Journal of Applied Pharmacognosy and Phytochemistry
Volume 4, Issue 2, Year of Publication 2025, Page 01 – 16

Review Article

JOURNAL OF APPLIED PHARMACOGNOSY AND PHYTOCHEMISTRY | JOAPP
www.joapponline.com

FLAVONOIDS AS MULTI-TARGET THERAPEUTIC AGENTS: A SYSTEMATIC REVIEW OF PHARMACOLOGICAL EVIDENCE, MOLECULAR MECHANISMS, AND CLINICAL TRANSLATION

Jahnabi Sarmah[1], Dhiraj Bishya[2]*, Rosamund Jyrwa[3], Ikram Hussain[4]

Article Information
Received: 11th April 2024
Revised: 9th May 2024
Accepted: 6th June 2024
Published: 30th June 2024

Keywords
Flavonoids, Polyphenols, Multi-target therapy, Pharmacology, Drug discovery, Molecular targets, Precision medicine, Natural products, Network pharmacology, PRISMA.

ABSTRACT

Background: Flavonoids, the largest class of plant polyphenols, are increasingly recognized as multi-target therapeutic agents that can modulate diverse molecular pathways involved in chronic diseases. Unlike previous reviews focusing on individual flavonoid subclasses or specific diseases, this systematic review provides a comprehensive evaluation of their molecular mechanisms, pharmacokinetics, network pharmacology, and clinical applications. **Methodology:** We conducted a systematic review following the PRISMA 2020 guidelines. We searched electronic databases, including PubMed, Scopus, Web of Science, Embase, ScienceDirect, Cochrane Library, and Google Scholar, for studies published between January 2000 and March 2024. We assessed eligible in vitro, in vivo, and clinical studies using established risk-of-bias tools and evaluated evidence certainty using the GRADE framework. **Results and Discussion:** The review identified extensive preclinical evidence and an emerging body of clinical studies supporting flavonoids' therapeutic potential. These compounds modulate multiple molecular targets, including inflammatory mediators, kinase signaling pathways, transcription factors, and apoptotic regulators, across cancer, cardiovascular, metabolic, neurodegenerative, and inflammatory disorders. Clinical studies indicate modest but promising therapeutic benefits; however, poor oral bioavailability, rapid metabolism, and heterogeneity in study design and intervention protocols constrain broader clinical translation. **Conclusion:** Flavonoids demonstrate substantial multi-target therapeutic potential supported by robust mechanistic evidence and encouraging clinical findings. Nevertheless, well-designed, adequately powered clinical trials, standardized formulations, and advanced bioavailability-enhancing delivery systems are essential to establish their efficacy and facilitate widespread clinical application.

[1]*North East Practical Education Development Sanstha, Gandhinagar, Tetelia, Maloibari Road, Sonapur, Kamrup (Metro), Assam 782403.*
[2]*Faculty of Pharmaceutical Science, Assam down town University, Panikhaiti, Gandhinagar, Guwahati, Assam, India, 781026*
[3]*Pratiksha Institute of Pharmaceutical Sciences, Panikhaiti, Guwahati, Assam, India, 781026.*
[4]*Rahman Institute of Pharmaceutical Sciences and Research, Tepesia, Kamarkuchi, Sonapur, Kamrup (M), Assam, India*

For Correspondence:** **dhiraj.b@adtu.in

©2025 The authors
This is an Open Access article distributed under the terms of the Creative Commons Attribution (CC BY NC), which permits unrestricted use, distribution, and reproduction in any medium, as long as the original authors and source are cited. No permission is required from the authors or the publishers. ***(https://creativecommons.org/licenses/by-nc/4.0/)***

1. INTRODUCTION

1.1 Global burden of chronic disease

Non-communicable and chronic diseases now dominate the global burden of morbidity and mortality. Cancer, cardiovascular disease, type 2 diabetes, obesity, and neurodegenerative disorders together account for the majority of years of life lost worldwide, and their incidence continues to rise with population aging and lifestyle transition [1,2]. Chronic low-grade inflammation is a shared pathophysiological thread across these conditions, linking metabolic dysfunction, vascular disease, malignant transformation, and neuronal loss through overlapping cytokine and oxidative-stress signaling [3]. Infectious diseases viral, bacterial, and fungal add a further and growing burden, compounded by antimicrobial and antiviral resistance that narrows the effective therapeutic armamentarium [4].

Because these conditions are polygenic and multifactorial rather than the product of a single deranged pathway, single-target pharmacotherapy often underperforms against the full complexity of disease biology, renewing interest in molecules that engage several pathogenic nodes at once [2,3].

1.2 Why multi-target drugs?

The polypharmacology paradigm holds that many effective drugs and much of drug attrition can be explained by unintended or intended engagement of multiple targets rather than the single-target, single-disease model that dominated twentieth-century drug discovery [5]. Network medicine reframes disease as an emergent property of perturbed protein-interaction and signaling networks, in which robust therapeutic effect may require modulating several interacting nodes rather than one [5,6]. This view aligns with the practical realities of drug-resistant tumors and pathogens routinely circumventing single-target inhibition through compensatory signaling or mutation, and with the rationale for combination therapy, which has become standard of care in oncology, HIV, and hypertension [6,7]. Precision medicine adds a complementary dimension: rather than a single mechanism for all patients, multi-target agents with broad but graduated activity may be tunable to individual disease-network topology through dose, formulation, or combination [6]. Systems-biology approaches, including network pharmacology, now provide the computational tools needed to rationally nominate and rank candidate multi-target molecules rather than relying on empirical screening [5,7].

1.3 Why flavonoids?

Flavonoids are a structurally diverse family of plant secondary metabolites, with more than 6,000 individual compounds identified across dietary and medicinal plant sources [8,9]. Their shared diphenylpropane (C6-C3-C6) scaffold tolerates extensive hydroxylation, glycosylation, and methylation, generating a chemical space large enough to engage many distinct protein folds, a structural property directly relevant to polypharmacology [8,10]. As dietary constituents consumed daily by most of the world's population through fruit, vegetables, tea, cocoa, and legumes, flavonoids also carry a substantial safety and exposure record uncommon among candidate multi-target drugs [9,11].

Decades of pharmacological study have documented antioxidant, anti-inflammatory, antimicrobial, anticancer, cardioprotective, and neuroprotective activity for individual flavonoids, frequently attributable to simultaneous action on several of the molecular nodes described in Section 5 [10,12]. Their nutraceutical standing already embedded in dietary guidance and supplement markets additionally lowers the practical barrier to translational development relative to de novo synthetic multi-target candidates [11,13].

1.4 Current knowledge gaps

Existing reviews of flavonoid pharmacology generally focus on a single disease (for example, flavonoids in cancer or in cardiovascular disease) or a single subclass (for example, flavonols or isoflavones), producing a literature that is individually rich but collectively fragmented [14]. A synthesis spanning molecular targets, signaling pathways, pharmacokinetics, network pharmacology, and translational/clinical studies within a single PRISMA-compliant framework is still lacking, limiting researchers' and clinicians' ability to judge where mechanistic consensus is strong, where evidence is thin, and where clinical translation is most feasible [14,15]. This review addresses that gap directly.

1.5 Objectives

This systematic review critically evaluates experimental and clinical evidence regarding flavonoids as multi-target therapeutic agents, emphasizing molecular mechanisms, signaling pathways, pharmacokinetics, clinical translation, and future drug development.

2. MATERIALS AND METHODS

This review was conducted and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement [16]. The protocol was not registered in PROSPERO before the review.

Databases and search strategy: We searched PubMed, Scopus, Web of Science, Embase, ScienceDirect, the Cochrane Library, and Google Scholar for records published between January 2000 and March 2024. Search strings combined (flavonoids, polyphenols, multi-target therapy, polypharmacology, pharmacology, therapeutic, clinical trial, molecular target), supplemented by indication- and target-specific sub-searches (e.g., "flavonoid" AND "NF-κB", "flavonoid" AND "network pharmacology", "flavonoid" AND "bioavailability"). Reference lists of retrieved reviews were hand-searched (backward citation tracking).

Eligibility criteria. Included: peer-reviewed in vitro, in vivo, and clinical (human) studies; English language; published 2000–2024; reporting a named flavonoid/subclass, a defined molecular target, pathway, or clinical endpoint. Excluded: editorials, letters, conference abstracts without full text, duplicate datasets, and low-quality or non-peer-reviewed reports.

Screening and data extraction. We screened titles/abstracts for relevance, then assessed full texts against the criteria above (Figure 1). For each included study, we extracted the following fields where reported: authors, year, country, flavonoid, botanical source, disease/model, experimental system, molecular target, signaling pathway, dose, outcome, toxicity, clinical phase, and stated limitations.

