



Targeting the NRF2 pathway to enhance lipid peroxidation: a novel therapeutic strategy in hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide and is characterized by a high recurrence rate, limited treatment options, and frequent resistance to systemic therapy. A key factor in this resistance is the persistent activation of nuclear factor erythroid 2-related factor 2 (NRF2), a transcription factor that normally protects against oxidative stress but, in malignant hepatocytes, suppresses ferroptosis by restricting lipid peroxidation. This dual function positions NRF2 as a key target for therapeutic modulation in HCC. Recent preclinical studies demonstrate that NRF2 maintains tumor survival by regulating antioxidant and iron management pathways, such as GPX4, SLC7A11, and ferritin, which together mitigate lipid peroxidation and prevent ferroptotic cell death. Multiple pharmacological strategies have been evaluated to counteract this effect, including direct NRF2 inhibitors such as camptothecin (CPT) and brusatol, preoperative modulators such as metformin and picropodophyllin (PPP), and natural compounds such as tiliroside, bavaquine, and arenobufagin. These interventions often show synergistic activity with sorafenib and other standard treatments, while postoperative effectors such as CYP4F11 and the NRF2-SLC7A11-GPX4 axis have emerged as promising additional intervention points. Despite compelling results in vitro and animal model results, several challenges limit its application to clinical practice. These include the lack of dedicated clinical trials, the limited specificity of available inhibitors, tumor heterogeneity, and potential safety concerns in cirrhotic livers. Future research focuses on the development of selective NRF2 modulators, hepatocyte-targeted approaches such as proteolysis-targeted chimeras (PROTACs) and GalNAc-conjugated oligonucleotides, and biomarker-based patient stratification using genomic, immunohistochemical, and transcriptomic indicators of NRF2 activation. Taken together, contextual NRF2 modulation represents a promising strategy to restore sensitivity to ferroptosis, overcome drug resistance, and improve outcomes in HCC patients.



Keywords

hepatocellular carcinoma, ferroptosis, drug resistance, NRF2 pathway, lipid peroxidation, sorafenib, oxidative stress, therapeutic targeting

Introduction

The transcription factor nuclear factor erythroid 2-related factor 2 (NRF2; encoded by the *NFE2L2*) plays a key role in regulating cellular redox homeostasis and the protective antioxidant detoxification mechanisms in mammals [1]. NRF2 is a cytosolic transcription factor that regulates redox homeostasis by activating the expression of antioxidant response element (ARE)-dependent genes [2, 3]. Under normal conditions, NRF2 is downregulated by Kelch-like ECH-associated protein 1 (KEAP1), leading to its degradation [4, 5]. Under oxidative or electrophilic stress, cysteine modifications in KEAP1 stabilize NRF2, which translocates to the nucleus, dimerizes with small musculoaponeurotic fibrosarcoma (sMAF) proteins, and binds AREs to induce the transcription of cytoprotective genes [4, 6]. In this way, NRF2 drives the expression of various enzymes and signaling proteins involved in drug metabolism, antioxidant defense, and oxidative signaling, playing a crucial role in managing cellular responses to oxidative stress [7]. These enzymes include glutathione *S*-transferase (GST), NAD(P)H:quinone oxidoreductase 1 (NQO1), and heme oxygenase-1 (HO-1), which protect cells from oxidative damage [8].

Although NRF2 activation is beneficial in diseases characterized by oxidative stress, including neurodegenerative, cardiovascular, and metabolic disorders [8, 9], in cancer, its persistent activation can be maladaptive.

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy [2, 3] and accounts for 70–90% of cases in patients with chronic liver disease [10]. It is among the leading causes of cancer-related mortality worldwide [2, 10] and is characterized by rapid progression, late diagnosis, and poor prognosis. Major risk factors include chronic hepatitis B and C virus infections [4], alcohol abuse, aflatoxin B1 exposure, diabetes mellitus, obesity, tobacco use, iron accumulation, and nonalcoholic fatty liver disease [10]. Outcomes remain poor, with a 5-year relative survival rate of only ~18% for all stages [11], despite available treatments such as resection, liver transplantation, and systemic or locoregional therapies [12, 13], increasing to ~31% for localized disease [2]. For advanced HCC, systemic therapies are the standard of care; these include molecularly targeted agents (MTAs), chemotherapeutic drugs (CTDs), and immune checkpoint inhibitors (ICIs) [14]. Sorafenib, a multikinase inhibitor, has been widely used as first-line systemic therapy [15]; however, resistance is common, and conventional chemotherapy has shown limited efficacy, prompting the evaluation of combination regimens [16].

NRF2 signaling and lipid peroxidation are closely involved in HCC chemoresistance [10]. Oxidative stress contributes to hepatocarcinogenesis by inducing DNA damage, generating reactive oxygen and nitrogen species (ROS/RNS), and disrupting protein expression. Increased ROS can induce increased mitochondrial membrane permeability and DNA damage. According to Gao et al. [17], SLC27A5 deficiency activates the NRF2/TXNRD1 pathway due to increased lipid peroxidation in HCC. This suggests that alterations in lipid metabolism and the resulting oxidative stress/lipid peroxidation influence HCC chemoresistance, mediated in part by pathways such as NRF2 activation.

