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Integrative Narrative Review

Network Pharmacology and Bioinformatics Perspectives on Quercetin from Moringa Oleifera in Cancer Therapy

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ABSTRACT

Background: Quercetin is a naturally occurring flavonol present in Moringa oleifera and several dietary plant sources and has attracted considerable interest because of its reported multitarget anticancer activity. Network pharmacology and bioinformatics provide systems-level approaches for interpreting the diverse molecular pathways potentially influenced by quercetin and for prioritizing cancer-associated targets for experimental investigation. Objective: This integrative narrative review aimed to synthesize current evidence on the phytochemical and pharmacological characteristics of quercetin in the context of Moringa oleifera, evaluate published network-pharmacology and bioinformatics findings concerning its cancer-associated targets and pathways, and examine its potential roles in tumor biology, combination therapy, and translational oncology. Methods: Published evidence was synthesized across predefined thematic domains, including quercetin phytochemistry and pharmacology, network pharmacology, protein–protein interaction networks, functional and pathway-enrichment analyses, molecular docking and molecular-dynamics studies, cancer-specific mechanisms, tumor-microenvironment modulation, combination-treatment strategies, pharmacokinetic limitations, formulation approaches, and translational challenges. Computational findings were interpreted separately from biochemical, cellular, animal, and clinical evidence, and studies of purified quercetin were distinguished from investigations involving multicomponent M. oleifera preparations. Results: Across the reviewed literature, quercetin-associated targets repeatedly converged on pathways regulating proliferation, apoptosis, oxidative and inflammatory signaling, angiogenesis, metastatic behavior, and treatment resistance. Network-based studies frequently identified cancer-associated proteins including TP53, AKT1, VEGFA, CCND1, and regulators of cell-cycle and survival signaling as highly connected candidate nodes. Reported cancer-related pathways included PI3K/AKT/mTOR, MAPK, NF-κB, JAK/STAT, p53, hormone-receptor, and EGFR-associated signaling. Preclinical evidence further suggested potential effects on tumor-associated macrophages, cytokine signaling, efferocytosis, and PD-1/PD-L1-related mechanisms. Molecular docking and molecular-dynamics studies provided structural hypotheses for several quercetin–protein interactions, while combination studies described potential enhancement of chemotherapy, radiotherapy, targeted therapy, and immune-checkpoint approaches. However, the strength of evidence varied substantially across computational, experimental, and translational levels. Conclusion: Quercetin represents a biologically plausible multitarget anticancer candidate with potential relevance to several interconnected cancer-associated pathways. Nevertheless, computational predictions and preclinical findings do not establish clinical efficacy. Translation remains limited by formulation-dependent bioavailability, extensive metabolism, variability among M. oleifera preparations, incomplete experimental validation of predicted molecular targets, and limited clinical evidence. Standardized formulations, pharmacologically relevant experimental models, direct target-engagement studies, rigorous evaluation of combination strategies, and carefully designed clinical investigations are required before quercetin can be established as an adjunctive cancer therapy. Keywords: Quercetin; Moringa oleifera; network pharmacology; bioinformatics; cancer therapy; molecular docking; molecular dynamics; tumor microenvironment; immunomodulation; precision oncology

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INTRODUCTION

Cancer remains a major therapeutic challenge because malignant progression is driven by heterogeneous and interconnected molecular processes rather than by a single abnormal pathway. Although surgery, radiotherapy, cytotoxic chemotherapy, targeted therapy, and immunotherapy have substantially improved outcomes in several malignancies, treatment failure continues to occur because of systemic toxicity,

acquired or intrinsic drug resistance, tumor heterogeneity, metastatic progression, and adaptive signaling within the tumor microenvironment (1,2). These limitations have intensified interest in agents capable of modulating multiple cancer-associated pathways simultaneously. Natural products have historically contributed substantially to anticancer drug discovery and continue to provide structurally diverse bioactive compounds with potential relevance to cancer prevention and treatment (3).

Moringa oleifera Lam., a member of the Moringaceae family, is a medicinal and nutritional plant widely distributed in tropical and subtropical regions. Its leaves, seeds, stems, and other tissues contain numerous bioactive constituents, including phenolic acids, flavonoids, glucosinolates, isothiocyanates, vitamins, and other secondary metabolites (4–6). Among its flavonoids, quercetin has attracted particular attention because of its broad biological activity and its potential to influence cellular processes involved in carcinogenesis and tumor progression. Quercetin is a flavonol characterized chemically as 3,5,7,3',4'-pentahydroxyflavone and is also present in several dietary plant sources. Experimental evidence has associated quercetin with antioxidant, anti-inflammatory, antiproliferative, pro-apoptotic, antiangiogenic, and antimetastatic activities (7). However, evidence derived from purified quercetin should be distinguished from studies examining whole M. oleifera extracts or multicomponent preparations, because the biological effects of the latter may reflect interactions among several phytochemicals rather than quercetin alone.

The anticancer actions attributed to quercetin involve multiple molecular mechanisms. Experimental and computational studies have implicated modulation of the PI3K/AKT/mTOR, MAPK/ERK, NF-κB, JAK/STAT, and p53-associated signaling systems, together with effects on apoptosis, cell-cycle regulation, angiogenesis, epithelial–mesenchymal transition, oxidative stress, and inflammatory signaling (8). Such multidimensional activity is difficult to characterize adequately through the traditional one-drug–one-target paradigm. Network pharmacology provides a systems-level framework for examining relationships among compounds, molecular targets, signaling pathways, and disease processes, while complementary bioinformatics approaches can help characterize protein–protein interaction networks, pathway enrichment, functional gene associations, and disease-relevant molecular patterns (9).

These approaches are particularly relevant to phytochemicals because natural compounds frequently exhibit polypharmacological activity. Published network-based investigations of M. oleifera and its constituents have identified interconnected cancer-associated targets and pathways that may contribute to their biological effects. For example, network pharmacology analysis of M. oleifera combined with gemcitabine in pancreatic cancer identified a complex target network involving apoptosis-related and survival-associated signaling, with genes including TP53, AKT1, VEGFA, and CCND1 occupying important network positions (10). Such findings are hypothesis-generating and can assist in prioritizing molecular targets for further experimental investigation; however, network centrality or computational prediction alone does not establish direct molecular binding, target engagement, therapeutic efficacy, or clinical benefit.

An additional emerging area of interest concerns the possible influence of quercetin on the tumor microenvironment. Beyond its direct effects on malignant cells, quercetin has been investigated in relation to inflammatory signaling, immune-cell function, tumor-associated macrophages, immune-checkpoint pathways, and other mechanisms involved in cancer immune escape. Its potential use in combination with chemotherapy, radiotherapy, targeted therapy, or immunotherapy has also attracted attention. Nevertheless, the strength of evidence varies substantially between computational predictions, in vitro experiments, animal studies, and human investigations, and many proposed mechanisms remain preclinical. Furthermore, the clinical translation of quercetin is constrained by limited aqueous solubility, extensive metabolism, formulation-dependent systemic exposure, and the relatively limited clinical validation of its proposed anticancer effects (11).

Accordingly, a critical synthesis is required that distinguishes computationally predicted mechanisms from experimentally supported effects and separates evidence concerning purified quercetin from that involving M. oleifera extracts or multicomponent preparations. The present integrative review therefore examines the

phytochemical and pharmacological relevance of quercetin in the context of M. oleifera, evaluates published network-pharmacology and bioinformatics evidence concerning cancer-associated targets and pathways, synthesizes findings across major cancer types and the tumor microenvironment, reviews computational evidence concerning quercetin–target interactions and potential combination strategies, and discusses the principal pharmacokinetic, formulation, standardization, and clinical challenges that currently limit translation into oncology practice.

MATERIALS AND METHODS

Review Design and Scope

This article was structured as an integrative narrative review examining the anticancer relevance of quercetin in the context of Moringa oleifera, with particular emphasis on network pharmacology, bioinformatics, molecular interaction studies, tumor biology, and translational oncology. The review was designed to integrate evidence from phytochemical and pharmacological studies, experimental cancer research, computational investigations, and translational literature rather than to generate a pooled quantitative estimate of treatment effect. Because the available evidence encompasses heterogeneous experimental designs, cancer types, molecular targets, computational approaches, and therapeutic contexts, findings were synthesized qualitatively according to their biological and translational relevance.

