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NARRATIVE REVIEW

Drug Repurposing Potential of Natural Products: Molecular Targets, Pharmacological Profiles, and Precision Therapeutic Strategies: A Narrative Review

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ABSTRACT

Repurposing compounds is an important way to look at new uses for approved drugs. Natural products have a wide range of structural and pharmacologic diversity and have the potential to be applied in repurposing, especially for complex and chronic diseases. This is a narrative review of molecular targets, pharmacological properties and therapeutic strategies for repurposed natural compounds. Natural products are predicted to modulate pathways that include PI3K/Akt, NF-κB, and AMPK, all of which play a role in cancer, neurodegenerative and metabolic diseases, according to computational and systems level studies. The predicted mechanisms have been studied preclinically and pharmacological effects have been observed in experimental models; structure-activity relationship studies and semi-synthetic modifications have been examined to gain more favorable bioavailability and target-related properties. Nevertheless, low solubility and high metabolism of phytochemicals, and their variable compositions, are significant limitations. While multi-omics and AI methods could help identify targets and aid precision medicine, predictions need experimental and clinical validation. The clinical evidence is limited and heterogeneous, and larger trials are needed to confirm efficacy and safety, and reported to have therapeutic effect for curcumin, resveratrol, and berberine. Standardization and regulatory variations are also barriers to translation. In summary, combining computational prediction, preclinical evidence, and strong clinical data is crucial for natural product drug discovery.

Keywords: Biological Availability; Drug Repositioning; Phytochemicals; Precision Medicine; Structure-Activity Relationship

INTRODUCTION

Drug repurposing is the discovery of new therapeutic uses for available pharmacological agents in a specific biological and molecular context [1,2]. Unlike traditional drug discovery, which requires de novo synthesis and subsequent validation, repurposing leverages known pharmacokinetic, toxicological, and safety profiles, minimizing uncertainty during development [3]. Repurposed agents are often polypharmacological, engaging with many signaling pathways [4] that are involved in the pathogenesis of cancer, inflammatory disorders, and metabolic diseases, including PI3K/Akt, NF-κB, and MAPK [2].

Natural products represent a chemically heterogeneous and biologically active group of compounds that have traditionally played a major role in approved therapeutic agents, specifically in the fields of oncology, infectious diseases, and metabolic disorders [5]. Recent pharmacological studies have shown that plant-produced secondary metabolites, such as alkaloids, flavonoids, terpenoids, and polyphenols, have structurally complex scaffolds that allow them to engage with a variety of molecular targets [6]. This multi-target binding ability is aided by the recent studies in network pharmacology which show that natural compounds can be able to mediate interconnected signaling pathways including NF-κB, PI3K/Akt/mTOR and MAPK cascades [7,8], which play a crucial role in inflammation, tumor progression, and cellular stress responses. The development of high-throughput screening and metabolomics has enabled the discovery of bioactive phytochemicals with specific molecular targets, such as enzymes, receptors, and transcription factors [9].

Ethnopharmacological evidence confirmed that drug repurposing is promising, since traditional medicinal systems are proven to have compounds that are experimentally verified to have pharmacological activity [10]. Curcumin, resveratrol, and berberine have been shown to have regulatory effects on oxidative stress, mitochondrial activity, and inflammatory mediators in preclinical and clinical trials [11,12]. Nevertheless, low aqueous solubility, rapid metabolism, and changes in the phytochemical composition caused by environmental and extraction variables limit the pharmacological translation of natural products [13]. The latest advances in formulation approaches such as nanoencapsulation and phytosome-

based delivery systems have demonstrated higher bioavailability and target specificity of natural products [14]. Thus, natural products are a mechanistically validated and ever-growing pool of drug repurposing, especially in the realm of multi-factorial and chronic diseases.