While NRF2 can act as a tumor suppressor under physiological stress, its sustained activation in HCC drives malignant progression [18]. Persistent NRF2 signaling, frequently mediated by the p62-KEAP1-NRF2 axis, promotes survival by activating ARE-dependent genes such as *SLC7A11*, glutathione peroxidase 4 (*GPX4*), *NQO1*, *HO-1*, and *FTH1*, which limit lipid peroxidation, regulate iron homeostasis, and protect against ferroptosis. These mechanisms confer resistance to ferroptosis-inducing agents such as erastin, sorafenib, and buthionine sulfoximine [19, 20].

Considering the interplay between oxidative stress, lipid peroxidation, and persistent NRF2 activation, targeting this pathway emerges as a promising strategy to overcome therapy resistance in HCC. The aim of

this review is, therefore, to examine the dual role of NRF2 in cancer, with particular emphasis on HCC, and to analyze how its regulation of lipid peroxidation and ferroptosis influences disease progression. We also summarize current therapeutic approaches proposed to modulate this pathway and discuss their potential to complement existing HCC treatments.

NRF2 in oxidative stress, disease, and therapeutic modulation

ROS/RNS are continuously being generated from both endogenous metabolism and external exposures. While controlled levels of oxidants are involved in physiological processes, such as cell division, immune regulation, and stress adaptation, their excessive accumulation causes oxidative stress, damaging lipids, proteins, and nucleic acids [7, 21].

Oxidative stress activates multiple signaling pathways, including MAPKs, PI3K/AKT, and the transcription factor NRF2 [22]. Once stabilized, NRF2 translocates to the nucleus, binds to AREs, and induces cytoprotective genes such as *HO-1*, *NQO1*, *SLC7A11*, and *GPX4*, which restore redox balance and limit lipid peroxidation [23]. This regulatory axis is not merely theoretical, but it has been consistently demonstrated using natural products that activate the NRF2-ARE pathway. For example, dithiolthiones and anethole have been shown to induce phase II detoxification enzymes by activating ARE, thereby strengthening the antioxidant and detoxification capacity of cells. Kou et al. [24] describe additional dietary phytochemicals—such as curcumin, resveratrol, and quercetin—that promote ARE-dependent expression of protective enzymes, supporting the idea that diet-derived compounds may enhance cellular defenses through NRF2 signaling. By incorporating these specific examples, it becomes clear that NRF2 represents a central regulator of the adaptive response to oxidative and electrophilic stress, with translational relevance extending from basic cellular models to preventive strategies based on natural compounds [25–27].

The regulatory role of the KEAP1-NRF2 pathway has been extensively investigated in a wide range of conditions where oxidative stress plays a pivotal role, including chronic, degenerative, pulmonary, cardiovascular, and even emerging infectious diseases [8, 26–30].

These findings highlight the broad relevance of NRF2 in health and disease. In this review, however, we focus specifically on how its dysregulation contributes to HCC.

NRF2 and cancer progression: mechanisms and implications in HCC

In the context of cancer, NRF2 has traditionally been considered a tumor suppressor because its cytoprotective functions are considered the main cellular defense mechanism against exogenous and endogenous insults, including xenobiotics and oxidative stress. However, several recent studies demonstrate that sustained activation of the NRF2 pathway creates an environment that favors the survival of normal and malignant cells, protecting them against oxidative stress, chemotherapeutic agents, and radiotherapy [11]. Cancer cells can exploit the protective function of this pathway to promote tumor growth and drug resistance, making NRF2 inhibitors a potential therapeutic strategy in personalized cancer treatments [12].

The NRF2 pathway can become oncogenic in cases of sustained activation, often due to somatic mutations in *KEAP1* or *NFE2L2*, the gene encoding for NRF2, or through non-genetic mechanisms such as accumulation of p62/SQSTM1, which competes for KEAP1 binding and allows NRF2 stabilization [3]. Furthermore, NRF2 interacts with oncogenic signaling pathways. It acts synergistically with the PI3K/AKT pathway, where AKT inhibits GSK-3 β , thereby preventing NRF2 phosphorylation at the DSGIS motif of its Neh6 domain, which would otherwise lead to its degradation via the E3 ligase complex β -TrCP-SKP1-CUL1-RBX1. This contributes to the persistent nuclear activity of NRF2. Furthermore, NRF2 interacts with the NOTCH1 signaling axis and promotes the expression of vascular endothelial growth factor C (VEGFC), platelet-derived growth factor C (PDGFC), and insulin-like growth factor 1 (IGF1), which promote angiogenesis and mitogenic signaling. NRF2 also antagonizes pro-inflammatory transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and activator protein 1 (AP-1),

contributing to an immunosuppressive tumor microenvironment by reducing cytokine expression and interfering with antigen presentation [8].

These alterations are prevalent in many cancer types and are particularly relevant in HCC, where chronic liver injury from hepatitis B or C infection, alcohol abuse, or metabolic dysfunction leads to persistent oxidative stress and inflammation. NRF2 is constitutively activated by somatic mutations in the gene *NFE2L2* or *KEAP1*, or by sequestration of KEAP1 by p62/SQSTM1. These alterations impair NRF2 degradation and result in sustained activation of its transcriptional program. In HCC, NRF2 overexpression drives a multifaceted program that includes metabolic reprogramming, immune evasion, and chemoresistance. NRF2 stimulates the pentose phosphate pathway by upregulating glucose-6-phosphate dehydrogenase (G6PD), transketolase (TKT), and 6-phosphogluconate dehydrogenase (PGD), which increases NADPH production, which is required for reductive biosynthesis and redox homeostasis. Simultaneously, NRF2 enhances serine/glycine biosynthesis by transcriptionally activating phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase 1 (PSAT1), and serine hydroxymethyltransferase 2 (SHMT2), through coregulation with transcription factor ATF4, which promotes proliferation and resistance to nutrient deprivation. This provides transformed hepatocytes with increased tolerance to ROS, increased metabolic flexibility, and resistance to cell death, all of which contribute to tumorigenesis, survival, and drug resistance [3, 12, 13]. The metabolic shift favors the rapid synthesis of nucleotides, lipids, and amino acids, which is necessary for tumor proliferation and maintenance of high intracellular levels of NADPH for reductive biosynthesis and ROS detoxification. Furthermore, NRF2 enhances drug resistance by inducing the expression of ATP-binding cassette (ABC) transporters such as ABC sub-family C member 1 (ABCC1) and ABC sub-family G member 2 (ABCG2), which efflux chemotherapeutic agents out of cells. It also contributes to immune evasion by repressing the antigen-presenting machinery and increasing the expression of immunosuppressive genes [14, 15].

