

ADVANCES IN NETWORK PHARMACOLOGY FOR CANCER THERAPY: INTEGRATING TUMOR BIOLOGY, SYSTEMS BIOLOGY, AND PRECISION MEDICINE

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ABSTRACT

Cancer is a multifactorial and heterogeneous disease characterized by complex genetic, epigenetic, and microenvironmental alterations that drive tumor initiation, progression, metastasis, and therapeutic resistance. Conventional "one drug-one target" strategies have demonstrated limited efficacy due to the intricate and interconnected nature of cancer signaling networks, tumor heterogeneity, and compensatory mechanisms that frequently lead to treatment failure and drug resistance. Consequently, cancer is increasingly recognized as a network disease involving dynamic interactions among genes, proteins, signaling pathways, and the tumor microenvironment. Network pharmacology has emerged as a promising systems-level approach that integrates systems biology, network science, multi-omics technologies, and computational modeling to elucidate these complex interactions. This review highlights the molecular basis of cancer, tumor biology, and the role of the tumor microenvironment in disease progression and therapy response. Furthermore, it discusses the significance of biological networks, including protein-protein interaction and gene regulatory networks, in understanding cancer pathogenesis. Particular emphasis is placed on the applications of network pharmacology in multi-target drug discovery, optimization of combination therapies, and personalized cancer treatment. The review also summarizes the contributions of genomics, proteomics, metabolomics, and key bioinformatics resources such as STRING, KEGG, Cytoscape, and TCGA in advancing precision oncology. Despite challenges related to data integration, standardization, and experimental validation, network pharmacology offers a comprehensive framework for deciphering cancer complexity and accelerating the development of safer, more effective, and personalized anticancer therapies.

KEYWORDS: Cancer; Network Pharmacology; Systems Biology; Precision Oncology; Multi-Target Therapy; Tumor Microenvironment; Protein-Protein Interaction Networks; Multi-Omics Integration; Drug Discovery; Personalized Medicine.

INTRODUCTION

Cancer ranks as the second most common cause of death globally. It develops through a sequence of mutations in

genes, which subsequently alter cellular functions. Chemical substances play a significant role in causing these genetic mutations and the formation of cancer cells.

Moreover, smoking introduces various carcinogenic chemicals that contribute to the development of lung cancer.^[1]

The advancement of targeted cancer treatments, particularly in identifying potential drug targets, necessitates a deeper comprehension of how molecular modifications and the transmission of biological signals contribute to the progression of the disease.

The broad rise of systems biology coincides with the growing demand for developing targeted therapies. By utilizing extensive omics data, systems biology is able to quantify all molecular components of biological systems, whether healthy or diseased, evaluate their interactions, and incorporate them into various graphical network models. This approach allows for the exploration of these networks to uncover the fundamental biological mechanisms.^[2]

Limitation of conventional one drug-one target approaches

The development of cancer is characterized by numerous signaling pathways and intricate interactions between genes and the environment. Consequently, drugs that target a single aspect often do not deliver the anticipated outcomes in clinical settings, particularly when confronted with the diversity of cancer and the issue of drug resistance. Firstly, cancer heterogeneity implies that even within the same cancer type, there are notable variations in gene expression and pathological features among different patients. This diversity results in certain targeted therapies being effective for some individuals while proving ineffective or even detrimental for others. Secondly, tumor cells possess a high degree of adaptability, and the prolonged use of a single targeted therapy frequently leads to drug resistance, which progressively diminishes or nullifies the treatment's effectiveness.^[3]

The primary reason that drugs targeting a single molecule often fail is that cancer functions through intricate, interconnected biological networks rather than isolated pathways. Even if a drug successfully targets and disables one protein or node within a disease pathway, alternative processes can be activated to compensate for the lost function. Moreover, altering or removing a single protein tends to have minimal impact on the functionality of cancer cells. Advances in network biology have significantly enhanced our understanding of the multifaceted interactions within cancer pathways. This knowledge may aid in interpreting signature datasets that collectively unravel the complex mechanisms of drug actions. Holistic strategies grounded in network biology and polypharmacology may establish network pharmacology as a viable tool for developing drugs to treat complex diseases like cancer. Consequently, network pharmacology is strengthening its role in cancer treatment.^[4]

