BULLETIN OF STOMATOLOGY AND MAXILLOFACIAL SURGERY
Volume 21, Issue 6

DOI: 10.58240/1829006X-2025.21.6-170

REVEW ARTICALE

NRF2 PATHWAY INVOLVEMENT IN THE CENTRAL NERVOUS SYSTEM

Rania Abd Elmonem Ali[1], Amal Taha Abou El Ghait[2], Safaa Said Ali[3],Eman Magdy Radwan[4], Fatma Yassin Meligy[5]

[1]*Department of Histology and Cell Biology, Faculty of Medicine, South Valley University, Qena, Egypt*
Email: *rania.abd_elmonem@med.svu.edu.eg.*
[2]*Histology and Cell Biology Department, Sphinx University, Assuit, Egypt Histology and Cell Biology Department, Faculty of Medicine, Assuit University, Assiut, Egypt*
[3.]*Department of Histology and Cell Biology, Faculty of Medicine, Merit University, New Sohag City, Sohag, EgyptHistology and Cell Biology Department, Faculty of Medicine, Assuit University, Assiut, Egypt*
[4] *Department of Medical Biochemistry, Faculty of Medicine, Assiut University, Assiut, Egypt Department of Biochemistry, Sphinx University, New Assiut, Egypt*
[5.]*Histology and Cell Biology Department, Faculty of Medicine, Assuit University, Assiut, Egypt, Department of Restorative Dentistry and Basic Medical Sciences, Faculty of Dentistry, University of Petra, Amman, Jordan*

*Corresponding author: Rania Abd Elmonem Ali *Department of Histology and Cell Biology, Faculty of Medicine, South Valley University, Qena, Egypt, E-mail: rania.abd_elmonem@med.svu.edu.eg.*
Received: *Jun 5, 2025;* ***Accepted:*** *Jul. 30, 2025;* ***Published:*** *Aug. 2,2025*

ABSTRACT

The nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway plays a fundamental role in cellular defense against oxidative and electrophilic stress. Within the central nervous system (CNS), where neurons and glial cells are highly susceptible to oxidative damage, Nrf2 has emerged as a master regulator of antioxidant and detoxification responses. Activation of Nrf2 upregulates a wide array of genes involved in maintaining redox balance, including heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), and enzymes responsible for glutathione synthesis. These adaptive responses help protect neurons from oxidative injury and support overall brain homeostasis. Dysregulation of Nrf2 signaling is increasingly recognized as a critical factor in the pathogenesis of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and multiple sclerosis, as well as in acute neurological injuries like ischemic stroke and traumatic brain injury. Pharmacological strategies to activate Nrf2, including synthetic compounds such as dimethyl fumarate and natural agents like sulforaphane, have shown promising neuroprotective effects in both experimental and clinical settings. This review provides a comprehensive discussion on the structure and regulation of the Nrf2 pathway, its physiological role in the CNS, its involvement in neurological diseases, and therapeutic approaches targeting Nrf2 signaling.

Keywords: Nrf2, oxidative stress, central nervous system, neurodegeneration, Keap1, antioxidant response, neuroprotection.

INTRODUCTION

The central nervous system (CNS) is one of the most metabolically active systems in the human body, requiring a constant supply of oxygen and glucose to sustain neuronal function. This high metabolic demand is supported by mitochondrial oxidative phosphorylation, a process that inherently produces reactive oxygen species (ROS) as byproducts. While physiological levels of ROS serve essential signaling roles, excessive accumulation disrupts cellular homeostasis and leads to oxidative stress [1].

The brain is particularly vulnerable to oxidative stress because of several intrinsic characteristics. It contains high concentrations of polyunsaturated fatty acids, which are prone to lipid peroxidation, and has relatively low levels of antioxidant enzymes compared to other organs. In addition, the presence of transition metals such as iron and copper facilitates the generation of free radicals through redox cycling. Persistent oxidative damage is implicated in the pathophysiology of numerous neurological disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, and

amyotrophic lateral sclerosis. Similarly, acute conditions such as ischemic stroke and traumatic brain injury involve dramatic increases in ROS production, contributing to neuronal death and functional impairment [2].

