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Review paper

New perspectives on the therapeutic potential of quercetin in non-communicable diseases: Targeting Nrf2 to counteract oxidative stress and inflammation

Li Zhang [a], Li-Yue Xu [a], Fei Tang [a], Dong Liu [a], Xiao-Lan Zhao [a], Jing-Nan Zhang [a], Jia Xia [a], Jiao-Jiao Wu [a], Yu Yang [a], Cheng Peng [a, **], Hui Ao [b, *]

[a] State Key Laboratory of Southwestern Chinese Medicine Resources, School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, 611137, China
[b] Innovative Institute of Chinese Medicine and Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, 611137, China

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ABSTRACT

Non-communicable diseases (NCDs), including cardiovascular diseases, cancer, metabolic diseases, and skeletal diseases, pose significant challenges to public health worldwide. The complex pathogenesis of these diseases is closely linked to oxidative stress and inflammatory damage. Nuclear factor erythroid 2-related factor 2 (Nrf2), a critical transcription factor, plays an important role in regulating antioxidant and anti-inflammatory responses to protect the cells from oxidative damage and inflammation-mediated injury. Therefore, Nrf2-targeting therapies hold promise for preventing and treating NCDs. Quercetin (Que) is a widely available flavonoid that has significant antioxidant and anti-inflammatory properties. It modulates the Nrf2 signaling pathway to ameliorate oxidative stress and inflammation. Que modulates mitochondrial function, apoptosis, autophagy, and cell damage biomarkers to regulate oxidative stress and inflammation, highlighting its efficacy as a therapeutic agent against NCDs. Here, we discussed, for the first time, the close association between NCD pathogenesis and the Nrf2 signaling pathway, involved in neurodegenerative diseases (NDDs), cardiovascular disease, cancers, organ damage, and bone damage. Furthermore, we reviewed the availability, pharmacokinetics, pharmaceutics, and therapeutic applications of Que in treating NCDs. In addition, we focused on the challenges and prospects for its clinical use. Que represents a promising candidate for the treatment of NCDs due to its Nrf2-targeting properties.

1. Introduction

Non-communicable diseases (NCDs), including cardiovascular diseases, cancer, metabolic diseases, and skeletal diseases, are becoming a global epidemic and pose a severe health threat to humanity. The World Health Organization (WHO) data reveals that NCDs account for 41 million annual deaths worldwide. They are the leading cause of death and disability and negatively affect the physical and emotional well-being of affected individuals [1]. Inflammation and oxidative stress play a key role in the development of NCDs [2]. Nuclear factor erythroid 2-related factor 2 (Nrf2) plays a crucial role in oxidative stress, autophagy, inflammation, endoplasmic reticulum stress/unfolded protein response, apoptosis, and mitochondrial biogenesis. Therefore, Nrf2 can be a potential therapeutic target for treating NCDs [3]. The Nrf2 pathway is abnormally activated or inhibited by some modifying enzymes during the development of NCDs. This restricts the function of Nrf2, thereby impairing the immune response of the body. Consequently, for NCD treatment, researchers are developing therapeutic strategies for activating Nrf2. However, effective and safe Nrf2-targeting drugs have not been developed to date. Natural products have minimal side effects, abundant active ingredients, and multiple therapeutic effects [4]. Therefore, they can be explored to identify lead compounds targeting the Nrf2 pathway for the treatment of NCDs.

Quercetin (Que) is one of the most extensively studied flavonoids. It belongs to the class of polyhydroxy-flavonoids and is widely found in plants, such as vegetables, fruits, and tea. It is often used as a natural antioxidant. Que has several pharmacologic effects including antioxidant [5], anti-inflammatory [6], hepatoprotective [7], antihypertensive [8], antitumor [9], hypoglycemic [10], antiallergic [11], antiviral [12], and cardiovascular protective effects [13]. Therefore,

* Corresponding author.
** Corresponding author.
E-mail addresses: aohui2005@126.com (H. Ao), pengchengcxy@126.com (C. Peng).

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Que has great potential in the treatment of NCDs [14]. Que modulates the Nrf2 pathway to activate the intracellular antioxidant defense systems and ameliorate oxidative stress and inflammation, thereby inhibiting the development and progression of NCDs. However, a systematic review summarizing the mechanisms by which Que modulates Nrf2 to achieve its anti-NCD effects is not available to date. Here, we comprehensively reviewed the role of Nrf2 in NCDs and explored the effects of Que on Nrf2 and the Nrf2-related pathways for alleviating NCDs. This review will be a valuable reference for researchers and clinicians working on the development of new treatments for NCDs, specifically those targeting the Nrf2 pathway with natural compounds such as Que.

2. Crosstalk between oxidative stress, inflammation, and NCDs

Inflammation and oxidative stress are closely associated with several common NCDs, such as neurodegenerative diseases (NDDs) [15], cardiovascular diseases [16], osteoporosis [17], cancers [18], liver and kidney diseases [19], and diabetes [20]. They trigger a range of secondary injuries such as apoptosis, cytotoxic impaired autophagy [21], DNA damage, and mitochondrial dysfunction [22], which contribute to the progression of NCDs (Fig. 1).

Nrf2 plays an important regulatory role in ameliorating inflammation and oxidative stress responses. It detects specific intracellular signals and activates various genes involved in antioxidant and anti-inflammatory responses. Therefore, targeteding the Nrf2 pathways can alleviate inflammation and oxidative stress for developing potential therapeutic strategies for NCDs.

3. Brief introduction of Nrf2

3.1. Structure of Nrf2

The therapeutic effects of Nrf2 protein are closely related to its structure. Nrf2 belongs to the cap 'n' collar (CNC) transcription factor family and comprises distinct structural domains, namely Neh1, Neh2, Neh3, Neh4, Neh5, Neh6, and Neh7 (Fig. 2). Each domain plays a specific role in regulating Nrf2 stability or transactivation. Neh1 is the CNC-bZIP domain that binds to DNA. The domain forms a dimer with small male neurofibrosarcoma protein to facilitate the recognition and binding of antioxidant response elements (AREs) to Nrf2 [23]. It also initiates target gene transcription and contains a nuclear localization signal [24]. Neh2 mediates the interaction of Nrf2 with the negative regulator Kelch-like epichlorohydrin (ECH)-associated protein 1 (Keap1) and regulates the ubiquitination of Nrf2. This domain contains important motifs involved in these processes, such as glutamic acid-threonine-glycine-glutamic acid (ETGE) and dialogue [25]. The C-terminal Neh3 structural domain has *trans*-activating properties. It binds to cyclic adenosine phosphate response element-binding (CREB) proteins and nuclear cofactors (RAC3, AIB1, and SRC-3) and cooperates with Neh4 and Neh5 to activate ARE-dependent gene transcription [26–28]. Neh6 (consisting of a serine-rich region) regulates the stability and degradation of Nrf2, independent of Keap1, by interacting with the E3 ubiquitin ligase β-transducer repeat protein [29,30]. Neh7 is associated with retinoic acid X receptor α, which inhibits the activity of Nrf2 [31]. To sum up, Nrf2 comprises receptor DNA and nuclear-binding structural domains with specific sequences. These structural domains play important roles in regulating gene expressions and protein functions to participate in the antioxidant and anti-inflammatory responses mediated by Nrf2.

3.2. Antioxidant and anti-inflammatory properties of Nrf2

Nrf2 plays an important role in protecting the cells from oxidative stress and inflammation induced damage.

3.2.1. Antioxidant properties of Nrf2

Nrf2 plays a critical role in maintaining cellular redox homeostasis and regulating inflammatory responses. Nrf2 inhibits the

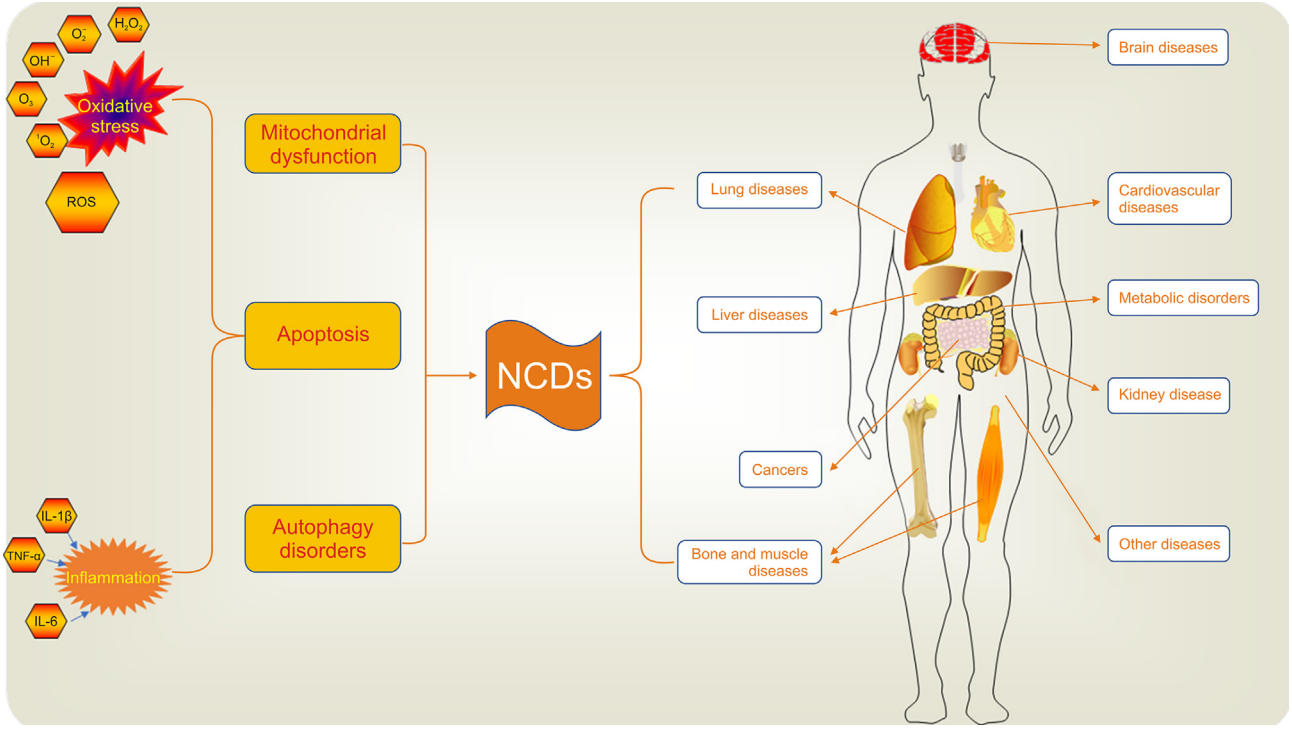

Fig. 1. The underlying pathogenesis of non-communicable diseases (NCDs). ROS: reactive oxygen species; IL: interleukin; TNF: tumor necrosis factor.

