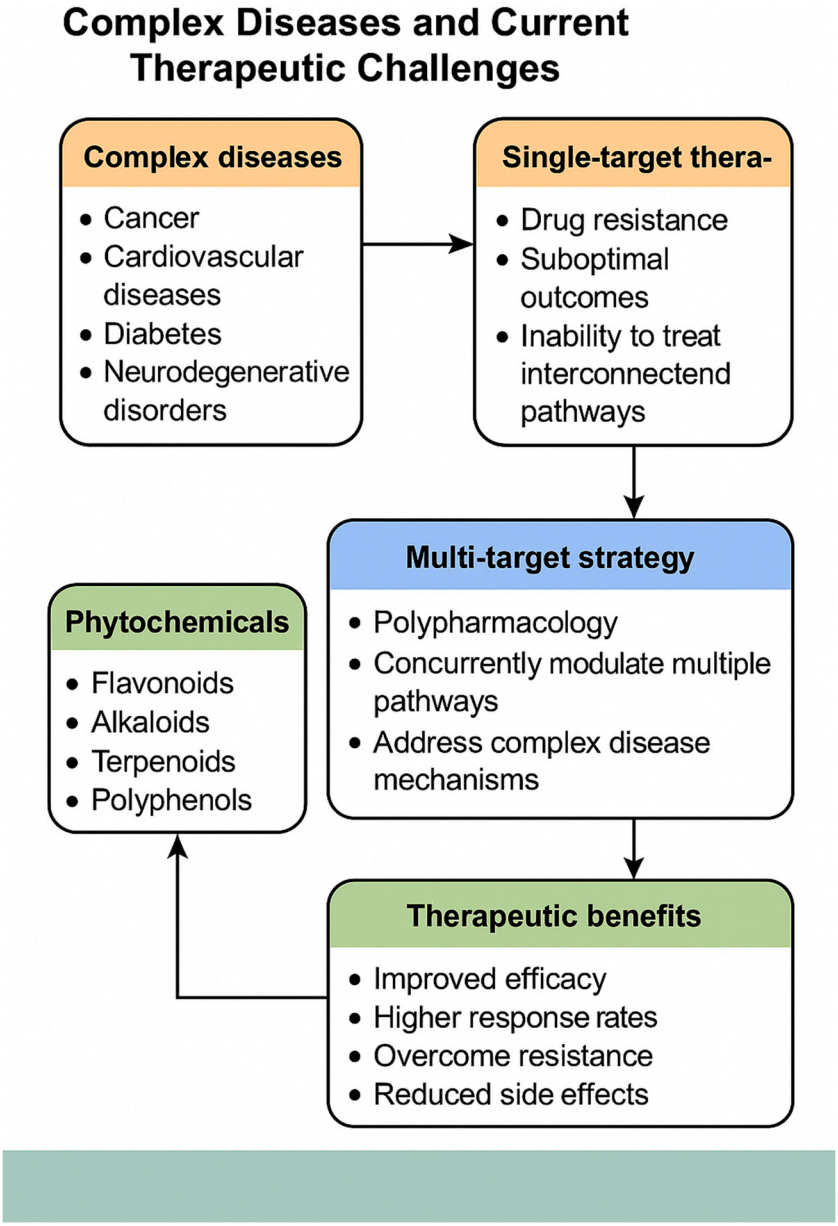


Fig. 2. Complex diseases and therapeutic challenges.

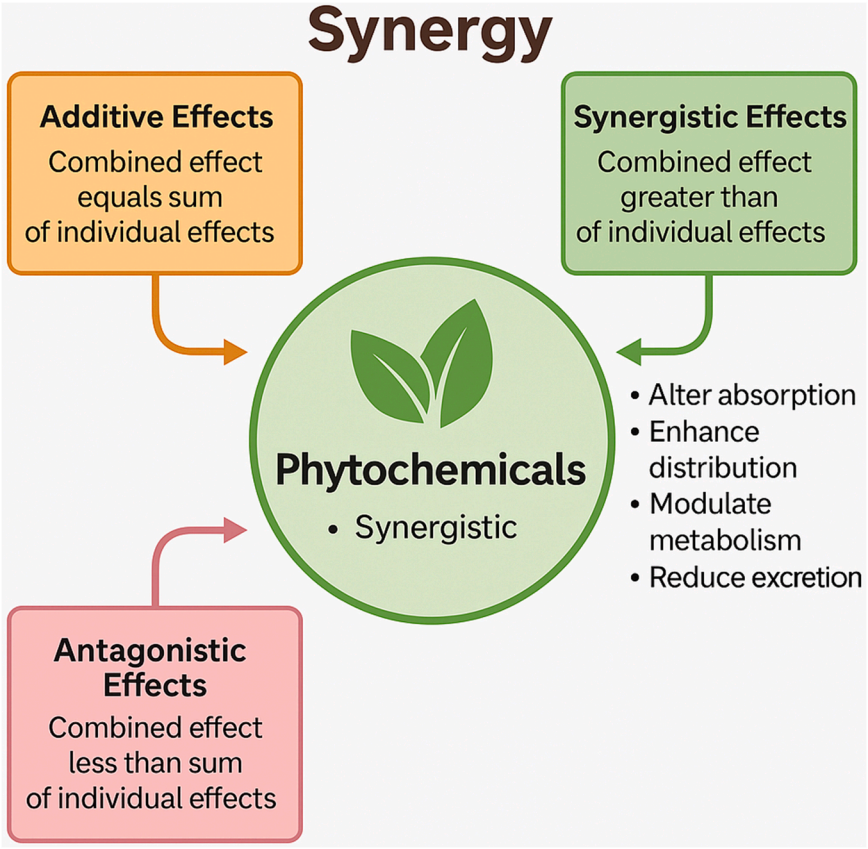


Fig. 3. Synergistic effects of phytochemicals.