Network Pharmacology

Network pharmacology is a research approach grounded in systems biology and network science, aiming to comprehend how drugs affect the entire biological system by examining the intricate interactions among drugs, genes, targets, and diseases. In contrast to the conventional "one disease-one target" model, network pharmacology emphasizes the holistic regulation of multiple targets and biological pathways. It employs multi-omics data and computational models to pinpoint potential multi-target drugs or drug combinations, thereby crafting more precise and comprehensive treatment strategies.^[3]

Molecular docking, a crucial tool for predicting target-drug interactions, is a component of NP, a comprehensive approach for discovering possible therapeutic drug targets. The method combines many data sources, including proteomics, metabolomics, transcriptomics, and genomes, to find critical target genes and pathways involved in the development and spread of tumors. The development of safer and more effective anticancer treatments depends on this system-level understanding of drug interaction with targets. Because NP techniques use multi-target tactics to address the complexity of disease, they are very effective in cancer therapy. The NP approach is a useful additional technique for determining drug targets and underlying mechanisms in the fight against cancer. It can be used to forecast the potency and toxicity of pharmacological compounds.^[5]

APPLICATION OF NETWORK PHARMACOLOGY IN CANCER THERAPY

Multi target drug design

By using network pharmacology, scientists can identify important target combinations that are directly linked to the pathogenic causes of cancer, making it easier to develop more potent medications. In order to support multifunctional medications that target several pathways and reduce resistance, researchers employ network analysis to find target combinations linked to cancer mechanisms. Natural products that control linked signaling, for instance, are filtered in this manner. Holistic approaches replace "one disease-one target" models.^[3]

Optimizing Combinations

Optimizing current drug combinations is another application of network pharmacology. We can find therapeutic combinations with synergistic benefits, increasing efficacy and lowering side effects, by examining how various treatments interact with one another and how this affects cancer pathology networks. It finds synergies that improve efficacy and reduce negative effects by simulating drug-pathway interactions, such as verified combinations in solid tumors and blood malignancies. Combinations with CI values ≤ 0.515 , which indicate substantial synergy, are predicted via network propagation. Efficacy is ensured without

overlapping toxicities by complementary exposure patterns.^[6]

Personalized treatment

Cancer patients can receive individualized treatment options from network pharmacology. Researchers can create customized disease networks and pinpoint patient-specific pathogenic pathways and important targets by examining multiomics data, such as patient genomes, transcriptomes, and proteomes. The basis for precision medicine is laid by this individualized network analysis, which enables each patient to receive a customized treatment plan to optimize the therapeutic outcome. By creating patient disease networks, multi-omics integration opens up new avenues for customized precision treatment. Genome-specific predictions are made possible by TCGA data, like as in regimens for metastatic colorectal cancer. By identifying the best combinations for resistant patients, subgroup clustering advances the concept of "right drug for right patient."^[7]

Basics of tumor biology

A tumor, also known as a neoplasm, is an aberrant cell mass found in the body. It is brought on by cells that either divide excessively or fail to die when they need to.

Classification of tumors

- **Benign Tumor:** Tumors classified as benign remain in their original spot without spreading to other parts of the body. They do not propagate to distant bodily organs or nearby structures.
- **Malignant Tumor:** Uncontrollably growing cells that spread locally and/or to distant locations are a feature of malignant tumors. Because they spread to other areas, malignant tumors are cancerous. Through the lymphatic or circulatory systems, they disperse to distant locations. We refer to this spread as metastasis.^[8]

Tumor cell biology is a rapidly evolving field that seeks to understand the complex mechanisms underlying cancer development, progression, and metastasis.

Tumor cells exhibit several hallmark traits

- Sustained proliferative signalling
- Evasion of growth suppressors
- Resistance to cell death
- Limitless replicative potential
- Induction of angiogenesis
- Activation of invasion and metastasis.

