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REVIEW

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Activation of Nrf2 with natural flavonoids and mesenchymal stromal/stem cells: mechanisms and therapeutic potential for inflammatory diseases

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Abstract

Redox balance is crucial for maintaining normal physiological functions. Its disruption by oxidative stress can trigger or exacerbate a series of pathological cascades, ultimately contributing to various chronic diseases, particularly inflammatory disorders. Inhibiting oxidative stress and its associated pathological cascades may alleviate these diseases, a process often linked to the activation of nuclear factor erythroid 2-related factor 2 (Nrf2). Initially characterized as a redox-sensitive transcription factor, Nrf2 is now recognized as a pivotal regulator of an extensive network of antioxidant genes, effectively counteracting oxidative stress and its detrimental effects. Consequently, advances in understanding Nrf2 activators and their regulatory mechanisms have accelerated the development of Nrf2-targeted therapies, demonstrating significant potential for preventing and treating chronic inflammation diseases. Many natural phytochemicals, particularly flavonoids, have been identified as Nrf2 activators that can ameliorate inflammatory responses. Furthermore, therapy with mesenchymal stromal/stem cells (MSCs) is a highly researched treatment approach with the potential to confer immunomodulatory, anti-inflammatory, anti-apoptotic and antimicrobial effects. Owing to their superior safety profile compared to conventional therapeutics, MSCs are gaining prominence as sustainable long-term treatment options, although their precise molecular mechanisms remain to be fully elucidated. This review focuses on the activation mechanisms of Nrf2 and its clinical and preclinical inducers, with particular emphasis on the mechanistic insights and therapeutic applications of natural flavonoids and MSCs in the prevention or treatment of inflammatory diseases. More importantly, it summarizes the profound role of flavonoid-MSCs combinatorial therapy in the intervention of inflammatory diseases, pointing out novel therapeutic strategies and future prospects for modulating the Nrf2 signaling pathway in the treatment of inflammatory disorders.

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Keywords Nuclear factor erythroid 2-related factor 2 (Nrf2), Natural flavonoids, Mesenchymal stromal/stem cells (MSCs), Inflammatory diseases

Introduction

Organisms face a persistent threat from oxidative stress, a condition resulting from an imbalance between reactive oxygen species (ROS) production and cellular antioxidant defenses [1]. These ROS, including superoxide anions, hydrogen peroxide, and hydroxyl radicals, are generated as natural metabolic byproducts or are induced by environmental factors, such as pollution, radiation and toxins. While low levels of ROS are essential for cellular signaling and homeostasis, their excessive accumulation damages cellular components such as lipids, proteins, and DNA, leading to dysfunction and cell death [2]. This also triggers inflammation by activating pro-inflammatory signaling pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK), ultimately promoting the expression of inflammatory cytokines (e.g., tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-1β) and chemokines [3]. This establishes a self-perpetuating cycle in which inflammation further enhances ROS production, exacerbating oxidative stress and tissue damage [4, 5].

To mitigate the resulting oxidative damage, organisms have evolved sophisticated adaptive mechanisms to preserve genomic integrity and maintain redox homeostasis. One of the most versatile mechanisms of adaptation is the Nrf2 antioxidant pathway [6]. Nrf2 is a critical transcription factor that plays a central role in regulating cellular defense mechanisms for mitigating inflammation, which are biological processes bidirectionally linked with oxidative stress [7, 8]. Emerging evidence from in vitro and in vivo studies indicates that dietary phytochemicals, particularly natural flavonoids, can activate the Nrf2-dependent signaling pathway through alternative mechanisms. This activity suggests a cost-effective, safe and accessible strategy for mitigating various inflammation-related pathologies. And their protective potential has been demonstrated in several conditions, such as non-alcoholic fatty liver disease (NAFLD), diabetes and its complications, ischemia/reperfusion injury, cellular senescence, atherosclerosis, hepatotoxicity and other inflammatory diseases [9–11]. These findings underscore the promise of flavonoids as therapeutic agents in the management of chronic inflammatory and metabolic diseases.

Mesenchymal stromal/stem cells (MSCs) are multipotent stem cells that can be isolated from various tissues and differentiated into multiple lineages under appropriate conditions. Their functional repertoire includes immunomodulation, homing, and differentiation, which collectively help establish a balanced inflammatory and regenerative niche within damaged tissues during severe inflammation. Furthermore, accumulating evidence demonstrates that MSCs-derived extracellular vesicles (MSCs-EVs) and conditioned medium (MSCs-CM) play remarkable roles, exhibiting potent anti-inflammatory and antioxidant properties that offer novel therapeutic alternatives for inflammatory diseases [12].

Pharmacological activation or inhibition of Nrf2 can directly regulate the survival and function of MSCs under various stress conditions through multiple key intracellular mechanisms [13, 14]. Thus, the integration of natural flavonoids with MSCs-based therapies offers a novel strategy to enhance the therapeutic potential of MSCs in inflammatory diseases.

As a result, this review systematically summarizes the therapeutic potential of Nrf2 as a treatment strategy for inflammation. It elucidates the mechanistic roles of Nrf2-targeting agents in managing inflammation-related diseases. Furthermore, this work explores the synergistic potential of combining natural flavonoids with MSCs as a drug delivery platform, aiming to establish a theoretical foundation for future research.

Materials and methods

Literature search strategy

The literature review for this study was conducted by searching Scopus, Science Direct, PubMed, and Google Scholar databases. The search was limited to articles published in English between January 1995 and June 2025, with a specific focus on research progress in this field over the past three decades.

Keywords

The search was performed using the following keywords and their combinations: "Nrf2", "mesenchymal stem/stromal cells" or "MSCs", "natural flavonoids", "inflammatory diseases", "oxidative stress", "Keap1", "Nrf2 inducers", "MSCs-derived exosomes/conditioned medium", "synergistic effects of flavonoids and MSCs", as well as specific disease terms such as "rheumatoid arthritis", "Alzheimer's disease", etc. or specific flavonoid such as "quercetin", "luteolin", etc.

Inclusion criteria

1. Original research articles and reviews focusing on Nrf2 activation by mesenchymal stem cells or flavonoids.

2. Studies involving "in vivo", "in vitro", or clinical models of inflammatory diseases.
3. Studies elucidating molecular mechanisms, particularly those involving the Nrf2 signaling pathway.

Exclusion criteria

1. Non-English publications.
2. Studies not directly associated with Nrf2, mesenchymal stem cells, or flavonoids.
3. Articles lacking a clear description of mechanisms or disease relevance.

The regulator role of Nrf2

The Nrf2 research field has undergone remarkable advancements in the last 30 years, during which paradigm-shifting discoveries have redefined our mechanistic comprehension of Nrf2 as a master regulator vitally involved in the maintenance of cellular homeostasis. In 1994, Nrf2 was identified as a member of the cap'n'collar (CNC) subfamily and was characterized by a bZIP structure containing seven functional domains (Neh1–Neh7) that regulate cellular defense genes (Fig. 1) [15, 16]. It was further validated through Nrf2 knockout (Nrf2 KO) mouse models in 1996 [17, 18], cementing its momentous role in cellular oxidative stress responses and defense pathways. Between 1999 and 2009, significant progress revealed that Kelch-like ECH-associated protein 1 (Keap1), as a substrate adaptor for the Cullin3-RBX1 E3 ubiquitin ligase, maintains low Nrf2 levels under physiological conditions. However, electrophilic compounds modify key cysteine residues in Keap1, particularly Cys151, disrupting the Nrf2-Keap1-Cullin3 complex, inhibiting Nrf2 ubiquitination, and promoting its stabilization and activation [19–22]. Prior to this, antioxidant response elements (AREs), located in the regulatory regions of phase II detoxification genes, were identified as key elements that facilitate the binding of Nrf2, which upregulates antioxidant and detoxifying enzymes such as NAD(P)H quinone oxidoreductase 1 (NQO1), glutamate-cysteine ligase catalytic subunit (GCLC), and heme oxygenase 1 (HO-1) in 1997 [23, 24]. Nrf2 mitigates excessive inflammatory responses by upregulating NQO1 and HO-1 expression in response to lipopolysaccharide (LPS), which in turn protects against the excessive production of inflammatory cytokines, such as TNF and IL-1β [25]. Therefore, as the master regulator of cellular defense mechanisms, the Nrf2-related pathway is essential for protecting against inflammatory tissue injury by upregulating antioxidant proteins and detoxifying enzymes [26]. This positions it as a critical molecular target in human disease research.

Thus, Nrf2 was predominantly recognized as a cytoprotective transcription factor that preserves cellular homeostasis and mitigates environmental toxin-induced damage between 1999 and 2009, however, a paradigm-breaking discovery revealed its dual role in cancer via augmenting chemoresistance in 2008 [27]. Elevated Nrf2 expression drives tumor progression and confers broad resistance to therapies including chemotherapy, radiotherapy and targeted-immunotherapy. This overexpression is further associated with aggressive metastasis, higher rates of tumor recurrence, and worse prognoses [22]. Although the duality of Nrf2 exemplifies its Janus-faced nature in oncogenesis, it exerts cytoprotective and tumor-suppressive functions in normal physiological contexts, which act as a gatekeeper to prevent cancer onset.

Pharmaceutical development of Nrf2 modulators

The identification of Nrf2 as a master regulator of cellular antioxidant defenses has revolutionized our understanding of its pivotal role as a therapeutic target in the pathogenesis of inflammatory diseases. This has driven the development of novel compounds designed to modulate Nrf2 for both disease prevention and targeted intervention. Numerous experimental studies have demonstrated that the activation of Nrf2 constitutes an essential prerequisite for the suppression of inflammation. However,

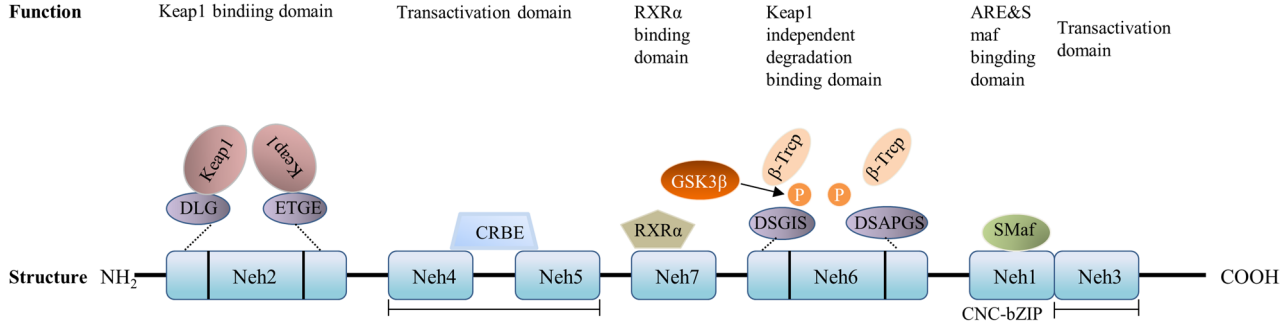


Fig. 1 Schematic representation of the basic structure and function of the Nrf2 protein. *Neh* Nrf2-ECH homology, *CNC-bZIP* Cap'n'Collar basic leucine zipper, NH_2 N-terminal, *COOH* C-terminal, *RXRα* retinoid X receptor-alpha, *β-TrCP* beta-transducin repeat containing E3 ubiquitin protein ligase, *ARE* antioxidant response element, *CRBE* Cyclic AMP response element-binding protein

the development of Nrf2 modulators has progressed through distinct stages, each characterized by a hierarchy of evidence. This progression begins with mechanistic discoveries in in vitro systems and animal models, then advances from preclinical investigation to clinical trials, and ultimately, aims to achieve clinical application. To date, three small-molecule Nrf2 activators (dimethyl fumarate [DMF], diroximel fumarate and omaveloxolone) have already been approved by the US Food and Drug Administration for specific indications (multiple sclerosis, psoriasis and Friedreich's ataxia), while numerous others under preclinical investigation.

Nrf2 inducers in clinic

The prototypical Nrf2 inducers are cysteine-reactive small molecules that specifically target cysteine residues on KEAP1, notably Cys151, which consequently disrupts the KEAP1-CUL3 E3 ubiquitin ligase complex and thus prevents Nrf2 degradation. Currently, the strongest evidence supporting Nrf2 activation as a therapeutic strategy comes from three approved drugs (Table 1), whose efficacy and safety profiles have been rigorously validated through standardized clinical trial processes. DMF, the pioneering Nrf2 activator approved for clinical applications, is commercially available under multiple brand names including Tecfidera, Skilarence, and Fumaderm. Notably, Tecfidera (BG-12), an orally administered formulation of DMF, is approved for relapsing-remitting multiple sclerosis (MS); Skilarence has received regulatory approval in the European Union, while Fumaderm, a combination of DMF and monoethyl fumarate salts, is specifically authorized in Germany for the treatment of psoriasis [22, 28]. Complementing these clinical advances, diroximel fumarate, with brand name as Vumerity, a structurally optimized derivative of DMF, has been approved for the management of MS [28]. These approved drugs highlight the significant clinical efficacy of DMF in treating chronic inflammatory and autoimmune disorders by promoting a shift from pro-inflammatory to anti-inflammatory cytokine profiles through dual mechanisms. This shift is partially mediated by activating the Nrf2 pathway through Keap1 modification, leading to Nrf2 accumulation and nuclear translocation, where it upregulates genes containing ARE to enhance the production of antioxidant and cytoprotective proteins. Additionally, Nrf2-independent actions contribute to this effect through the inhibition of NF-κB signaling and activation of the hydroxycarboxylic acid receptor 2 [29, 30]. However, both DMF and diroximel fumarate exhibit identical off-target interactions due to similar mechanistic pathways, resulting in overlapping adverse effects, though diroximel fumarate has been structurally optimized to mitigate gastrointestinal toxicity. A recent breakthrough in therapeutic innovation was achieved with the 2023 approval of omaveloxolone (commercially known as Skyclarys, also referred to as RTA 408), a synthetic oleanane triterpenoid derived from cyclic-28, 30-didehydro-28, 29-dimethyl-18β-oleano-12-oleanoic acid (CDDO). Omaveloxolone and its analogues directly target Keap1, PPARγ and IKKβ, leading to broad anti-inflammatory effects [22]. This landmark approval marked the first targeted treatment specifically designed for Friedreich's ataxia, addressing a critical unmet need in the management of this rare and debilitating neurodegenerative disorder.

