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Review

Systemic Preventive and Detoxifying Efficacy of Phenolics and Flavonoids Against Carcinogenesis: A Comprehensive Analysis of the Transition from Cellular Protection to Systemic Metabolic Resilience

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Abstract: Hepatocellular carcinoma (HCC) remains a formidable global health challenge, characterized by high mortality and strong links to chronic liver injury, metabolic dysfunction-associated steatotic liver disease (MASLD), and cirrhosis. Conventional therapeutic modalities show limited efficacy in advanced disease stages, highlighting an urgent need for effective chemopreventive and protective strategies. Dietary phenolics and flavonoids—secondary plant metabolites defined by their characteristic C6-C3-C6 phenylpropanoid scaffolds—have emerged as powerful bio-modulators capable of shifting cellular dynamics from localized antioxidant protection to systemic metabolic resilience. This review comprehensively synthesizes the multi-tiered mechanisms through which phenolic compounds exert anti-carcinogenic and detoxifying effects, with a particular focus on the transition from chronic inflammation to malignancy. Mechanistically, these compounds disrupt the pathogenic pro-inflammatory triad (NF-κB, STAT3, and COX-2), trigger apoptotic cascades (Bax/Bcl-2, caspases), and restore autophagic flux (AMPK/mTORC1) to eliminate damaged cellular components. At the core of their detoxifying potential is the activation of the Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)-Antioxidant Response Element (ARE) axis. Activation of Nrf2 upregulates Phase II biotransformation and antioxidant enzymes (GSTs, NQO1, HO-1, GCL), establishing a "metabolic shield" that neutralizes

and excretes electrophilic carcinogens while reinforcing cellular glutathione (GSH) pools. Furthermore, we address the dual role of Nrf2—the "Nrf2 paradox"—wherein transient activation confers chemoprevention in normal tissue, whereas constitutive hyperactivation drives chemoresistance and metabolic survival in established tumors. To bridge preclinical findings with clinical applications, we explore advanced delivery technologies (e.g., liposomes, nano-emulsions) that overcome poor phenolic bioavailability, alongside biosynthetic microbial chassis engineering and personalized, biomarker-driven supplementation.

Keywords: Hepatocellular Carcinoma, Flavonoids, Phenolics, Nrf2-ARE Pathway, Phase II Detoxification, Nrf2 Paradox, Metabolic Resilience, Tumor Microenvironment, Nanocarrier Delivery.

1. Introduction

Hepatocellular carcinoma (HCC) represents a major global health crisis, currently ranking as the sixth most commonly diagnosed cancer and the third leading cause of cancer-related mortality worldwide [1, 2]. According to recent data, there are over 900,000 new cases and approximately 830,000 deaths annually, highlighting a high mortality-to-incidence ratio that underscores the limited efficacy of interventions at advanced stages [3, 4]. The disease is strongly associated with chronic liver injury, with cirrhosis present in approximately 85% of cases [2, 5]. Primary risk factors include chronic Hepatitis B (HBV) and Hepatitis C (HCV) viral infections, heavy alcohol consumption, and the rapidly increasing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), which is becoming a dominant etiology in both Western and developing nations [6, 7, 8]. The socioeconomic burden is profound, as the condition disproportionately affects middle-aged and older populations, necessitating intensive clinical management and lifelong surveillance [2, 9].

Phenolics and flavonoids constitute a diverse group of plant-derived secondary metabolites whose potent biological activities are dictated by their unique chemical architectures [10, 11]. Flavonoids are characterized by a 15-carbon phenylpropanoid core (C6-C3-C6) comprising two aromatic rings linked by a heterocyclic pyran ring, with variations in oxidation and saturation levels yielding subclasses such as flavones, flavonols, and anthocyanidins [12- 14]. These compounds function as "hormetic stressors" due to their specific hydroxyl and ketonic functional groups, which allow them to engage in intricate redox reactions [15, 16]. Their structural capacity to undergo metabolic modifications—such as sulfation, glucuronidation, and methylation—modulates their bioavailability and facilitates their role as both direct radical scavengers and indirect modulators of cellular detoxification pathways [17, 18].

Phenolic and flavonoid compounds exhibit multifaceted antitumor potential by targeting critical checkpoints in malignant transformation and progression [19-23]. These agents are known to suppress proliferation, induce apoptosis in transformed cells, and inhibit angiogenesis, thereby limiting the metabolic support necessary for tumor expansion [24, 25]. Furthermore, they modulate the tumor microenvironment by reducing chronic, pro-inflammatory signaling—often mediated by nuclear factor kappa B (NF-κB)—which is essential for tumor promotion [10, 26]. By promoting cell cycle arrest and activating autophagy, these dietary compounds function as natural chemopreventive agents that maintain tissue homeostasis and prevent the transition from chronic inflammation to malignant growth [20, 27].

The antitumor and systemic detoxifying efficacy of these compounds is primarily mediated through the modulation of the Nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway [11, 28]. Under physiological stress, specific flavonoids act as ligands that facilitate the stabilization and nuclear translocation of Nrf2, which subsequently binds to the Antioxidant Response Element

(ARE) in the promoter regions of various cytoprotective genes [14, 15]. This activation triggers a coordinated expression of Phase II biotransformation enzymes, including Glutathione S-transferases (GSTs), NAD(P)H:quinone oxidoreductase 1 (NQO1), and Heme Oxygenase-1 (HO-1) [12, 16]. This process creates a "metabolic shield" by conjugating and facilitating the excretion of reactive electrophilic carcinogens, while simultaneously reinforcing redox homeostasis to prevent further genomic instability [18, 28].

Recent advancements in this field include the application of nanotechnology, such as lipid-based nanoparticles and liposomal carriers, to circumvent the issues of poor water solubility and low systemic bioavailability of many flavonoids [13, 17, 24]. Furthermore, biosynthetic engineering is opening new doors for the standardized production of high-purity bioactive metabolites [22, 27]. Despite these breakthroughs, significant gaps persist, most notably the "Nrf2 paradox": while transient activation is protective, chronic or constitutive activation in established tumors can promote chemoresistance and a more aggressive malignant phenotype [11, 15, 26]. Additionally, there is a lack of large-scale, long-term human clinical trials that can definitively translate preclinical findings into standardized clinical recommendations, indicating a need for more robust pharmacodynamic studies [19, 20].

This review aims to synthesize current evidence regarding the systemic preventive and detoxifying efficacy of dietary phenolics and flavonoids against carcinogenesis. By shifting the perspective from simple radical scavenging to the broader concept of systemic metabolic resilience, this analysis seeks to provide a comprehensive framework for how these compounds modulate redox homeostasis and Phase II biotransformation pathways across diverse malignant phenotypes. Ultimately, the review intends to clarify the dual nature of Nrf2-mediated signaling and offer evidence-based perspectives for utilizing these bioactive secondary metabolites as a strategic approach to cancer prevention and personalized oncological support.

2. Structural Chemistry, Bioavailability, and Metabolic Fate

2.1 Structure-Activity Relationships (SAR): Influence of C6–C3–C6 Backbone Variations, Degree of Hydroxylation, and C2=C3 Double Bonds on Redox Signaling and Radical Scavenging Potency

The biological efficacy of flavonoids as both direct antioxidants and active modulators of intracellular redox cascades is fundamentally governed by their structural topology [29]. The canonical flavonoid skeleton features a 15-carbon C6–C3–C6 framework consisting of two aromatic rings (Ring A and Ring B) interconnected via a three-carbon heterocyclic oxygen-containing ring (Ring C) [29, 30]. While traditional paradigm centered almost exclusively on stoichiometric free-radical scavenging, recent structural reviews emphasize that subtle variations across this central scaffold dictate a functional bifurcation between direct chemical radical quenching and catalytic, transcriptional redox signaling [31, 32].

2.1.1 Degree and Pattern of Hydroxylation

The number and positional distribution of hydroxyl (−OH) groups across the C6–C3–C6 backbone serve as the primary determinant of Hydrogen Atom Transfer (HAT) and Single Electron Transfer (SET) kinetics [29, 33].

The Ring B Catechol Motif (3′,4′-OH): The presence of an *ortho*-dihydroxy arrangement on Ring B represents the single most crucial structural feature conferring high radical scavenging capacity [29, 33]. Upon hydrogen abstraction by a reactive oxygen species (ROS) or nitrogen species (RNS), the catechol moiety forms a resonance-stabilized *semiquinone* radical, which readily undergoes a

second oxidation step to yield a stable *ortho*-quinone [29, 33]. This feature dramatically lowers the bond dissociation enthalpy (BDE) of the phenolic O–H bonds [29].

Ring A Hydroxylation (5,7-OH): Phenolic hydroxyl groups at the C5 and C7 positions of Ring A contribute secondary radical scavenging capacity [33]. Specifically, the C5–OH group forms a strong intramolecular hydrogen bond with the adjacent C4-carbonyl oxygen on Ring C [31, 33]. This intramolecular interaction stabilizes the parent molecule and alters the electron density of the pyrone ring, enhancing overall delocalization upon radical formation [31, 33].

Impact of Modification (O-Methylation and Glycosylation): Recent mechanistic evaluations demonstrate that masking free phenolic −OH groups through O-methylation or glycosylation drastically reduces direct thermodynamic radical scavenging capacity by increasing phenolic O–H BDE [31, 33].

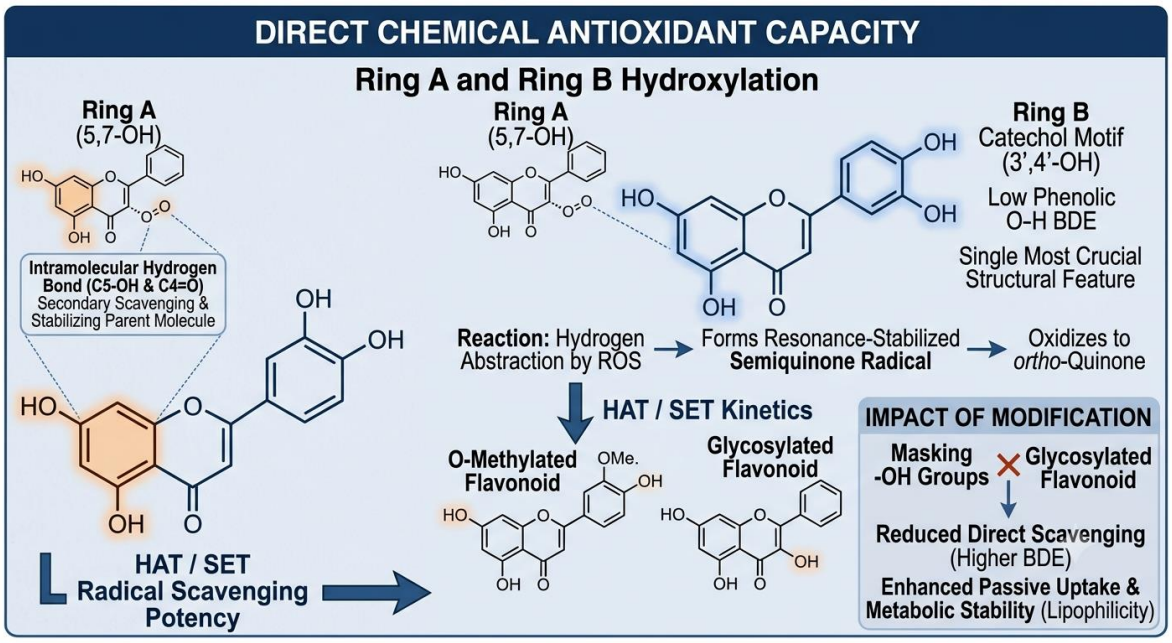

Figure 1. Overview of direct antioxidant actions of ring A and ring B hydroxyl groups in flavonoids.

However, O-methylation significantly increases lipophilicity and membrane permeability, frequently preserving or even enhancing intracellular redox signaling by improving passive uptake and metabolic stability in cell models [31- 35].

2.1.2 The C2=C3 Double Bond and C4-Oxo Conjugation Framework

The presence of a C2=C3 double bond in Ring C—characteristic of flavones and flavonols—exerts a profound dual effect on chemical stabilization and biochemical signaling [29, 32].

Planarity and Conjugation: The C2=C3 unsaturation flattens the heterocyclic C-ring, forcing the A- and B-rings into a coplanar orientation [29]. This coplanarity extends the π-electron conjugation across the entire C6–C3–C6 system, permitting radical electrons formed on Ring B to delocalize seamlessly across the C4-keto group and Ring A [29, 33]. Consequently, saturated analogues (such as flavanones and flavan-3-ols lacking the C2=C3 double bond) exhibit significantly lower electron delocalization capacity and lower radical quenching rate constants [29, 33].

Electrophilic Enone Formation and Keap1–Nrf2 Activation: Beyond direct radical neutralization, the combination of a C2=C3 double bond and a C4-carbonyl group creates an α,β-

unsaturated enone system [32, 34]. This conjugated structural motif acts as a soft electrophilic Michael acceptor capable of undergoing reversible alkylation with nucleophilic thiols [32, 34]. Specifically, this moiety targets hyper-reactive cysteine residues (most notably Cys151, Cys273, and Cys288) on the Kelch-like

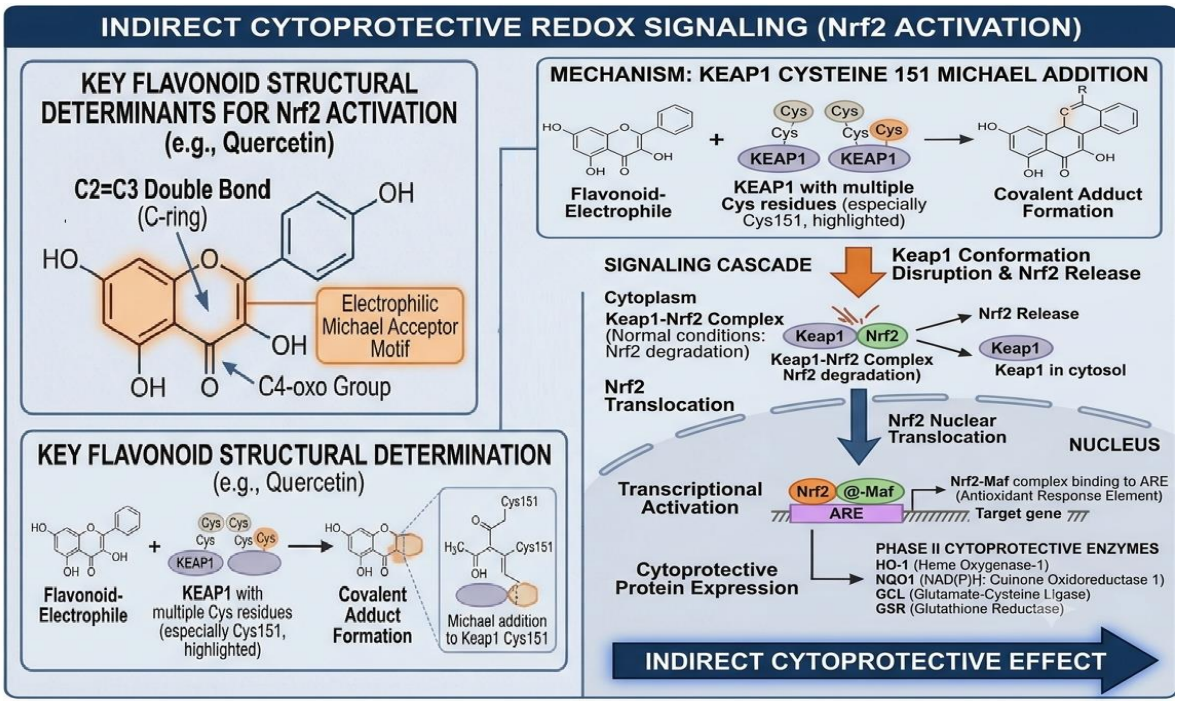

Figure 2. Overview of indirect cytoprotective redox signaling of flavonoids.

