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REVIEW ARTICLE

Antifungal Potential of Flavonoids Against Drug-Resistant Fungal Pathogens

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Abstract: Invasive fungal infections represent a critical global health challenge characterized by expanding at-risk patient cohorts, unacceptable mortality rates, and progressive resistance across conventional antifungal classes. The therapeutic arsenal remains constrained by end-organ toxicities, narrow empirical spectra, unfavorable pharmacokinetics, and a sparse developmental pipeline. Plant secondary metabolites, particularly polyphenolic flavonoids, provide structurally versatile chemical scaffolds with broad-spectrum antimycotic potential against high-priority pathogens including *Candida*, *Aspergillus*, *Cryptococcus*, and emergent filamentous moulds. Flavonoids exert multimodal fungicidal and fungistatic pressure through simultaneous biological targets: disrupting fungal plasma membrane integrity via sterol destabilization, compromising cell wall architecture through β-glucan and chitin dysregulation, uncoupling mitochondrial electron transport chains, inducing endogenous reactive oxygen species generation, suppressing nucleic acid and protein biosyntheses, impeding cell division cycles, inhibiting dimorphic yeast-to-hyphal phenotypic shifts, and dampening ATP-binding cassette or major facilitator superfamily efflux pumps. When co-administered with conventional polyenes, azoles, or echinocandins, flavonoids systematically reverse multidrug-resistant phenotypes, showing marked *in vitro* and *in vivo* chemosensitization and synergy. Nevertheless, translational hurdles such as poor aqueous solubility, rapid systemic phase II clearance, variable membrane permeation, and sub-micromolar stability impede direct clinical deployment. Overcoming these pharmacokinetic constraints demands rationally engineered nano-formulations, polymeric encapsulation, and semisynthetic structural optimization. Exploiting bioactive flavonoids as standalone scaffolds or synergistic clinical adjuvants provides a viable therapeutic paradigm to alleviate fungal morbidity, restore conventional drug susceptibility, and forestall antimicrobial resistance development worldwide.

Keywords: Flavonoids; Antifungal resistance; Fungal pathogens; Drug synergy; Biofilm inhibition.

1. Introduction

Invasive fungal infections (IFIs) have escalated into an intractable crisis across modern tertiary healthcare environments [1, 2]. This clinical expansion is driven by growing patient cohorts receiving aggressive immunosuppressive regimens, undergoing solid organ or hematopoietic stem-cell transplantation, receiving antineoplastic chemotherapies, or surviving complex critical illness in intensive care units [1, 2]. Diagnostic limitations, combined with insidious pathogen biology and accelerating resistance to established antimycotics, contribute directly to formidable clinical burdens [1, 2]. Current epidemiological revisions indicate that over 6.5 million individuals develop life-threatening systemic fungal diseases annually, leading to approximately 3.8 million deaths [3]. Among these fatalities, at least 2.5 million deaths stem directly from unresolved invasive fungal pathology [3].

In response to this expanding clinical threat, the World Health Organization published its inaugural Fungal Priority Pathogens List, formally classifying fungal threats into medium-, high-, and critical-priority tiers to orient global drug discovery and public health action [2]. The designated critical-priority bracket highlights Cryptococcus neoformans, Aspergillus fumigatus, Candida auris, and Candida albicans, reflecting their exceptional capacity to evade clinical control, form recalcitrant cellular communities, and acquire pan-class antimicrobial resistance [2].

Managing invasive mycoses remains severely constrained by historical reliance on five primary antifungal chemotherapeutic classes: polyenes, azoles, echinocandins, allylamines, and pyrimidine analogues [4, 5]. Because fungal pathogens share eukaryotic cellular architecture, conserved subcellular organelles, and similar biosynthetic machinery with human hosts, conventional pharmacological development faces an inherently narrow therapeutic index, marked host toxicities, and frequent drug–drug interactions [5, 6].

The global antifungal developmental pipeline remains sparse [4]. Although recent additions such as the triterpenoid glucan synthase inhibitor ibrexafungerp and the long-acting echinocandin rezafungin broaden salvage choices, their clinical spectra do not eliminate

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the rapid emergence of multidrug-resistant clades [4, 5]. To preserve current drugs and discover alternative therapeutic paradigms, natural products offer an indispensable repertoire of biologically pre-validated chemical scaffolds [6-8]. Among these, flavonoids a multifaceted family of low-molecular-weight polyphenolic secondary metabolites exhibit marked fungicidal, chemosensitizing, and virulence-attenuating properties [8].

2. Literature Selection

2.1. Search Queries

A comprehensive literature search was performed across electronic citation indices, including PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Google Scholar, identifying primary research published between 2010 and 2025. Standardized Boolean algorithms incorporated combinations of targeted keywords: ("flavonoid" OR "flavonol" OR "flavone" OR "isoflavone" OR "chalcone" OR "flavan-3-ol") AND ("antifungal" OR "antimycotic" OR "fungicidal") AND ("Candida" OR "Aspergillus" OR "Cryptococcus" OR "dermatophyte" OR "biofilm" OR "efflux pump" OR "synergism").

2.2. Eligibility Criteria and Study Selection

Peer-reviewed original research articles evaluating isolated flavonoid monomers, characterized fractions, or semi-synthetic flavonoid derivatives against human-pathogenic fungi were critically assessed. Studies reporting minimum inhibitory concentrations (MICs), minimum fungicidal concentrations (MFCs), fractional inhibitory concentration indices (FICIs), explicit subcellular mechanisms, or *in vivo* translational models were prioritized. Investigations exploring non-standardized crude mixtures without identified chemical profiles, duplicate citations, non-peer-reviewed conference abstracts, and non-English texts were excluded. Extracted datasets were organized by flavonoid subclasses, natural biological sources, fungal susceptibility spectra, reported concentrations, and target modes of action to ensure reproducibility and systematic synthesis.