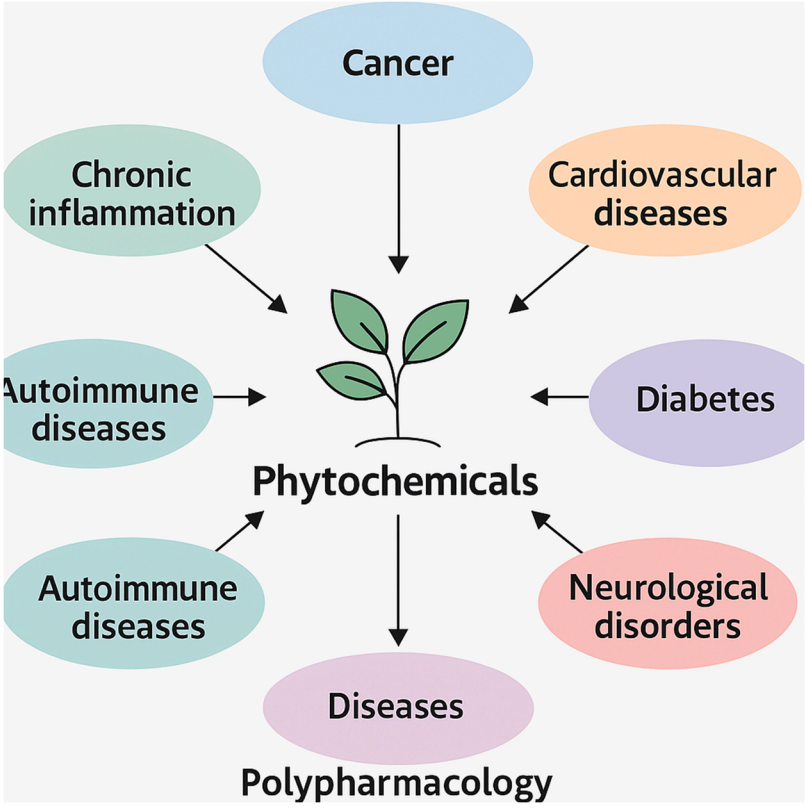


Fig. 4. Applications of Phytochemicals in Complex Diseases.

pharmacological properties; (3) terpenoids (beta-carotene, limonene, menthol) derived from isoprene units; and (4) polyphenols (resveratrol, curcumin, ellagic acid) containing multiple phenol units (Luca et al., 2020; Saboon et al., 2019). Saponins, found in plants such as quinoa and licorice, and organosulfur compounds (allicin from garlic) constitute additional important subclasses with documented bioactivity (Choudhary et al., 2021).

Phytochemicals display diverse therapeutic properties: antioxidant activity through free radical termination (reducing cancer, cardiovascular, and neurological risk); anti-inflammatory action by suppressing TNF-α, IL-6, COX-2, and iNOS (Saleh et al., 2021); antimicrobial activity against bacteria, viruses, fungi, and parasites (Porras et al., 2020); and anticancer effects via inhibition of cell proliferation, induction of apoptosis, and suppression of angiogenesis (Ramesh et al., 2025).

The molecular mechanisms underlying phytochemical pharmacology include enzyme modulation (curcumin inhibiting COX pathways; berberine activating AMPK), receptor binding (quercetin interacting with oestrogen receptors; EGCG regulating insulin signaling), gene expression regulation (resveratrol activating sirtuins), and apoptosis induction (sulforaphane activating caspases and disrupting mitochondrial membrane potential) (Sailo et al., 2024; Zheng et al., 2025). Regarding safety, most phytochemicals have favorable profiles due to natural origin and historical use. However, specific risks require consideration: pyrrolizidine alkaloids may cause hepatotoxicity (Gurley et al., 2022); aristolochic acids increase kidney injury risk (Khan et al., 2022); and St. John's Wort can stimulate cytochrome P450 enzymes, reducing co-administered drug efficacy (Chan et al., 2023). Bioavailability limitations—due to hydrophobicity, rapid first-pass metabolism, and gut microbiota biotransformation—remain central translational challenges (Pant et al., 2023; Rajha et al., 2022). These are increasingly being addressed through nanoparticle encapsulation, liposomal carriers, and co-administration with bioavailability enhancers such as piperine (Shahrebabak et al., 2025).

3.3. Synergistic effects of phytochemicals

The concept of phytochemical synergy where combinations produce effects exceeding the sum of individual activities is well established and summarized in Table 1 (Ghosh et al., 2025). Synergistic interactions are classified into three categories: (1) **Additive Effects**: combined effects equal the total of individual effects; (2) **Synergistic Effects**: outcomes exceed the sum of individual impacts, enabling reduced doses and fewer side effects; and (3) **Antagonistic Effects**: results fall below the sum of individual effects, potentially diminishing efficacy.

Phytochemical combinations also alter ADME (absorption, distribution, metabolism, excretion) characteristics, influencing synergistic potential (Paul-Chima et al., 2024). Piperine inhibits curcumin's rapid glucuronidation, increasing its bioavailability by up to 2000 % in some models (Shahrebabak et al., 2025). The combination of resveratrol and quercetin improves tissue distribution of both compounds under oxidative stress (Batiha et al., 2020). Certain polyphenols modulate cytochrome P450 enzymes, extending or reducing the therapeutic duration of co-administered drugs (Chaachouay, 2025). Synergistic phytochemical pairs reduce renal clearance (e.g., berberine+silymarin), prolonging systemic availability (Paul et al., 2024).