ECH-associated protein 1 (Keap1) sensor [32- 38]. Covalent modification or conformational disruption of Keap1 prevents the ubiquitination and degradation of Nuclear factor erythroid 2-related factor 2 (Nrf2), triggering Nrf2 nuclear translocation and binding to Antioxidant Response Elements (ARE) [30, 32, 38]. This signaling cascade induces Phase II cytoprotective enzymes, including Heme Oxygenase-1 (HO-1) and NAD(P)H:quinone oxidoreductase 1 (NQO1) [30, 32, 35].

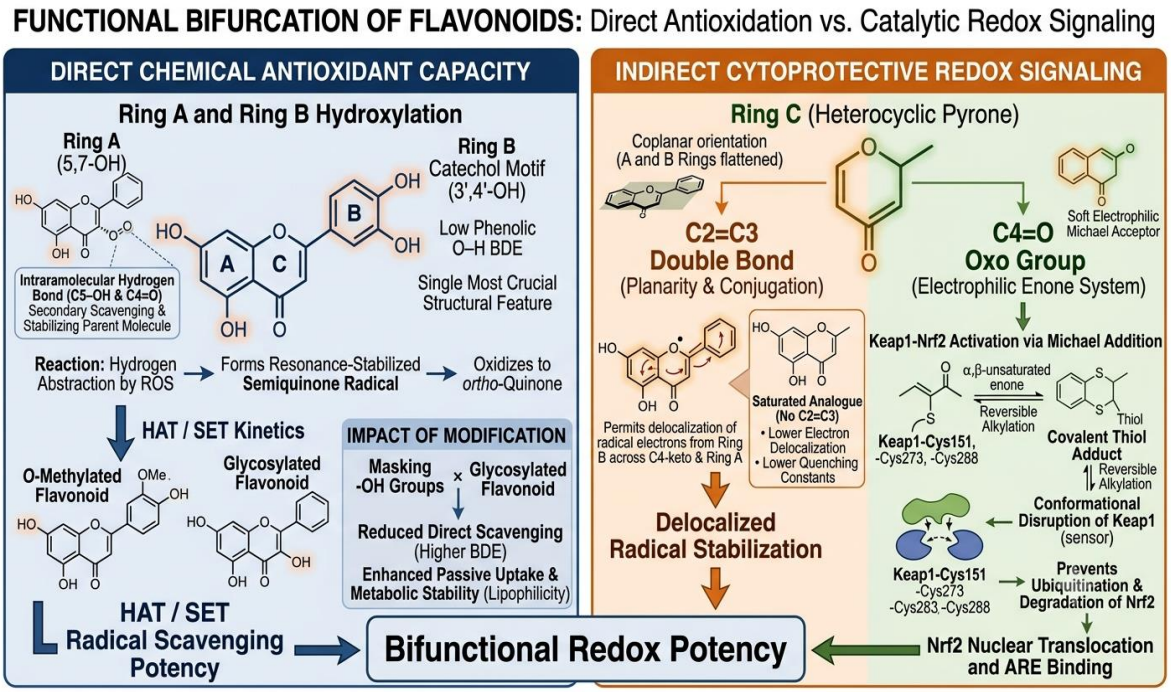

Figure 3. Diagramatic overview of functional bifurcation of flavonoids.

2.1.3 Backbone Variations and Functional Redox Modulation

Structural transformations that alter the geometry of the three-carbon bridge (C3) redistribute the molecule's redox activity profile [29, 34]:

Table 1. Structure-activity relationship (SAR) and redox potency of flavonoid subclasses.

Structural Subclass	Backbone Feature	Direct Radical Scavenging Potency	Nrf2/Keap1 Electrophilic Signaling	Key Structural SAR Driver
Flavonols (e.g., Quercetin, Kaempferol)	C2=C3 bond, C4=O, 3-OH, 3′,4′-OH	Very High	High	Full planarity, C3-OH extension, catechol B-ring, conjugated enone [29, 31].
Flavones (e.g., Luteolin, Apigenin)	C2=C3 bond, C4=O, lacks 3-OH	Moderate–High	High	Planar conjugation intact; lacks C3-OH driving thermodynamic radical stabilization [29, 30].
Flavanones (e.g., Naringenin, Hesperetin)	Saturated C2–C3 bond, C4=O	Low	Moderate	Non-planar C-ring limits π-delocalization; relies on metabolic activation or A/B ring hydroxylation [29, 36].

Chalcones (e.g., Isoliquiritigenin)	Open-chain C3 bridge, α,β-unsaturated enone	Moderate	Very High	Highly flexible open scaffold with an exposed, highly reactive Michael acceptor enone [34, 37].
Isoflavones (e.g., Genistein, Daidzein)	Ring B attached at C3 position	Low–Moderate	Moderate	Altered geometry disrupts classic catechol delocalization; distinct receptor binding profile [29, 39].

Recent investigations confirm that structural features optimizing direct stoichiometry (such as maximal polyhydroxylation) do not strictly parallel those optimizing adaptive, gene-mediated redox responses [32, 39]. Open-chain chalcones and planar flavones possessing strong electrophilic features often act as superior inductors of endogenous enzymatic defenses relative to highly hydroxylated but chemically labile flavonols [34, 38]. Thus, the C6–C3–C6 architecture acts as a structural switch, balancing immediate chemical radical trapping with sustained transcriptional cellular protection [31, 32, 39, 40].

2.2. Phase I and Phase II Xenobiotic Metabolism: Systemic Handling of Phenolics: Sulfation (SULTs), Glucuronidation (UGTs), and Methylation (COMT)

Following oral ingestion, dietary phenolics and polyphenols encounter an extensive metabolic barrier across the gastrointestinal tract and hepatic parenchyma [41- 47]. While minor Phase I oxidative processes (mediated by cytochrome P450 monooxygenases) modify select phenolic structures through hydroxylation or demethylation, the predominant pathway governing systemic disposition is Phase II enzymatic conjugation [43, 46]. Phase II metabolism functions as a critical biotransformation mechanism designed to convert lipophilic xenobiotics into highly polar, hydrophilic metabolites, facilitating rapid renal and biliary excretion while limiting direct cellular toxicity [47, 48].

The systemic disposition of phenolics is predominantly governed by three specialized enzyme families:

Sulfotransferases (SULTs): SULT enzymes, primarily SULT1A1, SULT1A3, and SULT1E1, catalyze the transfer of a sulfonate group from 3′-phosphoadenosine-5′-phosphosulfate (PAPS) to the hydroxyl groups of phenolic rings [46]. This modification imparts a negative charge, significantly increasing aqueous solubility and altering systemic distribution. Intestinal SULT1A3 demonstrates high affinity for dietary flavonoids during enterocyte transit, representing a primary presystemic metabolic barrier [41, 49-51].

UDP-Glucuronosyltransferases (UGTs): UGTs, located in the endoplasmic reticulum of enterocytes and hepatocytes (specifically UGT1A1, UGT1A8, UGT1A9, and UGT2B7), transfer glucuronic acid from UDP-glucuronic acid (UDPGA) to target phenolic hydroxyl moieties [46, 48]. Glucuronidation represents the quantitatively dominant conjugation pathway for bulk phenolics such as quercetin, resveratrol, and epigallocatechin gallate (EGCG) [43, 51]. Glucuronide conjugates are actively transported across apical or basolateral membranes via Multidrug Resistance-Associated Proteins (MRP2 and MRP3), directing them toward biliary excretion or systemic circulation, respectively [47].

Catechol-O-Methyltransferases (COMT): COMT specifically targets phenolic structures containing a catechol moiety (dihydroxylated benzene rings, such as caffeic acid or luteolin) [43, 46]. Utilizing S-adenosyl-L-methionine (SAM) as a methyl donor, COMT transfers a methyl group to either the meta or para hydroxyl position [46]. Methylation reduces the number of free, reactive hydroxyl groups, blunting direct ROS-scavenging potential while altering lipophilicity and cellular uptake kinetics [43, 48].

The concerted activity of SULTs, UGTs, and COMT creates a systemic profile dominated almost exclusively by conjugated metabolites (sulfates, glucuronides, and methyl ethers) rather than unesterified parent aglycones [41, 51]. Although conjugation typically dampens the immediate in vitro radical-scavenging capacity of parent phenolics, these phase II conjugates serve as circulating pro-drug reservoirs that can undergo localized tissue-specific deconjugation via β-glucuronidase or sulfatase enzymes during inflammatory or metabolic stress [43, 47].

2.3. Microbial Biotransformation: Gut Microbiota-Derived Metabolites and Their Enhanced Systemic Bioactivity Compared to Parent Compounds

A substantial fraction of ingested phenolics—frequently exceeding 90–95% for complex flavonoids, polymeric proanthocyanidins, and bound phenolic acids—evades small intestinal absorption due to bulky glycosylation, high molecular weight, or structural rigidity [41, 49]. Upon reaching the distal ileum and colon, these unabsorbed compounds interact with the dense enzymatic machinery of the gut microbiota [40, 45]. Microbial biotransformation breaks down parent structures through deglycosylation, C-ring cleavage, dehydroxylation, demethylation, and hydrogenation, producing smaller, low-molecular-weight phenolic catabolites [40, 50].

Key Pharmacokinetic Shift: Parent polyphenols often exhibit transient plasma concentrations in the low nanomolar range (C_{max} < 0.1μM) and short half-lives ($t_{1/2}$ < 2 hours). In contrast, microbial-derived catabolites reach micromolar systemic concentrations (1–10 μM) and maintain extended circulation times ($t_{1/2}$ = 12–24 hours), establishing them as the primary drivers of systemic pharmacological activity [40, 49].

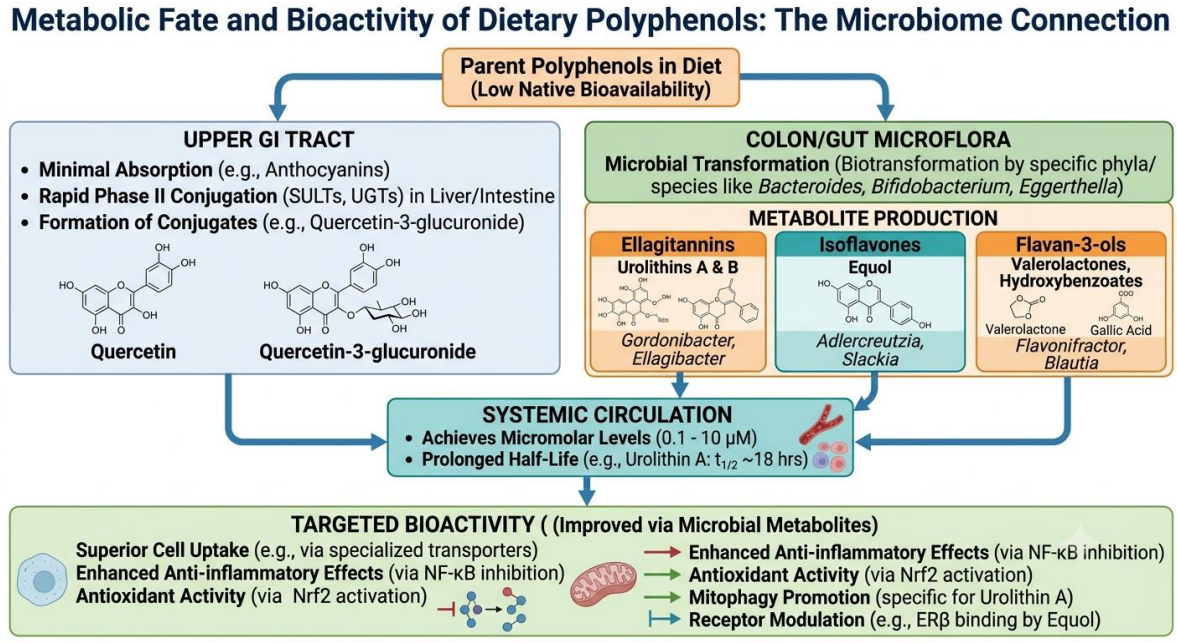

Figure 4. The metabolic fate and bioactivity of dietary polyphenols, emphasizing the crucial role of the gut microbiome.

Ellagitannins to Urolithins: High-molecular-weight ellagitannins and ellagic acid are cleaved by colonic microbiota (such as Gordonibacter urolithinfaciens and Ellagibacter isourolithinifaciens) through sequential loss of lactone rings and hydroxyl groups to form urolithins (Urolithin A, B, C, and D) [40, 50]. Urolithin A displays significantly superior lipophilicity and cellular permeation compared to ellagic acid, acting as a potent inducer of mitophagy and mitochondrial quality control in musculoskeletal and neural tissues [40, 49].

Isoflavones to Equol: Daidzein undergoes microbial reduction to form equol, a reaction executed by specific gut bacterial strains (e.g., Adlercreutzia equolifaciens) [40, 50]. Equol exhibits an elevated binding affinity for estrogen receptor-beta (ER-β) and higher antioxidant capacity compared to its parent isoflavone daidzein, driving enhanced vasculoprotective and bone-sparing effects [40, 51].

Flavan-3-ols to Valerolactones: Polymeric catechol-containing flavan-3-ols are degraded into 5-(3′,4′-dihydroxyphenyl)-γ-valerolactones and low-molecular-weight phenylpropionic or benzoic acids [40, 41]. These smaller catabolites readily cross the intestinal epithelium and blood-brain barrier, executing anti-neuroinflammatory signaling through Nrf2 activation and NF-κB inhibition at concentrations unattainable by parent polymers [43, 49].

Thus, gut microbiota-derived metabolites exhibit enhanced systemic bioactivity, prolonged plasma exposure, and distinct receptor-binding profiles relative to their native parent molecules [40, 45, 49].

2.4. Modern Formulation Strategies: Nanocarriers (Liposomes, Polymeric Nanoparticles, Nano-Emulsions) Overcoming Low Aqueous Solubility and Rapid Clearance

The translational and clinical application of native phenolics remains severely restricted by their unfavorable physicochemical features: poor aqueous solubility (BCS Class II/IV classification), susceptibility to pH-dependent chemical degradation, rapid Phase II metabolic inactivation, and swift systemic or biliary clearance [41, 42, 52, 53]. To circumvent these pharmacokinetic limitations, modern pharmaceutical engineering leverages advanced nanocarrier delivery systems to shield active payloads, enhance intestinal permeation, and sustain systemic residence [42, 54].

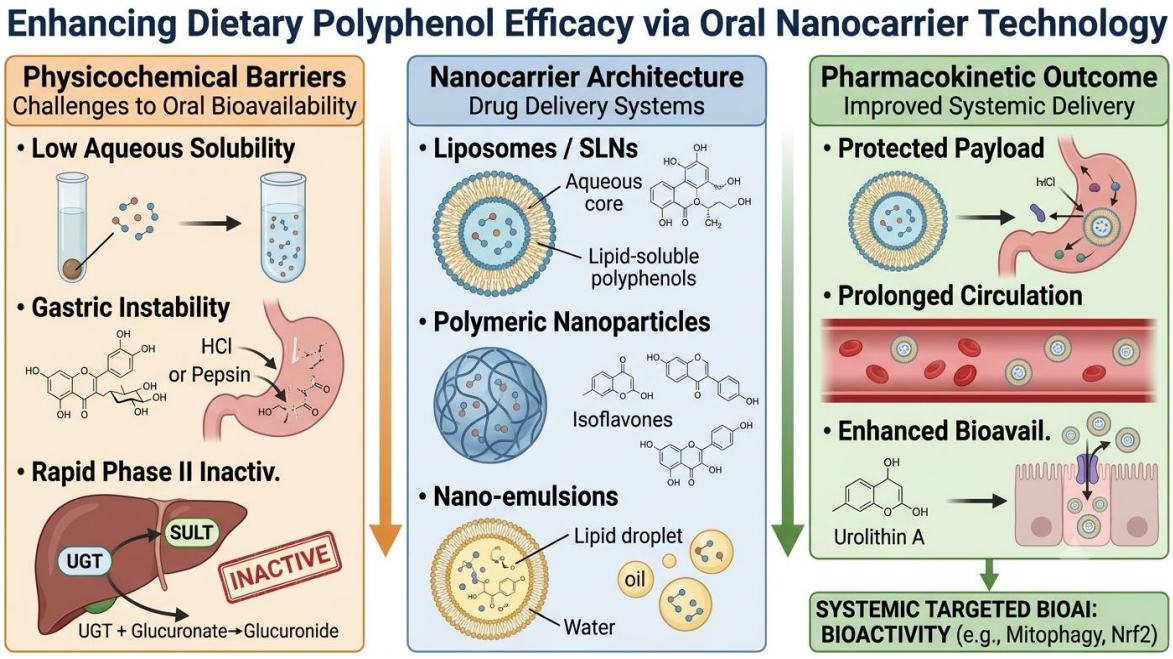

Figure 5. Nanotechnology-based strategies for enhancing the oral bioavailability and systemic efficacy of dietary polyphenols.