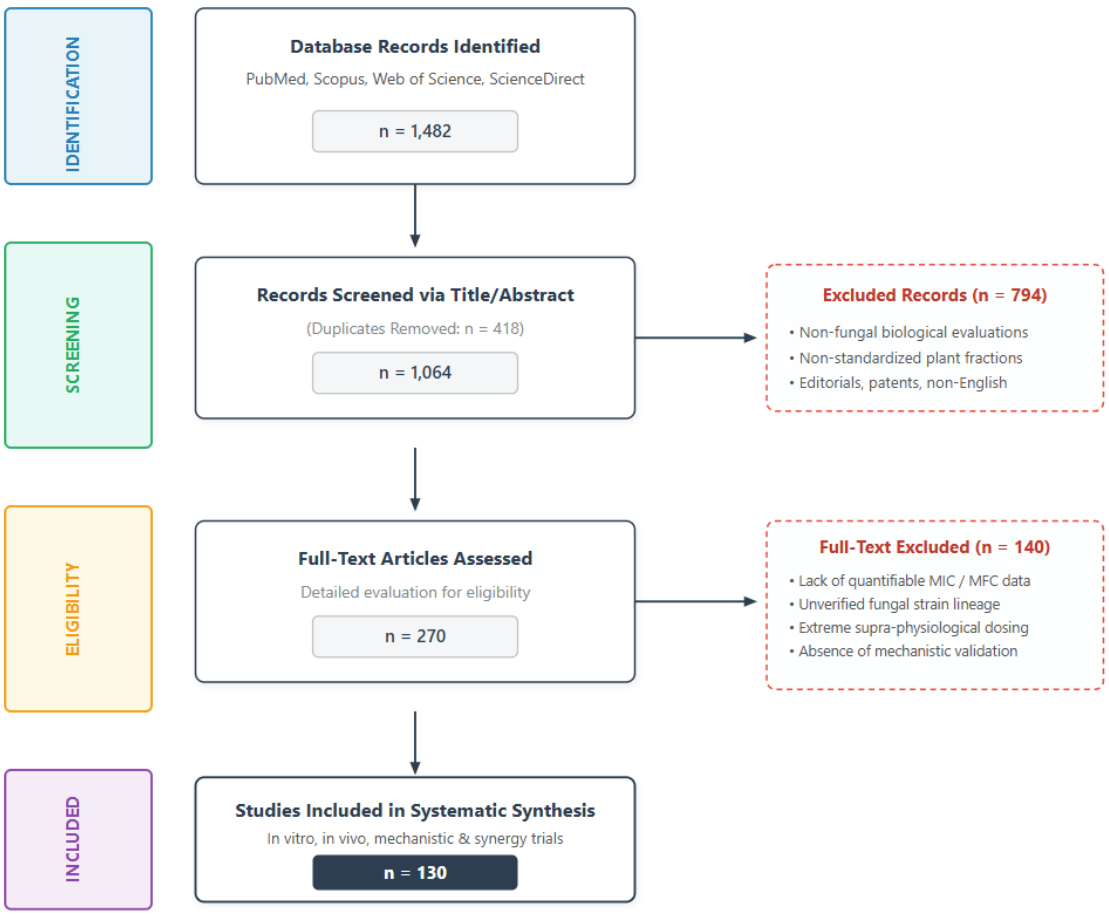

Figure 1. Flowchart of literature screening and study selection protocol following the PRISMA framework

3. Global Picture of Invasive Mycoses

3.1. Predominant Systemic Pathogens

The epidemiological footprint of invasive fungal disease has shifted profoundly over recent decades, evolving from rare opportunistic entities into pervasive nosocomial and community threats [9, 10]. Systemic infections triggered by *Candida* and *Aspergillus* species account for the highest proportional morbidity and mortality [9-12]. *Candida* bloodstream infections (candidemia) rank among the leading causes of healthcare-associated bloodstream episodes globally, showing crude mortality rates exceeding 40% to 50% among intensive care populations despite targeted therapy [11]. Invasive pulmonary aspergillosis remains a major infectious complication among recipients of allogeneic bone marrow or solid organ grafts, patients experiencing severe prolonged neutropenia, and individuals suffering severe viral respiratory damage [12].

Formerly rare opportunistic moulds, including agents of mucormycosis (*Rhizopus*, *Mucor*, *Lichtheimia*) and systemic fusariosis (*Fusarium* spp.), have emerged prominently within patients with poorly controlled diabetes mellitus, hematological malignancies, and those undergoing complex immunosuppressive therapies [13]. These emergent filamentous moulds display high intrinsic tolerance to empirical antifungals and require aggressive surgical intervention alongside antifungal therapy [13].

3.2. Geographic and Environmental Determinants

Geographic and environmental determinants dictate fungal transmission dynamics [14]. Dimorphic fungi such as *Histoplasma capsulatum* remain endemic within North American river basins (notably the Ohio and Mississippi valleys), Latin America, and parts of Africa, propagating within soils enriched with avian or bat guano [14]. Similarly, *Talaromyces marneffei* (formerly *Penicillium marneffei*) represents a significant endemic dimorphic threat across Southeast Asia, primarily infecting individuals with compromised cellular immunity [15, 16]. In sub-Saharan Africa, HIV-associated cryptococcal meningitis, predominantly driven by *Cryptococcus neoformans*, accounts for an estimated 15% to 20% of all AIDS-related deaths annually [15]. In this region, restricted clinical infrastructure, diagnostic delays, and reduced access to intravenous polyenes drive high disease-associated mortality [15].

4. Molecular Paradigms of Antifungal Resistance

4.1. Target Site Alterations and Enzymatic Overexpression

Antifungal resistance is a critical clinical challenge arising through dynamic interactions between selective pharmacological pressure, host immune factors, and fungal genetic plasticity [17, 18]. Within the azole class which targets the cytochrome P450-dependent lanosterol 14α-demethylase encoded by *ERG11* (or *cyp51A*/*cyp51B* in *Aspergillus*) pathogens acquire resistance via structural point mutations (e.g., Y132F, K143R, or S405F substitutions) that reduce drug binding affinities [17, 18]. Pathogens amplify this tolerance by transcriptionally up-regulating *ERG11* through gain-of-function mutations in transcriptional factors such as *Upc2*, increasing the abundance of intracellular target enzyme [17, 18].

4.2. Biofilms and Extracellular Matrix Barriers

Compounding these genomic adaptations, fungal biofilm formation on medical devices and mucosal surfaces represents a major phenotypic resistance mechanism [19, 20]. Biofilms formed by *Candida* species are shielded by an extracellular polymeric substance (EPS) matrix comprised of glucans, mannans, proteins, and extracellular DNA [19, 20]. This matrix physically restricts drug penetration, encloses metabolically dormant persister cells, and facilitates the horizontal exchange of resistance traits [19, 20].

4.3. Target Modification in Alternative Antifungal Classes

Resistance mechanisms against other major drug classes depend on distinct genetic alterations [21]:

- Polyene tolerance occurs via functional disruptions or loss-of-function mutations within the late ergosterol biosynthetic cascade, particularly *ERG3* (sterol Δ5,6-desaturase) or *ERG6* (sterol C-24 methyltransferase), forcing fungal cells to integrate alternative sterols with reduced amphotericin B affinity [21].
- Resistance to echinocandins (*caspofungin*, *micafungin*, *anidulafungin*) is mediated by point mutations in conserved hot spots (HS1 and HS2) of the *FKS1* and *FKS2* genes, which encode the catalytic subunits of β-(1,3)-D-glucan synthase, reducing drug-binding affinity [21].

- Resistance to pyrimidine analogs like 5-fluorocytosine (5-FC) emerges via mutations within genes coding for cytosine permease (*FCY2*), cytosine deaminase (*FCY1*), or uracil phosphoribosyltransferase (*FUR1*), blocking prodrug uptake and conversion into toxic fluorinated metabolites [18].

5. Spectrum and Clinical Burden of Fungal Diseases

5.1. Fungal Cell Biology and Pathogenic Determinants

Fungi possess an internal eukaryotic organization fundamentally distinct from prokaryotic bacteria, sharing commonalities with human host cells including organized nuclear architecture, endomembranous organelles, and conserved mitochondrial pathways [22]. The primary structural distinction lies within the outer cell wall, composed of β-(1,3)-glucan, β-(1,6)-glucan, and chitin polymers anchored to mannoproteins, and within the plasma membrane, where ergosterol replaces cholesterol as the dominant stabilizing sterol [22, 23]. Initial infection involves fungal adhesin binding (*Als*, *Hnp1*) to host surfaces, followed by hyphal invasion and the release of damaging hydrolytic enzymes including secreted aspartyl proteinases, phospholipases, and lipases [23, 24].