METHODOLOGY

This narrative review is organized in an informative literature synthesis approach to provide transparency and reproducibility. The major biomedical databases, such as PubMed, Scopus, and Web of Science, were used to identify relevant studies in the pharmacological and biomedical fields. Validated keyword combinations, including drug repurposing, natural products, phytochemicals, precision medicine, and molecular targets, were included as the search strings, and further refined with Boolean operators. The primary search string was: ("drug repurposing" OR "drug repositioning") AND ("natural products" OR phytochemicals) AND ("molecular targets" OR mechanisms OR "precision medicine"). Peer-reviewed original research papers, systematic reviews and meta-analyses were included to make sure that the most recent scientific evidence would be integrated. Research without experimental validation, those that were not published in English, and those that were not peer-reviewed were eliminated to maintain scientific rigor. The extraction of data was based on molecular mechanisms, pharmacological profiles, and clinical relevance of natural compounds. Critical appraisal was also carried out through reviewing of the study design, sample size, reproducibility, and methodology quality, which was in line with the use of narrative review standards. Where reviewer disagreement occurred during study selection or data interpretation, discrepancies were discussed and resolved through consensus unresolved disagreements were adjudicated by a third reviewer.

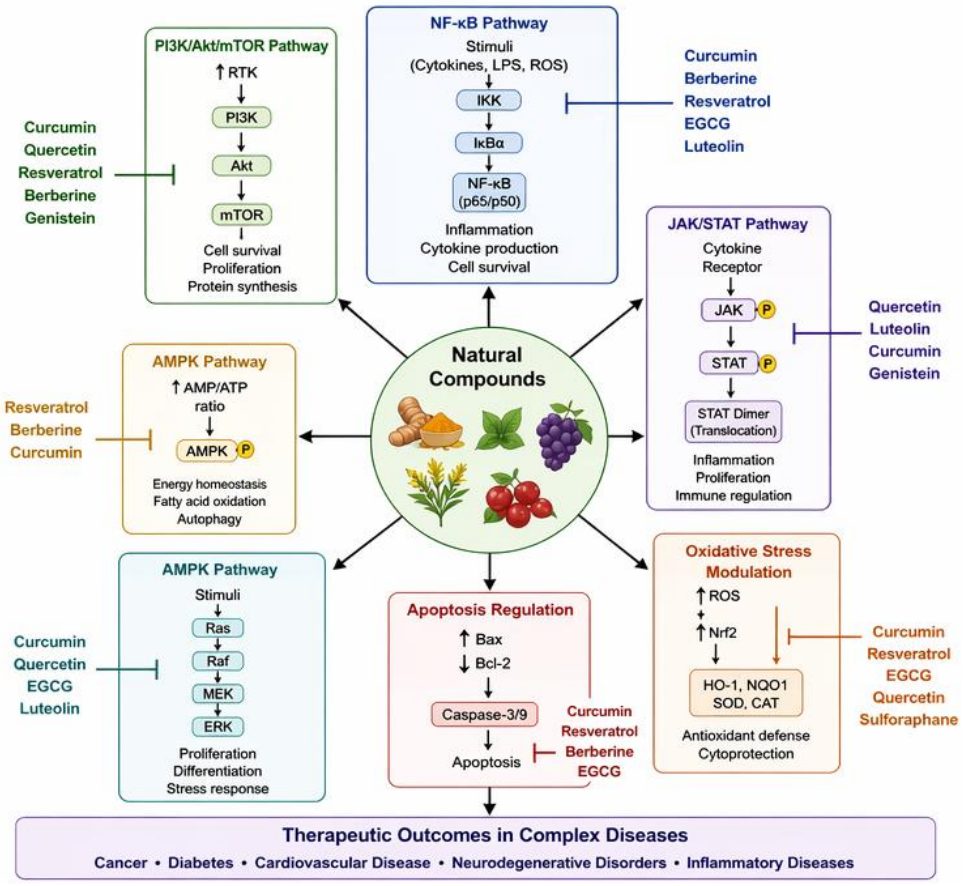

Figure 1: Multi-target mechanisms and network pharmacology of repurposed natural compounds in complex diseases: Natural compounds (e.g., curcumin, resveratrol, berberine, quercetin, EGCG, genistein) modulate interconnected signalling pathways including PI3K/Akt/mTOR, NF-κB, JAK/STAT, AMPK, and MAPK, regulating inflammation, apoptosis, proliferation, metabolism, and oxidative stress. Through pathway crosstalk and Nrf2-mediated antioxidant responses, these compounds exert network-level, pleiotropic effects relevant to cancer, metabolic, cardiovascular, and neurodegenerative diseases [8,11, 19,22,53].