2.4.1 Liposomes and Lipid-Based Nanocarriers

Liposomes—spherical vesicles composed of concentric phospholipid bilayers surrounding an aqueous core—can simultaneously encapsulate hydrophobic phenolics within the lipid membrane and hydrophilic derivatives within the core [42, 55]. Phospholipid complexes protect phenolic hydroxyl groups from premature luminal oxidation and early intestinal UGT/SULT conjugation [42, 52]. Furthermore, liposomal surface modification with polyethylene glycol (PEGylation) creates a sterically protective hydration layer, inhibiting opsonization and clearance by the reticuloendothelial system (RES), thereby prolonging systemic circulation half-life [42, 52].

2.4.2 Polymeric Nanoparticles

Polymeric nanoparticles fabricated from biocompatible, biodegradable polymers—such as poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), chitosan, or synthetic block copolymers—encapsulate phenolic molecules within a solid polymeric matrix [42, 54]. These carriers enable controlled, diffusion- or erosion-driven zero-order release profiles, maintaining systemic drug concentrations within the therapeutic window [42, 54]. Chitosan-coated polymeric nanoparticles impart mucoadhesive properties that prolong mucosal residence time in the small intestine, enhancing endocytic cellular uptake and transcytosis via enterocytes and M-cells while bypassing hepatic first-pass metabolism via lymphatic transport pathways [42, 52, 54].

2.4.3 Nano-Emulsions and Self-Nanoemulsifying Drug Delivery Systems (SNEDDS)

Nano-emulsions are isotropic, thermodynamically stable or kinetically stable oil-in-water dispersions stabilized by surfactant and co-surfactant combinations, characterized by droplet dimensions typically under 100 nm [42, 53]. Encapsulating lipophilic phenolics (e.g., curcumin, resveratrol) within the inner oil phase dramatically elevates their apparent aqueous solubility and dissolution kinetics [42, 53]. Upon oral administration, nano-emulsion droplets promote the formation of mixed intestinal micelles, stimulating chylomicron assembly in enterocytes and directing the phenolic payload into the lymphatic circulation [53, 54]. This lymphatic transport mechanism avoids portal vein transit, successfully bypassing hepatic Phase II metabolic clearance and raising oral bioavailability by up to several orders of magnitude [42, 53, 55].

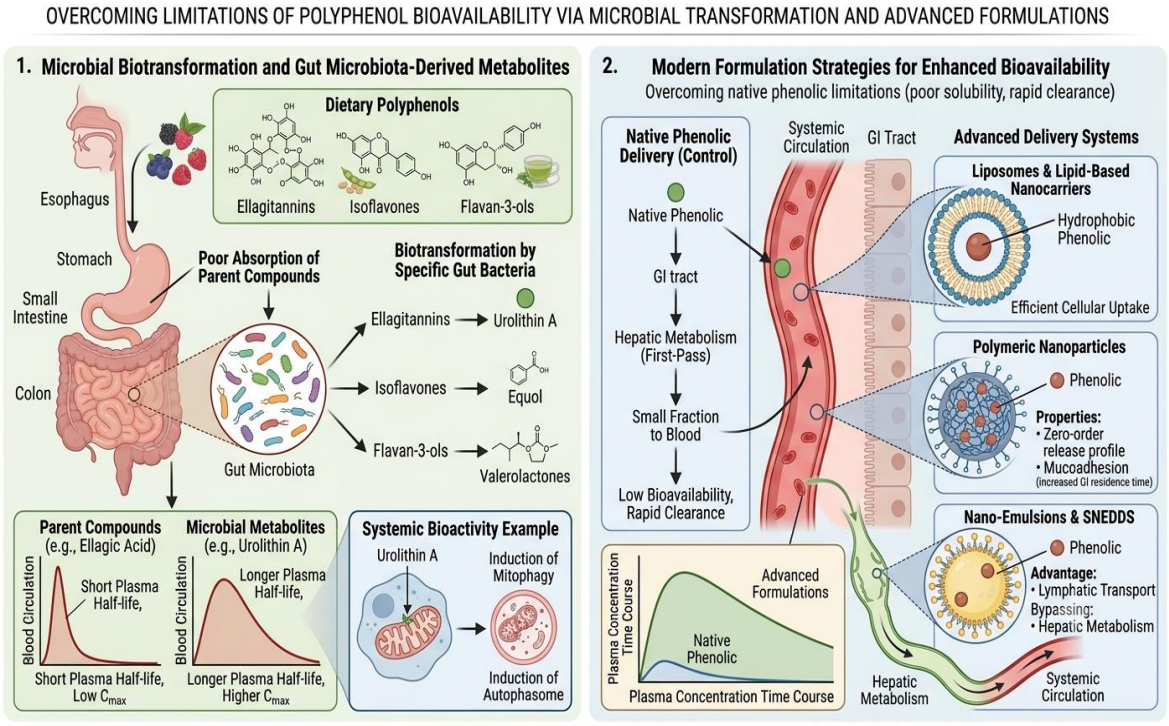

Figure 6. Overcoming limitations of polyphenol bioavailability: gut microbiota and advanced delivery systems. Panel 1: microbial biotransformation. Panel 2: modern formulation strategies.

3. Molecular Signaling Networks in Chemoprevention and Cellular Protection

Chemoprevention represents a proactive pharmacological strategy designed to arrest, reverse, or retard the multi-step process of carcinogenesis before clinical malignancy manifests [56]. In the liver, where sustained parenchymal injury, chronic necroinflammation, and regenerative hyperplasia create a fertile soil for malignant transformation, targeting specific molecular node networks provides a robust barrier against oncogenesis [57]. Effective chemopreventive agents modulate intricate signaling cascades that intersect inflammation, cell fate decisions, organelle quality control, and metabolic adaptation [58].

3.1. Suppression of Pro-Inflammatory Signaling: Cross-talk between NF-κB, STAT3, and COX-2 in Preventing Chronic Hepatitis-to-HCC Transition

The step-wise progression from chronic hepatitis and cirrhosis to hepatocellular carcinoma (HCC) is driven by persistent hepatic necroinflammation [59]. Central to this inflammatory-driven oncogenic continuum is a pathogenic signaling triad consisting of Nuclear Factor kappa B (NF-κB), Signal Transducer and Activator of Transcription 3 (STAT3), and Cyclooxygenase-2 (COX-2) [57]. Under conditions of chronic viral (HBV/HCV) infection, metabolic dysfunction-associated steatohepatitis (MASH), or toxic insults, activated kupffer cells and damaged hepatocytes continuously release pro-inflammatory cytokines, primarily Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α) [60, 61].

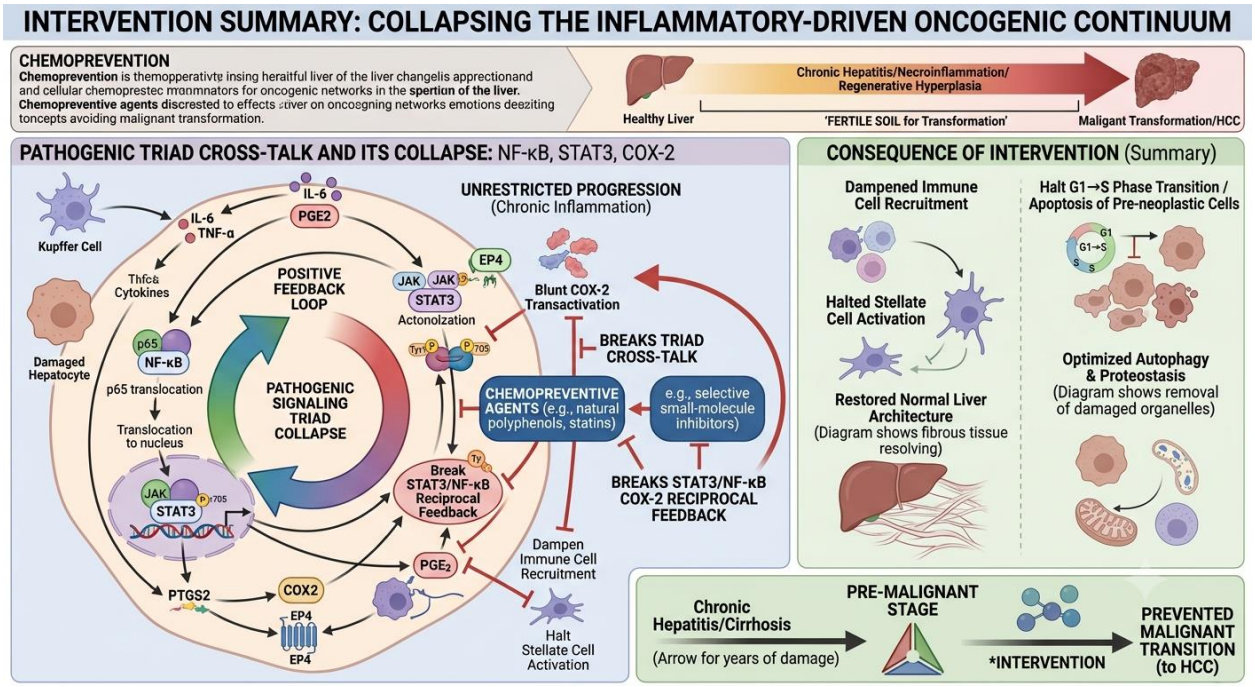

Figure 7. The pathogenic triad of NF-κB, STAT3, and COX-2 forms a self-sustaining feedback loop in the inflamed liver. Natural polyphenols and other chemopreventive agents can break this "triangular cross-talk," halting the transition from chronic hepatitis to liver cancer.

Mechanistically, NF-κB p65 translocation to the nucleus directly transactivates the PTGS2 gene (encoding COX-2), leading to elevated production of Prostaglandin E2 (PGE2) [60, 62]. Concurrently, IL-6-driven activation of Janus Kinases (JAK) induces STAT3 phosphorylation at Tyr705, promoting its dimerization and nuclear localization. Crucially, a positive feedback loop exists between NF-κB and STAT3; STAT3 prolongs NF-κB nuclear retention by mediating acetyltransferase-dependent p65 acetylation, while NF-κB maintains STAT3 activation through sustained cytokine output [60, 63]. PGE2 acting via its EP4 receptor further amplifies both pathways, creating a self-sustaining pro-survival, anti-apoptotic, and pro-angiogenic niche [62].

Suppressing this triangular cross-talk via targeted chemopreventive agents (e.g., natural polyphenols, statins, and selective small-molecule inhibitors) collapses this self-reinforcing loop [56, 59]. By blunting COX-2 transactivation and breaking the STAT3/NF-κB reciprocal feedback, chemopreventive intervention dampens hepatic immune cell recruitment, halts stellate cell activation, and restores normal liver architecture, effectively preventing malignant transition [61, 63].

3.2. Induction of Apoptosis and Cell Cycle Arrest: Extrinsic/Intrinsic Apoptotic Pathways (Bax/Bcl-2, Caspase Cascades) and Cyclins/CDKs Inhibition

Elimination of pre-neoplastic, dysplastic hepatocytes with accumulated DNA damage relies on the timely engagement of cell cycle arrest and programmed cell death mechanisms [64]. Chemopreventive molecules re-establish homeostatic surveillance by activating both intrinsic (mitochondrial) and extrinsic (death receptor-mediated) apoptotic cascades while simultaneously imposing checkpoints on hyper-proliferative cell cycles [64, 65].

At the mitochondrial level, the intrinsic apoptotic pathway is governed by the stoichiometric balance between pro-apoptotic (e.g., Bax, Bak) and anti-apoptotic (e.g., Bcl-2, Bcl-xL) members of the Bcl-2 family [65]. Dysplastic hepatocytes routinely overexpress Bcl-2, preventing outer mitochondrial membrane permeabilization (OMMP). Chemopreventive intervention shifts the Bax/Bcl-2 ratio

toward a pro-apoptotic state. Elevated Bax translocates to the outer mitochondrial membrane, inducing OMMP and releasing Cytochrome c into the cytosol [65]. Cytochrome c recruits Apaf-1 and pro-caspase-9 to assemble the apoptosome, triggering the cleavage-driven activation of executioner Caspase-3 and Caspase-7, leading to irreversible genomic DNA fragmentation and cell death [64, 65].

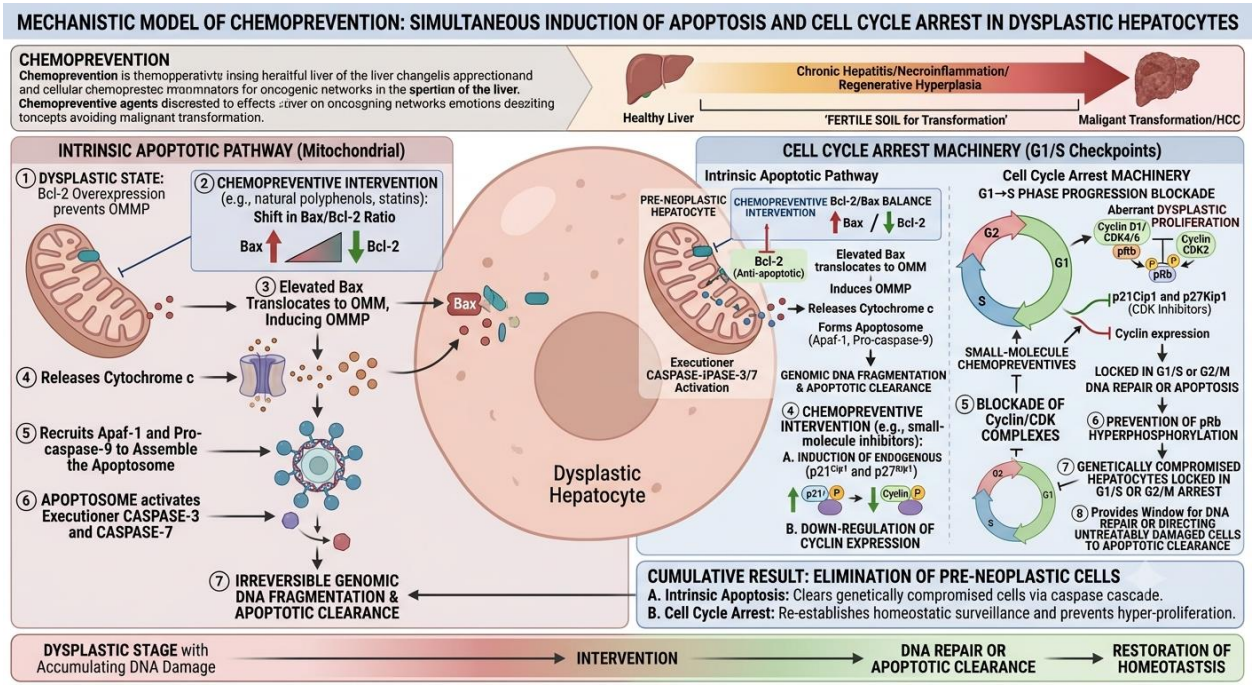

Figure 8. A comprehensive view of chemoprevention in pre-neoplastic hepatocytes, highlighting the shift in the Bax/Bcl-2 balance to trigger the intrinsic apoptotic pathway and the use of CDK inhibitors to impose essential G1/S checkpoints, leading to DNA repair or apoptotic clearance.