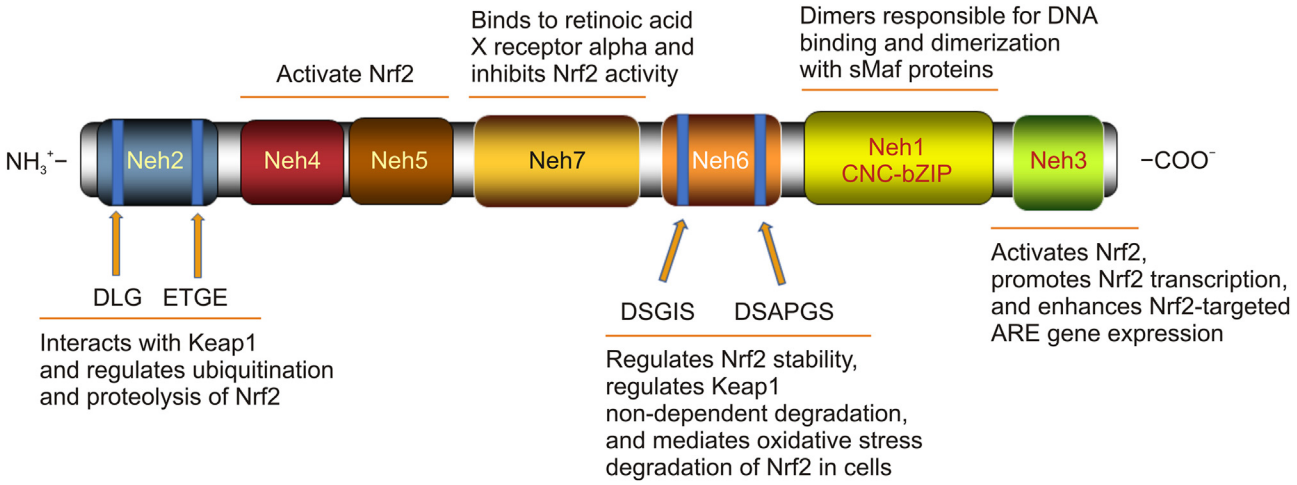

Fig. 2. The structure of nuclear factor erythroid 2-related factor 2 (Nrf2). DLG: aspartic acid-leucine-glycine; ETGE: glutamic acid-threonine-glycine-glutamic acid; DSGIS: aspartic acid-serine-glycine-isoleucine-serine; DSAPGS: aspartic acid-serine-alanine-proline-glycine-serine; CNC-bZIP: cap 'n' collar-basic leucine zipper; Keap1: kelch-like ech-associated protein 1; sMaf: small male neurofibrosarcoma; ARE: antioxidant response elements.

production of reactive oxygen species (ROS) and ameliorates inflammation to exert its antioxidant properties. It activates the antioxidant enzyme system by harmonizing DNA and regulating gene expression, which helps protect the cells from oxidative stress-induced damage. Nrf2 regulates the expressions of several target genes, including nicotinamide adenine dinucleotide phosphate/nicotinamide adenine dinucleotide (*NAD(P)H*):quinone oxidoreductase 1 (*NQO1*), *ferritin*, heme oxygenase-1 (*HO-1*), the catalytic subunit of glutamate-cysteine ligase complex (*GCLC*), and the modified subunit of glutamate-cysteine ligase complex (*GCLM*), which maintain the intracellular redox environment. Nrf2 activation controls the expressions of the key components of the antioxidant system in the nucleus, such as superoxide dismutase (SOD), glutathione (GSH), HO-1, NQO1, and GCLM, thereby reducing oxidative damage [32,33]. In addition, Nrf2 is activated during the regeneration of NADPH, ROS, and xenobiotic detoxification, thereby maintaining cellular redox balance [34]. Taken together, Nrf2 plays a crucial role in protecting cells from oxidative stress-induced damage and maintaining intracellular redox homeostasis and can be potentially targeted for the prevention and treatment of oxidative stress-related diseases.

3.2.2. Anti-inflammatory properties of Nrf2

Nrf2 can directly inhibit inflammation or indirectly exert inhibitory effects by targeting other pathways. *HO-1*, a target gene of *Nrf2*, is the key regulator of Nrf2-mediated nuclear factor-kappaB (NF-κB) inhibition. It is a rate-limiting enzyme that catalyzes the degradation of heme to produce carbon monoxide (CO), biliverdin, and free iron [35]. In addition, HO-1 indirectly inhibits the activation of NF-κB by inducing the expressions of adhesion molecules, such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) [36], thereby mitigating the generation of inflammatory factors. In addition, Nrf2 exerts anti-inflammatory effects by activating various kinases, such as mitogen-activated protein kinase (MAPK), intracellular phosphatidylinositol kinase (PI3K), extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 kinases [37]. The release and translocation of these kinases promote the translocation of Nrf2, ultimately enhancing the antioxidant capacity of the cell [38]. Therefore, Nrf2 is involved in antioxidant and anti-inflammatory effects, and it is a key target for the treatment of oxidative stress induced disorders and inflammatory diseases.

Additionally, Nrf2 inhibits the inflammatory signaling pathway, thereby reducing inflammation and influencing cellular processes such as apoptosis and autophagy. Moreover, it promotes the maintenance of mitochondrial function, enhances antioxidant capacity, and aids in the repair of mitochondria by regulating of specific genes. It also contributes to the stability of genes and facilitates DNA repair by regulating the expression and activity of repair enzymes. Overall, Nrf2 regulates oxidative stress, inflammation, and various essential biological processes.

4. Role of Nrf2 in NCDs

Nrf2 plays a crucial role in regulating oxidative stress and inflammation, making it a promising therapeutic target for the treatment of various NCDs [39]. Nrf2 regulates the expressions of target genes involved in different cellular processes, such as oxidative stress, inflammation, apoptosis, autophagy, mitochondrial dysfunction, and DNA repair, to exert its therapeutic effect on NCDs [40]. Moreover, Nrf2 controls the expression of AREs, drug-metabolizing enzymes, and GSH metabolism genes [41].

Additionally, Nrf2 regulates genes involved in cellular metabolism, specifically immune metabolism and hemoglobin and iron metabolism. Nrf2 interacts with various transcription factors to maintain cellular equilibrium and delay the onset and progression of NCDs [42]. However, excessive Nrf2 activity can have negative effects, such as promoting cancer metastasis, inducing drug resistance and forming malignant tumors [43]. Therefore, controlling Nrf2 activity is an effective approach for preventing and treating NCDs.

Taken together, Nrf2 effectively regulates antioxidant enzymes, detoxification enzymes, and anti-inflammatory mediators, thereby reducing oxidative stress, inhibiting inflammatory responses, and restoring metabolic homeostasis. Collectively, these effects contribute to the remission of NCDs.

4.1. NDDs

NDDs are age-related conditions that affect the nervous system, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). The pathogenesis of these diseases involves pathologic protein aggregation, synaptic and neuronal network dysfunction, abnormal protein homeostasis,

cytoskeletal abnormalities, altered energy homeostasis, DNA and RNA defects, inflammation, and ultimately neuronal cell death [44]. Oxidative stress and inflammation in the brain are the key contributors to neuronal dysfunction and death. Accumulation of β-amyloid (Aβ) plaques and the Tau protein tangles, oxidative stress-induced peroxides, and an abnormal expression of protein kinase D1 contribute to the progression of neuronal dysfunction and death.

Nrf2 binds to ARE and further activates a series of genes that encode important antioxidant enzymes, such as glutathione reductase, SOD, glutathione peroxidase (GPX), and NQO1, and involved in antioxidant defenses, detoxification, and cellular repair. In addition, Nrf2 promotes the breakdown of Aβ plaques and reduces the production of Aβ precursor protein by activating the key proteolytic enzymes. Moreover, Nrf2 enhances the transcription of neuronal protective genes, such as *nerve growth factor* and *BDNF*, which support neuronal survival and repair [45].

Additionally, Nrf2 activates molecular chaperones, such as heat shock protein 70, which maintain protein folding stability and cellular protein homeostasis [46]. Moreover, it inhibits neuronal apoptosis by suppressing the activity of apoptosis-related proteins, such as caspase-3 and B-cell lymphoma-2 (Bcl-2) assaciated X protein (Bax). Nrf2 also activates mitochondrial antioxidant enzymes, such as GPX and glutathione S-transferase (GST), to reduce the levels of free radicals in mitochondria. Furthermore, Nrf2 regulates the mitochondrial membrane potential to preserve normal mitochondrial function and providing protect them from NDDs.

Taken together, Nrf2 mitigates oxidative stress, regulates inflammation, inhibits neuronal apoptosis, promotes the breakdown of Aβ plaques, enhances neuronal survival and repair, activates molecular chaperones, and regulates mitochondrial function. Collectively, these effects contribute to ameliorating NDDs.

4.2. Brain injury diseases

Brain injury disorders, such as traumatic brain injury (TBI) and ischemic brain injury (IBI), result from trauma, hypoxia, poisoning, or infection. These conditions lead to neuronal death, disruption of the blood-brain barrier, mitochondrial dysfunction, and inflammation [47]. Activation of the Nrf2 pathway reduces neuronal death and inflammation and death by upregulating genes that encode key antioxidants, such as SOD, and anti-inflammatory cytokines such as interleukin (IL)-10. Moreover, Nrf2 activation promotes neural stem cell proliferation and differentiation, facilitating brain tissue regeneration through neurogenesis and synaptogenesis. Additionally, Nrf2 stimulates neuronal autophagy and enhances mitochondrial function, thereby improving cellular metabolism and energy supply, ultimately contributing to the amelioration of brain injury disorders [48,49].

4.3. Hepatic diseases

The liver is a crucial metabolic organ responsible for synthesizing, breaking down, and converting biomolecules in addition to detoxification. However, the liver can be damaged by several factors, including toxic substances, alcohol, drugs, and chemicals, resulting in oxidative stress, inflammation, and ultimately liver diseases.

Nrf2 plays a crucial role in protecting liver cells from damage. Activation of Nrf2 in the liver stimulates the expression of genes involved in antioxidants and anti-inflammatory responses, and detoxification [50]. These genes include *SOD*, *GPX*, *GST*, tumor necrosis factor-α (*TNF-α*), *IL-1β*, *IL-6*, *NQO1*, and *methionine transferase genes*. This protection is primarily mediated through several signaling pathways, such as the PI3K/Keap1/Nrf2, Nrf2/glutamate-cysteine ligase (GCL)/GSH, MAPK/Nrf2/HO-1, Nrf2/HO-1, and Nrf2/ARE pathway [51].

4.4. Cardiovascular diseases

Cardiovascular diseases include coronary heart disease, angina pectoris, myocardial infarction, arrhythmia, hypertension, and atherosclerosis. Nrf2 is critical to combating these diseases due to its antioxidative, anti-inflammatory, lipid metabolism regulatory, angiogenesis promotion, and repair capabilities [52,53]. Nrf2 mitigates the damage caused by oxidative stress by regulating important intracellular antioxidant enzymes (SOD, GPX, and GST) and reduces inflammation-induced damage by activating anti-inflammatory cytokines (IL-10 and IL-1RA). Additionally, Nrf2 activates lipid metabolism genes such as peroxisome proliferator-activated receptor-gamma (*PPAR-γ*), adenosine triphosphate (ATP)-binding cassette transporter A1 (*ABCA1*), and carnitine palmitoyltransferase I (*CPT1*), to promoting lipid β-oxidation and cholesterol efflux, resulting in decreased lipid levels and reduced deposition of plaques in the walls of blood vessels.

Furthermore, the activation of Nrf2 triggers the expressions of growth factors (vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF)), thereby supporting the proliferation and migration of vascular endothelial cells to promote angiogenesis [54]. Moreover, Nrf2 promotes the proliferation and repair of vascular smooth muscle cells, effectively restoring the optimal structure and function of blood vessels to improve cardiovascular health.

