**Kelch-like ECH-associated protein 1-nuclear factor erythroid 2-related factor 2 Pathway Activation in Neuroprotection and Cognitive Enhancement**

Abstract

Neurodegenerative diseases and cognitive decline pose significant global health challenges. The Kelch-like ECH-associated protein 1 (Keap1) – nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is a master regulator of cellular defense against oxidative stress and inflammation, factors implicated in these conditions. This review examines the pivotal role of Keap1-Nrf2 pathway activation in promoting neuroprotection and cognitive enhancement. A comprehensive literature search was conducted across databases such as PubMed, Scopus, and Web of Science. Studies investigating direct activation of the Keap1-Nrf2 pathway, its downstream targets, and its impact on neuronal health and cognitive function were included. Activation of the Keap1-Nrf2 pathway leads to the transcription of antioxidant and cytoprotective genes, mitigating neuronal damage caused by reactive oxygen species and inflammatory mediators. Studies demonstrate that enhanced Nrf2 activity can protect against insults in models of Alzheimer's disease, Parkinson's disease, and stroke, improving neuronal survival and reducing neuroinflammation. Furthermore, this pathway positively influences synaptic plasticity and memory formation. The Keap1-Nrf2 pathway's robust antioxidant and anti-inflammatory actions position it as a promising therapeutic target. Strategies aimed at inhibiting Keap1 or directly activating Nrf2 show significant potential for ameliorating neurodegenerative processes and improving cognitive function. Activating the Keap1-Nrf2 pathway represents a compelling therapeutic strategy for neuroprotection and cognitive enhancement, offering a promising avenue for combating debilitating neurological disorders.

**Keywords:** Keap1, Nrf2, Neuroprotection, Cognitive Enhancement, Oxidative Stress,

**Introduction**

The nervous system, an extraordinarily complex and sophisticated network, stands as the body's central command center. It meticulously orchestrates a vast array of bodily functions, ranging from the simplest reflexes, such as blinking and withdrawing from pain, to intricate motor skills like playing a musical instrument or performing athletic feats. Beyond these physiological imperatives, the nervous system is the seat of higher-level cognitive processes, underpinning our capacity for learning, memory formation, reasoning, and complex decision-making. This intricate network relies on the precise communication between billions of neurons, interconnected through trillions of synapses, making it exquisitely sensitive to disruption (Sabina et al., 2024; Jékely et al., 2021). The very complexity and high metabolic demands of the nervous system render it particularly vulnerable to the damaging effects of oxidative stress and inflammation. Oxidative stress arises from an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them with antioxidants. These ROS can damage cellular components, including DNA, proteins, and lipids, leading to cellular dysfunction and death. Similarly, inflammation, while a necessary immune response, can become chronic and detrimental within the brain, triggering a cascade of events that exacerbate neuronal damage. These two interconnected imbalances are often exacerbated by aging, environmental factors (such as exposure to toxins and pollutants), genetic predisposition, and lifestyle choices (such as diet and exercise). Prolonged exposure to oxidative stress and inflammation can disrupt cellular homeostasis, leading to neuronal dysfunction, synaptic loss, impaired neurogenesis, and ultimately, cognitive decline – a debilitating hallmark of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease (Oyovwi & Udi, 2025; Kıran et al., 2023; Udi et al., 2022).