Simultaneously, chemopreventive agents disrupt aberrant dysplastic cell proliferation by targeting the Cyclin/Cyclin-Dependent Kinase (CDK) machinery [66]. Dysregulated Cyclin D1/CDK4/6 and Cyclin E/CDK2 complexes hyperphosphorylate the Retinoblastoma protein (pRb), driving unchecked G1→S phase transitions [66]. Small-molecule chemopreventives induce endogenous CDK inhibitors (p21Cip1 and p27Kip1) and down-regulate Cyclin expression. This dual mechanism ensures that genetically compromised hepatocytes are locked in G1/S or G2/M arrest, providing a window for DNA repair or directing untreatably damaged cells to apoptotic clearance [64, 66].

3.3. Autophagy and Proteostasis: Dual Role of Autophagy Induction (mTOR Suppression/AMPK Activation) in Clearing Damaged Organelles and Preventing Malignant Transformation

Autophagy is an evolutionarily conserved catabolic pathway critical for maintaining hepatic proteostasis and metabolic homeostasis [67]. In the context of early liver disease and chemoprevention, autophagy exhibits a distinct, stage-dependent dual role [67, 68]. During early hepatocarcinogenesis, basal and induced autophagy functions as an indispensable tumor-suppressive mechanism by eliminating damaged mitochondria (mitophagy), clearing toxic protein aggregates, suppressing reactive oxygen species (ROS) accumulation, and limiting genomic instability [68, 69].

At the signaling apex, autophagy is governed by the dynamic antagonistic balance between Mechanistic Target of Rapamycin Complex 1 (mTORC1) and AMP-Activated Protein Kinase (AMPK) [68]. Nutrient excess and oncogenic driver mutations hyperactivate the PI3K/Akt/mTORC1 pathway,

shutting down autophagic flux and permitting the accumulation of damaged organelles and oncogenic proteins [69].

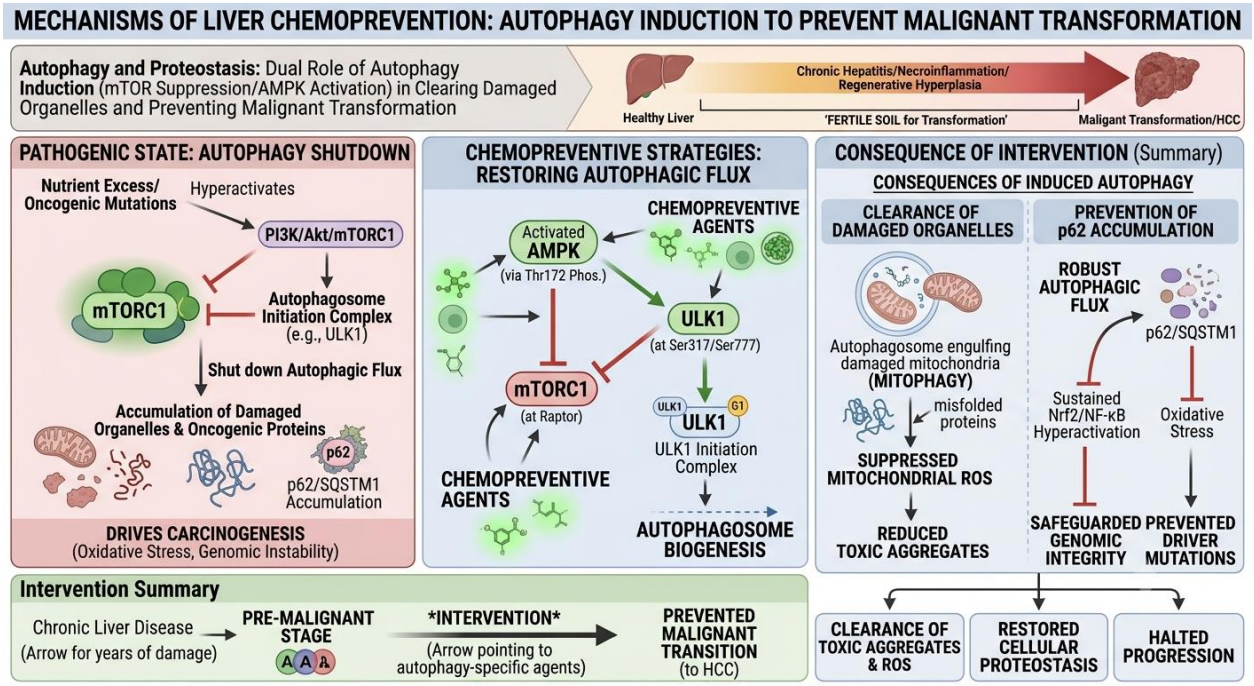

Figure 9. Mechanisms of liver chemoprevention via autophagy induction to prevent malignant transformation. The diagram illustrates the transition from a healthy liver to chronic inflammation and hepatocellular carcinoma (HCC), contrasting a pathogenic state of autophagy shutdown against chemopreventive strategies that restore autophagic flux.

At the signaling apex, autophagy is governed by the dynamic antagonistic balance between Mechanistic Target of Rapamycin Complex 1 (mTORC1) and AMP-Activated Protein Kinase (AMPK) [68]. Nutrient excess and oncogenic driver mutations hyperactivate the PI3K/Akt/mTORC1 pathway, shutting down autophagic flux and permitting the accumulation of damaged organelles and oncogenic proteins [69]. Chemopreventive strategies reactivate this cellular garbage-disposal system by either directly activating AMPK via Thr172 phosphorylation or inhibiting mTORC1 [68]. Activated AMPK phosphorylates ULK1 (at Ser317 and Ser777) and inhibits Raptor within mTORC1, thereby activating the initiation complex for autophagosome biogenesis [68, 70].

By sustaining robust autophagic flux, chemopreventive agents prevent p62/SQSTM1 accumulation—an adaptor protein whose pathological accumulation promotes oxidative stress and sustained Nrf2/NF-κB hyperactivation [69, 70]. Efficient clearance of depolarized mitochondria prevents mitochondrial ROS generation, thereby safeguarding genomic integrity and preventing dysplastic hepatocytes from acquiring driver mutations essential for malignant transformation [67, 70].

4. The Nrf2-ARE Axis and the "Metabolic Shield": Phase II Detoxification

The Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)–Antioxidant Response Element (ARE) signaling network serves as the primary master regulator of cellular xenobiotic detoxification and redox homeostasis. Functioning as a "metabolic shield," this pathway coordinates a multi-tiered defense system against oxidative stress, electrophilic insults, and reactive metabolic intermediates [71]. Under physiological baseline conditions, Nrf2 activity is kept tightly constrained to prevent metabolic waste and aberrant cell signaling. However, upon exposure to reactive oxygen species

(ROS) or electrophilic compounds, Nrf2 undergoes rapid stabilization and nuclear translocation, driving the transcriptional upregulation of a battery of cytoprotective, Phase II detoxifying, and antioxidant genes [72].

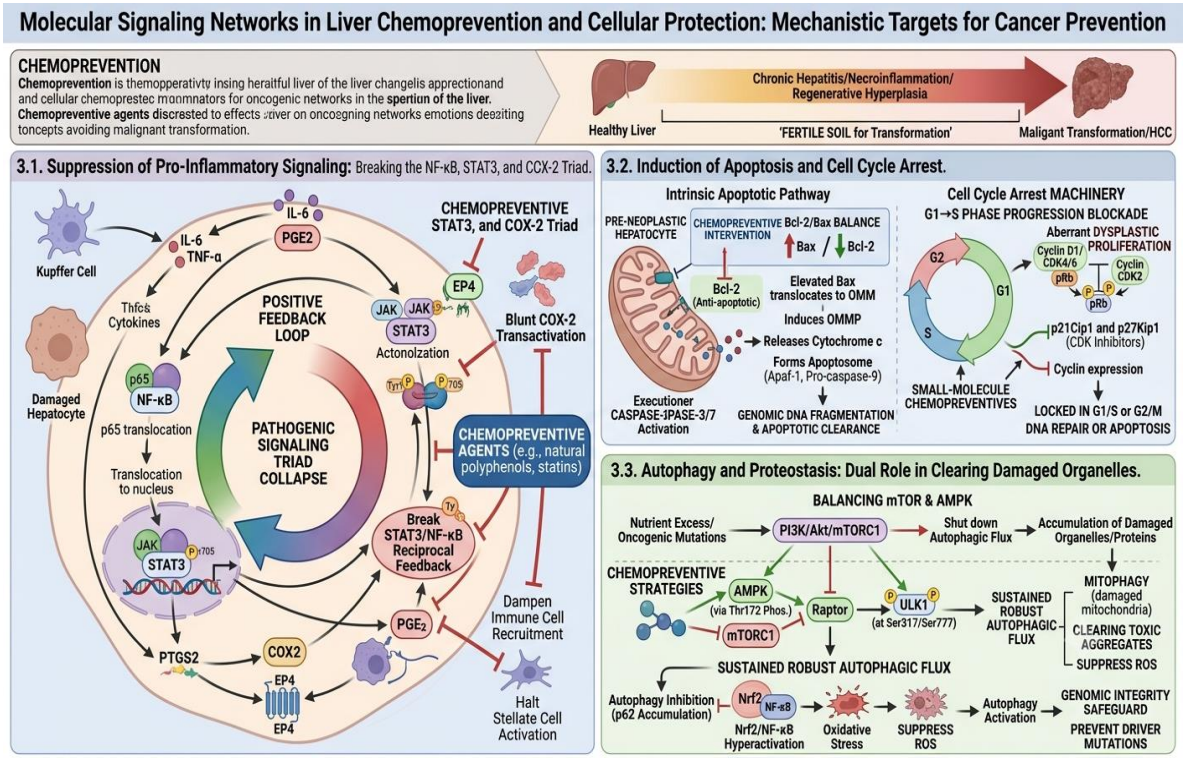

Figure 10. Figure X. Molecular signaling networks in liver chemoprevention and cellular protection. Schematic representation illustrating the primary mechanistic targets involved in preventing the progression of chronic hepatitis and necroinflammation toward malignant transformation into hepatocellular carcinoma (HCC).

4. The Nrf2-ARE Axis and the "Metabolic Shield": Phase II Detoxification

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4.1. Physiological Mechanics of Nrf2 Activation

Keap1-Dependent Regulation: Under homeostatic conditions, Nrf2 levels are regulated primarily through a Keap1-dependent degradation mechanism. Kelch-like ECH-associated protein 1 (Keap1) functions as a homodimeric substrate adaptor for the Cullin-3 (Cul3)–Ring Box Protein 1 (Rbx1) E3 ubiquitin ligase complex [73]. Keap1 binds Nrf2 in the cytoplasm via two distinct binding motifs within the Nrf2 Neh2 domain: a high-affinity "ETGE" motif and a low-affinity "DLG" motif [74]. This dual-latch interaction positions specific lysine residues within Nrf2 for polyubiquitination,

marking the transcription factor for rapid proteasomal degradation by the 26S proteasome, yielding a short half-life of approximately 15–20 minutes [75].

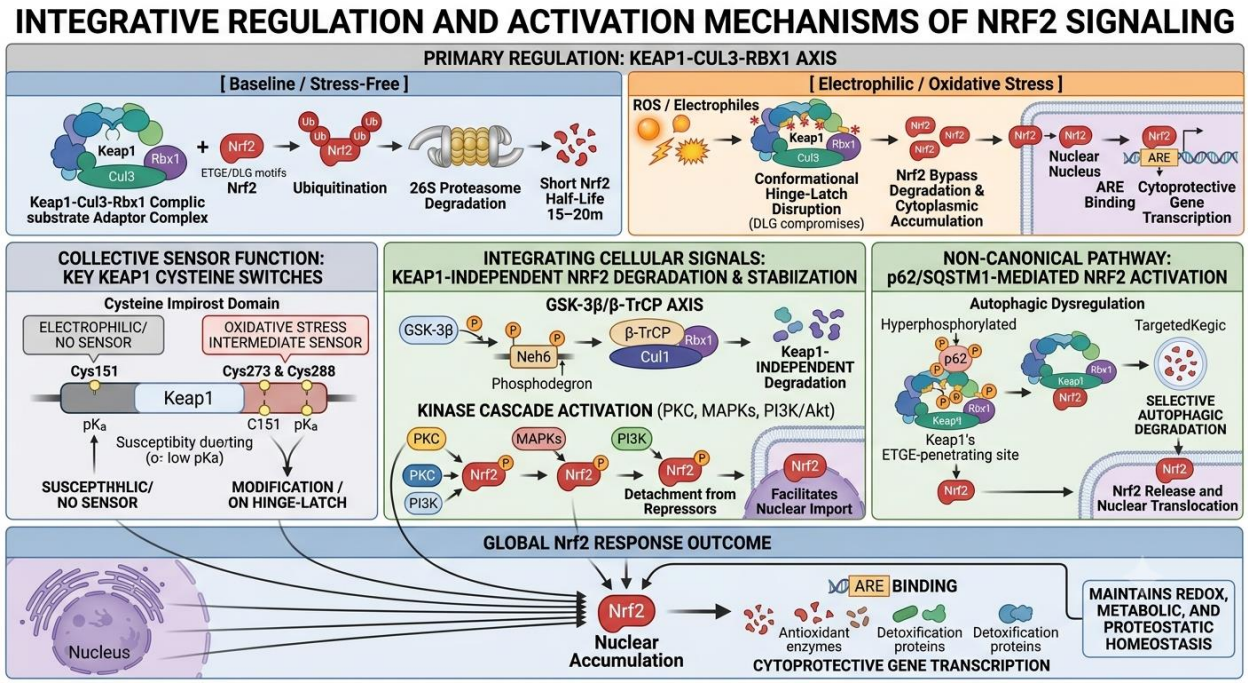

Figure 11. Integrative regulation and activation mechanisms of Nrf2 signaling. Schematic representation illustrating canonical, non-canonical, and kinase-mediated pathways governing Nrf2 stability and transcriptional activity.

The sensor capacity of Keap1 relies on its abundance of cysteine residues (27 cysteine residues in human Keap1), which exhibit low pK_a values and are highly susceptible to oxidation and electrophilic modification [76]. Specific reactive cysteines act as molecular switches:

Cys151: Primarily senses direct electrophilic stress and nitric oxide [77].

Cys273 and Cys288: Essential for sensing alkylating agents and oxidative stress intermediates [78].

When reactive species modify these critical thiol groups, Keap1 undergoes a conformational change that disrupts the "hinge-latch" mechanism, specifically compromising the low-affinity DLG interaction. Consequently, Nrf2 polyubiquitination ceases, causing Keap1 saturation and allowing newly synthesized Nrf2 to bypass degradation, accumulate in the cytoplasm, and translocate into the nucleus [79].

Keap1-Independent Regulation: Although Keap1 remains the primary repressor, Nrf2 stabilization is additionally governed by Keap1-independent mechanisms that integrate cellular energy, growth, and stress signals:

GSK-3β/ β-TrCP Axis: Glycogen synthase kinase-3 beta (GSK-3β) phosphorylates specific serine residues in the Neh6 domain of Nrf2, creating a phosphodegron recognized by the β-transducin repeat-containing protein (β-TrCP)–Cul1 E3 ligase complex, targeting Nrf2 for degradation independently of Keap1 [80].

Kinase Phosphorylation Cascades: Upstream signaling pathways—including Protein Kinase C (PKC), Mitogen-Activated Protein Kinases (MAPKs: p38, ERK, JNK), and Phosphoinositide 3-kinase

(PI3K/Akt)—phosphorylate Nrf2 at distinct residues (e.g., Ser40 by PKC), promoting its detachment from repressor complexes and facilitating nuclear import [81].

p62/SQSTM1 Autophagic Pathway: Non-canonical Nrf2 activation occurs via the autophagy receptor p62/SQSTM1. Upon autophagic dysregulation or p62 hyperphosphorylation, p62 directly binds to the ETGE-penetrating site on Keap1, competitively displacing Nrf2 and targeting Keap1 for selective autophagic degradation [82].