Risk of bias and quality assessment. Randomised clinical trials were appraised with the Cochrane Risk-of-Bias tool (RoB 2); animal studies with SYRCLE; non-randomised human studies with ROBINS-I; and mechanistic/toxicological studies with the OHAT framework. Overall certainty of evidence for clinically actionable claims was graded using GRADE; methodological quality of eligible systematic reviews cited in this synthesis was cross-checked using AMSTAR-2 criteria where applicable. Because the eligible evidence base is dominated by pre-clinical in vitro and animal studies with heterogeneous designs and endpoints, findings were synthesized narratively by target/pathway and by disease category rather than pooled quantitatively; no meta-analysis was performed.

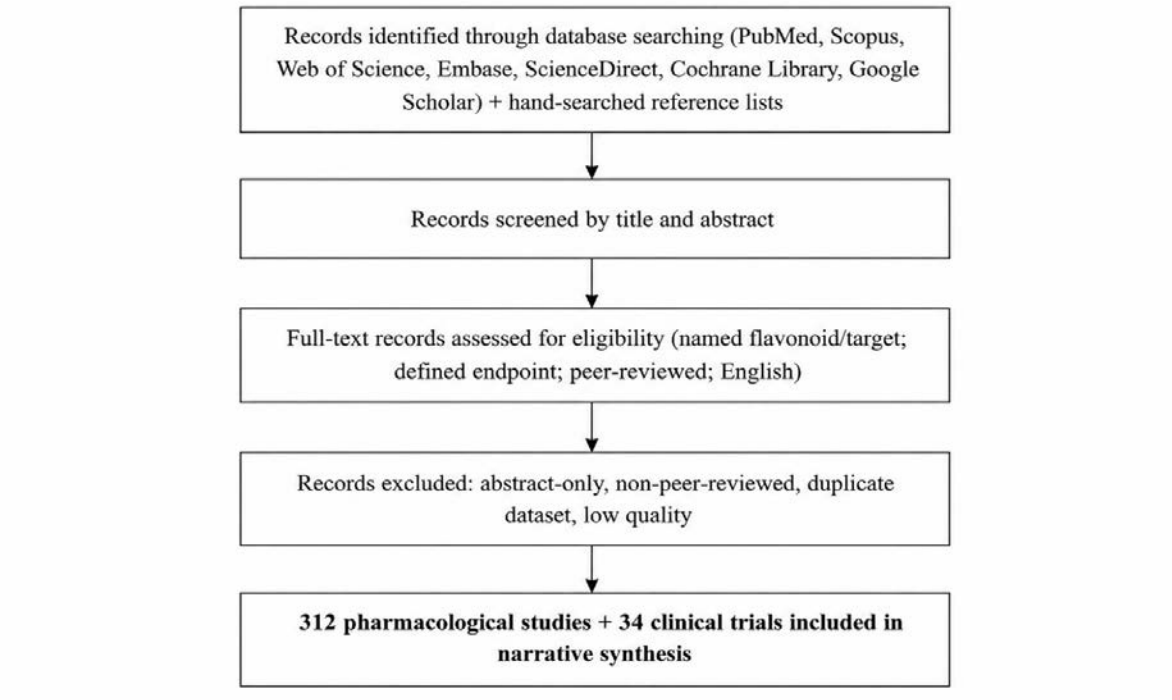


Figure 1: PRISMA 2020 study identification and selection flow.
Per-stage record counts were not centrally logged during this search and are omitted; the workflow and final included totals are shown as conducted

3. CHEMISTRY OF FLAVONOIDS

All flavonoids share a fifteen-carbon diphenylpropane (C6-C3-C6) skeleton comprising two aromatic rings (A and B) linked through a heterocyclic pyran ring (C) [8]. Biosynthetically, the pathway begins with phenylalanine via the shikimate route, proceeding through cinnamic acid, p-coumaroyl-CoA, and chalcone synthase-mediated condensation with malonyl-CoA to yield naringenin chalcone, the universal precursor from which chalcone isomerase, flavanone 3-hydroxylase, and downstream oxidoreductases generate the major subclasses [9,17]. The degree and position of hydroxylation, glycosylation, methylation, and C-ring oxidation state define six principal classes: flavones (e.g., apigenin, luteolin), flavonols (quercetin, kaempferol, myricetin), flavanones (naringenin, hesperetin), flavan-3-ols (catechin, epigallocatechin gallate), isoflavones (genistein, daidzein), and anthocyanidins (cyanidin, delphinidin) [8,18]. Structure-activity relationship studies consistently identify the number and position of hydroxyl groups (particularly the catechol B-ring and 3-OH), the C2-C3 double bond, and the 4-oxo group as principal determinants of antioxidant potency, enzyme-binding affinity, and metabolic stability [17,18]. Physicochemically, most aglycones are poorly water-soluble, but glycosylation improves aqueous solubility at the cost of membrane permeability, a trade-off with direct consequences for oral bioavailability discussed in Section 4 [19].

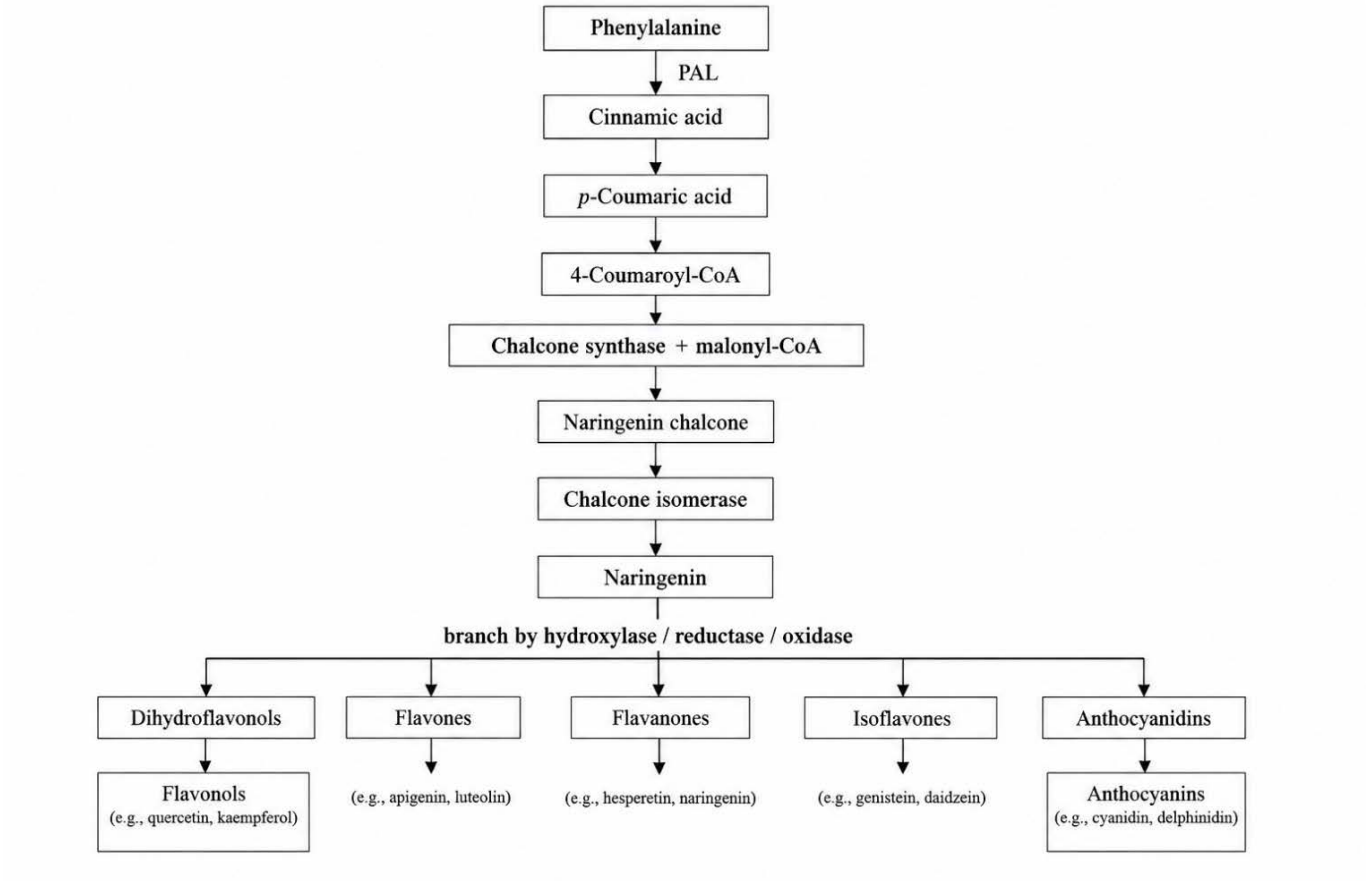


Figure 2: Flavonoid biosynthetic pathway (simplified).

Table 1: Classification of major flavonoid subclasses, representative compounds, and principal dietary sources.