Molecular Mechanisms and Systems-Level Approaches in Drug Repurposing

The molecular basis of drug repurposing lies in identifying novel drug–target interactions beyond the original therapeutic indication. Proteomics-based binding assays and transcriptomic profiling are examples of high-throughput screening technologies that have helped identify new molecular targets for repurposed compounds [15]; for example, transcriptomic signature-based analyses have prioritized statins such as simvastatin and atorvastatin for COVID-19 [16], whereas thermal proteome profiling has revealed celecoxib-targeted proteins for neurodegenerative disorders [17] such as Alzheimer's disease and supported its repurposing potential. To illustrate the multi-pathway and network-level mechanisms underlying the therapeutic effects of repurposed natural compounds, **Figure 1** summarized their interactions with key signaling cascades involved in complex diseases.

Recent research applying network pharmacology strategies revealed that drug-target interactions can be charted over biological networks, enabling the identification of key proteins and pivot regulatory nodes in the progression of diseases [7,18]. Natural compounds have been demonstrated to mediate central signaling pathways that include PI3K/Akt, JAK/STAT, NF-κB, and AMPK, which control cellular functions like proliferation, apoptosis, inflammation, and energy metabolism [8,19]. Curcumin has been reported to inhibit NF-κB signaling and reduce inflammatory mediator expression [20,21], while also suppressing PI3K/Akt activity in cancer cells and activating AMPK in inflammatory and injury models. Similarly, berberine attenuates NF-κB activation in cellular and animal systems, supporting its role in controlling inflammatory and apoptotic responses [22]. Resveratrol has been shown to activate AMPK in neurons and brain tissue, but its effects are not uniform across tissues or exposure conditions, underscoring the importance of context in interpreting pathway modulation [23].

Structure-Activity Relationships (SAR) and Chemical Optimization of Natural Compounds: The Structure-Activity Relationships (SAR) is an essential part of the current drug repurposing practices, which offers mechanistic understanding of how certain chemical attributes of natural compounds affect their biological action and target [24]. Various experimental studies have demonstrated that curcumin exerts its antioxidant activity through its phenolic hydroxyl groups and conjugated diketone structure, which enable binding and inhibition of NF-κB signaling proteins [25]. In another study, epigallocatechin-3-gallate (EGCG) from green tea demonstrated strong binding affinity to multiple protein targets, and may disrupt Oropouche virus infection through multi-target mechanisms [26].

The use of high-resolution structural biology methods, such as X-ray crystallography and cryo-electron microscopy, has enabled the specific mapping of ligand–target interactions to enable rational manipulation of natural compounds to increase their therapeutic effect [27-29]. X-ray crystallography provided high-resolution, static structural details of ligand–target complexes, making it ideal for precise binding-site analysis,

whereas cryo-EM allows visualization of large and dynamic macromolecular complexes in near-native states, offering advantages in studying membrane proteins and flexible systems [28]. For instance, rapamycin, a natural macrolide repurposed as an immunosuppressant and anticancer agent, was structurally characterized using X-ray crystallography, revealing its binding to FKBP12–mTOR complexes, which guided the development of improved analogs [30]. Similarly, ivermectin, originally derived from *Streptomyces avermitilis*, has been studied using cryo-EM to understand its interaction with glutamate-gated chloride channels, explaining its antiparasitic efficacy and enabling exploration of broader therapeutic roles [31]. In addition, paclitaxel (Taxol), a plant-derived anticancer drug, was characterized through X-ray crystallography, elucidating its binding to β-tubulin and stabilization of microtubules, forming the basis for its clinical activity [32].

Structural alteration, however, is limited by the necessity to maintain the basic bioactive scaffold that is responsible for the pharmacological effect. Thus, SAR-guided optimization can be considered an important connection between natural compound identification and a high-quality drug repurposing to create more powerful, selective, and bioavailable therapeutic compounds.