These characteristics result from genetic and epigenetic alterations that disrupt normal cellular functions and enable malignant transformation.^[9]

Tumor microenvironment

The intricate ecosystem that surrounds cancer cells, including immune cells, stromal cells, blood vessels, and the extracellular matrix (ECM), is referred to as the tumor microenvironment (TME). Tumor cells are

constantly interacting with this environment, which has a significant impact on how tumors develop, spread, and react to therapy. Understanding the TME is crucial because tumors cannot act on their own; in order to survive and grow, they need cues and assistance from their surroundings. Without the milieu that supports and shields it, a tumor cannot grow. Almost every aspect of cancer biology is impacted by the TME, including treatment resistance, secondary tumors, and the start of carcinogenesis.^[10]

Molecular Basis of Cancer

The molecular basis of cancer involves genetic and epigenetic alterations that disrupt normal cellular control, leading to uncontrolled proliferation and survival.^[11]

Genetics mutations

Tumor suppressors (like TP53 and PTEN) lose function due to deletions or inactivating mutations that hinder DNA repair and apoptosis, whereas oncogenes (like RAS and MYC) gain activity through point mutations or amplifications, promoting proliferation. Through genetic instability, these somatic alterations accumulate and enable characteristics like continuous growth.^[12]

Epigenetic changes

Histone acetylation loss compacts chromatin, inhibiting genes; DNA hypermethylation silences tumor suppressors (such the BRCA1 promoter); and non-coding RNAs like miR-21 stimulate carcinogenesis. In addition to mutations, these reversible changes promote advancement without altering the DNA sequence.^[13]

Signalling Pathway

PI3K/AKT/mTOR (PTEN loss) improves survival/metabolism; MAPK/ERK hyperactivation (by RAS/RAF mutations) increases proliferation; and NF-κB (IKK activation) causes inflammation/survival, frequently interacting with PI3K. Malignancy is sustained by feedback loops created by dysregulation.^[14]

Tumor microenvironment plays a major role in cancer therapy response

The tumor microenvironment (TME) critically influences cancer progression by promoting immunosuppression and therapy resistance, but targeting it enhances immunotherapy efficacy in advanced cancers.

Immunotherapy strategies

PD-1/PD-L1 inhibitors, such as pembrolizumab and nivolumab, reactivate T cells by blocking TME-driven immune checkpoints; the FDA has approved these drugs for melanoma, non-small cell lung cancer, and other conditions; response rates in PD-L1-high tumors can reach 68%. Hematological cancers respond well to CAR-T treatment, but solid tumors encounter TME obstacles such hypoxia; engineering (such as CRISPR PD-1 knockdown) enhances infiltration.

Combination therapies

When checkpoint blockers and radiation therapy are combined, CD8 T-cell penetration and DAMP release are increased, which works in concert to combat NSCLC (PFS 6.8 months). In melanoma/RCC, dual PD-1/CTLA-4 suppression (nivolumab+ipilimumab) produces an ORR of 35–71%; resistance is reversed by gut microbiota modification using FMT.

Emerging targets

Exosomal PD-L1 blockers and peptides/macrocycles (like BMS-57) overcome mAb limitations including limited penetration; vaccinations plus PD-1 inhibition reprogram TME in colon/ovarian animals. Using the approvals/combos tables in the PDF, highlight TME reshaping in your chapter to enhance progressive illness responses.^[15-16]

System biology approaches

By exposing the molecular complexity of cancer, omics technologies such as proteomics, metabolomics, and genomes have significantly improved our understanding of tumor biology. These methods aid in the identification of metabolic alterations, protein expression patterns, and genetic abnormalities that contribute to the development of tumors.

Genomics role

Genomics sequences DNA to detect mutations like TP53 or KRAS, revealing driver events and tumor heterogeneity in cancers such as breast or lung.

It maps copy number variations and structural rearrangements, linking them to oncogenesis across patient cohorts.^[17]

Proteomics role

Proteomics quantifies proteins and post-translational modifications via mass spectrometry, uncovering active signaling pathways like PI3K/AKT in tumors.

It identifies biomarkers for drug response, such as HER2 in gastric cancer, bridging genotype to phenotype.^[18]

Metabolism profile

Metabolomics profiles small molecules, highlighting Warburg effect shifts like lactate accumulation or glutamine dependency in proliferating cells.