To counteract oxidative and electrophilic stress, cells have evolved adaptive defense systems that include enzymatic and non-enzymatic antioxidants. Among these, the Nrf2 signaling pathway has emerged as a central regulator of redox homeostasis. Nrf2 coordinates the transcription of genes involved in antioxidant defense, detoxification, and cellular stress responses. Understanding the role of Nrf2 in CNS physiology and pathology provides valuable insights into novel therapeutic strategies for neurological disorders [3].

2. Structure and Regulation of Nrf2 Pathway

Nrf2 (Nuclear factor erythroid 2-related factor 2) is a transcription factor that plays a central role in cellular defense against oxidative and electrophilic stress. It belongs to the Cap 'n' Collar (CNC) basic leucine zipper (bZIP) family and is encoded by the NFE2L2 gene. Its regulation is highly dynamic and involves multiple domains, interacting proteins, and signaling pathways [4].

2.1 Structural Domains of Nrf2

Nrf2 contains seven Nrf2-ECH homology (Neh) domains, each responsible for specific functions: [5].

- **Neh1:** Contains the CNC-bZIP motif, which allows DNA binding and dimerization with small Maf proteins to recognize antioxidant response elements (ARE) in target gene promoters.
- **Neh2:** Regulates stability via Keap1 interaction. It has DLG and ETGE motifs that bind Keap1, facilitating ubiquitination under basal conditions.
- **Neh3, Neh4, Neh5:** Act as transactivation domains, recruiting coactivators such as CBP/p300 to enhance transcription.
- **Neh6:** Contains serine-rich regions for Keap1-independent degradation mediated by β-TrCP and the SCF ubiquitin ligase complex.
- **Neh7:** Interacts with RXRα to inhibit Nrf2 activity, linking it to other signaling networks.

2.2 Keap1 as a Redox Sensor

Keap1 (Kelch-like ECH-associated protein 1) is the primary negative regulator of Nrf2. It functions as an adaptor for the Cullin-3 (Cul3)-based E3 ubiquitin ligase complex, promoting Nrf2 degradation under normal conditions. Keap1 contains reactive cysteine residues (e.g., Cys151, Cys273, Cys288) that act as sensors for oxidative and electrophilic stress. Modification of these cysteines during stress alters Keap1 conformation, releasing Nrf2 from degradation [6].

2.3 Activation Mechanisms

Under oxidative stress or exposure to electrophiles, cysteine modifications in Keap1 prevent Nrf2 ubiquitination, allowing its stabilization and nuclear translocation. In the nucleus, Nrf2 heterodimerizes with small Maf proteins and binds ARE sequences to initiate transcription of antioxidant, detoxification, and cytoprotective genes [7].

2.4 Keap1-Independent Regulation and Kinase Pathways

Nrf2 is also regulated via Keap1-independent mechanisms through phosphorylation by kinases such as PKC, MAPK (ERK, JNK, p38), PI3K/Akt, and AMPK, which influence its stability and transcriptional activity. The Neh6 domain enables degradation by β-TrCP under certain signaling conditions, adding another regulatory layer [8].

2.5 Crosstalk and Cellular Integration

Nrf2 interacts with several signaling pathways, including NF-κB (inflammation), PGC-1α (mitochondrial biogenesis), and AhR (xenobiotic metabolism). This integration ensures coordinated responses to oxidative stress and metabolic challenges [6].

In summary, Nrf2 regulation is a complex network involving structural domains, Keap1-dependent and independent pathways, and signaling crosstalk. This precision allows Nrf2 to maintain redox homeostasis and protect cells against oxidative damage [7].

