Journal of Zhejiang University-SCIENCE B 2026 27(9):978-995
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Review

https://doi.org/10.1631/jzus.B2500053

Check for updates

Nrf2 signaling pathway and its molecular regulatory mechanism

Yunfei PAN[1], Xiaodong ZHANG[2], Yimin LU[2], Hao QIN[2], Rong CHEN[1]✉, Handong FAN[2]✉

[1]*School of Public Health and Nursing, Hangzhou Normal University, Hangzhou 311121, China*
[2]*College of Basic Medicine, Hangzhou Normal University, Hangzhou 311121, China*

Abstract: Nuclear factor erythroid 2-related factor 2 (Nrf2) is a crucial transcription factor that orchestrates the expression of genes involved in antioxidant defense, detoxification, and the maintenance of cellular homeostasis. This review provides a comprehensive analysis of the dual regulatory role of Nrf2 in both normal physiological and pathological conditions, focusing on the molecular mechanisms by which it modulates mitochondrial function, oxidative stress, inflammation, and autophagy. The review summarizes the current knowledge on the effects of various synthetic and natural compounds, such as flavonoids and resveratrol, on Nrf2 activity. The review also explores the therapeutic potential of Nrf2 in neurodegenerative diseases, cancers, diabetes, and other disorders, laying a foundation for the development of Nrf2-targeted pharmacological interventions.

Key words: Nuclear factor erythroid 2-related factor 2 (Nrf2); Kelch-like ECH-associated protein 1 (Keap1); Oxidative stress; Mitochondrial function; Inflammation; Autophagy

1 Introduction

The maintenance of homeostatic equilibrium is essential for organismal survival, yet exogenous environmental stressors invariably perturb cellular function. Organisms rely on specific regulatory mechanisms to cope with these challenges. Central to this adaptive response is the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), which orchestrates cellular protection against oxidative insult. Nrf2 regulates the expression of genes involved in the production of antioxidant enzymes, detoxification processes, and redox homeostasis, thereby helping cells adapt to stress and minimize oxidative damage. In addition to its antioxidative functions, Nrf2 modulates diverse cellular processes including DNA repair mechanisms, autophagic pathways, metabolic regulation, and mitochondrial dynamics (Schmidlin et al., 2021). Aberrant Nrf2 signaling contributes to the pathogenesis of neurodegenerative, cardiovascular, metabolic, inflammatory, oncological, and chronic obstructive pulmonary disorders. This is because oxidative stress, mitochondrial dysfunction, and inflammation constitute the cardinal pathophysiological mechanisms underlying these disease entities. Elucidating the regulatory mechanisms of Nrf2 activity and its broadening functional repertoire poses significant challenges for targeted therapeutic development while concurrently offering substantial opportunities for treating diverse disease states (Zgorzynska et al., 2021).

2 Structure of the Nrf2 gene and protein

The human Nrf2 protein is encoded by the *NFE2L2* gene, which maps to cytogenetic band 2q31.2 on chromosome 2. According to the National Center for Biotechnology Information (NCBI) GenBank database, *NFE2L2* spans base pairs 177 227 595 to 177 392 697, while more recent data from the AceView database place it on the reverse strand of chromosome 2q31.2, between base pairs 178 257 419 and 178 083 605, with a total length of 173.81 kb. The *NFE2L2* gene comprises 40 distinct introns, encoding 38 messenger RNA (mRNA) variants, including 31 alternatively spliced forms and seven unspliced

✉ Handong FAN, fanhandong@whu.edu.cn
Rong CHEN, rongchen1984@hznu.edu.cn
Handong FAN, https://orcid.org/0000-0001-7040-7744
Rong CHEN, https://orcid.org/0000-0002-8642-786X
Yunfei PAN, https://orcid.org/0009-0003-1286-1713

Received Jan. 31, 2025; Revision accepted July 21, 2025;
Crosschecked June 12, 2026; Published online July 1, 2026

© Zhejiang University Press 2026

transcripts (Ulasov et al., 2022). Further analysis indicates that 22 of these variants are translatable, generating 19 distinct protein isoforms. These isoforms exhibit distinct 5'- and 3'-untranslated region configurations, splice junction architectures, and exon–intron boundary organizations, underpinning the complex transcriptional and post-transcriptional regulation of Nrf2 (Huang et al., 2023).

The Nrf2 protein comprises six highly conserved domains (Neh1–Neh6), each contributing to different aspects of cellular regulation. The Neh1 domain contains a basic leucine zipper (bZIP) structural motif, which is essential for DNA binding and heterodimerization with small musculoaponeurotic fibrosarcoma (sMaf) proteins. The Neh2 domain harbors two critical motifs (ETGE and DLG) that mediate interaction with Kelch-like ECH-associated protein 1 (Keap1), the principal regulator of Nrf2 degradation under basal conditions. Neh3, Neh4, and Neh5 domains are indispensable for transcriptional activation: Neh3 recruits chromatin-modifying complexes, while Neh4 and Neh5 serve as transactivation domains that assemble transcriptional cofactors. The Neh6 domain contains two degron sequences (DSGIS and DSAPGS) that facilitate Keap1-independent, β-transducin repeat-containing protein (β-TrCP)-mediated ubiquitination and proteasomal degradation, particularly during oxidative stress. Finally, the Neh7 domain negatively modulates Nrf2 activity through retinoic acid receptor α binding, thereby inhibiting the recruitment of transcriptional coactivators (Fig. 1) (He et al., 2020; Zgorzynska, et al., 2021).

3 Nrf2 signaling pathway activation mechanism

The Nrf2 signaling pathway undergoes activation via canonical and non-canonical mechanisms. In the

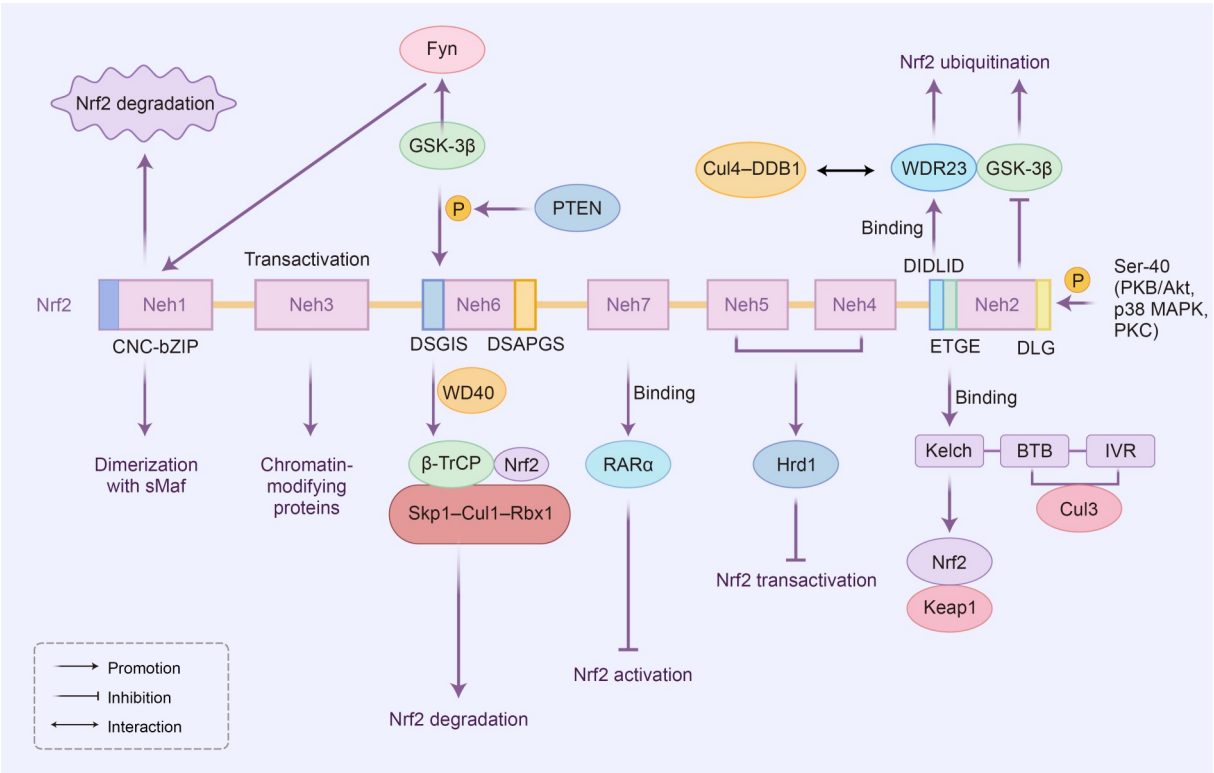

Fig. 1 Six domains of nuclear factor erythroid 2-related factor 2 (Nrf2) and their functions. CNC-bZIP: cap'n'collar-basic region leucine zipper; sMaf: small musculoaponeurotic fibrosarcoma; Fyn: tyrosine-protein kinase Fyn; GSK-3β: glycogen synthase kinase-3β; PTEN: phosphatase and tensin homolog; β-TrCP: β-transducin repeat-containing protein; Skp1: S-phase kinase-associated protein 1; Cul1: Cullin 1; Rbx1: RING-box protein 1; Skp1–Cul1–Rbx1: E3 ubiquitin ligase; RARα: retinoic acid receptor α; Hrd1: HMG-CoA reductase degradation 1; DDB1: damage-specific DNA-binding protein 1; Cul4–DDB1: ubiquitin ligase; WDR23: WD repeat-containing protein 23; BTB: bric-à-brac tramtrack broad complex; IVR: intervening region; Ser-40: serine-40; PKB/Akt: protein kinase B; MAPK: mitogen-activated protein kinase; PKC: protein kinase C.

predominant Keap1/Nrf2/antioxidant response element (ARE) regulatory axis, Keap1 functions as a substrate adaptor for the Cullin 3 (Cul3)–RING-box protein 1 (Rbx1) E3 ubiquitin ligase complex, targeting Nrf2 for constitutive ubiquitination and proteasomal degradation under basal conditions. Oxidative stressors or electrophilic compounds induce post-translational modifications of Keap1's cysteine sensor residues, disrupting Keap1–Nrf2 binding. Stabilized Nrf2 subsequently accumulates cytoplasmically and translocates to the nucleus. There, Nrf2 heterodimerizes with sMaf proteins and binds AREs in regulatory regions of target genes, transactivating cytoprotective enzymes essential for antioxidant defense and phase II detoxification. This orchestrated response confers cellular protection against oxidative insult mediated by reactive oxygen species (ROS) and ionizing radiation (Oh and Jun, 2018; Huang et al., 2023).

The activation of the Keap1/Nrf2/ARE signaling pathway is regulated not only through ubiquitination but also by multi-level mechanisms that control Nrf2 localization, trafficking, and stability. Nrf2's cellular distribution is dynamic, as it can shuttle between the nucleus, cytoplasm, and mitochondrial membrane. This distribution is influenced by processes such as Keap1-mediated degradation and signaling pathways that promote Nrf2's nuclear translocation. This spatial regulation critically depends on key mediators: ubiquitin-conjugating enzyme E2 E3 (UBE2E3) facilitates intracellular trafficking, while importin 11 (IPO11) governs nuclear translocation efficiency. Collectively, these coordinated mechanisms ensure Nrf2 stabilization and transcriptional competence for optimal oxidative stress responses (Zgorzynska et al., 2021).

Nrf2 stability is stringently modulated at transcriptional and post-transcriptional levels. Transcriptionally, Nrf2 expression is augmented via an autoregulatory positive feedback loop involving ARE-like sequences (Miao et al., 2005). The NFE2L2 promoter contains CpG-rich islands, wherein hypermethylation suppresses transcriptional activity, thereby reducing Nrf2 abundance (Zgorzynska et al., 2021). This multifaceted regulatory architecture ensures precise control of Nrf2 signaling, which is essential for maintaining cellular redox equilibrium and orchestrating effective antioxidant responses.