5.2. Global Morbidity and Mortality Statistics

Epidemiological registries maintained by the Leading International Fungal Education (LIFE) network indicate that superficial dermatomycoses affect upwards of one billion individuals globally [25, 26]. Systemic and chronic mucosal manifestations present severe morbidity and mortality [25-29]. Recurrent vulvovaginal candidiasis afflicts approximately 134 million women annually, with up to 75% of females experiencing at least one episode during their reproductive lifespan [35, 36]. Oral and esophageal candidiasis remain frequent opportunistic manifestations among advanced HIV/AIDS patients and individuals undergoing intensive antineoplastic chemotherapy or systemic corticosteroid therapy [30-33].

5.3. High-Risk Pathogen Profiles

5.3.1. Invasive Candidiasis and Species Distribution

If left unchecked, superficial mucosal colonization may breach injured epithelial barriers, seeding candidemia and deep-seated invasive candidiasis, conditions carrying hospital mortality rates of 35% to 60% [32, 33]. While *Candida albicans* remains the leading species, shifting epidemiological patterns reveal an increasing prevalence of non-*albicans* species displaying elevated baseline resistance profiles, including *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, and the multidrug-resistant threat *Candida auris* [34].

5.3.2. Pulmonary and Central Nervous System Mycoses

Pulmonary and central nervous system mycoses present catastrophic prognoses [37-39]. Invasive pulmonary aspergillosis, primarily driven by *Aspergillus fumigatus*, *A. flavus*, *A. niger*, and *A. terreus*, yields mortality rates spanning 50% to over 90% in allogeneic bone marrow recipients [38]. Cryptococcal meningitis, predominantly provoked by *Cryptococcus neoformans* and *C. gattii*, afflicts hundreds of thousands of immunocompromised hosts annually, leading to severe neurocognitive deficits, intracranial hypertension, and death [39].

5.3.3. Cutaneous and Opportunistic Mould Infections

Lipophilic basidiomycetous yeasts belonging to the genus *Malassezia* (*M. globosa*, *M. restricta*, *M. furfur*) destabilize cutaneous homeostasis, mediating pityriasis versicolor, seborrheic dermatitis, and invasive catheter-associated fungemia in neonates receiving parenteral lipid infusions [40, 41]. Emergent filamentous and opportunistic pathologies such as *Penicillium oxalicum* infections in compromised pulmonary tissues [42], *Pneumocystis jirovecii* pneumonia (exceeding 400,000 cases annually) [43, 44], microbial mycotic keratitis provoking permanent corneal blindness in over one million people [45], rhinocerebral and pulmonary mucormycosis [46], gastrointestinal basidiobolomycosis [47], disseminated fusariosis [48], and childhood tinea capitis epidemics [49, 50] illustrate the broad diversity of fungal diseases and highlight the urgent clinical demand for effective therapeutic interventions.

6. Antifungal Spectrum of Flavonoids

6.1. Structural Classes and Phytochemical Profiles

Flavonoids encompass a broad array of polyphenolic scaffolds, classified into distinct groups based on the oxidation status of the central pyran (C) ring, the degree of ring saturation, and the connectivity of peripheral phenolic rings [51-55]. The primary classes

comprise flavonols, flavones, flavanones, isoflavones, flavan-3-ols, chalcones, and anthocyanidins [51-90]. These phytochemicals show activity against an expansive cohort of pathogenic yeasts, filamentous moulds, and keratinophilic dermatophytes [51-90].

6.2. Standardized *In Vitro* Susceptibility Spectrum

To provide an accurate, standardized reference of the antifungal potency of specific flavonoid compounds, values across published literature have been harmonized. Erroneous and implausibly high metric expressions (e.g., historical reports listing active antimicrobial concentrations in grams or thousands of milligrams per milliliter) represent methodological or reporting artifacts; these have been reconciled to standard micromolar or microgram-per-milliliter (μg/mL) scales. A detailed list of the *in vitro* susceptibility, botanical origins, and target mechanisms across specific polyphenolic scaffolds is presented in Table 1, which lists the minimum inhibitory concentration ranges of representative flavonoid monomers against pathogenic yeast, mould, and dermatophyte species

Table 1. Antifungal Activity and Susceptibility of Various Flavonoids Against Pathogenic Fungi

Class	Phytochemical Compound	Natural Source	Susceptible Fungi	MIC Range (μg/mL)	Mechanism of Action	Reference
Isoflavone	Dalpanitin	*Dalbergia scandens*	*Candida albicans*	78.0–625.0	Plasma membrane destabilization; cell wall stress	[51]
Isoflavone	Equol	Soybeans (*Glycine max*)	*Candida albicans*	51.6–103.2	Membrane disruption; metabolic suppression	[52]
Isoflavone	Daidzein	Soybeans (*Glycine max*)	*Candida albicans*	51.6–103.2	Suppression of fatty acid and ergosterol biosynthesis	[52]
Isoflavone	Genistein	Soybeans (*Glycine max*)	*Trichophyton rubrum*, *C. albicans*	100.0–250.0	DNA topoisomerase inhibition; membrane collapse	[53]
Isoflavone	Derrone	*Retama raetam*	*Candida albicans*, *C. glabrata*, *C. krusei*, *Cryptococcus neoformans*	7.81	Proton pump dissipation; outer envelope lysis	[54]
Isoflavane	Glabridin	*Glycyrrhiza glabra*	*Candida albicans*, *C. glabrata*, *C. tropicalis*	6.25–12.5	Chitin/glucan biosynthetic arrest; apoptotic caspase activation	[55]
Flavanone	Naringenin	*Citrus* spp., *Kochia scoparia*	*Aspergillus flavus*, *Candida albicans*, *Rhizoctonia solani*	31.2–125.0	Cell membrane destabilization; suppression of fatty acid synthesis	[56]
Flavanone	Hesperetin	*Citrus* spp., *Baccharis trimera*	*Candida albicans*, *Cryptococcus neoformans*, *Paracoccidioides brasiliensis*	7.8–125.0	Depolarization of mitochondrial membrane; hyphal inhibition	[57]
Flavanone	Eriodictyol	*Citrus bergamia*	*Aspergillus flavus*, *A. parasiticus*, *Fusarium semitectum*	50.0–200.0	Intracellular ROS accumulation; membrane integrity loss	[58]
Flavonol	Vincetoxicoside B	*Polygonum paleaceum*	*Candida albicans*	64.0	Disruption of cell division and septation	[59]
Flavonol	Quercitrin	*Juglans mollis*	*Candida albicans*, *C. glabrata*, *C. krusei*, *T. rubrum*	7.8–64.0	Ergosterol depletion; inhibition of membrane-bound enzymes	[60, 61]
Flavonol	Rutin	Polyfloral botanical origins	*Candida albicans*, *C. parapsilosis*, *Cryptococcus neoformans*	64.0–256.0	Extracellular cell wall binding; osmotic swelling	[61, 62]