Evidence Domains

The literature incorporated into the review was organized into predefined thematic domains corresponding to the principal scientific questions addressed by the manuscript. These domains comprised the phytochemical distribution and pharmacological characteristics of quercetin in M. oleifera; pharmacokinetic and bioavailability limitations; principles and applications of network pharmacology; compound–target and protein–protein interaction networks; Gene Ontology and pathway-enrichment approaches; cancer-associated signaling pathways; mechanisms affecting proliferation, apoptosis, oxidative stress, inflammation, angiogenesis, and metastatic behavior; cancer type-specific evidence; modulation of the tumor microenvironment; molecular docking and molecular-dynamics evidence; combination strategies with conventional anticancer treatments; and translational barriers including formulation, clinical validation, and standardization of M. oleifera preparations.

Classification of Biological and Computational Evidence

Evidence was interpreted according to the type of investigation from which it originated. Computationally predicted targets, network hubs, enriched pathways, docking interactions, and molecular-dynamics findings were considered hypothesis-generating evidence and were distinguished from experimentally demonstrated molecular or cellular effects. Findings obtained from in vitro experiments and animal models were treated as preclinical evidence and were not interpreted as evidence of established clinical efficacy. Human or clinically oriented evidence, where represented in the included literature, was considered separately from computational and preclinical findings.

Particular attention was given to distinguishing studies of purified quercetin from investigations of M. oleifera extracts or multicomponent botanical preparations. Findings derived from whole-plant or leaf extracts were not attributed exclusively to quercetin when other biologically active constituents were also present. This distinction was maintained because M. oleifera contains multiple flavonoids, phenolic compounds, glucosinolates, isothiocyanates, and other constituents that may independently or collectively contribute to observed biological effects.

Network Pharmacology and Bioinformatics Evidence Synthesis

Published network-pharmacology findings were synthesized according to the relationships reported among compounds, predicted or experimentally documented molecular targets, protein–protein interaction networks, and cancer-associated signaling pathways. Particular attention was given to recurrently reported targets and network nodes, including proteins involved in cell-cycle regulation, survival signaling, apoptosis, angiogenesis, inflammation, and tumor progression. Hub status within a

computational network was interpreted as an indicator of network connectivity or topological importance rather than as proof of direct quercetin binding or causal therapeutic activity.

Bioinformatics findings were organized according to functional and pathway-level interpretation. Evidence involving Gene Ontology, KEGG, Reactome, protein–protein interaction analysis, transcriptomic resources, and cancer-associated molecular databases was considered in relation to the biological functions attributed to quercetin-responsive or predicted target genes. Where studies used different databases, algorithms, or analytical thresholds, their findings were interpreted within the context of the individual published analysis rather than assumed to be directly interchangeable.

Molecular Docking and Molecular-Dynamics Evidence

Molecular docking and molecular-dynamics findings reported in the included literature were considered as computational evidence supporting possible quercetin–protein interactions. Reported binding energies, interacting amino-acid residues, conformational stability measures, hydrogen-bond interactions, and other simulation outputs were interpreted according to the computational framework of the individual study. Docking scores generated by different proteins, software platforms, scoring functions, structures, or simulation conditions were not treated as directly equivalent measures of biological potency.

Computational interaction data were interpreted conservatively because predicted binding does not independently establish biochemical inhibition, intracellular target engagement, therapeutic selectivity, or clinical activity. Greater evidentiary weight was therefore assigned where computational predictions were accompanied by biochemical, cellular, animal, or other experimental validation.

Cancer-Specific and Mechanistic Synthesis

Evidence was further synthesized across major malignancies represented in the literature, including breast, colorectal, lung, prostate, hepatocellular, and hematological cancers. Within each cancer type, findings were organized according to the principal molecular mechanisms investigated, including regulation of proliferative signaling, cell-cycle progression, apoptosis, oxidative stress, inflammatory pathways, angiogenesis, metastatic processes, and treatment resistance. Common pathways reported across multiple cancer types were distinguished from mechanisms described primarily within individual malignancies.

Evidence concerning the tumor microenvironment was reviewed separately because these effects may involve immune and stromal components in addition to direct cancer-cell responses. Findings related to tumor-associated macrophages, lymphocyte responses, cytokine regulation, efferocytosis, MerTK signaling, and immune-checkpoint pathways were interpreted according to their experimental context and level of validation.

Combination-Therapy Evidence

Studies examining quercetin in combination with chemotherapy, radiotherapy, targeted therapy, or immunotherapeutic approaches were evaluated according to the type of combination effect reported. Evidence demonstrating increased treatment sensitivity or enhanced antitumor activity was distinguished from formally demonstrated pharmacological synergy. The term synergy was considered appropriate only when supported by the analytical approach reported in the underlying study; otherwise, combination effects were interpreted as enhancement, sensitization, or potential therapeutic interaction.

Translational Assessment

The translational potential of quercetin was assessed in relation to the principal barriers identified across the reviewed evidence. These included limited solubility and systemic exposure, extensive metabolism, formulation-related differences in bioavailability, variability in the phytochemical composition of M. oleifera preparations, uncertainty regarding the contribution of individual constituents within botanical extracts, limited clinical validation, and the need to establish whether computationally identified molecular interactions translate into biologically and clinically meaningful target engagement.

Novel delivery approaches described in the reviewed literature, including nanoparticle-based systems, phospholipid complexes, and other formulation strategies, were considered in relation to their potential to improve quercetin exposure. Such formulation approaches were interpreted as emerging translational strategies rather than established oncological treatments.

NETWORK PHARMACOLOGY APPROACHES IN ELUCIDATING QUERCETIN TARGETS

Network pharmacology provides a systems-level framework for investigating compounds that may influence multiple molecular targets and biological pathways simultaneously. This approach is particularly relevant to natural products such as quercetin because their biological effects are unlikely to be explained adequately by a single drug–single target model. Instead, network-based approaches integrate relationships among compounds, molecular targets, protein interactions, biological pathways, and disease-associated genes to generate hypotheses regarding the mechanisms through which a bioactive compound may influence complex disorders such as cancer (23). Within this framework, computationally identified targets and pathways should be regarded primarily as candidates for subsequent experimental validation rather than as confirmed mechanisms of therapeutic action.

Principles of Network Pharmacology

Network pharmacology is based on concepts from systems biology and graph theory, in which biological entities are represented as nodes and their functional or predicted relationships as edges. Several interconnected network types can be used to characterize the potential activity of a compound. Compound–target networks associate a bioactive molecule with predicted or experimentally reported protein targets, whereas target–pathway networks link these proteins with signaling cascades and biological processes. Disease-associated networks further relate molecular targets and pathways to pathological processes relevant to specific malignancies (24).

Protein–protein interaction networks provide an additional level of organization by illustrating known or predicted functional relationships among proteins. Network-topological measures may be used to identify highly connected nodes, commonly referred to as hubs, as well as nodes that occupy strategically important positions within network connectivity. Such proteins can be prioritized for mechanistic investigation because perturbation of highly connected components may influence multiple downstream processes (25). However, topological importance within a constructed network does not demonstrate that a protein is a direct molecular target of quercetin, nor does it establish biochemical inhibition or therapeutic efficacy. Network analysis should therefore be interpreted as a tool for target prioritization and hypothesis generation.

Databases and Computational Resources

Published investigations of quercetin and other phytochemicals have used multiple databases and computational resources to characterize chemical properties, predict molecular targets, identify cancer-associated genes, construct protein-interaction networks, and examine pathway enrichment. PubChem and ChEMBL provide chemical structures and experimentally reported bioactivity information, while the Traditional Chinese Medicine Systems Pharmacology Database has been used in natural-product research to obtain pharmacokinetic and drug-likeness characteristics (26). Computational platforms such as SwissTargetPrediction, PharmMapper, and the Similarity Ensemble Approach predict possible protein targets using approaches including chemical similarity, pharmacophore matching, and related computational strategies.

Cancer-associated genes may be obtained from disease-oriented resources such as DisGeNET, Online Mendelian Inheritance in Man, and the Therapeutic Target Database (27). Protein–protein interaction information can be explored using STRING, while Cytoscape is commonly used for network visualization and topological analysis. Functional interpretation of candidate targets can subsequently involve pathway resources such as KEGG, Reactome, and WikiPathways and enrichment-analysis platforms designed to identify biological processes or pathways represented disproportionately within a target set (28).

The results obtained through these databases depend on their underlying data sources, prediction algorithms, confidence thresholds, disease definitions, and dates of access. Consequently, targets obtained through different computational resources cannot automatically be regarded as equivalent, and predictions should be interpreted in relation to the methodological framework of the individual study.