NRF2 also interacts with oncogenic signaling pathways frequently deregulated in HCC, such as PI3K/AKT, mTOR, and NOTCH1. For example, PI3K/AKT signaling inhibits GSK-3 β , which prevents phosphorylation of the Neh6 degron on NRF2, thereby blocking its degradation by the β -TrCP E3 ligase complex. This results in increased stabilization of NRF2, generating a positive feedback loop. Furthermore, NRF2 activation promotes epithelial-mesenchymal transition (EMT) and cancer stem cell (CSC) maintenance through the induction of NOTCH1, SIRT1, and aldehyde dehydrogenase (ALDH) isoforms. These functions contribute to HCC metastasis, recurrence, and resistance. Notably, NRF2's dual role—as a protector in early liver injury and a promoter in advanced cancer—makes it a therapeutic target that requires context-specific modulation to avoid adverse effects [12, 15, 16].

Clinically, high NRF2 expression in HCC is associated with larger tumor size, vascular invasion, poor differentiation, and decreased overall survival. Therapeutic targeting of NRF2 in HCC remains challenging due to its dual nature: while inhibition can restore drug sensitivity and immunogenicity, it also risks disrupting the redox balance in normal hepatocytes. Several natural compounds and synthetic inhibitors are being investigated to modulate the KEAP1-NRF2 axis with greater specificity. Therefore, contextual modulation—guided by molecular profile of *KEAP1/NFE2L2* mutations and redox signatures—emerges as a promising strategy in precision medicine for HCC [3]. Importantly, one of the most relevant consequences of sustained NRF2 activation in this context is the evasion of ferroptosis through the suppression of lipid peroxidation, which directly links NRF2 activity with therapeutic resistance.

NRF2 and ferroptosis: a therapeutic crossroad in HCC

Ferroptosis is a distinctive form of non-apoptotic cell death characterized by its dependence on intracellular iron and oxidative stress. Triggered by compounds such as erastin, it is morphologically and biochemically distinct from apoptosis, necrosis, and autophagy, and results from decreased cystine uptake and diminished antioxidant defenses [17]. Ferroptosis is mediated through iron-dependent phospholipid peroxidation, making lipid metabolism a central regulator of this form of cell death and a critical link between oxidative damage and therapeutic vulnerability in diseases such as cancer [18]. In this context, ferroptosis represents a promising alternative to overcome therapy resistance in cancer, as its induction

can suppress tumor growth, improve immunotherapy responses, and offer a new strategy to attack cancer through regulated lipid peroxidation [19].

Mechanistically, NRF2 inhibits lipid peroxidation through five coordinated programs. First, it enhances cystine import and glutathione (GSH) synthesis by transactivating SLC7A11 (with the cooperation of ATF4) and GCLC/GCLM, which drives GPX4 to reduce phospholipid hydroperoxides (PLOOH→PLOH) and block ferroptosis [31]. Second, it supports the GPX4 axis—directly or GSH indirectly via GSH—to detoxify lipid peroxides at membranes [32]. Third, NRF2 maintains cytosolic NADPH by upregulating G6PD/PGD [oxidative picropodophyllin (PPP)] and ME1/IDH1 (alternative pathways), thereby supporting GSH recycling and lipid-peroxide repair systems [33]. Fourth, it shapes the labile iron pool by inducing ferritin (FTH1/FTL) and ferroportin (SLC40A1) and modulating HO-1 (HMOX1), which together tend to limit Fenton chemistry that propagates lipid peroxidation (with recognized context dependency for HO-1) [34]. Fifth, in KEAP1-deficient contexts, NRF2 can interact with the FSP1-CoQ10 system as an anti-ferroptotic pathway parallel to GPX4; the combined action of NRF2/FSP1 overcomes the resistance to ferroptosis [35].

In HCC, these NRF2 programs attenuate sorafenib-induced ferroptosis, whereas NRF2 inhibition or disruption of its downstream pathways restores lipid peroxidation and ferroptotic death (e.g., GSTZ1 sensitizes HCC to sorafenib by suppressing the NRF2/GPX4 axis) [36]. This positions NRF2 as a promising target to enhance the efficacy of ferroptosis-inducing therapies [37].