Preclinical Nrf2 inducers

In contrast to the three clinically approved Nrf2 activators described above, the following compounds remain investigational and require further validation to transition from candidates to clinically approved therapeutics (Table 2). CDDO-IM (imidazole derivative of CDDO) and CDDO-Me (methylester derivative of CDDO), two prominent bardoxolone derivatives, effectively mitigate sepsis by suppressing LPS-triggered cytokine expression and oxidative stress [31, 32]. Carbon monoxide (CO)-releaser/Nrf2 activator hybrids (HYCOs), a novel class of hybrid molecules, demonstrate their therapeutic efficacy

Table 1 FDA approved pharmaceutical Nrf2 inducers

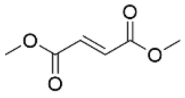
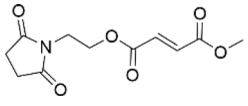
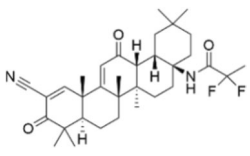
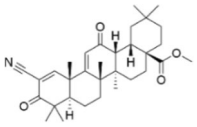
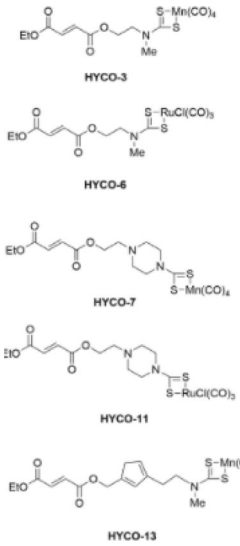
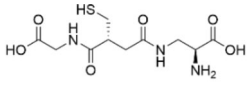
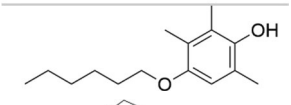
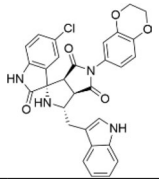
Inducer	Structures	Disease	Brand names	Refs.
Dimethyl fumarate		Multiple sclerosis; Psoriasis	Tecfidera, Skilarence, and Fumaderm	[22, 28]
Diroximel fumarate		Multiple sclerosis	Vumerity	[28]
Omaveloxolone		Friedreich's ataxia	Skyclarys, RTA 408	[22]

Table 2 Preclinical pharmaceutical Nrf2 inducers targeting inflammatory diseases

Inducer	Structures	Disease	Refs.
CDDO-Im and CDDO-Me		Sepsis	[31, 39]
HYCOs	 HYCO-3 HYCO-6 HYCO-7 HYCO-11 HYCO-13	Psoriatic symptoms	[33]
DMA		Diabetes-related complications	[35]
GSH		Hyperoxic lung injury	[36]
BTT-105		MASH	[37]
PHAR		NASH	[38]

by simultaneously activating Nrf2 and enabling controlled CO release, which collectively contribute to their potent anti-inflammatory effects and significant alleviation of psoriatic symptoms [33]. Meanwhile, expression quantitative trait loci (eQTLs) linked to Nrf2-regulated pathways provide a deeper understanding of the intricate relationship between Nrf2 and immune signaling within the skin compartment, shedding light on how genetic variations orchestrate the dynamic pathological changes observed in psoriatic skin [34]. Dimerumic acid (DMA) effectively mitigates diabetes-related complications by activating Nrf2. This activation suppresses inflammation and oxidative stress, enhances methylglyoxal (MGO) metabolism, and reduces the accumulation of advanced glycation end-product (AGEs) and inflammatory cytokines, thereby offering therapeutic benefits [35]. Supplementing hyperoxic lung injury mice with glutathione (GSH) significantly restored their recovery ability, highlighting the critical role of Nrf2-regulated GSH synthesis in lung tissue repair and inflammation resolution [36]. In the therapeutic approach for managing metabolic dysfunction-associated steatohepatitis (MASH) and its progression, various compounds have demonstrated significant efficacy by activating the Nrf2 signaling pathway. 1-*O*-hexyl-2,3,5-trimethylhydroquinone (BTT-105), an Nrf2 activator, alleviates MASH fibrosis by enhancing antioxidant pathways and suppressing phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling in hepatic stellate cells [37]. Rather than targeting Keap1, PHAR ((1 S,3R,3aR,6aS)-5′-chloro-5-(2,3-dihydro-1,4-benzodioxin-6-yl)-1-(1H-indol-3-ylmethyl) spiro [1,2,3a,6a-tetrahydropyrrolo [3,4-c]pyrrole-3,3′-1

H-indole]-2′,4,6-trione) presents a novel therapeutic approach by disrupting the Nrf2–β-TrCP–CULLIN1 E3 ubiquitin ligase complex, effectively mitigating liver fat accumulation and fibrosis in non-alcoholic steatohepatitis (NASH) while circumventing the adverse effects commonly associated with other Keap1-targeting Nrf2 activators [38].

While preclinical compounds show therapeutic promise, their development faces significant hurdles, as exemplified by CDDO-Me. This is illustrated by the termination of the BEACON (NCT01351675, Bardoxolone Methyl Evaluation in Patients with Advanced Chronic Kidney Disease and Type 2 Diabetes, 2011) and CARDINAL (NCT03019185, Patients with Alport Syndrome, 2017) trials due to cardiovascular safety concerns, despite achieving renal benefit-highlighting the imperative for rigorous long-term safety evaluation. An elevated rate of serious adverse events, including heart failure and other cardiovascular complications, prompted the trials' termination, providing compelling evidence of a heightened risk associated with CDDO-Me in this patient population [22]. Moreover, the anti-psoriatic effects attributed to other candidates such as HYCOs have not been independently verified. Significant promiscuity in protein interactions has also been observed with CDDO derivatives, which engage with over 500 proteins according to proteomic analyses, suggesting considerable off-target effects that may undermine their therapeutic utility. These challenges highlight the critical need to enhance both pharmacokinetic properties and target specificity in the ongoing development of Nrf2 modulators. Thus, preclinical candidates show mechanistic promise but remain distant from clinical application, with their potential contingent upon overcoming efficacy-, specificity-, and safety-related hurdles in human trials. Future success will depend on leveraging strong preclinical evidence while prioritizing clinical trial designs that rigorously assess long-term outcomes.

Phytochemicals as Nrf2 inducers

Despite the clinical success of some Nrf2 activators, their broad electrophilic reactivity with proteins containing reactive cysteine residues leads to significant off-target effects and challenges in achieving precise therapeutic outcomes, thereby presenting substantial barriers to clinical translation. These clinical setbacks underscore the complexities and challenges in future research in optimizing Nrf2 inducers by enhancing target specificity, reducing off-target toxicity, and refining their pharmacological profiles to achieve successful clinical outcomes. Therefore, advanced strategies to improve target specificity and refine pharmacological properties are therefore warranted. Protein-protein interaction (PPI) disrupting activators represent a promising high-specificity alternative to Nrf2, however, their clinical translation remains hindered by pharmacokinetic constraints. Consequently, ongoing research and refinement in the design of both PPI-based and conventional inducers are essential to maximize the therapeutic potential of Nrf2 activation.

In comparison to these strategies, a variety of medicinal materials containing bioactive small molecules, especially natural flavonoids derived from traditional Chinese medicine (TCM) and folk medicines, exhibit significant anti-inflammatory activity by effectively downregulating key pro-inflammatory cytokines such as IL-1β, IL-6, MCP-1 and TNF-α, especially. Importantly, this cytokine-suppressing activity is mechanistically dependent on the Nrf2 signaling pathway, as evidenced by the complete loss of anti-inflammatory efficacy upon genetic ablation or silencing of Nrf2 expression. Thus, the Nrf2-mediated anti-inflammatory properties of these natural compounds position them as promising therapeutic candidates that may offer enhanced safety profiles and serve as cost-effective alternatives to currently prescribed pharmacological interventions.

Flavonoids targeting Nrf2

Numerous medicinal plants contain over five thousand known flavonoid compounds, many of which have been utilized for centuries as essential bioactive components in traditional medical practices across East Asia, particularly in China, Japan, Korea, and Mongolia. Structurally characterized by a conserved three-ring (C6-C3-C6) skeleton, flavonoids exhibit a remarkable spectrum of biological activities and are classified into seven major subclasses (flavones, isoflavones, flavanols, flavanones, flavonols, anthocyanidins, and chalcones) based on distinct aromatic ring substitutions [40–43]. These structural variations confer the ability to modulate multiple pathological processes, with demonstrated efficacy in inflammatory disorders, predominantly through the activation of the Nrf2 signaling pathway. Here, the common chemical structure and sources of ten extensively studied flavonoid compounds with therapeutic potential in inflammatory diseases are depicted in Fig. 2. In addition, we summarize representative flavonoids (Table 3) and non-flavonoid phytochemicals (Table 4) to illustrate how these compounds target Nrf2 in the treatment of inflammation-related disorders.

Flavones

Flavones, including hesperidin, baicalein, luteolin, and naringin, exert profound regulatory effects by activating Nrf2 to enhance cellular defense mechanisms and mitigate oxidative stress-induced damage. Specifically, hesperidin has been shown to augment Nrf2 phosphorylation via the PI3K/AKT pathway, leading to elevated antioxidant capacity in HepG2 cells and hepatic tissues

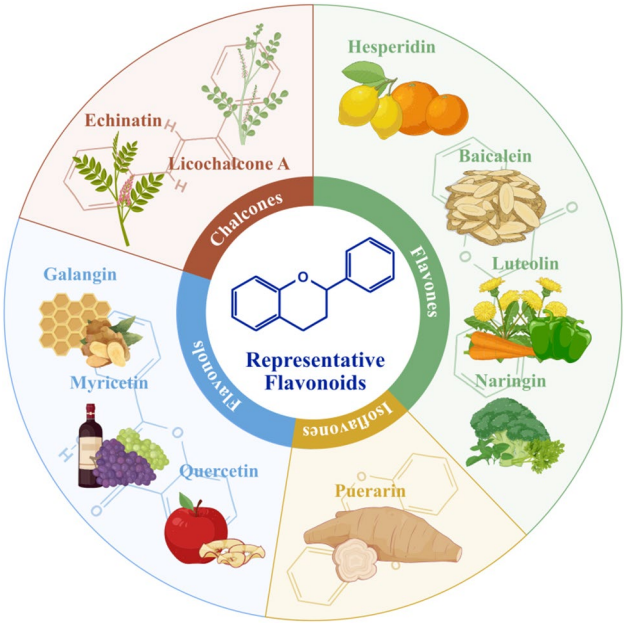


Fig. 2 Main sources of ten representative flavonoids. Hesperidin predominantly comes from lemons and oranges. A key source of baicalein is *Scutellarin baicalensis*. Luteolin is most often found in carrots, green peppers and chrysanthemum. Naringin commonly occurs in mint, parsley and broccoli. Puerarin is enriched in *Pueraria*. Quercetin mainly exists in apple peel. Myricetin is abundant in grape skins and wine. Galangal and propolis yield significant amounts of galangin. Echinatin and Licochalcone A are mainly extracted from *Glycyrrhiza glabra* and Xinjiang licorice (*Glycyrrhiza inflata*), respectively. Both *Scutellaria baicalensis* and *Glycyrrhiza* are well-known traditional Chinese medicines

[44]. Baicalein, a bioactive flavonoid isolated from *Scutellaria baicalensis*, demonstrates efficacy in attenuating NAFLD in high-fat diet-fed rats by activating the Nrf2-mediated antioxidant system through the PI3K/AKT signaling cascade [45]. Luteolin orchestrates dual modulation of Nrf2-mediated oxidative stress and NF-κB-mediated inflammatory responses, conferring protection against high glucose-induced cardiac fibrosis, hypertrophy, and dysfunction [46]. Furthermore, luteolin upregulates Nrf2 by activating sestrin2, which reduces the release of lactate dehydrogenase (LDH) and malondialdehyde (MDA), ameliorates mitochondrial dysfunction, and thereby enhances cardiac performance and myocardial resilience to prevent the diabetic rat heart from ischemia/reperfusion (I/R) injury [47]. Naringin inhibits streptozotocin (STZ)-induced apoptosis in MIN6 pancreatic β-cells by activating Nrf2 and its downstream target genes, glutathione S-transferase (GST) and NQO1 [48].

Isoflavones

As a bioactive isoflavone, puerarin significantly upregulated the mRNA expression of Nrf2 and HO-1, suppressed IL-1β levels, and conferred substantial retinal protection in STZ-induced diabetic rats [49].

Flavonols

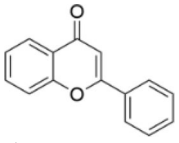
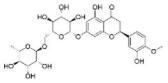
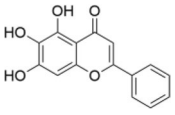
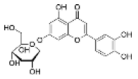
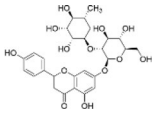
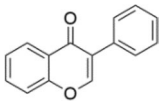
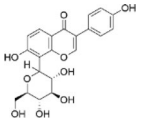
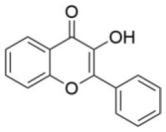
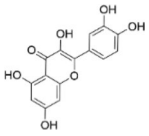
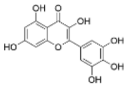
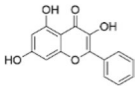
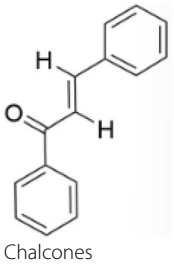
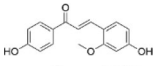
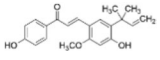
As prominent flavonols, quercetin and myricetin have been shown to significantly reduce the risk of diabetic cataract formation by modulating multiple molecular pathways, with a particularly notable impact on the Nrf2 signaling pathway [50]. Galangin exerts its anti-senescence effects by activating the SIRT1/PGC-1α/Nrf2 signaling pathway to prevent senescence in dermal fibroblasts [51].

Chalcones

Recent studies found that phytochemicals can regulate ferroptosis by promoting adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)-mediated Nrf2 activation, which elevates the expression levels of ferritin, SLC7A11, and glutathione peroxidase 4 (GPX4) thereby suppressing ferroptosis. Echinatin has been demonstrated to upregulate the expression of glutamate-cysteine ligase (GCL), including both the catalytic subunit (GCLC) and the modulatory subunit (GCLM) in vascular smooth muscle cells (VSMCs), thereby maintaining the homeostasis of GSH metabolism. Adequate availability of GSH is critical for counteracting arterial stiffening. By regulating GSH synthesis, echinatin inhibits both ferroptosis and matrix remodeling, which are considered significant contributors to arterial stiffening and atherosclerosis [52]. Moreover, Licochalcone A, a compound derived from Xinjiang licorice (*Glycyrrhiza inflata*), ameliorated aflatoxin B1 (AFB1)-induced hepatotoxicity. Its primary mechanisms include the inhibition of oxidative stress, apoptosis, liver fibrosis, inflammation, and pyroptosis, effects closely associated with activation of the Nrf2 signaling pathway [53].

Beyond their established capacity to activate the Nrf2 pathway, flavonoids also demonstrate significant anti-inflammatory properties through alternative molecular mechanisms. In addition to the shared Nrf2 activation previously described, luteolin directly binds IKKα/IKKβ, thereby suppressing the NF-κB/TOM6/PINK1 mitophagy axis and ameliorating vascular calcification [54]. Similarly, galangin exerts protective effects against vascular aging by binding SMAD3 and activating PINK1/LC3-mediated mitophagy, suggesting a novel therapeutic mechanism [55]. In addition to its involvement in Nrf2-mediated signaling in LPS-stimulated RAW264.7 cells, vitexin exerts multifaceted anti-inflammatory and lipid metabolic regulatory functions in NAFLD by coordinated downregulation of lipogenic pathways and selective inhibiting the TLR4/NF-κB signaling axis [56]. Apigenin significantly attenuates nitric oxide (NO) production and inhibits the secretion of pro-inflammatory cytokines, including IL-6 and IL-1β, while downregulating the protein expression of COX-2 and iNOS. Furthermore, it suppresses the phosphorylation of ERK and

Table 3 Subclass, chemical structure, biochemical properties and functions of representative flavonoids targeting Nrf2 in inflammation diseases

Subclasses	Compounds	Chemical Structure	Signal Pathway Targeting Nrf2	Disease	Refs.
 Flavones	Hesperidin		PI3K/AKT-Nrf2-ARE pathway	NAFLD	[44]
	Baicalein				[45]
	Luteolin		Nrf2- ARE	Diabetic cardiomyopathy	[46]
			Sestrin2- Nrf2	Ischemia/reperfusion injury	[47]
	Naringin		Nrf2- ARE	Diabetes	[48]
 Isoflavones	Puerarin		Nrf2- ARE		[49]
 Flavonols	Quercetin		Nrf2- ARE	Diabetic cataracts	[50]
	Myricetin				
	Galangin		SIRT1-PGC-1α/Nrf2	Senescence	[51]
 Chalcones	Echinatin		Nrf2-GSH-GPX4	Atherosclerosis	[52]
	Licochalcone A		Nrf2- ARE	Hepatotoxicity	[53]

JNK, key kinases within the MAPK signaling cascade in RAW264.7 cells [57]. In a dermal inflammation model, apigenin also exhibits remarkable protective effects against UVA-induced photodamage by substantially reducing metalloproteinase-1 expression. This protective mechanism is attributed to its interference with Ca^{2+} influx-dependent MAPK and AP-1 signaling pathways in HaCaT cells and normal human dermal fibroblasts [58]. Additionally, apigetrin exerts antioxidant and anti-inflammatory effects in RAW264.7 cells by alleviating free radical-induced oxidative damage to DNA, proteins, and erythrocytes, primarily through suppression of ROS and downregulation of IL-6, TNF-α, and the NF-κB signaling pathway [59]. In parallel with its ability to activate the Nrf2/HO-1 pathway [60], biochanin A contributes to vascular homeostasis and mitigates age-related vascular dysfunction by targeting the HDAC1/H3K4me3/NFKB1 axis to inhibit NF-κB-mediated senescence-associated secretory phenotype (SASP) production [61]. Kaempferol ameliorates bone loss by directly binding Sp1 to promote FUNDC1-mediated mitophagy, thereby attenuating bone density attenuating caused by postmenopausal osteoporosis and reducing senescence in BMSCs [62]. Baicalin alleviates ulcerative colitis (UC) through dual-targeting JAK2/STAT3 phosphorylation during Th17 differentiation and IL-17 production, while suppressing IL-17RA expression in macrophages to inhibit NF-κB activation and M1 polarization, thereby disrupting IL-17-mediated inflammatory crosstalk between the Th17/M1 macrophage immune pathways [63]. Even extracts derived from

P. nudicaule cultivars, which are rich in flavonoid-derived indole alkaloids, exert potent anti-inflammatory effects in RAW264.7 by attenuating LPS-induced NO production, and downregulating NO synthase 2 and cyclooxygenase 2, through inhibiting the activation of NF-κB and STAT3 signaling pathways [64, 65]. These findings collectively underscore the capacity of flavonoids to modulate inflammatory responses via coordinated regulation of multiple signaling networks across diverse pathological contexts and cell types. In summary, flavonoids, as a class of structurally diverse natural small molecules, exhibit more direct actions and more specific targets, enabling them to rapidly exert a multi-target synergistic pharmacological network. They provide us with a "chemical toolbox" for regulating redox and inflammatory homeostasis, which also forms the basis for the synergistic effects between flavonoids and MSCs ("Natural flavonoids synergize with MSCs to enhance Nrf2 activation" section).