Compound–Target–Disease Network Construction

Published network-pharmacology studies generally construct compound–target–disease networks through sequential identification of candidate compounds, potential molecular targets, disease-associated genes, and intersecting biological pathways. Chemical structures may initially be retrieved from databases such as PubChem, after which candidate compounds can be characterized using physicochemical or pharmacokinetic criteria. Some natural-product investigations using TCMSP have applied thresholds such as oral bioavailability greater than 30% and drug-likeness greater than 0.18; however, these thresholds are specific to particular analytical workflows and should not be considered universally applicable criteria for quercetin or other phytochemicals (29).

Potential targets may subsequently be obtained through computational prediction, literature-derived evidence, pharmacophore approaches, or drug–target databases. Cancer-related targets are then assembled from disease databases, and overlapping compound- and disease-associated genes may be used to construct protein–protein interaction or compound–target–disease networks. The resulting networks can be visualized and analyzed using tools such as Cytoscape, with network centrality measures used to prioritize candidate proteins for further investigation.

An illustrative example is the published network-pharmacology investigation of Moringa oleifera combined with gemcitabine in pancreatic cancer. In that study, TCMSP-based screening identified catechin, epicatechin, quercetin, and kaempferol among compounds meeting the specified screening requirements, while additional M. oleifera constituents, including glucomoringin, glucoraphanin, and moringinine, were retained on the basis of reported anticancer activity (30). Candidate targets for M. oleifera and gemcitabine were compiled from drug- and chemical-associated databases, whereas pancreatic cancer-associated genes were obtained from disease databases. Protein–protein interaction analysis subsequently demonstrated a complex network among overlapping targets (10).

The significance of such findings lies primarily in their ability to identify molecular relationships that may merit experimental investigation. Because M. oleifera is a multicomponent botanical preparation, network findings derived from whole-plant or extract-level analyses should not automatically be attributed specifically to quercetin. Likewise, the presence of a gene within a predicted network does not independently demonstrate direct ligand binding, functional inhibition, or clinical relevance.

Recurrently Reported Candidate Targets

Across the network-based evidence summarized in the manuscript, several cancer-associated proteins recur as highly connected or biologically relevant nodes. These include TP53, AKT1, VEGFA, CCND1, and proteins involved in apoptosis, cell-cycle regulation, inflammatory signaling, and angiogenesis. Their recurrence is biologically plausible because they participate in processes central to tumor survival and progression, including proliferative signaling, resistance to cell death, vascular development, and cell-cycle control.

Nevertheless, the evidentiary meaning of these findings should be carefully calibrated. A protein identified as a hub through computational network analysis is best described as a candidate or prioritized network-associated target. Stronger mechanistic conclusions require complementary evidence demonstrating direct interaction, target engagement, downstream functional consequences, and preferably reproducibility across independent experimental systems. Network pharmacology therefore provides a useful framework for organizing and prioritizing the complex molecular hypotheses associated with quercetin but should be integrated with biochemical, cellular, animal, and ultimately clinical evidence before therapeutic conclusions are drawn.

BIOINFORMATICS INSIGHTS INTO THE ANTICANCER MECHANISMS OF QUERCETIN

Bioinformatics approaches complement network pharmacology by enabling functional interpretation of predicted or experimentally reported target sets. Rather than establishing therapeutic efficacy independently, these analyses help determine whether candidate genes are concentrated within particular biological processes, molecular functions, cellular compartments, protein-interaction modules, or signaling pathways. In the context of quercetin and cancer, such approaches have been used to generate mechanistic hypotheses concerning cell-cycle control, apoptosis, inflammatory signaling, angiogenesis, survival pathways, oxidative stress, and other cancer-associated processes.

Gene Ontology and Functional Enrichment

Gene Ontology analysis categorizes genes and their encoded products according to three principal domains: Biological Process, Molecular Function, and Cellular Component. Within published quercetin-related and Moringa-associated analyses, candidate cancer-related targets have been linked to biological processes involving cell-cycle regulation, apoptotic signaling, inflammatory responses, angiogenesis, cellular stress responses, and epithelial–mesenchymal transition. Molecular-function categories may include protein kinase activity, ATP binding, transferase activity, transcription-factor interactions, and receptor-associated signaling, while cellular-component categories can reflect localization within the nucleus, plasma membrane, signaling complexes, cytoskeletal structures, or other intracellular compartments (32).

These enrichment results indicate that a target list contains more genes associated with particular functional annotations than would be expected under the analytical background model. They should not, however, be interpreted as direct evidence that quercetin experimentally regulates every enriched biological process. Functional enrichment is influenced by the composition of the input gene list, database annotation density, statistical thresholds, background-gene selection, and multiple-comparison procedures.

In the published investigation of Moringa oleifera combined with gemcitabine against pancreatic cancer, Gene Ontology enrichment was used to characterize biological processes, molecular functions, and cellular components associated with the identified targets (10). Findings from such a multicomponent Moringa intervention should be interpreted at the level of the analyzed preparation or target set unless a specific contribution from quercetin has been independently demonstrated.

Protein–Protein Interaction Networks

Protein–protein interaction analysis provides a means of examining how candidate molecular targets are functionally or physically interconnected. Published studies commonly use the STRING database for interaction retrieval, Cytoscape for network visualization, and clustering algorithms such as MCODE to identify densely connected functional modules. These modules may highlight groups of proteins participating in related biological processes.

The M. oleifera–gemcitabine pancreatic cancer study described in the reviewed literature reported a protein–protein interaction network comprising 33 nodes and 122 edges among common biotargets. Network analysis highlighted proteins including TP53, AKT1, VEGFA, and CCND1 as highly connected components of the reported network. These proteins are biologically relevant to cancer because they participate in tumor-suppressor signaling, cellular survival, angiogenesis, and cell-cycle progression, respectively.

Other target groupings described in the quercetin literature include cell-cycle-associated proteins such as CDK1, CCNA2, CCNB1, CDK2, and CDK4; apoptosis-related proteins including TP53, BCL2, CASP3, CASP8, and BAX; survival-signaling components such as AKT1, PIK3CA, MTOR, and PTEN; inflammatory mediators including PTGS2, TNF, NFKB1, and IL6; and angiogenesis-associated proteins such as VEGFA, MMP2, MMP9, and HIF1A (33,34).

These groupings provide a biologically coherent framework for understanding possible multitarget activity, but their presence within a computational network does not establish that all listed proteins are directly

bound or inhibited by quercetin. The most persuasive mechanistic interpretation is achieved when network predictions converge with independent biochemical, cellular, or in vivo evidence.

KEGG and Reactome Pathway Analyses

Pathway-enrichment analysis extends target-level interpretation by examining whether candidate genes are disproportionately represented within established signaling pathways. Published quercetin-related analyses frequently implicate pathways central to cancer-cell survival, proliferation, stress responses, inflammation, apoptosis, and angiogenesis.

The PI3K/AKT signaling axis is among the recurrently identified pathways and includes proteins such as AKT1, PIK3CA, MTOR, and BCL2 that participate in cellular growth and survival. MAPK-associated targets, including MAPK1, MAPK3, MAPK8, and EGFR, are involved in responses to mitogenic and stress-related stimuli. The p53 pathway includes proteins such as TP53, CDKN1A, BAX, and MDM2 that coordinate responses to DNA damage and cellular stress. Other reported pathway associations include NF-κB signaling through components such as NFKB1, RELA, TNF, and IL6; JAK/STAT signaling involving JAK1, STAT3, and SOCS3; FoxO-associated signaling involving FOXO1, FOXO3, and CDKN1B; and hypoxia-related signaling involving HIF1A, VEGFA, and NOS2 (35).

Reactome-based analyses can provide more detailed functional organization within these broader pathways and have associated quercetin-related target sets with processes including cell-cycle checkpoints, apoptotic signaling, regulation of TP53 activity, and receptor tyrosine kinase signaling (36). The convergence of several independent computational analyses on common cancer-associated pathways increases their biological plausibility but does not substitute for experimental demonstration of pathway modulation at pharmacologically relevant concentrations.

In the published M. oleifera–gemcitabine analysis, pathway enrichment implicated cancer-related and apoptosis-associated mechanisms in the predicted effects of the combination (10). As with other multicomponent preparations, these results should not be assigned specifically to quercetin unless constituent-specific evidence is available.