4.2. Transcriptional Profiling of Phase II Enzymes

Upon entry into the nucleus, Nrf2 heterodimerizes with small Maf proteins (sMaf: MafF, MafG, MafK). This heterodimer binds to the Antioxidant Response Element (ARE; core consensus sequence: 5'-TGACnnnGC-3'), located in the promoter regions of target genes, orchestrating the activation of Phase II detoxification enzymes [83].

Glutathione S-Transferases (GSTs): Glutathione S-transferases (e.g., GSTA, GSTP, GSTM families) catalyze the nucleophilic addition of reduced glutathione (GSH) to non-polar, electrophilic centers of exogenous xenobiotics and endogenously generated lipid hydroperoxides [84]. By neutralizing electrophiles, GSTs render hydrophobic toxins water-soluble, facilitating their active extrusion via multidrug resistance-associated proteins (MRPs/ABCC transporters) [85].

NAD(P)H: Quinone Oxidoreductase 1 (NQO1): NQO1 is a flavoprotein that catalyzes the obligate two-electron reduction of reactive quinones, quinone imines, and azo dyes directly to stable hydroquinones [86]. By bypassing single-electron reductions, NQO1 prevents the formation of unstable semiquinone radicals and the subsequent generation of superoxide anion radicals (O^{2-}), acting as a crucial enzymatic safeguard against redox cycling and oxidative membrane injury [87].

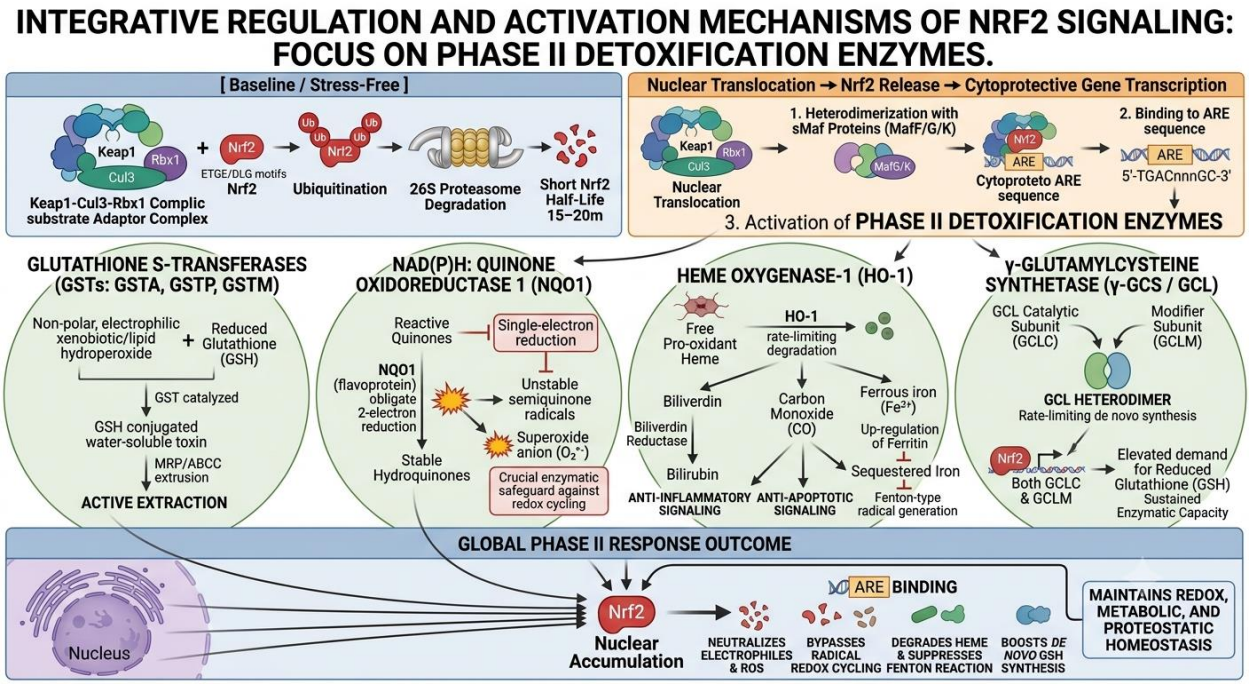

Figure 12. Integrative regulation of Nrf2 signaling with a focus on Phase II detoxification enzymes. Schematic representation showing Nrf2 suppression under basal conditions, its activation pathways, and downstream transcriptional upregulation of key Phase II cytoprotective enzymes.

Heme Oxygenase-1 (HO-1): HO-1 is an inducible stress-response enzyme that catalyzes the rate-limiting degradation of free pro-oxidant heme into carbon monoxide (CO), free ferrous iron (Fe^{2+}), and biliverdin [88]. Biliverdin is rapidly converted by biliverdin reductase into bilirubin, a potent lipophilic scavenger of peroxyl radicals. Simultaneously, CO exerts anti-inflammatory and anti-apoptotic signaling effects, while the released Fe^{2+} triggers the up-regulation of ferritin to sequester free iron, suppressing Fenton-type radical generation [89].

γ-Glutamylcysteine Synthetase (γ-GCS / GCL): γ-GCS (also designated Glutamate-Cysteine Ligase, GCL) is the rate-limiting enzyme in de novo glutathione synthesis. GCL operates as a heterodimer consisting of a catalytic subunit (GCLC) and a modifier subunit (GCLM) [90]. Nrf2 directly drives the transcription of both GCLC and GCLM, ensuring sustained enzymatic capacity to meet the elevated demand for reduced glutathione during Phase II conjugation and oxidative stress neutralization [91].

4.3. Glutathione System and Endogenous Antioxidant Repertoire

The protection conferred by the Nrf2-ARE axis extends beyond xenobiotic conjugation to encompass the maintenance of cellular redox potential through the continuous regeneration of antioxidant buffers and enzymatic ROS scavengers [92].

***4.3.1* Replenishment of GSH Pools:** Intracellular GSH pools are replenished through a coordinated two-pronged transcriptional program:

Biosynthesis and Import: Nrf2 transcriptionally upregulates the cystine/glutamate antiporter system x_c^-(specifically the sub-unit xCT/SLC7A11), which drives the cellular uptake of cystine—the rate-limiting amino acid precursor for GSH synthesis [93]. Concurrently, GCLC and GCLM synthesize γ-glutamylcysteine, which is subsequently converted into GSH by glutathione synthetase (GSS) [94].

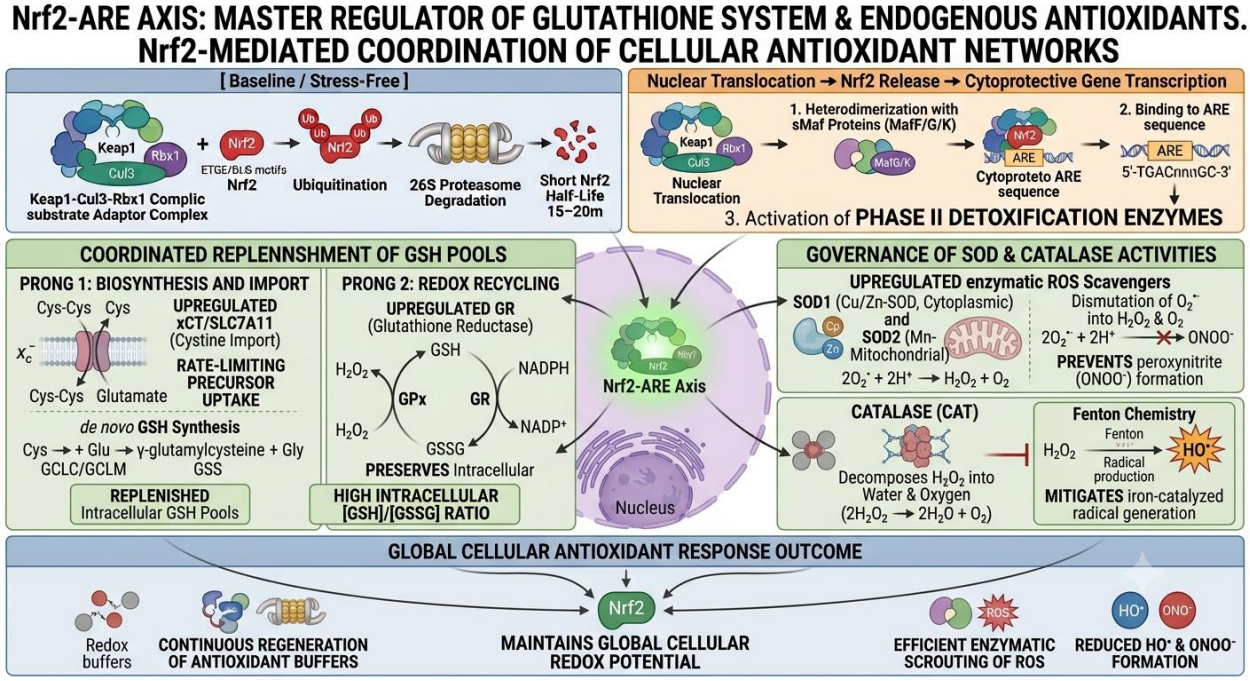

Figure 13. The Nrf2-ARE axis as a master regulator of the glutathione system and endogenous antioxidant networks. Schematic overview depicting basal regulation, nuclear transactivation, and downstream transcriptional control over cellular redox capacity.

Redox Recycling: During peroxide scavenging by glutathione peroxidase (GPx), GSH is oxidized to glutathione disulfide (GSSG). Nrf2 upregulates Glutathione Reductase (GR), an NADPH-dependent enzyme that reduces GSSG back to two molecules of GSH, preserving a high intracellular GSH/GSSG ratio essential for maintaining cellular thiol redox status [95].

4.3.2 Modulation of SOD and Catalase Activities

Nrf2 directly and indirectly governs the catalytic activity of primary enzymatic ROS scavengers:

Superoxide Dismutase (SOD): Nrf2 transcriptional programs promote the activity of SOD1 (Cu/Zn-SOD, cytoplasmic) and SOD2 (Mn-SOD, mitochondrial) [96]. SOD enzymes catalyze the dismutation of superoxide anions (O^{2-}) into hydrogen peroxide (H_2O_2) and molecular oxygen (O^2), preventing the formation of highly reactive peroxynitrite ($ONOO^-$) [97, 98].

Catalase (CAT): Catalase decomposes H_2O_2 into water and molecular oxygen without requiring electron donors. Nrf2 crosstalk regulates CAT expression, preventing the accumulation of H_2O_2 and mitigating the risk of iron-catalyzed hydroxyl radical (HO^-) production via Fenton chemistry [99].

4.4. Electrophilic Scavenging and Excretion Mechanics

Carcinogenesis frequently initiates through the metabolic bioactivation of pro-carcinogens by Phase I cytochrome P450 (CYP450) enzymes into highly reactive electrophilic intermediates. These electrophiles bind covalently to nucleophilic centers in DNA, forming bulky DNA adducts (e.g., 8-OHdG, N^7-guanine adducts) that induce replication fork arrest, double-strand breaks, and oncogenic mutations [100].

The Nrf2-mediated Phase II response interrupts this cascade through precise detoxification and excretion mechanics [100, 101]:

Direct Electrophilic Scavenging: Nrf2-driven GSTs accelerate the conjugation of GSH to electrophilic xenobiotic metabolites, sterically blocking their access to genomic DNA [102].

Mercapturic Acid Pathway and Efflux: Conjugated xenobiotics (GSH-electrophile adducts) are recognized by Phase III ATP-binding cassette (ABC) efflux transporters, such as MRP1 and MRP2, which are also target genes of Nrf2 [103]. These pumps actively export the conjugates across cell membranes into bile or systemic circulation for renal excretion. In the kidneys and liver, these conjugates undergo sequential enzymatic cleavage by γ-glutamyltranspeptidase and dipeptidases, followed by N-acetylation to yield water-soluble mercapturic acid derivatives excreted in urine [104].

Table 2. Integrated multi-step detoxification cascade for genomic integrity. Schematic summary of Phase I bioactivation (CYP450), Nrf2-mediated Phase II conjugation/reduction (GSTs, NQO1), and Phase III efflux (MRP/ABCC), demonstrating how coordinated xenobiotic clearance prevents DNA adduct formation and guards against carcinogenesis.

Pathway Component	Molecular Mechanism	Functional Outcome
Phase I Bioactivation	Cytochrome P450 oxidation	Converts inert pro-carcinogens into reactive electrophiles

Nrf2 Phase II Induction	GSTs and NQO1 upregulation	Conjugates GSH to electrophiles; reduces reactive quinones
Phase III Efflux	MRP/ABCC transporter activation	Translocates hydrophilic conjugates into bile and urine
Genomic Protection	Interruption of DNA adduct formation	Suppresses mutations, chromosome breaks, and carcinogenesis

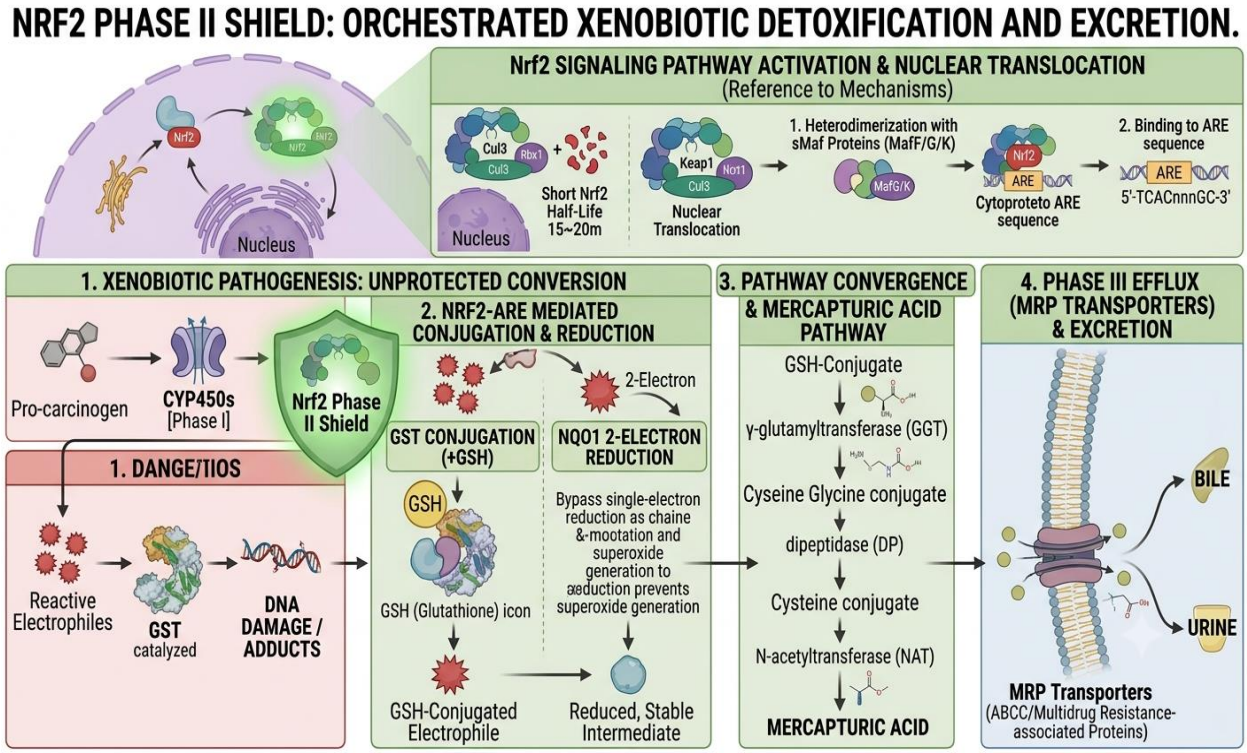

Figure 14. Coordinated multi-stage xenobiotic clearance via the Nrf2 Phase II shield. Cytochrome P450-mediated Phase I bioactivation converts inert pro-carcinogens into reactive electrophiles capable of inducing DNA adducts. Activation of the Nrf2-ARE pathway counteracts this toxicity by driving (1) GST-catalyzed glutathione (GSH) conjugation and NQO1-mediated two-electron reduction; (2) metabolic conversion through the mercapturic acid pathway (involving GGT, DP, and NAT enzymes); and (3) Phase III active transport via MRP/ABCC efflux pumps for final excretion into bile and urine.