4.5. Pulmonary diseases

Lung diseases, including chronic obstructive pulmonary disease, pulmonary hypertension, and pulmonary fibrosis, are characterized by tissue damage, apoptosis, oxidative stress, and inflammatory responses. The activation of Nrf2 plays a crucial role in protecting cells from these diseases. Nrf2 upregulates the expression of various antioxidant and detoxification genes (*SOD*, catalase (*CAT*), *GPX*, *NQO1*, *HO-1*, and *GCLC*) to reduce oxidative stress and toxic responses in the lung, safeguarding cells from damage. *Nrf2* inhibits the expression of inflammatory factors, such as NF-κB and activating protein-1 (AP-1) and enhances the expressions of anti-inflammatory factors, such as IL-10 and transforming growth factor-beta (TGF-β), to alleviate renal inflammation [55,56]. This dual action enhances the anti-inflammatory capacity of cells. Taken together, Nrf2 plays a critical role in protecting lung from diseases by reducing oxidative stress, inflammation, and apoptosis.

4.6. Renal diseases

Oxidative stress and inflammation are the primary causes of cell damage and death in renal diseases. Impaired Nrf2 activation attenuates the expressions of antioxidant- and anti-inflammatory enzymes, such as cyclooxygenase-2 (COX-2), NAD(P)H, HO-1, GCLC, and CAT, causing damage to renal cells [57,58]. Optimal Nrf2 activation protects renal cells from inflammation-induced injury by suppressing the expression of pro-inflammatory factors such as TNF-α and IL-6. Additionally, Nrf2 promotes the expression of Bcl-2 and its homologs and suppresses Bax expression, which results in the inhibition of renal cell apoptosis and preserves renal function [59].

Furthermore, Nrf2 regulates the expression of genes, such as FGF-23, involved in renal metabolism and excretion. This regulation enhances renal metabolic and excretory functions, thereby ameliorating the symptoms and improving the prognosis of renal diseases [60]. Overall, Nrf2 mitigates oxidative stress, suppresses

inflammation, inhibits apoptosis, and enhances renal metabolic and excretory functions.

4.7. Bone damage

Bone injuries induce oxidative stress to cause cellular damage. Nrf2 regulates the expressions of antioxidant genes, such as *SOD*, *CAT*, and *GPX*. These antioxidants scavenge ROS and ameliorate oxidative stress, consequently supporting normal bone tissue growth and repair [61]. In addition, bone injuries are accompanied by inflammation, which is characterized by swelling, redness, and pain. Nrf2 inhibits the production of pro-inflammatory factors, such as TNF-α and IL-1β [62].

Furthermore, Nrf2 regulates genes involved in osteoblast proliferation and differentiation and inhibits bone-resorbing cells. Nrf2 also modulates genes related to calcium metabolism and promotes VEGF expression, facilitating neoangiogenesis, maintaining capillary integrity, and promoting bone tissue repair [63]. Taken together, the activation of Nrf2 in response to bone injuries helps protect against oxidative stress, inflammation, and tissue damage. It promotes bone tissue growth and repair by regulating antioxidant and inflammatory responses and modulating osteoblast activity and calcium metabolism.

4.8. Muscle damage

Acute and chronic muscle injuries cause inflammation and oxidative stress, eventually damaging the muscles and impairing their function. However, activation of Nrf2 protects muscles from inflammation and oxidative stress-induced damage [64]. Nrf2 activation promotes the expression of genes involved in mitochondrial metabolism, antioxidant defense, and cellular redox homeostasis, thereby reducing the level of oxidative stress in muscle cells [65,66]. In addition, Nrf2 modulates the inflammatory response to muscle injury by inhibiting the production of pro-inflammatory cytokines and chemokines, while promoting the expression of anti-inflammatory factors [67,68]. In conclusion, Nrf2 activation plays a crucial role in protecting muscles from inflammation-induced damage and oxidative stress. Nrf2 regulates mitochondrial function, cellular redox homeostasis, and inflammatory responses to reduce muscle damage and promote tissue repair.

4.9. Metabolic disorders

Metabolic diseases, including obesity, diabetes, and non-alcoholic fatty liver disease, are closely associated with inflammation, oxidative stress, and insulin resistance. The accumulation of ROS and toxic substances triggers cellular damage and death, contributing to the development of metabolic diseases [69]. Nrf2 reduces oxidative stress damage by promoting the expressions of antioxidant genes, such as *GST*, *NQO1*, and *glutathione reductase*. In addition, it inhibits the expressions of pro-inflammatory factors, such as TNF-α and IL-6, and promotes the expression of anti-inflammatory factors such as IL-10. These regulatory actions ameliorate metabolic disorders and tissue damage associated with chronic low-grade inflammation. Additionally, Nrf2 influences adenosine monophosphate (AMP)-activated protein kinase (AMPK), PPAR-γ, and Sirtuin 1 (SIRT1) to alleviate metabolic disorders and reduce tissue damage [70–72].

Overall, Nrf2 plays a pivotal role in regulating metabolic diseases by reducing oxidative stress, suppressing inflammatory factors, modulating energy generation pathways (such as glucose, lipid, and cholesterol metabolism) through PPAR-γ and SIRT1, and preventing cardiovascular diseases.

4.10. Cancer

Cancer development is closely associated with the generation of oxidative stress, and Nrf2 exerts significant anti-cancer activity. Nrf2 acts as an antioxidant and inhibits the occurrence of oxidative stress. However, high expression of *Nrf2* can potentially induce malignant tumor formation. Therefore, maintaining Nrf2 level within a reasonable range is critical to the treatment of oncologic diseases [73]. The levels of oxidative stress are high in cancer cells, and Nrf2 activation counteracts this imbalance by regulating the expression of antioxidant genes. The activation of Nrf2 promotes cellular survival and inhibits the proliferation of cancer cells [74]. Moreover, Nrf2 promotes the release of mitochondrial cytochrome C (Cyt-c) and synergizes with the NF-κB/signal transducer and activator of transcription 3 (STAT3) pathway, resulting in the regulation of apoptosis-related genes (including *Bax*, *p53*, and *caspase-9*). Consequently, Nrf2 promotes apoptosis, a critical process in cancer therapy [75].

Tumor angiogenesis, a critical step in cancer development is intricately linked to Nrf2 activation. Nrf2 inhibits the expression of VEGF, thereby curtailing angiogenesis and impeding the migration and metastasis of cancer cells [76]. Notably, Nrf2 inhibition can inhibit tumor cell proliferation and metastasis and promote the sensitivity of cancer cells to conventional chemotherapeutic agents [77]. Therefore, modulating the expression of the Nrf2 pathway may improve the efficacy of cancer chemotherapy and radiotherapy, reduce side effects, and improve treatment outcomes.

4.11. Other diseases

Nrf2 protects intestinal epithelial cells from oxidative stress and inflammation. This protection improves the function of the intestinal mucosal barrier and promotes the balance of the intestinal microbiota. Consequently, it helps alleviate intestinal inflammation and reduces the risk of developing gastrointestinal diseases [78]. Nrf2 promotes the survival and function of eye tissues and protects them from oxidative damage. Therefore, Nrf2 plays a crucial role in the treatment of retinal diseases [79,80]. In addition, Nrf2 protects skin cells from ultraviolet (UV) radiation-induced damage and reduces oxidative and inflammatory responses. It also promotes skin cell repair and regeneration, thereby playing a therapeutic role in various skin diseases [81].

Overall, targeting Nrf2 can effectively decrease the occurrence and development of NCDs by combating oxidative stress and inflammatory responses. Therefore, identifying natural compounds that regulate Nrf2 is important to inhibit the onset and progression of NCDs. Notably, Que is a natural antioxidant, which efficiently regulates and activates Nrf2.

5. Interaction between Que and Nrf2

Que (2-phenylbenzo-r-pyrone) is a natural compound that has antioxidant and anti-inflammatory properties. Its chemical structure comprises two benzene rings and an indole backbone containing ketones and hydroxyl groups. The hydroxyl group, benzene ring, and double bond contribute to the potent antioxidant activity of Que. It effectively scavenges free radicals to reduce oxidative stress and inflammation and protect cells from damage [82]. In addition, Que interacts with antioxidant enzymes such as HO-1, CAT, and glutathione peroxidase (GSH-PX), and enhances their free radical scavenging activity [83,84]. These enzymes possess AREs in their gene promoters and protect against oxidative stress. The unique structure of Que enables its binding to Nrf2 and facilitates the translocation of Nrf2 into the nucleus, where Nrf2 forms a

complex with AREs [85]. This process upregulates the expressions of key antioxidant and detoxification genes, such as *HO-1* and *NQO1*, thereby inhibiting excessive intracellular ROS production.

We performed virtual molecular docking to validate the affinity between Que and Nrf2. The Protein Data Bank (PDB) database was searched for available templates that matched Nrf2, and molecule 6ytm from Homo sapiens was identified as the best-fitting molecule. The three-dimensional (3D) structure of Que for docking was built in Chemdraw 14.0 and energy was minimized using the molecular mechanics 2 (MM2) force field. The AutoDock Vina software was used for virtual docking, and ligands with the lowest energy and most favorable orientation were selected (Fig. 3). *In silico* analysis revealed that Nrf2 formed favorable hydrogen-bonding interactions with ARG-41. The hydrophobic side chains of Nrf2, comprised GLY-603, GLY-462, GLY-509, GLY-364, ILE-416, ILE-461, LEU-365, LEU-139, LEU-249, PHE-478, ALA-556, and ALA-366 and participated in Van der Waals interactions with Que.

In addition, Que has been reported to influences Nrf2-related signaling pathways, such as the NF-κB, PI3K/protein kinase B (Akt), MAPK, AMPK, glycogen synthase kinase 3 beta (GSK-3β), and protein kinase C (PKC). Consequently, Que promotes the expression of essential antioxidant enzymes such as SOD, CAT, GSH-PX, and GSH, and inhibiting lipid peroxidation, protein carbonylation, and DNA damage [86].

Overall, Que regulates the Nrf2 pathway through multiple mechanisms. It disrupts the negative regulation of Nrf2 by Keap1, facilitating its translocation to the nucleus and enhancing its binding to AREs (Fig. 4). Moreover, Que modulates various signaling pathways to promote Nrf2-mediated antioxidant responses.

6. Potential therapeutic action of Que against NCDs through the Nrf2 pathway

Que exerts antioxidant and anti-inflammatory activity by modulating the Nrf2 pathway (Fig. 5). The activated pathway attenuates cellular damage, such as mitochondrial dysfunction, autophagy, apoptosis, and DNA damage. Que has great therapeutic potential in managing NCDs, such as cardiovascular diseases, cancers, metabolic disorders, and musculoskeletal diseases.

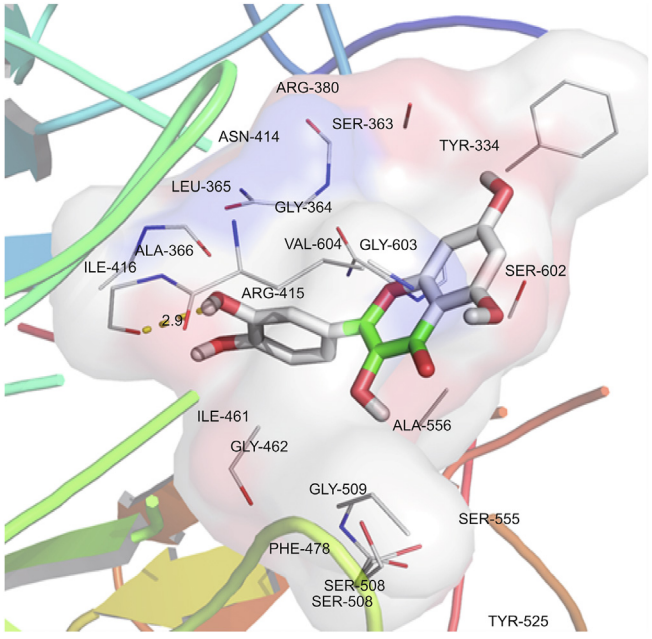

Fig. 3. Docking of quercetin (Que) and nuclear factor erythroid 2-related factor 2 (Nrf2). Low-energy binding conformation (−7.8 kcal/mol) of the complex between Que and ligand binding domain (LBD) of Nrf2 by virtual docking.