Cross-Validation Using Public Cancer Databases

Public molecular datasets can potentially strengthen the biological relevance of network-pharmacology predictions by determining whether candidate genes show disease-associated expression patterns or prognostic relationships in human cancer datasets. Resources such as The Cancer Genome Atlas provide genomic, transcriptomic, and clinical information across multiple malignancies, while the Gene Expression Omnibus contains independent datasets generated from diverse patient cohorts and experimental conditions. The Genotype-Tissue Expression resource provides information on gene expression in non-malignant human tissues that may support comparisons with tumor-derived data.

Single-cell cancer resources can provide an additional level of resolution by identifying the cellular populations within the tumor microenvironment in which particular genes are expressed. Such analyses may help determine whether a predicted target is predominantly associated with malignant cells, immune populations, stromal cells, or other cellular compartments within tumors.

The manuscript literature also identifies network-based approaches that can be used to compare molecular predictions with disease-associated datasets and human population-level evidence (37,38). However, the present review does not document the performance of an independent TCGA, GEO, GTEx, or single-cell analysis by the authors. These databases are therefore discussed as potential or previously used validation resources rather than as sources of original results generated in the present article.

Interpretation of Bioinformatics Evidence

Collectively, published bioinformatics findings support a model in which quercetin-associated targets intersect with several molecular systems involved in cancer biology, particularly pathways governing proliferation, survival, apoptosis, inflammatory signaling, angiogenesis, and cellular stress. Recurrent appearance of proteins such as TP53, AKT1, VEGFA, CCND1, and related signaling components across network and enrichment analyses provides a rational basis for prioritizing them in experimental research.

Nevertheless, computational convergence should not be equated with therapeutic validation. Predicted targets may arise partly because well-characterized cancer genes are highly represented within interaction and annotation databases, and enrichment results depend on the selected input targets and analytical thresholds. Consequently, the strongest evidence for a quercetin-mediated anticancer mechanism requires convergence between computational prediction and experimentally demonstrated target engagement, pathway modulation, phenotypic response, and in vivo relevance. Bioinformatics should therefore be regarded as a hypothesis-generating and prioritization framework that complements, rather than replaces, experimental and clinical investigation.

MODULATION OF CANCER HALLMARKS BY QUERCETIN

The hallmarks of cancer provide a useful framework for organizing the diverse biological processes that sustain malignant growth and progression. Evidence summarized in the reviewed literature suggests that quercetin may influence several of these processes, including sustained proliferative signaling, resistance to cell death, oxidative and inflammatory signaling, angiogenesis, and metastatic behavior. These effects have been described predominantly in computational and preclinical studies and should therefore be interpreted according to the experimental context in which they were observed rather than as established clinical anticancer effects (33).

Inhibition of Proliferative Signaling and Cell-Cycle Progression

Quercetin has been associated with reduced proliferation in several experimental cancer models through effects on both cell-cycle machinery and upstream growth-signaling pathways. Reported mechanisms include inhibition or downregulation of cyclin-dependent kinases such as CDK1, CDK2, CDK4, and CDK6, reduction in cyclins including cyclin D1 and cyclin B1, and increased expression of cell-cycle inhibitory proteins such as p21 and p27. Modulation of TP53 has also been implicated in quercetin-associated cell-cycle arrest (39).

At the signaling level, quercetin has been linked with suppression of the PI3K/AKT/mTOR and RAS/MAPK/ERK pathways, both of which regulate cell survival, growth, and proliferation. Additional effects involving transcriptional regulators such as NF-κB, AP-1, and c-Myc have been described in the reviewed literature. Computational network studies also repeatedly identify TP53 and AKT1 as highly connected cancer-associated nodes. However, their recurrent appearance in network analyses should be regarded as supportive of biological plausibility rather than proof that they are universally direct molecular targets of quercetin.

Taken together, the available evidence supports a model in which quercetin may interfere with proliferative signaling at several levels, including receptor-associated pathways, intracellular kinase networks, transcriptional regulation, and cell-cycle checkpoints. The relative contribution of each mechanism is likely to vary according to cancer type, concentration, experimental system, and molecular context.

Induction of Apoptotic Signaling

Induction of programmed cell death is one of the most consistently described anticancer effects of quercetin in preclinical models. Quercetin has been associated with activation of both intrinsic and extrinsic apoptotic pathways. Within the intrinsic pathway, reported effects include disruption of mitochondrial membrane potential, release of cytochrome c, activation of caspase-9 and caspase-3, downregulation of the anti-apoptotic protein Bcl-2, and increased expression of the pro-apoptotic protein Bax (40).

Effects on the extrinsic pathway have been linked to increased expression or activation of death-receptor signaling involving Fas, DR4, and DR5, with subsequent recruitment of caspase-8. Cross-talk between extrinsic and mitochondrial apoptosis may occur through cleavage of Bid and amplification of downstream caspase activation. Other reported mechanisms include endoplasmic-reticulum stress involving the PERK/ATF4/CHOP pathway and both p53-dependent and p53-independent apoptotic responses.

The biological relevance of these pathways is consistent with network-pharmacology findings in which apoptosis-associated proteins such as CASP3, BCL2-family members, and TP53 occur within highly

connected target networks. Nevertheless, the strongest evidence for apoptosis derives from experimental studies rather than computational centrality alone. In human HCT116 colon cancer cells, fractions derived from M. oleifera leaves containing quercetin together with other flavonoids were associated with morphological features of apoptosis and increased cleaved caspase-3-positive cells (41). Because these preparations contained multiple constituents, the observed effects cannot be attributed exclusively to quercetin.

Regulation of Oxidative Stress

Quercetin exhibits context-dependent effects on cellular redox balance. At lower concentrations and under some experimental conditions, it acts as an antioxidant through direct free-radical scavenging, metal-ion chelation, and activation of endogenous antioxidant defense mechanisms. Reported mechanisms include modulation of the Nrf2/ARE pathway and increased expression of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, glutathione S-transferase, and NAD(P)H:quinone oxidoreductase 1 (42).

In contrast, quercetin has also demonstrated pro-oxidant activity under certain experimental conditions. Autoxidation and redox cycling may increase intracellular reactive oxygen species, particularly in cells already exposed to high oxidative stress. Such effects have been proposed to contribute to selective cytotoxicity in some cancer models through mitochondrial dysfunction and apoptosis (43). These apparently opposing actions emphasize that quercetin should not be characterized simply as an antioxidant; its biological effect depends on dose, cellular redox state, metabolic environment, and experimental model.

Modulation of Inflammatory Signaling

Chronic inflammation contributes to tumor initiation, progression, angiogenesis, immune evasion, and treatment resistance. Quercetin has been associated with suppression of several inflammatory mediators, particularly through inhibition of NF-κB-related signaling. Reported effects include reduced degradation of IκBα, decreased nuclear translocation of NF-κB components, and lower expression of downstream inflammatory mediators such as cyclooxygenase-2 and inducible nitric oxide synthase.

Reductions in pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, and IL-8 have also been reported in experimental models. In the context of M. oleifera, modulation of inflammatory signaling has additionally been linked with PPAR-γ-associated mechanisms (44). These findings support a potential role for quercetin in modifying tumor-associated inflammatory processes, although such effects remain dependent on experimental context and do not establish therapeutic efficacy in patients with cancer.

Angiogenesis and Metastatic Processes

Quercetin has also been implicated in the regulation of processes required for tumor vascularization and metastatic progression. Network and experimental studies have associated quercetin-related activity with VEGFA, HIF1A, MMP2, and MMP9, which participate in angiogenesis, extracellular-matrix remodeling, invasion, and metastatic dissemination. Downregulation of VEGF-associated signaling and matrix metalloproteinases has therefore been proposed as one mechanism through which quercetin could suppress tumor vascularization and invasive behavior.

Effects on epithelial–mesenchymal transition have also been described, suggesting potential modulation of cellular plasticity and migration. However, these mechanisms have been evaluated predominantly in preclinical settings. Evidence that quercetin inhibits metastasis or angiogenesis in clinically relevant human exposure conditions remains limited.

Integrated Interpretation of Cancer-Hallmark Modulation

Rather than acting through a single molecular pathway, the reviewed evidence portrays quercetin as a pleiotropic bioactive compound associated with several interconnected cancer-related processes. A central feature of this proposed activity is the convergence of multiple mechanisms on common biological outcomes, particularly inhibition of proliferation, promotion of programmed cell death, modulation of inflammatory and oxidative signaling, and interference with angiogenic and metastatic pathways.