Post-transcriptional regulation of Nrf2 involves pivotal microRNA (miRNA/miR)-mediated mechanisms that target Nrf2 mRNA for degradation (O'Brien et al., 2018). Recent investigations with oxygen-glucose deprivation/reperfusion (OGD/R) models demonstrate that miR-380-5p potentiates Nrf2/Keap1 pathway activation by directly repressing bric-à-brac tramtrack broad complex (BTB) and cap'n'collar (CNC) homology 1 (Bach1) and Bach2, which are transcriptional competitors of Nrf2 for ARE genomic loci (Wang and Xu, 2021). Furthermore, miR-152-3p overexpression enhances Nrf2/ARE signaling by directly inhibiting postsynaptic density protein-93 (PSD-93), a Fyn kinase activator responsible for promoting Nrf2 degradation. This modulation alleviates OGD/R-induced neuronal damage, highlighting the neuroprotective role of miRNA-mediated Nrf2 regulation (Zhang et al., 2019). Post-translational modifications—including phosphorylation, acetylation, and small ubiquitin-like modifier-mediated modification (SUMOylation)—allosterically modulate the structural and functional interaction between Nrf2 and its principal regulatory partner Keap1 (Huang et al., 2015). These modifications can influence Nrf2 stability by altering its susceptibility to proteasomal degradation, thereby impacting its intracellular levels and availability for executing its protective cellular functions.

Non-canonical activation mechanisms involve additional signaling pathways and specific protein interactions (Huang et al., 2015). The sequestosome-1 (p62/SQSTM1) protein directly interacts with Keap1, disrupting the Keap1–Nrf2 complex and stabilizing Nrf2. This stabilization facilitates the cytosolic accumulation of Nrf2 and its consequent nuclear translocation (Komatsu et al., 2010). The tumor suppressor breast cancer susceptibility 1 (BRCA1) engages Nrf2 via direct protein–protein interaction, shielding it from Keap1-mediated ubiquitin-proteasomal degradation while enhancing its transactivation potential. PALB2 (partner and localizer of BRCA2) amplifies this stabilization by disassembling the Keap1–Cul3 E3 ubiquitin ligase complex, thereby potentiating Nrf2 activation (Yi et al., 2021). Pharmacological agents, including sulforaphane (SFN), bardoxolone methyl, and curcumin, activate Nrf2 through covalent adduction of reactive cysteine sensor residues within Keap1. This modification disrupts Keap1-mediated Nrf2 ubiquitination, facilitating Nrf2 stabilization (Bahar et al., 2017).

Nrf2 stability and activity are modulated by intersecting signaling cascades. The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway phosphorylates and inhibits glycogen synthase kinase-3β

(GSK-3β), attenuating β-TrCP-mediated Nrf2 degradation and oxidative insults. Extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (MAPK), and c-Jun N-terminal kinase (JNK) stabilize Nrf2 via site-specific phosphorylation (Joo et al., 2016). Protein kinase C (PKC) phosphorylates serine-40 (Ser-40) within the Neh2 domain, while casein kinase 2 phosphorylates serine/threonine residues in Neh4 and Neh5 domains. Collectively, they enhance Nrf2 nuclear translocation and transactivation capacity (Bloom and Jaiswal, 2003). Although p38 MAPK phosphorylates Nrf2, its contribution to transcriptional activation remains constrained, indicating indirect regulatory functions (Bloom and Jaiswal, 2003; Best et al., 2018). Additionally, silent mating-type information regulation 2 homolog 1 (SIRT1) enhances Nrf2 stability by reducing its ubiquitination and promoting its nuclear accumulation, further supporting its role in oxidative stress responses (Park et al., 2018). These non-canonical regulatory mechanisms establish a supplementary tier of Nrf2 control, suggesting novel therapeutic targets for pathophysiological conditions associated with oxidative stress and redox dysregulation (Fig. 2).

4 Regulation of Nrf2 by ubiquitin and proteasome degradation

Nrf2 degradation is orchestrated by multiple E3 ubiquitin ligase complexes through both Keap1-dependent and Keap1-independent mechanisms. The Keap1–Cul3–Rbx1 complex constitutes the principal E3 ligase governing constitutive Nrf2 turnover under basal conditions. In contrast, Keap1-independent degradation involves other pathways, such as the β-TrCP–Skp1–Cul1–Rbx1 complex, HMG-CoA reductase degradation 1 (Hrd1), and the WD repeat-containing protein 23 (WDR23)–Cul4–damage-specific DNA-binding protein 1 (DDB1) complex. These alternative systems contribute to Nrf2 degradation under specific

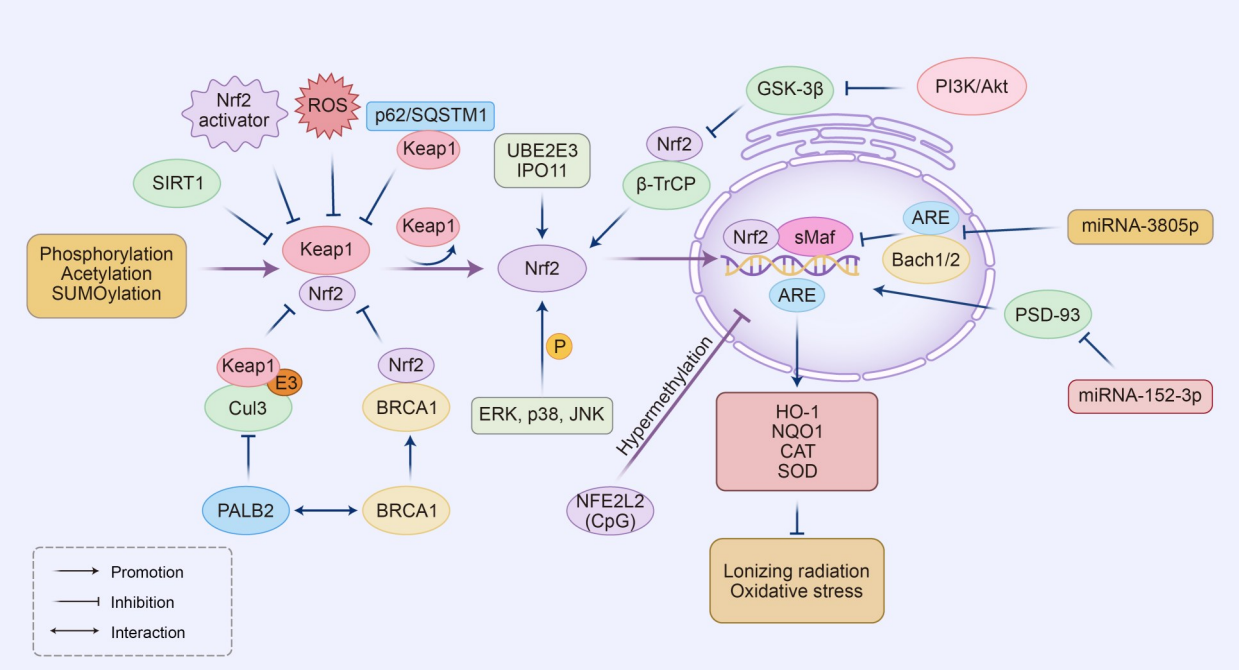

Fig. 2 Activation and stabilization mechanism of nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway. SIRT1: silent mating-type information regulation 2 homolog 1; ROS: reactive oxygen species; Keap1: Kelch-like ECH-associated protein 1; p62/SQSTM1: sequestosome-1; Cul3: Cullin 3; BRCA1: breast cancer susceptibility 1; PALB2: partner and localizer of BRCA2; UBE2E3: ubiquitin-conjugating enzyme E2 E3; IPO11: importin 11; ERK: extracellular signal-regulated kinase; JNK: c-Jun N-terminal kinase; CpG: cytosine-phosphate-guanine; β-TrCP: β-transducin repeat-containing protein; sMaf: small musculoaponeurotic fibrosarcoma; ARE: antioxidant response element; HO-1: heme oxygenase-1; NQO1: NAD(P)H:quinone oxidoreductase 1; CAT: catalase; SOD: superoxide dismutase; Bach1/2: bric-à-brac tramtrack broad complex (BTB) and cap'n'collar (CNC) homology 1/2; PSD-93: postsynaptic density protein-93; GSK-3β: glycogen synthase kinase-3β; PI3K/Akt: phosphatidylinositol 3-kinase/protein kinase B.

cellular conditions and environmental stressors (Zhao et al., 2015).

In the canonical Keap1-dependent degradation pathway, Keap1 serves as the primary sensor and regulator of Nrf2 turnover. Keap1 has three functionally critical domains: the BTB domain and the intervening region (IVR), which recruit Cul3 to form the Cullin–RING ubiquitin ligase complex, and the Kelch domain, which specifically binds to the Neh2 domain of Nrf2 (Iso et al., 2016; He et al., 2020). Under basal conditions, Keap1 constitutively facilitates Nrf2 polyubiquitination and proteasomal degradation. During oxidative or electrophilic stress, covalent modifications of specific Keap1 cysteine residues disrupt Nrf2 binding. This enables Nrf2 stabilization, nuclear translocation, dimerization with sMaf proteins, and subsequent activation of cytoprotective genes via AREs (Kobayashi et al., 2004; Hast et al., 2013; Liu et al., 2018).

The Keap1-independent GSK-3β/β-TrCP axis orchestrates Nrf2 degradation through GSK-3β-mediated phosphorylation of the DSGIS phosphodegron motif. This post-translational modification facilitates β-TrCP recognition via its WD40 domain and subsequent assembly of the Skp1–Cul1–Rbx1 E3 ubiquitin ligase complex, ultimately targeting Nrf2 for degradation (Rada et al., 2011; Chowdhry et al., 2013). The phosphatase and tensin homolog (PTEN) may further enhance GSK-3β-mediated phosphorylation of the DSGIS motif in Nrf2, amplifying this degradation pathway (Rojo et al., 2014). Conversely, kinases, including protein kinase B (PKB), p38 MAPK, and PKC, phosphorylate Ser-40 within Nrf2's Neh2 domain and inhibit GSK-3β through N-terminal phosphorylation, enhancing Nrf2 stability and expanding its functional pool (Hayes et al., 2015). Additionally, GSK-3β activation facilitates the nuclear accumulation of Fyn kinase, which phosphorylates Nrf2's Neh1 domain. This promotes the nuclear output of Nrf2, enabling its subsequent ubiquitin-mediated proteasomal degradation (Jain and Jaiswal, 2007). Cell-based ubiquitination assays reveal that Hrd1 attenuates Nrf2 signaling through cytosolic binding to its Neh4 and Neh5 domains, resulting in the suppression of transactivation capacity (Wu et al., 2014). Furthermore, WDR23 mediates the post-translational stabilization of Nrf2 by binding the DIDLID motif within its Neh2 domain and engaging the Cul4–DDB1 ubiquitin ligase complex (Fig. 1).

5 Protective effects of Nrf2 regulation on mitochondria, oxidative stress, inflammation, and autophagy

Nrf2 serves as a central regulator of mitochondrial homeostasis and cytoprotective responses. It orchestrates mitochondrial biogenesis through transcriptional upregulation of mitochondrial transcription factor A (TFAM), which governs mitochondrial DNA replication and transcription (Li PA et al., 2017). Nrf2 further promotes ubiquitin-mediated mitophagy through transcriptional induction of PTEN-induced putative kinase 1 (PINK1) and Parkin, enabling selective autophagic clearance of depolarized mitochondria. Concurrently, Nrf2-inducible antioxidant enzymes attenuate mitochondrial ROS generation, thereby preserving membrane potential and oxidative phosphorylation efficiency (Cores et al., 2020). These coordinated mechanisms sustain bioenergetic capacity while preserving mitochondrial structure and function under both homeostatic and pathophysiological conditions.