6.1. Protective effect against organ damage

Que has protective effects on the brain, eyes, liver, gastrointestinal tract, cardiovascular system, lungs, kidneys, reproductive system, bones, muscles, and skin.

6.1.1. Brain-protective effects

Que is considered as a potential drug for the treatment of NDDs, traumatic brain injury, IBI, and other cerebral disorders due to its ability to modulate Nrf2.

6.1.1.1. Protective effects against NDDs. Que activates the Nrf2 pathway to regulate inflammation, oxidative stress, and mitochondrial function in the neurons. Activation of this pathway promotes the production of intracellular antioxidants, inhibits the release of inflammatory factors, and enhances mitochondrial function and biosynthesis. Collectively, these effects attenuate the pathologic process of NDDs.

6.1.1.1.1. AD. Que emerges as a promising therapeutic agent for AD by modulating the Nrf2 pathway. Researches detailed in Table S1 [87,88] demonstrated the ability of Que to delay AD progression by inhibiting the accumulation of Aβ and Tau protein aggregation. It activated the Nrf2/HO-1 pathway, reversing neuronal damage and slowing down AD progression. The administration of Que enhanced antioxidant activity by upregulating Nrf2 expression and downregulating $A\beta_{1-42}$ expression in an AD animal model induced by Aβ [87]. This resulted in a decrease of lipid peroxidation and an increase in the levels of HO-1, SOD, CAT, and GSH in the brain tissues. Additionally, Que modulated the SIRT1/Nrf2/HO-1 signaling pathway, enhancing cellular antioxidant capacity and reducing Aβ-induced neuronal damage. Moreover, Que treatment decreased the levels of HO-1, acetylcholinesterase, and malondialdehyde (MDA) and increased the total antioxidant capacity (T-AOC) [88].

Que also showed promising anti-AD effect by preventing abnormal Tau aggregation and neuronal death, as indicated in Table S1 [89]. It suppressed the Tau protein aggregation, inhibited the ERK signaling, and promoted the tyrosine kinase receptor B and CREB signaling pathways. This ultimately protected neurons from oxidative stress-induced damage [89].

6.1.1.1.2. PD. Que has shown potential in treating PD by targeting the Nrf2 pathway. Valuable insights into the therapeutic effects of Que in PD are provided in literature [90–92].

The administration of Que increased Nrf2 expression in a mouse model of PD. Increased Nrf2 expression activated protein kinase D1 and Akt in dopaminergic neurons, protecting neurons from damage and inhibiting PD progression, as illustrated in Table S1 [90]. Additionally, Que alleviated PD by inducing Nrf2-mediated HO-1 expression and inhibiting NF-κB activation. Que enhanced Nrf2, HO-1, and ARE expressions, whereas reduced TNF-α, IL-1β, NF-κB, p50, p65, inducible nitric oxide synthase (iNOS), and nitric oxide (NO) expressions in microglial cells. The use of *Nrf2* small interfering RNA (siRNA) attenuated the beneficial effects of Que, as indicated in Table S1 [91,92], suggesting the potential of Que to restore cellular homeostasis and alleviate PD symptoms by modulating the Nrf2 pathway.

6.1.1.1.3. ALS. Que has been identified as a potential therapeutic molecule for ALS. It protects central neurons from chronic high glucose injury by modulating Nrf2 activity, as evidenced by literature [93,94].

Que increased the expressions of Nrf2 and HO-1 and decreased that of caspase-3, ROS, NF-κB, IκBα, iNOS, COX-2, IL-6, and TNF-α in dorsal root ganglion (DRG) neurons. These changes suggested that

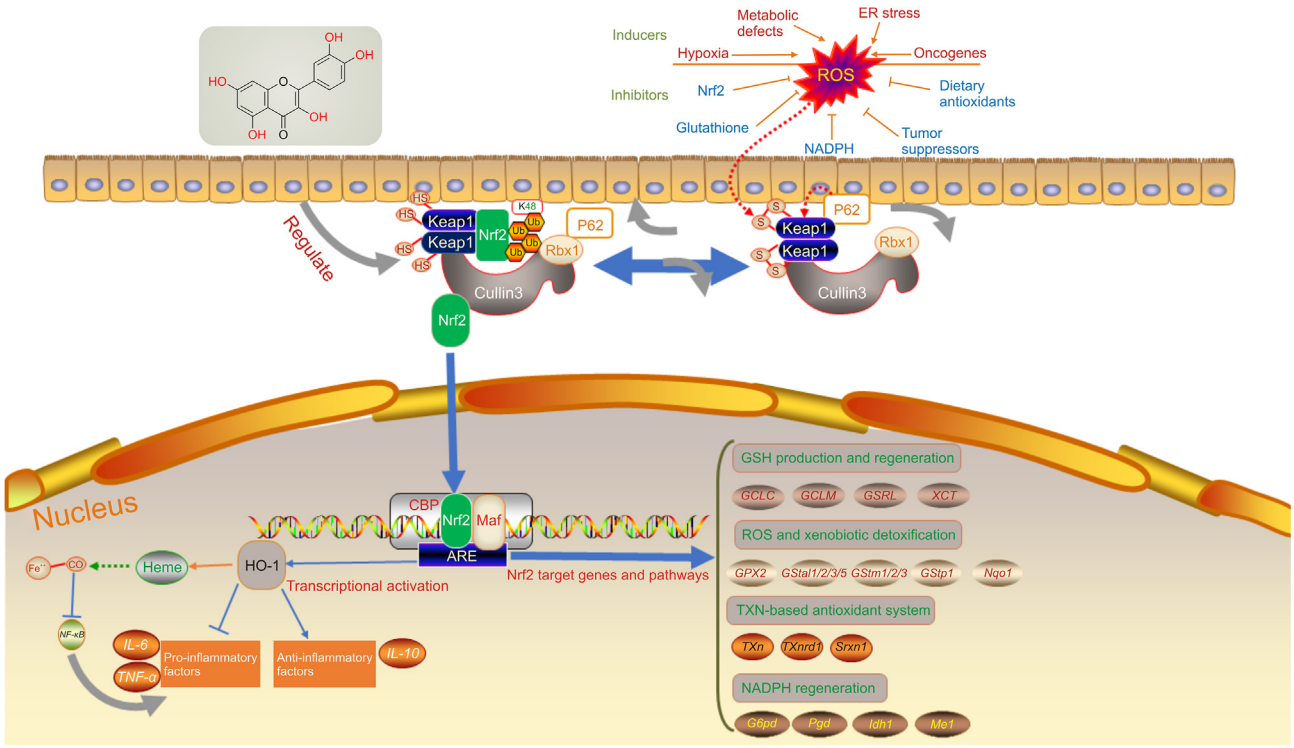

Fig. 4. Schematic summary of the major targets nuclear factor erythroid 2-related factor 2 (Nrf2) modulated by quercetin (Que) in non-communicable diseases (NCDs). ER: endoplasmic reticulum; ROS: reactive oxygen species; NAD(P)H: nicotinamide adenine dinucleotide phosphate/nicotinamide adenine dinucleotide; Keap1: kelch-like ech-associated protein 1; HS:heat shock ; Ub: ubiquitin ; CO: carbon monoxide; *NF-κB*: nuclear factor kappa-light-chain-enhancer of activated B cells; *IL*: interleukin; *TNF-α*: tumor necrosis factor-α; HO-1:heme oxygenase-1; CBP: cyclic adenosine phosphate response element-binding (CREB)-binding protein; sMaf: small male neurofibrosarcoma; ARE: antioxidant response elements; GSH: glutathione; *GCLC*: catalytic subunit of the glutamate-cysteine ligase complex; *GCLM*: subunit of the glutamate-cysteine ligase complex; *GSRL*: ghrelin receptor-like; *XCT*: cystine/glutamate transporter; *GPX2*: glutathione peroxidase 2; *GSTal1/2/3/5*: glutathione *S*-transferase alpha 1/2/3/5; *GStm1/2/3*: glutathione *S*-transferase mu 1/2/3; *GStp1*: glutathione *S*-transferase pi 1; *NQO1*: NAD(P)H:quinone oxidoreductase 1; *TXN*: thioredoxin; *TXnrd1*: TXN reductase 1; *Srxn1*: sulfiredoxin 1; *G6pd*: glucose-6-phosphate dehydrogenase; *Pgd*: phosphogluconate dehydrogenase; *Idh1*: isocitrate dehydrogenase 1; *Me1*: malic enzyme 1.

Que augments the antioxidant defenses of DRG neurons through the Nrf2/HO-1 axis, affording a protective effect against ALS. Furthermore, Que activated the Nrf2/ARE/glyoxalase-1 (Glo-1) pathway by increasing levels of Nrf2 and phosphorylated Nrf2, as delineated in Table S1 [93]. Additionally, Que increased the messenger RNA (mRNA) and protein levels of Glo-1, γ-glutamylcysteine synthetase (γ-GCS), GSH, and advanced glycosylation end products, as indicated in Table S1 [94]. The activation of this pathway was further enhanced after pretreatment of a p38MAPK inhibitor, whereas inhibition of PKC or activation of GSK-3β mitigated the effects of Que. These findings indicate that Que protects DRG neurons through the Nrf2/ARE/Glo-1 pathway.

6.1.1.2. Traumatic brain injury. Li et al. [95] explored the molecular mechanisms by which Que ameliorated TBI. Que administration substantially increased total Nrf2 expression after brain injury in a TBI mouse model. Que facilitated the movement of Nrf2 from the cytoplasm to the nucleus, activating the Nrf2 pathway and enhancing the anti-inflammatory and antioxidant responses. The restoration of key mitochondrial functional factors, including Bax, MDA, Cyt-c, SOD, and ATP, as well as the translocation of Nrf2 from the cytoplasm to the nucleus, was observed. This translocation triggered the activation of anti-inflammatory and antioxidant responses, as shown in Table S1 [95]. These outcomes suggested that Que-induced activation of Nrf2 enhanced mitochondrial function and decelerates TBI progression, positing Que as a potential novel therapeutic approach for TBI management.

6.1.1.3. IBI. Que shows neuroprotective effects in rats with IBI-induced blood-brain barrier injury. This was evident as depicted in Table S1 [96,97]. Notably, Que activated the Nrf2/HO-1 pathway, which was associated with the neuroprotective effects in an IBI rat model [96]. Que reduced ROS level and increased the expressions of Nrf2, HO-1, and proteins involved in blood-brain barrier integrity (Occludin, Claudin-5, and ZO-1). Furthermore, administration of Que promoted Sirt1 expression in rats subjected to ischemia/reperfusion, facilitating nuclear translocation and activation of Nrf2. EX527, an inhibitor of Sirt1, antagonized the neuroprotective effects of Que, providing further evidence of the involvement of the Sirt1/Nrf2/HO-1 pathway. Que alleviated neuronal cell death induced by oxygen-glucose deprivation (OGD) [97]. Que upregulated the levels of Nrf2, HO-1, and NOS1, and downregulated the level of Keap1 in SHSY5Y cells and rat cortical neurons. It also promoted SUMOylation level in neurons through the Nrf2 pathway and inhibited the activities of SENP1 and SENP2, thereby enhancing the antioxidant capacity against OGD and OGD restoration of oxygen/glucose-induced damage.