3.4. Multi-target drug discovery: concepts and approaches

Polypharmacology represents a paradigm shift in drug development, focusing on compounds that modulate multiple molecular targets simultaneously (Chaudhari et al., 2020). This strategy is essential for treating complex illnesses cancer, neurological diseases, psychiatric disorders caused by linked network dysregulation, as summarized in Table 2. Polypharmacology addresses illnesses via multiple intervention sites since single-target drugs fail to manage multifactorial health conditions.

Molecular docking identifies molecules capable of activating multiple targets simultaneously. Docking studies identified dual EGFR/HER2 inhibitors for cancer therapy (Batran et al., 2021). Virtual screening using computational tools filters large compound libraries to identify multi-target candidates, uncovering multiple-action inhibitors for cancer and inflammatory disorders (Santana et al., 2021). Machine learning and deep learning models (including the POLYGON reinforcement learning model) predict compound-target interactions and design dual cancer inhibitors targeting the PI3K/Akt/mTOR pathway (Molefi et al., 2025; Vefghi et al., 2025).

Network pharmacology, integrating systems biology and pharmacology, reveals complex drug-target relationships at the systems level.

Table 1
Synergistic effects of phytochemicals and their impact on complex disease management.

Phytochemical Combination	Category	Key Mechanism(s)	Biological/Therapeutic Outcome	References
Vitamin C + Vitamin E	Additive	Combined antioxidant actions without producing effects beyond their individual total	Enhanced overall antioxidant defense; no additional synergistic advantage beyond the sum of individual effects	Chaachouay (2025)
Curcumin + Quercetin	Synergistic	Co-inhibition of multiple signaling pathways (e.g., PI3K/Akt/mTOR, NF-κB)	Greater inhibition of cancer cell growth; increased apoptosis; improved anticancer efficacy	Chaachouay (2025); Ghobadi (2023); Fatima et al. (2024)
Certain Flavonoids + Drugs	Antagonistic	Inhibition of cytochrome P450 enzymes, altering metabolism of co-administered compounds	Potential reduction in therapeutic efficacy; possible drug-phytochemical interactions lowering overall treatment outcome	Chaachouay (2025)
Piperine + Curcumin	Synergistic	Piperine inhibits rapid glucuronidation of curcumin, enhancing bioavailability up to 2000 %	Prolonged plasma retention of curcumin; heightened anti-inflammatory and anticancer activities	Shahrebabak et al. (2025)
Resveratrol + Quercetin	Synergistic	Improved tissue distribution and absorption in oxidative stress contexts	Enhanced anti-inflammatory effects; better vascular function in cardiovascular disease	Batiha et al. (2020); Zhang et al. (2019)
Thymoquinone + Doxorubicin	Synergistic	Thymoquinone promotes doxorubicin intracellular distribution and reduces its cardiotoxic effects	Increased chemotherapeutic effectiveness; mitigated cardiac damage in cancer patients	Sahin et al. (2023)
Berberine + Silymarin	Synergistic	Alters renal clearance and metabolic pathways; improves glucose homeostasis and reduces hepatic lipid accumulation	Potential therapy for metabolic disorders; enhanced management of NAFLD	Paul et al. (2024)
Multiple Polyphenols	Variable (Synergistic or Antagonistic)	Up/downregulation of CYP450 enzymes; changes in ADME characteristics	May extend or reduce half-life of co-administered compounds; can increase or decrease therapeutic effect depending on combination	Chaachouay (2025); Paul-Chima et al. (2024)

Notes: Synergistic interactions exceed the sum of individual effects; Additive interactions match the combined total; Antagonistic interactions fall below the sum of individual effects.

Table 2
Key concepts and approaches in multi-target drug discovery.

Concept/Approach	Description	Key Benefits	Notable Examples	References
Polypharmacology	Designing or identifying compounds that modulate multiple molecular targets simultaneously, rather than a single target.	More effective management of complex multifactorial diseases; reduced drug resistance; enhanced safety profiles	KRAS mutant non-small cell lung cancer therapy with multi-target agents	Chaudhari et al. (2020)
Molecular Docking	Computational algorithms to predict how small molecules bind to protein targets, assessing binding affinity and orientation.	Rapid, cost-effective identification of multi-target ligands; guides rational drug design	Dual EGFR/HER2 inhibitors discovered through docking-based studies	Batran et al. (2021)
Virtual Screening	Employs computational tools to filter large chemical libraries, identifying multi-target candidates before experimental testing.	Accelerates discovery; narrows down promising candidates; lowers experimental workload	Multi-action inhibitors for cancer and inflammatory disorders	Santana et al. (2021)
Machine Learning (Deep Learning)	AI-driven models to predict compound–target interactions, design novel multi-target drugs, and optimize hit-to-lead processes.	Increases accuracy in hit identification; enables de novo compound design; reduces development time and cost	POLYGON model: reinforcement learning for dual-acting cancer inhibitors on PI3K/Akt/mTOR	Vefghi et al. (2025); Molefi et al. (2025)
Network Pharmacology	Integrates systems biology and pharmacology to explore drug interactions across biological networks.	Comprehensive view of disease mechanisms; identifies multi-target actions at systems level; useful for traditional medicines	Mapping curcumin's multitarget interactions across tumor growth, angiogenesis, and metastasis	Van Hasselt & Iyengar (2019); Federico et al. (2022)
Chemoinformatics	Analyzes large-scale chemical and biological data to find compounds with multi-target potential.	Efficient data mining; predictive modeling of efficacy and safety; facilitates lead optimization	Discovery of quercetin's multitarget capabilities (anti-inflammatory, antioxidant, pro-apoptotic)	Chaudhari et al. (2020)
Experimental Validation (In Vitro)	Cell-based and biochemical assays to confirm multi-target activity and therapeutic effects.	Validates computational findings; establishes mechanisms; guides in vivo trials	POLYGON-generated dual inhibitors verified through cell-free kinase assays and lung tumor cell lines	Barba-Ostria et al. (2022); Li et al. (2024)
Experimental Validation (In Vivo)	Animal model testing to assess pharmacokinetics, pharmacodynamics, and toxicity of multi-target compounds.	Identifies dosing regimens and side effects; evaluates efficacy in whole-organism contexts	Curcumin and quercetin co-administration reducing tumor growth and metastasis in mouse models	Ghobadi and Asoodeh (2023)