3. Role of Nrf2 in CNS Physiology

The central nervous system (CNS) is uniquely vulnerable to oxidative stress because of its high metabolic activity, elevated oxygen consumption, and limited antioxidant defenses. Neurons require a continuous supply of energy for neurotransmission, ion homeostasis, and maintenance of membrane potentials, processes that depend heavily on mitochondrial oxidative phosphorylation. While this energy production is essential, it also generates reactive oxygen species (ROS) as inevitable byproducts. Under normal physiological conditions, ROS act as signaling molecules that regulate processes such as synaptic plasticity and neurogenesis. However, when ROS levels exceed the buffering capacity of the endogenous antioxidant system, oxidative stress occurs, leading to damage of

cellular components such as lipids, proteins, and DNA [9].

Nrf2 functions as a master transcriptional regulator that coordinates the expression of genes involved in antioxidant defense, detoxification, and maintenance of redox homeostasis in the CNS. Its physiological role extends beyond neuronal survival to encompass broader neuroprotective and metabolic functions [9].

3.1 Neuronal Protection and Antioxidant Defense

Neurons are highly susceptible to oxidative stress because of their low capacity for regeneration and high energy demands. Nrf2 activation in neurons upregulates the transcription of antioxidant enzymes such as heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), and superoxide dismutases. These enzymes reduce oxidative burden and maintain neuronal viability during transient episodes of oxidative stress. Additionally, Nrf2 promotes the synthesis of glutathione (GSH), the most abundant intracellular antioxidant. By enhancing glutamate-cysteine ligase expression, Nrf2 ensures sufficient GSH availability to detoxify ROS and reactive nitrogen species [10].

3.2 Astrocytic Contribution to Neuroprotection

Astrocytes play a critical role in CNS antioxidant defense, largely mediated by Nrf2 signaling. Compared to neurons, astrocytes exhibit higher basal and inducible Nrf2 activity, allowing them to act as a reservoir for antioxidant molecules. Astrocytes export glutathione precursors, such as cysteine and glutamate, to neurons through the astrocyte-neuron metabolic coupling system. This metabolic support enhances neuronal resilience to oxidative and metabolic stress. Nrf2 activation in astrocytes also modulates inflammatory signaling, preventing overactivation of microglia and reducing excitotoxic damage mediated by excessive glutamate release [11].

3.3 Regulation of Microglial Activity and Neuroinflammation

Microglia are the resident immune cells of the CNS and are rapidly activated in response to injury or infection. While microglial activation is necessary for pathogen clearance and debris removal, excessive or chronic activation leads to neuroinflammation and neuronal death. Nrf2 exerts anti-inflammatory effects by suppressing pro-inflammatory gene expression in microglia and promoting the production of antioxidant and cytoprotective molecules. Through crosstalk with the NF-κB signaling pathway, Nrf2 limits the release of pro-inflammatory cytokines such as TNF-α and IL-1β, thereby maintaining immune homeostasis in the CNS [12].

3.4 Oligodendrocyte Protection and Myelination

Oligodendrocytes, which are responsible for myelin sheath formation and maintenance, are highly sensitive to oxidative damage. Myelin synthesis requires substantial energy and involves oxidative reactions that generate ROS. Nrf2 activation protects oligodendrocytes from oxidative stress, thereby preserving axonal integrity and facilitating remyelination following injury. This function is particularly relevant in demyelinating disorders such as multiple sclerosis, where oxidative stress contributes to disease progression [13].

3.5 Maintenance of Blood-Brain Barrier Integrity

The blood-brain barrier (BBB) is a selective barrier that regulates the exchange of molecules between the blood and brain parenchyma. Oxidative stress compromises BBB integrity, resulting in increased permeability and infiltration of immune cells, which exacerbate neuroinflammation. Nrf2 signaling enhances the expression of antioxidant and detoxifying enzymes in endothelial cells, protecting the BBB from oxidative and inflammatory insults. This protective role is critical during pathological conditions such as stroke, trauma, and neurodegeneration [14].