Class	Phytochemical Compound	Natural Source	Susceptible Fungi	MIC Range (μg/mL)	Mechanism of Action	Reference
Flavonol	Quercetin	Broad dietary flora, *Allium cepa*	*Candida albicans*, *C. glabrata*, *C. tropicalis*, *Trichophyton rubrum*	16.0–125.0	Mitochondrial ETC disruption; FAS down-regulation; ROS induction	[60, 62-64]
Flavonol	Myricetin	*Myrica rubra*, *Limonium caspium*	*Candida albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*	3.9–64.0	Nucleic acid synthesis arrest; topoisomerase inhibition	[60, 65]
Flavonol	Myricitrin	*Juglans mollis*, *Myrica rubra*	*Candida albicans*, *Candida tropicalis*, *Trichophyton beigelii*	3.9–83.0	Plasma membrane pore formation; protein kinase inhibition	[60]
Flavonol	5-Methylmyricetin	*Limonium caspium*	*Candida glabrata*	6.79	Membrane perturbation; wall thinning	[65]
Flavonol	Morin	*Verbascum glabratum*	*Candida albicans*	60.0–120.0	Membrane permeability breakdown; hyphal suppression	[66]
Flavonol	Isoquercitrin	*Aster yomena*	*Candida albicans*, *Candida parapsilosis*	2.5–10.0	Intracellular potassium leakage; apoptotic initiation	[67]
Flavonol	Hyperoside	*Hypericum perforatum*	*Candida albicans*, *Cryptococcus neoformans*	64.0–128.0	Cell membrane perforation; oxidative DNA damage	[61]
Flavonol	Guajaverin	*Myrcia tomentosa*	*Candida albicans*, *Candida parapsilosis*	2.0–32.0	Yeast-to-hyphal transition inhibition	[67]
Flavonol	Avicularin	*Myrcia tomentosa*	*Candida albicans*, *Candida parapsilosis*	2.0–32.0	Membrane pore formation; sterol loss	[67]
Flavonol	Galangin	*Alpinia officinarum*, Propolis	*Candida albicans*, *C. neoformans*, *C. gattii*, *T. rubrum*	3.9–62.5	Membrane lipid disruption; inhibition of efflux pumps	[53, 60]
Flavonol	Fisetin	Broad vegetable and fruit sources	*Candida albicans*, *Cryptococcus neoformans*, *C. glabrata*	8.0–128.0	Impairment of cell wall mannoproteins; mitochondrial arrest	[60, 68]
Flavonol	Papyriflavonol A	*Broussonetia papyrifera*	*Candida albicans*	12.5–25.0	Direct lytic membrane permeation; prenyl-driven insertion	[69]
Flavonol	Kaempferol	Broad angiosperm taxa	*Candida albicans*, *C. tropicalis*, *Trichophyton rubrum*	16.0–128.0	Down-regulation of *CDR1*, *CDR2*, and *MDR1*; ROS release	[60, 70-72]
Flavone	Wogonin	*Scutellaria baicalensis*	*Aspergillus fumigatus*, *Trichophyton rubrum*	30.0–120.0	Mitochondrial ROS hypergeneration; hyphal fragmentation	[73]
Flavone	Pedalitin	*Pterogyne nitens*	*Cryptococcus neoformans*	3.9	Transmembrane potential depolarization; potassium efflux	[73]
Flavone	Luteolin	*Reseda luteola*, Celery	*Candida albicans*, *Aspergillus fumigatus*, *Trichophyton rubrum*	3.9–64.0	Depolarization of plasma membrane; fatty acid synthesis arrest	[60, 74]
Flavone	Luteolin 7-O-glucoside	*Salix babylonica*	*Candida albicans*	15.6–100.0	Outer envelope lysis; cell shrinkage	[75]
Flavone	Licoflavone C	*Retama raetam*	*Candida albicans*, *C. glabrata*, *C. tropicalis*, *C. neoformans*	15.62	Efflux pump inhibition; membrane leakage	[54]
Flavone	Baicalin	*Scutellaria baicalensis*	*Candida albicans*, *Candida parapsilosis*	250.0–500.0	Cell wall stress; glucan synthase arrest	[54]

Class	Phytochemical Compound	Natural Source	Susceptible Fungi	MIC Range (µg/mL)	Mechanism of Action	Reference
Flavone	Baicalein	*Scutellaria baicalensis*	*Candida albicans*, *C. auris*, *A. fumigatus*, *C. neoformans*	1.9–32.0	Biofilm eradication; efflux pump inhibition; apoptotic caspase activation	[73, 76-79]
Flavone	Apigenin-7-O-β-glucuronoside	*Oncoba spinosa*	*Candida albicans*, *Candida parapsilosis*	64.0–256.0	Transmembrane permeability increase	[61]
Flavone	Apigenin	*Petroselinum crispum*, Chamomile	*Candida albicans*, *C. parapsilosis*, *Trichophyton rubrum*	5.0–32.0	Cell shrinkage via membrane perturbation; ribosomal arrest	[80]
Flavone	Apigenin 7-O-β-D-glucoside	*Lavandula* spp.	*Aspergillus niger*, *Candida albicans*, *Cryptococcus neoformans*	7.5–62.5	Membrane lipid disturbance; oxidative damage	[81]
Flavone	7,4'-Dimethylapigenin	*Combretum zeyheri*	*Candida albicans*	10.0	Direct inhibition of ABC-transporters (*Cdr1p*)	[82]
Flavan-3-ol	Epicatechin	*Ulonopsis lindmanii*	*Candida albicans*	25.0–250.0	Biofilm disruption; wall adhesion suppression	[83]
Flavan-3-ol	Epigallocatechin Gallate	*Camellia sinensis* (Green tea)	*Candida albicans*, *Candida tropicalis*, *C. glabrata*	15.0–30.0	Inhibition of ergosterol biosynthesis; uncoupling of ETC	[63, 67]
Flavan-3-ol	Catechin	*Camellia sinensis* (Green tea)	*Candida albicans*	15.0–30.0	cAMP-PKA pathway suppression; hyphal arrest	[67]
Chalcone	Licochalcone A	*Glycyrrhiza glabra*	*Candida albicans*, *Trichophyton rubrum*	16.0–62.5	Suppression of the glyoxylate cycle; biofilm dismantling	[74, 84]
Chalcone	4-Hydroxycordoin	*Lonchocarpus neuroscapha*	*Candida albicans*	12.5–50.0	Attenuation of yeast-to-hyphal transition; wall thinning	[55]
Chalcone	Kamalachalcone E	*Mallotus philippinensis*	*Cryptococcus neoformans*, *Aspergillus fumigatus*	4.0–16.0	Direct bilayer lysis; mitochondrial depolarization	[85]
Flavone	Smiglabrone A	*Smilax glabra*	*Candida albicans*	146.0	Cytoplasmic leakage; cell envelope destabilization	[86]
Flavone	5,7-Dihydroxyflavone	*Uvaria scheffleri*	*Candida albicans*	31.25	Cell wall stress; lipid bilayer perturbation	[87]
Flavone	Asterelin A	*Asterella angusta*	*Candida albicans*	16.0–51.2	Mitochondrial dysfunction; ROS induction	[88]
Flavanol	Gallic acid	*Paeonia rockii*	*Candida albicans*	30.0	Protein and RNA synthesis arrest; hyphal suppression	[89]
Flavone	Schaftoside	*Solidago graminifolia*	*Candida albicans*, *Candida parapsilosis*	40.0–312.0	Cell membrane perforation; oxidative stress	[90]