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Prevention of Genomic Instability: By accelerating the turnover and excretion of electrophiles, the Nrf2-ARE axis prevents the formation of mutagenic DNA adducts, maintains genomic fidelity, and prevents initial driver mutations in proto-oncogenes (e.g., RAS) and tumor suppressor genes (e.g., TP53) [105].

5. The "Nrf2 Paradox" and Dual Roles in Cancer Biology

Nuclear factor erythroid 2-related factor 2 (NRF2) represents a classic biological double-edged sword in oncology, giving rise to the well-documented "Nrf2 Paradox" [106, 107]. Under physiological homeostasis, NRF2 functions as the master transcription factor governing cellular defense against oxidative, electrophilic, and xenobiotic insults by transactivating genes bearing Antioxidant Response Elements (AREs) [106, 108]. However, while transient NRF2 activation shields non-malignant tissues from malignant transformation, sustained and constitutive hyperactivation of NRF2 in established neoplastic lesions drives tumorigenesis, metabolic reprogramming, immune evasion, and resistance to radio- and chemotherapy [107, 109].

5.1. Chemoprevention vs. Chemoresistance: The Biphasic/Hormetic Nature of Nrf2

The dual functionality of NRF2 operates along a distinct hormetic and temporal continuum. In healthy, non-transformed cells or pre-malignant microenvironments, **transient, tightly regulated activation** of NRF2 exhibits profound chemopreventive effects [106, 110]. By inducing Phase II detoxifying enzymes (e.g., NQO1, GSTs) and antioxidant systems (e.g., HO-1, GCLC, GCLM), NRF2 facilitates the rapid neutralization and clearance of chemical carcinogens and reactive oxygen species (ROS), thereby preventing oxidative DNA damage, genomic instability, and initial tumor initiation [107, 110].

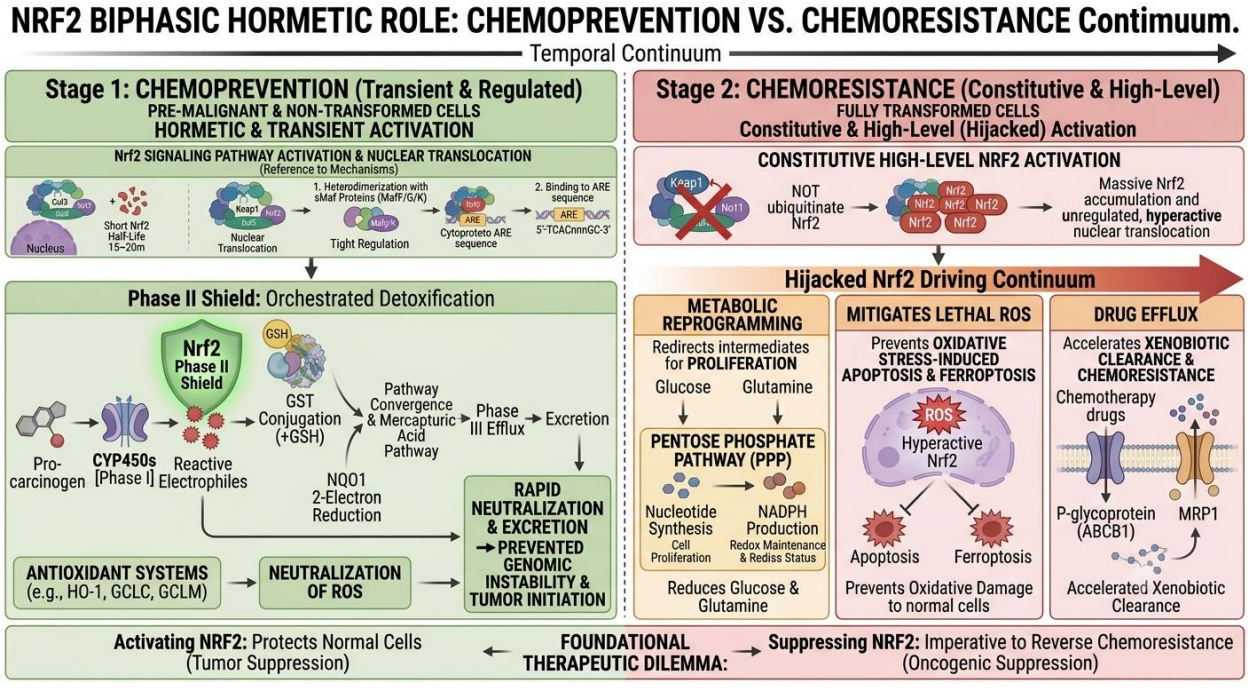

Figure 15. Conceptual overview of the biphasic role of Nrf2 signaling during tumor evolution. Stage 1 (Chemoprevention) and Stage 2 (Chemoresistance). This figure highlights the therapeutic challenge of activating Nrf2 for chemoprevention versus suppressing it to overcome drug resistance.

Conversely, once carcinogenesis progresses past the initiation phase to establish malignant lesions, cancer cells hijack this protective cellular defense mechanism [107- 118]. Under conditions of constitutive, high-level NRF2 activation, the transcription factor converts from a tumor suppressor into a potent oncogenic driver [109, 118]. In fully transformed cells, hyperactive NRF2:

Mitigates lethal ROS accumulation: Prevents oxidative stress-induced apoptosis and ferroptosis [107, 116].

Up-regulates drug efflux transporters: Boosts the expression of ATP-binding cassette (ABC) transporters, including P-glycoprotein (ABCB1) and MRP1, accelerating xenobiotic clearance [107, 111].

Drives metabolic reprogramming: Redirects glucose and glutamine intermediates toward the pentose phosphate pathway (PPP), bolstering nucleotide synthesis and NADPH production necessary for cell proliferation and redox maintenance [106, 108].

This biphasic dynamic creates the foundational therapeutic dilemma: activating NRF2 protects normal cells against carcinogenesis, whereas suppressing NRF2 is imperative to reverse chemoresistance in established refractory tumors [109, 110].

5.2. Somatic Mutations and Epigenetic Alterations

Constitutive activation of NRF2 in advanced malignancies rarely relies on transient physiological signaling; instead, it is primarily driven by permanent genetic, epigenetic, and post-translational dysregulations within the KEAP1–NRF2 axis [108, 112]. Under basal homeostatic conditions, Kelch-like ECH-associated protein 1 (KEAP1) acts as a substrate adaptor for the Cullin-3 (CUL3)-based E3 ubiquitin ligase complex, targeting NRF2 for rapid 26S proteasomal degradation [106, 108].

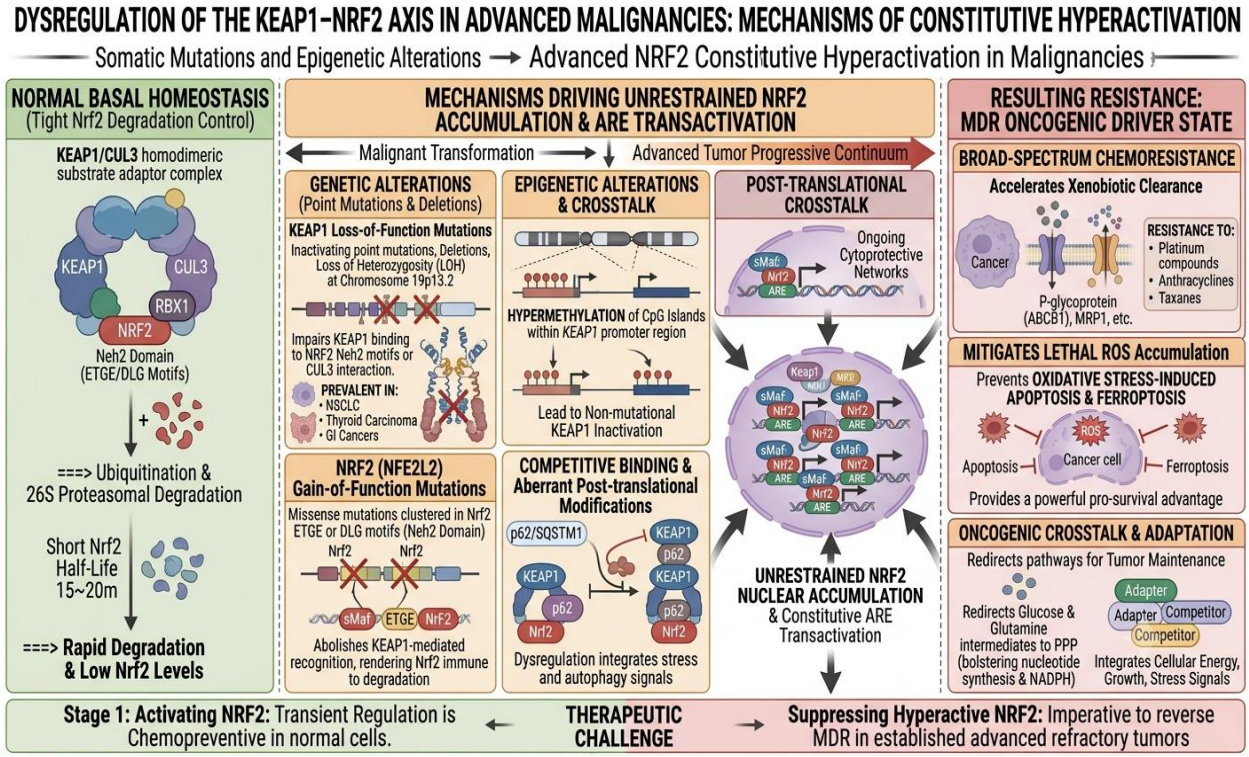

Figure 16. Dysregulation of the KEAP1–NRF2 axis in advanced malignancies and mechanisms of constitutive hyperactivation. Schematic overview illustrating the transition from normal physiological Nrf2 control to unrestrained constitutive transactivation driving a multidrug-resistant (MDR) oncogenic state.

Genetic disruptions resulting in persistent activation include:

KEAP1 Loss-of-Function Mutations: Inactivating point mutations, deletions, or loss of heterozygosity (LOH) at chromosome 19p13.2 impair KEAP1's ability to bind NRF2 or interact with

CUL3 [108, 112]. This is particularly prevalent in non-small cell lung cancer (NSCLC), thyroid carcinoma, and gastrointestinal cancers [106, 112].

NRF2 (NFE2L2) Gain-of-Function Mutations: Missense mutations occurring clustered within the high-affinity ETGE or low-affinity DLG motifs located in the Neh2 domain of NRF2 abolish KEAP1-mediated recognition, rendering NRF2 completely immune to ubiquitin-dependent degradation [106, 119].

Epigenetic Alterations: Hypermethylation of CpG islands within the KEAP1 promoter region, along with aberrant post-translational modifications or competitive binding by proteins such as p62/SQSTM1, further lead to non-mutational KEAP1 inactivation [106, 108, 119].

Together, these genetic and epigenetic alterations result in unrestrained NRF2 nuclear accumulation and ongoing expression of cytoprotective networks, rendering cancer cells resistant to broad-spectrum chemotherapeutics (e.g., platinum compounds, anthracyclines, taxanes) and radiation therapy [107, 112].

5.3. Strategic Timing of Interventions: Defining the Therapeutic Window

Exploiting the NRF2 axis in oncology requires precise temporal discrimination, matching the interventions strictly to the disease stage [110, 120].

Table 3. Therapeutic paradigm of NRF2 activation versus inhibition based on disease stage. Summary of stage-specific NRF2 strategies in oncology, contrasting transient activation against targeted inhibition.

Disease Phase	Primary Objective	Therapeutic Strategy	Bioactive Modulators / Agents
Healthy / Pre-Malignant (Prevention and Interception)	Boost endogenous redox defenses; clear electrophiles; prevent genomic instability	Transient NRF2 Activation	Dietary phenolics and electrophilic phytochemicals (e.g., Sulforaphane, Curcumin, Resveratrol) [110, 120]
Established Malignancy (Active Chemotherapy)	Collapse antioxidant barrier; restore drug sensitivity; trigger ROS-mediated death	Targeted NRF2 Inhibition	Small-molecule inhibitors (e.g., ML385), synthetic phenolics, or quassinoids (e.g., Brusatol) [111, 114, 117]

During early chemoprevention or disease interception, low-dose phenolic compounds act as mild electrophilic stressors that transiently modify critical cysteine residues on KEAP1 (e.g., Cys151), boosting cytoprotective capacity without causing long-term genetic dysregulation [110, 120].

In stark contrast, when treating established cancers exhibiting high baseline NRF2 expression or KEAP1 mutations, NRF2 activators are strictly counter-indicated as they further shield malignant cells from therapy [107, 109]. Instead, small-molecule NRF2 inhibitors—such as ML385 (which binds the CNC-bZIP domain of NRF2 to disrupt DNA binding) or Brusatol (which promotes NRF2 protein degradation)—must be co-administered alongside standard chemotherapy [111, 114, 117]. Inhibiting NRF2 during active treatment restores chemosensitivity, lowers the threshold for drug-induced oxidative damage, and overcomes multidrug resistance (MDR) in refractory solid tumors [107, 111, 114].

6. Transition to Systemic Metabolic Resilience in Chronic Liver Disease

Chronic liver pathology represents a dynamic, multi-stage continuum that spans metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis (MASH), progressive fibrosis, cirrhosis, and ultimately hepatocellular carcinoma (HCC) [121, 122]. A central driver throughout this continuum is the loss of metabolic resilience—the hepatic architecture's reduced capacity to buffer chronic nutrient surplus, oxidative stress, and lipotoxic strain [123]. Enhancing cellular stress defenses, particularly through master redox and metabolic regulators like the Nrf2-ARE pathway, restores metabolic homeostasis and provides therapeutic protection across all stages of chronic liver disease [124, 125].

6.1. MASLD/MASH to HCC Progression Pipeline

The progression from simple steatosis to MASH and HCC is driven by a "multi-hit" lipotoxic cascade within steatotic microenvironments [121, 123]. Under conditions of sustained caloric excess and peripheral insulin resistance, the liver receives an overwhelming flux of free fatty acids (FFAs), driving hyperactive de novo lipogenesis (DNL) [123].

Lipotoxicity and Lipid Peroxidation: When the influx of fat surpasses the oxidation and export capacities of hepatocytes, toxic lipid species accumulate—including saturated FFAs (e.g., palmitate), ceramides, diacylglycerols, and free cholesterol [126]. These lipotoxic intermediates directly induce organelle stress [126]. Excessive reactive oxygen species (ROS) attack polyunsaturated fatty acids (PUFAs) in hepatocellular membranes, initiating non-enzymatic lipid peroxidation (LPO) [127]. Highly reactive lipid aldehydes, such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), covalently modify cellular proteins and form mutagenic $M_{1\text{-}G}$ DNA adducts, directly promoting genomic instability and initiating hepatocarcinogenesis [124, 128, 129].