Repurposed Natural Compounds Pharmacokinetics and Pharmacodynamics: Pharmacodynamics (PD) and pharmacokinetics (PK) play a vital role in the therapeutic efficacy and safety of repurposed natural compounds, regulating their absorption, distribution, metabolism, excretion, and biological actions at target sites [33]. Recent pharmacological research indicated that natural compounds have poor aqueous solubility, intestinal permeability, and extensive first-pass metabolism through cytochrome P450 enzymes, which led to low oral bioavailability [34]. Curcumin and resveratrol were quickly converted to glucuronide and sulfate conjugates, respectively [12], and this greatly decreases the bioactive concentrations of the two compounds in the body. The development of novel drug delivery systems such as lipid-based nanoparticles, solid lipid carriers, and nanoemulsions increased the absorption capacity and extended systemic circulation of these substances [35]. These systems improved solubility of poorly water-soluble phytochemicals**,** protect them from chemical and enzymatic degradation, and increase intestinal absorption and bioavailability. Curcumin-loaded lipid nanoparticles have shown significantly higher plasma concentration and prolonged circulation time compared to free curcumin [36].

Pharmacodynamically, natural products tend to have pleiotropic effects, by acting on several signaling pathways akin to each other, such as inflammatory mediators, oxidative stress responses, and apoptosis regulators [33]. For example, curcumin has been reported to inhibit DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), leading to altered DNA methylation and increased histone acetylation, thus controlling gene expression in disease-relevant pathways [38,39]. Similarly, sulforaphane functions primarily as an HDAC inhibitor, promoting histone acetylation and enhancing anticancer gene expression [53]. Thus, pharmacokinetic profile optimization and mechanistic pharmacodynamic insight is critical to the successful clinical translation of repurposed natural products [40].

Computational Repurposing of Drugs: The latest developments in machine learning and artificial intelligence have made great progress in predicting compound-target binding, pharmacological activity, and toxicity profiles from large-scale biological data [41,42]. Computational methods, such as quantitative structure-activity relationship (QSAR) modeling and machine learning-based prediction systems, are also becoming popular to measure important pharmacophores and optimize lead compounds [43]. QSAR studies on curcumin analogs have demonstrated that the presence and position of methoxy and hydroxyl groups significantly influence anti-inflammatory and anticancer activity, guiding the design of more potent derivatives [44]. Similarly, QSAR modeling of flavonoids has shown that structural features such as hydroxylation patterns and planarity strongly correlate with antioxidant and enzyme inhibitory activity [45]. These semi-synthetic alterations target pharmacokinetic characteristics (such as solubility, metabolic stability, and membrane permeability) to optimize natural products for their pharmacokinetic behavior [48]. Derivatization of compounds like curcumin and resveratrol has been demonstrated to lead to increased bioavailability and decreased rapid metabolic degradation via methylation, glycosylation, and nanoparticle conjugation [49].