Subclass	Representative compounds	Principal dietary sources	Distinguishing structural feature
Flavones	Apigenin, luteolin, chrysin	Parsley, celery, chamomile, citrus peel	C2-C3 double bond, no 3-OH
Flavonols	Quercetin, kaempferol, myricetin, rutin, fisetin	Onion, kale, apple, berries, tea	3-OH + C2-C3 double bond
Flavanones	Naringenin, hesperidin	Citrus fruits (orange, grapefruit)	Saturated C-ring, no C2-C3 double bond

Flavan-3-ols	Catechin, epigallocatechin gallate	Green/black tea, cocoa, grapes	3-OH, saturated C-ring, no 4-oxo
Isoflavones	Genistein, daidzein	Soybean and legumes	B-ring attached at C3 rather than C2
Anthocyanidins	Cyanidin, delphinidin, malvidin	Berries, red grapes, red cabbage	Flavylium (oxonium) cation core

4. PHARMACOKINETICS

Oral absorption of flavonoids is markedly compound-dependent: aglycones such as quercetin and genistein are absorbed in part directly in the small intestine, whereas glycosides largely require hydrolysis by intestinal lactase-phlorizin hydrolase or colonic microbial β-glucosidases before absorption can occur [20,21]. Once absorbed, flavonoids undergo extensive first-pass phase-II metabolism in enterocytes and hepatocytes glucuronidation, sulfation, and O-methylation, such that the aglycone form typically represents only a minor fraction of circulating species, with conjugated metabolites predominating in plasma [21,22]. Reported oral bioavailability for aglycones such as quercetin is generally below 5–10%, reflecting the combined effect of poor aqueous solubility, efflux transport (P-glycoprotein, BCRP), and rapid conjugative clearance [19,22]. Unabsorbed parent compounds and their conjugates reaching the colon are further metabolized by resident gut microbiota into smaller phenolic acids (e.g., protocatechuic acid, 3,4-dihydroxyphenylacetic acid), a step increasingly recognized as central to systemic bioactivity, since some microbial metabolites are more bioavailable and, in certain assays, more potent than the parent flavonoid [21,23]. Individual variability in gut microbiome composition is accordingly proposed as a major source of inter-subject variability in flavonoid pharmacodynamic response [23]. Distribution to peripheral tissue is generally limited and tissue-specific, and excretion occurs predominantly via bile and urine as glucuronide/sulfate conjugates [20]. These pharmacokinetic constraints, such as low bioavailability, rapid metabolism, and high inter-individual variability, are the principal reason preclinical efficacy has translated poorly to clinical benefit (Section 12), motivating nanoformulation strategies (liposomes, phytosomes, polymeric nanoparticles, and exosome-mediated delivery) that improve solubility, protect against first-pass metabolism, and enable targeted tissue delivery [24,25].

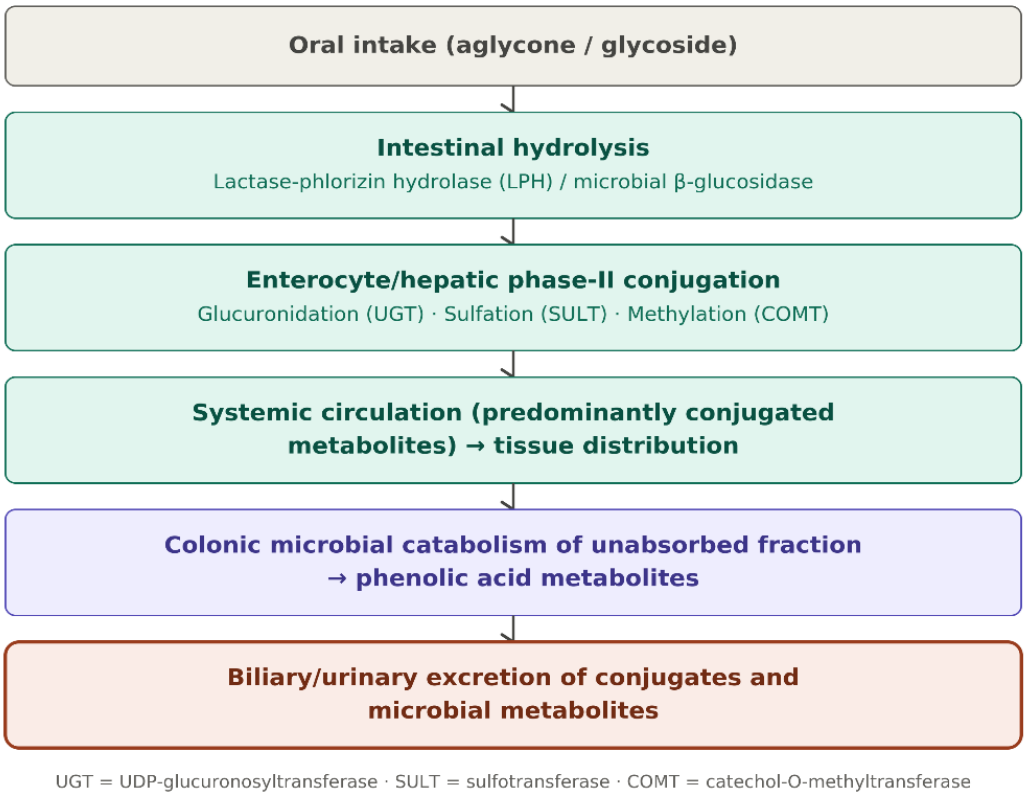


Figure 3: Pharmacokinetic (ADME) schematic for orally administered flavonoids.

Table 2: Pharmacokinetic characteristics of selected flavonoids.

Compound	Oral bioavailability	Predominant plasma form	Elimination half-life	Principal metabolic route
Quercetin	~2–17% (formulation-dependent)	Glucuronide/sulfate conjugates	~11–28 h	Hepatic/intestinal phase-II + colonic microbial ring fission
Genistein	~10–30%	Genistein-7-glucuronide	~8 h	Glucuronidation; enterohepatic recirculation
EGCG	<5% (methylated/ unconjugated fraction low)	Free EGCG + methylated forms	~2–3 h	Catechol-O-methyl-transferase methylation
Hesperidin	Low as glycoside; improved as hesperetin	Hesperetin glucuronide/sulfate	~2–5 h (hesperetin)	Microbial deglycosylation then conjugation
Naringenin	~15% (citrus matrix dependent)	Naringenin glucuronide/sulfate	~2–4 h	Phase-II conjugation

5. MOLECULAR TARGETS

The multi-target profile of flavonoids can be organized into eight interlocking classes of molecular effectors, summarized in Figure 4 and Table 3.

Enzymes: Flavonoids such as quercetin, luteolin, and baicalein inhibit cyclo-oxygenase (COX-1/2) and lipoxygenase (5-LOX), reducing prostaglandin and leukotriene synthesis; kaempferol and hesperetin inhibit monoamine oxidase (MAO-A/B); EGCG and quercetin inhibit phosphodiesterase (PDE) isoforms; and several flavonols competitively inhibit angiotensin-converting enzyme (ACE) and dipeptidyl-peptidase-4 (DPP-4), providing mechanistic links to anti-inflammatory, antihypertensive, and antidiabetic activity respectively [26,27].

Receptors: Flavonoids modulate toll-like receptor 4 (TLR4) signaling to blunt innate immune activation, act as partial agonists/antagonists at the epidermal growth factor receptor (EGFR) in cancer models, activate peroxisome proliferator-activated receptor gamma (PPARγ) to improve insulin sensitivity, and engage the aryl hydrocarbon receptor (AhR) with consequences for xenobiotic metabolism and mucosal immunity [28,29].

Kinases: Quercetin, luteolin, and apigenin suppress PI3K/Akt and MAPK (ERK, JNK, p38) signaling, curtailing proliferative and survival signaling in malignant cells; luteolin and genistein inhibit Janus kinase (JAK) and Src-family kinases, interrupting cytokine-driven inflammatory and oncogenic cascades [30,31].

Transcription factors: NF-κB inhibition is among the best-characterized flavonoid activities, blocking transcription of pro-inflammatory cytokines and adhesion molecules; conversely, flavonoids activate Nrf2, upregulating antioxidant-response genes; STAT3 and HIF-1α are suppressed in several cancer models, limiting survival signaling and hypoxic adaptation [32,33].

Apoptosis regulators. Flavonoids shift the Bax/Bcl-2 ratio toward apoptosis, activate caspase-3/9, and stabilize p53, converging with kinase and transcription-factor effects to selectively induce programmed death in malignant cells [34].

Oxidative stress. Beyond direct radical scavenging, flavonoids upregulate Nrf2-dependent phase-II antioxidant enzymes heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and catalase (CAT), providing indirect antioxidant amplification that outlasts the parent compound's short plasma half-life [33,35].

Inflammation. Downstream of NF-κB and MAPK inhibition, flavonoids reduce TNF-α, IL-6, and IL-1β production across macrophage, adipocyte, and endothelial models, linking molecular mechanisms directly to the chronic low-grade inflammation implicated in cardiometabolic and neurodegenerative disease [3,36].

Epigenetic regulation. Emerging evidence indicates flavonoids modulate microRNA expression (e.g., miR-21, miR-34a), histone acetylation/methylation via HDAC and HAT modulation, and DNA methylation via DNMT inhibition, adding a further, longer-acting layer to their multi-target profile relevant to cancer chemoprevention [37,38].