Other phytochemicals targeting Nrf2

Beyond flavonoids, many other natural compounds also potently activate the Nrf2 signaling pathway, demonstrating considerable therapeutic promise for diverse pathologies. These non-flavonoid agents, derived from various natural sources, possess distinct structural characteristics that allow them to interact with cellular machinery and bolster antioxidant defenses. Their structural diversity enables specific interactions with key regulatory proteins, thereby facilitating the activation of Nrf2 and the subsequent upregulation of cytoprotective genes. Research has extensively detailed how these compounds modulate oxidative stress pathways, particularly in inflammatory and degenerative diseases, underscoring their relevance to both traditional medicine and modern pharmacology.

Cardiovascular diseases

Nrf2-mediated HO-1 pathway modulation also exerts cardioprotective potential by mitigating oxidative damage in vascular endothelial cells, as demonstrated by hydroxytyrosol, a bioactive compound derived from olives [66]. Ginkgo biloba extract [67] exhibits anti-atherogenic and vascular protective properties by upregulating HO-1 expression in vascular tissues, a process mediated by the p38-Nrf2 signaling pathway. Also, a short-term dietary supplementation with broccoli sprouts provides robust cardioprotection against I/R-induced oxidative stress and cardiomyocyte apoptosis in rats, primarily through Nrf2 pathway activation [68]. Tanshinone I [69] exerts anti-apoptotic effects through Nrf2 pathway activation, which mitigates mitochondrial damage, alleviates myocardial oxidative stress, and ultimately improves cardiac function in mice .

Diabetes and diabetic complications

Ellagic acid [70, 71] and total sesquiterpenoid glycosides [70, 71] also activate Nrf2 by inhibiting Keap1 through upregulating miR-223 and enhancing IRS-1/GLUT4

Table 4 Non-flavonoids phytochemicals acting on inflammatory diseases by targeting Nrf2

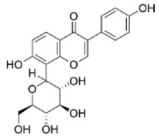
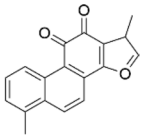
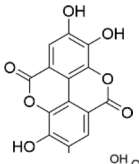
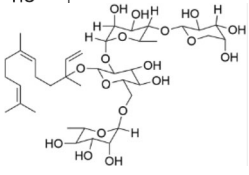
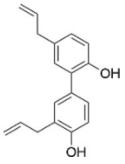
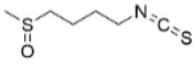
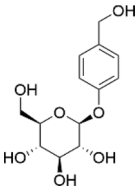
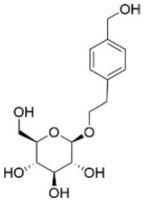
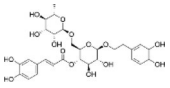
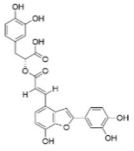
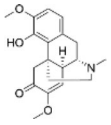
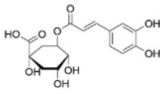
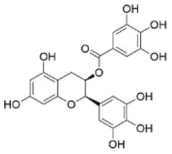
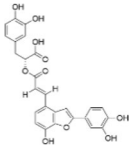
Inducer	Structure	Target signal pathway	Disease	Refs.
Hydroxytyrosol		p38- Nrf2/HO-1	Cardiovascular diseases	[66]
Ginkgo biloba extract	–			[67]
Broccoli sprouts	–	Nrf2-ARE		[68]
Tanshinone I				[69]
Ellagic acid		miR-223/keap1-Nrf2	Type 2 diabetes mellitus	[70]
Total sesquiterpenoid glycosides		SIRT6/Nrf2		[71]
Irisin	–	Nrf2-ARE	Diabetic cardiac microvascular injury	[72]

Table 4 (continued)

Inducer	Structure	Target signal pathway	Disease	Refs.
Garlic sartan isopropyl ester	–	SIRT1/Nrf2/NF-κB	Diabetic cardiomyopathy	[73]
Honokiol		SIRT1-Nrf2		[74]
Sulforaphane		AMPK/Nrf2		[75]
		Nrf2-ARE	Diabetic nephropathy (DN)	[76]
		AMPK/Nrf2	Neurodegenerative diseases	[77, 78]
Anthocyanins	–	PI3K/AKT/Nrf2/HO-1		[79]
Gastrodin		Nrf2/HO-1		[80]
Resveratrol		Nrf2/Keap1/SLC7A11		[81]
Forsythoside A		Nrf2/GPX4	Neuroinflammation	[82]
Salvianolic acid C		AMPK/Nrf2-NF-κB		[83]
Sinomenine		Nrf2-NF-κB		[84]
Chlorogenic acid		Nrf2-ARE	Cerebral ischemia/reperfusion injury	[85]
EGCG		Nrf2-NF-κB/NLRP3 inflammasome	Lupus nephritis	[86]
Fuzi	–	Nrf2-ARE	Rheumatoid arthritis	[87]
Polyphenol-rich grapes			Obesity-induced inflammation	[88]
Salidroside			Liver injury	[89]

signaling. They further activate AMPK and modulate TRPV1 and SIRT6/Nrf2 signaling to mitigate high glucose-induced insulin resistance in type 2 diabetes mellitus (T2DM). Irisin rescues diabetic cardiac microvascular injury by stimulating the phosphorylation and nuclear translocation of extracellular signal-regulated kinase (ERK) 1/2 and Nrf2, while increasing the mRNA expression of HO-1, superoxide dismutase (SOD) 1, and SOD2 [72]. Garlic sartan isopropyl ester demonstrates therapeutic efficacy by activating the SIRT1/Nrf2 axis to inhibit the NF-κB signaling pathway and downregulate NF-κB p65 and pro-inflammatory cytokines TNF-α and IL-1β, thereby alleviating diabetes-associated oxidative stress and inflammation in a high-fat diet and STZ-induced rat model [73]. Honokiol protects against myocardial I/R injury in type 1 diabetic rats by suppressing oxidative stress and apoptosis through activation of the SIRT1-Nrf2 signaling pathway [74]. Moreover, sulforaphane, a key compound in broccoli sprouts, suppresses diabetic cardiomyocyte damage through the activation of the AMPK/Nrf2 pathways [75], and protects against diabetes-induced renal damage in mice and humans by activating Nrf2 [76].

Neurodegenerative & neuroinflammation diseases

In addition, SFN exhibits protective effects in neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), and MS, all of which are closely related to neuroinflammation. Specifically, it offers neuroprotective effects in AD by activating Nrf2 to inhibit BACE1 and reduce Aβ production [77, 78]. Anthocyanins show protective effects against neurodegeneration and memory impairment in an AD mouse model by alleviating ROS and oxidative stress via the PI3K/AKT/Nrf2/HO-1 pathway activation [79].

Moreover, gastrodin upregulates the Nrf2/HO-1 pathway, inhibiting ferroptosis and providing neuroprotection [80]. In parallel, resveratrol mitigates rotenone-induced inflammation and oxidative stress by upregulating STAT1, Nrf2, and SLC7A11, leading to a marked suppression of pro-inflammatory cytokine production, such as IL-6, IL-1β and TNF-α in a microglia cell line to attenuate PD [81]. Forsythoside A also activates the Nrf2/GPX4 axis to inhibit iron deposition-mediated neuroinflammation and lipid peroxidation, preventing the IKK/IκB/NF-κB signaling, reducing pro-inflammatory cytokine secretion to improve memory and cognitive function in Alzheimer's-like pathology [82]. Additionally, salvianolic acid C exerts anti-inflammatory effects by targeting the AMPK/Nrf2 pathway, which in turn inhibits the NF-κB pathway to mitigate LPS-stimulated neuroinflammation [83]. Sinomenine exerts anti-inflammatory effects by promoting Nrf2-dependent microglia M1/M2 polarization and inhibiting the phosphorylation of IκBα as well as NF-κB nuclear translocation, contributing to the treatment of cerebral inflammatory disorders [84]. Moreover, chlorogenic acid has a similar effect in activating Nrf2 to regulate oxidative stress in cerebral I/R injury in rats [85].

Other inflammation disorders

Epigallocatechin gallate (EGCG), a green tea compound, alleviates lupus nephritis (LN) in mice by enhancing Nrf2 signaling and inhibiting nucleotide-binding oligomerization domain (NOD)-like receptor protein 3 (NLRP3) inflammasome activation, thereby reducing oxidative stress and inflammation, and improving renal function [86]. Fuzi, a traditional Chinese medicine derived from the lateral roots of *Aconitum carmichaeli Debx*, exerts beneficial effects on rheumatoid arthritis patients by modulating the Nrf2 pathway [87]. Additionally, the Nrf2-ARE pathway can be activated by polyphenol-rich grape compounds to target obesity-induced inflammation and metabolic diseases [88]. Salidroside alleviates hypoxia-induced hepatic injury by simultaneously modulating the JAK2/STAT3 pathway and enhancing Nrf2-driven antioxidant activation, thereby reducing inflammation and strengthening cellular antioxidant defenses [89].

MSCs and derivatives as potent activators of Nrf2 in inflammatory diseases

Nrf2 serves as a master regulator of redox and metabolic homeostasis in MSCs, playing a crucial role in maintaining their physiological integrity and functional properties. This positions Nrf2 as a valuable therapeutic target for MSCs-based regenerative medicine in inflammatory diseases. The therapeutic capacity of MSCs in inflammatory conditions is increasingly attributed to their potent paracrine activity rather than solely to their differentiation potential. A key mechanism underlying this paracrine effect is the activation of the Nrf2 antioxidant pathway. MSCs and their secreted products including exosomes (Exos)/extracellular vehicles (EVs) and CM, activate Nrf2 through multi-dimensional/target mechanisms, thereby enhancing cellular antioxidant defenses, modulating immune responses, and promoting tissue repair (Fig. 3). It is noteworthy that the therapeutic efficacy of MSCs and their derivatives can be enhanced through external modulation, including pretreatment with natural compounds; these synergistic strategies are discussed in "Natural flavonoids synergize with MSCs to enhance Nrf2 activation" section. This section first systematically reviews the intrinsic mechanisms by which MSCs and their derivatives activate the Nrf2 pathway. It then explores natural strategies and other reinforcement approaches for alleviating inflammatory pathology.

Different tissue derived MSCs as Nrf2 activators

Transplantation of MSCs derived from various human or animal sources-such as bone marrow (BM), umbilical cord (UC), adipose tissue (AD), dental pulp (DP) and placenta-has demonstrated therapeutic efficacy in multiple models of inflammatory diseases. The primary mechanism underlying this effect involves the suppression of oxidative stress and inflammatory responses through direct or indirect activation of the Nrf2 signaling pathway.

Pulmonary diseases

In pulmonary diseases, the downstream effects regulated by Nrf2 form a multidimensional defense network that enables MSCs to combat inflammation and injury. This protection is founded on the ability of MSCs to alleviate tissue damage by coordinately regulating redox homeostasis and programmed cell death via Nrf2. MSCs significantly alleviate lung injury through activation of the Nrf2 pathway. In a bleomycin-induced rat model of pulmonary fibrosis, intravenous infusion of bone marrow MSCs (BMSCs) markedly reduced collagen deposition and hydroxyproline content in lung tissue via activation of the Nrf2/ARE signaling pathway, while increasing SOD activity and decreasing MDA levels, thereby effectively attenuating oxidative stress and tissue fibrosis [90]. In a model of ALI associated with severe acute pancreatitis (SAP), BMSCs similarly exerted protective effects by activating the Nrf2 transcription factor and suppressing ferroptosis in lung tissue. This was evidenced by decreased Fe^{2+}, MDA, and ROS levels, along with increased GPX4 and GSH levels [91]. Furthermore, Nrf2 activation acts as a critical hub through which MSCs achieve a synergistic anti-inflammatory and anti-fibrotic effect. In an a model of aging, BMSCs suppressed the expression of the endoplasmic reticulum stress marker-BiP via the PERK-Nrf2 axis, thereby mitigating bleomycin-induced pulmonary inflammation and fibrosis [92]. In a LPS-induced acute lung injury (ALI) model, BMSCs transplantation alleviated pulmonary edema and tissue damage, a protective effect linked to upregulation of the Nrf2/HO-1 pathway and inhibition of the NLRP3 inflammasome [93].

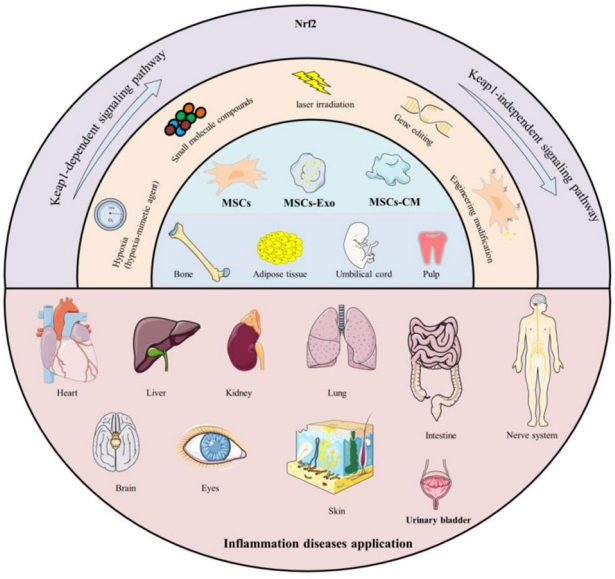


Fig. 3 The epigenetic regulatory mechanism of MSCs and their derivatives in activating Nrf2 for the treatment of inflammatory diseases. This figure provides an overview of the potential applications of MSCs derived from various tissues (such as bone, adipose tissue, umbilical cord, and dental pulp) or MSCs-derived products (e.g., exosomes or conditioned medium) in the treatment of inflammatory diseases across multiple organs (including the heart, liver, kidney, lung, brain, eye, skin, bladder and etc.) through the regulation of upstream and downstream signaling pathways of Nrf2. Pretreatment and engineering strategies-such as hypoxia mimetics, small molecule compounds, laser irradiation, and genetic editing-can further enhance the regulatory efficiency of the Nrf2 pathway via either Keap1-dependent or Keap1-independent signaling pathways, underscoring the multi-target and multi-directional regulatory role of the Nrf2 pathway in the treatment of inflammation

Investigations using different administration routes have yielded important insights into these mechanisms and their clinical translation. Positive outcomes have also been achieved through other routes of administration. Zhou et al. established a chronic obstructive pulmonary disease (COPD) model in mice through cigarette smoke and intranasal LPS administration. Their findings demonstrated that airway delivery of MSCs alleviated COPD progression, primarily by modulating the Nrf2 pathway and reversing oxidative stress, thereby improving pulmonary condition [94]. Notably, intranasal administration of human BMSCs also demonstrated therapeutic efficacy in an LPS-induced ALI mouse model, an effect mediated by the STC2 protein via the Nrf2/HO-1 pathway [95]. These findings significantly reinforce the generalizability of the Nrf2 pathway as a core effector mechanism for MSCs, which remain consistent across administration routes.