It reveals therapy resistance mechanisms, such as altered lipid metabolism, aiding metabolic-targeted interventions.^[19]

Integration benefits

Combining these omics layers via network models deciphers tumor microenvironment interactions, predicting multi-target therapies.

This holistic view enhances precision oncology, from early detection to overcoming resistance.^[20]

Tools and Databases Used

Key tools and databases like STRING, KEGG, Cytoscape, and TCGA are essential for systems biology analysis in tumor biology, enabling network visualization and omics data integration.

STRING Database

Protein-protein interactions are compiled by STRING using text mining, algorithmic predictions, curated literature, and experimental data. Each association is given a confidence value. It uses variational auto-encoders to predict co-expression from single-cell RNA-seq and proteomics data, and it allows custom networks for unique genomes. By simulating interaction networks for tumor-related proteins, these features support cancer research.^[21]

Kegg pathway

KEGG provides manually selected pathway maps that link genes to signaling cascades and metabolic activities like glycolysis or the TCA cycle. To find dysregulated functions in cancer, users compare their genomic data to these sources. This integration shows how tumor cellular pathways are changed by mutations.

Cytoscape software

Cytoscape overlays omics data, including gene expression patterns, and visualizes intricate molecular networks. Smooth STRING network imports, sophisticated layouts, clustering, and enrichment analysis for cancer pathways are made possible by its plugins, such as the stringApp. This makes it easier to investigate therapeutic targets and tumor microenvironments.^[22]

TCGA Database

TCGA produced 2.5 petabytes of public genomic, epigenomic, transcriptomic, and proteomic data by analyzing more than 20,000 cancer samples from 33 different tumor types. It reveals the epigenetic modifications, expression shifts, and somatic mutations that cause oncogenesis. By connecting genomic profiles to clinical outcomes, these discoveries drive precision oncology.

Multi-Target Mechanisms of Traditional Medicines Introduction to Traditional Medicines in Cancer

Cancer continues to be the world's biggest cause of death despite several advancements in treatment. Drug resistance, adverse effects, high costs, and decreased patient quality of life are some of the drawbacks of conventional therapy. Complementary and alternative medicine (CAM) is becoming more popular as a solution to these problems. Conventional therapies are increasingly being employed in conjunction with traditional medical systems, such as Chinese, Korean, Indian, Japanese, and South African medicine. These methods can lessen adverse effects, boost overall therapy results, and promote patient well-being.

Integrative oncology focuses on holistic therapy, including nutrition, lifestyle, and mental health, by fusing traditional therapies with current medicine. Bioactive phytochemicals included in traditional medicines work on a variety of biological targets, supporting their use in the treatment of cancer.

All things considered, combining conventional medicine with contemporary treatments presents a promising multi-target approach for enhancing cancer treatment and patient quality of life while also offering avenues for further interdisciplinary study.^[23]

Ayurveda, Traditional Chinese Medicine (TCM), herbal medicine

Traditional Chinese medicine and Ayurveda are two of the world's oldest medical systems still in use today. Global interest in these ancient remedies has grown in recent years, and efforts to standardize and regulate herbal medications have also increased. Because of its excellent integration with contemporary scientific research and evidence-based methodologies, China has been more effective in spreading TCM globally. Ayurveda, on the other hand, still needs more thorough scientific validation and study to increase its acceptance around the world.

Holistic concepts like harmonizing the body and emphasizing general well-being are shared by both systems. However, they must deal with important issues including quality assurance, scientific validation, and regulatory norms in order to successfully compete in international markets.^[24]

In order to boost immunity, lessen side effects, and enhance quality of life, traditional medicines including Ayurveda, TCM, and herbal systems provide comprehensive approaches to cancer care.

Traditional medicine Historical use in cancer treatment

Traditional Chinese medicine, Ayurveda, and Unani medicine are becoming increasingly popular among cancer patients. Globally, these methods have been in operation for centuries. They are frequently employed to delay metastases or preserve remission. Strong scientific and clinical data is still scarce, though.^[25]

Traditional Chinese Medicine

With records going back more than 3500 years, Traditional Chinese Medicine (TCM) is one of the earliest cancer therapy systems. According to books like *The Yellow Emperor's Inner Canon*, it takes a holistic approach, considering tumors as a component of a systemic imbalance brought on by elements including nutrition, environment, emotional stress, and internal organ malfunction.