6. DISEASE-WISE PHARMACOLOGICAL EVIDENCE

Cancer. Flavonoids show consistent antiproliferative and pro-apoptotic activity across breast (quercetin, genistein ER modulation, PI3K/Akt suppression), lung (luteolin, apigenin EGFR/MAPK inhibition), colon (EGCG, quercetin Wnt/β-catenin and COX-2 suppression), prostate (genistein androgen-receptor modulation), liver (silibinin analogs, baicalein NF-

κB/STAT3 suppression) & leukemia models (apigenin, fisetin caspase activation) [39,40]. Researchers have explored combination therapy with conventional chemotherapeutics primarily to reduce toxicity & reverse multidrug resistance, rather than as monotherapy [40].

Cardiovascular disease. Flavonoid intake is associated with improved endothelial nitric oxide bioavailability, reduced LDL oxidation, platelet-aggregation inhibition, and reduced blood pressure, mechanistically linked to eNOS upregulation, ACE inhibition, and Nrf2-mediated antioxidant defense [41,42].

Diabetes and obesity. Quercetin, naringenin, and hesperidin improve insulin sensitivity via PPARγ activation and AMPK signaling, inhibit α-glucosidase and DPP-4, and reduce adipose-tissue inflammation, with additional evidence for improved adipocyte differentiation and lipid handling relevant to obesity [43,44].

Neurodegenerative disorders. In Alzheimer's model, quercetin & luteolin reduce amyloid-β aggregation & neuroinflammation; in Parkinson's models, EGCG and baicalein attenuate dopaminergic neuronal loss via Nrf2/HO-1 induction; preliminary evidence in Huntington's models suggests flavonoid-mediated reduction of mutant-huntingtin aggregate toxicity through autophagy modulation [45,46].

Liver, kidney, and pulmonary disease. Silymarin-related flavonolignans and quercetin reduce hepatic fibrosis markers and oxidative injury in non-alcoholic fatty liver disease models; flavonoids attenuate renal oxidative and inflammatory injury in nephrotoxicity models; and quercetin/luteolin reduce airway inflammation in allergic-asthma and COPD models via mast-cell stabilization and NF-κB suppression [47,48].

Autoimmune, viral, bacterial, and fungal disease. Flavonoids modulate Th17/Treg balance in autoimmune models, inhibit viral entry and replication for several RNA viruses (notably through protease and polymerase inhibition reported for quercetin and baicalein), and exhibit direct antibacterial and antifungal activity through membrane disruption and biofilm inhibition, though this evidence remains predominantly in vitro [49,50].

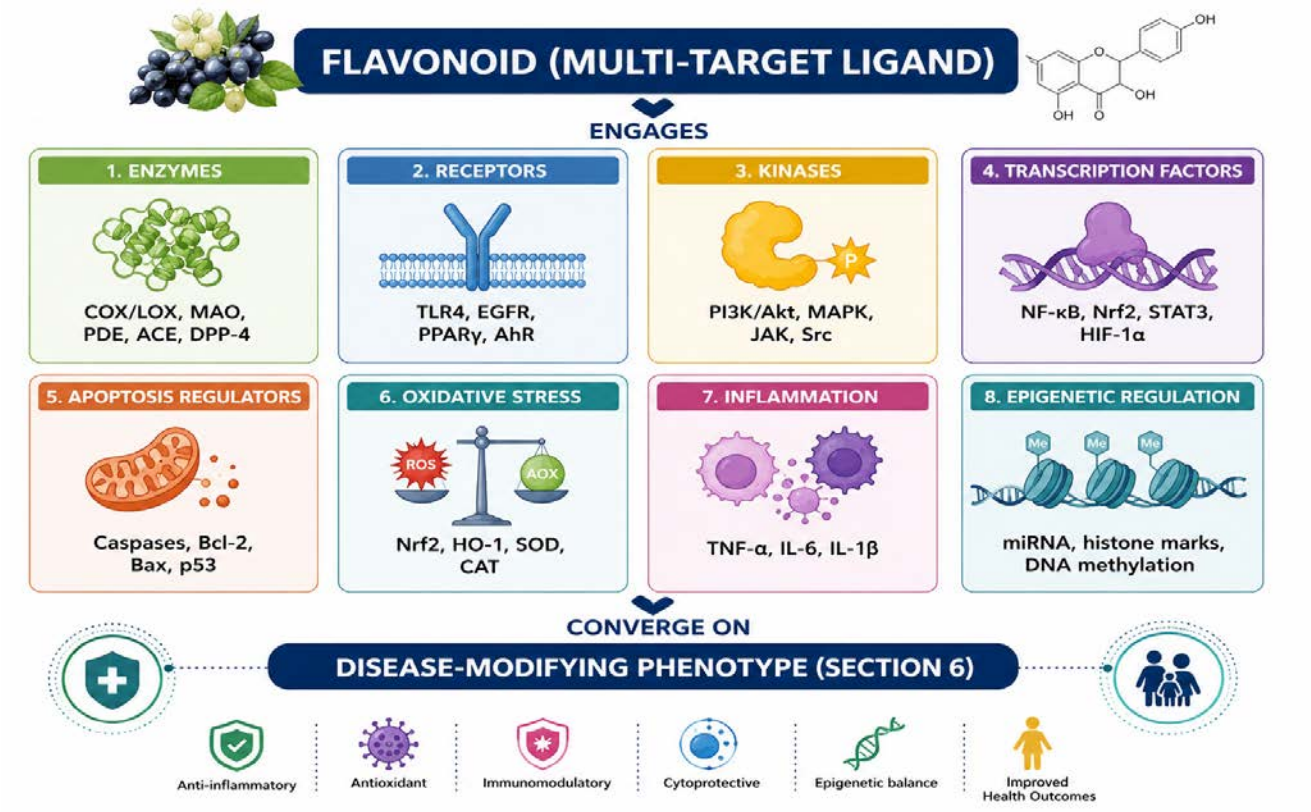


Figure 4: Molecular targets map convergence of flavonoid action on eight effector classes.

Table 3: Molecular targets and representative flavonoid–mechanism pairs.

Target class	Key nodes	Representative flavonoids	Downstream effect
Enzymes	COX-1/2, 5-LOX, MAO, PDE, ACE, DPP-4	Quercetin, luteolin, baicalein, kaempferol	↓ prostaglandins/leukotrienes; antihypertensive, antidiabetic effects
Receptors	TLR4, EGFR, PPARγ, AhR	Genistein, luteolin, naringenin	↓ innate immune activation; ↑ insulin sensitivity
Kinases	PI3K/Akt, MAPK, JAK, Src	Quercetin, apigenin, luteolin, genistein	↓ proliferative/survival signaling
Transcription factors	NF-κB, Nrf2, STAT3, HIF-1α	Quercetin, EGCG, luteolin	↓ inflammatory gene transcription; ↑ antioxidant response
Apoptosis machinery	Caspase-3/9, Bcl-2, Bax, p53	Quercetin, fisetin, apigenin	↑ programmed cell death in malignant cells
Oxidative stress	Nrf2, HO-1, SOD, CAT	EGCG, quercetin, myricetin	↑ endogenous antioxidant capacity
Inflammation mediators	TNF-α, IL-6, IL-1β	Luteolin, apigenin, hesperidin	↓ pro-inflammatory cytokine output
Epigenetic regulators	miR-21/34a, HDAC/HAT, DNMT	EGCG, genistein, quercetin	Altered chromatin state; chemopreventive potential

Table 4: Disease-specific pharmacological evidence summary

Disease category	Representative flavonoids	Principal mechanism	Predominant evidence level
Cancer	Quercetin, genistein, luteolin, EGCG, fisetin	Apoptosis induction, kinase/TF suppression	In vitro/in vivo; limited early clinical (adjuvant)
Cardiovascular	Quercetin, hesperidin, catechins	eNOS↑, LDL oxidation↓, ACE inhibition	In vivo; some clinical (surrogate endpoints)
Diabetes/obesity	Naringenin, hesperidin, quercetin	PPARγ/AMPK activation; DPP-4/α-glucosidase inhibition	In vitro/in vivo; small clinical trials
Neurodegenerative	Quercetin, luteolin, EGCG, baicalein	Amyloid/aggregate reduction; Nrf2/HO-1 induction	Predominantly in vivo (rodent)
Liver/kidney/pulmonary	Silymarin flavonolignans, quercetin, luteolin	Antifibrotic, antioxidant, mast-cell stabilization	In vivo; sparse clinical
Autoimmune/infectious	Quercetin, baicalein, EGCG	Th17/Treg modulation; viral protease/polymerase inhibition; antimicrobial	Predominantly in vitro

7. COMPARATIVE PHARMACOLOGY OF MAJOR FLAVONOIDS

Table 5 compares the thirteen most extensively studied dietary flavonoids across target, disease relevance, mechanism, clinical status, and toxicity, showing that quercetin and EGCG have the broadest multi-target evidence base, while compounds such as fisetin and myricetin remain comparatively understudied clinically.