Table 1. Principal cancer hallmarks and quercetin-associated mechanisms described in the reviewed literature

Cancer-related process	Representative molecular components reported	Principal reported effect	Evidence interpretation
Proliferation and cell-cycle progression	CDK1, CDK2, CDK4, CDK6, cyclin D1, cyclin B1, p21, p27, TP53	Cell-cycle arrest and reduced proliferative signaling	Primarily preclinical; supported by computational pathway associations
Survival signaling	PI3K, AKT1, mTOR, MAPK/ERK	Suppression of growth- and survival-associated pathways	Computational and experimental evidence; direct target status varies
Intrinsic apoptosis	BCL2, BAX, caspase-9, caspase-3, TP53	Mitochondrial dysfunction and caspase-dependent apoptosis	Predominantly experimental/preclinical
Extrinsic apoptosis	Fas, DR4, DR5, caspase-8, Bid	Activation and amplification of death-receptor signaling	Preclinical mechanistic evidence
Oxidative stress	Nrf2/ARE, antioxidant enzymes, ROS	Antioxidant or pro-oxidant effects depending on biological context	Strongly context- and concentration-dependent
Inflammatory signaling	NF-κB, COX-2, iNOS, TNF-α, IL-1β, IL-6, IL-8, PPAR-γ	Reduction in pro-inflammatory signaling	Predominantly preclinical
Angiogenesis	VEGFA, HIF1A	Suppression of proangiogenic signaling	Primarily computational and preclinical
Invasion and metastasis	MMP2, MMP9, EMT-associated pathways	Reduced matrix remodeling, migration, and invasive signaling	Predominantly preclinical

The convergence of these mechanisms is biologically consistent with the multitarget profile proposed by network pharmacology. However, the evidence varies substantially in strength. Computationally predicted pathway associations, biochemical observations, cultured-cell findings, animal data, and clinical evidence should not be treated as equivalent. Consequently, quercetin is best regarded at present as a biologically plausible multitarget anticancer candidate whose cancer-hallmark effects require further validation under pharmacologically and clinically relevant conditions.

QUERCETIN ACROSS DIFFERENT CANCER TYPES

Quercetin has been investigated across several malignancies, with reported mechanisms reflecting both shared cancer-associated pathways and tumor-specific molecular features. Across breast, colorectal, lung, prostate, hepatocellular, and hematological cancers, recurrent mechanisms include modulation of PI3K/AKT/mTOR signaling, p53-associated apoptosis, NF-κB-related inflammatory signaling, cell-cycle regulation, and angiogenesis. At the same time, individual cancer types show additional mechanisms related to their characteristic molecular drivers (45). The available evidence is predominantly computational and preclinical, and the strength of support for individual mechanisms varies between tumor types.

Breast Cancer

In breast cancer models, quercetin has been investigated across hormone receptor-positive, HER2-positive, and triple-negative disease. In estrogen receptor-positive models, reported effects include modulation of estrogen-receptor signaling, including reduced ERα-associated activity and relative enhancement of ERβ-associated signaling. In HER2-positive models, quercetin has been associated with suppression of HER2 phosphorylation and downstream MAPK and AKT signaling (46).

Cell-cycle regulation represents another proposed mechanism. CDK1 has been identified in computational studies as a potentially relevant quercetin-associated target, and molecular-docking analyses of quercetin and related flavonoids have reported favorable predicted binding interactions with CDK1. These computational findings should, however, be interpreted as structural hypotheses rather than evidence of therapeutic inhibition in patients.

Quercetin has additionally been investigated in relation to tumor-microenvironment regulation, including MerTK-associated efferocytosis and PD-L1 expression. Combination studies have explored quercetin together with tamoxifen, trastuzumab, doxorubicin, and paclitaxel, with reports of increased treatment sensitivity in preclinical models. The available evidence supports further mechanistic investigation but is insufficient to establish quercetin as a clinically validated adjunct in breast cancer (47).

Colorectal Cancer

In colorectal cancer models, quercetin has been studied in both treatment-sensitive and chemoresistant cellular systems. Reported mechanisms include modulation of thymidylate synthase, p53-associated apoptosis, mitochondrial dynamics, Nrf2/HO-1 signaling, Wnt/β-catenin-related pathways, and inflammatory signaling associated with treatment resistance (48).

Quercetin has also been evaluated in combination with 5-fluorouracil, with preclinical studies reporting enhanced cytotoxic or sensitizing effects in colorectal cancer cell models. Mechanisms proposed for these effects include modulation of ERK/NLRP3 signaling and pathways associated with resistance. Such combination effects should be described as synergistic only where the underlying study performed an appropriate formal analysis of synergy.

Evidence involving M. oleifera leaf fractions provides additional support for anticancer activity in colorectal models. In HCT116 cells, fractions containing quercetin together with other flavonoids were reported to suppress proliferation and promote apoptotic features, including increased cleaved caspase-3-positive cells (41). Because the fractions were chemically complex, these effects cannot be assigned to quercetin alone.

Lung Cancer

In lung cancer, particularly non-small cell lung cancer, quercetin has been linked with modulation of receptor tyrosine kinase and intracellular survival pathways. Reported targets and pathways include EGFR, PI3K/AKT/mTOR, and MAPK-associated signaling. Computational and experimental studies have suggested that quercetin may interact with the ATP-binding region of EGFR and influence downstream proliferative signaling.

Additional investigations have examined possible effects on ALK-related signaling and natural-killer-cell activity. Quercetin has also been studied in combination with tyrosine kinase inhibitors such as gefitinib and erlotinib as a potential strategy for modifying acquired resistance. Its possible role as a radiosensitizing agent has similarly been explored through effects on DNA-damage and survival pathways (49).

These findings remain largely preclinical. Particularly for kinase-targeted mechanisms, predicted binding should be differentiated from direct biochemical inhibition and from clinically meaningful target engagement.

Prostate Cancer

Quercetin has been investigated in androgen-dependent and castration-resistant prostate cancer models. A principal reported mechanism involves modulation of androgen-receptor signaling, including downregulation of androgen receptor activity and reduced expression of androgen-responsive genes such as prostate-specific antigen. Quercetin has also been associated with inhibition of PI3K/AKT signaling, activation of AMPK, and suppression of mTOR-associated survival pathways (50).

These mechanisms are potentially relevant in castration-resistant prostate cancer because androgen-receptor signaling and PI3K/AKT/mTOR activity can contribute to continued tumor survival. Nevertheless, the evidence summarized in the manuscript is primarily mechanistic and preclinical, and clinical efficacy cannot be inferred from these molecular observations alone.

Hepatocellular Carcinoma

A broad range of mechanisms has been reported for quercetin in hepatocellular carcinoma models. These include modulation of PI3K/AKT/mTOR, JAK/STAT, NF-κB, and MAPK signaling, together with activation of the p53/p21 axis, reduction of cyclin D1, and inhibitinow pon of the anti-apoptotic protein Bcl-2 (51).

Other reported effects include induction of autophagy, suppression of angiogenic signaling, and increased sensitivity to agents such as sorafenib and doxorubicin in preclinical systems. Quercetin has also been discussed in relation to metabolic liver injury and viral-associated mechanisms relevant to hepatocellular carcinoma development. These latter observations may provide biological context but should not be interpreted as direct evidence that quercetin prevents or treats hepatocellular carcinoma in humans.

Hematological Malignancies

In leukemia, lymphoma, and multiple myeloma models, quercetin has been associated with mechanisms involving NF-κB signaling, topoisomerase II, proteasome activity, and apoptosis. In chronic myeloid leukemia models, effects on the BCR-ABL oncoprotein have also been reported, generating interest in possible combination approaches with tyrosine kinase inhibitors such as imatinib (52).

The molecular biology of hematological malignancies differs substantially from that of solid tumors, and mechanisms derived from one disease cannot automatically be generalized to another. The available findings should therefore be interpreted according to the specific disease and experimental model in which they were generated.

Common and Cancer-Specific Mechanisms

Comparison across malignancies indicates that several pathways recur despite substantial differences in tumor biology. PI3K/AKT/mTOR signaling, p53-associated apoptosis, NF-κB-related inflammatory regulation, cell-cycle control, and VEGF-associated angiogenesis represent recurring themes. Network analyses similarly identify highly connected cancer-associated genes such as TP53, AKT1, VEGFA, and CCND1 across different biological contexts (53).