Neurological injuries

MSCs exert comprehensive neuroprotective effects in neurological disorders by modulating Nrf2-mediated redox homeostasis. Firstly, MSCs alleviate neuropathological damage and symptoms directly via an Nrf2-mediated synergistic antioxidant and anti-inflammatory effect. In a model of oxaliplatin-induced sensory neuropathy (OISN), a single intravenous injection of BMSCs completely reversed mechanical and cold allodynia, demonstrating a longer-lasting analgesic effect than gabapentin [96]. Mechanistically, BMSCs elevated the levels of anti-inflammatory cytokines IL-10 and transforming growth factor-beta (TGF-β) in the spinal cord and, more importantly, upregulated the gene expression of spinal Nrf2 and SOD. This reinforced the capacity to scavenge ROS, thereby reducing levels of oxidative stress markers

(nitrite and malondialdehyde, MDA) and reestablishing redox homeostasis. More profoundly, the precise Nrf2-dependent regulation of microglial phenotype polarization by MSCs is particularly critical for neuroprotection and regeneration. In a chronic stress-induced depression model, transplantation of adipose-derived MSCs (ADSCs) significantly reversed depression-like behaviors. The central mechanism involves the activation of the Nrf2/HO-1 pathway and inhibition of the toll-like receptor 4 (TLR4)/NF-κB pathway, which modulates microglial polarization by suppressing the M1 phenotype while promoting the M2 phenotype. This regulation reduced the release of pro-inflammatory cytokines and restored the expression of brain-derived neurotrophic factor (BDNF) and its receptor TRKB expression in the brain. Knockdown and overexpression experiments confirmed that Nrf2 is a key molecule mediating the antidepressant effects of ADSCs [97]. In an AD model, human dental pulp stem cells (hDPSCs) transplanted into the hippocampus of 3xTg-AD mice promoted Nrf2 nuclear translocation via the AKT-GSK3β-Nrf2 pathway. This led to the upregulation of antioxidant enzymes, including HO-1 and SOD1. Subsequently, M1 microglial polarization was inhibited, oxidative stress and neuronal apoptosis were alleviated, and ultimately, cognitive impairments and hippocampal pathology in the mice improved [98]. However, the upstream activation mechanisms may vary depending on the cell source or disease context. This diversity in upstream signaling implies that MSCs adapt to distinct pathological microenvironments through specific factors, which ultimately converge to activate Nrf2.

Hepatic diseases

The hepatoprotective effect of MSCs depends on the activation of Nrf2, with its core mechanism residing in the coupled enhancement of hepatic antioxidant defenses and suppression of excessive inflammatory responses. In a model of LPS-induced acute liver injury during sepsis, transplantation of BMSCs significantly ameliorated hepatic pathological architecture. This protective effect was mediated by the upregulation of Nrf2 mRNA expression, which alleviated oxidative stress (restoring GSH and GPX levels) and inflammatory responses (reflected in reduced TNF-α and IL-6 levels) [99]. In a carbon tetrachloride (CCl_4)-induced model of chronic liver injury and fibrosis, BMSCs homed to the damaged liver and activated the Nrf2/HO-1 signaling pathway. This activation enhanced hepatic antioxidant capacity (reducing MDA and restoring GSH) and suppressed inflammation (via NF-κB downregulation) [100]. Studies further revealed that allogeneic (rat-derived) BMSCs conferred superior therapeutic efficacy compared to xenogeneic (mouse-derived) BMSCs, suggesting that immunological compatibility may influence treatment outcomes [101]. This finding further suggests that the survival, paracrine activity, and host immune interactions of transplanted MSCs in vivo directly influence the capacity of host hepatocytes to activate the Nrf2 pathway, thereby offering an additional explanation for the observed variations in clinical efficacy. In a model of D-galactose-induced aging-associated liver injury, treatment with umbilical cord-derived MSCs (UC-MSCs) effectively mitigated mitochondrial dysfunction (restoring membrane potential and adenosine triphosphate [ATP] levels while reducing ROS), alleviated histopathological damage, and reduced senescence markers. These benefits were achieved primarily through activation of the Nrf2/HO-1 pathway, rather than the FOXO3a pathway [102]. Unlike the mechanistic emphasis in acute or toxin-induced injury models, these findings suggest that when confronting intrinsic programmed damage like cellular senescence, MSCs may use Nrf2 to prioritize repairing core organelle functions related to cellular energy metabolism.

Heart and kidney diseases

In high-metabolism terminal organs susceptible to oxidative damage, such as the heart and kidneys, MSCs confer protection by activating Nrf2. This Nrf2-mediated protection encompasses not only fundamental anti-inflammatory, antioxidant, and anti-fibrotic actions but also, more profoundly, the regulation of programmed cell death and metabolic remodeling. In cardiac diseases, BMSCs exhibit protective effect against isoproterenol-induced myocardial infarction, with efficacy even surpassing that of the clinical drug digoxin. Mechanistically, BMSCs home to the damaged myocardium and mitigate oxidative stress, inflammatory response, and apoptosis by upregulating Nrf2 while downregulating TLR-4 and p53 [103]. In kidney disease, MSCs exert protective effects in various kidney injury models via the Nrf2 pathway. In a DN model, human UCMSCs promote Nrf2 nuclear translocation through the PI3K/AKT signaling pathway, upregulate antioxidant factors such as HO-1 and SOD2, and consequently alleviate glomerulosclerosis and mesangial cell apoptosis [104]. Further studies reveal that hUCMSCs can also activate Nrf2 by inhibiting the JNK/KEAP1 signaling pathway, thereby modulating ferroptosis-related proteins (downregulating ACSL4 and upregulating GPX4 and FTH1, among others) and ultimately inhibiting ferroptosis in the diabetic kidney [105]. In LN, UCMSCs have similarly been shown to inhibit ferroptosis in glomerular podocytes by upregulating Nrf2 [106]. In a methotrexate (MTX)-induced nephrotoxicity model, both ADSCs and platelet-rich plasma (PRP) alleviated renal oxidative stress, inflammation, and apoptosis by activating the Nrf2/PPARγ/HO-1 pathway and inhibiting the NF-κB/Keap1/Caspase-3 pathway, with comparable efficacy observed between the two treatments [107]. In

both isoproterenol-induced myocardial infarction and kidney damage models induced by various factors (such as diabetes, lupus, and drugs), the core role of MSCs begins with the activation of Nrf2. And this activation directly enhances the organ's fundamental defense capacity. However, certain limitations remain. For instance, in studies claiming efficacy superior to that of digoxin, whether the dosing regimens and efficacy evaluation criteria are entirely fair and comparable requires careful assessment. More importantly, post-myocardial infarction repair involves multiple stages, including inflammation resolution, angiogenesis, and fibrosis regulation. Current research has not yet provided a spatiotemporally resolved answer as to whether Nrf2 activation predominantly governs a specific stage or provides protection throughout the entire process.

Intestinal diseases

In studies on MSCs therapy for colitis, multiple lines of evidence have demonstrated that MSCs can exert antioxidant, anti-inflammatory, and mucosal repair effects through activation of the Nrf2 pathway. Liu et al. [108] administered MSCs or MSCs-CM via rectal instillation and found that both treatments alleviated inflammation, improved intestinal barrier function, and enhanced antioxidant enzyme activity in a dextran sodium sulfate (DSS)-induced mouse colitis model. This protective effect was shown to depend on activation of the Nrf2/Keap1/ARE pathway, as the therapeutic benefits were abolished upon administration of the inhibitor ML385. In another study [109], ADSCs were administered intraperitoneally in a rat model of acute colitis induced by acetic acid. The results showed a reduction in inflammatory factors (TNF-α, PTX-3) and oxidative indicators (MDA), along with an increase in the anti-inflammatory factor IL-10 and in Nrf2 expression, which collectively attenuated intestinal tissue damage. However, this study lacked direct functional validation of the Nrf2/HO-1 pathway and did not clarify the effector mechanisms of MSCs. Collectively, these findings suggest that MSCs may alleviate colitis by modulating oxidative stress and immune responses through the Nrf2 pathway. Nevertheless, the specific mechanisms involved, long-term safety, and feasibility of clinical translation require further systematic investigation.

Skeletal and metabolic diseases

In skeletal diseases, MSCs promote bone repair and counteract apoptosis via the Nrf2 pathway. In a rat model of finger amputation, human BMSCs mitigated inflammation and oxidative stress by activating the SIRT1/Nrf2 pathway, thereby promoting angiogenesis and osteogenesis [110]. In a glucocorticoid-induced osteonecrosis of the femoral head (GC-ONFH) model, human UCMSCs co-cultured with osteoblasts significantly alleviated dexamethasone (Dex)-induced oxidative stress and osteoblast apoptosis through activation of the Nrf2-ARE signaling pathway, while also enhancing osteogenic mineralization potential. This protective effect was abolished upon administration of an Nrf2 inhibitor [111]. In metabolic diseases, specifically type 1 diabetes mellitus (T1DM), intravenous infusion of human UCMSCs has demonstrated therapeutic potential. Studies have found that MSCs can migrate to the damaged pancreas, reduce the generation of ROS, inhibit β-cell apoptosis, and improve insulin secretion by activating the Nrf2/HO-1 pathway, ultimately ameliorate hyperglycemia [112]. Knockdown experiments have further confirmed the critical role of the Nrf2 pathway in this process. MSCs primarily alleviate local inflammation and oxidative stress by activating Nrf2, which is consistent with the fundamental protective effects observed in other organs, aiming to create a clean microenvironment for tissue regeneration. However, during bone repair, do the transplanted MSCs act as activators of Nrf2, or do they themselves differentiate into bone cells? Furthermore, how do systemically administered MSCs efficiently home to bone, and does local application offer greater advantages? Addressing these questions may contribute to further enhancing therapeutic efficacy.

Other inflammatory conditions

The therapeutic efficacy of MSCs extends to other fields as well. In obstructive sleep apnea-hypopnea syndrome (OSAHS), intermittent hypoxia leads to oxidative damage in the genioglossus muscle. Human UCMSCs enhance the antioxidant capacity of the genioglossus by regulating upstream factors of DJ-1 and MEF2A, promoting the dissociation of Nrf2 from Keap1, and activating downstream expression of HO-1 and NQO1. However, direct evidence is still required to confirm their functional improvement effects [113]. In a rat model of interstitial cystitis (IC), intrathecal injection of human UMSCs alleviates neuroinflammation and oxidative stress in the dorsal horn of the spinal cord via activation of the Sirt1/Nrf2/HO-1 pathway, thereby improving pain, urinary function, and depression-like behaviors [114]. This contrasts with the aforementioned direct protective effects targeting the brain or spinal cord in neurological diseases, yet shares a consistent mechanistic core: upregulating Nrf2 at central nervous system sites can significantly influence the pathological progression of systemic or multi-system diseases. And in the field of fat grafting, ADSCs significantly improve the survival rate of transplanted fat by suppressing inflammation, reducing ROS, and promoting angiogenesis through interactions between the Nrf2 and TLR4/NF-κB pathways, highlighting their potential application in regenerative medicine [115]. It suggests that co-transplanting MSCs as a "biological adjuvant"

with tissue grafts, leveraging their Nrf2-mediated microenvironment remodeling capacity, can effectively promote clinical tissue regeneration.

In a word, MSCs consistently exert therapeutic effects by activating the Nrf2 signaling pathway, thereby alleviating oxidative stress, suppressing inflammatory responses, and promoting tissue healing in various disease models. However, numerous challenges remain to be addressed in order to translate these promising preclinical findings into clinical practice. Future research should focus on the following aspects: (i) elucidating the precise upstream molecular mechanisms by which MSCs activate Nrf2; (ii) employing more clinically relevant chronic disorder models; (iii) systematically evaluating the long-term safety, optimal delivery strategies (including dosage and route of administration), and immunogenicity of MSCs-based therapies; and (iv) validating the selection criteria (optimal source), quality control, batch-to-batch consistency of MSCs, and addressing the regulatory and ethical barriers to clinical translation.

Cell-free therapy: harnessing MSCs-derived exos/EVs and CM

In contrast to flavonoids, which directly target Keap1 or upstream kinases, MSCs can indirectly modulate the Nrf2 pathway in target cells through their secretome, for example via exosomes containing specific miRNAs. This paracrine mechanism represents a distinct, cell-derived strategy for Nrf2 activation. MSCs-derived products-particularly Exos/EVs and CM retain most of the therapeutic functions of MSCs while circumventing limitations associated with cell-based therapies, such as immune rejection, tumorigenic risks, and low cell survival rates. Exos/EVs are nano-sized extracellular vesicles secreted by MSCs and are enriched with bioactive molecules, including proteins, lipids, and nucleic acids (e.g., miRNA, lncRNA). They modulate recipient cell functions via paracrine mechanisms. CM, on the other hand, comprises the full spectrum of soluble factors secreted by MSCs during in vitro culture, including cytokines, growth factors, and metabolites, and is characterized by multi-factor synergistic effects. Both Exos/EVs and CM can replicate the immunomodulatory, antioxidant, and anti-inflammatory effects of MSCs. These products have demonstrated considerable potential in modulating the Nrf2 signaling pathway, thereby offering novel therapeutic avenues for the treatment of inflammatory diseases. This section will systematically review the mechanisms and research related to Exos/EVs and CM in treating various disease models via activation of the Nrf2 pathway, with a particular emphasis on their unique advantages as "cell-free therapy" strategies.

Pulmonary diseases

In recent years, studies have revealed that Exos/EVs and CM exert multifaceted protective effects in hyperoxia-, LPS-, or sulfur mustard (SM)-induced ALI, diabetes, and sepsis-associated lung injury through modulation of the Nrf2 signaling pathway. Across various ALI models, multiple MSCs-derived products have demonstrated significant protective efficacy. For instance, exosomes derived from BMSCs (BMSCs-Exos) alleviate high glucose and LPS-induced dysfunction, inflammation, and ferroptosis in human pulmonary microvascular endothelial cells (HPMECs) via activation of the Nrf2/HO-1 pathway [116]. Further mechanistic studies have identified that human UCMSCs derived exosomes (hUCMSCs-Exos) are enriched with miR-199a-5p, which targets caveolin-1 (CAV1), thereby relieving its inhibitory effect on Nrf2, promoting its nuclear translocation, and enhancing the expression of downstream antioxidant genes [117]. This cascade ultimately mitigates SM-induced oxidative stress and apoptosis. Moreover, both human UCMSCs-CM and induced pluripotent stem cells conditioned medium (iPSCs-CM) have been shown to ameliorate LPS- or hyperoxia-induced ALI through activation of Nrf2 and suppression of the NF-κB pathway [118]. Specifically, iPSCs-CM enhances the Nrf2-mediated antioxidant response, potentially through its key component α-Klotho [119]. Regarding administration routes, inhaled MSCs-EVs were found to be superior to tail vein injection in promoting macrophage M2 polarization, attenuating inflammation, and reducing oxidative damage, with these effects also dependent on the adaptive regulation of Nrf2 [120]. This provides direct comparative evidence for the optimal delivery strategy of cell-free therapies, suggesting that local inhalation enables more efficient enrichment of effector molecules in lung tissues.