Collectively, these findings highlight the neuroprotective properties of Que mediated by the activation of the Sirt1/Nrf2/HO-1 pathway, which increases the antioxidant capacity of neurons.

6.1.1.4. Other cerebral disorders. The susceptibility of the nervous system to oxidative stress, which often leads to mitochondrial dysfunction, can precipitate various neurological disorders. Activation of the Nrf2 pathway plays a crucial role in combating this, as

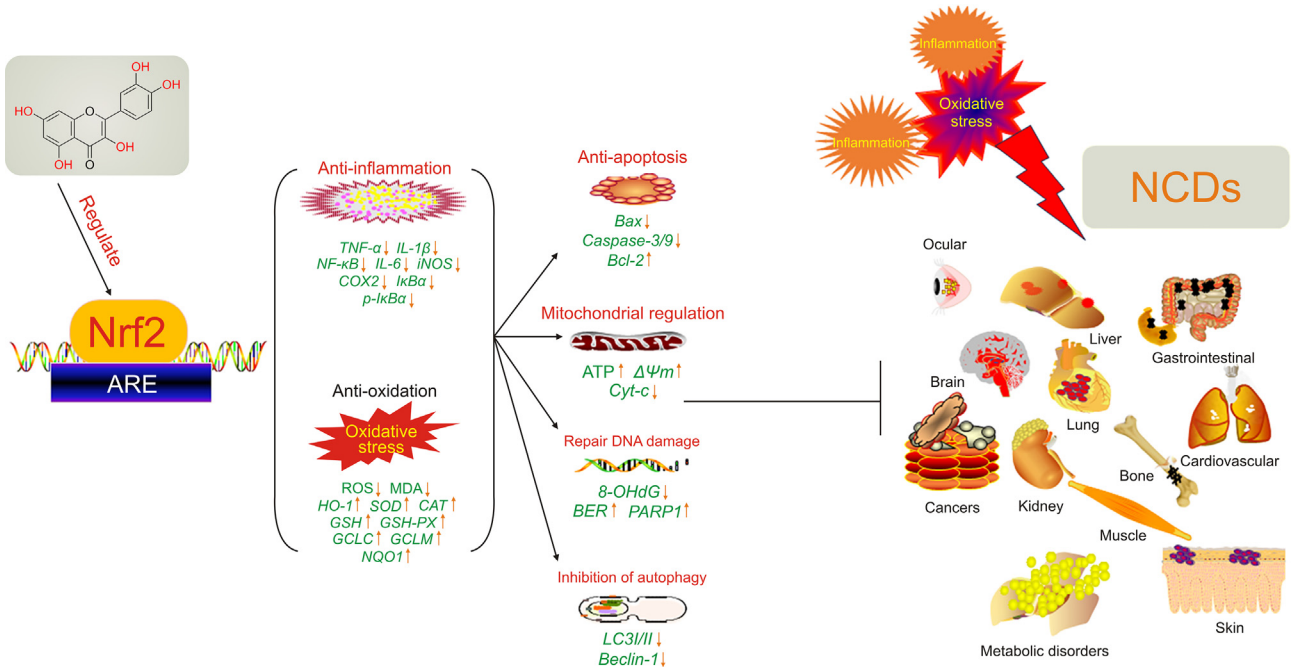

Fig. 5. The pharmacological activity of quercetin (Que) exerted mainly through nuclear factor erythroid 2-related factor 2 (Nrf2) and its effective amelioration of non-communicable diseases (NCDs). ARE: antioxidant response elements; *TNF-α*: tumor necrosis factor-α; *IL*: interleukin; *NF-κB*: nuclear factor kappa-light-chain-enhancer of activated B cells; *iNOS*: inducible nitric oxide synthase; *COX-2*: cyclooxygenase-2; *P-IκBα*: phosphorylated IκBα; ROS: reactive oxygen species; *MDA*: malondialdehyde; *HO-1*: heme oxygenase-1; *SOD*: super oxide dismutase; *CAT*: catalase; *GSH*: glutathione; *GSH-PX*: GSH peroxidase; *GCLC*: catalytic subunit of the glutamate-cysteine ligase complex; *GCLM* :subunit of the glutamate-cysteine ligase complex; *NQO1*: nicotinamide adenine dinucleotide phosphate/nicotinamide adenine dinucleotide (NAD(P)H):quinone oxidoreductase 1; *Bax*: B-cell lymphoma 2 (Bcl-2) associated X protein; ATP: adenosine triphosphate; *ΔΨm*: mitochondrial membrane potential; *Cyt-c*: cytochrome C; *8-OHdG*: 8-hydroxy-2'-deoxyguanosine; *LC3I/II*: microtubule-associated proteins 1A/1B light chain 3B, form I/II. *Beclin-1*: Bcl-2-interacting myosin-like coiled-coil protein 1.

it enhances mitochondrial biosynthesis and cellular respiration, reduces mitochondrial DNA damage and apoptosis, and promotes antioxidant capacity within the mitochondria. This ensures the maintenance of intracellular energy homeostasis.

Que has been effective in alleviating neurological dysfunction caused by mitochondrial damage, chiefly by activating the Nrf2 pathway, enhancing antioxidant and anti-inflammatory capacities in neurons. Que has shown potential in reversing Mn-induced oxidative damage and neuroinflammation in the brain, upregulating expressions of HO-1 and Nrf2, promoting activities of SOD and CAT, and increasing intracellular GSH levels [98]. It also reduced neuroinflammation by downregulating the levels of phosphorylated IκBα (P-IκBα), NF-κB P65, iNOS, TNF-α, IL-1β, IL-6, and COX-2, and inhibiting the release of lactate dehydrogenase (LDH), restoring mitochondrial membrane potential in SK-N-MC cells [99]. Furthermore, Que restored mitochondrial membrane potential and mitochondrial dysfunction by elevating Nrf2 expression, increasing the levels of AMPK-α, SIRT1, and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) proteins, and improving antioxidant capacity (SOD1 and SOD2 expressions) in 7-ketocholesterol-treated N2a cells [100]. These effects of Que on mitigating mitochondrial damage and reducing oxidative stress and inflammation are detailed in Table S1 [98–100].

Furthermore, the role of Que in addressing cognitive dysfunction induced by external factors like high-fat and high-sugar diets has been significant. It regulated the Nrf2 pathway, affecting proteins such as PI3K, Akt, total antioxidant capacity, SOD, GSH/GSSG, CREB, and brain-derived neurotrophic factor (BDNF), thus reversing cognitive impairments and improving learning and memory abilities. The effectiveness of Que in attenuating neural damage induced by dietary stimulants was complemented by its antioxidant and anti-inflammatory actions, as demonstrated in various studies [101–103]. These actions included enhancing antioxidant activity in the cerebral cortex and reducing oxidative stress, alongside decreasing levels of pro-inflammatory markers and increasing brain-derived neurotrophic factors, further promoting neural health. The comprehensive effects of Que on neural health and cognitive functions are illustrated in Table S1 [101–103].

6.1.2. *Ocular protective effects*

Que has emerged as a promising agent in treating eye-related disorders, offering protective and therapeutic benefits against various forms of retinal damage [104–106]. Que has demonstrated significant efficacy in reducing toxicity and preventing apoptosis in retinal pigment epithelium (RPE) cells. This effect is primarily attributed to the activation of the Nrf2/Sirt1/PGC-1α detoxification pathway, as detailed in Table S1 [104]. By activating this pathway, Que effectively reduces intracellular ROS accumulation induced by oxidative stress and enhances cellular antioxidant defense mechanisms. This include the upregulation of Sirt1 and PGC-1α expressions via Nrf2, which collectively contributed to reversing pathological changes in RPE cells and modulating cellular responses such as autophagy.

Further insights, as shown in Table S1 [105], revealed the protective effect of Que against retinal oxidative stress in *Nrf2* knockout (KO) mice. It activated the Keap1/Nrf2/ARE pathway, significantly reducing retinal oxidative stress and inflammatory responses. This involved promoting expressions of key antioxidant enzymes, including SOD, GSH-PX, and CAT, and suppressing pro-inflammatory markers. Moreover, in the context of cigarette smoke extract's impact on RPE cells, Que has been found to reverse the adverse effects on proteins involved in the Keap1/Nrf2/ARE pathway, as indicated in Table S1 [106].

6.1.3. Hepatoprotective effects of Que

Activation of the Nrf2 pathway plays a crucial role in preventing acute liver injury and the development of chronic liver diseases. Que has shown great efficacy in combating oxidative stress and inflammation by modulating the Nrf2 signaling pathway.

Que promotes the antioxidant defenses in hepatocytes by activating Nrf2. Chronic liver diseases, including alcoholic liver injury and hepatotoxicity, are characterized by persistent inflammation and oxidative stress. Que helps alleviate these symptoms by increasing the production of detoxifying enzymes and antioxidant proteins, thereby protecting the liver from oxidative damage. In addition, Que inhibits the activation of inflammatory pathways and the production of pro-inflammatory molecules by activating Nrf2, thereby inhibiting the inflammatory response in the liver and improving liver health. Therefore, Que is a potential therapeutic molecule for mitigating liver injury and promoting liver health.

6.1.3.1. Heavy metal induced liver damage. Que mitigated heavy metal-induced liver damage by enhancing the expression of antioxidant and detoxification enzymes in hepatocytes via the Nrf2 signaling pathway [107]. In nickel-toxicity models, Que administration significantly upregulated HO-1 and Nrf2 activities, while reducing key liver damage markers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and DNA methyltransferase, in mice exposed to nickel toxicity. Moreover, Que diminished DNA methylation of Nrf2 and phosphorylation of inflammatory factors like TNF-α, IL-1β, iNOS, NF-κB p65, p38, and STAT1, suggesting its efficacy in rectifying liver function abnormalities caused by nickel toxicity, as shown in Table S1 [107].

6.1.3.2. Drug-related liver damage. Que counteracted liver damage caused by the inappropriate use of certain anti-cancer drugs, as outlined in Table S1 [108–111]. Que bolstered the antioxidant defenses against cyclophosphamide-induced hepatotoxicity by upregulating Nrf2 and HO-1 expressions, increasing the levels of GSH, SOD, and CAT, while reducing Keap1, ROS, MDA, NO, and TNF-α levels in rats [108]. Further, the protective effect of Que in monocrotaline-induced hepatic sinusoidal syndrome involved in decreasing MDA level and modulating the MAPK and PI3K/Akt pathways via Nrf2-mediated regulation of phosphatase and tensin homolog (PTEN), ERK, JNK, and p38 protein expressions [109]. This compound played a crucial role in activating the Nrf2/GSH signaling pathway, a key element in mitigating liver injury induced by toosendanin. This efficacy was evidenced by increasing Nrf2 expression, elevating intracellular GSH level, and reducing ROS and MDA levels, coupled with altered the expressions of Keap1, Nrf2, p62, and GCL/GCLM [110]. Furthermore, Que combated hepatocyte injuries induced by clivorine and acetaminophen by activating *Nrf2* transcription, enhancing nuclear *Nrf2* expression, and consequently increasing the levels of c-Jun N-terminal kinase (c-JNK), p62, GCLC, GCLM, and HO-1 in human normal liver L-02 cells. The mitigation of these effects by inhibitors of HO-1 and GCL, as well as JNK inhibitors and siRNA, further substantiated the primary role of the Nrf2 pathway in the hepatoprotective mechanism of Que [111].