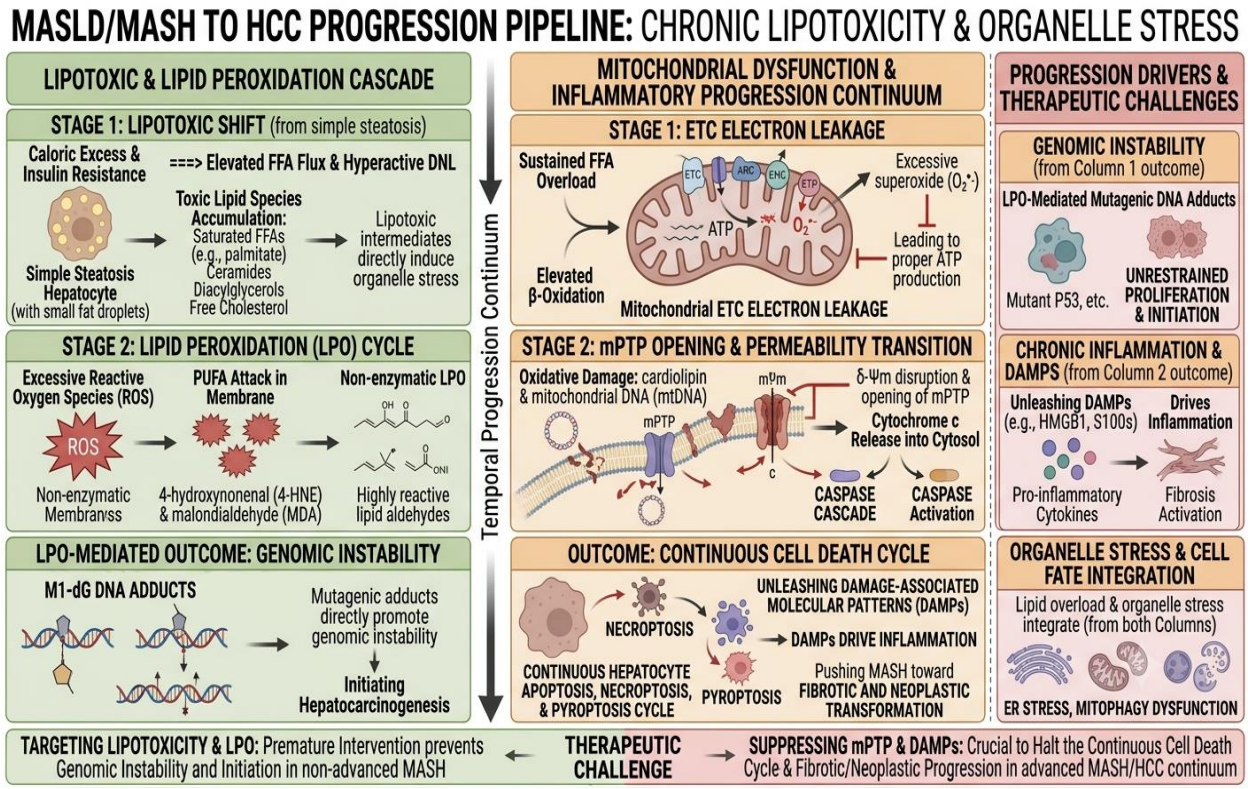

Figure 17. MASLD/MASH to HCC progression pipeline driven by chronic lipotoxicity and organelle stress. Schematic depicting the temporal continuum connecting metabolic lipid accumulation to

genomic instability, mitochondrial dysfunction, and malignant transformation into hepatocellular carcinoma (HCC).

Mitochondrial Dysfunction: Sustained FFA overload forces elevated β-oxidation within hepatic mitochondria, leading to electron transport chain (ETC) electron leakage and excessive superoxide (O^{2-}) generation [124]. Oxidative damage to mitochondrial DNA (mtDNA) and cardiolipin disrupts mitochondrial membrane potential δ-Psi_m, inducing the opening of the mitochondrial permeability transition pore (mPTP) [124]. The resulting release of cytochrome-c into the cytosol triggers caspase cascades and activates necroptosis and pyroptosis pathways [122]. This continuous cell death cycle unleashes damage-associated molecular patterns (DAMPs), driving inflammation and pushing MASH toward fibrotic and neoplastic transformation [125, 126].

6.2. Mitigation of Cirrhosis and Fibrogenesis

Hepatic fibrogenesis is the principal determinant of long-term liver mortality [127, 128]. The transition from reversible inflammation to irreversible cirrhosis depends on the persistent activation of hepatic stellate cells (HSCs), the primary cellular source of extracellular matrix (ECM) deposition [128, 129].

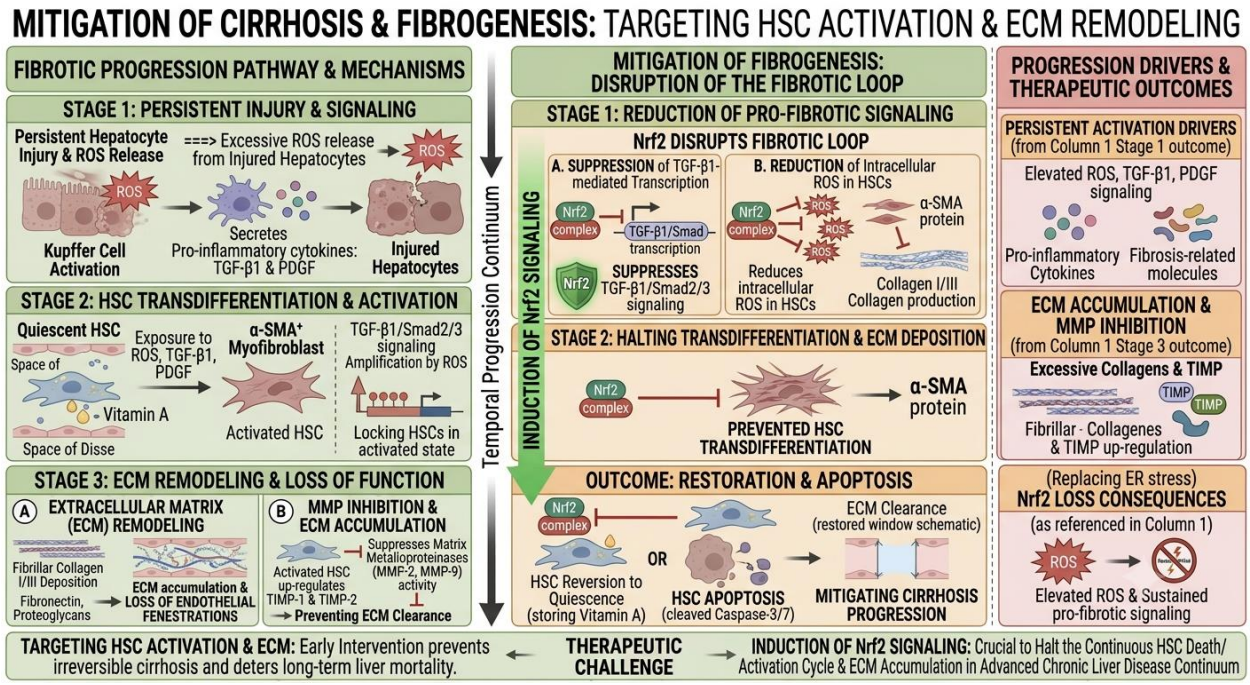

Figure 18. Mitigation of cirrhosis and fibrogenesis through targeting hepatic stellate cell (HSC) activation and extracellular matrix (ECM) remodeling. Schematic depicting the temporal continuum of fibrotic liver disease and the therapeutic disruption of the fibrotic loop by Nrf2 activation.

HSC Activation and Transdifferentiation: In a healthy liver, HSCs reside in the space of Disse in a quiescent, vitamin A-storing state [128]. Upon chronic oxidative damage and exposure to pro-inflammatory cytokines—primarily Transforming Growth Factor-beta 1 (TGF-β1) and Platelet-Derived Growth Factor (PDGF) secreted by injured hepatocytes and activated Kupffer cells—quiescent HSCs transdifferentiate into contractile, proliferative α-smooth muscle actin (α-SMA)-positive myofibroblasts [129, 130]. Intracellular ROS act as key second messengers that amplify TGF-β1 Smad2/3 signaling, locking HSCs in a activated, pro-fibrotic state [127, 131].

Extracellular Matrix Remodeling: Activated HSCs excessively secrete fibrillar collagens (Types I and III), fibronectin, and proteoglycans, leading to ECM accumulation and loss of endothelial fenestrations [129]. Simultaneously, HSCs up-regulate Tissue Inhibitors of Metalloproteinases (TIMP-1 and TIMP-2), suppressing Matrix Metalloproteinase (MMP-2, MMP-9) activity and preventing ECM clearance [129]. Induction of Nrf2 signaling disrupts this fibrotic loop by suppressing TGF-β1-mediated transcription, reducing intracellular ROS in HSCs, down-regulating α-SMA and collagen production, and promoting HSC apoptosis or reversion to quiescence [127, 131].

6.3. Tumor Microenvironment (TME) Remodeling

As MASH and cirrhosis progress to HCC, the tumor microenvironment (TME) undergoes extensive structural, metabolic, and immunological remodeling that supports tumor growth, immune evasion, and metastasis [132, 133].

6.3.1 Polarization of Tumor-Associated Macrophages (TAMs)

In the steatotic and cirrhotic TME, tumor-derived metabolic byproducts—particularly high concentrations of lactate—drive the repolarization of infiltrating monocytes and resident Kupffer cells into pro-tumorigenic M2-like Tumor-Associated Macrophages (TAMs) [132, 134]. These M2 TAMs (characterized by high expressions of CD163, CD206, and Arginase-1) secrete immunosuppressive cytokines (IL-10, TGF-β) that inhibit cytotoxic T-lymphocyte (CTL) activation, impair natural killer (NK) cell function, and recruit regulatory T cells (Tregs), forming an immune-evasive barrier around neoplastic foci [132, 133].

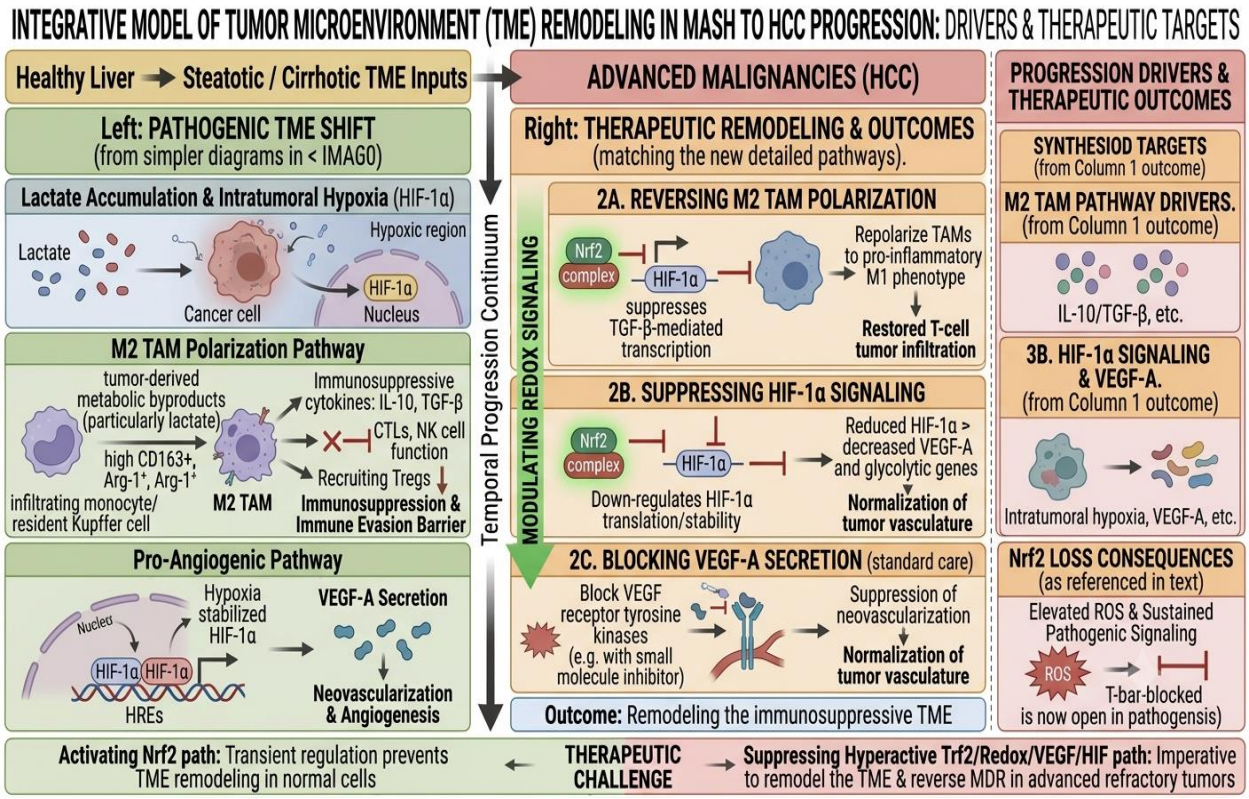

Figure 19. Integrative model of tumor microenvironment (TME) remodeling in MASH to HCC progression: Drivers and therapeutic targets. Schematic diagram depicting the pathogenic TME shift driven by metabolic and hypoxic stress, alongside therapeutic intervention strategies aimed at remodeling the immunosuppressive microenvironment in hepatocellular carcinoma (HCC).

6.3.2 Anti-Angiogenic Modulation via VEGF and HIF-1α Down-Regulation

Rapid tumor proliferation outpaces the local vascular supply, generating regions of severe intratumoral hypoxia [135]. Hypoxia stabilizes Hypoxia-Inducible Factor 1-alpha (HIF-1α) by preventing its prolyl-hydroxylation and degradation [134]. Nuclear HIF-1α forms a heterodimer with HIF-1β and binds Hypoxia Response Elements (HREs) to drive robust transcription of Vascular Endothelial Growth Factor A (VEGF-A), promoting abnormal neovascularization, vascular permeability, and metastatic dissemination [135, 136].

Modulating redox signaling pathways suppresses HIF-1α accumulation, decreases downstream VEGF expression, and reverses M2 TAM polarization [132, 135]. Restoring metabolic resilience attenuates pro-angiogenic signaling, normalizes tumor vasculature, and remodels the immunosuppressive microenvironment to improve therapeutic outcomes in advanced chronic liver disease and HCC [133, 136].

Table 4. Targeted strategies for remodeling the immunosuppressive and pro-angiogenic tumor microenvironment. Overview of TME progression pathways detailing their baseline pathological contributions: immunosuppressive M2 TAM polarization, hypoxia-driven HIF-1α stabilization, and VEGF-A-mediated neovascularization.

Pathway / Axis	Baseline Pathological Role in TME	Therapeutic Target and Outcome
M2 TAM Polarization	Secretes IL-10/TGF-β; suppresses CTLs; promotes immune evasion [132, 134]	Repolarize TAMs to pro-inflammatory M1 phenotype; restore T-cell tumor infiltration [132]
HIF-1α Signaling	Stabilized under intratumoral hypoxia; drives VEGF-A and glycolytic genes [135]	Down-regulate HIF-1α translation/stability; normalize tumor vasculature [135, 136]
VEGF-A Secretion	Induces abnormal angiogenesis, hyperpermeability, and metastasis [135, 136]	Block VEGF receptor tyrosine kinases; suppress neovascularization [136]

7. Translational Challenges, Clinical Evidence, and Future Horizons

7.1. Analysis of Preclinical vs. Clinical Data: Critical Evaluation of Human Clinical Trials

Despite robust preclinical evidence demonstrating the potent chemopreventive and anti-inflammatory mechanisms of bio-active phenolic compounds, translation into human clinical settings remains hampered by systemic discrepancies [137].