Nrf2 mediates anti-inflammatory cytoprotection by transcriptionally repressing pro-inflammatory mediators such as interleukin-6 (IL-6) and IL-1β. In microglia, Nrf2 activation reduces the production of neurotoxic mediators. In Alzheimer's disease (AD), it attenuates amyloid-β genesis by suppressing β-site APP cleaving enzyme 1 (BACE1), thereby reducing amyloid plaque and neurofibrillary tangle formation (Yi et al., 2023). Similarly, in Parkinson's disease (PD), Nrf2 mitigates pathological α-synuclein aggregation and preserves dopaminergic neuron viability (Huang et al., 2020). In amyotrophic lateral sclerosis (ALS), Nrf2 enhances motor neuron viability by reducing proteotoxic stress from misfolded 43-kDa transactive response DNA-binding protein (TDP-43)/superoxide dismutase 1 (SOD1) aggregates while augmenting autophagic flux (Soejima-Kusunoki et al., 2022).

Nrf2 orchestrates the transcriptional regulation of autophagy, an essential cellular proteostatic mechanism. It enhances autophagic flux by modulating the expression of core autophagy machinery genes, including autophagy-related gene (ATG) family members and p62/SQSTM1, which mediate the clearance of damaged organelles, protein aggregates, and depolarized mitochondria. The p62–Keap1 interaction establishes a critical autoregulatory amplification circuit: p62 sequesters competitive Keap1, liberating and

stabilizing Nrf2, while Nrf2 transcriptionally activates p62 expression. This reciprocal regulation amplifies autophagic capacity, enhancing proteostatic competence and cellular stress adaptation (Yi et al., 2023). Nrf2 also promotes lysosome biogenesis via transcription factor EB (TFEB), accelerating misfolded protein clearance. These coordinated mechanisms reduce oxidative stress, inflammation, protein aggregation, and mitochondrial dysfunction—characteristic pathological features of neurodegenerative disorders. Elucidation of these Nrf2-mediated pathways informs targeted therapeutic development for neurodegenerative pathologies (Yu et al., 2022) (Fig. 3).

6 Nrf2 mechanisms and signal regulation by natural and chemically synthesized drugs

Diverse natural and synthetic compounds have been extensively investigated as pharmacological modulators of the Nrf2 signaling axis (Table 1), which orchestrates pivotal cytoprotective responses. Substances such as SFN, bardoxolone methyl, tert-butylhydroquinone (TBHQ), resveratrol (RSV), curcumin, catechins, genistein, diallyl trisulfide, and epigallocatechin gallate have been identified as effective natural activators. Synthetic compounds like oltipraz also stimulate this pathway (Yi et al., 2021).

Flavonoids represent potent Nrf2 activators, primarily due to their antioxidant and anti-inflammatory pharmacophores. Their bioactive aglycone moieties induce Nrf2 nuclear translocation, demonstrating therapeutic potential in mitigating oxidative stress and inflammation. Genistein, a principal phytoestrogen abundant in legumes, significantly modulates the Nrf2 pathway. Empirical data indicate that genistein enhances both transcription and translation of Nrf2-governed cytoprotective enzymes—notably heme oxygenase-1 (HO-1), cyclooxygenase-2, and inducible nitric oxide synthase (iNOS)—through phosphorylation of the PI3K p85 subunit. This activation of PI3K p85 phosphorylation contributes to mitigating neuronal damage and alleviating β-amyloid peptide-mediated oxidative stress in astrocytes, thereby exerting a protective effect on cells (Guo et al., 2021). Beyond conferring neuroprotection, genistein activates the Nrf2 pathway to mitigate oxidative damage in the cardiovascular system, impeding cardiovascular disease pathogenesis. Under

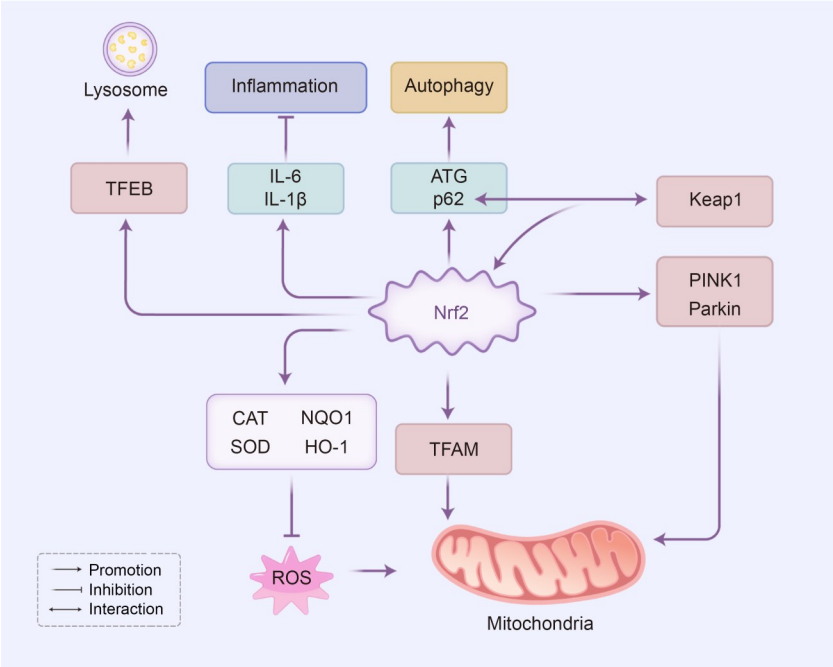

Fig. 3 Regulatory effects of nuclear factor erythroid 2-related factor 2 (Nrf2) on mitochondrial function, oxidative stress, neuroinflammation, and autophagy. TFEB: transcription factor EB; IL: interleukin; CAT: catalase; NQO1: NAD(P)H: quinone dehydrogenase 1; SOD: superoxide dismutase; HO-1: heme oxygenase-1; ROS: reactive oxygen species; ATG: autophagy-related gene; p62: sequestosome-1; TFAM: mitochondrial transcription factor A; Keap1: Kelch-like ECH-associated protein 1; PINK1: phosphatase and tensin homolog (PTEN)-induced putative kinase 1.

specific conditions, genistein inhibits tyrosine kinase activity, diminishing phospho-Nrf2 nuclear accumulation and attenuating Nrf2/ARE signaling (Liang et al., 2018).

Catechins and their partial derivatives (e.g., RSV and oxalic acid) activate the Keap1–Nrf2–ARE pathway by interacting with cysteine residues of Keap1, thereby dissociating the Keap1–Nrf2 complex. This liberation facilitates Nrf2 nuclear translocation and subsequent transcriptional activation of cytoprotective genes encoding antioxidant and detoxification enzymes. Consequently, catechin-mediated Nrf2 signaling elevates the expression and catalytic activity of multiple antioxidative enzymes, establishing a comprehensive intracellular cytoprotective network that effectively counteracts oxidative insults. In lipopolysaccharide-induced PD models, activated Nrf2 restores dopamine and γ-aminobutyric acid levels while reducing glutamate content. Nrf2 activation antagonizes nuclear factor-κB (NF-κB) signaling, suppressing the synthesis and secretion of pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), IL-1β, and IL-6 (Zhang et al., 2022). In addition, catechins modulate apoptotic pathways via Nrf2 activation, elevating anti-apoptotic protein expression while suppressing pro-apoptotic protein activity, reducing the rate of cell apoptosis (Shen et al., 2024). This mechanism of action helps to protect cells from apoptotic death induced by harmful external stimuli such as oxidative stress and inflammatory reactions, as well as to maintain tissue stability and function.

Luteolin, a flavonoid ubiquitous in plant-derived foods, exhibits potent anti-inflammatory, antioxidant, and antitumorigenic properties (Zhu et al., 2024). Luteolin activates Nrf2 signaling, elevating antioxidant enzyme expression, including HO-1, thereby attenuating pathological progression in blue light-induced retinal degeneration and hyperuricemic nephropathy (Yu et al., 2024; Hayakawa et al., 2025). However, when acting as an inhibitor, luteolin suppresses Nrf2 activation by upregulating $p47^{phox}$ and $p22^{phox}$ expression, inducing aberrant ROS accumulation and apoptosis in HT29 colon carcinoma cells (Yang et al., 2020). At physiological concentrations, it potentiates the chemosensitivity of A549 lung adenocarcinoma cells to oxaliplatin, bleomycin, and doxorubicin. Small interfering RNA (siRNA)-mediated Nrf2 knockdown abrogates luteolin-induced chemosensitization, indicating that pharmacological Nrf2 inhibition may potentiate therapeutic responsiveness to chemotherapeutic agents (Tang et al., 2011).

RSV, a non-flavonoid polyphenolic compound, represents a naturally occurring phytoalexin biosynthesized by plants upon exposure to environmental stressors. It stabilizes the Nrf2 protein by inhibiting its ubiquitin-mediated degradation and facilitating its nuclear translocation, enabling Nrf2 to function as a transcription factor. RSV administration in an AD murine model exerts neuroprotective effects and enhances survival, which is attributed to the attenuation of amyloid-β accumulation and the suppression of tau protein hyperphosphorylation (Porquet et al., 2013). RSV further activates the PI3K/Akt signaling cascade, inducing serine phosphorylation of Nrf2. This post-translational modification disrupts the Nrf2–Keap1 complex, facilitating Nrf2 nuclear translocation and the subsequent transactivation of ARE-regulated genes (Yang et al., 2018). Nrf2 upregulates the expression of phase II detoxifying enzymes and antioxidants, including glutathione peroxidase (GPX) and SOD, significantly augmenting cellular antioxidant defense systems and mitigating oxidative stress-induced damage. This regulatory pathway is integral to cell survival, proliferation, and metabolic homeostasis. RSV extends its protective effects beyond antioxidative activity by exerting significant anti-inflammatory properties. This action is mediated through Nrf2-dependent pathways, resulting in the inhibition of key inflammation mediators such as NF-κB. Consequently, RSV attenuates the synthesis and secretion of pro-inflammatory cytokines and mediators, thereby facilitating the resolution of inflammatory cascades (Xia et al., 2024).

SFN, an isothiocyanate derived from cruciferous vegetable glucosinolates, functions as an electrophilic compound that covalently modifies key cysteine residues within Keap1. This modification disrupts the Keap1-Nrf2 protein–protein interaction, enabling Nrf2 to evade Keap1-mediated ubiquitination and proteasomal degradation, facilitating its nuclear accumulation. Following nuclear translocation, Nrf2 dimerizes with sMaf proteins and binds to ARE, transactivating the expression of phase II detoxifying enzymes such as glutathione *S*-transferase (GST), uridine diphosphate glucuronosyltransferase, and NAD(P)H:quinone dehydrogenase 1 (NQO1). Concurrently, SFN indirectly inhibits the activity of phase I enzymes by modulating

the Nrf2 pathway, thereby reducing the metabolic conversion of pro-carcinogens into carcinogens. SFN also enhances cellular antioxidant capacity by promoting the synthesis of antioxidants such as glutathione (GSH), further strengthening the cell's defense against oxidative stress (Chen GX et al., 2024). Beyond its chemopreventive properties, SFN facilitates the detoxification of harmful substances, including pesticide residues and heavy metals, by activating Nrf2-regulated detoxification enzymes. These enzymes convert toxic compounds into water-soluble, less toxic metabolites, which are subsequently excreted via the liver or kidneys. SFN suppresses inflammatory pathways, including the NF-κB signaling axis, through activation of the Nrf2 cascade, resulting in the attenuation of pro-inflammatory cytokine production (Ma et al., 2023).