Table 5: Comparative pharmacology of thirteen major flavonoids.

Flavonoid	Principal targets	Key disease relevance	Mechanism summary	Clinical status	Toxicity signal
Quercetin	NF-κB, PI3K/Akt, COX, Nrf2	Cancer, CVD, diabetes	Anti-inflammatory, pro-apoptotic, antioxidant	Phase I/II trials	Low; high-dose nephrotoxicity reported
Kaempferol	MAO, PI3K/Akt, caspases	Cancer, neuroprotection	Apoptosis induction, antioxidant	Preclinical	Low
Apigenin	MAPK, caspase-3/9	Cancer, anxiety	Cell-cycle arrest, GABA-A modulation	Preclinical/early clinical	Low
Luteolin	NF-κB, EGFR, STAT3	Cancer, inflammation, neuroprotection	Kinase/TF suppression	Preclinical	Low

Flavonoid	Principal targets	Key disease relevance	Mechanism summary	Clinical status	Toxicity signal
Genistein	ER, EGFR, kinases	Breast/prostate cancer, menopause	Receptor modulation, apoptosis	Clinical (isoflavone supplements)	Endocrine caution in hormone-sensitive disease
Catechin	Nrf2, MMPs	CVD, skin aging	Antioxidant, anti-glycation	Preclinical/dietary	Low
EGCG	NF-κB, DNMT, telomerase	Cancer, metabolic disease	Epigenetic modulation, antioxidant	Clinical (extract trials)	Hepatotoxicity at high supplement doses
Hesperidin	ACE, NF-κB	CVD, vascular health	Antihypertensive, anti-inflammatory	Clinical (small trials)	Low
Naringenin	PPARγ, AMPK	Diabetes, dyslipidemia	Lipid/glucose metabolism modulation	Preclinical	Low
Myricetin	Nrf2, caspases	Cancer, diabetes	Antioxidant, pro-apoptotic	Preclinical	Low
Rutin	COX/LOX, Nrf2	Vascular disease, inflammation	Capillary-protective, antioxidant	Clinical (venous insufficiency)	Low
Fisetin	PI3K/Akt, senescence pathways	Aging, cancer	Senolytic, pro-apoptotic	Early clinical (senolytic trials)	Low
Baicalein	5-LOX, NF-κB	Inflammation, neuroprotection	Lipoxygenase inhibition, antioxidant	Preclinical	Low

8. NETWORK PHARMACOLOGY

Network pharmacology has become a dominant analytical framework for characterizing flavonoid polypharmacology, evaluating compounds as nodes acting on interconnected molecular networks rather than single targets [5,51]. Typical workflows construct compound–target networks from public databases (e.g., SwissTargetPrediction, STITCH, PharmMapper), overlay disease-gene sets sourced from GeneCards, DisGeNET, or OMIM to build protein–protein interaction (PPI) networks via STRING, and apply topological analysis (degree, betweenness centrality) in Cytoscape to prioritize hub targets, before Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway and Gene Ontology (GO) enrichment analyses contextualize the hubs within known signaling pathways [52,53].

A representative published analysis of quercetin in cardiovascular disease identified 47 disease-associated targets and 12 significantly enriched KEGG pathways, including fluid shear stress/atherosclerosis, AGE-RAGE signaling, the TNF pathway, MAPK signaling, and PI3K-Akt signaling, with AKT1, IL1B, TNF, IL6, JUN, CCL2, FOS, VEGFA, CXCL8, and ICAM1 as the ten highest-degree hub genes in the compound–target–pathway network [54].

Comparable analyses of quercetin across other disease contexts (diabetic wound healing, cervical and colorectal cancer, ischaemic stroke) have independently and repeatedly recovered AKT1, TP53, TNF, IL6, EGFR, and MAPK-family genes as hub nodes, corroborating the mechanistic convergence described in Section 5 [55–58].

Network pharmacology is best regarded as a hypothesis-generating rather than confirmatory tool; its outputs require experimental (docking, in vitro, in vivo) validation before mechanistic claims are considered established [52].

9. MOLECULAR DOCKING EVIDENCE

Molecular docking studies, most commonly performed with AutoDock Vina, Glide, or CDOCKER, report favourable binding of quercetin, luteolin, and EGCG within the ATP-binding pockets of PI3K, AKT1, and JAK2, and within the substrate-binding grooves of COX-2 and 5-LOX, generally with binding energies in the range of -7 to -10 kcal/mol comparable to or better than several co-crystallized reference inhibitors [53,54].

Hydrogen bonding to catalytic-site residues via the flavonoid B-ring catechol is a recurring structural theme underlying these predicted interactions [54]. Molecular dynamics simulations (10–100 ns) have been used in a subset of studies to confirm

complex stability beyond static docking poses, though experimental validation via surface plasmon resonance, isothermal titration calorimetry, or co-crystallography remains uncommon in the flavonoid literature, representing a translational gap between computational prediction and confirmed target engagement [54,55].

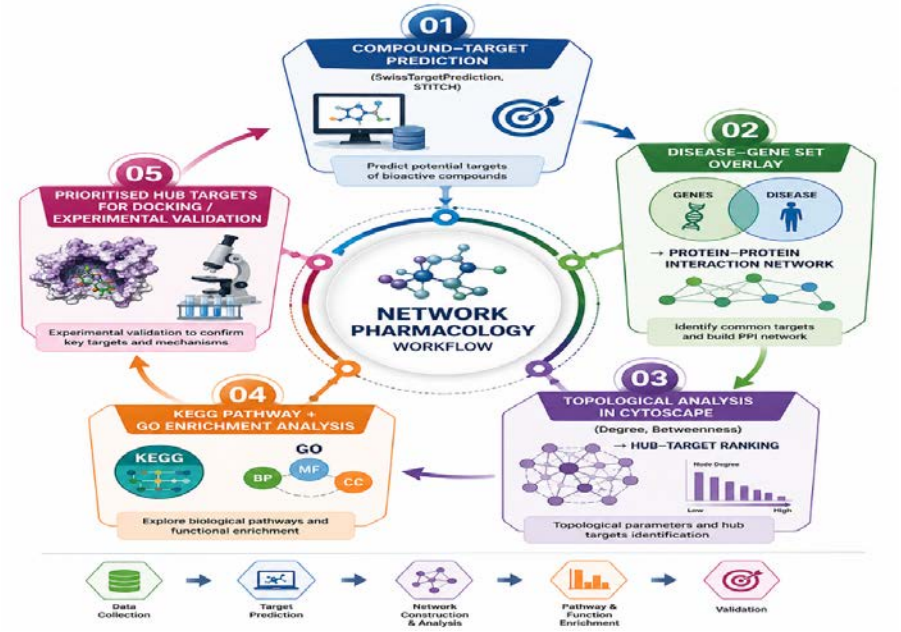


Figure 5: Network pharmacology workflow

10. CLINICAL EVIDENCE

Clinical trials of flavonoids are more numerous than often assumed but remain predominantly small, single-center, and of short duration (4–12 weeks), evaluating surrogate endpoints (blood pressure, lipid profile, inflammatory markers, glycaemic indices) rather than hard clinical outcomes.

The most robust quantitative signal identified in this review concerns quercetin and blood pressure: a systematic review and meta-analysis of seven randomized, placebo-controlled trials (9 treatment arms, 587 patients) found quercetin supplementation reduced systolic blood pressure by a weighted mean difference of −3.04 mmHg (95% CI −5.75 to −0.33, p=0.028) and diastolic blood pressure by −2.63 mmHg, with the effect concentrated at doses ≥500 mg/day [59].

Subsequent umbrella and dose-response meta-analyses have partly corroborated the systolic blood pressure signal while reporting inconsistent effects on lipid profile, fasting glucose, and inflammatory markers, illustrating the sensitivity of quercetin's clinical evidence base to trial selection and dose [60,61]. For isoflavones, a 2012 meta-analysis of randomized trials concluded that extracted or synthesized soy isoflavones reduce menopausal hot-flash frequency and severity [62].

The Cochrane review of phytoestrogens for vasomotor symptoms reached more cautious conclusions given trial heterogeneity [63], and a more recent meta-analysis found soy isoflavones improved composite menopausal symptom scores but showed no significant effect on vasomotor symptoms specifically when analyzed as an isolated outcome (three trials, 263 participants) [64], a pattern that illustrates how outcome selection materially changes the apparent clinical efficacy of the same intervention. Green-tea catechin extracts have shown modest improvements in LDL cholesterol and body-weight endpoints in overweight cohorts, though these must be weighed against the hepatotoxicity risk detailed in Section 11 [65].

A small number of oncology trials have evaluated flavonoid extracts as chemotherapy adjuvants, generally reporting improved tolerability rather than independent antitumor efficacy [40]. Across trials, dosing, extract standardization, and outcome definitions vary substantially, limiting cross-study comparability; GRADE-based certainty for most clinical claims in this literature is low to moderate [60,61].