Cancer-specific mechanisms are also apparent. Estrogen- and HER2-associated signaling is particularly relevant to breast cancer, androgen-receptor signaling to prostate cancer, thymidylate-synthase and Wnt/β-catenin-associated mechanisms to colorectal cancer, EGFR-associated signaling to lung cancer, and BCR-ABL or proteasome-related processes to selected hematological malignancies.

Table 2. Comparative summary of quercetin-associated mechanisms across cancer types

Cancer type	Principal mechanisms/ targets described	Combination approaches described	Evidence profile in reviewed literature
Breast cancer	ER signaling, HER2, AKT/MAPK, CDK1, MerTK, PD-L1	Tamoxifen, trastuzumab, doxorubicin, paclitaxel	Computational and preclinical
Colorectal cancer	Thymidylate synthase, p53, mitochondrial dynamics, Nrf2/HO-1, Wnt/β-catenin, ERK/NLRP3	5-fluorouracil	Predominantly preclinical; additional evidence from M. oleifera fractions
Lung cancer	EGFR, PI3K/AKT/mTOR, MAPK, ALK-associated signaling, DNA-damage responses	Gefitinib, erlotinib, radiotherapy	Computational and preclinical
Prostate cancer	Androgen receptor, PSA-associated signaling, PI3K/AKT, AMPK, mTOR	Not specifically established in the supplied section	Predominantly preclinical
Hepatocellular carcinoma	PI3K/AKT/mTOR, JAK/STAT, NF-κB, MAPK, p53/p21, Bcl-2, autophagy, angiogenesis	Sorafenib, doxorubicin	Predominantly preclinical
Hematological malignancies	NF-κB, topoisomerase II, proteasome activity, BCR-ABL	Imatinib in CML-related models	Predominantly mechanistic and preclinical

The comparative evidence therefore supports a multitarget model in which quercetin-associated mechanisms converge on a limited number of core cancer pathways while also interacting with disease-specific molecular drivers. This pattern is compatible with the systems-level interpretation advanced by network pharmacology but also illustrates a major translational limitation: broad pathway involvement does not necessarily predict therapeutic selectivity, clinically achievable activity, or efficacy across all tumor types.

The strongest future evidence would require integration of computational predictions with biochemical target-engagement studies, disease-specific cellular models, pharmacologically relevant in vivo exposure, and ultimately controlled clinical investigation. Until such evidence is available, cancer-specific quercetin effects should be presented primarily as preclinical and hypothesis-generating rather than as established therapeutic actions.

QUERCETIN AND THE TUMOR MICROENVIRONMENT

The tumor microenvironment (TME) comprises malignant cells together with immune cells, stromal populations, extracellular-matrix components, vascular structures, soluble mediators, and metabolic factors that collectively influence tumor progression and therapeutic response. Increasing evidence indicates that the biological effects attributed to quercetin may extend beyond direct cytotoxic or antiproliferative actions on malignant cells to modulation of inflammatory and immune processes within the TME (54). However, these effects appear strongly dependent on cellular context, dose, model system, and the immune population investigated.

Effects on Immune-Cell Function

Quercetin has been investigated in relation to several immune-cell populations involved in antitumor immunity. Preclinical studies have described effects on T lymphocytes, natural killer cells, macrophages, and dendritic cells. Some experimental evidence suggests that quercetin may influence CD8+ T-cell

responses, regulatory T-cell activity, and Th1/Th2 balance, while effects on natural killer cells have been associated with altered expression of activating receptors and cytotoxic mediators.

Macrophage polarization represents another potentially important mechanism because tumor-associated macrophages frequently acquire phenotypes that support angiogenesis, tissue remodeling, immune suppression, and tumor progression. Quercetin has been associated in some experimental systems with reduced M2-like polarization and enhancement of M1-associated features. Nevertheless, macrophage phenotypes exist along a functional continuum rather than as strictly binary M1/M2 states, and these findings should therefore be interpreted as evidence of immune modulation rather than complete phenotypic reprogramming.

The effect of quercetin on dendritic cells appears particularly context dependent. Although some literature has proposed enhanced antigen-presenting or immune-regulatory activity, other evidence indicates suppression of dendritic-cell activation and function (55). Accordingly, quercetin should not be characterized as uniformly immunostimulatory. Instead, its effects on dendritic-cell biology and adaptive immunity should be presented as model dependent and incompletely resolved.

Cytokine and Inflammatory Modulation

Quercetin has been associated with modulation of cytokines and inflammatory mediators that contribute to the TME. Reported effects include reduction of mediators such as TNF-α, IL-1β, IL-6, and IL-8, together with suppression of cyclooxygenase-2, inducible nitric oxide synthase, and prostaglandin-associated signaling in selected experimental systems (56). Effects on immunoregulatory cytokines, including TGF-β and IL-10, have also been described.

These observations are potentially relevant because persistent inflammatory signaling can promote tumor growth, angiogenesis, immune evasion, and treatment resistance. However, individual cytokines may exert different or even opposing effects depending on tumor type, disease stage, immune-cell composition, and treatment context. Consequently, reduction of a particular cytokine cannot automatically be interpreted as beneficial antitumor immune modulation.

Tumor-Associated Macrophages and Efferocytosis

Tumor-associated macrophages are important regulators of immune suppression and tissue remodeling in many solid tumors. Published evidence has linked quercetin with pathways involved in macrophage polarization and signaling through transcription factors such as STAT3 and STAT6. Suppression of these pathways has been proposed as one mechanism through which quercetin may reduce tumor-supportive macrophage activity.

An emerging area of interest concerns efferocytosis, the clearance of apoptotic cells by phagocytes. MerTK, a member of the TAM receptor tyrosine kinase family, contributes to efferocytosis and can promote immunoregulatory signaling within tumors (57). Because efficient clearance of apoptotic tumor cells may induce mediators such as TGF-β and IL-10, inhibition of MerTK-associated efferocytosis has been proposed as a strategy for modifying the immunosuppressive microenvironment. Quercetin-related modulation of this pathway has therefore generated mechanistic interest.

Nevertheless, evidence connecting quercetin directly with clinically meaningful MerTK inhibition remains preclinical. Efferocytosis is also physiologically important for tissue homeostasis and resolution of inflammation; therefore, its inhibition should not automatically be assumed to be therapeutically advantageous in all settings.

Immune-Checkpoint Pathways

The PD-1/PD-L1 pathway is a major mechanism through which tumors suppress T-cell activity and evade antitumor immunity. Experimental evidence summarized in the manuscript indicates that quercetin may reduce PD-L1-associated signaling under some conditions, and relationships between MerTK activity, efferocytosis, and checkpoint regulation have been proposed (58).

Computational studies have additionally explored possible direct interactions between quercetin and immune-checkpoint proteins. Such docking predictions are hypothesis generating and do not independently establish functional checkpoint blockade. Evidence concerning other checkpoint pathways, including CTLA-4, TIM-3, and LAG-3, remains comparatively limited within the supplied literature.

Combination approaches involving quercetin and PD-1/PD-L1-directed therapy have shown encouraging effects in preclinical investigations (59). These observations provide a rationale for further study but should not be interpreted as evidence that quercetin currently functions as a clinically validated immune-checkpoint modulator.

Integrated Interpretation of Tumor-Microenvironment Effects

The TME represents an important extension of the proposed anticancer profile of quercetin because potential effects on macrophages, cytokine signaling, efferocytosis, and checkpoint pathways could complement direct effects on malignant cells. However, immune modulation is intrinsically context dependent, and some reported actions of quercetin appear divergent across experimental systems.

Table 3. Tumor-microenvironment processes potentially influenced by quercetin

TME component/process	Principal mechanisms described	Potential biological consequence	Current evidentiary interpretation
T lymphocytes	CD8+ responses, Treg activity, Th1/Th2 balance	Altered antitumor adaptive immunity	Preclinical and context dependent
Natural killer cells	Activating-receptor and cytotoxic-effector modulation	Potential enhancement of tumor-cell killing	Preclinical
Dendritic cells	Altered activation, maturation, and antigen presentation	Variable effects on adaptive immune priming	Conflicting/context-dependent evidence
Tumor-associated macrophages	STAT3/STAT6-associated signaling, macrophage polarization	Potential reduction of tumor-supportive macrophage functions	Preclinical
Efferocytosis	MerTK-associated signaling	Possible reduction of immunoregulatory clearance pathways	Emerging preclinical evidence
Cytokine environment	TNF-α, IL-1β, IL-6, IL-8, TGF-β, IL-10 and related mediators	Modification of inflammatory and immunosuppressive signaling	Context dependent
Immune checkpoints	PD-1/PD-L1; proposed relationships with other checkpoints	Potential modification of immune escape	Predominantly preclinical; some computational evidence

Overall, current evidence supports further investigation of quercetin as a potential modulator of the TME, but the complexity of immune regulation requires substantially greater experimental validation before these effects can be translated into therapeutic recommendations.