TBHQ, a synthetic electrophilic compound, is a well-characterized activator of the Nrf2 signaling pathway that has been extensively investigated for its capacity to ameliorate oxidative stress and associated cellular damage (Ujah et al., 2021). TBHQ mediates its effects through the electrophile-mediated covalent modification of specific cysteine residues within Keap1, thereby disrupting Keap1-mediated repression of Nrf2 and facilitating Nrf2 nuclear translocation. Within the nucleus, Nrf2 heterodimerizes with sMaf proteins, binds to ARE, and activates the transcription of cytoprotective enzymes and antioxidants (Baxter et al., 2021). TBHQ demonstrates significant cardioprotective efficacy, particularly against doxorubicin-induced pathophysiological alterations, via Nrf2-dependent attenuation of oxidative damage. The compound further ameliorates ROS generation, exhibiting broad cytoprotection across diverse cellular systems. In H9C2 cardiomyocyte models, TBHQ mitigates oxidative stress, apoptosis, and cellular injury elicited by deleterious agents, including ethanol and xenobiotics (Deng et al., 2021).

Metformin, a low-cost first-line biguanide antidiabetic agent with a favorable safety profile, manifests pleiotropic therapeutic efficacy extending beyond glycemic control to encompass pulmonary fibrosis, oncological conditions, obesity, and hepatopathies (Lv and Guo, 2020). In hyperglycemic models, metformin ameliorates renal inflammatory injury in diabetic murine models through Keap1/Nrf2 pathway modulation and enhanced mitophagy in renal tubular epithelial cell senescence (Sun D et al., 2024). Within oncology, metformin significantly potentiates cisplatin chemosensitivity in gastric carcinoma via Nrf2 suppression, metabolic reprogramming, and concomitant activation of oxidative stress, p53 tumor suppression, and adenosine monophosphate-activated protein kinase (AMPK) signaling cascades (Duan et al., 2025). Clinically, the

Table 1 Mechanisms of Nrf2 regulation by various drugs

Drug	Mechanisms	References
Genistein	Increasing the phosphorylation of PI3K p85 synergistically enhances the expression of HO-1 at mRNA and protein levels	Huang et al., 2023
Catechin	Acting on the Nrf2 pathway; reducing ROS levels; inducing ARE-mediated expression of antioxidant genes; including phase II detoxifying enzymes	Yang et al., 2022
Luteolin	Keap1/Nrf2/HO-1 signaling pathway; suppressing Nrf2 activation by modulating $p47^{phox}$ and $p22^{phox}$ expression; inducing a decrease in Nrf2 expression, resulting in reduced binding of Nrf2 to ARE; depletion of reduced glutathione	Tang et al., 2011; Yang et al., 2020; Hayakawa et al., 2025
Resveratrol	Increasing *Nrf2* gene expression; upregulating downstream antioxidant enzymes such as SOD, GPX, and CAT	Majhi et al., 2023
Sulforaphane	Keap1/Nrf2 pathway, promoting its nuclear translocation; inducing Nrf2/ARE/PRDX6 activity; inducing antioxidant enzyme expression; increasing mitochondrial biogenesis; preventing dopaminergic neuronal loss	Shore et al., 2024
Tert-Butylhydroquinone	Keap1/Nrf2/ARE signal pathway; stimulating transcription of phase 2 genes	Satoh et al., 2009
Metformin	Keap1/Nrf2 pathway and enhancing mitophagy; suppressing Nrf2 expression and activating p53 and AMPK pathways; Keap1/Nrf2/HO-1 signal pathway	Tang et al., 2022; Sun D et al., 2024; Duan et al., 2025

PI3K: phosphatidylinositol 3-kinase; HO-1: heme oxygenase-1; mRNA: messenger RNA; Nrf2: nuclear factor erythroid 2-related factor 2; ROS: reactive oxygen species; ARE: antioxidant response element; Keap1: Kelch-like ECH-associated protein 1; SOD: superoxide dismutase; GPX: glutathione peroxidase; CAT: catalase; PRDX6: peroxiredoxin 6; AMPK: adenosine monophosphate-activated protein kinase.

combination of sorafenib and metformin for the treatment of hepatocellular carcinoma suppresses cancer cell proliferation by inducing ferroptosis through modulation of the p62–Keap1–Nrf2/HO-1 pathway (Tang et al., 2022).

7 Regulatory roles of Nrf2 in several diseases

Nrf2 is a critical transcription factor that regulates cellular homeostasis by controlling the expression of protective genes involved in antioxidant defense, detoxification, and redox balance. Due to its central role in mitigating oxidative stress and inflammation, the Nrf2 pathway influences the progression of numerous diseases, making it a promising target for therapeutic intervention.

7.1 Neurodegenerative diseases

Oxidative stress and neuroinflammation are pathophysiological hallmarks of neurodegenerative disorders. In AD models, Nrf2 nuclear translocation within substantia nigra dopaminergic neurons mediates homeostatic regulation of intracellular ROS balance and confers cytoprotection to this vulnerable neuronal population. Decreased nuclear Nrf2 expression is documented in AD, with a recent meta-analysis of microarray datasets identifying 31 downregulated ARE-driven genes in AD patients (Wang et al., 2017). Correspondingly, transgenic AD mouse models demonstrate that enhanced Nrf2 expression and downstream antioxidant enzymes (e.g., HO-1) ameliorate spatial learning deficits and cognitive impairment. These findings underscore Nrf2's potential to mitigate early AD pathological processes, including neuroprotection mediated by the regulation of amyloid-β peptide and phosphorylated tau protein (Yang et al., 2025).

PD manifests as the progressive degeneration of substantia nigra dopaminergic neurons and the accumulation of neuronal inclusion bodies (Lewy bodies) containing ubiquitinated α-synuclein aggregates (Funayama et al., 2023). Proximity proteomics analyses demonstrate that ZNF746 (Paris), a PD-associated zinc finger transcription repressor, significantly downregulates endogenous NQO1 expression. This repression induces oxidative stress and apoptotic cascades, driving dopaminergic neurodegeneration in PD models. Mechanistically, ZNF746 interacts with Nrf2-MAFG heterodimers, repressing ARE-driven cytoprotective gene expression. Pharmacological Nrf2 activation counteracts these pathological processes by attenuating ROS production, inhibiting apoptotic pathways, reducing α-synuclein aggregation, and ultimately conferring neuroprotection (Lapak et al., 2023).

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by progressive neuronal loss and the accumulation of mutant huntingtin protein aggregates. An analysis of HD brain tissue revealed elevated oxidative stress markers, mitochondrial dysfunction, and sustained neuroinflammation (Valadão et al., 2020). Nrf2-deficient mice are more susceptible to the effect of mitochondrial complex II inhibitor 3-nitropropionic acid (3-NP), while Nrf2 overexpression confers striatal neuroprotection against 3-NP and malonate toxicity (Shih et al., 2005; Hamouda et al., 2024). Pharmacological activation of the Nrf2/ARE pathway by synthetic triterpenoids upregulates endogenous antioxidant defenses, including cerebral HO-1 expression, reduces lipid peroxidation biomarkers such as malondialdehyde (MDA), ameliorates motor deficits, and extends survival in transgenic HD murine models (Stack et al., 2010).

ALS is a rapidly progressive and invariably fatal neurodegenerative disorder characterized by the selective degeneration of cortical and spinal motor neurons. Oxidative damage, neuroinflammation, and mitochondrial dysfunction constitute key pathogenic contributors. In human $SOD1^{G93A}$ ($hSOD1^{G93A}$) transgenic murine models, mutant SOD1 expression induces profound oxidative stress that suppresses total Nrf2 expression and impedes its nuclear translocation. This impairment downregulates the solute carrier family 7 member 11 (SLC7A11) and GPX4, thereby potentiating ferroptosis in motor neurons. Pharmacological activation of Nrf2 abrogates ferroptosis and confers neuroprotection in both in vitro and in vivo ALS models (Yang et al., 2023). Complementary investigations demonstrate that in the $hSOD1^{G93A}$ mouse model, desloratadine administration exerts multifaceted protective effects through the 5-hydroxytryptamine receptor 2A ($5HTR_{2A}$)/cyclic adenosine monophosphate (cAMP)/AMPK signaling axis by promoting autophagy to reduce mutant hSOD1 levels, suppressing oxidative stress via the downstream Nrf2–HO-1/NQO1 pathway, and inhibiting astrocyte-mediated neuroinflammation through the NF-κB/NOD like receptor family containing pyrin domain protein 3 (NLRP3) cascade in the spinal cord (Lu et al., 2024).

7.2 Cancers

In breast cancer murine models, Nrf2 activity is principally orchestrated by its epigenetic regulator zinc finger MYND-type containing 8 (ZMYND8). ZMYND8 enhances Nrf2 stability by mitigating Keap1-mediated ubiquitination, impeding Nrf2 proteasomal degradation. It recruits Nrf2 to the promoters of antioxidant genes, leading to their increased expression, reduced iron levels within breast cancer stem cells (BCSCs), and the protection of BCSCs from oxidative stress and ferroptosis. The critical interaction between the PBP domain of ZMYND8 and the Neh1 domain of Nrf2 facilitates direct binding and mutual regulation. Furthermore, Nrf2 can enhance ZMYND8 transcription by binding to the ARE located on the ZMYND8 promoter, establishing a positive feedback loop. This regulatory mechanism underscores Nrf2's dual role in promoting antioxidant defense and maintaining BCSC survival. Therefore, a critical investigation is warranted to examine whether ZMYND8-mediated Nrf2 activation within BCSCs promotes therapeutic resistance in breast cancer (Luo MW et al., 2024).

In prostate cancer (PCa) cellular models, Nrf2 regulation is principally mediated through the speckle-type POZ protein (SPOP)–p62 interaction axis. SPOP functions as a substrate recognition component of the Cul3–RING E3 ubiquitin ligase complex, with frequent mutations observed in prostate carcinogenesis. Conversely, p62—a multifunctional scaffolding protein integral to selective autophagy and stress response pathways—exhibits pathological elevation in diverse disease states and modulates Nrf2 activation through competitive Keap1 sequestration. Structural analyses establish that SPOP's meprin and TRAF-C homology (MATH) domain directly engages the substrate-binding consensus (SBC) motif of p62. Under normal physiological conditions, SPOP facilitates the non-degradable ubiquitination of p62, thereby negatively regulating p62-mediated sequestration of Keap1 and suppressing Nrf2-mediated stress responses. However, recurrent SPOP mutations abrogate this regulatory function. This molecular dysfunction promotes the pathological accumulation of p62, enhances autophagic flux, and sustains aberrant Nrf2 pathway activation (Shi et al., 2022).

Nrf2 demonstrates a biphasic regulatory function in pulmonary carcinogenesis, exhibiting tumor-suppressive or oncogenic activity modulated by disease progression stage. During initial tumorigenesis in pulmonary neoplasia murine models, Nrf2 exerts cytoprotective effects by sustaining cellular redox homeostasis, regulating phase II detoxification enzyme expression, preventing genomic instability, mediating cell cycle control, and inhibiting pro-inflammatory cascades. Nrf2 facilitates the progression of established tumors, whether the activation mechanism is pharmacological or genetic (Kalpana Deepa Priya et al., 2011; Tao et al., 2018). Non-small cell lung carcinoma (NSCLC) exhibits frequent Nrf2/Keap1 pathway mutations resulting in aberrant activation. This sustained Nrf2 upregulation confers cytoprotective advantages to malignant cells, consequently underpinning the development of chemoresistance in NSCLC (Chen et al., 2014).