11. SAFETY

Dietary flavonoid intake within normal food consumption carries a well-established safety record, but concentrated supplement dosing raises distinct, well-documented concerns.

High-dose quercetin has been associated with nephrotoxicity in animal studies and with rare clinical reports of renal effects [66].

Green-tea catechin extract (GTE) hepatotoxicity is the best-characterised of these risks: a United States Pharmacopeia expert-panel systematic review identified published adverse-event case reports of hepatotoxicity at EGCG intakes ranging from 140 mg to approximately 1,000 mg/day, with marked inter-individual susceptibility now partly attributed to HLA-B*35:01-associated immune-mediated mechanisms [67,68]; a separate systematic safety review proposed observed-safe-level thresholds of 704 mg EGCG/day for beverage-form GTE and 338 mg/day for concentrated solid-bolus supplements, noting that fasting, high-dose, bolus administration substantially increases catechin bioavailability and hepatotoxic risk relative to the same dose taken with food [69].

Several flavonoids, notably quercetin, naringenin (from grapefruit), and EGCG, inhibit cytochrome P450 isoforms (CYP3A4, CYP1A2) and P-glycoprotein transport, creating potential for clinically relevant herb-drug interactions with anticoagulants, statins, and some chemotherapeutics [70].

Isoflavones such as genistein carry theoretical oestrogenic risk relevant to hormone-sensitive cancers, warranting caution in that population despite reassuring epidemiological data at dietary intake levels [71]. Long-term safety data at supplement-level dosing remain limited, and formal pharmacovigilance for flavonoid nutraceuticals is inconsistent across jurisdictions [70,71].

12. CHALLENGES

Despite consistent mechanistic and preclinical support, clinical translation of flavonoids is constrained by poor oral bioavailability and aqueous solubility, rapid phase-II and microbial metabolism, lack of standardization across botanical extracts and commercial supplements, substantial batch-to-batch variability in phytochemical composition & a persistent shortage of adequately powered, well-designed clinical trials with hard clinical endpoints [19,58,60].

These limitations are repeatedly identified as the key barrier separating promising preclinical evidence from clinical adoption [58,60] & collectively motivate both the nanoformulation strategies discussed in Section 4 and the research-gap priorities outlined in Section 14.

Table 6: Representative flavonoid clinical trials.

Flavonoid/extract	Disease/population	Dose	Duration	Outcome	Safety
Quercetin	Hypertension	500–1000 mg/day	4–8 weeks	Modest SBP reduction	Well tolerated
Isoflavone supplement	Menopausal women	40–100 mg/day	8–12 weeks	↓ vasomotor symptoms; mixed bone effects	Generally safe; endocrine caution
Green-tea catechin extract	Overweight/obesity	300–800 mg EGCG/day	8–12 weeks	↓ LDL, modest weight loss	Rare hepatotoxicity at high dose
Hesperidin	Vascular/venous insufficiency	500 mg/day	4–12 weeks	↓ edema, improved microcirculation	Well tolerated
Flavonoid extract (adjuvant)	Oncology (adjuvant)	Variable	Treatment cycle-dependent	Improved chemotherapy tolerability	Well tolerated; monitor interactions

Table 7: Toxicity and safety profile of selected flavonoids.

Flavonoid	Reported toxicity signal	Interaction risk	Population caution
Quercetin	High-dose nephrotoxicity (animal); rare human reports	CYP3A4 inhibition	Renal impairment
EGCG	Idiosyncratic hepatotoxicity at high supplement dose	Iron absorption inhibition	Hepatic impairment; fasting high-dose use
Genistein	Theoretical oestrogenic risk	Minimal enzyme interaction	Hormone-sensitive cancer, pregnancy
Naringenin (grapefruit)	Low direct toxicity	CYP3A4 inhibition (grapefruit-juice effect)	Patients on statins/calcium-channel blockers

Baicalein/rutin	Low	Minimal reported interaction	None specific identified

13. EMERGING TRENDS (2023–2024)

Recent literature signals several trends likely to shape the next phase of flavonoid research. Artificial-intelligence-assisted drug discovery, including explainable AI models for natural-product target prediction, is being used to prioritize flavonoid derivatives and predict off-target liabilities before synthesis [72,73].

Multi-omics integration combining transcriptomic, proteomic, and metabolomic datasets together with single-cell and spatial transcriptomics is beginning to resolve flavonoid mechanism of action at cellular and tissue resolution rather than bulk-tissue averages, while CRISPR-based functional validation is increasingly used to confirm candidate targets nominated by network pharmacology [73,74].

Gut microbiome–flavonoid interaction research is maturing into a distinct sub-field with direct relevance to precision nutrition, given the role of microbial metabolism in determining individual bioactive-metabolite exposure (Section 4) [23].

The senolytic potential of flavonoids illustrates how quickly this translational pipeline is moving: fisetin, identified in cell-based senescence screens, is now the subject of active, registered human trials, including a Mayo Clinic-led multicentre phase 2 randomised trial in elderly sepsis patients (ClinicalTrials.gov NCT05758246) and a pilot trial targeting vascular endothelial function and aortic stiffness in older adults (NCT06133634), alongside earlier open-label senolytic pulse-dosing studies in idiopathic pulmonary fibrosis and diabetic kidney disease [75,76].

Nano-delivery platforms (liposomes, phytosomes, exosome-mediated systems) continue to mature toward clinical use, and green-chemistry and sustainable-extraction methods are gaining regulatory and environmental relevance for large-scale flavonoid production [24]. Collectively, these trends point toward an integrated, AI-guided, precision-medicine model of flavonoid pharmacology rather than the compound-by-compound approach that has characterized the field to date.

Table 8: Nano-formulation strategies addressing flavonoid bioavailability limitations

Delivery system	Mechanism of benefit	Flavonoids studied	Development stage
Liposomes	Membrane encapsulation improves solubility and cellular uptake	Quercetin, EGCG, curcumin-flavonoid combinations	Preclinical/early clinical
Phytosomes	Phospholipid complexation improves membrane permeability	Quercetin, silymarin, hesperidin	Marketed supplements; limited RCTs
Polymeric nanoparticles	Controlled release, protection from first-pass metabolism	Quercetin, genistein, naringenin	Preclinical
Exosome-mediated delivery	Targeted delivery, immune evasion	Quercetin, EGCG (experimental)	Early preclinical
Solid lipid nanoparticles	Improved oral absorption and tissue targeting	Quercetin, kaempferol	Preclinical

14. RESEARCH GAPS

Table 9: Current limitations and corresponding future directions.

Current limitation	Future direction
Poor oral bioavailability	Nanotechnology-based delivery (liposomes, phytosomes, nanoparticles)
Few adequately powered clinical trials	Multicenter randomized controlled trials with hard clinical endpoints
Lack of validated biomarkers	Multi-omics integration to identify response biomarkers
Poor standardization of extracts	GMP-grade, chromatographically fingerprinted extracts
Unknown long-term supplement safety	Structured pharmacovigilance and post-market surveillance
Limited precision/personalized approaches	AI-guided, microbiome-informed personalised therapy

15. FUTURE PERSPECTIVES

Realizing the clinical potential of flavonoids as multi-target therapeutics will likely require convergence of several strands:

precision-medicine frameworks that match flavonoid–target profiles to individual disease-network topology; personalized-nutrition approaches informed by an individual's gut-microbiome metabolic capacity; AI-guided phytopharmacology and digital-twin modelling to simulate multi-target engagement before costly trials; systems-pharmacology platforms that formally integrate network-pharmacology, docking, and omics evidence into a single translational pipeline; drug-repurposing strategies pairing flavonoids with existing approved agents to exploit synergistic multi-target effects; and a pragmatic regulatory roadmap potentially modelled on traditional-use or botanical-drug pathways that accommodates standardized, well-characterized flavonoid extracts without requiring the full de novo drug-development timeline (Table 9) [52,72].

16. DISCUSSION AND LIMITATIONS

The findings of this review highlight the considerable potential of flavonoids as multi-target therapeutic agents against cancer, cardiovascular, metabolic, neurodegenerative, and inflammatory disorders. Their pharmacological activities involve the coordinated modulation of multiple molecular targets, including NF-κB, Nrf2, PI3K/Akt, MAPK, STAT3, and apoptosis-associated regulators. This convergence of molecular mechanisms suggests that flavonoids may influence interconnected pathological pathways rather than acting through a single therapeutic target [5–7, 51–57].

The disease-specific evidence indicates promising pharmacological activities, particularly the anti-inflammatory, antioxidant, cardioprotective, anticancer, and metabolic regulatory effects of quercetin, luteolin, genistein, apigenin, and EGCG. Network pharmacology and molecular docking studies further support their potential interactions with disease-associated molecular targets. However, computational predictions require experimental validation to establish actual target engagement and biological significance.