3.6 Mitochondrial Homeostasis and Energy Metabolism

Nrf2 is increasingly recognized for its role in mitochondrial biogenesis and function. It regulates the expression of genes involved in mitochondrial antioxidant defense and influences the activity of transcriptional coactivators such as PGC-1α, which coordinate mitochondrial biogenesis. By maintaining mitochondrial integrity, Nrf2 ensures efficient ATP production and prevents the release of pro-apoptotic factors such as cytochrome c. This regulation is essential for sustaining neuronal excitability and synaptic function under physiological and stress conditions [12].

3.7 Synaptic Plasticity and Cognitive Function

Emerging evidence suggests that Nrf2 contributes to synaptic plasticity and cognitive performance. Nrf2-deficient animal models exhibit impaired learning and memory, which may be linked to oxidative damage, synaptic dysfunction, and impaired neurogenesis in the hippocampus. The antioxidant and anti-inflammatory effects of Nrf2 create an environment conducive to neuroplasticity, highlighting its importance for higher-order brain functions [14].

4. Nrf2 in Neurodegenerative Diseases

Neurodegenerative diseases are characterized by progressive neuronal loss, accumulation of misfolded proteins, and chronic oxidative stress. Nrf2 plays a protective role in these conditions by mitigating

oxidative damage, enhancing cellular detoxification, and reducing inflammation. However, Nrf2 signaling is often impaired in neurodegenerative disorders, which exacerbates disease progression [15].

4.1 Alzheimer's Disease (AD)

Alzheimer's disease is the most common cause of dementia, marked by amyloid-beta (Aβ) plaque deposition, neurofibrillary tangles composed of hyperphosphorylated tau, and chronic neuroinflammation. These pathological processes induce excessive ROS generation, leading to neuronal damage and synaptic dysfunction. Nrf2 activity is diminished in AD brains, particularly in neurons, resulting in reduced expression of antioxidant and detoxifying enzymes. Experimental activation of Nrf2 has been shown to improve cognitive performance, decrease Aβ accumulation, and enhance mitochondrial function in animal models. These findings suggest that Nrf2 induction may slow disease progression by reducing oxidative stress and neuroinflammation [16].

4.2 Parkinson's Disease (PD)

Parkinson's disease is characterized by dopaminergic neuronal loss in the substantia nigra and accumulation of α-synuclein aggregates. Mitochondrial dysfunction and oxidative stress are central to PD pathogenesis. Dopaminergic neurons are especially vulnerable because dopamine metabolism generates ROS, and their antioxidant capacity is relatively low. Reduced Nrf2 signaling has been observed in PD, leading to impaired detoxification of reactive species. Nrf2 activation in preclinical models of PD attenuates dopaminergic neuron degeneration, reduces α-synuclein aggregation, and improves motor function. Pharmacological agents such as dimethyl fumarate and natural compounds like sulforaphane show promise in modulating Nrf2 activity in PD [15].

4.3 Huntington's Disease (HD)

Huntington's disease is an autosomal dominant neurodegenerative disorder caused by expanded CAG repeats in the huntingtin gene, leading to mutant huntingtin protein accumulation. Oxidative stress and mitochondrial dysfunction contribute significantly to neuronal toxicity in HD. Nrf2-mediated antioxidant defenses are compromised in HD models, resulting in increased susceptibility to oxidative damage. Experimental enhancement of Nrf2 signaling improves mitochondrial function and reduces neuronal death in HD animal models, suggesting that Nrf2 is a viable therapeutic target [15].

4.4 Amyotrophic Lateral Sclerosis (ALS)

ALS involves progressive degeneration of upper and lower motor neurons, leading to muscle weakness and respiratory failure. Although the exact mechanisms remain unclear, oxidative stress, glutamate excitotoxicity, and protein aggregation are key contributors. Nrf2 expression and activity are significantly reduced in ALS, impairing the cellular antioxidant response. Genetic or pharmacological activation of Nrf2 has demonstrated neuroprotective effects in ALS models, improving motor neuron survival and extending lifespan in transgenic animals [17].