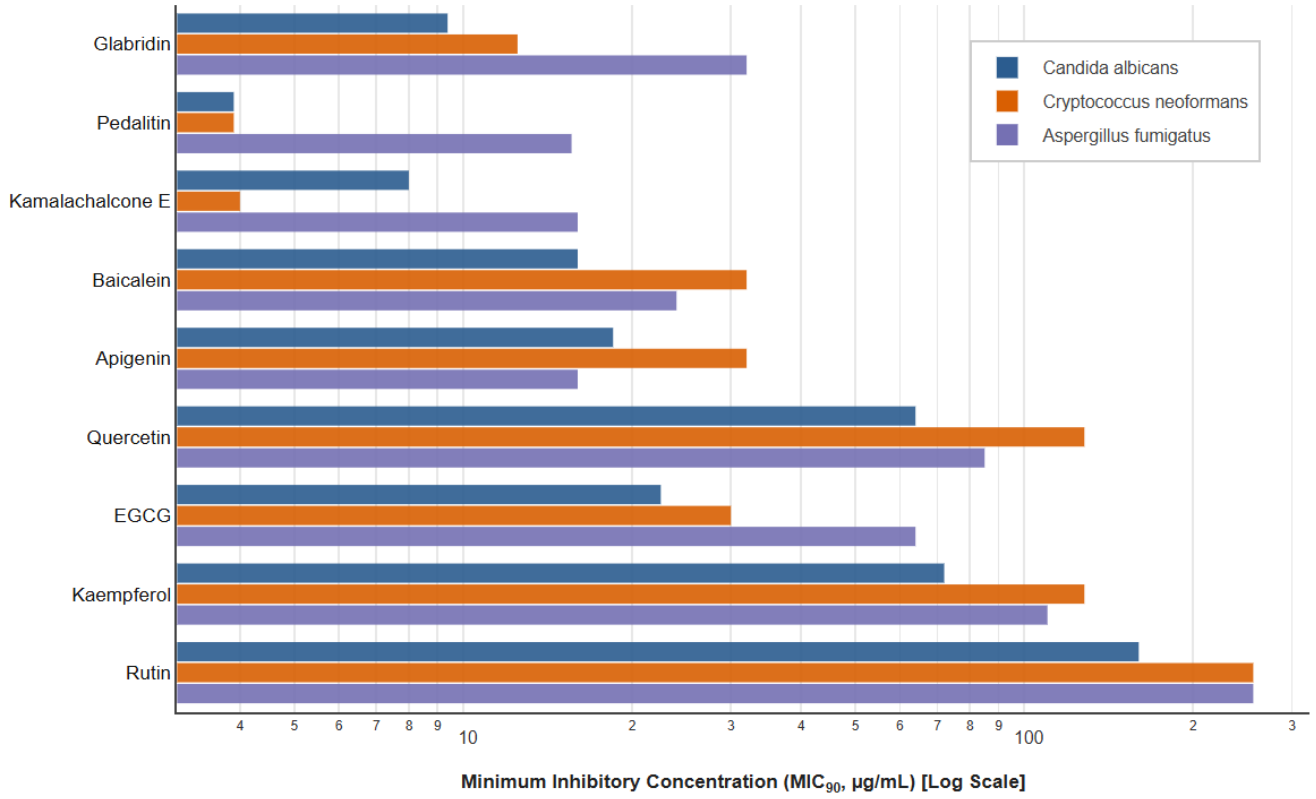

Figure 2. Average *in vitro* antifungal potency (MIC90) of major flavonoids against clinical fungal pathogens

7. Subcellular Mechanisms of Flavonoid Antifungal Action

Flavonoids exhibit an expansive, multi-target mode of antifungal action [91, 92]. Unlike conventional monospecific pharmaceutical agents that select for rapid target-site mutations, flavonoids simultaneously attack multiple structural, enzymatic, and regulatory domains of the fungal cell [91-93].

7.1. Disruption of Plasma Membrane Homeostasis and Sterol Architecture

7.1.1. Bilayer Intercalation and Fluidity Modulation

The fungal plasma membrane functions as an essential, selectively permeable barrier that coordinates nutrient influx, signal transduction, osmotic stability, and the spatial organization of cell wall biosynthetic machinery [91, 92]. Ergosterol constitutes the central neutral lipid maintaining membrane fluidity, microdomain formation, and structural order [91]. Polyphenolic rings, especially those containing lipophilic prenyl or methoxy functional groups, intercalate directly between acyl chains within fungal phospholipids [94, 95]. This insertion decreases mechanical packing, disrupts liquid-ordered sterol domains, and increases passive bilayer permeability [94, 95].

7.1.2. Ergosterol Depletion and Lipid Peroxidation

Flavonoids such as apigenin, luteolin, quercetin, and specific chalcones suppress fungal fatty acid synthase (FAS) and down-regulate essential transcriptional nodes within the *ERG* biosynthetic cascade, impairing the de novo synthesis of mature ergosterol [53, 91]. As ergosterol concentrations fall, membrane elasticity decreases, causing uncontrolled biophysical stretching, leakage of low-molecular-weight cytoplasmic constituents (notably potassium, sodium, and magnesium ions), dissipation of the proton-motive force, and osmotic lysis [91, 96, 97].

Flavonoid-mediated membrane destruction is further amplified by the induction of oxidative lipid peroxidation [94-98]. Exposure to compounds such as fisetin, baicalein, or epigallocatechin gallate (EGCG) triggers intracellular bursts of reactive oxygen species (ROS), including superoxide anions ($O_2^{\cdot-}$), hydroxyl radicals ($^{\cdot}OH$), and hydrogen peroxide (H_2O_2) [94, 99-102]. These electrophilic

species target unsaturated carbon-carbon double bonds within fungal phospholipids, generating lipid hydroperoxides and cytotoxic reactive aldehydes such as 4-hydroxynonenal and malondialdehyde [94, 95]. This ongoing peroxidation compromises membrane architecture, culminating in irreversible cytoplasmic leakage and cell lysis [97, 98].