HCC remains a significant global health burden due to its aggressiveness and high recurrence rates. Traditional therapies such as resection, radiofrequency ablation, or systemic agents such as sorafenib offer limited survival benefits, often due to inherent or acquired chemoresistance. A key mechanism involved in such resistance is the sustained activation of NRF2, a key regulator of ferroptosis evasion in tumor cells [20, 21]. The function of NRF2 is twofold: while protecting normal cells from oxidative damage, sustained NRF2 activation in cancer cells promotes survival under stress by upregulating antioxidant genes (e.g., *SLC7A11*, *HO-1*, *GPX4*), GSH biosynthesis, and regulating iron metabolism to suppress lipid peroxidation and ferroptotic cell death, thereby facilitating tumor progression [22, 23]. For this reason, there is growing interest in targeting the NRF2 signaling axis as a therapeutic strategy in HCC, with the aim of altering its antioxidant defenses and promoting ferroptotic cell death by improving lipid peroxidation.

Targeting the NRF2 pathway in HCC: studies and mechanisms

Various therapies have been studied to modulate the NRF2 pathway in the context of HCC. Sorafenib, a multi-kinase inhibitor widely used in the treatment of HCC, frequently presents therapeutic resistance. Studies with sorafenib-resistant HCC cell lines have shown that NRF2 signaling contributes to enhanced cell proliferation and migration, as well as cancer pluripotency, through upregulation of pluripotency markers and ABC transporter genes. Notably, NRF2 inhibition reduces these aggressive features, implying that NRF2 is a key driver of sorafenib resistance in HCC [26].

In this context, various cotreatment strategies have been developed to reduce tumor cell resistance to sorafenib, while novel compounds have also been studied. Furthermore, key intracellular targets have been identified, whose modulation has shown promising effects in improving ferroptosis and regulating NRF2 activity. These findings are summarized in Table 1 and illustrated in Figure 1.

Table 1. Pharmacological modulators targeting the NRF2 pathway in HCC and their impact on lipid peroxidation and ferroptosis.

Compound	Model	Doses	NRF2 pathway targeting strategy	Effect on lipid peroxidation/NRF2	Conclusion	Study
In vitro studies						
CPT + sorafenib	HepG2 and Huh7 cells	CPT 1–5 μM + sorafenib 5 μM	CPT inhibits NRF2's expression, synergizing with sorafenib to induce ferroptosis	↓ NRF2 intracellular levels, ↑ lipid peroxidation	CPT synergizes with sorafenib to induce ferroptosis	Elkateb et al., 2023 [38]

Table 1. Pharmacological modulators targeting the NRF2 pathway in HCC and their impact on lipid peroxidation and ferroptosis. (continued)

Compound	Model	Doses	NRF2 pathway targeting strategy	Effect on lipid peroxidation/NRF2	Conclusion	Study
Metformin + sorafenib	HCC cell lines, mouse xenograft	PPI 1–4 μ M	Metformin + sorafenib inhibits p62-KEAP1-NRF2 pathway	↓ NRF2's translocation to the nucleus, ↑ ferroptosis with combo therapy	Reverses NRF2-driven resistance to sorafenib	Tang et al., 2022 [41]
Picropodophyllin (PPP)	In vitro and in vivo HCC models	PPP 2.5–10 μ M	PPP inhibited the PI3K-AKT-NRF2 pathway	↓ NRF2 target genes, ↑ lipid ROS; ferroptosis via iron overload	Induces ferroptosis through NRF2 inhibition	Zheng et al., 2025 [42]
Arsenic trioxide (ATO)	HCC cell lines	ML385 10 μ M	ATO-induced ferroptosis enhanced by silencing NRF2	↑ Lipid ROS, MDA, Fe ²⁺ , ↑ NRF2 knockdown ferroptosis	Ferroptosis enhanced by NRF2 silencing	Huang et al., 2025 [43]
Tiliroside	HCC cell lines and tumor xenografts in nude mice	Not applicable	Tiliroside promotes the ubiquitination of NRF2 and sensitizes cells to ferroptosis inducers	↓ NRF2 intracellular levels, ↑ lipid peroxidation, and enhanced ferroptotic cell death	Sensitizes HCC cells to ferroptosis inducers	Yang et al., 2023 [44]
Bavachin	Huh7 and HepG2 cells	Bavachin 20–40 μ M	Bavachin mildly activates NRF2/HO-1 pathway	↑ ROS, MDA, exceeding the protective effect of NRF2's activation	Promotes ferroptosis via oxidative stress	Li et al., 2024 [45]
Brusatol	Cell lines and patient tissue	Brusatol 100 nM; sulforaphane 5 μ M	NRF2-driven CYP4F11 expression promotes HCC and resistance	↑ NRF2 inhibition sensitizes cells, ↑ lipid peroxidation	Suppresses HCC via CYP4F11-NRF2 inhibition	Chen et al., 2025 [39]
In vivo studies						
DSF/Cu	HCC cell lines	DSF 1 μ M + Cu 1 μ M	DSF/Cu treatment elevates NRF2 as a compensatory response	↑ Lipid peroxidation impairs mitochondrial homeostasis	Potentiated by NRF2 inhibition	Ren et al., 2021 [48]
Arenobufagi	HepG2 cells, nude mice	Arenobufagin 20 μ M	Arenobufagin modulates p62-KEAP1-NRF2 to induce autophagy-dependent ferroptosis	↓ NRF2 intracellular levels, ↑ MDA, lipid ROS	Induces autophagy-dependent ferroptosis	Yang et al., 2024 [46]
NSC48160	HepG2, SMMC-7721 and BEL-7402 cells	NSC48160 36 μ M	Disrupts TCA cycle metabolism and indirectly inhibits the NRF2-SLC7A11-GPX4 axis	↑ Lipid peroxidation and ferroptosis, ↓ NRF2 expression, and its downstream effectors	Promotes ferroptosis via NRF2 suppression	Zhang et al., 2025 [47]