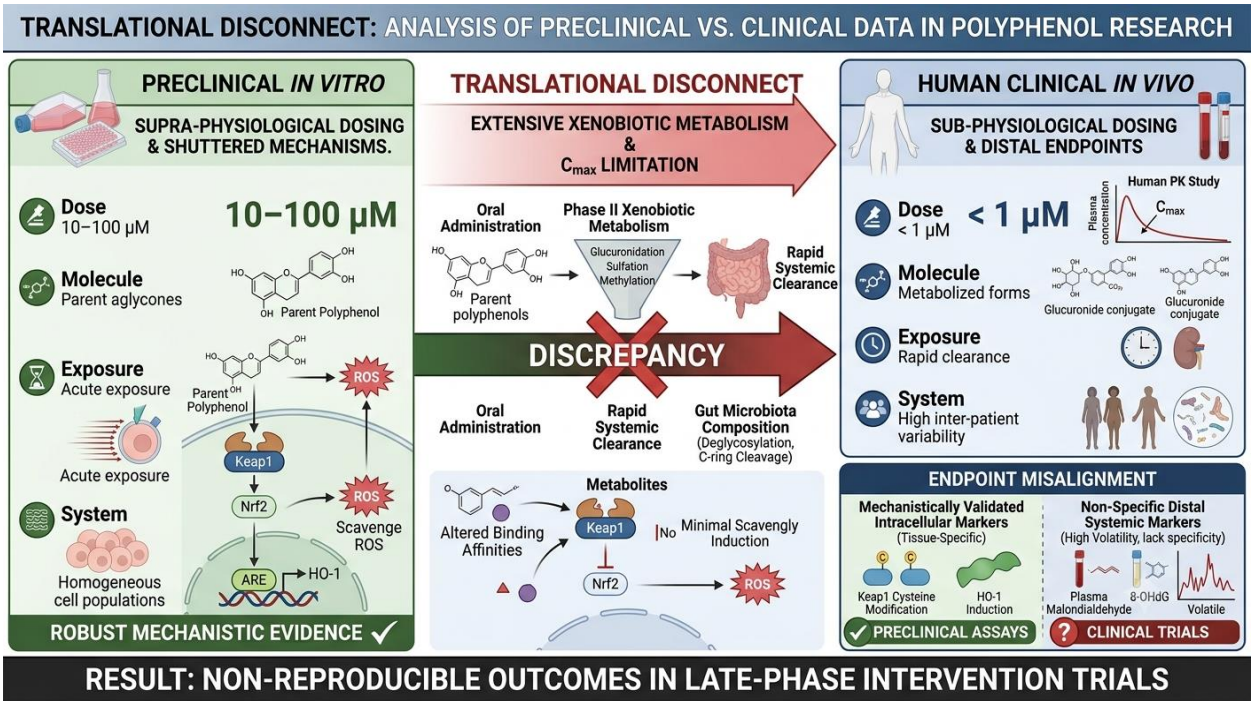

Figure 20. Translational disconnect: analysis of preclinical versus clinical data in polyphenol research. Schematic comparison illustrating the methodological and pharmacokinetic discrepancies that drive non-reproducible outcomes in late-phase clinical trials.

In vitro assays routinely utilize supra-physiological concentrations (e.g., 10–100\ µM) of un-metabolized parent polyphenols to demonstrate nuclear factor erythroid 2-related factor 2 (Nrf2) activation and reactive oxygen species (ROS) scavenging [138]. However, human pharmacokinetic (PK) studies reveal that oral administration yields peak plasma concentrations (C_{max}) rarely exceeding 1 µM due to extensive phase II xenobiotic metabolism—principally glucuronidation, sulfation, and methylation—and rapid systemic clearance [1367, 139]. Consequently, circulating bio-active metabolites often exhibit altered binding affinities for target proteins compared to their parent aglycones [140].

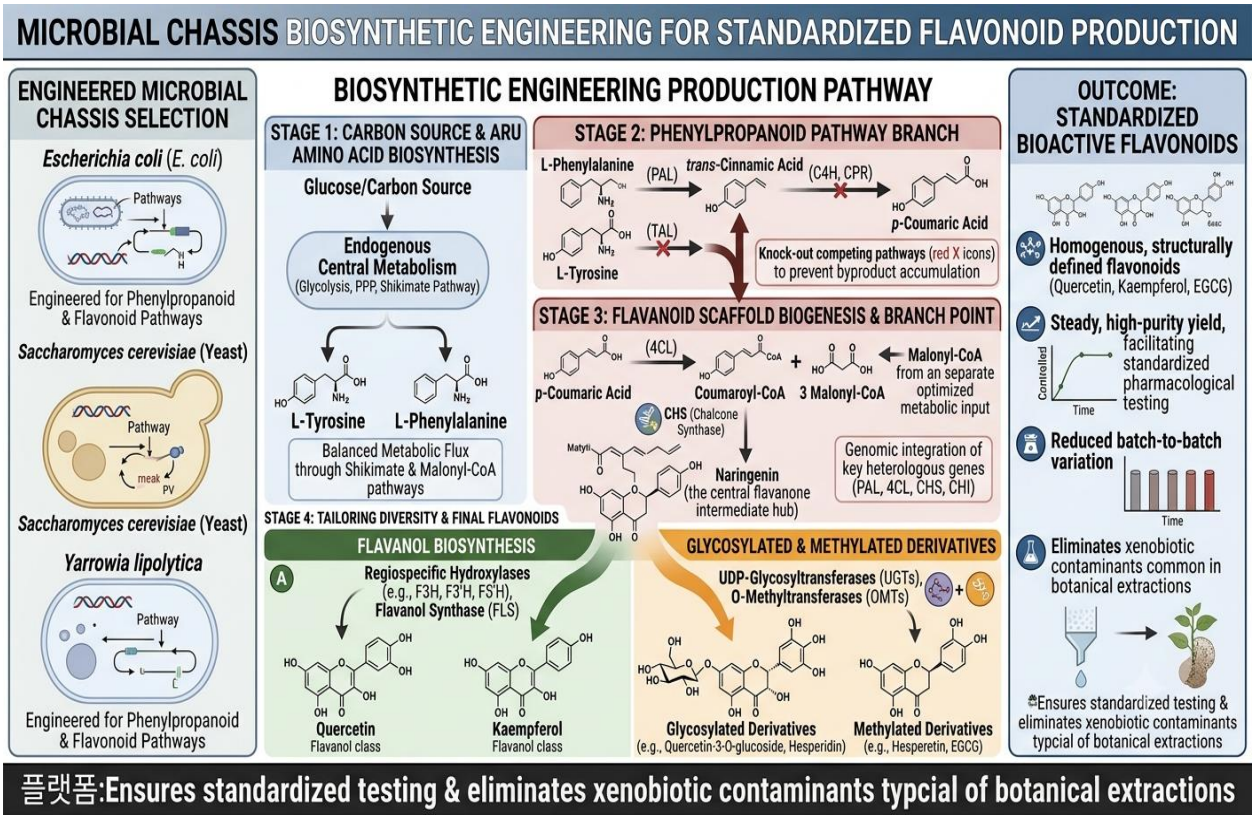

Figure 21. Microbial chassis biosynthetic engineering for standardized flavonoid production. Schematic workflow depicting host selection, metabolic pathway reconstruction, and production of structurally defined, high-purity flavonoids.

Furthermore, dosing discordances are compounded by variable phase I and phase II metabolic rates, as well as distinct inter-individual gut microbiota compositions that govern phenolic deglycosylation and C-ring cleavage [141]. Clinical endpoints in human trials frequently rely on distal systemic markers of oxidative stress, such as plasma malondialdehyde or 8-hydroxy-2'-deoxyguanosine (8-OHdG), which lack tissue specificity and display high baseline volatility [142]. This misalignment between preclinical mechanistically validated intracellular markers (e.g., Keap1-cysteine modification, HO-1 induction) and non-specific clinical endpoints accounts for the non-reproducible outcomes observed across late-phase intervention trials [137, 142, 143].

7.2. Biosynthetic Engineering and Synthetic Biology: Microbial Chassis Production

To overcome the challenges of low natural extraction yields, seasonal variations, and complex chemical synthesis of bio-active flavonoids, synthetic biology offers a scalable pathway through heterologous expression in engineered microbial chassis [144]. Microorganisms such as Escherichia coli, Saccharomyces cerevisiae, and Yarrowia lipolytica have been successfully metabolic-engineered to express plant-derived phenylpropanoid and flavonoid pathways [145].

Standardization of microbial chassis production involves precise enzyme scaffolding, balancing metabolic flux through the shikimate and malonyl-CoA pathways, and knocked-out competing endogenous pathways to prevent byproduct accumulation [146]. Direct genomic integration of heterologous genes—such as phenylalanine ammonia-lyase (PAL), 4-coumarate: CoA ligase (4CL), chalcone synthase (CHS), and chalcone isomerase (CHI)—enables the de novo biosynthesis of central flavanone intermediates like naringenin [147]. Subsequent tailoring with regiospecific hydroxylases, O-methyltransferases, and UDP-glycosyltransferases yields homogenous, structurally defined

bioactive flavonoids (e.g., quercetin, kaempferol, epigallocatechin gallate) with reduced batch-to-batch variation [148, 149]. This platform ensures steady, high-purity yield, facilitating standardized pharmacological testing and eliminating xenobiotic contaminants typical of botanical extractions [144, 149].

7.3. Personalized Chemoprevention: Biomarker Profiling and Targeted Supplementation

The paradigm of chemoprevention is shifting from population-wide dietary recommendations to personalized phenolic supplementation strategies guided by comprehensive biomarker profiling [150]. Central to this approach is the baseline functional status of the Keap1-Nrf2-ARE signaling axis, which governs endogenous antioxidant and phase II detoxifying gene networks [151]. Individuals exhibiting distinct Nrf2 transcriptional baselines, somatic KEAP1 or NFE2L2 gene mutations, or epigenetic hypermethylation respond differently to electrophilic phenolic phytochemicals [152].

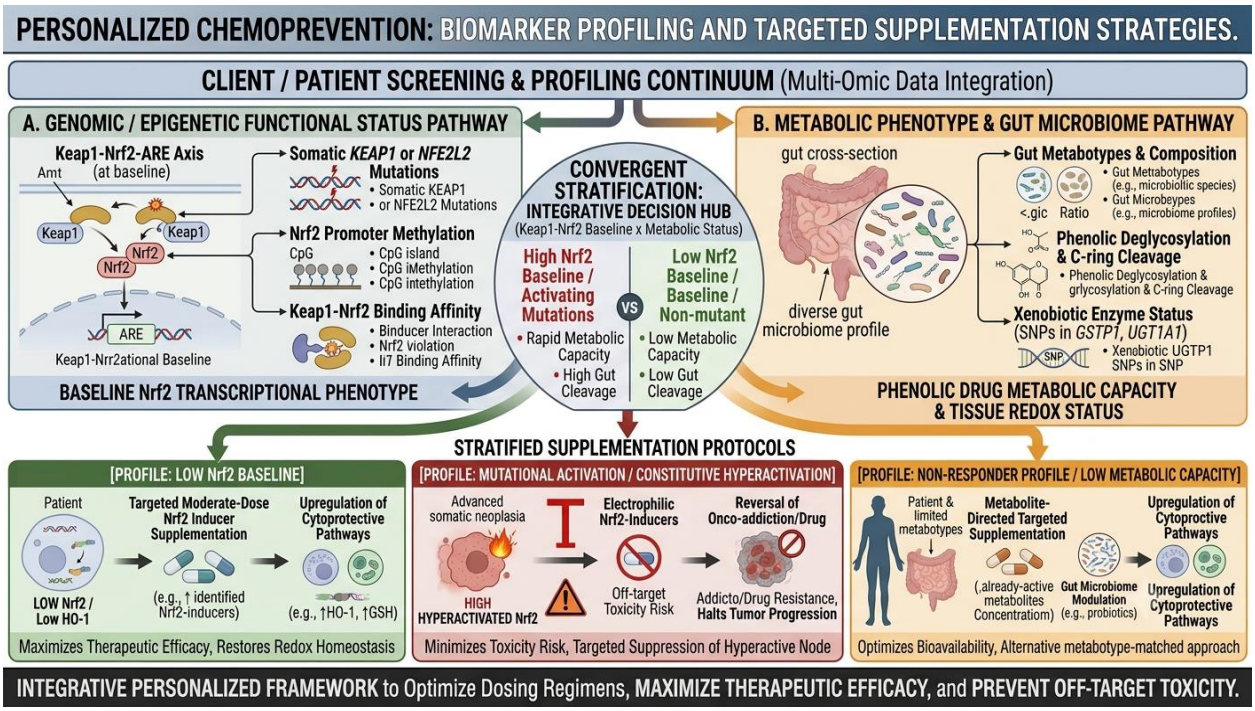

Figure 22. Personalized chemoprevention: Biomarker profiling and targeted supplementation strategies. Schematic framework illustrating multi-omic data integration for client/patient stratification to optimize dosing regimens, maximize therapeutic efficacy, and minimize off-target toxicity.

Integrating multi-omic profiles—including single nucleotide polymorphisms (SNPs) in xenobiotic-metabolizing enzymes (e.g., GSTP1, UGT1A1) and deep sequencing of gut microbiome metabotypes—allows precise stratification of patient responsiveness [153]. For instance, patients with low baseline Nrf2 expression benefit from targeted supplementation with electrophilic Nrf2-inducers to upregulate cytoprotective pathways [151], whereas individuals with constitutively hyperactivated Nrf2 (frequently observed in advanced somatic neoplasia) require targeted Nrf2 inhibitors rather than induction therapy [154]. Stratifying patients by metabolic phenotype and tissue-specific redox status provides a framework to optimize dosing regimens, maximize therapeutic efficacy, and prevent off-target toxicity [150, 155].

8. Conclusions

Shift to Systemic Metabolic Resilience: The anti-cancer efficacy of phenolics and flavonoids extends far beyond direct, stoichiometric free-radical scavenging. Their true power lies in their ability to serve as hormetic electrophilic stressors that systematically reconfigure cellular signaling, boosting endogenous biotransformation capacity (Phase II enzymes) and maintaining systemic metabolic resilience under chronic oxidative strain.

Disruption of the Oncogenic Microenvironment: Through the simultaneous suppression of the NF-κ B/STAT3/COX-2 inflammatory network, restoration of autophagic flux, and induction of cell cycle checkpoints, dietary phenolics interrupt the step-wise transition from chronic liver injury and cirrhosis to hepatocellular carcinoma.

Resolution of the "Nrf2 Paradox": The temporal and contextual state of the tissue dictates Nrf2 function. Transient Nrf2 induction in healthy or pre-malignant tissue acts as a vital guardian against genomic instability. Conversely, in established tumors with somatic KEAP1 or NRF2 mutations, sustained Nrf2 hyperactivation becomes an oncogenic driver that confers chemoresistance and facilitates metabolic adaptation.

Overcoming Bioavailability Bottlenecks: Modern nanocarrier systems (e.g., SNEDDS, polymeric nanoparticles, liposomes) and gut microbiome-derived metabolites (such as urolithins and equol) represent the actual systemic drivers of efficacy, successfully surmounting the traditional limitations of low oral absorption and rapid phase II metabolic clearance.

9. Recommendations and Future Perspectives

Stage-Specific Clinical Protocol Design: Future clinical trials must rigidly define patient cohorts based on disease stage. Phenolic Nrf2 activators should be utilized exclusively during early interception, high-risk chemoprevention, or pre-malignant phases. In contrast, in advanced, established malignancies with elevated baseline Nrf2 expression, natural or synthetic Nrf2 inhibitors (e.g., ML385, Brusatol) should be combined with standard chemotherapy to restore treatment sensitivity.

Biomarker-Driven Personalization: Clinical translation requires multi-omic stratification. Patients should be profiled for baseline Nrf2 activity, KEAP1/NFE2L2 mutational status, single nucleotide polymorphisms (SNPs) in phase II enzymes (GSTP1, UGT1A1), and individual gut microbiome metabotypes to tailor phenolic dosing and maximize therapeutic responses.

Standardization via Synthetic Biology: To overcome batch-to-batch variability and contaminants in botanical extracts, industry and research efforts should pivot toward heterologous microbial chassis production (E. coli, S. cerevisiae, Y. lipolytica). This ensures consistent, high-purity yield for standardized pharmacological evaluation and clinical translation.

Validation of Pharmacodynamic Biomarkers: Clinical trial design must shift away from non-specific systemic markers (e.g., serum MDA) and adopt tissue-specific, mechanistically validated target biomarkers (e.g., target gene occupancy, HO-1/NQO1 induction in circulating mononuclear or biopsy cells, and intra-tumoral metabolite concentrations) to establish accurate dose-response relationships in humans.

Patents: N/A

Supplementary Materials: N/A

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