The goals of TCM treatment are to improve blood circulation, eliminate infections, enhance bodily

resistance, and restore equilibrium. Additionally, it introduced stage-based therapy, which supports the body in later phases while focusing on disease in its early stages. Numerous traditional herbal remedies created in antiquity are still in use today.^[25]

Ayurveda

Since ancient times, Ayurveda, the oldest indigenous Indian medical system, has used plant-based medicines to prevent or reduce a variety of cancers. Additionally, researchers are becoming more interested in studying complementary and alternative medicine for the treatment of cancer. According to the Ayurvedic notion of "Charaka" and "Sushruta Samhitas," cancer is referred to as either "Granthi" (small neoplasm) or "Arbuda" (large neoplasm) and is defined as either inflammatory or non-inflammatory swelling. Three fundamental Ayurvedic systems—the artery system (Kapha or water), the venous system (Pitta or fire), and the nerve system (Vata or air)—are crucial for proper bodily function. All three systems (Tridoshas) become out of control and lose mutual coordination in malignant tumors, which results in tissue destruction and a severe condition. Excessive metabolic crises brought on by tridoshas lead to proliferation. Herbs aid in complete recovery and lessen side effects and issues related to cancer. *Andrographis paniculata*, *Phyllanthus niruri*, *Piper longum*, *Podophyllum hexandrum*, *Tinospora cordifolia*, *Vitis vinifera*, *Baliospermum montanum*, *Madhuca indica*, *Pandanus odoratissimus*, *Pterospermum acerifolium*, *Raphanus sativus*, *Barleria prionitis*, *Prosopis cineraria*, *Amorphophallus campanulatus*, *Oxoxylum indicum*, *Flacourtia romantchi*, *Ficus bengalensis*, *Curcuma domestica*, *Allium sativum*, *Calotropis gigantea*, *Datura metel*, *Hygrophila spinosa*, *Juniperus indica*, and *Picrorrhiza kurroa*.^[26]

Herbal medicine

Since ancient times, herbal remedies have been utilized to cure and prevent a variety of illnesses, including cancer. Herbal remedies treat cancer and are safe for human health. *Astragalus*, *turmeric*, *ginger*, *aloe vera*, and other herbs are utilized as complementary therapies because they may have anticancer properties. When used in conjunction with traditional therapies, they may enhance immunity, survival, and quality of life; however, some may result in adverse effects or interactions. Their mechanisms are the focus of current study, and traditional therapies are being standardized for safe and efficient usage.^[26]

The various bioactive substances found in natural goods, such as flavonoids, alkaloids, and polyphenols, make them attractive anticancer agents. They work in a variety of ways, including triggering apoptosis, preventing the growth of tumors, preventing angiogenesis, and boosting the immune system. Herbal remedies can lessen side effects, increase chemotherapy tolerance, and work in concert to treat cancer. However, further study is still

needed to address issues including dose, safety, standardization, and clinical validation.^[27]

Advantages use of traditional medicines over synthetic drugs in cancer treatment

Traditional medicines offer several advantages over synthetic drugs in cancer treatment, including multi-target effects, reduced toxicity, and synergy with chemotherapy.

Reduced side effect

Although there is little data on the pharmacodynamic effects of herbal medications, many cancer patients take them in addition to chemotherapy. Natural products have the ability to treat cancer and can lessen the toxicity and mucositis associated with chemotherapy. By working in concert with traditional medicines, they could improve the effectiveness of treatment. However, additional clinical research is required to verify their efficacy, safety, and appropriate application.