Beyond ALI, MSCs derivatives products also exhibit therapeutic potential in sepsis-associated acute respiratory distress syndrome (ARDS) and pulmonary fibrosis. BMSCs-Exos activate the Nrf2 pathway, reverse sepsis-induced impairments in mitochondrial biogenesis and fission-fusion balance in alveolar epithelial type II cells, and consequently reduce apoptosis and decrease mortality [121]. Notably, in a bleomycin-induced pulmonary fibrosis model, conditioned medium from human embryonic stem cell-derived stromal cells (hESC-MSC-IMRC-CM) alleviated oxidative stress and fibrosis by suppressing the Nox4/Nrf2 signaling axis while concurrently antagonizing Tlr4/MyD88-mediated inflammation [122]. This suggests that Nrf2 may play context-dependent roles across different pathological conditions. It also indicates that the regulation of Nrf2 requires precise spatiotemporal alignment with disease stages, and its "double-edged sword" role urgently warrants systematic investigation.

In summary, both Exos/EVs and CM can effectively replicate the core functions of intact MSCs, including antioxidant, anti-inflammatory, anti-cell death (e.g., ferroptosis, apoptosis), and pro-repair effects, through activation of the Nrf2 pathway. This finding is of fundamental significance: it confirms that the paracrine mechanism, rather than direct cell replacement, is the primary route for the therapeutic efficacy of MSCs. Furthermore, compared to the research model using intact cells, the study of MSC derivatives allows for a clearer dissection of the "signaling cascade" leading to Nrf2 activation, reflecting a refinement in mechanistic understanding.

Neurological injuries

In neurological disorders, Exos/EVs and CM demonstrate broad neuroprotective potential by modulating a network of pathways centered around Nrf2. Studies have shown that human UCMSCs-derived Exos can alleviate LPS-induced neuroinflammation and microglial M1 polarization by activating Nrf2 and inhibiting the NF-κB/NLRP3 inflammasome [123]. In models of neuronal damage and cognitive impairment induced by the chemotherapeutic agent MTX or surgical intervention, MSCs-Exos significantly ameliorated oxidative stress, ferroptosis, and neurological function through activation of the Nrf2-ARE or SIRT1/Nrf2/HO-1 pathways [124, 125]. In acute spinal cord injury (SCI), Exos derived from various MSCs sources effectively inhibited microglial ferroptosis, attenuated inflammation, promoted autophagy, and improved motor function by delivering specific miRNAs (e.g., miR-124, miR-219-5p) to target UBE2Z [126], by activating Nrf2 and its downstream effectors (e.g., HO-1, GCH1/BH4) [127, 128], and by reversing p62 accumulation [129].

In traumatic and ischemic injuries, such as traumatic brain injury (TBI), cerebral ischemia–reperfusion injury (CIRI), and hypoxic-ischemic brain damage (HIBD), MSCs-Exos activated Nrf2 downstream effectors (e.g., Lin28a), effectively suppressing microglial ferroptosis, reducing inflammation, and mitigating injury [130]. Ferroptosis was inhibited and inflammation alleviated through activation of the long non-coding RNA TUBB6/Nrf2 axis [131], or via delivery of specific miRNAs (e.g., miR-653-3p) that targe the TRIM21/p62/Nrf2/CYLD axis, thereby suppressing the NF-κB signaling pathway and counteracting protein aggregation, oxidative stress, and neuroinflammation [132]. Furthermore, in an intracerebral hemorrhage (ICH) model, neural stem cell secretions inhibited hemin-induced ferroptosis and cerebral edema via the Nrf2 pathway, with the key component HSPE1 protein potentially mediating this protective effect [133]. In a PD model, miR-100-5p in trophoblast-derived MSCs Exos protected dopaminergic neurons and improved behavioral performance by targeting NOX4 and regulating the Nox4/ROS/Nrf2 axis [134]. Finally, in amyotrophic lateral sclerosis (ALS), conditioned medium exerted potent antioxidant effects by activating the Nrf2/HO-1 signaling pathway, improving cell viability, and reducing cytoplasmic aggregation of TDP-43 M337V [135].

In summary, stem cell derivatives exhibit significant therapeutic potential in various neurological disease models owing to their favorable penetrability of the central nervous system and multi-targeting regulatory capabilities. These derivatives exert regulation over neuronal and glial cell fate, as well as their interactions, by a signaling network centered on Nrf2. Their effects are mediated through Nrf2-associated antioxidant, anti-inflammatory and anti-cell death mechanisms, which together provide experimental foundation for clinical translation. While most studies have demonstrated effects at the tissue level, several critical questions remain unclear. For instance, which neural cell types, for example, neurons, astrocytes, microglia, or oligodendrocytes, was served as the primary targets for the delivery of these acellular components and the activation of Nrf2? How can these components efficiently cross or evade the blood–brain barrier? Although specific miRNA or protein molecules have been identified as key mediators, do other components act synergistically or antagonistically?

Hepatic diseases

In the field of chronic liver disease, MSCs-Exos, through the precise modulation of the Nrf2 network, not only retain the protective effects of intact cells but also demonstrate unique mechanistic advantages in targeting core pathological processes of chronic liver disease, such as autophagy, cellular transdifferentiation, and metabolic dysregulation. In a CCl_4-induced liver fibrosis model, MSCs-Exos restored autophagy function, suppressed endothelial–mesenchymal transition (EMT), and modulated the expression of multiple miRNAs (such as miR-153-3p and miR-27a) through the non-canonical Nrf2/Keap1/p62 signaling pathway, thereby reducing collagen deposition, apoptosis, and inflammatory responses [136]. In a nonalcoholic steatohepatitis (NASH) model, human UCMSCs derived Exos significantly alleviated hepatocellular steatosis and suppressed inflammatory responses and oxidative stress by activating the Nrf2/NQO-1 pathway [137]. Their action extends beyond merely addressing the consequences of lipid peroxidation (oxidative stress); they may also intervene in the intrinsic balance of lipid metabolism within hepatocytes via the Nrf2 downstream network (potentially involving lipid metabolism-related genes).

Heart and kidney diseases

In cardiac and renal diseases, MSCs derivatives demonstrate significant therapeutic potential due to their potent antioxidant, anti-inflammatory and novel anti-ferroptosis properties. In the context of heart disease, Exos derived from iPSCs ameliorate myocardial injury induced by SAP in rats by activating the Akt/Nrf2/HO-1 signaling pathway, thereby improving cardiac function and suppressing oxidative stress [138]. In myocardial I/R injury, EVs from dexmedetomidine-pretreated human UCMSCs (hUC-MSC-EVs) deliver miR-24 to inhibit KEAP1, activate the Nrf2/HO-1 pathway, and promote macrophage M2 polarization, thereby enhancing cardioprotection [139]. Furthermore, MSCs-CM improves mitochondrial biogenesis and function in aged rats following I/R injury by upregulating the SIRT-1/PGC-1α/Nrf2 pathway, reducing infarct size and suppressing inflammation [140]. Notably, although MSCs-CM does not protect against H_2O_2- and *S*-Nitroso-*N*-acetyl-DL-penicillamine (SNAP)-induced oxidative damage, it specifically counteracts erastin- and RSL3-induced ferroptosis. This effect is closely associated with significant upregulation of iron metabolism-related genes (FPN), redox regulatory genes (GPX4, AIFM2), and key transcription factors (Nrf2, ATF4), offering new insights into stem cell derivative-based therapies for ferroptosis-related cardiac diseases [141]. In kidney disease, MSCs-EVs alleviate oxidative stress and tubular damage in acute kidney injury (AKI) models by enhancing the activation of the Nrf2/ARE signaling pathway and the expression of its downstream antioxidant gene HO-1, a protective effect that appears to be cell source-specific [142]. Collectively, these studies indicate that therapeutic strategies employing stem cell derivatives to target the Nrf2 and its associated pathways provide novel avenues for the preventing and treating cardiac and renal diseases through the multidimensional regulation of redox balance, iron metabolism, and inflammatory responses. However, their clinical translation warrants further investigation.

Skin injuries

In dermatology, stem cell-derived exosomes also exert significant effects by modulating the Nrf2 pathway. Human UCMSCs-derived Exos mitigate ultraviolet (UV) A/B-induced skin oxidative damage, DNA damage, and inflammatory responses while improving mitochondrial function in mice through adaptive regulation of the Nrf2 defense system [143]. ADSCs derived Exos effectively counteract UVB-induced photoaging in human dermal fibroblasts by synergistically activating the Nrf2 pathway, inhibiting the MAPK/AP-1 pathway, and activating the TGF-β/Smad pathway to promote collagen synthesis [144]. Furthermore, Exos have been extensively demonstrated to modulate multiple key signaling pathways, such as TLR4 and PI3K/AKT, thereby comprehensively regulating macrophage polarization, oxidative stress, angiogenesis, and collagen synthesis, ultimately ameliorating various types of skin damage [145]. Despite promising prospects, research in this field has predominantly focused on preventive protection (e.g., against ultraviolet radiation) or cellular models, while validation of efficacy in complex pathological models remains insufficient. Furthermore, strategies for the effective penetration of the skin barrier and targeted delivery to specific skin layers (epidermis, dermis) by Exos represent a critical technological bottleneck that must be addressed for clinical translation.

Skeletal and metabolic diseases

In bone and metabolic diseases, Exos demonstrate novel therapeutic potential through precise modulation of the Nrf2 pathway. In the model of IVDD, studies have untangled the multi-layered and profound mechanisms by which Exos regulate Nrf2. For example, BMSCs-Exos can effectively neutralize excessive ROS by inhibiting Keap1 and promoting the expression and nuclear translocation of Nrf2, thereby alleviating inflammation, apoptosis, and extracellular matrix degradation in nucleus pulposus (NP) cells and ultimately delaying IVDD progression [146]. Furthermore, Exos specifically inhibit tert-butyl hydroperoxide (TBHP)- or RSL3-induced ferroptosis in NP cells via the p62/KEAP1/Nrf2 signaling axis, and animal studies have confirmed their efficacy in mitigating IVDD in rats [147]. More in-depth studies reveal that Exos can also stabilize Nrf2 through epigenetic mechanisms: Exos can upregulate the expression of the demethylase FTO by promoting H3K27ac modification, which subsequently induces m^6A demethylation of Nrf2 and reduces its recognition by YTHDF2. This ultimately enhances the stability of Nrf2 expression, thereby inhibiting oxidative stress-induced lysosomal membrane permeabilization (LMP) and the senescence of nucleus pulposus cells (NPCs), offering a novel epigenetic strategy for treating IVDD [148]. Collectively, these findings indicate that targeting the Nrf2 pathway represents a central mechanism by which stem cells-derived exosomes treat IVDD, laying a theoretical foundation for clinical translation.

In glucocorticoid-induced osteoporosis (GIOP), exosomes derived from adipose-derived mesenchymal stem cells (ADSCs-Exos) can reverse Dex-induced oxidative stress and mitochondrial dysfunction in osteoblasts by activating the Nrf2/HO-1 signaling pathway. They also upregulate the expression of osteogenic markers and improve bone microstructure in rats. This protective effect is attenuated upon silencing of Nrf2 [121]. In a T2DM model, hUCMSCs-Exos activated the AKT/ERK pathway by delivering functional proteins that promote

NRF2 phosphorylation and nuclear translocation, thereby inhibiting ferroptosis in β-cells and enhancing pancreatic islet function. To further improve targeting specificity, an aptamer-PEG-modified exosome system (Apt-EXO) was developed, which significantly prolongs circulation time and enriches within the pancreas, demonstrating superior protective effects compared to unmodified exosomes. This provides a novel strategy for cell-targeted therapy in T2DM [149]. This represents a direct technological innovation in moving from leveraging the natural tropism of Exos to rationally designing targeted delivery tools, and the construction of an engineered exosome platform may emerge as a potential future research direction.

Reproductive system diseases

In reproductive system diseases, stem cell derivatives provide innovative therapeutic strategies for various refractory functional impairments by targeting the Nrf2 signaling pathway. In premature ovarian insufficiency (POI), hUCMSCs-EVs carry insulin-like growth factor 1 (IGF-1) to activate the Nrf2/HO-1 pathway, thereby suppressing cyclophosphamide-induced excessive autophagy and damage in granulosa cells. This mechanism improves ovarian structure, regulates serum sex hormone levels, and restores ovarian function in mice [150].

In the context of male reproduction, the secretome derived from human amniotic mesenchymal stem cells (hAMSCs-secretome) significantly alleviates oxidative stress, inflammation, and spermatogenic cell apoptosis in mice following testicular torsion/detorsion by modulating the SIRT1/NRF2/TNF-α pathway. It also elevates serum testosterone levels, improves sperm parameters, and effectively restores testicular structure and function [151]. As for diabetic erectile dysfunction (DMED), MSC-EVs, particularly engineered vesicles enriched with miR-200a-3p (EVs-200a), directly target and inhibit Keap1 through miR-200a-3p. This action relieves the suppression of Nrf2, activates the Nrf2/HO-1 antioxidant pathway, reduces oxidative stress in the corpus cavernosum, decreases smooth muscle cell apoptosis and fibrosis, and ultimately reverses erectile dysfunction in diabetic rats [152]. In the context of reproductive system diseases, stem cell derivatives offer an innovative perspective for treating traditionally intractable organ-specific functional failure by targeting the Nrf2 pathway. These studies not only reaffirm the core mechanisms of antioxidant and anti-inflammatory actions but, more profoundly, untangle the feasibility of precisely modulating Nrf2 activity within reproductive glands and accessory organs through the remote delivery of specific signaling molecules (e.g., proteins, miRNAs), thereby restoring their complex endocrine and physiological functions.

Other inflammatory conditions

In the fields of ophthalmology, surgery, and immunomodulation, stem cell-derived exosomes also demonstrate multifaceted therapeutic potential through precise regulation of the Nrf2 pathway. In diabetic retinopathy (DR), MSCs-Exos activate the PI3K/AKT signaling pathway to promote the expression of Nrf2 and its downstream target genes, thereby inhibiting high glucose-induced senescence, apoptosis, and oxidative stress in retinal pigment epithelial cells and ultimately improving retinal structure and function in mice [153]. ADSCs-EVs, through their specific miRNA cargo, activate the Nrf2/HO-1/NQO1 pathway, attenuate hydrogen peroxide-induced damage in ARPE-19 cells, and temporarily delay retinal degeneration in RCS rats [154]. In the context of flap surgery, intravenous administration of BMSCs-Exos significantly enhances the survival rate of random skin flaps in rats by activating the Keap1/Nrf2 signaling pathway. This mechanism is closely associated with the mitigation of oxidative stress, reduction of apoptosis, and promotion of angiogenesis [155]. Regarding immunosenescence regulation, human placental mesenchymal stem cell-derived exosomes (hPMSC-Exo) carry miR-21, which targets and inhibits PTEN, thereby activating the PTEN/PI3K-Nrf2 axis. This enhances the antioxidant capacity of $CD4^+$T cells in aged mice, reduces oxidative damage, and suppresses senescence-associated phenotypes [156].

In brief, MSCs derivatives activate the Nrf2 signaling pathway through multiple mechanisms and demonstrate significant antioxidant, anti-inflammatory and anti-cell death effects across various inflammatory disease models, including those affecting the skin, lung, nervous system, heart, and kidney. The protective effects are primarily reflected in the alleviation of oxidative stress, inhibition of inflammatory cytokine release, improvement of mitochondrial function, and promotion of tissue healing. However, current research still exhibits notable limitations, including the unidentified nature of most active components (such as specific miRNAs or proteins), a reliance on ex vivo or murine models without clinical validation, insufficient long-term safety and pharmacokinetic data, and a lack of standardization in administration methods and dosages. These factors collectively hinder their translation into clinical applications.

Strategic enhancement: preconditioning and engineering for superior Nrf2 activation

Although MSCs and their derivatives demonstrate considerable potential in the treating inflammation-related diseases, their clinical application is limited by several challenges, including low survival rates, poor homing efficiency, and functional suppression within inflammatory microenvironments. To further enhance the Nrf2-activation capacity and therapeutic efficacy of MSCs,

researchers have developed various external strategies, which can be broadly categorized into preconditioning and engineering modification. These approaches significantly improve the antioxidant, anti-inflammatory and survival capabilities of MSCs, thereby boosting their effectiveness in treating inflammatory diseases.