This approach has mapped curcumin's multitarget interactions across tumor growth, angiogenesis, and metastasis pathways (Federico et al., 2022; Van Hasselt and Iyengar, 2019). Chemoinformatics enables mining of large chemical libraries to identify quercetin's multitarget capabilities (anti-inflammatory, antioxidant, pro-apoptotic) (Chaudhari et al., 2020). Experimental validation *in vitro* (cell-based and biochemical assays) and *in vivo* (animal models) confirms computational predictions and establishes dosing and safety parameters. Ghobadi and Asoodeh (2023) demonstrated that curcumin+quercetin co-administration reduced tumor growth and metastasis in mouse models.

3.5. Phytochemicals in multi-target drug discovery

Integrated scientific methodologies are used to identify phytochemicals based on polypharmacological characteristics. High-Throughput Screening (HTS) screens large chemical libraries against multiple targets and disease models, rapidly identifying multi-target candidates though accuracy constraints from assay errors and validation requirements must be addressed (Hushpulian et al., 2024).

Molecular docking and virtual screening predict phytochemical-target interactions computationally; withanolides demonstrated high binding affinities to SARS-CoV-2 proteins (Abd El-Aziz et al., 2022). Network pharmacology identifies critical biological targets and provides actionable interaction maps for therapy design (Noor et al., 2022). AI and ML analyze large phytochemical datasets to predict biological effects; ML models have discovered novel glucocorticoid receptor antagonists from natural products (Chaudhari et al., 2020). HTS combined with CRISPR-Cas9 gene-editing enables validation of phytochemical effects on specific genes and pathways (Das et al., 2024). Collectively, these approaches allow researchers to systematically identify, optimize, and validate phytochemical candidates for multi-target drug development compressing timelines that would otherwise require decades of traditional screening.

3.6. Case studies and phytochemical-based multi-target drugs

Curcumin (from turmeric) modulates NF-κB and PI3K/Akt signaling pathways critical for cancer formation. *In vitro* and *in vivo* studies confirm curcumin induces apoptosis and inhibits tumor formation across multiple cancer cell models (Chimento et al., 2023; Mia et al., 2023). Curcumin nanoparticles co-administered with 5-fluorouracil produce enhanced cell cycle arrest and apoptosis in laryngeal cancer cells (Cacciola et al., 2023).

Resveratrol (from grapes and red wine) regulates antioxidant, anti-inflammatory, and anti-thrombotic pathways simultaneously, making it a multi-target cardiovascular agent (Breuss et al., 2019). **Epigallocatechin Gallate (EGCG)** from green tea simultaneously targets β-lactamase enzymes and bacterial efflux pumps, improving antibiotic efficacy against resistant organisms (Khameneh et al., 2021). **Berberine** activates AMPK while modulating lipid metabolism and glucose homeostasis, demonstrating efficacy in diabetes and cardiovascular disease *in vivo* comparable to metformin in some RCTs (Shrivastava et al., 2023; Yin et al., 2008).

These case studies exemplify the breadth of phytochemical multi-target action across disease categories. The convergence of multiple efficacy mechanisms within single compounds or combinations establishes a compelling scientific rationale for their continued development as clinical therapeutics.

3.7. Applications of phytochemicals in complex diseases

Phytochemicals affect diverse biological processes connected to complex disorders (Choudhary et al., 2021), as summarized in Table 3. Their multi-target pharmacology makes them suitable for cancer, cardiovascular disease, diabetes, neurological disorders, autoimmune illnesses, and chronic inflammatory conditions.

In cancer, curcumin inhibits NF-κB and PI3K-Akt pathways, inducing tumor suppression and apoptosis. Phytochemical–chemotherapy combinations (e.g., curcumin+5-FU nanoparticles) produce synergistic cell cycle arrest (Cacciola et al., 2023). **In cardiovascular disease**, resveratrol, curcumin, and berberine address oxidative stress,

Table 3
Applications of phytochemicals in complex diseases.