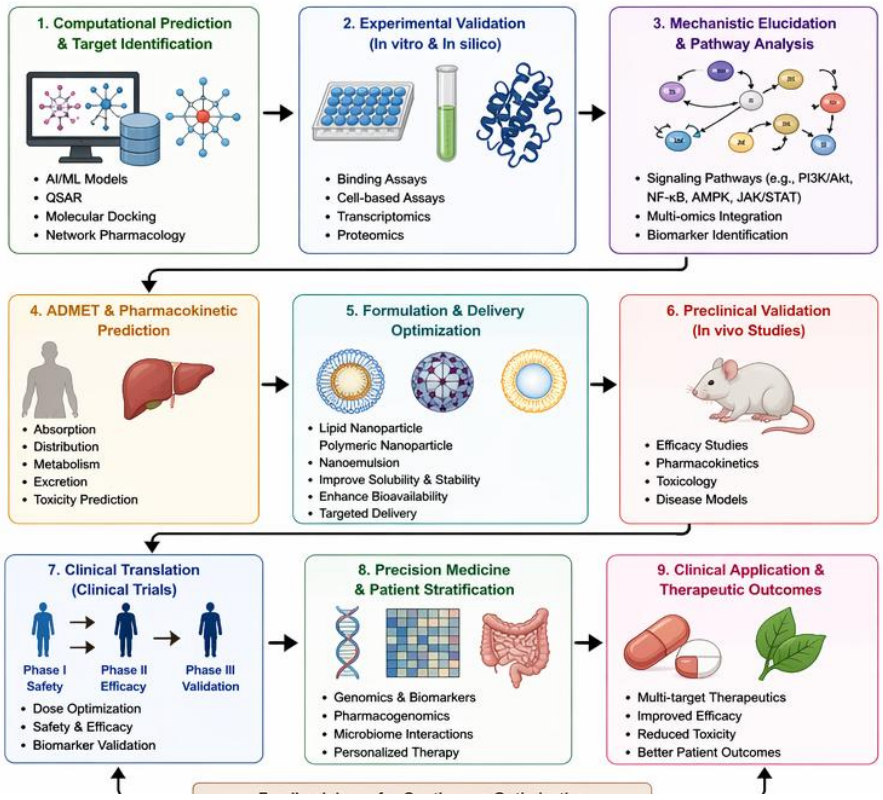

Figure 2: Integrated framework of drug repurposing of natural compounds: from computational prediction to clinical translation. A stepwise framework for natural product repurposing, encompassing AI/QSAR-based target prediction, experimental validation, mechanistic pathway analysis, ADMET/PK profiling, and formulation optimization, followed by preclinical studies and clinical trials. Integration of multi-omics and precision medicine enables patient stratification, with iterative feedback improving therapeutic efficacy and safety [1,2,26,39,48].

Additionally, molecular docking and molecular dynamics simulations are extensively employed to predict binding affinity and stability of compound-target interactions, and the use of artificial intelligence is extensively employed to enhance prediction quality [50]. Nonetheless, target identification is limited by issues like off-target effects, binding specificity variability, and pathway activation depending on context [51]. Hence, the molecular architecture of drug repurposing is based on the combination of experimental verification with computational prediction to generate mechanistically accurate and therapeutically relevant results. The integrated pipeline from computational prediction to clinical translation of natural compounds provided a systems-level overview of the drug repurposing process, as shown in **Figure 2.**

A recent study demonstrated that machine learning-guided virtual screening achieved up to a fivefold increase in hit rates compared to conventional high-throughput screening, while also reducing false positives by 20-30% [52]. Network pharmacology combines genomics, proteomics, and metabolomics data to build interaction networks that can reveal major regulatory nodes and pathways in disease progression.

Natural Products Multi-Pathway Targeting in Complex Diseases: It is also becoming evident that natural products have the capacity to tune a variety of molecular pathways at once, which can be especially useful in the treatment of complex and multifactorial diseases [19]. Natural compounds regulate these pathways by targeting key signaling molecules involved in phosphorylation and transcriptional activation. Curcumin inhibits NF-κB by blocking IKK activity and suppresses PI3K/Akt/mTOR signaling, while activating AMPK [21]. Quercetin inhibits PI3K/Akt and JAK/STAT (STAT3 phosphorylation), reducing cell survival and inflammation [22]. Berberine activates AMPK (via increased AMP/ATP ratio) and suppresses NF-κB and PI3K/Akt/mTOR, thereby regulating inflammation, apoptosis, and metabolic homeostasis [53].

Natural products have been reported to decrease oxidative stress, prevent protein aggregation, and control neuroinflammatory responses, all of which are core factors in conditions like Alzheimer and Parkinson disease in neurodegenerative disease [54]. Nonetheless, there is a difficulty in predicting dose-response relationships and possible off-target effects due to the complexity of multi-pathway interactions [55]. Thus, natural compounds show integrated network effects that are necessary to understand to maximize their use in drug repurposing strategies to complex diseases.

Precision Medicine Approaches in Natural Product Repurposing: Drug repurposing with precision medicine methods centers on developing therapeutic interventions that are customized to specific genetic, molecular, and phenotypic characteristics to enhance treatment efficacy and minimize adverse effects. Emerging technologies in genomics and molecular diagnostics identified that disease-specific biomarkers may help in the selection of natural compounds that have specific pharmacological effects [56]. Whole-genome and transcriptome analysis have shown that there are patient-specific differences in gene expression and activation of signaling pathways, which determine responsiveness to therapy, and are revealed by high-throughput sequencing technologies [57]. It is demonstrated that natural products can regulate critical molecular targets in a context-specific way, suggesting their potential in precision-based therapeutic approaches.