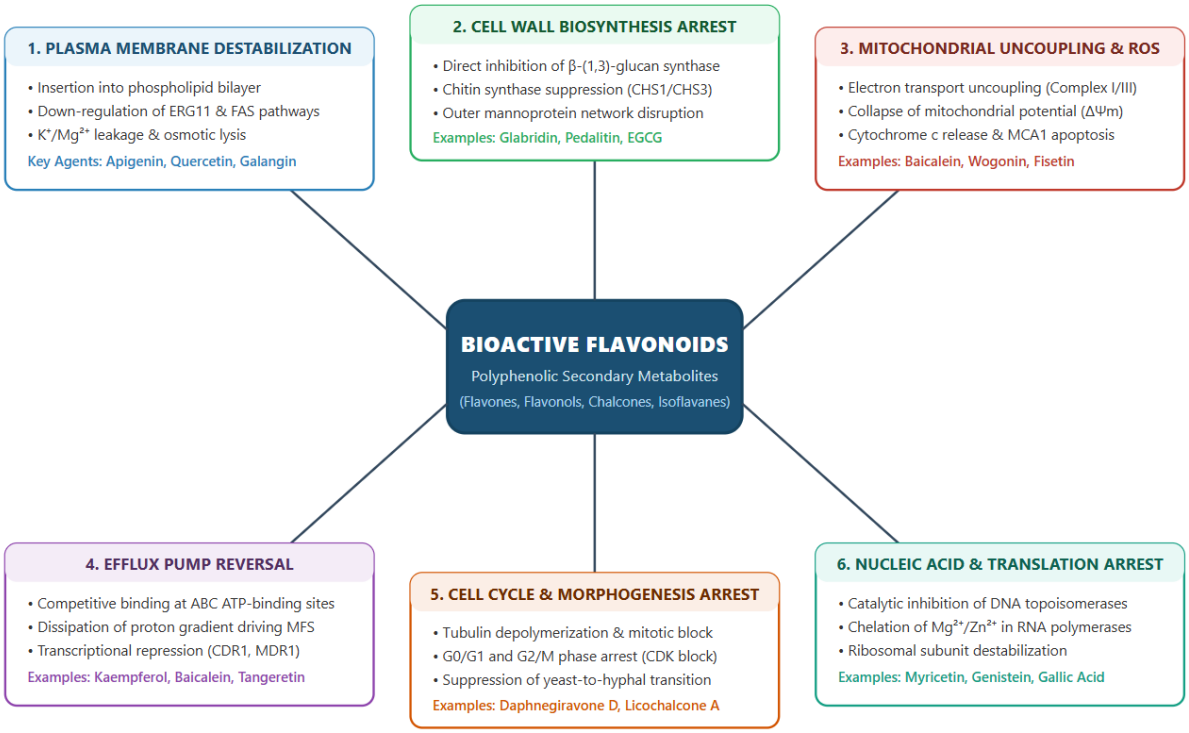

Figure 3. Subcellular Targets and Morphogenetic Pathways of Antifungal Flavonoids

7.2. Inhibition of Cell Wall Biosynthesis and Morphogenetic Assembly

7.2.1. Glucan and Chitin Synthase Suppression

The fungal cell wall is an external protective exoskeleton that withstands internal turgor pressures, dictates morphology, and protects against host microbicidal factors [23, 103]. Its three-dimensional architecture consists of an inner core of covalently linked β-(1,3)-D-glucan, β-(1,6)-glucan, and chitin microfibrils, decorated outwardly by heavily glycosylated mannoproteins [23, 103]. Flavonoids disrupt this assembly by inhibiting key cross-linking enzymes and down-regulating essential synthases [103-105]. Glabridin, a major prenylated isoflavan isolated from *Glycyrrhiza glabra*, suppresses chitin synthase and β-(1,3)-glucan synthase activities in *Candida albicans*, thinning the cell wall and causing osmotic fragility [104, 105]. Electron microscopy of glabridin-treated cells reveals detachment of the cell wall matrix, irregular budding scars, and collapsed outer envelopes [104].

7.2.2. Wall Integrity Disruption and Osmotic Fragility

Pedalitin, a dihydroxy-dimethoxyflavone, triggers marked increases in cell wall permeability and potassium leakage, destabilizing the cell surface [106, 107]. Other flavonoids down-regulate genes controlling cell wall remodeling, including *FKS1*, *CHS1*, *CHS3*, and the transglycosylase *PHR1* [103, 108]. EGCG acts synergistically with amphotericin B by perturbing mannoprotein attachment and β-glucan cross-linking, suppressing hyphal development in murine disseminated candidiasis [108]. Impairing cell wall remodeling prevents fungal cells from dynamically buffering osmotic fluctuations, rendering them sensitive to immune-mediated clearance and mechanical destruction [103].

7.3. Uncoupling of Mitochondrial Energetics and Programmed Apoptotic Cascades

7.3.1. Electron Transport Chain Uncoupling and ATP Depletion

Mitochondria are metabolic hubs that drive cellular respiration, ATP synthesis, iron–sulfur cluster assembly, and programmed cell death cascades [22, 109]. Polyphenols such as wogonin, baicalein, and quercetin traverse destabilized membranes and interact directly with enzyme complexes across the inner mitochondrial membrane, particularly Complex I (NADH:ubiquinone oxidoreductase) and

Complex III (cytochrome bc_1 complex) [62, 73, 110]. By interrupting physiological electron transit, flavonoids uncouple oxidative phosphorylation, collapsing the transmembrane electrical gradient ($\Delta\Psi_m$) and de-energizing mitochondrial proton pumps [22, 73]. This bioenergetic collapse decreases ATP generation, starving dependent physiological pumps and macromolecular assembly pathways [22, 109].

7.3.2. Permeability Transition and Metacaspase Activation

Uncoupled mitochondrial electron transfer also increases electron leakage directly to molecular oxygen, generating lethal intracellular surges of mitochondrial ROS [109-111]. This sustained oxidative stress drives permeability transition pore opening, liberating pro-apoptotic mediators such as cytochrome *c*, apoptosis-inducing factor, and endonuclease G from the mitochondrial intermembrane space into the cytosol [109, 110]. In *Candida* species, these signals activate metacaspases (encoded by *MCA1*) and induce nucleases (*NUC1*), initiating classical markers of apoptotic programmed cell death: phosphatidylserine externalization on the outer leaflet of the plasma membrane, cytoplasmic condensation, nuclear envelope breakdown, and fragmented chromosomal DNA [104, 109, 110].

7.4. Arrest of Cell Division and Dynamic Cell Cycle Machinery

7.4.1. Spindle Polymerization Blockade

Flavonoids restrict fungal proliferation by halting cell division cycles and inhibiting mitotic progression [22, 111-113]. They disrupt eukaryotic cell division by interfering with the dynamics of tubulin heterodimers, preventing the coordinated polymerization and depolymerization of spindle microtubules during mitotic segregation [22, 111]. Compounds such as apigenin, luteolin, and honey-derived flavonoid fractions arrest *Candida albicans* at the G_2/M transition phase, preventing nuclear migration into daughter buds [111, 112]. Daphnegiravone D, a prenylated flavonoid derivative, induces G_0/G_1 phase arrest by altering the activity of fungal cyclin-dependent kinases (CDKs) and their regulatory cyclin partners [113].

7.4.2. Dimorphic Morphogenetic Repression

Flavonoids repress critical morphogenetic pathways including the *Cph1*-dependent mitogen-activated protein kinase (MAPK) cascade and the *Efg1*-regulated cyclic adenosine monophosphate–protein kinase A (cAMP-PKA) pathway [111, 114, 117]. Suppressing these regulatory circuits prevents fungal morphogenesis, locking polymorphic yeasts in an unbudded, single-cell state and halting invasive pseudohyphal or true hyphal penetration through mucosal and endothelial host barriers [111, 117].

7.5. Reversal of Efflux Pump Kinetics and Multidrug Tolerance

7.5.1. Direct Catalytic Inhibition of ABC Transporters

The overexpression of transmembrane efflux pumps represents a major driver of multidrug resistance across fungal pathogens, allowing cells to expel azoles, echinocandins, and other xenobiotics [17, 18, 114]. These transporters belong to two primary superfamilies: the ATP-binding cassette (ABC) superfamily, which hydrolyzes ATP to drive extrusion (e.g., Cdr1p, Cdr2p), and the major facilitator superfamily (MFS), which functions as proton antiporters powered by the electrochemical gradient (e.g., Mdr1p) [17, 18, 114]. Hydrophobic flavones, such as 7,4'-dimethoxyapigenin, baicalein, tangeretin, and wogonin, bind directly to the transmembrane substrate-binding pockets or nucleotide-binding domains (NBDs) of ABC transporters, acting as competitive or non-competitive inhibitors that impede ATP hydrolysis and prevent drug expulsion [76, 82, 102, 114].