7.3 Diabetes

Gestational diabetes mellitus (GDM) is a pregnancy-specific metabolic disorder characterized by insulin resistance, the unmanaged progression of which has profound adverse repercussions for both maternal health and fetal-neonatal outcomes across perinatal and lifelong timescales. Hyperglycemic conditions downregulate Nrf2 expression while significantly upregulating miR-142-5p in human trophoblastic BeWo cells. Notably, there is a strong inverse correlation between miR-142-5p levels and Nrf2 expression in GDM patients. This dysregulation leads to a marked decrease in the expression of Nrf2-regulated antioxidant genes, including *NQO1*, *SOD*, and catalase (*CAT*), as well as decreased angiogenic markers such as hypoxia-inducible factor 1 alpha (HIF-1α) and stromal cell-derived factor (SDF). The suppression of miR-142-5p may restore Nrf2 activity, thereby promoting placental angiogenesis in GDM (Milan et al., 2024). *N*-Acetyl-L-cysteine-mediated activation of the Nrf2/HO-1 signaling axis in GDM murine liver tissue ameliorates oxidative stress, inflammatory responses, and hyperlipidemia, thereby attenuating gestational complications and improving reproductive outcomes (Wang et al., 2023).

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder characterized by the immune-mediated destruction of pancreatic β-cells, which results in absolute insulin deficiency and persistent hyperglycemia (Li W et al., 2017). In alloxan-damaged MIN6 β-cells, formononetin competitively binds Keap1 to activate the cytoprotective Nrf2 pathway, suggesting

that it may have therapeutic potential for mitigating oxidative stress in T1DM pathogenesis (Chen HP et al., 2024). Urolithin C administration in non-obese diabetic (NOD) mice significantly suppresses Keap1 expression and activates the Nrf2 antioxidant pathway, upregulating NQO1 and HO-1. This intervention improves β-cell functional integrity and preserves normoglycemia and insulin homeostasis, thereby attenuating T1DM pathogenesis (Luo et al., 2023).

Type 2 diabetes mellitus (T2DM) is a multifactorial, chronic, and complex metabolic disorder influenced by genetic predisposition, family history, age, lifestyle, and dietary habits (Ortiz-Martínez et al., 2022). Under high-glucose and high-fat conditions, poliumoside treatment of bone mesenchymal stem cells has been shown to enhance Nrf2 nuclear translocation. This activation consequently induces the transcriptional upregulation of the cytoprotective enzymes HO-1 and GPX4, thereby attenuating ferroptosis and promoting the biosynthesis of osteogenic regulatory proteins (Xu et al., 2024). In streptozotocin-induced T2DM mouse models, treatment with gentisic acid significantly increases *p21* gene expression while reducing the binding of Keap1 to Nrf2. This interference decreases Nrf2 ubiquitination and subsequent degradation, thereby enhancing the activation of the antioxidant redox signaling pathway (Razliqi et al., 2023).

7.4 Cardiovascular diseases

Atherosclerosis (AS) features lipid deposition in the arterial intima, forming uneven plaques. These induce lumen narrowing, impaired compliance, and fibrotic vessel walls. Using micheliolide (MCL) pretreatment in both oxidized low-density lipoprotein (ox-LDL)-stimulated macrophages and apolipoprotein E knockout ($ApoE^{-/-}$) mice, the results demonstrated that MCL increased the transcriptional activity of GPX4 and Xap5 circadian timekeeper (xCT) by activating the Nrf2 pathway, thereby inhibiting macrophage ferroptosis. Simultaneously, MCL competitively inhibits Keap1 at Arg483, inducing dissociation of the Keap1–Nrf2 complex. This facilitates Nrf2 nuclear translocation and attenuates AS (Luo X et al., 2024). In AS mouse models, itaconate exerts anti-atherosclerotic effects in vivo by inducing Nrf2 activation, which results in the downregulation of proinflammatory cytokine and chemokine expression and secretion, the inhibition of macrophage infiltration, and the suppression of inflammatory polarization (Song JR et al., 2023).

Hypertension is a prevalent cardiovascular disease that imposes significant global health burdens. Chronic microinjection of 5-aminoimidazole-4-carboxamide ribonucleotide into the rat hypothalamic paraventricular nucleus activates the AMPK/Nrf2 axis, downregulating NADPH oxidase 2 (NOX2)/NOX4 expression, reducing ROS production, and upregulating SOD1 expression. This activation also reduces TNF-α expression while increasing IL-10 levels, ultimately lowering plasma norepinephrine levels. These combined effects reduce systolic blood pressure and ameliorate hypertension (Fu et al., 2024). In wild-type Nrf2 ($Nrf2^{+/+}$) mice, the co-administration of angiotensin II (to induce oxidative stress) and TBHQ for 12–14 d activates Nrf2, upregulating dimethylarginine dimethylamino hydrolase-1 (*DDAH-1*) and *DDAH-2* gene expression. This reduces ROS levels, promotes nitric oxide (NO) production, and metabolizes asymmetric dimethylarginine, thereby inhibiting NO synthase (NOS). The inhibition of NOS reduces the production of endothelial-derived contraction factors, mitigating microvascular hyperreactivity to thromboxane A2 and endothelin-1. In Nrf2 knockout ($Nrf2^{-/-}$) mice, these protective effects are abolished, demonstrating that Nrf2 mediates protection against microvascular endothelial dysfunction and pathological hypertension induced by angiotensin II (Wang et al., 2018).

7.5 Respiratory diseases

In acute lung injury (ALI), inflammatory cascades and oxidative stress mediate accumulating intracellular ions and lipid peroxidation, triggering ferroptosis and pulmonary tissue damage. In mouse models of intestinal ischemia-reperfusion (IIR)-induced ALI, characteristic features of ferroptosis are observed, including decreased GSH and GPX4 levels, increased MDA expression and Nrf2 activation. Nrf2 knockdown accelerates ferroptosis, suppresses the expression of TERT and SLC7A11, and exacerbates lung tissue damage. These findings suggest that Nrf2 may mitigate ferroptosis in IIR ALI by regulating TERT and SLC7A11 expression levels (Dong et al., 2021). In murine models of sepsis-induced ALI, supplementation with 4-octyl itaconate (4-OI) rescues attenuated Nrf2/HO-1 signaling, elevates GPX4 expression, suppresses prostaglandin G/H synthase 2 (PTGS2), and

reduces MDA and intracellular iron levels, protecting against pulmonary injury (He et al., 2022).

Chronic cigarette smoke exposure in chronic obstructive pulmonary disease (COPD) induces pulmonary iron deposition, oxidative stress, and inflammation, culminating in lung tissue damage. Nrf2 counteracts this progression by suppressing ferroptosis through ROS scavenging and GSH biosynthesis to maintain redox homeostasis. Murine studies demonstrate that smoke-exposed lungs exhibit increased Fe^{3+} deposition, diminished Nrf2 and GPX4 expression, alveolar space enlargement, and airflow limitation. Nrf2 induction upregulates GPX4 and SOD expression, reduces ROS accumulation, and inhibits pro-inflammatory cytokine (e.g., IL-1β and IL-8) release. These findings establish that Nrf2/GPX4 axis activation mitigates ferroptosis and inflammatory cascades, thereby attenuating COPD-associated pulmonary parenchymal damage (Zhang et al., 2021).

7.6 Inflammatory diseases

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by synovial hyperplasia, pannus formation, and progressive bone/cartilage destruction, ultimately causing functional disability and joint deformity (Smolen et al., 2016). Genetic ablation of the Nrf2 transcriptional repressor Keap1 activates the Nrf2 pathway, suppressing pro-inflammatory cytokines (e.g., IL-6, IL-1β, TNF-α, and C-C motif chemokine 2 (CCL2)) and upregulating antioxidant enzymes in SKG murine joint tissues, thereby attenuating arthritis progression. The synthetic triterpenoid 1-[2-cyano-3,12-dioxooleana-1,9(11-dien-28-oyl)] imidazole (CDDO-Im), administered orally, elicits both prophylactic and therapeutic effects in SKG mice through Nrf2-dependent mechanisms (Zhang AQ et al., 2023). In synovial tissues of RA, lysine acetyltransferase 2A (KAT2A)-mediated histone H3 lysine 9 acetylation constrains Nrf2 activation, driving unchecked pro-inflammatory cytokine IL-1β production and promoting inflammatory pathogenesis. Consequently, pharmacological inhibition of KAT2A represents a promising therapeutic strategy for RA management (Zhang YK et al., 2023).

Inflammatory bowel disease (IBD) is a chronic relapsing-remitting gastrointestinal disorder characterized by intestinal inflammation with multifactorial etiology involving mucosal immunity, environmental triggers, and host genetics (Sahoo et al., 2023). In dextran sulfate sodium salt (DSS)-induced murine colitis models, Ginkgo biloba-derived nanoparticles significantly induce p62 upregulation. p62 sequesters Keap1, liberating Nrf2 from cytoplasmic retention. Subsequent Nrf2 nuclear translocation transactivates cytoprotective genes, including *HO-1* and glutamate-cysteine ligase modifier subunit (*GCLM*), attenuating oxidative damage, enhancing cytoprotection, and modulating mucosal immunity to promote epithelial restitution (Yang et al., 2024).

7.7 Chronic kidney diseases

Chronic kidney disease refers to a group of kidney disorders caused by primary kidney diseases, various secondary kidney diseases, and congenital and hereditary kidney conditions. In erastin-treated HK2 cells, vitexin competitively inhibits Keap1, preventing Nrf2 ubiquitination and proteasomal degradation, activating the Nrf2/HO-1 signaling pathway. This transcriptional activation upregulates GPX4 expression, subsequently inhibiting lipid peroxidation and ferroptosis (Song JY et al., 2023). Diabetic nephropathy is one of the most significant complications of diabetes. In $Nrf2^{-/-}$ mice with diabetic kidney disease (DKD), the downregulation of GSH synthesis and transferases, along with the increase of 8-hidroxy-2-deoxyguanosine (8-OHdG, a marker of oxidative stress), exacerbates renal oxidative stress. This results in mesangial expansion, glomerular capillary enlargement, and heightened inflammation characterized by the overexpression of CCL2, IL-6, and monocyte chemoattractant protein-1 (MCP-1), leading to macrophage infiltration and further cytokine release. These changes aggravate DKD progression, causing renal cortical thinning and fibrosis. Nrf2 dysfunction exacerbates DKD pathogenesis, whereas pharmacological restoration of Nrf2 activity confers renoprotection by attenuating disease progression (Liu et al., 2022). In DKD murine models, mitoQ administration upregulates Nrf2 expression/activity, induces PINK1 transcription, attenuates oxidative cytotoxicity, and restores mitochondrial homeostasis (Xiao et al., 2017).

7.8 Liver diseases

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological entity characterized by excessive hepatocellular lipid deposition in the absence of significant alcohol intake or other defined hepatic insults. Danshen Zexie decoction ameliorates high-fat-diet-induced

murine NAFLD via Nrf2 activation, suppressing ROS generation, reducing NLRP3 inflammasome assembly, and inhibiting pro-caspase-1 autocleavage into active caspase-1 (Biao et al., 2022). In vitro free fatty acid-induced NAFLD models demonstrate that garcinia cambogia activates the Nrf2/ARE pathway, reduces oxidative stress, suppresses lipogenic transcription factors CCAAT/enhancer-binding protein α (C/EBPα) and peroxisome proliferator-activated receptor γ (PPARγ), and decreases lipid accumulation and apoptosis (Han et al., 2021).