6.1.3.3. Alcoholic liver damage. Que ameliorates alcoholic liver disease by modulating the *Nrf2* pathway, as summarized in Table S1 [112–116].

Acute alcohol exposure activated NF-κB p65 and upregulated the nucleotide-binding and oligomerization (NACHT), leucine-rich repeat (LRR), and pyrin domain (PYD) domains-containing protein 3 (NLRP3) inflammasome components (NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain (CARD), and caspase-1) in a rat model, which Que inhibited by enhancing IL-10 expression and reducing TNF-α, IL-1β, IL-18, MDA, and ROS levels in the liver. The crucial role of the HO-1/Nrf2 pathway in the hepatoprotection of Que was evident, especially as HO-1 inhibition by ZnppIX attenuated these effects [112]. In a zebrafish model, Que modulated the P2X7 receptor (P2X7R)-mediated PI3K/Keap1/Nrf2 signaling pathway of oxidative stress, reducing fat accumulation and levels of ALT, AST, gamma-glutamyltransferase (γ-GT), triglycerides, and cholesterol in ethanol-induced hepatic injury. It also decreased ROS and MDA production in hepatocytes while increasing the expressions of GSH, CAT, SOD, HO-1, CAT1, GPX8, and Akt [113].

Several authors have elaborated on the effect of Que on alcoholic liver injury through the Nrf2 pathway. Lee et al. [114] observed that Que markedly alleviated ethanol-induced cytotoxicity in HepG2 cells, such as decreasing ALT, AST, NO, ROS, iNOS, and TNF-α levels, and increasing GSH production. Yao et al. [115] found that Que activated HO-1 via ERK, JNK, and p38 pathways in ethanol-induced HepG2 cells, with pathway inhibitors exacerbating liver injury and blocking the protective effects of Que. Lee et al. [116] showed that Que and its metabolites, 30-*O*-methylquercetin and Que 3-glucoside, significantly inhibited ROS production in ethanol-damaged HepG2 cells, enhancing Nrf2, HO-1, and AP-1 expressions, reducing lipid peroxidation, restoring GSH level, and increasing antioxidant enzyme activities (SOD and CAT).

6.1.3.4. Liver fibrosis. Que exhibited notable protective effects against liver inflammation and fibrosis in CCl_4-induced mice and $CdCl_2$-induced liver fibrosis, as outlined in Table S1 [117–119]. Activation of the *Nrf2* pathway by Que upregulated the levels of hepatoprotective markers (HO-1, AST, ALT), while downregulating those of inhibitory factors (iNOS, 3-nitrotyrosine (3-NT), TGF-β1, MDA, GSH, SOD, NF-κB, TNF-α, and COX-2). Que also enhanced antioxidant enzymes (peroxidases and thioredoxins), improving liver antioxidant capacity [117,118]. Notably, this effect was attributed to the modulation of Nrf2, GSH, and SOD levels and a reduction in TNF-α, IL-6, ROS, MDA, NF-κB, and NF-κB p65 levels, mitigated oxidative stress and inflammatory responses. Que inhibited miR-21 through the Nrf2 pathway, leading to reduced sterol regulatory element binding protein 1 (SREBP1) expression and increased levels of TGF-β1, mothers against decapentaplegic homolog 3 (Smad3), collagen 1 A, PPAR-α, CPT1, and mothers against Smad7. This modulation effectively mitigated liver steatosis and fibrosis. The use of miR-21 antagonists further supported the inhibitory effect of Que on miR-21 via the Nrf2 pathway [119].

6.1.3.5. Other liver injuries. The Nrf2/Keap1 pathway is critical to ameliorating the effects of Que on liver injury induced by chemical drugs, as shown in Table S1 [120–125]. Que upregulated Nrf2 and HO-1 expressions in thioacetamide-induced rat liver tissues, boosting antioxidant levels and reducing toxicity [120]. Que also enhanced Nrf2-related expressions in H_2O_2-induced HepG2 cells, with the effect inhibited by ML385. Additionally, Que inhibited BACH1 activity, a negative regulator of the Nrf2 pathway in HepG2 cells, promoting cell survival and NQO1 and HO-1 expressions [121,122]. Weng et al. [123] proposed a positive correlation between the antioxidant activity of Que and metallothionein expression. Que attenuated *t*-butylhydroperoxide induced hepatocyte injury by inducing metallothionein, activating JNK, p38, and PI3K/Akt, and enhancing Nrf2 DNA-binding activity. Moreover, Que alleviated cytotoxicity and genotoxicity induced by ochratoxin A in HepG2 cells, restoring cell viability and reducing oxidative stress and inflammation [124]. Que and its metabolite benzo(α)pyrene induced cellular damage in HepG2 cells, promoting aryl hydrocarbon receptor (AhR) and Nrf2 translocation and regulating the expression of detoxification enzymes. They decreased intracellular

levels of DNA adducts and 8-oxo-2′-deoxyguanosine through the Nrf2 pathway, while increasing the expressions of phase I, II, and III enzymes [125].

6.1.4. Gastrointestinal protective effects

The intestinal mucosa is vital for maintaining health, but improper dietary intake can induce oxidative stress. The protective effects of Que were evident in various scenarios, as shown in Table S1 [126,127]. In broiler chickens, Que alleviated lipopolysaccharide-induced intestinal injury by activating *Nrf2* and downstream genes, reducing ROS and MDA levels and mitigating mitochondrial damage [126]. In oxidized soybean oil-fed broilers, Que promoted Nrf2-related gene transcription, decreased inflammation, and enhanced *mucin 2* expression, contributing to improved intestinal barrier function [127].

Long-term use of certain medications, such as indomethacin (an anti-inflammatory drug) severely damages the gastrointestinal tract, as shown in Table S1 [128,129]. In cases of indomethacin-induced gastric mucosal damage, Que's activation of Nrf2 blocked NF-κB activation, increased antioxidant enzyme activities, and inhibited inflammation in rats and Caco-2 cells [128]. Furthermore, Que protected an intestinal porcine epithelial cell line from diquat-induced damage by enhancing *Nrf2* activity, increasing GSH synthesis and reducing ROS level [129]. This safeguarding effect was evidenced by the attenuation of diquat-induced disruptions, including decreased mitochondrial membrane potential and reduced levels of tight junction proteins (ZO-1, ZO-2, ZO-3, Occludin, and Claudin-4).

6.1.5. Cardiovascular protective effects

Que alleviates cardiovascular diseases by activating the Nrf2 pathway and primarily targeting lipid peroxidation and inflammation through its antioxidant and anti-inflammatory effects, as shown in Table S1 [130–133]. Que effectively reversed hemodynamic changes, decreased left ventricular end-diastolic pressure, increased left ventricular systolic pressure, and prevented myocardial infarction-induced left ventricular remodeling in a rat model. Mechanistically, Que activated Nrf2 in these rats, which significantly increased the levels of SOD, GSH, bone morphogenetic protein 7, and Smad7 proteins and decreased the nuclear activity and protein levels of MDA, ROS, angiotensin II, TNF-α, IL-6, and NF-κB p65. Furthermore, inhibition of the phosphorylation of Smad3 was one of the mechanisms by which Que exerted antioxidant, anti-inflammatory, and anti-fibrotic effects [130]. Sharma et al. [131] emphasized the mediatory role of the Nrf2 pathway in the cardioprotective effects of Que, reducing adriamycin-induced cardiomyopathy by enhancing antioxidant defense and maintaining cell membrane integrity.

Que also attenuated atherosclerosis by activating p38, subsequently activating Nrf2, which promoted the transcription of antioxidant enzyme genes and inhibited adhesion factors associated with atherosclerosis. Moreover, in lipopolysaccharide-induced endothelial cells, Que activated Nrf2, leading to increased expressions of HO-1, NQO1, and GCL, with p38 MAPK inhibition reducing Nrf2 activation and supporting the antioxidative role of Que [132].

In the context of a high-cholesterol diet in hyperglycemic rats, Que activated the Nrf2 pathway, reversing lipid and glucose alterations, improving nuclear translocation of 8-isoprostane, normalizing antioxidant enzyme activity, and mitigating high-cholesterol-induced cardiac insufficiency. Que further enhanced ATP level, upregulated PGC-1α expression, and suppressed cardiac uncoupling protein 2 and PPAR-γ expression, collectively reducing high-cholesterol-induced oxidative stress [133].

6.1.6. Pulmonary protective effects

Que plays a pivotal role in alleviating lung diseases by activating the Nrf2 pathway, as shown in Table S1 [134–137]. Que reduced oxidative stress and inflammation by activating Nrf2 and inhibiting NF-κB, preventing pulmonary vascular leakage. Que initiated Nrf2 under hypoxic conditions, resulting in a decrease in ROS and MDA levels, an increase in antioxidant defenses, and a reduction in inflammatory mediators. Que also ameliorated lung pathology, inhibited the expression of adhesion molecules, and reduced tissue leakage, collectively reducing lung inflammation and vascular leakage [134]. Boots et al. [135] investigated the effects of Que on pulmonary fibrosis in mice and found that it reversed the increased expression of collagen markers such as collagen, type I, alpha 2 and fibronectin 1 associated with the extracellular matrix in bleomycin-induced mice. Notably, Que treatment was ineffective in reversing bleomycin-induced lung injury in mice lacking *Nrf2*. In NIH3T3 cells, Que induced nuclear translocation of Nrf2 and activated the Smad and MAPK pathways, leading to ERK and JNK phosphorylation. Interestingly, the HO-1 inhibitor tin protoporphyrin IX (SNPP) significantly reversed Que-induced reduction in collagen production [136]. In clinical studies, Que exhibited a protective effect against idiopathic pulmonary fibrosis, improving antioxidant levels, plasma GSH, and uric acid in patients. Que administration reversed dose-dependent ROS increase, reduced *Nrf2* gene expression, and lowered *TNF-α* and *IL-8* in bleomycin-induced BEAS-2B cells. Additionally, Que pretreatment enhanced expressions of *Nrf2* and related genes like *HO-1* and *γ-GCS*, mitigating oxidative stress and lung injury [137].

6.1.7. Kidney protective effects

Que alleviates renal damage induced by toxic chemicals such as $CuSO_4$, $CdCl_2$, and ochratoxin A by activating the Nrf2 pathway, in specific reference to Table S1 [138–140]. Que alleviated nephrotoxicity by reducing $CuSO_4$-induced inflammation and oxidative stress through upregulation of antioxidant genes and inhibition of inflammatory factors in mice [138]. In $CdCl_2$-induced nephrotoxicity, Que regulated endoplasmic reticulum stress through SIRT1 activity, ameliorating renal pathologic features and increasing Nrf2 activity. However, the kidney protective effect of Que was abolished in the presence of EX-527, an SIRT1 inhibitor, emphasizing the importance of Nrf2 activation in inhibiting endoplasmic reticulum stress and promoting antioxidant and anti-inflammatory effects in the kidney [139]. Additionally, Que alleviated ochratoxin A-induced DNA damage and micronuclei formation in kidney cells, enhancing resistance to genotoxicity by diminishing LDH and NO release through Nrf2 activation [140].

Que can mitigate the disruption of normal ovarian cell development caused by elevated ROS levels, as shown in Table S1 [141–143]. Que enhanced Nrf2 and NQO1 expressions, reducing serum 17β-estradiol and TNF-α levels. It also affected mammalian target of rapamycin (*mTOR*) mRNA level and endometriosis in rats [141]. In goat luteinized granulosa cells, Que via the Nrf2 pathway reduced apoptosis, modulated the *Bax*/*Bcl-2* ratio, and enhanced antioxidative gene expressions [142]. It treated reproductive dysfunction in granulosa cells by activating the Nrf2/ARE pathway, influencing *Trx* gene expression, and inhibiting the thioredoxin-interacting protein (*TXNIP*) gene, alleviating reproductive disorders [143].