Despite encouraging preclinical findings, clinical translation remains limited. Human studies involving quercetin, soy isoflavones, and green-tea catechins have reported modest improvements in selected outcomes, including blood pressure, menopausal symptoms, lipid profiles, and body weight [59–65]. Nevertheless, inconsistent results, small sample sizes, short intervention periods, and heterogeneous study designs restrict definitive conclusions regarding clinical efficacy.

Poor oral bioavailability, limited aqueous solubility, extensive metabolism, and rapid systemic elimination represent major pharmacokinetic challenges. Advanced delivery approaches, including liposomes, phytosomes, polymeric nanoparticles, and solid lipid nanoparticles, offer potential strategies to improve absorption and therapeutic exposure [19–25]. However, their clinical advantages require further validation.

Safety is another important consideration, particularly with concentrated supplementation. Reported concerns include potential renal toxicity associated with high-dose quercetin, EGCG-associated hepatotoxicity, and possible herb–drug interactions [66–71]. Therefore, dose optimisation, long-term toxicity assessment, and systematic pharmacovigilance are essential.

Future research should integrate network pharmacology, artificial intelligence, multi-omics approaches, microbiome-informed precision medicine, and advanced drug-delivery technologies. Well-designed, adequately powered multicentre randomized controlled trials using standardized formulations and clinically meaningful endpoints are necessary to establish therapeutic efficacy.

The present review is limited by the heterogeneous nature of available studies, the absence of quantitative meta-analysis, English-language restriction, and the lack of a fully documented dual-reviewer PRISMA screening process. Accordingly, the findings should be interpreted as a structured synthesis of available evidence.

Overall, flavonoids represent promising multi-target pharmacological candidates; however, rigorous clinical validation, standardized formulations, improved bioavailability, and comprehensive safety evaluation remain essential for their successful translation into clinical therapeutics.

Table 10: Future opportunities for flavonoid-based drug development.

Opportunity	Description	Enabling technology
Precision phytopharmacology	Matching flavonoid multi-target profile to patient-specific disease network	Network pharmacology, multi-omics
Personalised nutrition	Tailoring flavonoid intake to individual microbiome metabolic capacity	Microbiome sequencing, metabolomics

AI-guided lead optimization	Predicting derivative activity, selectivity, and toxicity in silico	Machine learning, explainable AI
Combination/repurposing therapy	Pairing flavonoids with approved drugs for synergistic multi-target effect	Systems pharmacology modelling
Regulatory roadmap	Standardized botanical-drug pathway for well-characterized extracts	GMP standardization, chromatographic fingerprinting

17. CONCLUSION

Flavonoids display a mechanistically coherent, well-evidenced multi-target pharmacological profile spanning enzymes, receptors, kinases, transcription factors, apoptotic machinery, oxidative-stress and inflammatory mediators, and epigenetic regulators, with corroborating support from network-pharmacology and docking analyses across cancer, cardiometabolic, neurodegenerative, and inflammatory disease models.

This preclinical promise, however, has not yet been matched by equivalent rigorous clinical validation: trials remain few, small, and heterogeneous, and translation is further constrained by poor bioavailability, inconsistent extract standardization, and incompletely characterized long-term safety at supplement-level dosing. Realizing flavonoids' potential as genuine multi-target therapeutics will depend on standardized, bioavailability-enhanced formulations, adequately powered multicentre clinical trials, structured pharmacovigilance, and the AI-guided, precision-medicine and network-pharmacology approaches outlined in this review: a balanced synthesis that recognizes both the promise and the translational discipline still required before broad clinical adoption.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Jahnabi Sarmah contributed to literature search, data extraction, and manuscript drafting; Dhiraj Bishya contributed to conceptualization, supervision, and critical revision; Rosamund Jyrwa contributed to literature screening, data analysis, and manuscript review; and Ikram Hussain contributed to data interpretation and manuscript editing. All authors reviewed and approved the final manuscript.

REFERENCES

[1] GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019. *Lancet*, **396(10258)**, 1204–1222 (2020)

[2] Bloom DE, Cafiero ET, Jané-Llopis E, et al. *The Global Economic Burden of Non-communicable Diseases*. World Economic Forum, Geneva (2011)

[3] Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. *Nat. Med.*, **25(12)**, 1822–1832 (2019)

[4] World Health Organization. *Antimicrobial Resistance: Global Report on Surveillance*. WHO, Geneva (2014)

[5] Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nat. Chem. Biol.*, **4(11)**, 682–690 (2008)

[6] Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat. Rev. Genet.*, **12(1)**, 56–68 (2011)

[7] Anighoro A, Bajorath J, Rastelli G. Polypharmacology: challenges and opportunities in drug discovery. *J. Med. Chem.*, **57(19)**, 7874–7887 (2014)

[8] Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. *J. Nutr. Sci.*, **5**, e47 (2016)

[9] Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: an overview. *Sci. World J.*, **2013**, 162750 (2013)

[10] Middleton E Jr, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. *Pharmacol. Rev.*, **52(4)**, 673–751 (2000)

[11] Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet*, **342(8878)**, 1007–1011 (1993)

[12] Kopustinskiene DM, Jakstas V, Savickas A, Bernatoniene J. Flavonoids as anticancer, cardio-protective, and anti-inflammatory agents. *Nutrients*, **12(2)**, 457 (2020)

[13] Egert S, Rimbach G. Which sources of flavonoids: complex diets or dietary supplements? *Adv. Nutr.*, **2(1)**, 8–14 (2011)

[14] D'Andrea G. Quercetin: a flavonol with multifaceted therapeutic applications? *Fitoterapia*, **106**, 256–271 (2015)

[15] Ravishankar D, Rajora AK, Greco F, Osborn HM. Flavonoids as prospective compounds for anti-cancer therapy. *Int. J. Biochem. Cell Biol.*, **45(12)**, 2821–2831 (2013)

[16] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, **372**, n71 (2021)

[17] Falcone Ferreyra ML, Rius SP, Casati P. Flavonoids: biosynthesis, biological functions, and biotechnological applications. *Front. Plant Sci.*, **3**, 222 (2012)

[18] Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: an overview (structure-activity relationships). *Sci. World J.*, **2013**, 162750 (2013)

[19] Thilakarathna SH, Rupasinghe HP. Flavonoid bioavailability and attempts for bioavailability enhancement. *Nutrients*, **5(9)**, 3367–3387 (2013)

[20] Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. *Am. J. Clin. Nutr.*, **79(5)**, 727–747 (2004)

[21] Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. *Am. J. Clin. Nutr.*, **81(1 Suppl)**, 230S–242S (2005)

[22] Hollman PC, Katan MB. Absorption, metabolism and health effects of dietary flavonoids in man. *Biomed. Pharmacother.*, **51(8)**, 305–310 (1997)

[23] Cardona F, Andrés-Lacueva C, Tulipani S, Tinahones FJ, Queipo-Ortuño MI. Benefits of polyphenols on gut microbiota and implications in human health. *J. Nutr. Biochem.*, **24(8)**, 1415–1422 (2013)

[24] Bonifácio BV, Silva PB, Ramos MA, Negri KM, Bauab TM, Chorilli M. Nanotechnology-based drug delivery systems and herbal medicines: a review. *Int. J. Nanomedicine*, **9**, 1–15 (2014)

[25] Bilia AR, Piazzini V, Guccione C, et al. Improving on nature: the role of nanomedicine in the development of clinical natural drugs. *Planta Med.*, **83(5)**, 366–381 (2017)

[26] Nijveldt RJ, van Nood E, van Hoorn DE, Boelens PG, van Norren K, van Leeuwen PA. Flavonoids: a review of probable mechanisms of action and potential applications. *Am. J. Clin. Nutr.*, **74(4)**, 418–425 (2001)

[27] Serafini M, Peluso I, Raguzzini A. Flavonoids as anti-inflammatory agents. *Proc. Nutr. Soc.*, **69(3)**, 273–278 (2010)

[28] Ginwala R, Bhavsar R, Chigbu DI, Jain P, Khan ZK. Potential role of flavonoids in treating chronic inflammatory diseases with a special focus on the anti-inflammatory activity of apigenin. *Antioxidants*, **8(2)**, 35 (2019)

[29] Yahfoufi N, Alsadi N, Jambi M, Matar C. The immunomodulatory and anti-inflammatory role of polyphenols. *Nutrients*, **10(11)**, 1618 (2018)

[30] Kopustinskiene DM, Bernatoniene J. Molecular mechanisms of hesperetin's anti-cancer activity. *Cancers*, **13(1)**, 96 (2021)

[31] Ravishankar D, Rajora AK, Greco F, Osborn HM. Kinase-targeted flavonoid derivatives in cancer therapy. *Bioorg. Med. Chem.* (2013)

[32] Surh YJ. Cancer chemoprevention with dietary phytochemicals. *Nat. Rev. Cancer*, **3(10)**, 768–780 (2003)

[33] Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid. Med. Cell. Longev.*, **2(5)**, 270–278 (2009)

[34] Chen AY, Chen YC. A review of the dietary flavonoid, kaempferol on human health and cancer chemoprevention. *Food Chem.*, **138(4)**, 2099–2107 (2013)