Recognizing this inherent vulnerability of the nervous system and the devastating consequences of neurodegenerative diseases, the fields of neuroprotection and cognitive enhancement have emerged as critical and rapidly evolving areas of scientific research. Neuroprotection aims to shield neurons from damage caused by various insults, including oxidative stress, inflammation, excitotoxicity, and genetic mutations, while simultaneously promoting their survival and functional integrity. Cognitive enhancement, on the other hand, seeks to improve cognitive abilities such as memory, attention, processing speed, and executive function, as well as enhance cognitive resilience against age-related decline and disease. These two fields are closely intertwined, as protecting neurons from damage is often a prerequisite for maintaining and improving cognitive function (Obukohwo et al., 2024; Karvandi et al., 2023; Andrew et al., 2017). At the heart of cellular defense mechanisms against oxidative stress and inflammation lies the Kelch-like ECH-associated protein 1 (Keap1) – Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway (Tao et al., 2024). This pathway functions as a master regulator, acting as a crucial sensor of cellular stress and orchestrating the expression of a diverse array of antioxidant, anti-inflammatory, and cytoprotective genes. In normal conditions, Keap1 binds to Nrf2 in the cytoplasm, targeting it for degradation. However, when cells are exposed to oxidative stress or inflammatory stimuli, Keap1 releases Nrf2, allowing it to translocate to the nucleus. Once in the nucleus, Nrf2 binds to antioxidant response elements (AREs) in the promoter regions of target genes, triggering their transcription. By modulating the levels of key enzymes and proteins involved in detoxification (e.g., glutathione S-transferases, heme oxygenase-1), redox balance (e.g., superoxide dismutase, catalase), and cellular repair (e.g., heat shock proteins, proteasome subunits), the Keap1-Nrf2 pathway plays a vital role in maintaining neuronal health, preserving synaptic function, and promoting cellular survival. Given its pivotal role in cellular defense and its ability to counteract the detrimental effects of oxidative stress and inflammation in the brain, activating the Keap1-Nrf2 pathway presents a promising and increasingly recognized therapeutic avenue for bolstering neurological health and enhancing cognitive performance. Modulating this pathway holds the potential to mitigate neuronal damage by reducing oxidative stress and inflammation, promote neuronal survival by enhancing cellular resilience, and improve cognitive outcomes in both healthy individuals seeking to optimize brain function and those at risk for or suffering from neurological disorders. This could involve preventing the onset of neurodegenerative diseases, slowing their progression, or alleviating their symptoms (Panda et al., 2022; Song et al., 2021; Saha et al., 2020).

This review will delve into the mechanistic details of the Keap1-Nrf2 pathway, elucidating its intricate regulatory mechanisms, including post-translational modifications and protein-protein interactions, and its diverse downstream effects on cellular function and gene expression. Furthermore, the study explore the pathway's potential to provide neuroprotection against a variety of insults, including ischemic stroke, traumatic brain injury, and neurotoxic exposure. We will also examine its ability to enhance cognitive function in different contexts, such as aging, stress, and neurodegenerative diseases, highlighting the evidence from preclinical and clinical studies. Finally, the review also shown the challenges and opportunities associated with targeting this pathway for therapeutic intervention, including the development of selective and potent Nrf2 activators, the optimization of treatment strategies, and the consideration of potential side effects. The ultimate goal of this review is to underscore the importance of the Keap1-Nrf2 pathway in combating neurological disorders, promoting healthy brain aging, and potentially unlocking novel strategies for preserving and enhancing cognitive function throughout the lifespan. The study also explore existing research and evidence that highlights the current understanding of the pathway's benefits and the potential for future development. This includes examining the latest findings on the efficacy of Nrf2 activators in clinical trials and identifying promising areas for future research, such as exploring the role of the Keap1-Nrf2 pathway in specific brain regions and in interaction with other cellular signaling pathways. By synthesizing the current knowledge and identifying remaining knowledge gaps, this review aims to contribute to the development of effective strategies for harnessing the power of the Keap1-Nrf2 pathway to protect and enhance the human brain.

**The Keap1-Nrf2 Pathway: Molecular Mechanisms**

The Keap1-Nrf2 pathway stands as a cornerstone of cellular defense, orchestrating a critical response to oxidative and electrophilic insults. This intricate mechanism is essential for maintaining cellular homeostasis and protecting cells from damage caused by reactive oxygen species (ROS) and other harmful electrophilic compounds. Central to the pathway's function are three key players: Keap1 (Kelch-like ECH-associated protein 1), Nrf2 (Nuclear factor erythroid 2-related factor 2), and the ARE (Antioxidant Response Element). Under normal physiological conditions, Keap1 acts as a vigilant repressor of Nrf2. This protein functions as an adaptor for a Cullin-based E3 ubiquitin ligase complex, constantly tagging Nrf2 for ubiquitination, which marks it for degradation by the proteasome. In essence, Keap1 ensures that Nrf2 levels remain low under basal conditions, preventing the unnecessary activation of antioxidant and detoxification pathways (Mukherjee & Gopalakrishnan, 2023; Panier et al., 2022).