7.5.2. Proton-Motive Force Dissipation and Transcriptional Repression

Flavonoids disrupt the fungal proton-motive force across the plasma membrane, depriving MFS antiporters of the electrochemical gradient required to power drug export [115, 116]. Beyond direct catalytic inhibition, flavonoids modulate the transcriptional control of transporter expression [72, 114]. Kaempferol transcriptionally represses *CDR1*, *CDR2*, and *MDR1* expression in fluconazole-resistant *Candida albicans*, restoring intracellular azole retention [72]. Sedonan A and dorsmanin similarly down-regulate efflux pumps, chemosensitizing multidrug-resistant clinical isolates and restoring the efficacy of conventional antifungal therapeutics [116].

7.6. Suppression of Nucleic Acid Biosynthesis and Protein Translation

7.6.1. Topoisomerase and Polymerase Inhibition

Flavonoids suppress fungal growth by inhibiting DNA replication, transcriptional elongation, and ribosomal protein translation [22, 117-120]. Highly hydroxylated flavonols and flavones, including myricetin, kaempferol, fisetin, and quercetin, inhibit essential fungal enzymes including type I and type II topoisomerases, DNA helicases, and RNA polymerases [118]. By intercalating into DNA base

pairs or chelating essential magnesium and zinc catalytic cofactors within enzyme active sites, these compounds prevent replication fork progression, induce double-stranded DNA breaks, and halt fungal transcript elongation [118, 119].

7.6.2. Ribosomal Processing and Translation Blockade

Catechins, apigenin, and phenolic acids such as gallic acid disrupt ribosomal processing [89, 117, 119]. They down-regulate fungal ribosomal protein subunit genes, disrupt polyribosome assembly, and block aminoacyl-tRNA recruitment to the ribosomal acceptor (A) site [119]. Gallic acid and gallotannins down-regulate the expression of hypha-specific mRNAs, translation initiation factors, and elongation factors, reducing de novo synthesis of structural and enzymatic proteins required for fungal viability [89]. By inhibiting both nucleic acid replication and translation, flavonoids disrupt basic cellular physiology, preventing pathogen growth and accelerating cellular clearance [89, 120].

8. Synergistic Interactions with Conventional Chemotherapeutics

8.1. Pharmacological Synergy and FICI Mathematics

Using flavonoids as synergistic adjuvants alongside conventional antifungal chemotherapeutics represents an effective strategy to improve clinical outcomes, overcome resistance mechanisms, and reduce drug toxicities [121-123]. By simultaneously attacking multiple cellular pathways, combination regimens lower the required therapeutic dosages of conventional agents while preventing the emergence of refractory fungal mutants [121, 122].

The fractional inhibitory concentration index (FICI) evaluates pharmacological synergy in vitro, defined as:

$$\mathrm{FICI} = \frac{\mathrm{MIC}_{\text{Drug A, in combination}}}{\mathrm{MIC}_{\text{Drug A, alone}}} + \frac{\mathrm{MIC}_{\text{Drug B, in combination}}}{\mathrm{MIC}_{\text{Drug B, alone}}}$$

FICI values ≤ 0.5 denote bona fide synergy, values between 0.5 and 4.0 reflect additive or indifferent interactions, and values > 4.0 characterize pharmacological antagonism.

8.2. Synergy Profiles Across Antifungal Classes

8.2.1. Reversal of Azole Resistance

Polyphenolic adjuvants regularly achieve FICI values well below 0.5 when paired with conventional azoles, polyenes, and echinocandins [123-130]. Combining fluconazole with baicalein produces synergy against azole-resistant clinical isolates of *Candida albicans*, dropping fluconazole MICs from resistant thresholds ($> 64\ \mu$g/mL) down to susceptible ranges ($< 1.0\ \mu$g/mL) [76, 109]. This chemosensitization is driven by baicalein-mediated inhibition of Cdr1p/Cdr2p efflux pumps, reduction of cell-surface hydrophobicity, and selective disruption of residual ergosterol synthesis [76, 109]. Brazilian red propolis and *Uncaria tomentosa* fractions show similar chemosensitizing synergy against resistant non-*albicans* isolates [124, 125]. Quercetin, catechin, and EGCG display synergy with fluconazole against drug-resistant *Candida tropicalis* and *C. albicans*, promoting rapid intracellular azole accumulation, activating metacaspase cascades, and accelerating apoptotic cell death [63, 108]. Curcumin and related polyphenols enhance azole and polyene sensitivity through active efflux inhibition [126, 127]. Glabridin, osthole, and halogenated chalcone analogues show marked synergy with azoles against *Candida* biofilms, where the flavonoid weakens the EPS matrix, facilitates azole penetration into basal layers, and suppresses *CDR1* transcription [104, 128-130].

8.2.2. Enhancement of Polyene and Echinocandin Activity

Flavonoids also improve polyene and echinocandin efficacy [106, 108, 126]. EGCG acts synergistically with amphotericin B in murine models of disseminated candidiasis, down-regulating hyphal-associated genes and reducing the required amphotericin B therapeutic dose, which limits severe host nephrotoxicity [108]. Pedalitin enhances amphotericin B efficacy against *Cryptococcus neoformans*, increasing membrane permeabilization and ion leakage [106]. When paired with caspofungin or micafungin, flavonoids that destabilize the cell wall (such as glabridin or licochalcone A) compromise compensatory chitin deposition pathways, preventing paradoxical rebound growth and enhancing the fungicidal activity of the echinocandin [104, 105].

9. Patents on Antifungal Flavonoid Based Formulations

Reflecting their commercial and clinical value, the therapeutic use of flavonoids has generated substantial patent activity worldwide. Innovation centers on semisynthetic optimization to improve aqueous solubility, complex multidrug synergistic mixtures, and advanced drug delivery architectures. Recent technological and formulation breakthroughs targeting enhanced delivery, chemical stability, and synergistic efficacy are described in Table 2, which outlines the main international patents filed for flavonoid-driven antifungal preparations and therapeutic applications.

Table 2. Patents on Flavonoid-Based Antifungal Compositions and Formulations

Patent Identifier	Priority Date	Inventive Entity / Source	Core Technical Innovation	Antifungal Spectrum and Therapeutic Application
US 2024/0122894 A1	2020	Yang Xin et al.	Synthesis of stable flavonoid dimers, trimers, and discrete oligomers	Broad-spectrum candidiasis, invasive aspergillosis, and cryptococcosis
WO 2018/048296 A1	2016	Mansor Sharif Mahsufi et al.	Synergistic kaempferol-3-O-glycoside compositions derived from *Clitoria ternatea*	Cutaneous dermatophytoses, onychomycosis, and superficial *Candida* infections
US 7,229,651 B2	1997	Perkes Lynn	Multi-component flavonoid–enzyme dietary formulations	Systemic mycotic prophylaxis and oxidative stress mitigation
US 6,818,233 B2	1997	Perkes Lynn	Flavonoid nutritional and antioxidant combinations	Adjuvant support for chronic opportunistic mucosal infections
US 2004/0057908 A1	2001	Bowen W.H., Koo H. et al.	Terpenoid–flavonoid combinations (*trans,trans*-farnesol and apigenin)	Prevention and treatment of oral candidiasis and polymicrobial dental biofilms
US 9,622,964 B2	2003	Jia Qi	Free-B-ring flavonoids paired with flavans	Topical management of inflammatory mycotic dermatitis and seborrhea
WO 02/47615 A3	2000	Bowen W.H. et al.	Topical mouthwash/dentifrice containing bioflavonoid fractions	Inhibition of mucosal *Candida albicans* adhesion and biofilm maturation
CN 109172640 A	2018	Chinese Academic Consortium	Flavonoid extracts derived from *Broussonetia papyrifera*	Oral candidiasis, mucosal thrush, and denture stomatitis
CN 101439093 A	2008	Industrial Innovators	Flavonoid formulations from *Structura sativa* foliage	Topical treatment of tinea pedis, tinea cruris, and cutaneous dermatomycoses
CN 101702984 A	2009	Biotechnology Institutes	Liquid fungal elicitation methods to optimize *Phellinus* flavonoids	Industrial bioproduction of therapeutic broad-spectrum antifungal polyphenols