The pharmacogenomic research suggested that genetic polymorphisms in drug-metabolizing enzymes, transporters, and receptors can have a considerable influence on the pharmacokinetics and pharmacodynamics of natural compounds. Indicatively, the activity of cytochrome P450 enzyme has been linked to variability in metabolism and bioavailability of phytochemicals [58]. Moreover, new evidence suggests the involvement of gut microbiota in altering the bioactivity of natural products by means of biotransformation processes, thus affecting the outcome of individual treatment. Multi-omics integration, such as genomics, proteomics, and metabolomics, has made it possible to create predictive models of personalized choice of therapy [59]. Nonetheless, the application of precision medicine to natural product repurposing is limited due to the lack of clinical validation, inconsistency in compound standardization and the multi-target interaction. Thus, to advance the personalized therapeutic use of natural compounds, it is necessary to integrate biomarker-based strategies with mechanistic insights.

Clinical Evidence and Translational Research of Repurposed Natural Products: Over the past few years clinical and translational studies on repurposed natural products have increased dramatically with the growing interest in multi-target therapeutics in chronic and complex disease therapy [60]. Recent clinical trials suggest that various natural products, such as curcumin, resveratrol, and berberine, have now been developed beyond the preclinical validation to human trials, with demonstrated effects on inflammation, metabolic homeostasis, and tumor development. Randomized controlled trials have documented that curcumin supplementation (500–1000 mg/day) was able to lower biomarkers of inflammation including C-reactive protein and interleukin-6 in patients with inflammatory and metabolic disorders [61,62]. Similarly, clinical studies on resveratrol (150–500 mg/day) have shown improved endothelial function and increased insulin sensitivity, along with reduced oxidative stress markers in patients with type 2 diabetes [63]. A consolidated overview of the mechanistic, pharmacokinetic, and translational characteristics of key repurposed natural compounds was provided in **Table I**.

Table I: A Summary of Mechanistic and Translational Profile of Repurposed Natural Compounds in Drug Discovery

Natural Compound	Primary Molecular Targets	Key Signaling Pathways	Experimentally Validated Mechanisms	Pharmacokinetic Limitations	Repurposing Relevance	Level of Evidence
Curcumin [11,12,20,21,39,60,61,62]	NF-κB, STAT3, COX-2, DNMTs, HDACs	PI3K/Akt, NF-κB, MAPK, AMPK	Inhibits IKK → NF-κB suppression; epigenetic modulation (DNMT/HDAC); antioxidant activity	Poor solubility; rapid metabolism	Cancer, inflammation, metabolic disorders	Clinical trials
Resveratrol [23,47,63]	SIRT1, AMPK, NF-κB	AMPK, mTOR	Activates AMPK/SIRT1; improves mitochondrial function; anti-inflammatory	Rapid metabolism; low bioavailability	Diabetes, cardiovascular diseases	Clinical trials
Berberine [22,59]	AMPK, NF-κB	AMPK, PI3K/Akt	AMPK activation via AMP/ATP; NF-κB suppression	Moderate absorption; microbiota metabolism	Type 2 diabetes, dyslipidemia	Clinical + preclinical
Quercetin [33,53]	PI3K, MAPK, NF-κB	PI3K/Akt, MAPK	Inhibits kinase signaling; reduces oxidative stress and cytokines	Poor solubility; low stability	Cancer, inflammation	Preclinical + limited clinical
EGCG [26,33]	EGFR, VEGF	MAPK, PI3K/Akt	Inhibits receptor tyrosine kinases; anti-angiogenic	Moderate bioavailability; instability	Cancer prevention, antiviral	Preclinical + emerging clinical