Preconditioning strategies to enhance Nrf2 activation efficiency

Preconditioning refers to the brief treatment of MSCs or their derivatives with physical, chemical, or biological factors prior to application, aiming to enhance their ability to counteract oxidative stress and improve their therapeutic efficacy. The effectiveness of preconditioning strategies has been validated in numerous studies. Ahmed et al. found that the combined application of BMSCs and indomethacin (IMC) ameliorated complete Freund's adjuvant (CFA)-induced arthritis by upregulating IL-4 and suppressing IL-1β and rheumatoid factor (RF) through the Nrf2 pathway [157]. Esmaeilzade et al. [158] demonstrated that dimethyloxalylglycine (DMOG), a prolyl hydroxylase inhibitor enhanced the viability, migration, and antioxidant capacity of BMSCs by stabilizing HIF-1α and upregulating migration-related genes (CXCR4, CCR2) and antioxidant genes (Nrf2). In Aβ-treated rats, DMOG-preconditioned BMSCs elevated hippocampal BDNF levels and antioxidant capacity, thereby restoring cognitive function. Zhang et al. [159] pretreated BMSCs with a low concentration H_2O_2, which activated the Nrf2 pathway by relieving Keap1-mediated inhibition of Nrf2, promoted its nuclear translocation, and initiated the expression of antioxidant enzyme genes (e.g., SOD, CAT). This process reduced ROS levels and alleviated mitochondrial dysfunction and DNA damage. The pretreatment markedly improved the survival rate of BMSCs under post-transplantation oxidative stress induced by a high concentration H_2O_2. Liu et al. [160] showed that pretreatment with 25 μM H_2O_2 boosted the proliferation, migration, and survival of BMSCs. Conditioned medium from H_2O_2-pretreated BMSCs (H_2O_2-BMSCs-CM) also activated the Nrf2/Keap1/ARE pathway, enhanced antioxidant capacity, and promoted tissue repair in DSS-induced colitis model. Wang et al. [161] reported that low-level laser irradiation (LLLI; 635 nm, 5.7 J/cm^2) similarly enhanced the antioxidant capacity of UC-MSCs, thereby promoting hematopoietic recovery in mice with radiation-induced acute radiation syndrome (ARS).

Preconditioning of hair follicle mesenchymal stem cells (HFSCs) with valproic acid (VPA) and rapamycin (RAPA), either individually or in combination, enhanced Nrf2 nuclear translocation, upregulated NQO1 and GPx activity as well as GSH levels, and increased VEGF and BDNF mRNA expression. These effects improved MSCs survival and reparative potential in ischemic injury, thereby enhancing transplantation efficiency [162]. Additionally, Gai et al. showed that exosomes derived from NaHS-preconditioned MSCs (H_2S-EVs) mitigated oxidative stress and mitochondrial dysfunction. Mechanistically, NaHS triggered Parkinson's disease protein 7 (PARK7)-mediated Nrf2/Keap1 dissociation, leading to cytoplasmic accumulation of Nrf2. Subsequently, free Nrf2 was loaded into EVs via recognition of its KFERQ motif by 70-kDa heat shock proteins (HSP70) and lysosomal-associated membrane protein 2 A (LAMP2A). Intranasal delivery of H_2S-EVs reduced oxidative damage and mitochondrial impairment in HI brain injury [163].

Given that the microenvironment of injured tissues is often hypoxic, preconditioning MSCs-derived products with hypoxia or hypoxia- mimicking agents can enhance their adaptability and therapeutic efficacy in vivo. Rao et al. demonstrated that hypoxia-preconditioned small extracellular vesicles (H-sEVs) derived from MSCs reversed H_2O_2-induced oxidative damage in PC12 cells by activating the SIRT1/Nrf2/HO-1 signaling pathway [164].

Hypoxia-preconditioned exosomes derived from iPSCs were enriched with antioxidant proteins (e.g., PRDX1, PRDX6, GSTP1, HSP90B), which promoted Nrf2 nuclear translocation and upregulated antioxidant genes (e.g., HMOX1, SOD2), thereby reducing ROS generation [165]. Furthermore, Hong et al. discovered that hypoxia-preconditioned ADSCs-CM exhibited enhanced Nrf2 activation capacity, increased Nrf2 nuclear translocation, and upregulated expression of SOD, GPx, and CAT, accompanied by reduced ROS production. This intervention significantly enhanced antioxidant enzyme activity and attenuated ROS toxicity in mice subjected to 70% hepatectomy [166]. Similarly, pretreatment of ADSCs with deferoxamine (DFX), a hypoxia-mimetic agent, yielded a secretory profile with comparable effects. Intranasal administration of DFX-preconditioned ADSCs-CM was found to reverse hippocampal oxidative stress, mitigate neuroinflammation, reduce apoptosis, and markedly improve neurobehavioral development (including righting reflex, negative geotaxis, and cliff avoidance), as well as motor coordination and memory function in neonatal rats [167]. The core logic of these strategies lies in simulating or inducing adaptive stress, such as employing specific chemical molecules or drug stimuli, or utilizing physical/microenvironmental preconditioning to mimic specific physical conditions of the in vivo injury environment. This pre-activates defense and repair pathways, such as the Nrf2 pathway, within MSCs, thereby empowering the cells. Consequently, after implantation into a harsh pathological microenvironment, the cells can maintain enhanced viability, superior paracrine function, and greater therapeutic resilience.

Engineered modification: precise modulation of the Nrf2 pathway

Gene engineering and nanotechnology have provided novel strategies for developing MSCs and their derivatives that target the Nrf2 pathway. The most straightforward strategy is the overexpression of Nrf2 or its key downstream effector molecules. Studies have demonstrated that Nrf2-overexpressing HFSCs (Nrf2-HFSCs) exhibit enhanced migration to intestinal injury sites, thereby improving the disease activity index (DAI) and histopathology outcomes in DSS-induced ulcerative colitis (UC) rats [168]. Similarly, Nrf2-overexpressing olfactory mucosa mesenchymal stem cells (OM-MSCs Nrf2) displayed improved cell survival and angiogenic potential [169]. Chen et al. [170] reported that in HO-1-overexpressing MSCs, Nrf2 and HO-1 synergistically inhibit the TLR4/MyD88 pathway, reduce the release of proinflammatory cytokines (TNF-α, IL-1β), and promote macrophage polarization toward the anti-inflammatory M2 phenotype. Wang et al. [171] found that in S-adenosylhomocysteine hydrolase (SAHH)-overexpressing MSCs, SAHH facilitates the dissociation of Nrf2 from Keap1, promotes Nrf2 nuclear translocation, and activates the Nrf2 pathway, thereby upregulating HO-1 and SOD1/2 expression, reducing ROS and MDA production, restoring paracrine functions (e.g., increased VEGF and IGF-1 secretion) in diabetic BMSCs, and ameliorating oxidative stress damage. And the exosomes derived from Nrf2-overexpressing BMSCs could suppress arrhythmias in atrial fibrillation models via the Nrf2/HO-1 pathway. This effect was primarily attributed to the ability of EVs derived from Nrf2-overexpressing MSCs to inhibit inflammatory responses, apoptosis, and fibrosis through activation of the Nrf2/HO-1 pathway [172, 173]. Additionally, to address complex diseases, some studies also employ co-expression or fusion expression strategies. MSCs co-overexpressing CXCL10 and Nrf2 while carrying the ferritin heavy chain (Fth) reporter gene (CXCL10-Nrf2-FTH-MSCs) were demonstrated to enhance T lymphocyte recruitment capacity and oxidative stress resistance. Consequently, these modified MSCs promoted T cell recruitment and induced iron accumulation, thereby suppressing tumor growth in glioblastoma (GBM) [174]. Transfection of ADSCs with the pIRES2-Nrf2-DKK1 plasmid, which enables co-expression of Nrf2/DKK1, significantly enhanced their anti-inflammatory/antioxidant capacity as well as paracrine effects. These genetically modified ADSCs demonstrated beneficial effects that promoted liver regeneration in acute-on-chronic liver failure (ACLF) mice [175]. Furthermore, a more refined and physiologically relevant regulatory approach involves the targeted inhibition of Keap1 through the introduction or upregulation of specific miRNAs. Regarding lentivirus-mediated miR-200a-modified BMSCs, miR-200a suppresses the 3' untranslated region activity of Keap1, thereby activating Nrf2 and strengthening antioxidant capacity. The miR-200a-modified BMSCs significantly promoted motor function recovery in rats with SCI [176]. Similarly, hsa-miR-532-3p enhances the antioxidant capacity of human decidual mesenchymal stem cells (hDMSCs) by activating the Nrf2 signaling pathway through targeting Keap1, thereby reducing the embryonic resorption rate in recurrent spontaneous abortion (RSA) [177]. The core logic of these strategies lies in simulating or inducing adaptive stress, such as employing specific chemical molecules or drug stimuli, or utilizing physical/microenvironmental preconditioning to mimic specific physical conditions of the in vivo injury environment. This pre-activates defense and repair pathways, such as the Nrf2 pathway, within MSCs, thereby empowering the cells. Consequently, after implantation into a harsh pathological microenvironment, the cells can maintain enhanced viability, superior paracrine function, and greater therapeutic resllience.

MSCs and their derivatives activate the Nrf2 signaling pathway through multiple mechanisms, exerting profound antioxidant, anti-inflammatory, and anti-apoptotic effects in various inflammatory disease models of the nervous system, lungs, heart, liver, kidneys, and bone. These protective roles primarily involve mitigating oxidative stress, suppressing the release of inflammatory factors, improving mitochondrial function, and promoting tissue healing. However, the majority of existing studies remain at the level of observing correlations with Nrf2 upregulation, and there is still a lack of precise causal validation regarding the key upstream signals-such as specific cytokines, miRNAs, or proteins-through which MSCs or derivatives initiate Nrf2 activation. Furthermore, the mechanistic insights are predominantly derived from in vivo or rodent (mouse/rat) model experiments, with a notable absence of clinical validation, insufficient long-term safety and pharmacokinetic data, and a lack of standardization in administration routes and dosages, all of which hinder clinical translation. Finally, and most critically, the essential role of the Nrf2 pathway has not been rigorously confirmed, as most studies have not employed reverse genetic validation using Nrf2-knockout animals or specific inhibitors. Consequently, it remains unclear whether the therapeutic effects are necessarily and exclusively dependent on Nrf2, and potential synergistic contributions from other pathways may have been overlooked. Therefore, future research must accomplish a triple transition: from descriptive phenomenology to mechanistic investigation, from short-term verification to long-term evaluation, and from idealized models to clinical scenarios, in order to overcome the current bottlenecks.

Moreover, the challenges in the clinical translation of MSCs and their derivatives cannot be overlooked. Firstly, regarding manufacturing processes, key bottlenecks include donor variability, maintenance of functional stability during large-scale expansion, batch-to-batch consistency, and the standardization of potency assays. These issues must be addressed through stringent donor screening, the use of animal component-free culture media, and unified functional testing standards. Long-term safety concerns, particularly the risk of tumorigenicity, require evaluation via genomic monitoring and long-term follow-up.

In particular, as for pharmacokinetics, the absorption, distribution, metabolism, and excretion of MSCs differ significantly from those of conventional small-molecule drugs. Different administration routes also lead to distinct pharmacokinetic outcomes. For instance, intravenously infused MSCs are prone to entrapment in pulmonary capillaries, resulting in limited systemic distribution. Moreover, their homing relies on chemotactic signals, so their in vivo survival time is short, and their clearance mechanisms remain unclear. Conventional pharmacokinetic parameters are not directly applicable, underscoring the urgent need to develop cell kinetic models based on labeling and tracking technologies.

From a regulatory perspective, MSCs are classified as advanced therapy medicinal products (ATMPs). They must be manufactured under Good Manufacturing Practice (GMP) conditions, with comprehensive quality control and traceability systems established throughout the entire production process. Additionally, they are subject to rigorous ethical and clinical approval procedures. Ethically, emphasis is placed on non-embryonic origin, informed consent, and review of allogeneic use. Clinical applications require the submission of non-clinical safety and pharmacodynamic data, along with the implementation of long-term follow-up studies.

Natural flavonoids synergize with MSCs to enhance Nrf2 activation

Although MSCs and their derivatives act as effective "executors" of Nrf2-mediated cytoprotection ("MSCs and derivatives as potent activators of Nrf2 in inflammatory diseases" section), their clinical application is hampered by practical limitations such as poor survival, restricted homing, and functional suppression within hostile inflammatory microenvironments [178]. Natural flavonoids, in contrast, are established "inducers" of the Nrf2 pathway with broad-spectrum antioxidant and anti-inflammatory activities ("Phytochemicals as Nrf2 inducers" section), but their therapeutic use is often limited by low bioavailability and rapid metabolism [179]. A direct comparison of these two strategies is provided in Table 5. A dual strategy therefore presents a novel alternative, in which flavonoids serve not only as co-therapeutic agents but also as pharmacological modulators that prime, protect, and potentiate MSCs (Table 6). This synergistic approach seeks to overcome the individual limitations of each component, building a more effective therapeutic alliance founded on robust Nrf2 activation (Fig. 4). The following section examines how the natural flavonoid compounds characterized in "Phytochemicals as Nrf2 inducers" section for the Nrf2-activating properties could be applied to pretreat or co-treat MSCs, thereby addressing key challenges in cell therapy. It presents a structured argument for this synergy: first, by explaining how flavonoids improve MSCs viability; second, by analyzing how they remodel MSC paracrine efficacy; and finally, by demonstrating how the combined strategy yields superior therapeutic outcomes in preclinical disease models. The discussion will also critically assess the translational pathway and future challenges for this approach.