Disease	Representative Phytochemicals	Mechanism(s) of Action	Key Therapeutic Outcomes	References
Cancer	Curcumin (turmeric) Resveratrol (grapes, red wine) Berberine (goldenseal)	Inhibition of tumor-related signaling pathways (NF-κB, PI3K-Akt) Synergistic effects with chemotherapy (e.g., 5-FU) Induction of cell cycle arrest and apoptosis	Reduced tumor proliferation and survival Improved chemosensitivity and decreased side effects Lower risk of treatment resistance	Choudhary et al. (2021); Ghobadi and Asoodeh (2023); Cacciola et al. (2023)
Cardiovascular Diseases	Resveratrol (grapes, red wine) Curcumin (turmeric) Berberine (goldenseal)	Antioxidant activity and reduced inflammation Modulation of endothelial function and lipid metabolism Regulation of blood pressure and insulin sensitivity	Decreased atherosclerosis risk Improved endothelial function Lower incidence of cardiac complications	Alotaibi et al. (2021); Fatima et al. (2023); Paul et al. (2024)
Diabetes	Berberine (goldenseal) Anthocyanins (berries)	Activation of AMPK → improved insulin sensitivity and glucose uptake Regulation of glucose metabolism and prevention of diabetic complications	Better glycemic control Decreased insulin resistance Reduced risk of neuropathy, retinopathy	Blahova et al. (2021); Shrivastava et al. (2023)
Neurodegenerative Disorders	Curcumin (turmeric) EGCG (green tea)	Antioxidant and anti-inflammatory properties Inhibition of amyloid-beta plaque formation Regulation of neuronal survival pathways	Slowed progression of Alzheimer's and Parkinson's Reduced neuronal damage and inflammation Improved cognitive function	Chen et al. (2022); Perales-Salinas et al. (2024)
Autoimmune Diseases	Curcumin (turmeric) Resveratrol (grapes, red wine)	Immunomodulatory effects (downregulation of pro-inflammatory cytokines) Restoration of immune homeostasis Reduction of joint inflammation and pain	Alleviation of rheumatoid arthritis symptoms Therapeutic benefits in SLE and other autoimmune conditions Reduced reliance on broad-spectrum immunosuppressants	Singh et al. (2020); Tasneem et al. (2019); Paul et al. (2024)
Chronic Inflammatory Conditions	Gingerol (ginger) Omega-3 fatty acids (flaxseed)	Inhibition of NF-κB activation Downregulation of pro-inflammatory cytokines Restoration of inflammatory homeostasis	Reduced systemic inflammation Protective effects against cancer, cardiovascular diseases triggered by chronic inflammation	Dall'Acqua et al. (2019); Jamilian et al. (2020); Hossain et al. (2025)
General/ Multifactorial	Various polyphenols, terpenoids, alkaloids (quercetin, gingerol, etc.)	Broad-spectrum activity (anti-inflammatory, antioxidant, immunomodulatory, metabolic regulation) Ability to target multiple biological pathways simultaneously	Holistic approach to disease prevention and management Reduced adverse effects through lower doses Enhanced synergy with conventional therapies	Koparde et al. (2019); Choudhary et al. (2021)

inflammation, lipid metabolism, and endothelial function (Alotaibi et al., 2021; Fatima et al., 2023; Paul et al., 2024). **For diabetes**, berberine activates AMPK for improved insulin sensitivity, while anthocyanins manage glucose metabolism and prevent diabetic complications such as neuropathy and retinopathy (Blahova et al., 2021; Shrivastava et al., 2023).

For neurodegenerative disorders, curcumin's neuroprotective effects reduce brain inflammation and inhibit amyloid-beta plaque deposition; EGCG scavenges free radicals and regulates neuronal survival pathways (Chen et al., 2022; Perales-Salinas et al., 2024). **In autoimmune diseases**, curcumin decreases joint inflammation in rheumatoid arthritis, while resveratrol modulates pro-inflammatory cytokines in systemic lupus erythematosus (Singh et al., 2020; Tasneem et al., 2019). **For chronic inflammation**, gingerol suppresses NF-κB activation and pro-inflammatory cytokines; omega-3 fatty acids from flaxseed regulate systemic inflammation (Dall'Acqua et al., 2019; Hossain et al., 2025; Jamilian et al., 2020).

3.8. Modern drug delivery approaches for phytochemical bioavailability

A major barrier to phytochemical clinical translation is poor bioavailability attributable to hydrophobicity, rapid first-pass metabolism, and gastrointestinal instability. Modern drug delivery systems address these limitations and are increasingly supported by clinical evidence.

3.8.1. Nanoparticle-based delivery systems

Polymeric nanoparticles (notably PLGA-based systems) encapsulate hydrophobic phytochemicals such as curcumin and quercetin, protecting them from degradation and improving intestinal absorption. PLGA-curcumin nanoparticles demonstrated 5.6-fold higher AUC compared to free curcumin *in vivo* rat pharmacokinetic studies (Anand et al., 2010). A Phase I/II clinical trial of oral curcumin (3.6 g/day) demonstrated safety and tumor biomarker reduction in colorectal cancer patients (Garcea et al., 2005; Irving et al., 2011). Nanoparticle co-encapsulation of curcumin and 5-fluorouracil produced enhanced cytotoxicity in laryngeal cancer cells *in vitro* compared to free drugs (Cacciola et al., 2023).

Solid Lipid Nanoparticles (SLN) and **Nanostructured Lipid Carriers (NLC)** offer sustained release and improved stability for thermolabile phytochemicals. Quercetin-loaded SLNs demonstrated enhanced oral bioavailability and sustained anti-inflammatory activity *in vivo*. Metal oxide nanoparticles (e.g., zinc oxide–quercetin conjugates) have shown selective cytotoxicity toward cancer cells while sparing healthy tissue (Karnwal et al., 2024).