Viral hepatitis is an infectious inflammatory liver disease caused by hepatotropic viruses that potentially progresses to acute/chronic hepatic dysfunction with severe sequelae, including cirrhosis and hepatocellular carcinoma. The hepatitis B virus (HBV) X protein competitively disrupts Keap1–Nrf2 binding, while Nrf2 overexpression enhances its occupancy at the HBV core promoter region, significantly attenuating promoter activity and viral replication (Ariffianto et al., 2023). A study of liver biopsy specimens from 24 patients with chronic hepatitis C revealed that TGF-β1 enhances GSK-3β activity, which subsequently modulates Nrf2 as its homologous substrate. This regulation promotes Nrf2 nuclear translocation and degradation, impairing antioxidant responses and exacerbating hepatic injury. Consequently, GSK-3β-targeted therapy may exert hepatoprotective effects in hepatitis by enhancing Nrf2-mediated antioxidant responses (Jiang et al., 2015).

Cirrhosis represents a major global health burden with diverse etiological factors including obesity, NAFLD, chronic excessive alcohol consumption, hepatitis B and C infections, autoimmune disorders, cholestatic diseases, and pathological iron or copper accumulation. In carbon tetrachloride-induced hamster models, curcumin administration activates the Nrf2 signaling axis, suppressing NF-κB expression and inflammatory cytokine production while conferring hepatoprotection (Macías-Pérez et al., 2019). In bile duct ligation-induced cirrhotic murine models, Nrf2 protein expression is significantly downregulated. Naltrexone treatment substantially increases Nrf2 levels, enhancing its mediated antioxidant responses and attenuating hepatic fibrogenesis (Hosseini-Fard et al., 2022).

7.9 Aging

Aging is intricately associated with cumulative oxidative damage and cellular dysfunction. The Nrf2 pathway—a principal regulator of cytoprotective responses—experiences progressive age-related decline, with diminishing cellular capacity to maintain redox homeostasis and repair oxidized macromolecules, including proteins, nucleic acids, and lipids. The enhancement of Nrf2 signaling has been proposed as a promising strategy for mitigating aging-related processes, improving mitochondrial function, reducing inflammation, and potentially preventing the onset of age-related degenerative diseases (Sun et al., 2020). An aging model was established using D-galactose to induce senescence in both mice and HT22 cells. Vitamin D administration activates the Nrf2/HO-1 axis via vitamin D receptor signaling, attenuating NLRP1 inflammasome activation. This mechanism mitigates ferroptosis-mediated hippocampal neurodegeneration and cognitive decline in aging murine models (Guo et al., 2022). In vitro ultraviolet B (UVB)-irradiated human dermal fibroblasts and subsequent in vivo validation demonstrate that salvianolic acid B activates PI3K signaling while suppressing the IL-17/MAPK pathway. This dual action promotes Nrf2 nuclear translocation and the transcriptional activation of antioxidant genes, enhancing ROS clearance in photoaging models (Sun JM et al., 2024).

8 Conclusions

Nrf2 functions as a master transcriptional regulator that orchestrates cellular homeostasis by modulating antioxidant defense mechanisms, metabolic pathways, inflammatory responses, autophagic flux, and mitochondrial biogenesis. Its activity is dynamically regulated by multiple determinants such as activating signals, cell type-specific factors, protein interactions, and crosstalk with other transcriptional networks. Under physiological conditions, Nrf2 activation typically mediates cytoprotective effects. However, in cancer biology, this protective mechanism can be coopted to support tumor survival and progression. This pathway also exhibits a dual role during viral infection, potentially leading to either host-protective or pathogen-advantageous outcomes. Future research should focus on clarifying the mechanisms by which the Nrf2-dependent signaling pathway transitions from providing physiological benefits to promoting pathological conditions. Elucidating this mechanistic shift may provide critical insights into the pathogenesis of diverse disease pathologies.

Acknowledgments

We would like to thank all staff involved for their contribution.

Author contributions

Handong FAN and Rong CHEN contributed to the conception and design of the review. Yunfei PAN and Xiaodong ZHANG wrote the first draft of the manuscript and created all the figures. Yimin LU and Hao QIN critically revised the manuscript. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Yunfei PAN, Xiaodong ZHANG, Yimin LU, Hao QIN, Rong CHEN, and Handong FAN declare that they have no conflicts of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

Declaration on the use of generative AI tools

The authors declare that DeepSeek was used to refine the language of this manuscript during its preparation. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

References

Ariffianto A, Deng L, Abe T, et al., 2023. Oxidative stress sensor Keap1 recognizes HBx protein to activate the Nrf2/ARE signaling pathway, thereby inhibiting hepatitis B virus replication. *J Virol*, 97(10):e01287-23. https://doi.org/10.1128/jvi.01287-23

Bahar E, Kim JY, Yoon H, 2017. Quercetin attenuates manganese-induced neuroinflammation by alleviating oxidative stress through regulation of apoptosis, iNOS/NF-κB and HO-1/Nrf2 pathways. *Int J Mol Sci*, 18(9):1989. https://doi.org/10.3390/ijms18091989

Baxter PS, Márkus NM, Dando O, et al., 2021. Targeted de-repression of neuronal Nrf2 inhibits α-synuclein accumulation. *Cell Death Dis*, 12(2):218. https://doi.org/10.1038/s41419-021-03507-z

Best SA, de Souza DP, Kersbergen A, et al., 2018. Synergy between the KEAP1/NRF2 and PI3K pathways drives non-small-cell lung cancer with an altered immune microenvironment. *Cell Metab*, 27(4):935-943.e4. https://doi.org/10.1016/j.cmet.2018.02.006

Biao YN, Chen J, Liu CX, et al., 2022. Protective effect of Danshen Zexie decoction against non-alcoholic fatty liver disease through inhibition of ROS/NLRP3/IL-1β pathway by Nrf2 signaling activation. *Front Pharmacol*, 13:877924. https://doi.org/10.3389/fphar.2022.877924

Bloom DA, Jaiswal AK, 2003. Phosphorylation of Nrf2 at Ser^{40} by protein kinase C in response to antioxidants leads to the release of Nrf2 from INrf2, but is not required for Nrf2 stabilization/accumulation in the nucleus and transcriptional activation of antioxidant response element-mediated NAD(P)H:quinone oxidoreductase-1 gene expression. *J Biol Chem*, 278(45):44675-44682. https://doi.org/10.1074/jbc.M307633200

Chen GX, Shen L, Hu H, et al., 2024. Sulforaphane inhibits oxidative stress and may exert anti-pyroptotic effects by modulating NRF2/NLRP3 signaling pathway in *Mycobacterium tuberculosis*-infected macrophages. *Microorganisms*, 12(6):1191. https://doi.org/10.3390/microorganisms12061191

Chen HP, Lou YM, Lin SY, et al., 2024. Formononetin, a bioactive isoflavonoid constituent from *Astragalus membranaceus* (Fisch.) Bunge, ameliorates type 1 diabetes mellitus via activation of Keap1/Nrf2 signaling pathway: an integrated study supported by network pharmacology and experimental validation. *J Ethnopharmacol*, 322:117576. https://doi.org/10.1016/j.jep.2023.117576

Chen ZW, Ye XY, Tang NW, et al., 2014. The histone acetyltransferase hMOF acetylates Nrf2 and regulates anti-drug responses in human non-small cell lung cancer. *Br J Pharmacol*, 171(13):3196-3211. https://doi.org/10.1111/bph.12661

Chowdhry S, Zhang Y, McMahon M, et al., 2013. Nrf2 is controlled by two distinct β-TrCP recognition motifs in its Neh6 domain, one of which can be modulated by GSK-3 activity. *Oncogene*, 32(32):3765-3781. https://doi.org/10.1038/onc.2012.388

Cores Á, Piquero M, Villacampa M, et al., 2020. NRF2 regulation processes as a source of potential drug targets against neurodegenerative diseases. *Biomolecules*, 10(6):904. https://doi.org/10.3390/biom10060904

Deng SH, Wu DM, Li L, et al., 2021. TBHQ attenuates ferroptosis against 5-fluorouracil-induced intestinal epithelial cell injury and intestinal mucositis via activation of Nrf2. *Cell Mol Biol Lett*, 26:48. https://doi.org/10.1186/s11658-021-00294-5

Dong H, Xia YY, Jin SL, et al., 2021. Nrf2 attenuates ferroptosis-mediated IIR-ALI by modulating TERT and SLC7A11. *Cell Death Dis*, 12(11):1027. https://doi.org/10.1038/s41419-021-04307-1

Duan GH, Qi M, Xun LT, et al., 2025. Metformin enhances the chemosensitivity of gastric cancer to cisplatin by down-regulating Nrf2 level. *Anal Cell Pathol (Amst)*, 2025:5714423. https://doi.org/10.1155/ancp/5714423

Fu LY, Yang Y, Tian H, et al., 2024. Central administration of AICAR attenuates hypertension *via* AMPK/Nrf2 pathway in the hypothalamic paraventricular nucleus of hypertensive rats. *Eur J Pharmacol*, 974:176373. https://doi.org/10.1016/j.ejphar.2024.176373

Funayama M, Nishioka K, Li YZ, et al., 2023. Molecular genetics of Parkinson's disease: contributions and global trends. *J Hum Genet*, 68(3):125-130. https://doi.org/10.1038/s10038-022-01058-5

Guo J, Huang XQ, Dou L, et al., 2022. Aging and aging-related diseases: from molecular mechanisms to interventions and

treatments. *Signal Transduct Target Ther*, 7:391. https://doi.org/10.1038/s41392-022-01251-0

Guo JB, Yang GQ, He YQ, et al., 2021. Involvement of α7nAChR in the protective effects of genistein against β-amyloid-induced oxidative stress in neurons via a PI3K/Akt/Nrf2 pathway-related mechanism. *Cell Mol Neurobiol*, 41(2):377-393. https://doi.org/10.1007/s10571-020-01009-8

Hamouda HA, Sayed RH, Eid NI, et al., 2024. Azilsartan attenuates 3-nitropropinoic acid-induced neurotoxicity in rats: the role of IκB/NF-κB and KEAP1/Nrf2 signaling pathways. *Neurochem Res*, 49(4):1017-1033. https://doi.org/10.1007/s11064-023-04083-8

Han JH, Park MH, Myung CS, 2021. *Garcinia cambogia* ameliorates non-alcoholic fatty liver disease by inhibiting oxidative stress-mediated steatosis and apoptosis through NRF2-ARE activation. *Antioxidants*, 10(8):1226. https://doi.org/10.3390/antiox10081226

Hast BE, Goldfarb D, Mulvaney KM, et al., 2013. Proteomic analysis of ubiquitin ligase KEAP1 reveals associated proteins that inhibit NRF2 ubiquitination. *Cancer Res*, 73(7):2199-2210. https://doi.org/10.1158/0008-5472.Can-12-4400

Hayakawa R, Ishii T, Fushimi T, et al., 2025. Luteolin protects human ARPE-19 retinal pigment epithelium cells from blue light-induced phototoxicity through activation of Nrf2/Keap1 signaling. *Free Radic Res*, 59(4):356-368. https://doi.org/10.1080/10715762.2025.2503832

Hayes JD, Chowdhry S, Dinkova-Kostova AT, et al., 2015. Dual regulation of transcription factor Nrf2 by Keap1 and by the combined actions of β-TrCP and GSK-3. *Biochem Soc Trans*, 43(4):611-620. https://doi.org/10.1042/bst20150011

He F, Ru XL, Wen T, 2020. NRF2, a transcription factor for stress response and beyond. *Int J Mol Sci*, 21(13):4777. https://doi.org/10.3390/ijms21134777

He RY, Liu BH, Xiong R, et al., 2022. Itaconate inhibits ferroptosis of macrophage via Nrf2 pathways against sepsis-induced acute lung injury. *Cell Death Discov*, 8:43. https://doi.org/10.1038/s41420-021-00807-3