Augmented viability and functional potency of MSCs

Natural flavonoids can activate Nrf2 through direct or indirect mechanisms, thereby enhancing the antioxidant, anti-apoptotic, and anti-aging capacities as well as the differentiation potential of MSCs. The primary mechanisms can be summarized into the following three categories:

1. Enhancing the intrinsic resistance of MSCs

Scutellarin (SCU), a bioactive flavonoid isolated from *Scutellaria baicalensis*, exhibits potent antioxidant and anti-inflammatory effects. Leptin receptor-positive ($LepR^+$) BMSCs, key regulators of bone remodeling, undergo senescence in diabetic osteoporosis (DOP), exacerbating bone deterioration. Wang et al. [180] demonstrated that SCU upregulates Ezh2 expression, enhancing H3K27me3 methylation at the Keap1 promoter to transcriptionally inhibit Keap1. This mechanism stabilizes Nrf2, activating its signaling cascade and ultimately attenuating $LepR^+$ BMSCs senescence in DOP. Based on its known Nrf2-activating properties (see "Phytochemicals as Nrf2 inducers" section), the study found that EGCG could be used to pretreat MSCs. Another study [181] demonstrated that EGCG mitigates H_2O_2-induced oxidative stress and cellular senescence in BMSCs through Nrf2 activation and p53/p21 downregulation, with Nrf2 knockdown abolishing these protective effects. Simultaneously, EGCG potentiates the functional efficacy of ADSCs by orchestrating a dual-pronged enhancement of the antioxidant defense system [182]. Specifically, it not only antagonizes Keap1 to activate Nrf2, alleviating ROS-induced cellular damage, but also elevates cystathionine γ-lyase (CTH) expression, thereby augmenting GSH biosynthesis and fortifying endogenous antioxidant

Table 5 Comparative analysis of Nrf2 activation by natural flavonoids versus MSCs and their derivatives

Feature	Natural flavonoids	MSCs and their derivatives
Primary mode of action	Direct pharmacological/chemical modulation	Biological/paracrine signaling and cell-cell communication
Core molecular targets	Keap1 (directly), upstream kinases such as PI3K/AKT, AMPK, or other pathways (e.g., NF-κB)	Keap1 (indirectly), via regulation of its upstream (e.g., PI3K/AKT, SIRT1) or downstream pathways through secreted factors (miRNAs, proteins)
Representative signaling pathway	Keap1-Nrf2-ARE(★★★★★), PI3K/AKT-Nrf2(★★★★☆), AMPK-Nrf2(★★★☆☆)	Nrf2/ARE (★★★★★); PI3K/AKT-Nrf2 (★★★☆☆), SIRT1-Nrf2 (★★☆☆☆), p62/Keap1/Nrf2 (★★★☆☆); miRNAs-Nrf2 (★★★☆☆)
Primary advantages	Well-defined structure, ease of chemical modification, potential for oral administration, relatively low cost	Multi-targeting capability, intelligent responsiveness to the microenvironment, potent tissue healing and immunomodulatory capacities, high safety profile as an "acellular" therapy
Major limitations/challenges	Low bioavailability, rapid metabolism, potential for off-target effects	Heterogeneity, low survival and homing rates, complex manufacturing and quality control, risk of immunogenicity (cell therapy)
Synergistic potential	Preconditioning MSCs to enhance their antioxidant, anti-apoptotic, and survival capabilities	Providing a protective niche during regeneration to amplify the long-term therapeutic efficacy of flavonoids.
Exemplary disease	Diabetic complications, neurodegenerative diseases, metabolic syndrome.	Acute organ injury (lung, liver, kidney), autoimmune disorders, difficult-to-heal wounds
Key evidence gaps	Low targeting efficiency and bioavailability, lack of long-term safety data	Specific miRNA or protein factor not yet identified, lack of long-term safety data
Research maturity	Experiment research	Experiment research

★★★★☆ The rating is based on the depth and reproducibility of the mechanistic studies included in this review, with five stars representing the most thoroughly investigated mechanisms

Table 6 Natural flavonoids-MSCs synergy in Nrf2 pathway

Flavonoids	MSCs	Model	Dosage	Synergistic mechanism	Refs.
Scutellarin (SCU)	$LepR^{+}$BMSCs	A high fat diet combined with low-dose STZ injections(35 mg/kg,7 days) induced DOP	In vivo: 10 mg/kg, twice a week for 8 weeks; In vitro: 50 μM SCU for 48 h	Ezh2↑-H3K27me3 methylation↑-Keap1↓-Nrf2 in MSCs↑-cellular senescence↓	[180]
EGCG	BMSCs	200 μM H_2O_2 induced cellular senescence	In vivo: EGCG (50/100 μM) for 6 h	Nrf2 in MSCs↑-p53/p21↓-cellular senescence↓	[181]
	ADSCs	Aging brain	In vivo: 1×10^6 rats ADSCs (or pre-conditioned with 10 μM EGCC for 2 h) by tail vein injection	CTH↑-GSH↑- antioxidant↑; SIRT1, PGC-1α, p-AMPKα↑- mitochondrial function↑; Keap1↓-Nrf2↑- antioxidant↑; p-AKT↑-survival↑; BDNF↑-TRKB↑-neurotrophy↑	[182]
7,8-DHF	BMSCs	Postmenopausal osteoporosis (PMO) mouse model with bilateral ovariectomy (OVX) surgery	In vivo: 2 mg/kg or 4 mg/kg through gavage every day for 8 weeks; In vitro: 0.5-25 μM	TRKB↑-PI3K/AKT↑-Nrf2↑-oxidative stress↓, osteogenic differentiation↑	[185]
Silibinin (SBN)		skin wound	–	Keap1↓-Nrf2↑- survival↑	[183]
Chrysin	BMSCs	Calvarial bone defect in T1DM model induced by intraperitoneal injections of streptozotocin (65 mg/kg)	In vitro: 0.2-5 μM	PI3K↑-p-AKT↑-ROS↓, mitochondrial function↑-survival↑, apotosis↓, osteogenic differentiation↑	[186]
Baicalin	BMSCs	D-Galactosamine and lipopolysaccharide (D-GalN/LPS)-induced ALI model	In vivo: 150 μg/mice	p62 in MSCs-Exos↑-p62 binds to Keap1↑-Nrf2↑-ferroptosis↓	[188]
Cyanidin	C3H10T1/2 MSCs	–	In vitro: 10 μg/mL;20 μg/mL	Nrf2↑-autophagy↓-chondrogenesis↓; p-IκBα/p-p65↓, autophagy↓-hypertrophic differentiation↓	[189]
Naringin	ADSCs	Cisplatin-induced nephrotoxicity	In vivo: naringin 100 mg/kg, 1×10^6 cells	Synergistic activation: SIRT-1↑-Nrf2↑HO-1↑-antioxidant↑, anti-inflammation↑	[190]

mechanisms in ADSCs. EGCG synergistically enhances mitochondrial optimization through coordinated activation of the SIRT1/PGC-1α axis and AMP-dependent protein kinase (p-AMPKα) signaling, thereby augmenting cellular energetics. Concurrently, its paracrine modulation upregulates neurotrophic factor secretion and improves blood–brain barrier (BBB) permeability, significantly amplifying the therapeutic efficacy of ADSCs in neurological restoration. EGCG orchestrates a synergistic interplay between the SIRT1 /PGC-1α axis and the p-AMPKα cascade, driving mitochondrial biogenesis and metabolic optimization to amplify the energetic

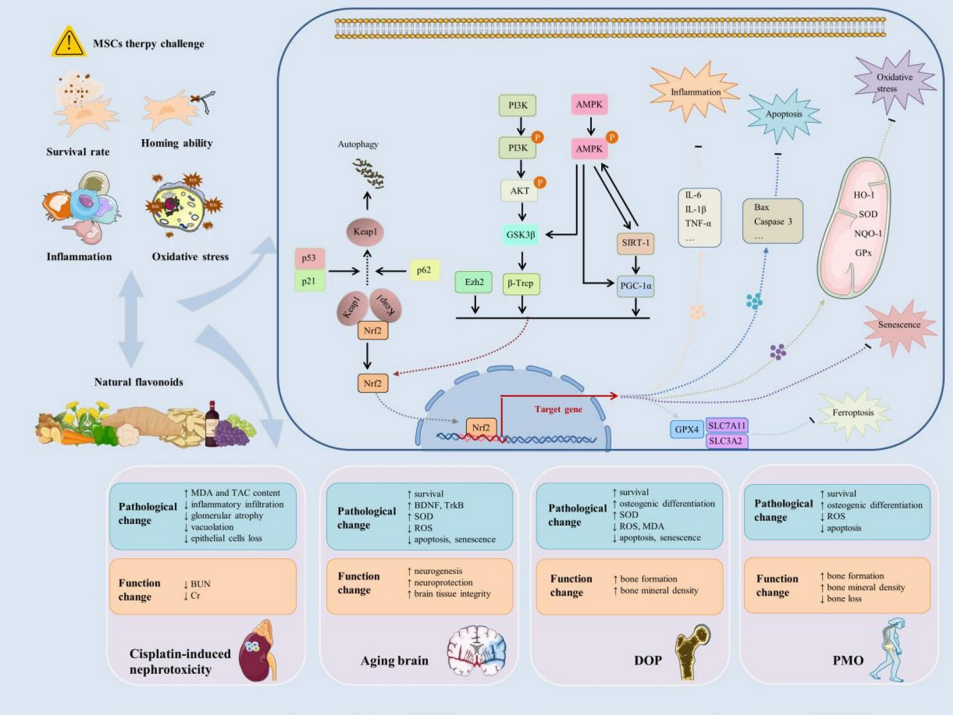


Fig. 4 Schematic illustration of the synergistic mechanism by which natural flavonoids and MSCs treat inflammatory diseases through Nrf2 signaling pathway activation. This diagram summarizes how natural flavonoids enhance the therapeutic efficacy of MSCs by improving their survival, homing capacity, and resistance to oxidative stress and inflammation. Key signaling molecules involved include those associated with autophagy (p62), cellular senescence (p53, p21), ferroptosis (SLC7A11, SLC3A2), apoptosis (Bax, Caspase-3), and antioxidant response (HO-1, SOD, NQO-1, GPx), as well as factors related to inflammation and senescence. This combined treatment ameliorates pathological and functional changes in various inflammatory disease models, including cisplatin-induced nephrotoxicity, aging, diabetic osteoporosis (DOP) and postmenopausal osteoporosis (PMO). ↑indicates increase; ↓indicates decrease

capacity of ADSCs. Concurrently, it recalibrates the ADSCs secretome, elevating neurotrophic factor output and enhancing BBB permeability, thereby augmenting their neuroregenerative capacity. Furthermore, the study also demonstrated that ADSCs preconditioned with EGCG significantly ameliorated disorganization in cortical tissue of aged rats, enhanced tissue integrity, and exhibited notable neuroprotective effects [182]. Shen et al. [183] pioneered an advanced therapeutic strategy by functionalizing MSCs with silibinin (SBN)-encapsulated poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles. Following efficient cellular internalization, the nanoparticles enabled sustained SBN release, which robustly activated the Keap1/Nrf2 axis, culminating in a threefold reduction in ROS accumulation. This intervention significantly enhanced MSCs survival under oxidative stress conditions. Notably, these modified cells demonstrated superior viability and retention post-transplantation, markedly accelerating wound healing and improving skin regeneration quality.

For the aforementioned flavonoids, the differences in their efficacy are essentially determined by their molecular structures, binding affinity to target proteins, and pharmacokinetic properties in vivo [184]. Future studies could integrate molecular docking, ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) prediction, and in vitro and in vivo validation to further elucidate the regulatory effects of flavonoids and enhance the understanding of their mechanisms of action.7, 8-Dihydroxyflavone (7,8-DHF), a neurotrophic flavonoid, confers cytoprotection against hydrogen peroxide-induced oxidative damage in BMSCs by attenuating apoptosis, enhancing proliferative capacity, and potentiating osteogenic differentiation, thereby promoting bone formation and alleviating bone loss in postmenopausal osteoporosis (PMO) mice. These pleiotropic effects are orchestrated through 7,8-DHF's selective activation of TRKB, which subsequently activates Nrf2 via the TRKB/PI3K/AKT signaling pathway, thereby constituting a critical molecular defense mechanism against oxidative stress-mediated cellular dysfunction [185]. Chrysin (5,7-dihydroxy-2-phenyl-4H-chromen-4-one) is a bioactive dihydroxyflavonoid predominantly found in plants such as *Scutellaria baicalensis* and *Elaeagnus angustifolia*. Under high-glucose conditions, chrysin demonstrates significant cytoprotective and proliferative-enhancing effects on BMSCs through activation of the PI3K/AKT/Nrf2 signaling pathway [186]. Furthermore, it enhances osteogenesis in

calvarial defects of T1DM rats, suggesting a novel therapeutic strategy for diabetes-associated impairment of bone regeneration. Curcumin (CUR), the predominant polyphenolic curcuminoid derived from *Curcuma longa*, demonstrates remarkable cytoprotective efficacy against H_2O_2-induced lung mesenchymal stem cells (LMSCs) [187]. CUR exhibits concentration-dependent capabilities in reducing apoptosis rates, decreasing ROS levels, and augmenting mitochondrial membrane potential. Its cytoprotective effects in LMSCs are primarily mediated through the activation of the Akt/Nrf2/HO-1 signaling pathway, leading to markedly higher potency compared to the conventional antioxidant *N*-Acetyl-L-cysteine (NAC).

2. Remodeling the MSCs secretome to achieve remote synergistic regulation

Pretreatment with flavonoids not only protects MSCs themselves but also optimizes their paracrine function, enabling the secretion of exosomes and cytokines with greater therapeutic potential. Zhao et al. [188] demonstrated that baicalin pretreatment elevates p62 protein levels in MSCs-EVs. P62 competitively binds to Keap1, thereby relieving the latter's inhibition of Nrf2 and facilitating Nrf2 nuclear translocation to activate antioxidant gene expression, ultimately enhancing cellular antioxidant capacity. In the d-galactosamine/LPS (D-GaIN/LPS)-induced ALI model, intervention with exosomes derived from baicalin-preconditioned MSCs-Exo (Ba-Exo) yielded the following outcomes: Ba-Exo effectively reduced hepatic Fe^{2+} accumulation and MDA production, increased GSH levels, and decreased ROS. Concurrently, it modulated key ferroptosis markers (inhibition of 5-lipoxygenase [5-LOX] concurrently with upregulation of GPX4 and SLC7A11), leading to significant improvements in hepatic function and inflammatory responses, thereby alleviating ALI. Supporting evidence reveals that cyanidin treatment during MSCs chondrogenesis markedly increases Nrf2 and p62 protein expression while downregulating microtubule-associated protein 1 light chain 3B (LC3B) expression [189]. Notably, during chondrocyte hypertrophy, cyanidin effectively blocks both IκBα phosphorylation and LC3B activation.

Bidirectional synergistic activation of Nrf2 by natural flavonoids and MSCs

A multi-tiered positive feedback loop is established through the interaction between natural flavonoids and MSCs. Flavonoids precondition and prime MSCs via the direct Keap1-Nrf2 pathway or the indirect PI3K-AKT pathway, which enhances cellular resilience to adverse conditions by reducing apoptosis and promoting survival. The primed MSCs, in turn, remodel the microenvironment through an altered secretory profile, releasing bioactive factors that create more favorable conditions for their own persistence. These improvements encompass attenuated oxidative stress, reduced inflammation, and decreased iron accumulation. Ultimately, this cooperative interaction achieves a functional synergy, producing therapeutic effects that surpass those attainable by either component administered alone.

Naringin exhibits potent synergy with ADSCs in the Nrf2 signaling pathway. NAR enhances the survival and homing capacity of ADSCs, while ADSCs amplify the antioxidant effects of naringin. Together, they promote the cascade activation of the SIRT1/Nrf2/HO-1 pathway, achieving a dual synergistic response comprising antioxidant and anti-inflammatory effects. The combined intervention with naringin and ADSCs significantly reduces serum levels of BUN and creatinine, attenuates inflammatory reactions and oxidative stress, ameliorates cisplatin-induced immune cell infiltration, thereby alleviating structural renal damage, including glomerular atrophy and tubular dysfunction, in cisplatin-induced nephrotoxicity models [190]. These findings collectively demonstrate synergistic therapeutic efficacy at the whole-animal level.

In addition to the aforementioned natural flavonoids with clearly defined compositions, certain flavonoid-rich plant extracts also exhibit bidirectional synergistic effects with MSCs. In a study evaluating the combination of *Rhus coriaria* (sumac) extract with rat BMSCs against MTX-induced nephrotoxicity in rats, 22 phytochemical constituents, primarily flavonoids, were identified in the sumac extract. Network pharmacology analysis further revealed that 7-*O*-methylcyanidin-3-*O*-(2″-galloyl)-galactoside exhibited high binding affinity to Keap1 [191]. The combined administration of sumac liposome via intraperitoneal injection and BMSCs via tail vein injection significantly ameliorated oxidative stress and inflammation, thereby attenuating MTX-induced kidney damage. This protective effect was mediated through activation of the Nrf2/Keap1/HO-1 signaling pathway.

Current studies indicate that the combination of natural flavonoids with MSCs exhibits significant synergistic effects. This combination can activate the Nrf2 signaling pathway through multiple routes, thereby enhancing the survival rate, functional activity, and paracrine capacity of MSCs. This leads to superior therapeutic outcomes compared to single interventions in various disease models. The core mechanism of this synergy involves the activation of the Nrf2/HO-1 axis, which exerts anti-inflammatory, antioxidant, and anti-apoptotic effects. Concurrently, it promotes tissue healing by inhibiting ferroptosis, protecting mitochondrial function, and modulating cellular metabolism. However, few of the aforementioned studies simultaneously included both in

vitro mechanistic validation (e.g., gene knockdown/overexpression, specific inhibitors) and in vivo disease model validation with adequate combined controls. Therefore, the synergistic mechanisms and efficacy between natural flavonoids and MSCs still require further investigation.