This table is of the author's own elaboration based on the review literature. This table summarizes in vitro and in vivo studies evaluating compounds that modulate the NRF2 pathway in HCC, including their models, doses, molecular mechanisms, effects on lipid peroxidation, and therapeutic implications in improving ferroptosis or overcoming drug resistance. AKT: protein kinase B; CPT: camptothecin; Cu: copper; DSF: disulfiram; GPX4: glutathione peroxidase 4; GSH: glutathione; HCC: hepatocellular carcinoma; HO-1: heme oxygenase-1; KEAP1: Kelch-like ECH-associated protein 1; MDA: malondialdehyde; NRF2: nuclear factor erythroid 2-related factor 2; p62: sequestosome 1; PI3K: phosphatidylinositol 3-kinase; ROS: reactive oxygen species; SLC7A11: solute carrier family 7 member 11; TCA: tricarboxylic acid.

Therapeutic strategies targeting NRF2 modulation in HCC can be classified into three categories: direct NRF2 inhibitors, upstream signaling modulators, and natural compounds with paradoxical or dual effects. These approaches converge on specific molecular nodes—including the KEAP1-NRF2 interaction, NRF2 stability and degradation, and downstream effectors such as CYP4F11—and often demonstrate synergistic potential when combined with standard therapies such as sorafenib.

Direct NRF2 inhibitors

Several agents act by directly suppressing NRF2 expression or activity. Camptothecin (CPT) inhibits NRF2 transcription, which potentiates sorafenib-induced ferroptosis in HCC cells by increasing lipid peroxidation and iron accumulation [38]. Similarly, brusatol promotes ubiquitination and proteasomal degradation of NRF2, reducing the expression of its target CYP4F11, thereby amplifying ferroptosis [39, 40]. These