Hosseini-Fard SR, Dehpour AR, Emamgholipour S, et al., 2022. Naltrexone protects against BDL-induced cirrhosis in Wistar rats by attenuating thrombospondin-1 and enhancing antioxidant defense system via Nrf-2. *Life Sci*, 300:120576. https://doi.org/10.1016/j.lfs.2022.120576

Huang BX, Liu JX, Fu SP, et al., 2020. α-Cyperone attenuates H_2O_2-induced oxidative stress and apoptosis in SH-SY5Y cells *via* activation of Nrf2. *Front Pharmacol*, 11:281. https://doi.org/10.3389/fphar.2020.00281

Huang WK, Zhong Y, Gao BT, et al., 2023. Nrf2-mediated therapeutic effects of dietary flavones in different diseases. *Front Pharmacol*, 14:1240433. https://doi.org/10.3389/fphar.2023.1240433

Huang Y, Li WJ, Su ZY, et al., 2015. The complexity of the Nrf2 pathway: beyond the antioxidant response. *J Nutr Biochem*, 26(12):1401-1413. https://doi.org/10.1016/j.jnutbio.2015.08.001

Iso T, Suzuki T, Baird L, et al., 2016. Absolute amounts and status of the Nrf2-Keap1-Cul3 complex within cells. *Mol Cell Biol*, 36(24):3100-3112. https://doi.org/10.1128/mcb.00389-16

Jain AK, Jaiswal AK, 2007. GSK-3β acts upstream of Fyn kinase in regulation of nuclear export and degradation of NF-E2 related factor 2. *J Biol Chem*, 282(22):16502-16510. https://doi.org/10.1074/jbc.M611336200

Jiang YF, Bao H, Ge Y, et al., 2015. Therapeutic targeting of GSK3β enhances the Nrf2 antioxidant response and confers hepatic cytoprotection in hepatitis C. *Gut*, 64(1):168-179. https://doi.org/10.1136/gutjnl-2013-306043

Joo MS, Kim WD, Lee KY, et al., 2016. AMPK facilitates nuclear accumulation of Nrf2 by phosphorylating at serine 550. *Mol Cell Biol*, 36(14):1931-1942. https://doi.org/10.1128/mcb.00118-16

Kalpana Deepa Priya D, Gayathri R, Sakthisekaran D, 2011. Role of sulforaphane in the anti-initiating mechanism of lung carcinogenesis in vivo by modulating the metabolic activation and detoxification of benzo(a)pyrene. *Biomed Pharmacother*, 65(1):9-16. https://doi.org/10.1016/j.biopha.2010.08.009

Kobayashi A, Kang MI, Okawa H, et al., 2004. Oxidative stress sensor Keap1 functions as an adaptor for Cul3-based E3 ligase to regulate proteasomal degradation of Nrf2. *Mol Cell Biol*, 24(16):7130-7139. https://doi.org/10.1128/mcb.24.16.7130-7139.2004

Komatsu M, Kurokawa H, Waguri S, et al., 2010. The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1. *Nat Cell Biol*, 12(3):213-223. https://doi.org/10.1038/ncb2021

Lapak KM, Saeidi S, Bok I, et al., 2023. Proximity proteomic analysis of the NRF family reveals the Parkinson's disease protein ZNF746/PARIS as a co-complexed repressor of NRF2. *Sci Signal*, 16(815):eadi9018. https://doi.org/10.1126/scisignal.adi9018

Li PA, Hou XL, Hao SC, 2017. Mitochondrial biogenesis in neurodegeneration. *J Neurosci Res*, 95(10):2025-2029. https://doi.org/10.1002/jnr.24042

Li W, Huang E, Gao SJ, 2017. Type 1 diabetes mellitus and cognitive impairments: a systematic review. *J Alzheimers Dis*, 57(1):29-36. https://doi.org/10.3233/jad-161250

Liang BH, Peng LQ, Li RX, et al., 2018. *Lycium barbarum* polysaccharide protects HSF cells against ultraviolet-induced damage through the activation of Nrf2. *Cell Mol Biol Lett*, 23:18. https://doi.org/10.1186/s11658-018-0084-2

Liu XF, Zhou DD, Xie T, et al., 2018. The Nrf2 signaling in retinal ganglion cells under oxidative stress in ocular neurodegenerative diseases. *Int J Biol Sci*, 14(9):1090-1098. https://doi.org/10.7150/ijbs.25996

Liu YX, Uruno A, Saito R, et al., 2022. *Nrf2* deficiency deteriorates diabetic kidney disease in *Akita* model mice. *Redox Biol*, 58:102525. https://doi.org/10.1016/j.redox.2022.102525

Lu J, He AX, Jin ZY, et al., 2024. Desloratadine alleviates

ALS-like pathology in hSOD1^{G93A} mice via targeting 5HTR$_{2A}$ on activated spinal astrocytes. *Acta Pharmacol Sin*, 45(5):926-944. https://doi.org/10.1038/s41401-023-01223-2

Luo C, Hou C, Yang DY, et al., 2023. Urolithin C alleviates pancreatic β-cell dysfunction in type 1 diabetes by activating Nrf2 signaling. *Nutr Diabetes*, 13:24. https://doi.org/10.1038/s41387-023-00253-3

Luo MW, Bao L, Xue YY, et al., 2024. ZMYND8 protects breast cancer stem cells against oxidative stress and ferroptosis through activation of NRF2. *J Clin Invest*, 134(6): e171166. https://doi.org/10.1172/jci171166

Luo X, Wang YH, Zhu XX, et al., 2024. MCL attenuates atherosclerosis by suppressing macrophage ferroptosis via targeting KEAP1/NRF2 interaction. *Redox Biol*, 69:102987. https://doi.org/10.1016/j.redox.2023.102987

Lv ZQ, Guo YJ, 2020. Metformin and its benefits for various diseases. *Front Endocrinol*, 11:191. https://doi.org/10.3389/fendo.2020.00191

Ma CJ, Gu CD, Lian PP, et al., 2023. Sulforaphane alleviates psoriasis by enhancing antioxidant defense through KEAP1-NRF2 pathway activation and attenuating inflammatory signaling. *Cell Death Dis*, 14(11):768. https://doi.org/10.1038/s41419-023-06234-9

Macías-Pérez JR, Vázquez-López BJ, Muñoz-Ortega MH, et al., 2019. Curcumin and *α*/*β*-adrenergic antagonists cotreatment reverse liver cirrhosis in hamsters: participation of Nrf-2 and NF-κB. *J Immunol Res*, 2019:3019794. https://doi.org/10.1155/2019/3019794

Majhi S, Kumar S, Singh L, 2023. A review on autism spectrum disorder: pathogenesis, biomarkers, pharmacological and non-pharmacological interventions. *CNS Neurol Disord Drug Targets*, 22(5):659-677. https://doi.org/10.2174/1871527321666220428134802

Miao WM, Hu LG, Scrivens PJ, et al., 2005. Transcriptional regulation of NF-E2 p45-related factor (NRF2) expression by the aryl hydrocarbon receptor-xenobiotic response element signaling pathway: direct cross-talk between phase I and II drug-metabolizing enzymes. *J Biol Chem*, 280(21):20340-20348. https://doi.org/10.1074/jbc.M412081200

Milan KL, Gayatri V, Kriya K, et al., 2024. MiR-142-5p mediated Nrf2 dysregulation in gestational diabetes mellitus and its impact on placental angiogenesis. *Placenta*, 158: 192-199. https://doi.org/10.1016/j.placenta.2024.10.021

O'Brien J, Hayder H, Zayed Y, et al., 2018. Overview of microRNA biogenesis, mechanisms of actions, and circulation. *Front Endocrinol*, 9:402. https://doi.org/10.3389/fendo.2018.00402

Oh YS, Jun HS, 2018. Effects of glucagon-like peptide-1 on oxidative stress and Nrf2 signaling. *Int J Mol Sci*, 19(1):26. https://doi.org/10.3390/ijms19010026

Ortiz-Martínez M, González-González M, Martagón AJ, et al., 2022. Recent developments in biomarkers for diagnosis and screening of type 2 diabetes mellitus. *Curr Diab Rep*, 22(3):95-115. https://doi.org/10.1007/s11892-022-01453-4

Park SY, Choi MH, Park G, et al., 2018. *Petasites japonicus* bakkenolide B inhibits lipopolysaccharide-induced proinflammatory cytokines via AMPK/Nrf2 induction in microglia. *Int J Mol Med*, 41(3):1683-1692. https://doi.org/10.3892/ijmm.2017.3350

Porquet D, Casadesús G, Bayod S, et al., 2013. Dietary resveratrol prevents Alzheimer's markers and increases life span in SAMP8. *AGE*, 35(5):1851-1865. https://doi.org/10.1007/s11357-012-9489-4

Rada P, Rojo AI, Chowdhry S, et al., 2011. Scf/β-TrCP promotes glycogen synthase kinase 3-dependent degradation of the Nrf2 transcription factor in a Keap1-independent manner. *Mol Cell Biol*, 31(6):1121-1133. https://doi.org/10.1128/mcb.01204-10

Razliqi RN, Ahangarpour A, Mard SA, et al., 2023. Gentisic acid ameliorates type 2 diabetes induced by Nicotinamide-Streptozotocin in male mice by attenuating pancreatic oxidative stress and inflammation through modulation of Nrf2 and NF-κB pathways. *Life Sci*, 325:121770. https://doi.org/10.1016/j.lfs.2023.121770

Rojo AI, Rada P, Mendiola M, et al., 2014. The PTEN/NRF2 axis promotes human carcinogenesis. *Antioxid Redox Signal*, 21(18):2498-2514. https://doi.org/10.1089/ars.2014.5843

Sahoo DK, Heilmann RM, Paital B, et al., 2023. Oxidative stress, hormones, and effects of natural antioxidants on intestinal inflammation in inflammatory bowel disease. *Front Endocrinol (Lausanne)*, 14:1217165. https://doi.org/10.3389/fendo.2023.1217165

Satoh T, Saitoh S, Hosaka M, et al., 2009. Simple *ortho*- and *para*-hydroquinones as compounds neuroprotective against oxidative stress in a manner associated with specific transcriptional activation. *Biochem Biophys Res Commun*, 379(2):537-541. https://doi.org/10.1016/j.bbrc.2008.12.106

Schmidlin CJ, Shakya A, Dodson M, et al., 2021. The intricacies of NRF2 regulation in cancer. *Semin Cancer Biol*, 76:110-119. https://doi.org/10.1016/j.semcancer.2021.05.016

Shen ML, You YT, Xu CN, et al., 2024. Epigallocatechin-3-gallate attenuates lipopolysacharide-induced pneumonia via modification of inflammation, oxidative stress, apoptosis, and autophagy. *BMC Complement Med Ther*, 24: 147. https://doi.org/10.1186/s12906-024-04436-y

Shi Q, Jin XF, Zhang PZ, et al., 2022. SPOP mutations promote p62/SQSTM1-dependent autophagy and Nrf2 activation in prostate cancer. *Cell Death Differ*, 29(6):1228-1239. https://doi.org/10.1038/s41418-021-00913-w

Shih AY, Imbeault S, Barakauskas V, et al., 2005. Induction of the Nrf2-driven antioxidant response confers neuroprotection during mitochondrial stress *in vivo*. *J Biol Chem*, 280(24):22925-22936. https://doi.org/10.1074/jbc.M414635200

Shore R, Behlen J, McBee D, et al., 2024. Lactational transfer of sulforaphane-*N*-acetylcysteine in vivo and in human

breast milk. *Toxicol Appl Pharmacol*, 482:116796. https://doi.org/10.1016/j.taap.2023.116796