Nrf2, a basic leucine zipper (bZIP) transcription factor, is the master regulator of the antioxidant response (Bathish et al., 2022). However, under normal circumstances, it remains largely quiescent in the cytoplasm, effectively tethered by Keap1. While present, Nrf2 is prevented from carrying out its transcriptional duties due to Keap1's constant surveillance and proteasomal targeting. The ARE is a specific and highly conserved DNA sequence located within the promoter regions of genes regulated by Nrf2. This cis-acting element serves as the binding site for the Nrf2 transcription factor, effectively acting as a switch that controls the expression of a wide array of cytoprotective genes. In a quiescent cell, Keap1's primary function is to facilitate the continuous ubiquitination and subsequent proteasomal degradation of Nrf2, thereby maintaining low basal levels of this key transcription factor. This ensures that the cell does not expend unnecessary resources on antioxidant defenses when not facing significant stress. However, when cells are confronted with oxidative or electrophilic stress, or exposed to other activating stimuli, the Keap1-Nrf2 pathway is rapidly activated. These stressors often trigger conformational changes in Keap1, often through the modification of critical cysteine residues within the protein. This modification disrupts Keap1's ability to effectively bind and ubiquitinate Nrf2. The disruption of the Keap1-Nrf2 interaction leads to Nrf2 stabilization. Freed from Keap1's grasp, Nrf2 escapes the clutches of the proteasome and accumulates in the cytoplasm. Stabilized Nrf2 can then undergo phosphorylation by various kinases, a modification that further enhances its stability and promotes its activation. Subsequently, Nrf2 translocates from the cytoplasm to the nucleus, the command center of the cell (Yu & Xiao, 2021; Otsuki & Yamamoto, 2020). Once inside the nucleus, Nrf2 is able to bind to the ARE. This binding event initiates the transcription of a diverse battery of cytoprotective genes, effectively launching a coordinated cellular defense program (Cuadrado, 2022; Shaw & Chattopadhyay, 2020). These downstream target genes encode a variety of proteins crucial for maintaining cellular health in the face of stress, including:

Antioxidant Enzymes: Proteins like heme oxygenase-1 (HO-1), superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) work to neutralize free radicals and ROS, mitigating oxidative damage.

Detoxification Enzymes: Enzymes such as glutathione S-transferases (GSTs) and NAD(P)H quinone oxidoreductase 1 (NQO1) facilitate the detoxification of harmful electrophiles and xenobiotics, protecting the cell from chemical damage.

Chaperones and Proteasomal Components: These proteins assist in protein folding, repair, and degradation, ensuring the proper function of cellular machinery and removing damaged or misfolded proteins.

Other Cytoprotective Proteins: A wide range of other proteins, including those involved in DNA repair, anti-inflammatory responses, and metabolic regulation, contribute to the overall cellular protection and adaptation to stress.

**Keap1-Nrf2 Pathway in Neuroprotection: A Critical Defense Against Neurodegenerative Diseases**

Oxidative stress and inflammation are recognized as central contributors to the pathogenesis of a wide range of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic Lateral Sclerosis (ALS), stroke, and Traumatic Brain Injury (TBI). These debilitating conditions are characterized by progressive neuronal damage, leading to loss of neurological function and ultimately, widespread deterioration (Anderson et al., 2023; Udi et al., 2018). Oxidative stress, an imbalance between the production of reactive oxygen and nitrogen species (ROS/RNS) and the body's antioxidant defense mechanisms, coupled with chronic inflammation, creates a toxic environment within the central nervous system, accelerating neuronal dysfunction and death (Oyovwi et al., 2025; Oyovwi et al., 2025; Udi, 2025). In the context of this neurodegenerative cascade, the Kelch-like ECH-associated protein 1 (Keap1)-Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway has emerged as a potent and promising therapeutic target for neuroprotection. Under normal physiological conditions, Nrf2 is sequestered in the cytoplasm by its repressor protein, Keap1. Keap1 facilitates the ubiquitination and subsequent proteasomal degradation of Nrf2, maintaining its levels low. However, in response to oxidative stress or exposure to certain chemical inducers, Nrf2 is released from Keap1. This allows Nrf2 to translocate to the nucleus, where it binds to the antioxidant response element (ARE) in the promoter region of numerous cytoprotective genes. These target genes encode a diverse array of antioxidant enzymes, detoxification proteins, and anti-inflammatory factors, including heme oxygenase-1 (HO-1), superoxide dismutase (SOD), glutathione S-transferase (GST), and NAD(P)H quinone oxidoreductase 1 (NQO1). Mounting evidence suggests that impaired Keap1-Nrf2 signaling is implicated in the progression of neurological disorders. Studies have shown that the expression and activity of Nrf2 are often reduced in affected brain regions of patients with neurodegenerative diseases, further emphasizing the importance of its activation. This compromised pathway weakens the brain's natural defense mechanisms, leading to increased vulnerability to oxidative damage and inflammation (Dong et al., 2023; Srivastava et al., 2022; Wang et al., 2021). Preclinical studies, utilizing both in vitro cell culture models and in vivo animal models, have consistently demonstrated the neuroprotective benefits of activating the Keap1-Nrf2 pathway (Segura-Aguilar & Mannervik. 2023). Activation strategies, often employing pharmacological agents that disrupt the Keap1-Nrf2 interaction, have been shown to:

**Protect against oxidative stress-induced neuronal damage:** By upregulating antioxidant enzymes, Nrf2 activation effectively neutralizes excessive ROS/RNS, preventing oxidative damage to lipids, proteins, and DNA within neurons.

**Reduce inflammation and glial activation:** Nrf2 activation can suppress the production of pro-inflammatory cytokines and chemokines, and modulate the activation of glial cells (astrocytes and microglia), thereby mitigating neuroinflammation.

**Attenuate neuronal apoptosis:** By promoting cell survival signaling pathways and inhibiting pro-apoptotic factors, Nrf2 activation helps to prevent programmed cell death in neurons.

**Preserve neuronal structure and function:** Through its protective mechanisms, Nrf2 activation contributes to the maintenance of neuronal integrity and the preservation of synaptic connectivity, crucial for proper brain function.

Furthermore, Nrf2 activation has shown promise in modulating protein aggregation, a hallmark of many neurodegenerative diseases. Specifically, it has been shown to influence the clearance and degradation of misfolded proteins, such as amyloid-beta plaques in AD and alpha-synuclein aggregates in PD. In animal models of these diseases, Nrf2 activation has demonstrated improvements in motor deficits, cognitive function, and other disease-related phenotypes, suggesting a potential for disease modification. While preclinical data are compelling, clinical studies investigating the efficacy of Keap1-Nrf2 activators in treating neurological diseases are still limited. However, the existing studies offer a glimmer of hope for future therapeutic interventions. Several clinical trials are currently underway, evaluating the safety and efficacy of Nrf2 activators in patients with AD, PD, ALS, and other neurological disorders. These trials are crucial for determining the translation potential of this therapeutic strategy (Mohan et al., 2025; Michalska & León, 2020).

Despite the promise, it is important to acknowledge the challenges and limitations associated with targeting the Keap1-Nrf2 pathway for neuroprotection. These include:

**Blood-brain barrier penetration:** Ensuring that Nrf2 activators can effectively cross the blood-brain barrier and reach the target brain regions is crucial for their therapeutic efficacy.

**Potential side effects:** Some Nrf2 activators may have off-target effects that could lead to adverse consequences. Careful consideration must be given to the safety profile of each activator.

**Disease stage specificity:** The effectiveness of Nrf2 activation may vary depending on the stage of the disease. It is possible that Nrf2 activation is more beneficial in the early stages of neurodegeneration.

**Individual variability:** Genetic factors and lifestyle factors can influence the responsiveness to Nrf2 activators, leading to variability in treatment outcomes.

**Keap1-Nrf2 Pathway and Cognitive Enhancement**

The Keap1-Nrf2 pathway has emerged as a promising therapeutic target for cognitive enhancement, particularly in the context of age-related cognitive decline and cognitive impairment seen in neurodegenerative diseases. Mounting evidence implicates oxidative stress and inflammation as significant contributors to these conditions. These processes inflict damage upon neuronal cells and disrupt crucial cognitive processes like learning, memory, and executive function. Notably, research suggests that Keap1-Nrf2 activity is diminished both in normal aging and in individuals suffering from cognitive disorders such as Alzheimer's disease, Parkinson's disease, and vascular dementia, further exacerbating the underlying pathology. Fortunately, preclinical models have demonstrated the potential of activating the Keap1-Nrf2 pathway to counteract these detrimental effects. Studies in animal models have shown a range of cognitive benefits following Keap1-Nrf2 activation, including improvements in learning and memory consolidation, enhancement of synaptic plasticity (the ability of synapses to strengthen or weaken over time, a crucial aspect of learning), increased neurogenesis (the generation of new neurons in the brain), and modulation of neurotransmitter systems, such as the glutamatergic, cholinergic, and dopaminergic systems, which are vital for optimal cognitive function. This activation appears to protect against cognitive deficits induced by a variety of stressors, including exposure to environmental toxins, traumatic brain injury, chronic stress, and the natural aging process itself (Bhat et al., 2024; Uruno& Yamamoto, 2023; Yu & Xiao, 2021).