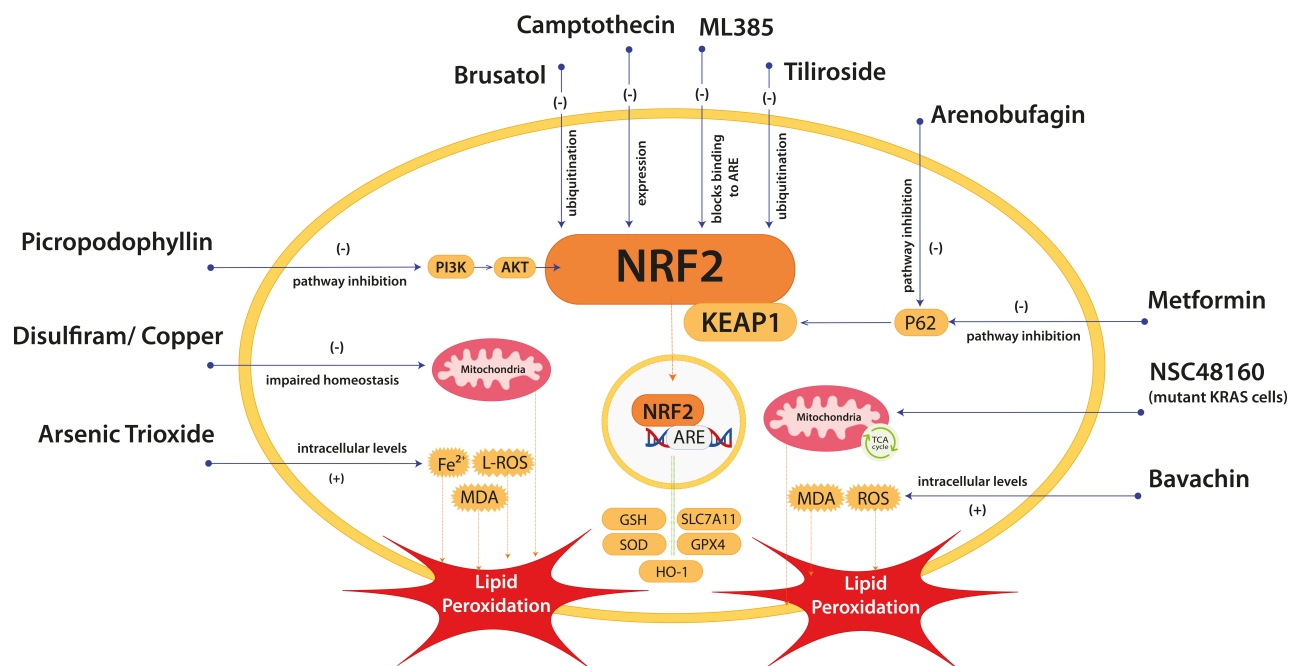


Figure 1. Mechanism in potential therapeutic modulation of the NRF2 pathway to enhance lipid peroxidation and ferroptosis. The figure is of the author's own elaboration. The figure presents a schematic representation of the NRF2 signaling pathway in HCC cells, highlighting its role in regulating oxidative stress and ferroptosis, along with points of pharmacological intervention. Under normal conditions, NRF2 is bound in the cytoplasm to its inhibitor KEAP1, which targets it for degradation. In response to oxidative stress, NRF2 dissociates from KEAP1 and translocates into the nucleus, where it promotes the transcription of antioxidant and cytoprotective genes, including *SLC7A11*, *GPX4*, *HO-1*, etc. These genes collectively suppress lipid peroxidation and inhibit ferroptosis, contributing to tumor cell survival and therapy resistance. The diagram illustrates how various compounds—such as camptothecin, tiliroside, PPP, ATO, bavachin, and metformin—target different components of the NRF2 pathway. These interventions either block NRF2 translocation, reduce the expression of its downstream targets, or enhance oxidative damage by increasing ROS, depleting GSH, and promoting lipid peroxidation. The cumulative effect is the induction of ferroptosis in cancer cells, making the pathway a promising therapeutic target. The image underscores the potential of combining NRF2 inhibitors with existing treatments like sorafenib to overcome resistance in HCC. AKT: protein kinase B; ARE: antioxidant response element; ATO: arsenic trioxide; GPX4: glutathione peroxidase 4; GSH: glutathione; HCC: hepatocellular carcinoma; HO-1: heme oxygenase-1; KEAP1: Kelch-like ECH-associated protein 1; MDA: malondialdehyde; NQO1: NAD(P)H:quinone oxidoreductase 1; NRF2: nuclear factor erythroid 2-related factor 2; P62: sequestosome 1; PI3K: phosphatidylinositol 3-kinase; PPP: picropodophyllin; ROS: reactive oxygen species; SLC7A11: solute carrier family 7 member 11.

compounds illustrate the feasibility of directly destabilizing NRF2 to overcome drug resistance, although concerns remain regarding off-target specificity and toxicity.

Upstream pathway modulators

Other interventions disrupt the signaling cascades that underpin NRF2 activation. Metformin, for example, suppresses the p62-KEAP1-NRF2 axis, blocking NRF2 nuclear translocation and improving sensitivity to sorafenib in both cell lines and xenograft models [41]. PPP, a natural IGF1R inhibitor, disrupts the PI3K-AKT-NRF2 pathway, downregulating antioxidant targets such as *SLC7A11* and *SLC40A1*, and triggering GSH depletion and ferroptosis [42]. Arsenic trioxide (ATO) also acts upstream: although it induces oxidative stress, NRF2 silencing significantly potentiates ATO-induced ferroptosis, confirming that NRF2 functions as a protective barrier in this context [43].

Natural compounds with paradoxical or dual effects

A specific group of natural agents shows more complex, dose- or context-dependent effects on NRF2 signaling. Tiliroside promotes NRF2 ubiquitination and degradation, sensitizing HCC cells to ferroptosis inducers and enhancing sorafenib efficacy in vitro and in vivo [44]. Bavachin, on the other hand, mildly activates NRF2/HO-1 signaling, while driving excess ROS and lipid peroxidation, ultimately neutralizing the antioxidant response and inducing ferroptotic cell death [45]. Arenobufagin modulates the p62-KEAP1-NRF2 axis to trigger autophagy-dependent ferroptosis, reducing NRF2 levels and promoting tumor suppression in xenograft models [46].

Downstream effectors of NRF2

Targeting NRF2-dependent antioxidant programs represents another therapeutic strategy. *CYP4F11*, recently identified as an NRF2 target gene, mitigates lipid peroxidation through the metabolism of polyunsaturated fatty acids (PUFAs). Inhibiting NRF2 or CYP4F11 increases ROS accumulation and ferroptosis in HCC cells [39]. NSC48160, a Kirsten rat sarcoma viral oncogene homolog (KRAS) inhibitor, indirectly suppresses the NRF2-SLC7A11-GPX4 axis by disrupting the tricarboxylic acid (TCA) cycle, thereby promoting ferroptosis in KRAS-mutant HCC models [47].

Synergistic mechanisms and combination approaches

In these categories, synergy with existing therapies is a recurring theme. Cotreatments such as sorafenib plus CPT [38], sorafenib plus metformin [41], or disulfiram/copper (DSF/Cu) combinations [48] demonstrate that NRF2 inhibition sensitizes tumor cells to ferroptosis and markedly improves therapeutic efficacy. These findings support the idea that NRF2 modulation is more effective when integrated into multidrug regimens rather than administered as monotherapy.

Limitations

Despite promising preclinical evidence, several limitations constrain the translational potential of NRF2-targeted therapies in HCC. First, the lack of clinical trials remains a major obstacle. While numerous compounds have demonstrated efficacy *in vitro* and in murine models, no phase I or II trials directly targeting NRF2 have been conducted in HCC patients, raising concerns about their applicability in clinical practice. Second, many current NRF2 inhibitors, such as brusatol or trigonelline, lack specificity and are associated with undesirable effects and systemic toxicity. This hampers dose optimization and increases the risk of adverse outcomes.

Tumor heterogeneity represents another limitation, as mutations or non-genetic mechanisms leading to NRF2 activation are not uniformly present across HCC subtypes. This highlights the need to stratify patients using molecular profiling before considering NRF2-targeted interventions. Furthermore, the dual role of NRF2—as a protective factor in early liver disease and a promoter of tumor survival in advanced stages—poses a therapeutic dilemma. Broad NRF2 inhibition risks exacerbating oxidative stress in non-tumorous hepatocytes, particularly in patients with cirrhosis or steatohepatitis.

Finally, there is a lack of robust biomarkers for monitoring NRF2 activity and treatment response in real time. Current studies rely on surrogate indicators, such as lipid peroxidation or GPX4 expression, which may not accurately capture NRF2 modulation. Together, these limitations underscore the need for more specific inhibitors, validated biomarkers, and carefully designed clinical studies to translate NRF2-targeted strategies into effective therapies for HCC.

These challenges, along with potential strategies to overcome them, are summarized in [Figure 2](#), which highlights the translational barriers of NRF2-targeted therapies and outlines proposed solutions such as patient-derived models, selective inhibitors, and biomarker development.