Smolen JS, Aletaha D, McInnes IB, 2016. Rheumatoid arthritis. *Lancet*, 388(10055):2023-2038. https://doi.org/10.1016/s0140-6736(16)30173-8

Soejima-Kusunoki A, Okada K, Saito R, et al., 2022. The protective effect of edaravone on TDP-43 plus oxidative stress-induced neurotoxicity in neuronal cells: analysis of its neuroprotective mechanisms using RNA sequencing. *Pharmaceuticals*, 15(7):842. https://doi.org/10.3390/ph15070842

Song JR, Zhang YL, Frieler RA, et al., 2023. Itaconate suppresses atherosclerosis by activating a Nrf2-dependent antiinflammatory response in macrophages in mice. *J Clin Invest*, 134(3):e173034. https://doi.org/10.1172/jci173034

Song JY, Wang HR, Sheng JY, et al., 2023. Vitexin attenuates chronic kidney disease by inhibiting renal tubular epithelial cell ferroptosis via NRF2 activation. *Mol Med*, 29:147. https://doi.org/10.1186/s10020-023-00735-1

Stack C, Ho D, Wille E, et al., 2010. Triterpenoids CDDO-ethyl amide and CDDO-trifluoroethyl amide improve the behavioral phenotype and brain pathology in a transgenic mouse model of Huntington's disease. *Free Radic Biol Med*, 49(2):147-158. https://doi.org/10.1016/j.freeradbiomed.2010.03.017

Sun D, Li HM, Du YK, et al., 2024. Metformin modulates mitochondrial autophagy in renal tubular epithelial injury induced by high glucose via the Keap1/Nrf2 pathway. *Mol Cell Biochem*, 479(9):2483-2496. https://doi.org/10.1007/s11010-023-04843-8

Sun JM, Liu YX, Liu YD, et al., 2024. Salvianolic acid B protects against UVB-induced skin aging via activation of NRF2. *Phytomedicine*, 130:155676. https://doi.org/10.1016/j.phymed.2024.155676

Sun LY, Zhao Q, Xiao Y, et al., 2020. Trehalose targets Nrf2 signal to alleviate D-galactose induced aging and improve behavioral ability. *Biochem Biophys Res Commun*, 521(1): 113-119. https://doi.org/10.1016/j.bbrc.2019.10.088

Tang KZ, Chen Q, Liu YM, et al., 2022. Combination of metformin and sorafenib induces ferroptosis of hepatocellular carcinoma through p62-Keap1-Nrf2 pathway. *J Cancer*, 13(11):3234-3243. https://doi.org/10.7150/jca.76618

Tang XW, Wang HY, Fan LF, et al., 2011. Luteolin inhibits Nrf2 leading to negative regulation of the Nrf2/ARE pathway and sensitization of human lung carcinoma A549 cells to therapeutic drugs. *Free Radic Biol Med*, 50(11): 1599-1609. https://doi.org/10.1016/j.freeradbiomed.2011.03.008

Tao SS, Rojo de la Vega M, Chapman E, et al., 2018. The effects of NRF2 modulation on the initiation and progression of chemically and genetically induced lung cancer. *Mol Carcinog*, 57(2):182-192. https://doi.org/10.1002/mc.22745

Ujah GA, Nna VU, Suleiman JB, et al., 2021. Tert-butylhydroquinone attenuates doxorubicin-induced dysregulation of testicular cytoprotective and steroidogenic genes, and improves spermatogenesis in rats. *Sci Rep*, 11:5522. https://doi.org/10.1038/s41598-021-85026-7

Ulasov AV, Rosenkranz AA, Georgiev GP, et al., 2022. Nrf2/Keap1/ARE signaling: towards specific regulation. *Life Sci*, 291:120111. https://doi.org/10.1016/j.lfs.2021.120111

Valadão PAC, Santos KBS, Ferreira e Vieira TH, et al., 2020. Inflammation in Huntington's disease: a few new twists on an old tale. *J Neuroimmunol*, 348:577380. https://doi.org/10.1016/j.jneuroim.2020.577380

Wang C, Luo ZM, Carter G, et al., 2018. NRF2 prevents hypertension, increased ADMA, microvascular oxidative stress, and dysfunction in mice with two weeks of ANG II infusion. *Am J Physiol Regul Integr Comp Physiol*, 314(3):R399-R406. https://doi.org/10.1152/ajpregu.00122.2017

Wang P, Ma HH, Hou XZ, et al., 2023. *N*-Acetyl-L-cysteine ameliorates gestational diabetes mellitus by inhibiting oxidative stress. *Biotechnol Appl Biochem*, 70(3):1128-1136. https://doi.org/10.1002/bab.2426

Wang Q, Li WX, Dai SX, et al., 2017. Meta-analysis of Parkinson's disease and Alzheimer's disease revealed commonly impaired pathways and dysregulation of NRF2-dependent genes. *J Alzheimers Dis*, 56(4):1525-1539. https://doi.org/10.3233/jad-161032

Wang YB, Xu M, 2021. miR-380-5p facilitates NRF2 and attenuates cerebral ischemia/reperfusion injury-induced neuronal cell death by directly targeting BACH1. *Transl Neurosci*, 12(1):210-217. https://doi.org/10.1515/tnsci-2020-0172

Wu TD, Zhao F, Gao BX, et al., 2014. Hrd1 suppresses Nrf2-mediated cellular protection during liver cirrhosis. *Genes Dev*, 28(7):708-722. https://doi.org/10.1101/gad.238246.114

Xia SG, Yan CY, Gu JH, et al., 2024. Resveratrol alleviates zearalenone-induced intestinal dysfunction in mice through the NF-κB/Nrf2/HO-1 signalling pathway. *Foods*, 13(8): 1217. https://doi.org/10.3390/foods13081217

Xiao L, Xu XX, Zhang F, et al., 2017. The mitochondria-targeted antioxidant MitoQ ameliorated tubular injury mediated by mitophagy in diabetic kidney disease via Nrf2/PINK1. *Redox Biol*, 11:297-311. https://doi.org/10.1016/j.redox.2016.12.022

Xu CY, Xu C, Xu YN, et al., 2024. Poliumoside protects against type 2 diabetes-related osteoporosis by suppressing ferroptosis via activation of the Nrf2/GPX4 pathway. *Phytomedicine*, 125:155342. https://doi.org/10.1016/j.phymed.2024.155342

Yang BY, Pan JR, Zhang XN, et al., 2023. NRF2 activation suppresses motor neuron ferroptosis induced by the $SOD1^{G93A}$ mutation and exerts neuroprotection in amyotrophic lateral sclerosis. *Neurobiol Dis*, 184:106210. https://doi.org/10.1016/j.nbd.2023.106210

Yang CS, Chen TT, Ho CT, 2022. Redox and other biological activities of tea catechins that may affect health: mechanisms and unresolved issues. *J Agric Food Chem*, 70(26): 7887-7899.

https://doi.org/10.1021/acs.jafc.2c02527

Yang H, Tang CY, Luo C, et al., 2018. Resveratrol attenuates the cytotoxicity induced by amyloid-$\beta_{1\text{-}42}$ in PC12 cells by upregulating heme oxygenase-1 via the PI3K/Akt/Nrf2 pathway. *Neurochem Res*, 43(2):297-305. https://doi.org/10.1007/s11064-017-2421-7

Yang H, Liu BF, Xie FJ, et al., 2020. Luteolin induces mitochondrial apoptosis in HT29 cells by inhibiting the Nrf2/ARE signaling pathway. *Exp Ther Med*, 19(3):2179-2187. https://doi.org/10.3892/etm.2020.8464

Yang S, Li WJ, Bai XY, et al., 2024. Ginseng-derived nanoparticles alleviate inflammatory bowel disease via the TLR4/MAPK and p62/Nrf2/Keap1 pathways. *J Nanobiotechnol*, 22:48. https://doi.org/10.1186/s12951-024-02313-x

Yang W, Yu QX, Wang N, et al., 2025. Far-infrared radiation ameliorates the cognitive dysfunction in an Alzheimer's disease transgenic mouse via modulating Jak-2/Stat3 and Nrf-2/HO-1 pathways. *Neuromol Med*, 27:34. https://doi.org/10.1007/s12017-025-08860-2

Yi LL, Luo M, Wang MJ, et al., 2023. Fangchinoline alleviates cognitive impairments through enhancing autophagy and mitigating oxidative stress in Alzheimer's disease models. *Front Cell Dev Biol*, 11:1288506. https://doi.org/10.3389/fcell.2023.1288506

Yi SQ, Chen SX, Xiang J, et al., 2021. Genistein exerts a cell-protective effect via Nrf2/HO-1/PI3K signaling in A$\beta_{25\text{-}35}$-induced Alzheimer's disease models *in vitro*. *Folia Histochem Cytobiol*, 59(1):49-56. https://doi.org/10.5603/FHC.a2021.0006

Yu HF, Huang LS, Gui LL, et al., 2024. Luteolin ameliorates hyperuricemic nephropathy by activating urate excretion and Nrf2/HO-1/NQO1 antioxidant pathways in mice. *Food Sci Nutr*, 12(10):8053-8066. https://doi.org/10.1002/fsn3.4403

Yu Y, Li Y, Qi KM, et al., 2022. Rosmarinic acid relieves LPS-induced sickness and depressive-like behaviors in mice by activating the BDNF/Nrf2 signaling and autophagy pathway. *Behav Brain Res*, 433:114006. https://doi.org/10.1016/j.bbr.2022.114006

Zgorzynska E, Dziedzic B, Walczewska A, 2021. An overview of the Nrf2/ARE pathway and its role in neurodegenerative diseases. *Int J Mol Sci*, 22(17):9592. https://doi.org/10.3390/ijms22179592

Zhang AQ, Suzuki T, Adachi S, et al., 2023. Nrf2 activation improves experimental rheumatoid arthritis. *Free Radic Biol Med*, 207:279-295. https://doi.org/10.1016/j.freeradbiomed.2023.07.016

Zhang AX, Qian YJ, Qian J, 2019. MicroRNA-152-3p protects neurons from oxygen-glucose-deprivation/reoxygenation-induced injury through upregulation of Nrf2/ARE antioxidant signaling by targeting PSD-93. *Biochem Biophys Res Commun*, 517(1):69-76. https://doi.org/10.1016/j.bbrc.2019.07.012

Zhang BY, Pan CY, Feng C, et al., 2022. Role of mitochondrial reactive oxygen species in homeostasis regulation. *Redox Rep*, 27(1):45-52. https://doi.org/10.1080/13510002.2022.2046423

Zhang YK, Gao Y, Ding YY, et al., 2023. Targeting KAT2A inhibits inflammatory macrophage activation and rheumatoid arthritis through epigenetic and metabolic reprogramming. *MedComm*, 4(3):e306. https://doi.org/10.1002/mco2.306

Zhang ZX, Fu CL, Liu JX, et al., 2021. Hypermethylation of the Nrf2 promoter induces ferroptosis by inhibiting the Nrf2-GPX4 axis in COPD. *Int J Chron Obstruct Pulmon Dis*, 16:3347-3362. https://doi.org/10.2147/copd.S340113

Zhao CY, Wang XL, Peng Y, 2015. Role of Nrf2 in neurodegenerative diseases and recent progress of its activators. *Acta Pharm Sin*, 50(4):375-384 (in Chinese). https://doi.org/10.16438/j.0513-4870.2015.04.012

Zhu MT, Sun YP, Su Y, et al., 2024. Luteolin: a promising multifunctional natural flavonoid for human diseases. *Phytother Res*, 38(7):3417-3443. https://doi.org/10.1002/ptr.8217