The observed cognitive benefits are likely mediated through a complex interplay of mechanisms. Activation of the Keap1-Nrf2 pathway leads to the upregulation of antioxidant enzymes, effectively reducing oxidative stress and protecting neurons from free radical damage (Deshmukh et al., 2017). Furthermore, it mitigates inflammation by suppressing the production of pro-inflammatory cytokines and chemokines, thereby preventing neuronal damage caused by inflammatory processes. Keap1-Nrf2 activation appears to promote neuronal survival by enhancing the expression of neurotrophic factors and anti-apoptotic proteins (Mukherjee et al., 2025). While clinical studies examining the use of Keap1-Nrf2 activators for cognitive enhancement in humans are still limited, the preclinical data provides a strong rationale for further investigation into this pathway as a therapeutic target for improving cognitive function. However, several challenges remain. These include optimizing drug delivery methods to ensure sufficient brain penetration of Keap1-Nrf2 activators, addressing potential off-target effects of these activators, and accounting for individual variability in response to treatment based on genetic background, lifestyle factors, and disease stage. Overcoming these challenges will be crucial for translating the promising preclinical findings into effective therapies for age-related cognitive decline and neurodegenerative diseases.

**Strategies for Keap1-Nrf2 Pathway Activation**

Strategies for activating the Keap1-Nrf2 pathway, a critical regulator of cellular defense against oxidative stress, encompass a diverse range of approaches designed to bolster the body's natural antioxidant and detoxification systems (Li et al., 2025; Zhou et al., 2019). These approaches can be broadly categorized into pharmacological interventions and the utilization of dietary and natural compounds. Pharmacological interventions include the development and application of synthetic molecules specifically designed to modulate the Keap1-Nrf2 interaction. Direct Nrf2 activators, such as bardoxolone methyl, directly stimulate Nrf2 activity, bypassing the need to disrupt the Keap1 complex. Alternatively, Keap1 inhibitors, such as sulforaphane, commonly found in cruciferous vegetables like broccoli, and dimethyl fumarate, disrupt the binding affinity between Keap1 and Nrf2. This disruption leads to the release of Nrf2 from Keap1, allowing it to translocate to the nucleus, bind to antioxidant response elements (AREs), and initiate the transcription of genes encoding antioxidant and detoxification enzymes. Numerous other synthetic compounds are also under investigation for their Nrf2-activating capabilities, each with unique mechanisms and potential advantages. Understanding the specific mechanisms of action, efficacy, bioavailability, and potential side effects of these pharmacological agents is crucial for their safe and effective use in clinical settings and therapeutic applications. This includes evaluating potential drug interactions and long-term effects on cellular homeostasis (Crisman et al., 2023; Cuadrado et al., 2019).

Beyond pharmaceuticals, dietary and natural compounds offer promising and often more accessible avenues for Nrf2 activation. Cruciferous vegetables like broccoli, cabbage, and kale, turmeric (containing curcumin), green tea (containing epigallocatechin gallate, or EGCG), and resveratrol, found in grapes and red wine, are all known to possess Nrf2-activating properties. These compounds often act through diverse mechanisms, including directly or indirectly modulating Keap1 activity, influencing upstream signaling pathways that impact Nrf2 expression or stability, or acting as mild stressors that trigger the Nrf2 response. The potential benefits of these natural compounds extend beyond direct Nrf2 activation, as they often possess other health-promoting properties, such as anti-inflammatory and anti-cancer effects. While these natural compounds generally exhibit good safety profiles and are well-tolerated, their bioavailability, metabolism, and the extent of their health benefits require careful consideration. Factors such as individual variability in gut microbiome composition, dietary co-factors, and the specific form of the compound consumed can significantly influence their effectiveness. Further research is needed to optimize the delivery and utilization of these natural Nrf2 activators to maximize their therapeutic potential (Torrente & DeNicola, 2022; Thiruvengadam et al., 2021).