COMPUTATIONAL VALIDATION OF QUERCETIN–TARGET INTERACTIONS

Computational approaches have been widely employed to investigate possible molecular interactions between quercetin and cancer-associated proteins. Molecular docking can generate hypotheses regarding ligand-binding orientations and relative interaction scores, while molecular-dynamics simulations can examine the temporal stability and conformational behavior of predicted protein–ligand complexes (60). These methods provide structural information that can guide experimental prioritization but do not independently establish biochemical inhibition or therapeutic activity.

Molecular Docking Studies

Molecular docking typically involves preparation of a three-dimensional protein structure and ligand, definition of a potential binding region, computational exploration of ligand orientations, and ranking of predicted poses using an algorithm-specific scoring function. Published studies investigating quercetin have used platforms such as AutoDock Vina, GLIDE, GOLD, and MOE, among others (61).

The reviewed literature reports predicted interactions of quercetin with several cancer-associated proteins, including CDK1, AKT1, EGFR, PI3K-related proteins, and p53-associated targets. Reported docking scores vary substantially between studies. Values cited in the manuscript include approximately −8.2 to −9.5 kcal/mol for CDK1, −7.5 to −8.8 kcal/mol for AKT1, −7.8 to −9.2 kcal/mol for EGFR, and approximately −7.2 to −8.5 kcal/mol for PI3Kγ in individual computational investigations (62). Other published work has reported stronger predicted interactions between quercetin and CDK1, including values around −12.249 kcal/mol with interactions involving residues such as TRP79, TRP111, and THR113 (63).

These numerical scores should not be compared directly across studies unless the same protein structures, docking platforms, scoring functions, ligand-preparation methods, binding-site definitions, and validation procedures were used. Docking energy is a model-dependent computational score rather than a directly measured thermodynamic binding affinity.

Molecular-Dynamics Simulations

Molecular-dynamics simulations extend docking analysis by examining predicted protein–ligand complexes over time. Published simulations commonly evaluate parameters such as root-mean-square deviation, root-mean-square fluctuation, radius of gyration, and hydrogen-bond persistence. Force fields such as AMBER, CHARMM, and GROMOS and explicit-solvent models may be used depending on the study design.

The reviewed literature describes quercetin–protein simulations conducted over time scales commonly ranging from tens to hundreds of nanoseconds, with some complexes showing relatively stable trajectories and persistent intermolecular interactions (64). Measures such as RMSD and hydrogen-bond occupancy can support assessment of whether a predicted docked configuration remains structurally stable within the simulated environment.

However, there is no universal RMSD threshold that confirms biologically meaningful binding, and simulation stability does not demonstrate functional inhibition. Interpretation must therefore remain specific to the protein, simulation protocol, comparator ligands, and experimental question.

Reliability and Limitations of In Silico Evidence

Computational approaches offer important advantages, including relatively rapid screening of multiple targets, visualization of possible binding orientations, and prioritization of hypotheses for subsequent laboratory testing. They are particularly valuable in natural-product research, where a single compound may potentially interact with numerous proteins.

Their limitations are equally important. Docking often simplifies protein flexibility, solvent effects, entropic contributions, protonation states, and dynamic conformational changes. Scoring functions may produce false-positive or false-negative predictions, and high predicted affinity does not guarantee adequate cellular uptake, target exposure, biochemical inhibition, or therapeutic selectivity (65).

Pharmacokinetic processes also remain outside the scope of most docking analyses. A compound may interact favorably with an isolated protein in silico but fail to reach that protein at sufficient concentrations in vivo because of limited absorption, metabolism, protein binding, or tissue distribution.

Experimental validation is therefore essential. Biophysical methods such as surface plasmon resonance, isothermal titration calorimetry, or microscale thermophoresis can examine direct binding, while cellular target-engagement approaches and functional assays can establish whether the proposed interaction occurs within a biological system and produces the predicted downstream effect (66). Computational findings are best regarded as a prioritization framework within a broader validation pathway.

POTENTIAL INTERACTIONS WITH CONVENTIONAL CANCER THERAPIES

Combination treatment is central to modern oncology because tumors frequently engage multiple survival pathways and can acquire resistance to individual therapies. The broad molecular effects attributed to quercetin have therefore stimulated investigation of its potential to modify responses to chemotherapy, radiotherapy, targeted treatments, and immunotherapy (22). Most of this evidence remains preclinical.

Combination with Chemotherapy

Quercetin has been investigated alongside several cytotoxic and targeted anticancer drugs. In colorectal and other gastrointestinal cancer models, combinations with 5-fluorouracil have been associated with modulation of thymidylate synthase, p53-associated apoptosis, mitochondrial processes, and signaling pathways implicated in treatment resistance. In experimental models involving cisplatin, proposed

sensitizing mechanisms include modulation of oxidative stress, Nrf2-associated defenses, and DNA-damage responses.

Table 4. Hierarchy for interpreting computational quercetin–target evidence

Evidence stage	Principal question addressed	What it can support	What it cannot establish independently
Target prediction/network pharmacology	Which proteins may be associated with quercetin?	Candidate-target prioritization	Direct binding or functional inhibition
Molecular docking	Can quercetin adopt a plausible predicted binding pose?	Structural hypothesis and relative scoring within a defined protocol	Measured binding affinity or cellular activity
Molecular dynamics	Does the predicted complex remain structurally stable during simulation?	Conformational stability within the simulated model	Therapeutic efficacy or target engagement in vivo
Biochemical/biophysical validation	Does direct molecular interaction occur experimentally?	Direct binding or biochemical effect	Whole-cell or clinical efficacy
Cellular validation	Does target engagement alter biological function in cells?	Functional mechanism in a cellular model	Clinical benefit
In vivo/clinical validation	Does the mechanism translate to an organism or patients?	Translational and therapeutic relevance	Generalizability beyond the tested context

Quercetin has also been studied with doxorubicin, with proposed mechanisms involving apoptosis-associated pathways and Bcl-2-family regulation, and with paclitaxel, where effects on drug-efflux mechanisms and survival signaling have been investigated (67). Combination studies involving sorafenib have similarly explored whether quercetin can influence resistance-associated signaling in hepatocellular carcinoma.

In a published network-pharmacology study of M. oleifera combined with gemcitabine in pancreatic cancer, apoptosis-associated pathways and highly connected proteins including TP53, AKT1, VEGFA, and CCND1 were identified within the predicted interaction network (10). Because this analysis examined a multicomponent botanical preparation rather than purified quercetin alone, the reported combination effects should not be attributed exclusively to quercetin.

Importantly, improved activity of a drug combination does not necessarily demonstrate pharmacological synergy. Where formal interaction analysis was not reported, terms such as enhanced activity, sensitization, or combination effect are more appropriate.

Radiosensitizing Effects

Preclinical evidence suggests that quercetin may alter cellular responses to ionizing radiation. Proposed mechanisms include modulation of DNA-damage repair, cell-cycle distribution, oxidative stress, apoptosis, and prosurvival signaling. Arrest of cells in radiosensitive phases of the cell cycle has also been proposed as a potential mechanism. Experimental work involving M. oleifera preparations has reported enhanced effects of ionizing radiation on survival and metastatic activity in pancreatic cancer cells (68). As with other extract-based evidence, the contribution of quercetin cannot be isolated unless constituent-specific experimentation is performed. The possibility that quercetin might simultaneously sensitize malignant cells while limiting normal-tissue injury is of considerable interest, but such differential effects require rigorous dose- and tissue-specific validation before translational conclusions can be made.

Combination with Immunotherapy

The potential interaction between quercetin and immune-checkpoint therapy has emerged from its reported effects on PD-1/PD-L1-associated signaling, inflammatory pathways, macrophages, and efferocytosis. Experimental evidence has suggested that quercetin may interfere with PD-1/PD-L1 interactions or PD-L1-associated immune suppression under selected conditions (69).

These observations provide a rationale for evaluating quercetin alongside checkpoint inhibitors, particularly where immune suppression and compensatory signaling contribute to treatment resistance. However, current evidence remains preclinical, and computational or cellular observations should not be interpreted as establishing clinical synergy with anti-PD-1 or anti-PD-L1 therapy.