Discussion

The NRF2 pathway has been established as a central regulator of oxidative stress, cellular redox balance, and resistance to ferroptosis. Under normal physiological conditions, NRF2 protects cells by inducing the expression of antioxidant and detoxifying enzymes such as HO-1, GPX4, and NQO1. However, in HCC, its sustained activation acts as a double-edged sword: rather than acting solely as a cytoprotective factor, NRF2 facilitates tumor survival, proliferation, and resistance to treatment by preventing ferroptotic cell death and enabling metabolic reorganization [49, 50].

While promising, it is important to highlight that the studies by Elkateb et al. [38] and Yang et al. [44] were mainly based on *in vitro* models, which might not fully reflect the complex tumor microenvironment of HCC. To reinforce the translational relevance of these findings, additional *in vivo* evidence is essential. In this regard, Chang et al. [51] demonstrated in a murine model of alcohol-induced chronic liver injury that

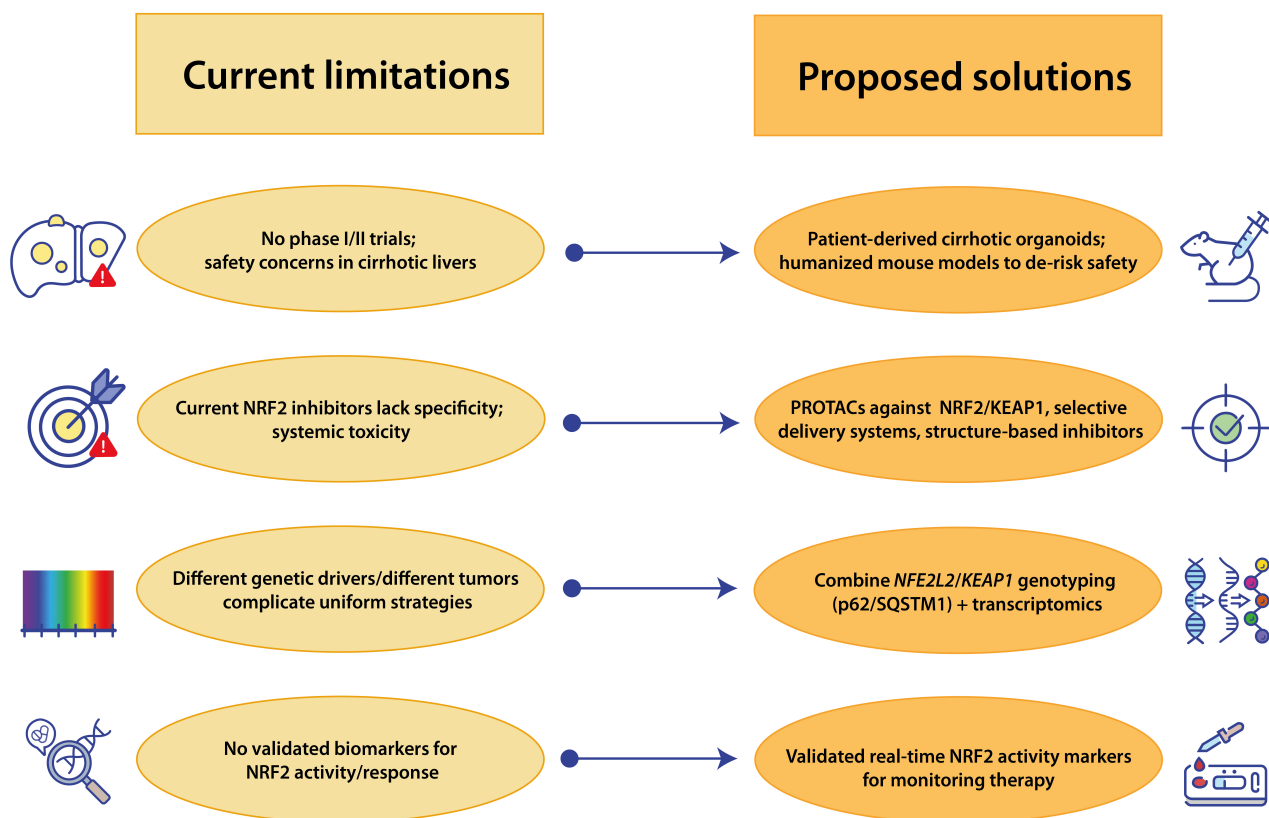


Figure 2. Current limitations and proposed solutions for nuclear factor erythroid 2-related factor 2 (NRF2)-targeted therapies in hepatocellular carcinoma (HCC). The figure is our own work. The figure summarizes the main challenges identified in the [Discussion](#) regarding the translation of NRF2 modulation into clinical practice. Current limitations include the lack of early-phase clinical trials and safety concerns in cirrhotic livers, the lack of specificity and systemic toxicity of available NRF2 inhibitors, the genetic and molecular heterogeneity in HCC tumors, and the absence of validated biomarkers for NRF2 activity and therapeutic response. On the right, proposed solutions are highlighted, including the use of patient-derived cirrhotic organoids and humanized mouse models to evaluate safety, the development of proteolysis-targeted chimeras (PROTACs) and other structure-based inhibitors with targeted delivery systems, the integration of *NFE2L2*/Kelch-like ECH-associated protein 1 (*KEAP1*) genotyping with immunohistochemistry and transcriptomics for accurate patient stratification, and the validation of real-time NRF2 activity markers for therapy monitoring. Together, these strategies illustrate a roadmap for overcoming current barriers and improving the specificity, safety, and translational potential of NRF2-targeted interventions in HCC.

the Xie Zhuo Tiao Zhi formula alleviates liver dysfunction by modulating the NRF2/KEAP1 signaling pathway. Similarly, Sun et al. [52] demonstrated using H22 mouse and VX2 rabbit tumor models that CPT enhances the antitumor efficacy of sorafenib, with reductions in tumor size and downregulation of NRF2, HO-1, and NQO1 expression. This in vivo validation supports the broader relevance of targeting NRF2 in liver diseases and complements the existing in vitro evidence, thus reinforcing the therapeutic potential of NRF2 modulation in HCC.