Herbal treatments frequently improve the quality of life for patients by reducing chemotherapy-induced side effects include nausea, exhaustion, thrombocytopenia, and cardiotoxicity. For example, curcumin increases response rates and lessens tiredness with paclitaxel, while astragalus guards against cisplatin side effects.^[28]

Multi target action

In contrast to single-target synthetics, network pharmacology allows traditional therapies like TCM to target several pathways at once, potentially bypassing resistance and addressing the complexity of cancer. TCM formulae contain a variety of bioactive substances that simultaneously regulate several signaling pathways, including PI3K-Akt, MAPK, and NF-κB. This disrupts the progression of cancer at different nodes and mimics the systemic aspect of the disease. This all-encompassing strategy allows for more therapeutic coverage and is in line with the complexity of cancer, where tumors develop through redundant pathways.^[20]

Synergy and efficacy

Combinations improve the efficacy of chemotherapy; *Rauwolfia vomitoria* enables gemcitabine dose reduction in pancreatic cancer, while green tea extract increases 5-FU cytotoxicity in resistant cells. Many chemotherapy drugs come from traditional plants. For example, vincristine from the Madagascar periwinkle (*Catharanthus roseus*) was used for generations in traditional medicine until being isolated in the 1960s. This demonstrates how network pharmacology techniques in cancer treatment are inspired by natural materials.^[21]

Reduced Toxicity

Traditional medicines generally cause fewer adverse effects than synthetic chemotherapy agents, improving patient tolerability and quality of life. They protect against myelosuppression, nausea, and gastrointestinal

damage from chemo/radiation while enhancing treatment efficacy as adjuvants.^[25]

Immune Modulation

Many traditional remedies boost innate immunity, stimulate progenitor cell recovery, and act as adaptogens (e.g., ginseng, ashwagandha), countering immunosuppression from cancer or therapy. They also exhibit antioxidant effects, scavenging free radicals to prevent mutagenesis.^[26]

Concept of Multi-Target Therapy

Definition and Importance

Instead of concentrating on a single target, multi-target therapy is a method of treating cancer in which a medication—or a combination of medications—is intended to work on several biological targets or pathways concurrently or sequentially. Since cancer is a multigenic illness involving numerous genes and signaling pathways, treating it by focusing on just one route is frequently insufficient.^[31]

Importance of Multi-Target Therapy

When treating complicated, multifactorial illnesses including cancer, neurological diseases (such Parkinson's and Alzheimer's), chronic inflammation, and mood disorders, multi-target ligands are particularly helpful.

Since many disorders involve several molecular pathways, single-target therapies are less successful. Compared to combo therapy, multi-target medicines provide a number of benefits, such as:

- Improved and more consistent pharmacokinetics
- Enhanced adherence to treatment
- A lower chance of drug-drug interactions.^[32]

In diseases including cancer, neurodegeneration, and infections, where single agents frequently fail despite significant R&D investment, it addresses adaptive resistance and redundancy. It increases advantages and reestablishes biological equilibrium by coordinating interconnected processes.

Reducing resistance and side effects: Compared to combinations beset by interactions and poor compliance, multi-target medications reduce the risk of multidrug resistance, allow for lower dose to limit toxicity, and simplify treatment. They offer cost savings and more consistent pharmacokinetics.^[32]

Difference between single target and multi target drug

Single-target drugs focus on one primary biological target, while multi-target drugs (or ligands) modulate multiple targets simultaneously for broader therapeutic effects.

Core paradigm

The traditional "one drug, one target" approach assumes high potency and specificity at a single site minimizes

off-target effects, fitting the lock-and-key model where one key fits one lock. Multi-target agents act as "skeleton keys" unlocking several locks (targets), often isoforms, pathway-related proteins, or unrelated ones via combined pharmacophores.

Efficacy in complex diseases

Single-target drugs suit single-gene disorders but falter in multifactorial conditions due to system resilience, compensatory mechanisms, and poor in vitro-to-in vivo translation. Multi-target drugs better address robust disease states from multiple genetic/environmental factors, like cancer or neurodegeneration, by simultaneous modulation.