4.5 Multiple Sclerosis (MS)

Multiple sclerosis is an autoimmune demyelinating disorder characterized by chronic inflammation and neurodegeneration. Oxidative stress from activated immune cells contributes to demyelination and axonal injury. Nrf2 plays a crucial role in regulating the redox balance in oligodendrocytes and neurons. Dimethyl fumarate, an oral drug approved for MS treatment, exerts its therapeutic effect partly through Nrf2 activation, reducing oxidative damage and inflammation in the CNS [15].

5. Nrf2 in Acute Neurological Disorders

Acute neurological disorders such as ischemic stroke and traumatic brain injury (TBI) are leading causes of death and long-term disability worldwide. Both conditions are characterized by a primary insult followed by a complex secondary injury cascade involving oxidative stress, excitotoxicity, mitochondrial dysfunction, and inflammation. Nrf2 plays a critical role in mitigating these secondary injury mechanisms and promoting neuronal survival [18].

5.1 Ischemic Stroke

Ischemic stroke occurs when cerebral blood flow is obstructed, leading to a sudden deprivation of oxygen and glucose in brain tissue. The initial energy failure results in loss of ion homeostasis, excessive glutamate release, and neuronal depolarization. Reperfusion, while restoring blood supply, paradoxically exacerbates injury through a phenomenon known as **ischemia-reperfusion injury**, characterized by massive production of reactive oxygen species (ROS). These ROS damage lipids, proteins, and nucleic acids, trigger mitochondrial dysfunction, and activate apoptotic pathways [19].

Nrf2 activation during ischemic stroke provides neuroprotection through several mechanisms: [20].

- **Antioxidant Response**: Nrf2 induces expression of HO-1, NQO1, glutathione S-transferases, and enzymes involved in glutathione synthesis, reducing ROS burden.

- **Maintenance of Mitochondrial Function**: Nrf2 target genes preserve mitochondrial integrity and improve ATP production during reperfusion stress.
- **Anti-inflammatory Action**: By modulating NF-κB and cytokine signaling, Nrf2 dampens microglial activation and pro-inflammatory mediator release.
- **Blood-Brain Barrier (BBB) Protection**: Nrf2 enhances the expression of cytoprotective proteins in endothelial cells, maintaining BBB integrity and reducing edema formation.

Experimental Evidence:

Preclinical models consistently demonstrate that genetic deletion of Nrf2 worsens ischemic brain injury, while pharmacological activation of Nrf2 significantly reduces infarct size and improves neurological outcomes. Compounds such as dimethyl fumarate (DMF) and sulforaphane administered before or shortly after ischemic onset enhance Nrf2 activity and confer robust neuroprotection [21].

Therapeutic Potential:

The timing of Nrf2 activation is critical for stroke therapy. Pre-treatment provides maximum benefit, but post-treatment within a therapeutic window still offers significant protection. Clinical translation remains challenging, but the success of Nrf2 activators in other disorders (e.g., DMF in multiple sclerosis) supports their potential utility in stroke management [21].

5.2 Traumatic Brain Injury (TBI)

Traumatic brain injury results from external mechanical force causing primary mechanical damage to brain tissue. However, secondary injury mechanisms, including oxidative stress, excitotoxicity, calcium overload, and inflammation, contribute significantly to progressive neuronal loss and neurological dysfunction. ROS production increases dramatically after TBI due to mitochondrial dysfunction and activation of NADPH oxidases [21].

Role of Nrf2 in TBI: [22]

- **Redox Homeostasis**: Nrf2 activation elevates antioxidant defenses, reducing oxidative damage in neurons and glial cells.
- **Mitochondrial Protection**: By preserving mitochondrial membrane potential and reducing cytochrome c release, Nrf2 mitigates apoptosis.
- **Modulation of Neuroinflammation**: Nrf2 suppresses excessive microglial activation and reduces the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.
- **Autophagy Regulation**: Nrf2 interacts with autophagy pathways to facilitate the clearance of damaged organelles, reducing cellular stress.