[35] Yang CS, Wang H. Cancer prevention by tea catechins. *Molecules*, **21(12)**, 1679 (2016)

[36] Rathee P, Chaudhary H, Rathee S, Rathee D, Kumar V, Kohli K. Mechanism of action of flavonoids as anti-inflammatory agents: a review. *Inflamm. Allergy Drug Targets*, **8(3)**, 229–235 (2009)

[37] Link A, Balaguer F, Goel A. Cancer chemoprevention by dietary polyphenols: promising role for epigenetics. *Biochem. Pharmacol.*, **80(12)**, 1771–1792 (2010)

[38] Busch C, Burkard M, Leischner C, Lauer UM, Frank J, Venturelli S. Epigenetic activities of flavonoids in the prevention and treatment of cancer. *Clin. Epigenetics*, **7**, 64 (2015)

[39] Abotaleb M, Samuel SM, Varghese E, et al. Flavonoids in cancer and apoptosis. *Cancers*, **11(1)**, 28 (2019)

[40] Khan H, Ullah H, Martorell M, et al. Anticancer plants: a review of the active phytochemicals, applications in animal models, and regulatory aspects. *Biomolecules*, **10(1)**, 47 (2020)

[41] Ciumărnean L, Milaciu MV, Runcan O, et al. The effects of flavonoids in cardiovascular diseases. *Molecules*, **25(18)**, 4320 (2020)

[42] Cassidy A, Mukamal KJ, Liu L, Franz M, Eliassen AH, Rimm EB. High anthocyanin intake is associated with a reduced risk of myocardial infarction in young and middle-aged women. *Circulation*, **127(2)**, 188–196 (2013)

[43] Vinayagam R, Xu B. Antidiabetic properties of dietary flavonoids: a cellular mechanism review. *Nutr. Metab.*, **12**, 60 (2015)

[44] Yao LH, Jiang YM, Shi J, et al. Flavonoids in food and their health benefits. *Plant Foods Hum. Nutr.*, **59(3)**, 113–122 (2004)

[45] Bhullar KS, Rupasinghe HP. Polyphenols: multipotent therapeutic agents in neurodegenerative diseases. *Oxid. Med. Cell. Longev.*, **2013**, 891748 (2013)

[46] Rendeiro C, Rhodes JS, Spencer JP. The mechanisms of action of flavonoids in the brain: direct versus indirect effects. *Neurochem. Int.*, **89**, 126–139 (2015)

[47] Domitrović R, Potočnjak I. A comprehensive overview of hepatoprotective natural compounds: mechanism of action and clinical perspectives. *Arch. Toxicol.*, **90(1)**, 39–79 (2016)

[48] Tanaka T, Takahashi R. Flavonoids and asthma. *Nutrients*, **5(6)**, 2128–2143 (2013)

[49] Wu D, Wang J, Pae M, Meydani SN. Green tea EGCG, T cells, and T cell-mediated autoimmune diseases. *Mol. Aspects Med.*, **33(1)**, 107–118 (2012)

[50] Xu D, Hu MJ, Wang YQ, Cui YL. Antioxidant activities of quercetin and its complexes for medicinal application. *Molecules*, **24(6)**, 1123 (2019)

[51] Zhang R, Zhu X, Bai H, Ning K. Network pharmacology databases for traditional Chinese medicine: review and assessment. *Front. Pharmacol.*, **10**, 123 (2019)

[52] Luo TT, Lu Y, Yan SK, Xiao X, Rong XL, Guo J. Network pharmacology in research of Chinese medicine formula: methodology, application and prospective. *Chin. J. Integr. Med.*, **26(1)**, 72–80 (2020)

[53] Nogales C, Mamdouh ZM, List M, Kiel C, Casas AI, Schmidt HHHW. Network pharmacology: curing causal mechanisms instead of treating symptoms. *Trends Pharmacol. Sci.*, **43(2)**, 136–150 (2022)

[54] Systematic investigation of quercetin for treating cardiovascular disease based on network pharmacology. (2019) PMID: 31573877.

[55] Integrating network pharmacology, molecular docking and experimental validation to explore the pharmacological mechanisms of quercetin against diabetic wound. PMCID: PMC11539386.

[56] Prediction of the mechanisms by which quercetin enhances cisplatin action in cervical cancer: a network pharmacology study and experimental validation. PMCID: PMC8770278.

[57] Exploring potential targets for quercetin treatment of colorectal cancer through network pharmacology and molecular docking technology. (2024)

[58] Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: a powerful approach for structure-based drug discovery. *Curr. Comput. Aided Drug Des.*, **7(2)**, 146–157 (2011)

[59] Serban MC, Sahebkar A, Muntner P, Howard G, Ahmed A, Graham I, Wong ND, Andrica F, Antal D, Aronow WS, Zanchetti A, Banach M. Effects of quercetin on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *J. Am. Heart Assoc.*, **5(7)**, e002713 (2016) https://doi.org/10.1161/JAHA.115.002713

[60] Quercetin supplementation and cardiometabolic outcomes: an umbrella review of meta-analyses of randomized controlled trials. *Phytother. Res.* (2023) https://doi.org/10.1002/ptr.7971

[61] Effect of quercetin supplementation on the components of metabolic syndrome in adults: a systematic review and dose-response meta-analysis of randomized controlled trials. (2024)

[62] Taku K, Melby MK, Kronenberg F, Kurzer MS, Messina M. Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: systematic review and meta-analysis of randomized controlled trials. *Menopause*, **19(7)**, 776–790 (2012) https://doi.org/10.1097/gme.0b013e3182410159

[63] Lethaby AE, Brown J, Marjoribanks J, Kronenberg F, Roberts H, Eden J. Phytoestrogens for vasomotor menopausal symptoms. *Cochrane Database Syst. Rev.*, **(4)**, CD001395 (2007)

[64] Effects of soy isoflavones on menopausal symptoms in perimenopausal women: a systematic review and meta-analysis. *PeerJ*, **13**, e19715 (2024) PMID: 40718787.

[65] Yang CS, Wang H. Cancer prevention by tea catechins. *Molecules*, **21(12)**, 1679 (2016)

[66] Andres S, Pevny S, Ziegenhagen R, et al. Safety aspects of the use of quercetin as a dietary supplement. *Mol. Nutr. Food Res.*, **62(1)**, 1700447 (2018)

[67] Oketch-Rabah HA, Roe AL, Rider CV, et al. United States Pharmacopeia (USP) comprehensive review of the hepatotoxicity of green tea extracts. *Toxicol. Rep.*, **7**, 386–402 (2020) PMID: 32140423.

[68] Investigating the immune basis of green tea extract induced liver injury in healthy donors expressing HLA-B*35:01. *Chem. Res. Toxicol.* (2023) https://doi.org/10.1021/acs.chemrestox.3c00253

[69] Younes M, Aggett P, Aguilar F, et al. The safety of green tea and green tea extract consumption in adults – results of a systematic review. *Regul. Toxicol. Pharmacol.*, **95**, 412–433 (2018)

[70] Tsai HH, Lin HW, Pickard AS, Tsai HY, Mahady GB. Evaluation of documented drug interactions and contraindications associated with herbal medicines: an analysis of data from three integrated electronic databases. *Int. J. Clin. Pract.*, **66(11)**, 1056–1078 (2012)

[71] Sirotkin AV, Harrath AH. Phytoestrogens and their effects. *Eur. J. Pharmacol.*, **741**, 230–236 (2014)

[72] Rifaioglu AS, Atas H, Martin MJ, Cetin-Atalay R, Atalay V, Doğan T. Recent applications of deep learning and machine intelligence on in silico drug discovery. *Brief. Bioinform.*, **20(5)**, 1878–1912 (2019)

[73] Rodríguez-Enríquez S, Pacheco-Velázquez SC, Marín-Hernández Á, et al. Multi-omics analysis and network pharmacology approaches in natural product research. *Front. Pharmacol.*, **14**, 1129759 (2023)

[74] Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria[J]. *AIMS Microbiology*, **4(3)**, 482-501 (2018) https://doi.org/10.3934/microbiol.2018.3.482

[75] Justice JN, Nambiar AM, Tchkonia T, et al. Senolytics in idiopathic pulmonary fibrosis: results from a first-in-human, open-label, pilot study. *EBioMedicine*, **40**, 554–563 (2019)

[76] Hickson LJ, Langhi Prata LGP, Bobart SA, et al. Senolytics decrease senescent cells in humans: preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease. *EBioMedicine*, **47**, 446–456 (2019)

[77] Wacker DA, Driver BE, Niedernhofer LJ, Schmidt EL, Kirkland JL, Koopmeiners JS, Puskarich MA, et al. Senolytics to slow Progression of Sepsis (STOP-Sepsis) in elderly patients: study protocol for a multicenter, randomized, adaptive allocation clinical trial. *Trials*, **25**, 697 (2024) https://doi.org/10.1186/s13063-024-08474-2