Translational potential of combination treatment

The synergistic interaction between natural flavonoids and MSCs represents a novel combination therapy paradigm. By activating the Nrf2 pathway, flavonoids act as potentiators that comprehensively enhance the survival, functionality, and secretome of MSCs, thereby overcoming the key bottlenecks in MSCs-based therapies. Substantial evidence indicates that this strategy has broad application prospects in various fields including metabolic bone diseases, liver injury, neural damage, and reproductive system disorders. However, the clinical translation still faces optimization challenges concerning key parameters such as dosing regimens, administration strategy, delivery routes, and long-term safety. Systematically reviewing these parameters in existing research and analyzing their impact on efficacy and safety are crucial for advancing the practical application of this combination therapy.

1. Optimization and challenges of dosing regimens

Dosing strategies in current studies are primarily based on concentration-effect relationships from in vitro-preconditioning and explorations of tolerability in animal models. For instance, EGCG is commonly used at concentrations below 100 μM to pretreat MSCs to enhance their resistance to oxidative stress [181], while SCU effectively inhibits Keap1 expression at 50 μM in vitro [180]. Naringin is administered at 100 mg/kg in combination with ADSCs [190], and 7,8-DHF is delivered via oral gavage at 2-4 mg/kg [185]. Although these doses are effective in specific models, their dose-dependency is significant: flavonoid concentrations that are too low may be insufficient to adequately activate pathways such as Nrf2, while excessively high concentrations may induce cytotoxicity or interfere with normal physiological functions. Furthermore, the compatibility between the transplantation dose of MSCs (typically 1×10^6 cells per rat) and different tissue sources or disease states lacks systematic investigation. Future studies require dose-matrix experiments and pharmacodynamic modeling to precisely define the optimal molar ratio and absolute dose for the combination therapy.

2. Strategic selection of administration

The administration strategy is another critical variable affecting synergistic efficacy. The current mainstream strategy is pretreatment, involving short-term incubation (e.g., 2-6 h) of MSCs with flavonoids prior to transplantation to pre-enhance their antioxidant, anti-apoptotic, and paracrine functions [182]. Additionally, a few studies have attempted co-administration or sequential administration, suggesting that different strategies may influence the homing efficiency of MSCs and their dynamic regulatory capacity in the lesion microenvironment [185, 190]. Therefore, selecting an appropriate administration strategy can maximize synergistic effects.

3. Exploration of delivery routes and novel delivery systems

The effective delivery of therapeutic components relies on a route that ensures their targeted accumulation. Common delivery routes for MSCs include tail vein injection (systemic distribution) and local injection (targeted repair), with the choice depending on the lesion site and disease nature. However, most natural flavonoids face challenges such as low oral bioavailability, rapid metabolism, and poor targeting. Developing novel delivery systems, such as MSCs surface-modified PLGA nanoparticles loaded with silibinin, to improve targeting efficiency and reduce systemic toxicity represents a key future direction [183]. Furthermore, the combination of natural flavonoid active ingredients with Exos/EVs-based delivery successfully overcomes the central challenge of low bioavailability for TCM components [192, 193]. Exos/EVs effectively load and reprogram the bioactive characteristics of natural flavonoids. By capitalizing on the inherent advantages of Exos/EVs as nanocarriers, this method not only bypasses the poor bioavailability resulting from low solubility and rapid clearance but also enables targeted delivery. And as a natural delivery system, Exos/EVs shield natural flavonoids from enzymatic degradation in vivo, which extends their duration of action. This approach establishes a novel paradigm for the modern application of TCM active ingredients.

4. Safety and toxicological considerations

Current preclinical studies have reported that combination therapies can repair damaged tissues and organs without causing additional injury. For example, the combination of naringin and ADSCs has been shown to improve renal function in cisplatin-induced nephropathy models [190]. However, long-term safety data remain relatively scarce. Potential risks include: long-term or high-dose flavonoid intervention may disrupt cellular homeostasis through excessive activation of the Nrf2 pathway and may even be potentially associated with tumorigenesis and progression; the immunomodulatory properties of MSCs may promote immunosuppression or

abnormal differentiation in specific microenvironments. Therefore, future studies should incorporate long-term toxicological evaluations to systematically assess the effects of combination regimens on major organs, the immune system, and potential tumorigenicity. Further in-depth mechanistic studies, such as elucidating the crosstalk between Nrf2 and critical signaling pathways including AMPK and mTOR in cellular metabolic reprogramming, as well as long-term evaluations of safety and efficacy, are essential to establish a more solid foundation for clinical application.

Conclusions and future perspectives

Over the past three decades of investigation, Nrf2 has been characterized as a pleiotropic core regulator of a broad functional spectrum, which reflects its physiological indispensability and the highly complex and context-dependent nature of its regulatory effects [194]. Given its pivotal role in the regulation of multiple cellular processes, this review systematically summarizes three major therapeutic strategies for Nrf2 activation: clinical and preclinical small-molecule agents with DMF and CDDO-Im as representative examples; natural product-derived compounds, particularly flavonoids; and cell-based and cell-free therapeutics utilizing MSCs and their derivatives. Although all these strategies converge on exerting anti-inflammatory and antioxidant effects via Nrf2-dependent signaling cascades, they exhibit distinct characteristics and confront unique challenges.

Yet the translation of Nrf2-targeted therapies from bench to clinic has progressed slowly, with only a few drugs, such as DMF, having been approved for clinical use to date. Notably, phytochemicals, especially flavonoids, that modulate the Nrf2 signaling pathway exhibit substantial potential for chemoprevention, thereby accelerating the development of plant-derived therapeutics characterized by low toxicity and high efficacy in the management of chronic diseases. Redox and metabolic processes constitute pivotal mechanisms governing MSCs' activity and functionality. The Nrf2 transcription factor plays a critical role in regulating MSCs redox balance and metabolic pathways, thereby influencing, to some extent, the therapeutic efficacy of MSCs in inflammatory disorders. Meanwhile, the Nrf2 transcription factor critically influences the therapeutic efficacy of MSCs in inflammatory disorders by regulating their redox balance and metabolic pathways. Furthermore, evidence exists for the individual therapeutic effects of both flavonoids and MSCs across inflammatory disease models in multiple organ systems, and thus the synergistic strategy of combining them has demonstrated potential value in overcoming the limitations of monotherapies. Specifically, flavonoids can effectively "precondition" or "empower" MSCs by directly targeting Keap1 or activating upstream signals such as PI3K/Akt and SIRT1; on the other hand, MSCs and MSCs-Exos can act as delivery vehicles to improve the enrichment and retention efficiency of flavonoids in target tissues, while modulating the Nrf2 network through paracrine actions (e.g., delivering specific miRNAs). In vivo studies using diabetic osteoporosis and cisplatin-induced nephrotoxicity models have confirmed that this synergistic effect can significantly enhance therapeutic efficacy.

However, current research in this field still has notable limitations. First, existing evidence is predominantly derived from in vitro and in vivo experiments with a lack of robust clinical data, which raises concerns regarding safety and efficacy. Second, the synergistic mechanisms remain insufficiently elucidated. Most studies are confined to correlative observations and lack rigorous causal validation using reverse genetic approaches, such as Nrf2 knockout models or specific inhibitors. Accordingly, it remains difficult to ascertain whether the observed therapeutic effects are necessarily and exclusively dependent on Nrf2 signaling. Furthermore, the high intrinsic heterogeneity of MSCs and variable efficacy across different tissue sources pose significant challenges to verifying the reproducibility and generalizability of these synergistic effects. Finally, systematic investigations into the dynamic regulatory mechanisms of Nrf2 across diverse pathophysiological contexts are still limited. In particular, the understanding of its bidirectional regulatory roles in various diseases and at different disease stages, as well as the environmental and time-dependent influences on these roles, is still insufficient.

Previous studies have shown that pharmacologically induced activation of Nrf2 holds therapeutic potential in multiple diseases, yet this process exhibits significant complexity: prolonged or excessive activation of Nrf2 may, through redox adaptation mechanisms, instead promote carcinogenesis and the development of multidrug resistance [195, 196]. Such complexity is also reflected in disease heterogeneity. For example, For instance, nuclear localization of Nrf2 is persistently elevated in the substantia nigra of PD patients [197], whereas Nrf2 protein levels are reduced in the primary motor cortex and spinal cord of ALS patients [198].

Thus, despite their certain translational potential, flavonoids-MSCs combination products may be categorized as complex ATMPs from a regulatory standpoint, and thus are required to comply with stringent GMP standards, standardized potency assessments, and comprehensive non-clinical safety data submissions. Specifically, systematic research on this therapy is urgently required for this therapy to determine the optimal flavonoid-to-MSCs dose ratio and administration strategy and timing; clarify whether flavonoid preconditioning impacts the long-term genomic stability or differentiation propensity

of MSCs; and establish standardized, scalable production processes for preconditioned MSCs, all of which constitute substantial bottlenecks hindering their clinical translation.

To advance this therapeutic strategy, future research should prioritize accelerating its clinical translation. On one hand, efforts should be directed toward deepening mechanistic insights. Advanced methodologies including AI-assisted screening and multi-omics analyse, could be leveraged to dissect the regulatory principles of microenvironmental remodeling following flavonoid-MSCs combinatorial therapy. Identifying the key upstream and downstream Nrf2-mediated targets that orchestrate synergistic effects will lay the groundwork for elucidating the underlying mechanisms. On the other hand, a more rigorous framework for causal verification should be established (e.g., mandatory use of Nrf2 knockout models), while prioritizing efficacy and safety evaluations in clinically relevant animal models, such as aged or comorbid models. Furthermore, breakthroughs should extend beyond the discovery of novel activating molecules to focus on developing intelligent regulatory tools. For example, protein–protein interaction inhibitors or conditionally activated prodrugs could enable spatiotemporal-specific regulation, as well as engineer MSCs or their Exos to enable targeted delivery and controlled release of Nrf2 modulators. Ultimately, a successful therapeutic paradigm will likely emerge as an integrated composite system that combines the pharmacological optimization potential of natural products with the microenvironment-remodeling capabilities of cell-based therapies. This necessitates closer interdisciplinary collaboration across the field, alongside a commitment to collectively translate foundational insights into the Nrf2 signaling pathway into safe, effective, and accessible novel anti-inflammatory therapies. In light of the foregoing considerations, the journey ahead remains arduous and thus sustained, concerted efforts are required.

Abbreviations

Aβ	β-amyloid
ACLF	Acute-on-chronic liver failure
ACSL4	Acyl-CoA synthetase long-chain family member 4
AD	Alzheimer's disease
ADSCs	Adipose-derived mesenchymal stem cells
AGEs	Advanced glycation end-product
AIS	Acute ischemic stroke
AKI	Acute kidney injury
AKT	Protein kinase
ALI	Acute lung injury
ALS	Amyotrophic lateral sclerosis
AREs	Antioxidant response elements
ARS	Acute radiation syndrome
ATP	Adenosine triphosphate
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
BLM	Bleomycin
BMSCs	Bone marrow mesenchymal stem cells
BUN	Blood urea nitrogen
CAT	Catalase
CAV1	Caveolin-1
CFA	Complete Freund's adjuvant
CMS	Chronic mild stress
CNC	Cap'n'collar
CO	Carbon monoxide
Cx43	Connexin43
COPD	Chronic obstructive pulmonary disease
CUR	Curcumin
DAI	Disease activity index
Dex	Dexamethasone
DOP	Diabetic osteoporosis
CTH	Cystathionine γ-lyase
DFX	Deferoxamine
D-Gal	D-Galactose
DMA	Dimerumic acid
DMF	Dimethyl fumarate
DMOG	Dimethyloxalylglycine
DN	Diabetic nephropathy
dNCR	Delayed neurocognitive recovery
DPSCs	Dental pulp mesenchymal stem cells
DSS	Dextran sodium sulfate
EGCG	Epigallocatechin gallate
EMT	Endothelial–mesenchymal transition
Exos	Exosomes
EVs	Extracellular vesicles
eQTLs	Expression quantitative trait loci
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FTH	Ferritin heavy chain
GBM	Glioblastoma
GCL	Glutamate-cysteine ligase
GCLC	Glutamate-cysteine ligase catalytic subunit
GCLM	Glutamate-cysteine ligase modulatory subunit
GC-ONFH	Glucocorticoid-induced osteonecrosis of the femoral head
GCs	Granulosa cells
GFAP	Glial fibrillary acidic protein
GPX4	Glutathione peroxidase 4
GSH	Glutathione
GSH-Px	Glutathione peroxidase
GSIS	Glucose-stimulated insulin secretion
GST	Glutathione *S*-transferase
hAMSCs	Human amniotic mesenchymal stem cells
HAT	Histone acetyltransferase
hDMSCs	Human decidual mesenchymal stem cells
hDPSCs	Human dental pulp stem cells
HFSCs	Hair follicle mesenchymal stem cells
HO-1	Heme oxygenase 1
HSP	Heat shock protein
IC	Interstitial cystitis
ICH	Intracerebral hemorrhage
iPSCs	Induced pluripotent stem cells
I/R	Ischemia–reperfusion
IGF-1	Insulin-like growth factor-1
IL	Interleukin
IMC	Indomethacin
IVDD	Intervertebral disc degeneration
Keap1	Kelch-like ECH-associated protein 1
LCA	Licochalcone A
LDH	Lactate dehydrogenase
LMSCs	Lung mesenchymal stromal/stem cells
LN	Lupus nephritis
LPS	Lipopolysaccharide
MASH	Metabolic dysfunction-associated steatohepatitis
MDA	Malondialdehyde
MGO	Methylglyoxal
miRNA	MicroRNA
MS	Multiple sclerosis
MSCs	Mesenchymal stromal/stem cells
MSCs-CM	MSCs-conditioned medium
MSCs-EVs	MSCs-derived extracellular vesicles
MSCs-Exo	MSCs-derived exosomes

MTX	Methotrexate
NAFLD	Nonalcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP3	Nucleotide-binding oligomerization domain (NOD)-like receptor protein 3
NO	Nitric oxide
NQO1	NAD(P)H quinone oxidoreductase 1
Nrf2	Nuclear factor erythroid 2-related factor 2
OISN	Oxaliplatin-induced sensory neuropathy
OGD/R	Oxygen-glucose deprivation/reperfusion
OSAHS	Obstructive sleep apnea-hypopnea syndrome
OXL	Oxaliplatin
PAPK7	Parkinson disease protein 7
PD	Parkinson's disease
PERK	Protein kinase R-like endoplasmic reticulum kinase
PI3K	Phosphatidylinositol 3-kinase
PKCα	Protein kinase Cα
PLGA	Poly(lactic-*co*-glycolic acid)
POI	Premature ovarian insufficiency
PPI	Protein–protein interaction
PRP	Platelet-rich plasma
PUN	Punicalagin
RAPA	Rapamycin
RF	Rheumatoid factor
ROS	Reactive oxygen species
RSA	Recurrent spontaneous abortion
SAHH	*S*-adenosylhomocysteine hydrolase
SAP	Severe acute pancreatitis
SASP	Senescence-associated secretory phenotype
SBN	Silibinin
SCI	Spinal cord injury
Scr	Serum creatinine
SCU	Scutellarin
SIRT	Sirtuin
SOD	Superoxide dismutase
STZ	Streptozotocin
T-AOC	Total antioxidant capacity
TCM	Traditional Chinese medicine
T1/2DM	Type 1/2 diabetes mellitus
TLR4	Toll-like receptor 4
TNF-α	Tumor necrosis factor-α
TGF-β	Transforming growth factor-beta
UCMSCs	Umbilical cord mesenchymal stem cells
VEGF	Vascular endothelial growth factor
VIM	Vimentin
VPA	Valproic acid
VSMCs	Vascular smooth muscle cells
vWF	von Willebrand factor
WT-1	Wilms tumor protein 1

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Author contributions
LS and LM conceived the review, designed the framework, and supervised the overall project. FS and YQ performed the literature search, selected relevant studies, extracted data, and drafted the initial manuscript. ZW, LD and AL contributed significantly to writing the preliminary draft and participated in its revision based on feedback. DZ, YG, QB and SG supported the literature search and data extraction process. All authors contributed substantially to revising and approving the submitted version, and all read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

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Competing interests
The authors declare no competing interests.

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