**Challenges and Future Directions**

The road ahead for Keap1-Nrf2 activator research presents a landscape of complex challenges intertwined with promising avenues for advancement (Mukherjee & Gopalakrishnan, 2023; Srivastava et al., 2022). A major obstacle remains the need for highly specific and selective targeting of the Keap1-Nrf2 interaction. Achieving this precision is critical to avoid inadvertently affecting other cellular processes and minimizing potential off-target effects that could lead to toxicity. Closely related to this is the challenge of deciphering dose-response relationships. Determining the optimal dosage of Keap1-Nrf2 activators is crucial, particularly given the considerable individual variability observed in response. This variability is influenced by a complex interplay of factors including an individual's genetic predisposition to Nrf2 activity and their history of environmental exposures.

To overcome these obstacles, future research must prioritize the development of more potent and highly selective Keap1-Nrf2 activators. These enhanced activators might also be used in conjunction with combination therapies that target complementary pathways, potentially leading to synergistic and more robust therapeutic outcomes. The promise of personalized medicine also looms large. Tailoring treatment strategies based on an individual's Nrf2 genotype and phenotype could revolutionize the way we approach Nrf2-based therapies, maximizing efficacy while minimizing adverse effects. Equally important is a thorough and rigorous evaluation of the long-term safety and efficacy profiles of Keap1-Nrf2 modulators. Comprehensive preclinical and clinical studies are essential to ensure that these interventions are both safe and effective before widespread clinical application. The successful translation of promising preclinical findings into clinically relevant treatments for neuroprotection and cognitive enhancement hinges on a more complete understanding of Nrf2's nuanced role within different brain cell types. This includes elucidating its intricate interplay with other vital signaling pathways operating within the brain, allowing for a more targeted and effective therapeutic approach. Ultimately, a multi-faceted approach addressing specificity, dosage, individual variability, and long-term effects is necessary to unlock the full therapeutic potential of Keap1-Nrf2 activation.

**Conclusion**

In conclusion, this exploration has illuminated the pivotal role of the Keap1-Nrf2 pathway in neuroprotection and cognitive enhancement, underscoring its significance as a central regulator of cellular defense against harmful stressors within the brain. Key findings demonstrate that activating this pathway, through various pharmacological or dietary interventions, can effectively combat oxidative stress (a major contributor to neuronal damage), dampen inflammation (a chronic process implicated in neurodegenerative diseases), and mitigate cellular damage (including protein aggregation and mitochondrial dysfunction). These protective effects are particularly crucial given that oxidative stress, inflammation, and cellular damage are all critical factors in the pathogenesis of neurological disorders and cognitive decline. Given its ability to bolster the brain's natural defense mechanisms by upregulating the expression of antioxidant enzymes, detoxification proteins, and anti-inflammatory mediators, modulation of the Keap1-Nrf2 pathway presents a promising therapeutic strategy for a range of debilitating conditions. This includes, but is not limited to, Alzheimer's disease (characterized by amyloid plaques and tau tangles), Parkinson's disease (marked by dopaminergic neuron loss), and age-related cognitive impairment (a gradual decline in memory and cognitive abilities).

Future research should focus on several crucial areas to translate the promise of Keap1-Nrf2 modulation into effective clinical therapies. This includes developing targeted and safe Nrf2 activators with improved bioavailability, specificity, and reduced off-target effects. Furthermore, exploring synergistic therapeutic combinations involving Nrf2 activators alongside existing treatments or other neuroprotective agents holds significant potential. Critically, rigorous clinical trials are needed to evaluate the efficacy and safety of Nrf2-based interventions in human populations, carefully assessing cognitive outcomes, biomarkers of brain health, and potential adverse effects. Such trials are essential to fully realize the potential of this pathway in improving neurological health and cognitive function. This avenue of research holds considerable promise for revolutionizing the treatment landscape for individuals affected by neurological and cognitive disorders, moving beyond symptomatic management to address the underlying cellular vulnerabilities. By harnessing the power of the Keap1-Nrf2 pathway, we can offer hope for enhanced quality of life, improved cognitive resilience, and ultimately, a future where age-related cognitive decline and neurodegenerative diseases are effectively managed and even prevented.

**Disclaimer (Artificial intelligence)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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