Que, by activating the Nrf2 pathway, effectively alleviates reproductive toxicity, reducing oxidative stress-induced damage to the reproductive system, as shown in Table S1 [144,145]. Triptolide is a potent natural compound with anticancer properties that induces oxidative stress in rat Leydig cells, adversely impacting their reproductive function. Que counteracted this situation by

modulating antioxidant and inflammatory factors, reducing ROS accumulation and alleviating cellular damage induced by triptolide [144]. Additionally, oxidative stress triggered the expression of *Nrf2*-microRNAs (miRNAs) such as miR-153, miR-28, and miR-708. Que effectively mitigated this phenomenon by enhancing expressions of *Nrf2* and its downstream genes (*NQO1* and *peroxiredoxin 1*), thereby suppressing reproductive toxicity. However, blocking miRNA undermines the effect of Que, underscoring the critical role of Nrf2 in Que's preventive action against reproductive disorders [145].

6.2. Protective effects against bone diseases

Que promoted osteoblast production and maintained skeletal cell homeostasis by reducing inflammation, oxidative stress, and ROS levels through the Nrf2 pathway, as shown in Table S1 [146–149]. Que and its metabolites regulated the Nrf2 pathway by modulating the ERK1/2 and NF-κB p65 signaling pathways. Notably, this pathway is crucial for the antioxidant response in osteoclasts [146]. It is worth noting that Que downregulated expressions of *Nrf2*-related genes (*HO-1* and *GCLC*) and phosphorylated ERK1/2, NF-κB, and NF-κB p65 levels in fetal rat calvarial osteoblasts [147]. Moreover, Que alleviated oxidative stress and ameliorated cellular senescence in rats with intervertebral disc degeneration [148]. This effect was achieved by activating Nrf2 to inhibit the NF-κB signaling pathway and attenuating the inflammatory response. Moreover, *Nrf2*-siRNA counteracted the effects of Que, indicating that Que regulated the NF-κB pathway through Nrf2 to ameliorate intervertebral disc degeneration lesions. Additionally, Que reduced alveolar bone loss in oxidized periodontal ligaments through the Nrf2 pathway [149]. It ameliorated DNA damage by decreasing p21 and p53 mRNA levels in human periodontal ligament cells. Moreover, it promoted osteogenesis and slowed alveolar bone resorption by enhancing the expression and activity of osteogenic biomarkers. Further, Que increased the expression of *Nrf2* and antioxidant genes (*HO-1*, *GPx3*, and *CAT*), while decreased those of ROS and MDA levels in human periodontal ligament cells. Taken together, Que mitigated skeletal injuries by regulating the Nrf2 pathway.

6.3. Protective effects against muscle diseases

Que alleviates muscle damage through the *Nrf2* pathway, as illustrated in Table S1 [150,151]. Kim et al. [150] found that Que inhibited key factors associated with muscle atrophy, increased HO-1 protein level, and activated the Nrf2/HO-1 pathway, effectively preventing muscle damage in both myotubes and *Nrf2*-deficient mice. Additionally, Borghi et al. [151] reported that Que alleviated skeletal muscle pain by suppressing various inflammatory and oxidative markers, enhancing Nrf2 and HO-1 expressions and modulating NF-κB activation, ultimately providing relief from pain induced by physical activity.

6.4. Protective effects against skin diseases

Que exhibits therapeutic potential in mitigating skin diseases by activating the Nrf2 pathway, as shown in Table S1 [152,153]. Que alleviated atopic dermatitis induced by destructive stimuli in mice by activating the Nrf2 pathway and suppressing the release of high mobility group box-1 protein (HMGB1) and inflammatory cytokines [152]. Que increased the expression of Nrf2, which subsequently inhibited the expression of inflammatory factors, resulting in the amelioration of skin inflammation induced by oxidative stress. Additionally, Que mitigated intracellular mitochondrial damage by inhibiting ROS production and enhancing GSH level in human keratinocyte HaCaT cells [153]. The deletion of *Nrf2* attenuated the protective effects of Que, highlighting the crucial role of Nrf2 activation in the skin-protective effect of Que.

6.5. Protective effects against metabolic disorders

Que regulates blood glucose and lipid levels by activating the Nrf2 signaling pathway. This finding highlighted the therapeutic benefits of Que for metabolic disorders. Que-induced activation of the Nrf2 pathway is a promising strategy to ameliorate oxidative stress and inflammation, which are the key contributors to metabolic disorders.

6.5.1. Anti-diabetic effect

Diabetes is a common metabolic disease, which is often linked to neurologic impairments. Que coupled with superparamagnetic iron oxide nanoparticles (QcSpions) reversed the streptozotocin-induced damage to pancreatic islets of Langerhans in rats [154]. This positive effect was primarily achieved through the activation of Nrf2. Que increased the expression of Nrf2 in the hippocampus of streptozotocin-induced diabetic rats, and Nrf2 enhanced the expression of antioxidant enzymes, as shown in Table S2 [154]. In addition, Que inhibited the expression of miR-27A, which improved memory function in diabetic rats.

6.5.2. Anti-obesity effect

Obesity is a major contributor to metabolic diseases, as indicated in Table S2 [155,156]. By activating the Nrf2 pathway, Que alleviated hepatic fat accumulation in high-fat diet-fed mice, promoting mitochondrial biogenesis and oxidative metabolism [155]. This resulted in improved liver function markers and the upregulation of pivotal genes associated with lipid metabolism, including *PGC-1α*, *PPAR-α*, *CTP-1*, and *Cyt-c oxidase* (complex IV), thus reducing lipid peroxidation and enhancing liver function markers in obese mice. In vitro experiments using co-cultured hepatocytes and macrophages further confirmed this finding [156]. Que activated the Nrf2 pathway, leading to the upregulated expressions of *HO-1*, *Arg-1*, and *Mrc1* and the suppressed expressions of inflammatory factors. These effects were impaired by the inhibition of HO-1 or the deficiency of *Nrf2*, highlighting the crucial role of the Nrf2/HO-1 pathway in mediating the beneficial effects of Que.

6.5.3. Anti-non-alcoholic fatty liver effect

Non-alcoholic fatty liver disease is closely associated with metabolic disorders, as detailed in Table S2 [157]. Que had a protective effect against L-thyroxin (LT4)-induced liver damage in hyperthyroid rats by activating the Nrf2 pathway [157]. Que mitigated the increase in the levels of thyroid hormones and oxidative stress markers while restoring the antioxidant markers and Nrf2 level in LT4-induced rats. Moreover, Que increased various protective markers and decreased detrimental markers in the liver. The liver-protective effect of Que was diminished in *Nrf2*-deficient rats, indicating the role of Nrf2 in mediating the protective mechanism of Que.

6.5.4. Effects on metabolic syndrome

Oxidative stress plays a crucial role in the development of metabolic syndrome. According to the data in Table S2 [158,159], Que alleviated oxidative stress in fatty liver of metabolic syndrome rats with metabolic syndrome through the Nrf2 pathway. In addition, Que increased the expression of key antioxidant enzymes, thereby improving the antioxidant capacity and reducing liver damage caused by metabolic syndrome [158]. Que treatment in high-fat diet-fed rats enhanced the expression of proteins associated with

antioxidant and fatty acid metabolism, such as HO-1, caspase-3, and CPT1, through Nrf2 activation [159]. Moreover, Que reduced NF-κB expression through Nrf2 activation, thereby attenuating oxidative stress and inflammation in metabolic syndrome.

6.6. Protective effects against cancer

Que has emerged as a potential drug for the treatment of cancer, because it can bidirectionally regulate the activity of the Nrf2 pathway. Que plays a crucial role in ameliorating oxidative stress-induced injury, inhibiting cancer cell proliferation and invasion, and maintaining intracellular redox homeostasis by regulating the Nrf2 pathway.

Que not only enhances the antioxidant capacity of cancer cells by activating Nrf2 but also inhibits the inflammatory response and counteracts the damaging effects of oxidative stress. In addition, Que also regulates other key processes during cancer progression, such as apoptosis and autophagy.

6.6.1. Liver cancer

Nrf2 deficiency is critical to cancer development, and Que inhibits cancer development by upregulating Nrf2 expression, as shown in Table S3 [160,161]. Granado-Serrano et al. [160] found that Que activated Nrf2 and promoted GSH-related antioxidant levels in HepG2 cells by targeting the p38/MAPK pathway, thereby attenuating apoptosis. Furthermore, the inhibition of p38 stabilized expression of *Nrf2*, which mechanistically explained the Que-mediated activation of the Nrf2 pathway through the p38/MAPK pathway. Moreover, Que enhanced the antioxidative capacity of the cells by activating the Nrf2/ARE signaling pathway, which promoted tumor apoptosis [161]. Que mediated activation of *Nrf2* resulted in a decrease in ROS level and an increased in ARE level in HepG2-C8 cells. Notably, Que increased the mRNA expressions of *HO-1*, *GST*, and *NQO1* through the Nrf2 pathway, highlighting its significant involvement in this process.

Interestingly, some authors have reported that Que inhibits the Nrf2 activity to inhibit cancer development. Marina et al. [162] found that Que reduced radiation-induced oxidative stress and Nrf2 expression, inhibiting the survival of hepatocellular carcinoma cells. Furthermore, Que demonstrated efficacy in attenuating hepatocellular carcinoma associated with hyperglycemia by inhibiting Nrf2 [163]. These findings provide valuable insights into the role of Que in mitigating Nrf2-associated cancers, as summarized in Table S3 [162,163].

6.6.2. Colon cancer

Organic compounds induce oxidative stress to cause cancer. Que inhibited colon cancer induced by 1,2-dimethylhydrazine in rats by enhancing the Nrf2/Keap1 signaling pathway [164]. Que increased the expression of Nrf2 by decreasing Keap1 expression, leading to the activation of antioxidant enzymes. This resulted in an inhibition of cell proliferation and a reduction in the production of ROS, MDA, and protein carbonyls in the colon tissues. Furthermore, Que inhibited 1,2-dimethylhydrazine-induced oxidative stress and DNA damage by activating Nrf2. This might be attributed to the induction of the base excision repair, which counteracted the oncogenic effects of 1,2-dimethylhydrazine.

Nevertheless, excessive upregulation of Nrf2 can contribute to the proliferation of colon cancer cells. Benzo(α)pyrene activated the AhR and Nrf2 pathways, promoting the proliferation of Caco-2 cells by increasing *AhR* expression, suppressing *AhR repressor* (*AhRR*) mRNA, and inducing the expression of cytochrome P450 family 1 (CYP1) target genes. Que, on the other hand, inhibits the production of Nrf2 and the expression of its target genes, such as glutathione reductase (*GR*), *GST*, and *CAT*. Additionally, Que reducesd *AhR* level, upregulatesd *AhRR* mRNA expression, and inhibits the proliferation of Caco-2 cells [165]. This dual mechanism highlighted the ability of Que to modulate Nrf2, effectively counteracting the oncogenic effects induced by compounds, as shown in Table S3 [164,165].