These findings highlight multiple therapeutic access points within the NRF2 regulatory network, including transcriptional repression, interference with upstream regulators such as KEAP1, and targeting of downstream effectors such as SLC7A11 or CYP4F11 [39]. Together, they support the notion that precise modulation of NRF2, particularly in combination with ferroptosis inducers or existing systemic therapies, could overcome resistance and improve outcomes in HCC.

Several studies highlight that many current NRF2 inhibitors and modulators suffer from insufficient targeting specificity, leading to off-target effects in normal tissues, disruption of systemic redox homeostasis, and increased toxicity. For example, in a review of natural NRF2 inhibitors, Zhang et al. [53] report sensitization of HCC lines but warn of potential toxicity when general antioxidant defenses are extensively suppressed. Similarly, adverse reactions such as hypotension, nausea, and vomiting have been documented with NRF2 inhibitors such as brusatol, and the use of tumour-targeted delivery systems, such as nanoparticle encapsulation, has been proposed to reduce systemic exposure [54]. In HCC-specific contexts, CPT has been shown to suppress NRF2-ARE activity in HepG2 and SMMC-7721 cell lines and in

xenograft models, enhancing chemosensitivity with comparatively less effect in adjacent normal tissues, indicating some degree of tumour specificity [55].

A major limitation for translating NRF2-targeted strategies into clinical practice is the substantial genetic and molecular heterogeneity of HCC, which is due to diverse etiologies and distinct oncogenic alterations. Variability in *NFE2L2* and *KEAP1* mutations, coupled with nongenetic mechanisms such as p62/SQSTM1 accumulation, results in highly variable NRF2 activity across tumors, complicating the unification of therapeutic approaches [5, 56]. This heterogeneity underscores the need for robust patient stratification strategies. A viable solution would be to implement a multimodal framework that combines *NFE2L2/KEAP1* genotyping to identify genetic drivers of NRF2 activation, immunohistochemistry for p62/SQSTM1 to detect post-translational stabilization of NRF2, and transcriptomic profiling of NRF2 downstream targets such as *NQO1*, *SLC7A11*, and *GPX4* to capture pathway activation at the functional level [57, 58]. Integrating these complementary layers of information would allow for accurate stratification of patients with hyperactive NRF2 signaling, guiding the rational use of NRF2 inhibitors and combination regimens in HCC.

To improve specificity, several strategies are being investigated, including the development of proteolysis-targeted chimeras (PROTACs) against NRF2 or KEAP1, and structure-based targeted delivery systems (e.g., nanoparticles), inhibitors that exploit tumour-specific mutations in *KEAP1* or *NFE2L2* genes (encoding NRF2), and careful dose optimization in combination therapies to reduce unwanted effects. Preclinical and early-phase clinical trials consistently indicate that monitoring protocols should include serial assessments of liver function (ALT, AST), redox biomarkers (GSH/GSSG, ROS levels), and signs of systemic oxidative stress. Biomarker studies suggest that measuring NRF2 target gene expression (e.g., *NQO1*) in accessible tissues or blood components may guide therapy and detect early adverse reactions [57, 59].

Conclusions

Inhibition of the NRF2 pathway offers a promising strategy to overcome ferroptosis resistance in HCC and improve therapeutic outcomes. Preclinical studies consistently demonstrate that NRF2 inhibition enhances lipid peroxidation and synergizes with agents such as sorafenib. However, its translation into clinical practice remains complex due to tumor heterogeneity, the limited specificity of available inhibitors, and safety concerns in diseased livers. In the future, the development of selective NRF2 modulators, integration of patient stratification based on genetic and molecular profiles, and the validation of reliable biomarkers will be essential. By combining these advances with rational therapeutic regimens, NRF2-targeted approaches could open new avenues for precision medicine in drug-resistant liver cancer.

Abbreviations

ABC: ATP-binding cassette

ARE: antioxidant response element

ATO: arsenic trioxide

CPT: camptothecin

G6PD: glucose-6-phosphate dehydrogenase

GPX4: glutathione peroxidase 4

GSH: glutathione

HCC: hepatocellular carcinoma

HO-1: heme oxygenase-1

IGF1: insulin-like growth factor 1

KEAP1: Kelch-like ECH-associated protein 1

KRAS: Kirsten rat sarcoma viral oncogene homolog

NQO1: NAD(P)H:quinone oxidoreductase 1

NRF2: nuclear factor erythroid 2-related factor 2

PGD: 6-phosphogluconate dehydrogenase

PPP: picropodophyllin

RNS: reactive nitrogen species

ROS: reactive oxygen species

Declarations

Author contributions

SGC: Conceptualization, Writing—original draft, Writing—review & editing, Visualization. BEJ: Conceptualization, Writing—original draft, Writing—review & editing, Visualization. SC: Supervision. LS: Supervision. RR: Writing—original draft, Writing—review & editing, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

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