Practical Advantages and challenges

Compared to combinations, multi-target alternatives have fewer interactions, improved compliance, predictable pharmacokinetics, and resistance mitigation (reduced single-mutation vulnerability). Design challenges include unfavorable energetics, reduced ligand efficiency, and lower screening hit rates from multiple constraints.^[32]

Synergistic effects

Synergistic effects occur when drug combinations produce greater therapeutic outcomes than the sum of individual effects, often enhancing selectivity by targeting multiple pathways in specific disease contexts

- **Enhanced Efficacy:** When used in combination, drugs can produce more potent anti-tumor effects compared to using them individually, as demonstrated by targeting kinases and inducing apoptosis.^[33]
- **Overcoming Resistance:** Multi-target approaches, such as combining venetoclax (BCL2 inhibitor) and AZD5991 (MCL1 inhibitor), can bypass tumor resistance mechanisms.
- **Reduced Toxicity:** By targeting multiple pathways simultaneously with lower doses, the overall side effects are often reduced compared to high-dose monotherapy.^[34]
- **Improved Targeting:** By integrating phototherapeutics with chemotherapy or nanodrugs, specialized treatments enhance the accuracy of targeting and eliminating diseased cells.^[35]

Bioactive Compounds in Traditional Medicines

Medicinal plants contain diverse bioactive compounds such as alkaloids, flavonoids, phenolics, terpenoids, and essential oils, which serve as important sources for antibiotic development. Natural products from plants and other sources (fungi, marine organisms) show strong potential in combating resistant pathogens. Plant-derived phytochemicals exhibit **antioxidant, antibacterial, and antifungal activities** and can enhance the effectiveness of existing antibiotics, helping to reduce resistance. Their mechanisms include disrupting bacterial cell membranes, interacting with membrane components, and causing cell lysis through structural destabilization.^[36]

Bioactive compounds like curcumin, resveratrol, quercetin, and berberine are key phytochemicals from traditional medicines such as Ayurveda, Traditional Chinese Medicine, and herbal remedies, valued for their pleiotropic effects on inflammation, cancer, metabolic disorders, and oxidative stress.

These compounds act via

- Antioxidant defense (Nrf2/HO-1 upregulation)
- Anti-inflammatory signaling (NF- κ B/TLR4 $\downarrow$, cytokines like TNF- α /IL-6 $\downarrow$)
- Cell death induction (apoptosis/autophagy via Bcl-2 $\downarrow$, caspases $\uparrow$, SIRT1 $\uparrow$).

In cancer, they hit stem cells and senescence pathways.^[36]

Mechanisms of action on multiple pathways

Curcumin

Curcumin is a naturally occurring lipophilic polyphenol that acts through several biological pathways to produce a variety of pharmacological actions, including as anti-inflammatory, antioxidant, antibacterial, antiparasitic, antimalarial, analgesic, and wound-healing properties. However, due to low absorption, fast metabolism, and rapid elimination, its poor bioavailability restricts its therapeutic application. Several formulations have been created to get around this. Additionally covered in this review are formulation strategies, analytical methods for identification and quantification, and extraction procedures (such as Soxhlet and microwave extraction). It emphasizes the need for more investigation to fully comprehend the mechanics, safety, and therapeutic potential of curcumin.^[36]

Curcumin inhibits NF- κ B/TLR4 for anti-inflammation (TNF- α , IL-6), activates Nrf2/AMPK for antioxidative defense (HO-1, SOD), and triggers apoptosis/autophagy in cancer via Bcl-2 $\downarrow$, caspases, and p53 $\downarrow$. It works well in neurodegeneration, metabolic diseases, and chemoprevention; it often enhances absorption when combined with drugs like piperine.^[37]

Resveratrol

Resveratrol is a stilbenoid polyphenol bioactive compound, best known as a phytoalexin produced by plants like grape skins, blueberries, peanuts, and Japanese knotweed under stress, and a hallmark of Traditional Chinese Medicine (e.g., Hu Zhang).^[37]

It mimics the effects of calorie restriction on NAD⁺, FOXO3A, and AMPK by activating SIRT1 (longevity enzyme), while mTOR/NF- κ B provides anti-aging, anti-inflammatory (IL-6/TNF- α), and metabolic advantages. Wnt inhibition, apoptosis (Bcl-2, caspase), and p53 are anticancer; endothelial NO and LDL oxidation are cardioprotective.^[61]

Quercetin

Quercetin is a flavonoid polyphenol and potent bioactive compound abundant in traditional medicines, found in

onions, apples, berries, capers, and herbs like Ginkgo biloba and St. John's wort.^[36]