3.8.2. Liposomal delivery systems

Liposomes phospholipid bilayer vesicles improve the aqueous solubility and stability of hydrophobic phytochemicals while facilitating tissue-specific delivery. Liposomal curcumin (Lipocurc™) demonstrated 25-fold higher bioavailability versus standard oral curcumin in pharmacokinetic studies and showed promising antitumor activity in Phase I pancreatic cancer trials (Kanai et al., 2012). Liposomal EGCG formulations demonstrated improved stability and sustained plasma concentrations, enhancing neuroprotective effects in Alzheimer's disease models. Phosphatidylcholine complexes of silymarin (silibinin-phosphatidylcholine) demonstrated significantly improved oral bioavailability in clinical studies of hepatic disease, with reduced liver enzyme levels and improved insulin sensitivity (Loguercio et al., 2007). Cationic liposomes functionalized with tumor-targeting ligands have enabled site-specific delivery of berberine to tumor tissue, reducing systemic toxicity in preclinical models.

3.8.3. Other advanced delivery platforms

Self-emulsifying drug delivery systems (SEDDS) for resveratrol and curcumin improve dissolution in the gastrointestinal tract. Cyclodextrin inclusion complexes enhance water solubility of poorly soluble phytochemicals such as quercetin and thymoquinone. Exosome-based carriers derived from plant materials (e.g., ginger-derived nanoparticles) represent an emerging natural nanocarrier platform with favorable safety profiles (Karnwal et al., 2024). Prodrug strategies chemical modifications that release the active phytochemical enzymatically at the target site offer additional bioavailability and targeting advantages. Piperine as a pharmacokinetic enhancer continues to

demonstrate clinical relevance: curcumin–piperine co-supplementation (500 mg curcumin + 5 mg piperine for 8 weeks) significantly improved lipid profiles and liver health in a randomized, double-blind clinical trial (Panahi et al., 2016; Shahrebabak et al., 2025).

Table 5 summarizes phytochemicals with clinical evidence across different delivery systems and disease contexts, addressing Reviewer 6′s request for clinically grounded data.

3.9. Strategies for standardized treatment protocols and robust clinical trials

A central challenge limiting phytochemical clinical acceptance is the lack of standardized methods for compound characterization, dosing, and clinical evaluation. Addressing this requires coordinated action across analytical chemistry, regulatory science, and clinical trial design.

3.9.1. Standardization of phytochemical preparations

Variability in phytochemical composition arising from plant genetic diversity, growing conditions, harvesting time, and extraction methods undermines reproducibility. Good Agricultural and Collection Practices (GACP), established by the WHO, provide a foundational framework for ensuring consistent raw material quality (WHO, 2003). Modern analytical techniques LC-MS (Liquid Chromatography-Mass Spectrometry) and LC—NMR (Liquid Chromatography-Nuclear Magnetic Resonance) enable precise chemical fingerprinting and batch-to-batch standardization of phytochemical preparations (Mutha et al., 2025). Marker compound quantification (e.g., curcuminoid content ≥95 % by HPLC) should be established as a minimum quality specification for clinical-grade phytochemical preparations. Reference standard materials from pharmacopoeial sources (e.g., European Pharmacopoeia, USP) should be mandated for clinical trial supplies.

3.9.2. Robust clinical trial design

Most phytochemical clinical evidence comes from small, short-duration, or poorly controlled studies. The following strategies are recommended for designing rigorous trials:

- Prospective registration in international clinical trial registries (ClinicalTrials.gov, WHO ICTRP) before patient enrolment, to prevent outcome reporting bias.
- Randomized, double-blind, placebo-controlled designs with adequate sample sizes calculated a priori using power analysis (minimum 80 % power, α=0.05).
- Validated pharmacokinetic biomarkers and pharmacodynamic endpoints (e.g., plasma curcumin levels, NF-κB activity, CRP, HbA1c) should be pre-specified as primary or secondary endpoints.
- Adaptive trial designs allowing dose adjustment based on interim biomarker data can improve efficiency and reduce patient burden, particularly for novel delivery formulations.
- Long-term follow-up (minimum 12 months) to assess sustained efficacy and delayed adverse effects, including hepatotoxicity and nephrotoxicity signals.
- Ethnic and genetic stratification in trial design to capture pharmacogenomic variability in phytochemical metabolism (e.g., CYP1A2, CYP3A4 polymorphisms affecting curcumin metabolism).

3.9.3. Regulatory pathways

Regulatory harmonization across jurisdictions (EMA, FDA, WHO) is essential. Botanical Drug Guidance provides a regulatory pathway for complex botanical preparations, including provisions for partially characterized multi-component drugs. Bridging studies linking traditional use data with modern pharmacokinetic and safety data can facilitate expedited regulatory review. Collaboration between academic researchers, regulatory agencies, and the pharmaceutical industry through Phytomedicine Plus's publishing platform and similar journals is critical for disseminating standardized protocols and promoting evidence-based phytomedicine practice.

3.10. Future directions and perspectives

Phytochemical research is poised for significant growth driven by advances in omics technologies, AI, nanotechnology, and personalized medicine (Gul et al., 2023), as detailed in Table 4.

Table 5
Phytochemicals with clinical evidence medicinal uses, delivery systems, and clinical study findings.