Network-based approaches may help identify combinations in which agents affect complementary but interconnected signaling nodes, thereby generating hypotheses for rational multidrug treatment design

(70). Such predictions require experimental confirmation using appropriate interaction models, pharmacological exposures, and clinically relevant endpoints.

Table 5. Conventional treatment modalities investigated in combination with quercetin or M. oleifera-associated preparations

Treatment modality	Examples described in the reviewed literature	Proposed basis for enhanced response	Interpretation
Antimetabolite chemotherapy	5-fluorouracil, gemcitabine	Apoptosis, thymidylate synthase, survival-signaling and resistance pathways	Predominantly preclinical
Platinum chemotherapy	Cisplatin	Oxidative stress, Nrf2-associated defenses, DNA-damage responses	Preclinical
Anthracyclines	Doxorubicin	Apoptotic signaling and Bcl-2-family regulation	Preclinical
Microtubule-directed chemotherapy	Paclitaxel	Drug-efflux and survival-pathway modulation	Preclinical
Targeted therapy	Sorafenib, gefitinib, erlotinib, imatinib	Modulation of resistance-associated signaling	Preclinical
Radiotherapy	Ionizing radiation	DNA-damage responses, cell-cycle effects, apoptosis	Preclinical
Immunotherapy	PD-1/PD-L1-directed approaches	Checkpoint modulation and TME-related mechanisms	Emerging preclinical evidence

Overall, combination therapy represents a biologically plausible direction for quercetin research, but claims of synergy should remain restricted to studies in which pharmacological interaction has been formally demonstrated.

TRANSLATIONAL CHALLENGES AND FUTURE OPPORTUNITIES

Despite extensive mechanistic and preclinical investigation, substantial barriers remain before quercetin can be considered a clinically useful anticancer adjunct. These challenges involve pharmacokinetics, formulation, botanical standardization, evidence quality, target validation, and the limited extent of prospective clinical investigation (71).

Bioavailability and Formulation

Poor and variable systemic exposure is among the most important translational limitations of quercetin. The reviewed literature attributes this limitation to low aqueous solubility, intestinal and hepatic metabolism, conjugation, and transport processes. The parent aglycone undergoes extensive metabolic conversion, producing glucuronidated, sulfated, and methylated metabolites whose biological properties may differ from those observed for unconjugated quercetin in cell-culture experiments.

For this reason, anticancer effects observed at relatively high concentrations of free quercetin in vitro cannot automatically be assumed to occur following conventional oral administration. Pharmacological interpretation should consider the chemical form administered, formulation, dose, circulating metabolites, and achievable tissue exposure.

Several formulation strategies have been investigated to improve delivery, including liposomes, polymeric nanoparticles, solid-lipid nanoparticles, phospholipid complexes or phytosomes, cocrystals, and related delivery technologies (72). These approaches may improve solubility, stability, membrane permeability, or systemic exposure, but enhancement of pharmacokinetics does not itself establish anticancer efficacy.

Limited Clinical Validation

The evidence summarized throughout this review is dominated by computational, cellular, and other preclinical investigations. Human clinical evidence remains comparatively limited, creating a substantial gap between mechanistic plausibility and therapeutic application.

Future clinical development should therefore proceed beyond demonstration of biological activity toward characterization of formulation-specific pharmacokinetics, clinically achievable exposure, safety, drug–drug interactions, target engagement, biomarkers of biological response, and well-defined clinical outcomes. Combination-treatment trials would additionally require careful evaluation of whether quercetin modifies efficacy or toxicity of established anticancer therapies. Biomarker-informed approaches may eventually help identify tumors in which quercetin-associated pathways are particularly

relevant. However, patient stratification based purely on computationally predicted targets would be premature without prospective biological and clinical validation.

Standardization of Moringa oleifera Preparations

Translation of M. oleifera-based interventions presents additional challenges beyond those associated with purified quercetin. The phytochemical composition of botanical preparations can vary according to plant part, geographical source, environmental conditions, harvest timing, processing, storage, and extraction method. Consequently, two M. oleifera preparations may contain substantially different concentrations and combinations of biologically active constituents. In addition to quercetin, M. oleifera contains compounds such as kaempferol, chlorogenic acid, isothiocyanates, glucomoringin, glucoraphanin, and other phytochemicals. Reported biological effects of a whole extract therefore may reflect additive, antagonistic, or interactive actions among multiple constituents rather than quercetin alone (73). Future studies involving M. oleifera should characterize the plant material, extraction procedure, chemical composition, and quercetin content sufficiently to permit reproducibility and meaningful comparison between studies. Where the scientific objective concerns quercetin specifically, purified-compound experiments should be distinguished from whole-extract investigations.

Experimental Validation of Computational Predictions

A further translational challenge is the gap between computationally predicted mechanisms and experimentally established target engagement. Hub genes and enriched pathways identified by network pharmacology may represent biologically important nodes, but their prominence within a computational network can also reflect annotation density and the interconnected nature of well-studied cancer genes. Future research should therefore prioritize candidate targets using convergent evidence. High-priority interactions should progress from computational prediction to direct binding studies, biochemical assays, cellular target-engagement experiments, functional perturbation, pharmacologically relevant animal models, and ultimately human investigation where justified. This validation hierarchy is especially important for multitarget compounds because broad computational connectivity can otherwise produce mechanistically attractive but experimentally weak narratives.

Integration of Multi-Omics and Precision-Oncology Approaches

Transcriptomic, proteomic, metabolomic, and other molecular datasets may provide opportunities to identify tumor contexts in which quercetin-associated pathways are particularly active. Integration of these data with network pharmacology could support biomarker discovery, mechanistic stratification, and prioritization of candidate combination therapies. However, multi-omics integration should be treated as a means of generating and refining testable hypotheses rather than as a substitute for experimental validation. Predictive models require independent validation, and associations between molecular signatures and quercetin response would need to be demonstrated prospectively before they could inform patient selection.

Priorities for Future Research

The next phase of quercetin research should emphasize translational depth rather than continued accumulation of isolated computational predictions. Important priorities include standardized characterization of purified quercetin and M. oleifera preparations; determination of pharmacologically achievable concentrations; direct confirmation of prioritized molecular targets; comparison of parent quercetin with circulating metabolites; rigorous evaluation of combination treatments; and development of formulations supported by pharmacokinetic evidence.

Cancer-specific studies should also identify whether molecular responses differ according to tumor genotype, signaling dependencies, immune context, and treatment history. Ultimately, the therapeutic relevance of quercetin will depend not on the number of pathways predicted to interact with the compound but on whether reproducible target engagement can be achieved safely at clinically relevant exposure and translated into meaningful patient outcomes.

CONCLUSION

Quercetin is a biologically active flavonoid present in Moringa oleifera and other plant sources that has been associated with multiple cancer-related molecular processes. The evidence synthesized in this integrative review indicates recurrent involvement of pathways regulating cellular proliferation, apoptosis, inflammatory and oxidative signaling, angiogenesis, treatment resistance, and components of the tumor microenvironment. Published network-pharmacology and bioinformatics studies frequently identify cancer-associated proteins such as TP53, AKT1, VEGFA, and CCND1 within highly connected target networks, while molecular-docking and simulation studies provide structural hypotheses for interactions with several cancer-relevant proteins. These computational findings strengthen mechanistic prioritization but should not be interpreted as confirmation of direct target engagement or therapeutic efficacy.

Across individual cancer types, quercetin-associated effects appear to combine common signaling mechanisms with tumor-specific molecular features. Preclinical studies further suggest that quercetin or M. oleifera-associated preparations may modify responses to chemotherapy, radiotherapy, targeted therapy, and immune-checkpoint pathways. However, evidence derived from purified quercetin must be distinguished from that obtained using multicomponent M. oleifera extracts, and enhancement of combination treatment should not be equated with pharmacological synergy unless formally demonstrated.

Clinical translation remains constrained by formulation-dependent bioavailability, extensive metabolism, variability in botanical preparations, incomplete experimental validation of computationally prioritized targets, and limited clinical evidence. Consequently, quercetin should presently be regarded as a promising preclinical and translational candidate rather than an established anticancer therapy. Future progress will require standardized preparations, pharmacokinetically relevant experimental models, direct target-engagement studies, rigorous evaluation of combination strategies, and carefully designed clinical investigations linking molecular mechanisms with measurable patient outcomes.

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