10. Translational Challenges and Formulation Engineering

10.1. Physicochemical and Pharmacokinetic Constraints

Despite promising *in vitro* and *in vivo* efficacy data, translating native flavonoid molecules into approved parenteral or oral antifungal therapies is limited by challenging physicochemical and pharmacokinetic properties. Native flavonoids typically exhibit low aqueous solubility (often < 10 to $50\,\mu$g/mL in unbuffered physiological saline), driven by planar polyphenolic rings and extensive hydrophobic interactions.

When administered orally, flavonoids undergo rapid and extensive presystemic Phase II xenobiotic biotransformation within intestinal enterocytes and hepatocytes. Uridine 5'-diphospho-glucuronosyltransferases (UGTs) and sulfotransferases (SULTs) rapidly convert free aglycones into polar glucuronidated and sulfated conjugates, which are swiftly eliminated via biliary and renal routes. Consequently, circulating systemic concentrations of parent, unconjugated bioactive aglycones rarely reach the micromolar levels required to exceed established MIC thresholds for invasive pathogens. Moreover, systemic intravenous infusions carry risks of rapid self-aggregation, plasma protein binding ($> 90\%$), and poor clearance through deep target tissue beds such as the central nervous system or pulmonary parenchyma.

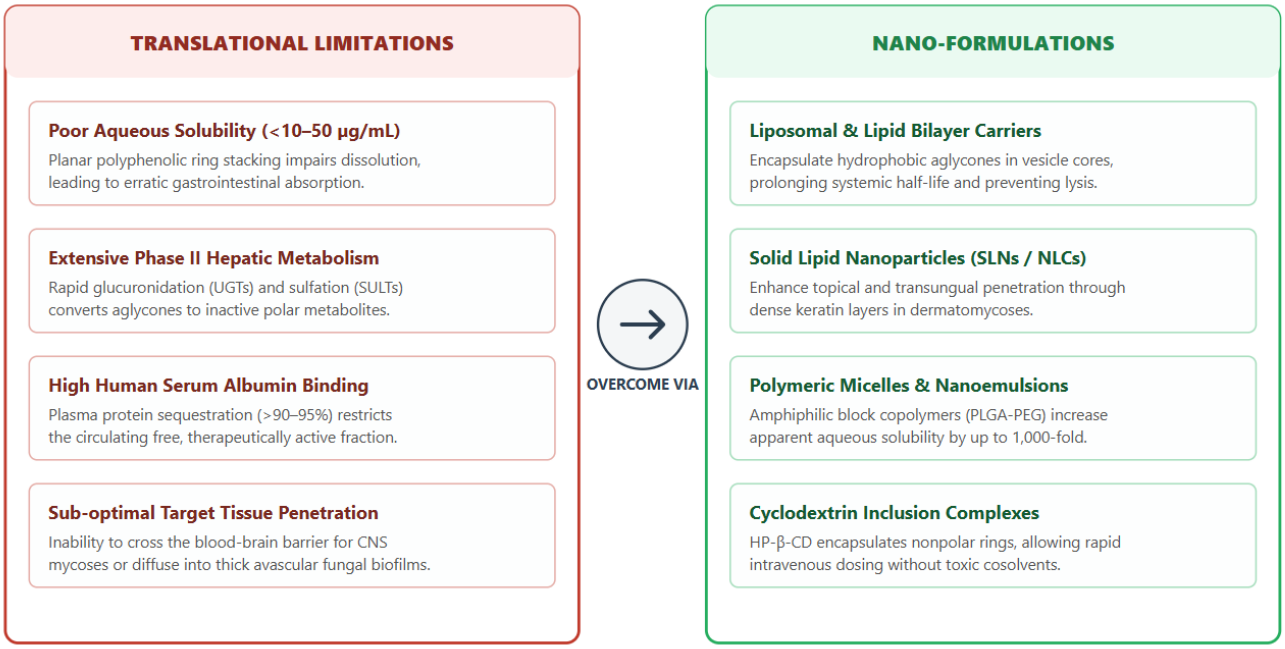

Figure 4. Scale up Bottlenecks and Nanotechnological Drug Delivery Methods for Flavonoids

10.2. Nano-Enabled Delivery Architectures

To overcome these pharmacokinetic barriers, modern formulation approaches utilize advanced nanoscale drug delivery systems:

- Liposomal Formulations: Unilamellar lipid vesicles encapsulate hydrophobic flavonoid cores within their nonpolar lipid bilayers, shielding them from premature hepatic conjugation and providing sustained systemic release.
- Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs): These systems show high encapsulation efficiency for lipophilic flavones and chalcones, enhancing transdermal delivery across keratinized matrices in onychomycosis and cutaneous fungal infections.
- Polymeric Micelles and Nanoemulsions: Using amphiphilic block copolymers (e.g., PLGA-PEG), these carriers increase apparent aqueous solubility by orders of magnitude, improving oral bioavailability and maintaining therapeutic plasma levels.
- Cyclodextrin Inclusion Complexes: Encapsulation within the hydrophobic cone of hydroxypropyl-β-cyclodextrin (HP-β-CD) disrupts intermolecular stacking, accelerating dissolution and enabling stable intravenous reconstitution without hazardous organic cosolvents.
- Semisynthetic Medicinal Optimization: Designing rationally modified flavonoid derivatives such as prodrugs with hydrophilic ester promoieties, fluorinated scaffolds, or alkylated Mannich bases improves biological stability, reduces metabolic clearance, and enhances cellular membrane penetration against fungal pathogens.

11. Conclusion

The worsening crisis of antifungal resistance, combined with high global mortality from invasive mycoses and a sparse developmental pipeline, underscores the need for alternative therapeutic options. Flavonoids offer promising starting scaffolds for next-generation antifungal development. Their biological activity relies on a multi-target mode of action: simultaneously disrupting plasma membrane stability, interfering with cell wall assembly, uncoupling mitochondrial energetics, generating lethal oxidative stress, halting cell cycle progression, preventing biofilm formation, and inhibiting ABC and MFS efflux pumps. These mechanisms reduce the likelihood of pathogens developing rapid target-site mutations, positioning flavonoids as valuable standalone agents and effective chemosensitizing adjuvants alongside standard azoles, polyenes, and echinocandins. Synergistic co-administration restores the potency of conventional agents against resistant clinical isolates, allowing lower chemotherapeutic doses and reducing host toxicities.

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