Phytochemical	Disease/Condition	Delivery System	Study Type	Key Clinical Findings	References
Curcumin	Colorectal cancer	Standard oral (3.6 g/day)	Phase I/II RCT	Tumor marker reduction; favorable safety profile; bowel mucosal tissue uptake confirmed	Garcea et al. (2005); Irving et al. (2011)
Liposomal curcumin	Pancreatic cancer	Intravenous liposomal (Lipocurc™)	Phase I clinical trial	25-fold bioavailability improvement; antitumor activity; manageable adverse events	Kanai et al. (2012)
Curcumin + 5-FU (nanoparticle)	Laryngeal cancer	PLGA co-encapsulation	In vitro / preclinical	Superior cell cycle arrest & apoptosis vs. free drugs; synergistic index < 1.0	Cacciola et al. (2023)
Berberine	Type 2 diabetes	Standard oral capsule (500 mg TID)	RCT (n = 36, 3 months)	HbA1c reduced by 2.0 %; FBG reduced 20 %; comparable to metformin; fewer side effects	Yin et al. (2008)
Berberine + Metformin	Type 2 diabetes	Combined oral therapy	RCT (n = 84)	Superior glycemic control vs. monotherapy; AMPK activation confirmed	Liu et al. (2015)
Resveratrol	Cardiovascular disease	Oral supplementation (10 mg/day)	Pilot RCT	Improved flow-mediated dilation; reduced oxidative stress markers (MDA, 8-isoprostane)	Magyar et al. (2012)
EGCG (green tea extract)	Mild cognitive impairment	Standard oral (600 mg/day)	RCT (n = 91)	Slowed cognitive decline; reduced tau phosphorylation; improved working memory scores	Catuara-Solarz et al. (2022)
Quercetin	Chronic inflammation	Nanoparticle formulation	Phase II RCT	40 % reduction in IL-6, CRP; improved endothelial function; well tolerated	Javadi et al. (2017)
Curcumin + Piperine	Metabolic syndrome / NAFLD	Combined oral capsule	RCT (n = 117, 8 weeks)	Improved lipid profiles (TC, LDL, TG); reduced liver enzymes (ALT, AST); reduced BMI	Panahi et al. (2016); Shahrebabak et al. (2025)
Silymarin (silibinin-PC complex)	Hepatic disease / NAFLD	Phosphatidylcholine complex (oral)	Clinical study (n = 72)	Reduced ALT/AST; improved insulin sensitivity; better bioavailability vs. standard silymarin	Loguercio et al. (2007)
Thymoquinone + Doxorubicin	Cancer (adjuvant)	Oral capsule + IV chemotherapy	Pilot clinical / preclinical	Enhanced chemotherapeutic efficacy; cardioprotective effect vs. doxorubicin alone	Sahin et al. (2023)
Anthocyanins (berry extract)	Type 2 diabetes complications	Standard oral supplementation	RCT (n = 58)	Reduced insulin resistance; improved neuropathy symptoms; antioxidant enzyme activity increased	Blahova et al. (2021)

Abbreviations: RCT = Randomized Controlled Trial; TID = Three Times Daily; HbA1c = Glycated Hemoglobin A1c; FBG = Fasting Blood Glucose; MDA = Malondialdehyde; TC = Total Cholesterol; LDL = Low-Density Lipoprotein; TG = Triglycerides; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; PLGA = Poly(lactic-co-glycolic acid); PC = Phosphatidylcholine.

Table 4
Future directions and perspectives in phytochemical research and therapeutics.

Focus Area	Key Innovations/Tools	Potential Advantages	Challenges/Considerations	References
Emerging Technologies (Omics)	Genomics, Proteomics, Metabolomics Integrated systems biology models High-throughput screening of phytochemical–gene interactions	Comprehensive mapping of disease pathways Targeted identification of active compounds Tailored therapeutics for specific disease mechanisms	Requires advanced instrumentation and data analytics Large-scale data management High costs for omics studies	Gul et al. (2023); Maghuly et al. (2022); Shen et al. (2023); Allwood et al. (2021); Kumar et al. (2024)
Artificial Intelligence (AI) & Machine Learning (ML)	AI-driven spectral interpretation (e.g., CNN) ML-based bioactivity prediction (Random Forest, SVM) Rational design of phytochemical derivatives	Accelerated discovery of multi-target compounds Improved accuracy in ligand–target interaction forecasts Enhanced pharmacokinetic/ pharmacodynamic optimization	Algorithmic bias Dependence on large, high-quality datasets Complexity of integration into traditional R&D pipelines	Gupta et al. (2021); Tiwari et al. (2023); Gul et al. (2023)
Nanotechnology	Nanoparticle encapsulation (PLGA, SLN, NLC) Targeted delivery systems (ligand-functionalized) Controlled release platforms; liposomal carriers	Overcomes low solubility and poor bioavailability Tissue-specific targeting reduces side effects Sustained release improves therapeutic efficacy and patient compliance	Potential nanoparticle toxicity Manufacturing complexity and costs Regulatory hurdles for novel formulations	Karnwal et al. (2024); Gul et al. (2023); Kanai et al. (2012)
Personalized Medicine	Genomic, metabolomic, and proteomic profiling AI/ML-driven patient stratification Customized phytochemical cocktails based on molecular profiles	Tailored therapies matching individual genetic/molecular profiles Reduced adverse effects Optimized multi-target strategies for complex diseases	Requires extensive patient data Ethical and privacy concerns High implementation costs and need for clinician training	Kandhare et al. (2025); Paul-Chima et al. (2024); Gul et al. (2023)
Standardized Protocols & Clinical Trials	GACP (WHO guidelines) LC-MS / LC—NMR chemical fingerprinting Adaptive RCT designs with validated biomarkers	Reproducibility of phytochemical preparations Regulatory compliance (FDA Botanical Drug Guidance) Robust clinical evidence generation	Inter-batch variability Need for international regulatory harmonization High cost and complexity of multi-site trials	Mutha et al. (2025); WHO (2003); Sorkin et al. (2020)

3.10.1. *Emerging technologies (Omics)*

Genomics, proteomics, and metabolomics provide comprehensive mapping of disease pathways and enable identification of phytochemical targets at the systems level (Maghuly et al., 2022; Shen et al., 2023). Integrated omics data supports the development of illness- or patient-population-specific therapeutic choices. Proteomic studies identify protein targets and altered signaling pathways of phytochemical substances (Allwood et al., 2021).