Quercetin suppresses NF- κ B/PI3K/Akt for anti-inflammatory (TNF- α , IL-6, COX-2), modifies Nrf2/ARE for endogenous antioxidants (GSH, SOD, HO-1), and interferes with biofilms and quorum sensing in bacteria like *Pseudomonas*. Antiviral, cardioprotective, and anticancer by apoptosis (caspases, Bcl-2).^[38]

Berberine

Barberry (*Berberis vulgaris*), goldenseal (*Hydrastis canadensis*), and coptis (*Coptis chinensis*) are examples of traditional remedies that include berberine, an isoquinoline alkaloid bioactive chemical that is essential to Ayurveda and Traditional Chinese Medicine for infections, digestion, and metabolic problems.

Berberine modulates gut microbiota (short-chain fatty acids, harmful bacteria), inhibits NF- κ B for anti-inflammation (TNF- α /IL-6), activates AMPK (mimicking metformin for glucose uptake, lipid metabolism), lowers lipids via PCSK9 and eNOS, and has anticancer/autophagy via mTOR regulation; neuroprotective potential.^[39]

Advantages of Traditional Multi-Target Therapy

By treating complicated disorders holistically, traditional multi-target therapies—such as those employing curcumin, resveratrol, quercetin, and berberine—offer significant advantages over single-target medications.^[40]

Reduced resistance

By blocking efflux pumps (like P-gp), reversing apoptosis resistance through Bax/Bcl-2 modulation, and simultaneously targeting heterogeneous cancer clones—curcumin/berberine restores chemosensitivity in resistant breast/colon lines without affecting healthy cells—these treatments fight multidrug resistance (MDR).^[41]

Lower toxicity

Multi-target herbals exhibit selective cytotoxicity against tumors while sparing normal tissues; combinations increase quality of life, prevent medication interactions by predictable pharmacokinetics versus polypharmacy, and minimize the amount of chemotherapy required (e.g., β -elemene with platinum lowers neuro/hepatotoxicity).^[32]

Holistic approach

By treating root causes across pathways (inflammation, metabolism, immunity) rather than isolated targets, they mimic physiological networks. For example, curcumin/NF- κ B synergies align with Lehar et al.'s selectivity bias for disease-specific effects, while berberine reshapes gut microbiota along with AMPK activation.^[40]

Integration with Modern Medicine

Combining herbal and conventional therapies

The use of herbal medicine in conjunction with conventional therapy is becoming more and more popular, but only when it is supported by research, controlled, and integrated with standard care. Although it can enhance symptom management, promote wellness, and occasionally supplement medication therapy, there are actual concerns associated with herb-drug interactions and issues with product quality.

Integration with modern medicine

Modern integration means herbal products are used alongside conventional medicine within a clinical framework, not outside it. WHO says this should be done appropriately, effectively, and safely, with decisions grounded in the latest scientific evidence. In practice, this requires collaboration between clinicians, careful product standardization, and attention to quality, safety, and efficacy.

Combining therapies

There are two primary approaches to combine herbal and conventional therapies: either to enhance conventional treatment or to lessen side effects, such symptom relief or improved tolerance. However, the combination needs to be carefully considered because some herbs can change pharmacodynamic effects or drug metabolism, particularly when used with medications like immunosuppressants, anticoagulants, or anticancer treatments. One of the most well-known herbs for clinically significant interactions is St. John's wort.^[42]

Personalized medicines

Because people react differently depending on their genetics, disease status, lifestyle, and co-medications, herbal medicine is a good fit for customized treatment. According to recent evaluations, personalized or precision herbal therapy is a strategy that matches the appropriate herbal intervention to the appropriate patient using biomarkers, genomes, and health profiling. This is particularly important for complicated illnesses like cancer, where customized treatment choices may take into account both traditional medications and natural remedies.

Future Prospects

More integrated care models, stricter regulations, improved biomarker-guided prescribing, and digital tools for monitoring and adherence are all expected to be features of the future. Research, regulation, and patient safety are highlighted by WHO and current policy talks as the cornerstones of wider adoption. Precision, where herbal treatments are standardized and chosen based on quantifiable patient factors rather than just tradition, is probably going to be the largest growing sector.^[43]

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