6.6.3. Leukemia

Leukemia is characterized by the release of high levels of free radicals and peroxides from cancer cells, which result in increased oxidative stress and damage to DNA and other biomolecules, Que inhibits the development of leukemia through the Nrf2 pathway, as indicated in Table S3 [166,167]. Que suppressed the growth of rat basophilic leukemia (RBL-2H3) cells by inducing the expressions of Nrf2 and HO-1. However, this effect was reversed by the HO-1 inhibitor SnPP [166]. Furthermore, Que facilitated the translocation of Nrf2 into the nucleus, upregulated HO-1 expression, and inhibited IgE-mediated degranulation in rodent mast cells. These observations indicated that Que activated Nrf2, leading to the induction of HO-1 and its metabolite carbon monoxide, which, in turn, inhibited the proliferation of leukemia cells.

Rubio et al. [167] further suggested the inhibitory effect of Que on the metabolic activity of NB4 leukemia cells through the Nrf2 pathway. Que inhibited Nrf2 expression in the nucleus by increasing the level of NF-κB p65. In addition, it decreased NF-κB p65 expression in the cytoplasm by increasing the level of Nrf2. Moreover, Que increased the levels of lipoxygenase, SOD, and antioxidants by upregulating Nrf2 expression.

6.6.4. Other cancers

The overexpression of Nrf2 contributes to cancer cell proliferation, as shown in Table S3 [168–170]. Que hindered breast cancer cell proliferation by modulating the Nrf2 pathway. By inhibiting Nrf2 expression, Que reduced the activities of antioxidant enzymes (HO-1 and NQO1), leading to decreased intracellular ROS production and enhanced cancer cell apoptosis [168]. Que and vitamin C (VC) downregulated Nrf2 gene and protein levels in PC3 cells, diminishing enzyme activities and improving sensitivity to both compounds.

In a 3D tumor model, Hundsberger et al. [169] validated the anti-tumor effect of Que mediated by Nrf2. Que activated the Nrf2/ARE pathway, suppressed ROS production, and relied on Nrf2-mediated ERK and NF-κB phosphorylation in melanoma spheroid cells. Additionally, Que induced overexpressions of *Nrf2*, *SOD*, *NQO1*, and *GCLC*, promoting ERK1/2 phosphorylation and inhibiting malignant tumor growth through Nrf2/ARE-related pathways.

Excessive Nrf2 proliferation was associated with certain malignancies. The upregulation of Nrf2 by Que impacted the drug sensitivity of malignant mesothelioma cells [170]. The knockdown of *Nrf2* resulted in increased levels of Bax, caspase-3, and PARP, while inhibiting the levels of Bcl-2 and Bcl-extra large (Bcl-xL). This shift highlighted heightened sensitivity to cisplatin, underscoring the detrimental impact of Nrf2 overexpression.

7. Availability, pharmacokinetics, pharmaceutics, and clinical studies on Que

7.1. Availability of Que

The flavonoid compound Que can be obtained from various plant parts. It is found in the stem bark, flowers, leaves, buds, seeds, and fruits of plants commonly consumed in our daily diet, such as hawthorn, sea buckthorn, onion, radish, root, tomato, pomegranate, japonica rice, and blackberry [171]. Que is also present in medicinal plants, such as Ginkgo biloba, Ginseng, Centella asiatica, and Hypericum [172,173]. However, the content of Que varies in different plants and their parts. The highest Que content was found in the outermost ring and the part closest to the root in red onions

[174]. Que can be obtained through plant extraction or chemical synthesis. However, traditional extraction methods are complex and environmentally unfriendly. Que extraction rates ranged from 13.38% to 15.64% from onion peel and 49.46%−56.88% from the pulp using the ultrasound-assisted extraction method [175]. The microwave-assisted extraction technique improved the extraction rates from onion peels by 20.3%−30.8% [176]. Interestingly, the use of nanobiocatalysts for extracting Que from onion peel demonstrated higher efficiency compared with other methods [177].

7.2. Pharmacokinetics of Que

Que, known for its diverse pharmacologic effects, is sourced from various plants. However, poor solubility, low bioavailability, and chemical instability posed challenges to its clinical applications.

7.2.1. Absorption

Que is orally administered, and stomach acids hydrolyze the glucose groups in the Que molecules to release free Que. The small intestine is the primary site of Que absorption [178−180]. The intestinal surface is covered with numerous villi that enhance the absorption. Que enters intestinal cells from the intestinal lumen through passive diffusion across cell membranes, driven by a concentration gradient. Following absorption, a fraction of Que molecules enter the circulation, whereas the remaining is transported to the liver through the portal system.

7.2.2. Distribution

Que is distributed in multiple organs, including the small intestine, colon, liver, and kidneys, after absorption. The highest concentration of Que was observed in the lungs of rats and the liver and kidneys of pigs [181]. These findings suggested that the tissue distribution of Que was variable among different species.

7.2.3. Metabolism

The biotransformation of Que primarily occurs through enzymes present in the small intestine and liver, resulting in the formation of methylated, sulfonyl-substituted, and glucuronidated metabolites [182]. Furthermore, Que undergoes ring fission in the small intestine and colon due to the activities of the intestinal microbiota. Consequently, the skeletal structure of Que is disrupted, giving rise to smaller phenolic compounds [183]. *Bacteroides fragilis*, *Lactobacillus rhamnosus, Clostridium perfringens, Bacteroides* JY-6, *Bifidobacterium* B-9, *Lactobacillus* L2, and *Streptococcus* S-2 converted Que into metabolites [184,185]. These findings underscore the crucial role played by biotransformation enzymes and intestinal microbiota for the effective use of Que, resulting in the generation of Que metabolites with modified chemical structures.

7.2.4. Excretion

Que tends to accumulate in organs involved in metabolism and excretion, and the highest concentrations are often observed in the mitochondria. The kidneys play a crucial role in the excretion of Que, and its urinary concentration increases in a dose and duration dependent manner [186]. Interestingly, carbon dioxide is identified as the primary metabolite of Que in humans, which is eliminated through the lungs [187]. Moreover, the glycosylated Que has higher absorption rates. The co-administration of Que with VC, folic acid, and other flavonoids enhances its bioavailability [188].

7.3. Pharmaceutics of Que

The clinical applications of Que are hindered by several factors, such as poor solubility, low bioavailability, and chemical instability. However, recent advancements in drug formulations research have paved way to improve the bioavailability of Que. Several nanoparticle drug carriers, such as liposomes, silver nanoparticles, silica nanoparticles, poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles, poly(lactic acid) (PLA) nanoparticles, polymeric micelles, and chitosan nanoparticles, have enhanced the antitumor effects of Que. Moreover, the formulation of antioxidant nanoparticles (QTiO2) improved the stability of Que, resulting in enhanced anti-fibrotic effects [189,190]. Que-loaded casein nanoparticles showed improved pharmacokinetic parameters in rat models [191]. Riva et al. [192] conducted a clinical trial and reported improvements in the oral absorption of Que-phospholipid complexes. Furthermore, Pluronic F127-coated Que micelles showed enhanced bioavailability and mitigated cisplatin-induced nephrotoxicity [193]. Some formulations, such as shell-type Que (ZCP-QE) and nuclear-type Que (ZCPE-Q), were prepared by encapsulating Que in a corn alcohol-soluble protein-based pilin emulsion. These formulations showed improved gastrointestinal absorption and oral bioavailability [194].

7.4. Clinical studies on Que

Several clinical studies have been conducted on the efficacy and safety of Que as a potential drug for the treatment of NCDs. Ferry et al. [195] conducted clinical trials using an intravenous injection of Que in patients with cancer, and demonstrated its safety and anticancer activity at a dose of 945 mg/m^2. However, higher doses of Que led to side effects, such as vomiting, hypertension, nephrotoxicity, and decreased serum potassium. A systematic review and meta-analysis of randomized controlled trials revealed that Que supplementation for $\geq$8 weeks at a dose of $\geq$500 mg/day substantially reduced fasting glucose levels in patients with metabolic syndrome and related disorders [196]. In addition, combining Zynamite®, a mango leaf extract containing the natural polyphenol mangostin, with Que enhanced recovery from exercise-induced muscle damage. Zynamite® (140 mg) and Que (140 mg) were administered 1 h before the strenuous damaging exercise, and three more doses were administered every 8 h after exercising. This regimen effectively reduced muscle pain and injury and accelerated the recovery of muscle performance [197]. The results of a randomized clinical trial indicated that consuming Que rich onion powder for 12 weeks might help prevent obesity and improve liver function [198]. No significant effects on the serum ICAM-1 or VCAM-1 concentrations were observed in patients with myocardial infarction after daily supplementation of 500 mg/day Que for 8 weeks. This finding suggested that Que supplementation does not have a significant effect on endothelial dysfunction biomarkers and depression levels [199].

Overall, Que has the potential to treat NCDs with promising efficacy and safety. It has anticancer activity, beneficial effects on blood glucose levels, enhances muscle recovery, ameliorates obesity, and improves liver function. However, its effects are variable on certain biomarkers and conditions. Therefore, the potential benefits and limitations of Que supplementation should be comprehensively evaluated in future studies.

8. Conclusions and future prospects

This review focuses on the potential of the role of Que in the treatment of NCDs, specifically focusing on its ability to counteract oxidative stress and inflammation by activating the Nrf2 signaling pathway. Oxidative stress and inflammation are particularly emphasized as key factors in the pathogenesis of NCDs such as neurodegenerative, cardiovascular, and metabolic diseases. The action of Que by the Nrf2 pathway not only enhances cellular

antioxidant defense mechanisms but also impacts on key cellular processes such as DNA repair and apoptosis, thus highlighting its importance in the treatment of NCDs.

However, the current research on Que also has limitations, primarily focusing on correlation analysis rather than causation. This limits the ability to translate laboratory findings into clinical practice. Future research should utilize rigorous experimental designs, such as randomized controlled trials and longitudinal cohort studies, to clarify the direct effects of Que on NCDs. Furthermore, the research should focus on identifying relevant biomarkers and delving into the mechanism of action of Que at the molecular level.

In terms of clinical application, it is crucial to determine the optimal dose, mode of administration, and treatment strategy for specific patient groups. It is also essential to conduct in-depth studies on the safety and tolerability of Que, including its interactions with other drugs, and its use in special populations such as pregnant women, children, and chronically ill patients. To comprehensively assess the therapeutic efficacy and safety of Que, extensive multicenter clinical trials are necessary. These trials should cover different populations and disease types to assess its long-term effects, optimal dosage, and potential side effects.

In addition, the study of the chemical stability of Que is essential to safeguard its therapeutic efficacy. Developing strategies to reduce oxidative degradation as well as optimizing absorption and metabolism processes are important to improve its bioavailability and stability. At the same time, a comprehensive risk assessment is necessary considering the safety and potential side effects of Que in long-term use, such as hepatotoxicity.

In conclusion, this review highlights the potential of Que to alleviate oxidative stress and inflammation in the treatment of NCDs by targeting the Nrf2 pathway. Future researches should focus on establishing causality, optimizing dosing, ensuring safety in different populations, and improving bioavailability and stability to effectively translate the therapeutic potential of Que into clinical practice for NCDs.

CRediT author statement

Li Zhang: Writing - Original draft preparation, Conceptualization, Visualization; **Li-Yue Xu** and **Fei Tang:** Writing - Original draft preparation, Data curation; **Dong Liu** and **Xiao-Lan Zhao:** Data curation, Investigation; **Jing-Nan Zhang** and **Jia Xia:** Writing - Reviewing and Editing, Visualization; **Jiao-Jiao Wu:** Writing - Reviewing and Editing, Supervision; **Yu Yang:** Data curation, Investigation; **Cheng Peng** and **Hui Ao:** Conceptualization, Writing - Reviewing and Editing, Funding acquisition.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

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