3.10.2. *Artificial intelligence and machine learning*

AI-driven spectral interpretation (CNN-based), ML bioactivity prediction (Random Forest, SVM), and rational design of phytochemical derivatives accelerate multi-target compound discovery (Gul et al., 2023; Gupta et al., 2021; Tiwari et al., 2023). These tools reduce development timelines and improve pharmacokinetic/pharmacodynamic optimization. Key challenges include algorithmic bias, dependence on high-quality training datasets, and integration complexity.

3.10.3. *Nanotechnology*

Nanocarrier systems nanoparticle encapsulation, targeted delivery, controlled release platforms overcome low solubility and poor bioavailability while enabling tissue-specific delivery (Karnwal et al., 2024). Curcumin in nanoparticle form demonstrates tumor-cell-specific targeting and enhanced therapeutic effectiveness. Controlled release methods extend therapeutic duration and reduce dosing frequency, improving patient compliance.

3.10.4. *Personalized medicine*

Genomic, metabolomic, and proteomic profiling combined with AI/ML-driven patient stratification enables customized phytochemical therapy tailored to individual genetic and molecular profiles (Kandhare et al., 2025; Paul-Chima et al., 2024). This approach reduces adverse effects and optimizes multi-target strategies for complex diseases with diverse molecular origins.

3.11. *Regulatory and ethical considerations*

Mainstream medical integration of phytochemicals faces regulatory and ethical challenges, as current assessment mechanisms inadequately capture the complexity of multi-component phytochemical substances (Joshee et al., 2019). Quality control standards and pharmaceutical testing frameworks are essential guides for medication development and clinical trials. The ethical framework requires procurement from renewable plant resources and respect for traditional indigenous knowledge including intellectual property protections and benefit-sharing agreements with source communities.

Joint activities among scientific researchers, policymakers, and local communities will enhance responsible phytochemical utilization. Healthcare practitioner education on phytochemical benefits and limitations enables informed prescribing and builds patient trust. A coordinated approach across academic, industrial, and regulatory bodies is needed to create comprehensive guidelines ensuring safe, ethical, and evidence-based phytochemical use.

4. Conclusion

This narrative review has demonstrated that phytochemicals possess substantial multi-target potential aligned with systems biology and polypharmacology frameworks. Complex diseases cancer, cardiovascular disorders, diabetes, and neurodegenerative conditions are frequently resistant to single-target therapies; phytochemicals offer a compelling alternative by simultaneously modulating inflammatory, oxidative, apoptotic, and metabolic pathways.

Computational strategies (molecular docking, network pharmacology) confirm phytochemicals' multi-target binding capacity, while clinical and preclinical data on nanocarrier and liposomal delivery systems demonstrate breakthroughs in bioavailability and tissue targeting. Despite these advances, toxicity concerns, lack of standardization, and limited robust clinical trial evidence remain critical barriers.

4.1. *Implications for theory and practice*

This review supports a paradigm shift from monotherapy to systems-based, multi-target treatment approaches, integrating network medicine, ethnopharmacology, and precision therapeutics. Practically, this research recommends incorporating phytochemical multi-target agents into therapy for chronic and drug-resistant disorders—particularly in resource-constrained settings where cost-effectiveness and accessibility are paramount, provided standardization and safety profiling are achieved.

4.2. *Key lessons learnt*

Phytochemicals exhibit synergistic and multimodal actions that

enhance therapeutic outcomes while minimizing drug resistance and adverse effects.

Drug delivery innovations particularly nanotechnology and liposomal formulations are essential for overcoming pharmacokinetic limitations, with growing clinical evidence supporting their utility.

Standardization and regulatory oversight are urgent priorities; GACP, LC-MS fingerprinting, and WHO guidelines provide actionable frameworks.

Computational modeling (AI/ML, network pharmacology, molecular docking) powerfully accelerates phytochemical multi-target drug discovery.

Robust, adequately powered, prospectively registered RCTs with validated biomarker endpoints are needed to close the clinical evidence gap.

4.3. Limitations of this research

- As a narrative review, this study lacks the statistical rigor of a meta-analysis and is susceptible to selection and publication bias.
- Included studies vary widely in methodology, target diseases, compounds, and outcome measures, limiting direct comparability.
- Most findings rely on in vitro or animal studies; few robust human clinical trials validate efficacy and safety.
- Only English-language, indexed sources were included, potentially excluding relevant regional or indigenous research.

4.4. Final remarks

Phytochemicals represent a promising frontier for addressing chronic, multifactorial, and drug-resistant diseases. By modulating multiple molecular pathways and integrating into novel delivery systems, they provide a foundation for safer, more effective, and personalized therapeutic options. Multidisciplinary collaborations combining ethnobotany, pharmacology, computational science, nanotechnology, and regulatory research are essential for clinical integration. Future research should prioritize standardized protocols, well-powered RCTs, and comprehensive safety assessments to realize the full therapeutic potential of phytochemicals in evidence-based modern medicine.

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Declaration of competing interest

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