Genistein [5,6]	Tyrosine kinases, ER receptors	PI3K/Akt	Tyrosine kinase inhibition; hormonal pathway modulation	Moderate absorption; endocrine effects	Hormone-dependent cancers	Clinical + epidemiological
Artemisinin [5]	ROS-related targets	MAPK, oxidative stress	ROS generation → cytotoxicity	Good bioavailability; resistance concerns	Malaria, cancer repurposing	Approved + trials
Paclitaxel [32]	β-tubulin	Cell cycle pathways	Microtubule stabilization → mitotic arrest (32)	IV administration; toxicity	Cancer	FDA-approved
Sulforaphane [33,38]	HDACs, Nrf2	Nrf2/ARE	HDAC inhibition; Nrf2 activation → antioxidant gene expression	Rapid metabolism; variable PK	Cancer prevention	Clinical + preclinical
Luteolin [8]	JAK/STAT, NF-κB	JAK/STAT	Inhibits STAT3 signaling; anti-inflammatory	Low solubility; limited PK data	Cancer, inflammation	Preclinical

AMPK= AMP-activated protein kinase; ARE= Antioxidant response element; COX-2= Cyclooxygenase-2; DNMTs= DNA methyltransferases; EGCG= Epigallocatechin-3-gallate; ER= Estrogen receptor; HDACs= Histone deacetylases; IKK= IκB kinase; JAK= Janus kinase; MAPK= Mitogen-activated protein kinase; mTOR= Mammalian target of rapamycin; NF-κB= Nuclear factor kappa B; Nrf2= Nuclear factor erythroid 2–related factor 2; PI3K= Phosphoinositide 3-kinase; PK= Pharmacokinetics; ROS= Reactive oxygen species; SIRT1= Sirtuin 1; STAT3= Signal transducer and activator of transcription 3

Natural products are also being considered in the field of oncology as an adjunct to conventional therapies to improve the efficacy of conventional therapies and minimize treatment-related toxicity [64]. Nonetheless, clinical translation has been limited by variability in standardization of compounds, heterogeneity in study design, and lack of large-scale multicenter studies. Another issue that leads to regulatory obstacles is the variation in the classification of natural products as dietary supplements or pharmaceuticals among jurisdictions [65]. Thus, a strong clinical validation of repurposed natural products should be established with standard protocols and large-scale trials to determine the therapeutic credibility.

Future Opportunities: Precision Therapeutics with Natural Products: Integration of artificial intelligence, multi-omics data, and precision medicine frameworks are likely to lead future developments in drug repurposing of natural products. Recent findings show that AI-based predictive models are capable of increasing the discovery of new drug-target interactions and can select compounds more accurately. Single-cell sequencing and spatial transcriptomics are emerging technologies that are helping to gain a deeper insight into the heterogeneity of different diseases, allowing more targeted therapeutic targeting of natural compounds [66]. Secondly, nanotechnology-based delivery carriers, such as liposomal and polymeric carriers, have demonstrated enhanced bioavailability, targeted delivery, and decreased systemic toxicity in preclinical and early clinical trials [67].

Integrative treatments using natural substances and traditional medications are also becoming a subject of study to improve their effectiveness and counter drug resistance, especially in cancer and metabolic diseases [68]. Moreover, innovations in synthetic biology, and metabolic engineering are facilitating the scaleable production and structural optimization of bioactive natural products [69]. Nonetheless, standardized formulations, large-scale clinical trials, and harmonized regulatory frameworks are prerequisites to successful clinical integration. Thus, the intersection of computational innovation, molecular precision, and translational research is likely to make natural products an essential part of future therapeutic approaches.

CONCLUSION

Drug repurposing of natural compounds is a scientifically sound and potentially resource-efficient approach for the management of complex and chronic diseases. Many natural products are capable of modulating interconnected disease pathways through their multi-target pharmacology and is further facilitated by the advances in systems biology, omics technologies, and computational modeling. Nonetheless, clinical translation is limited by issues such as, standardization, pharmacokinetics, and regulatory heterogeneity. To improve the reliability of therapeutics, integration of precision medicine strategies, efficient delivery systems, and intense clinical validation is needed. The way forward is to incorporate mechanistic knowledge with translational research to make natural products effective and evidence-based candidates in the modern therapeutic development.

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