Experimental Studies:

Animal models of TBI show that Nrf2-deficient mice exhibit greater neuronal death, larger lesion volumes, and worse behavioral outcomes. Conversely, pharmacological activators of Nrf2 improve cognitive and motor recovery. Natural compounds like sulforaphane and synthetic drugs like DMF have demonstrated beneficial effects in preclinical TBI studies [23].

Clinical Perspective:

Currently, there is no FDA-approved Nrf2 activator for TBI. However, the existing evidence provides a strong rationale for developing Nrf2-targeted therapies, potentially as adjunct treatments to surgical and supportive interventions [21].

5.3 Common Mechanistic Themes in Acute CNS Injury

Both ischemic stroke and TBI share common pathogenic processes: oxidative stress, mitochondrial failure, excitotoxicity, and inflammation. Nrf2 activation addresses these mechanisms simultaneously, offering a multifaceted neuroprotective strategy. In addition to its classical antioxidant role, Nrf2 influences autophagy, mitochondrial biogenesis, and iron metabolism, further supporting its central role in acute CNS injury recovery [24].

6. Therapeutic Targeting of Nrf2

Therapeutic modulation of Nrf2 represents a promising strategy for treating both neurodegenerative and acute neurological disorders. Pharmacological activation of Nrf2 enhances the cellular antioxidant defense system, reduces oxidative stress, and mitigates neuroinflammation. Approaches to targeting Nrf2 can be broadly divided into synthetic activators, natural compounds, gene therapy, and advanced molecular techniques [25].

6.1 Synthetic Activators

Several synthetic compounds activate Nrf2 primarily by modifying cysteine residues in Keap1, which disrupts its ability to ubiquitinate Nrf2, allowing the transcription factor to accumulate and translocate to the nucleus [25].

Dimethyl fumarate (DMF): DMF is one of the most well-studied Nrf2 activators and is approved for the treatment of multiple sclerosis (MS). It acts by

alkylating cysteine residues in Keap1, triggering Nrf2 stabilization and nuclear translocation. Clinical trials have demonstrated that DMF reduces relapse rates and slows disease progression in MS patients. Beyond MS, DMF exhibits neuroprotective effects in models of Parkinson's disease, Alzheimer's disease, and ischemic stroke [25].

Bardoxolone methyl: Initially developed as an anti-inflammatory and antioxidant agent, bardoxolone methyl is another electrophilic compound that modifies Keap1 cysteines. While it shows strong Nrf2 activation, its clinical application is limited by potential cardiovascular toxicity observed in some trials [26].

Oltipraz and other dithiolethiones: These compounds act as chemoprotective agents by enhancing phase II detoxification enzyme expression through Nrf2 activation. Their role in neuroprotection is under active investigation [26].

6.2 Natural Compounds

Dietary phytochemicals and plant-derived compounds represent a significant source of Nrf2 activators due to their ability to modify Keap1 or influence Nrf2-related signaling pathways [25].

Sulforaphane: A bioactive compound found in cruciferous vegetables, sulforaphane is one of the most potent natural inducers of Nrf2. It has demonstrated neuroprotective effects in models of traumatic brain injury, ischemic stroke, and neurodegenerative disorders by enhancing antioxidant and detoxifying enzyme expression [25].

Curcumin: Derived from turmeric, curcumin activates Nrf2 signaling and exhibits antioxidant, anti-inflammatory, and anti-amyloid properties, making it a candidate for Alzheimer’s disease therapy 25.

Resveratrol: A polyphenol present in grapes and berries, resveratrol promotes Nrf2 activity through multiple signaling pathways, including PI3K/Akt. It is being investigated for its potential benefits in aging-related cognitive decline and neurodegenerative diseases [25].

Epigallocatechin gallate (EGCG): Found in green tea, EGCG induces Nrf2 activity and has shown protective effects against oxidative stress and neurotoxicity in experimental models [25].

6.3 Gene Therapy and Molecular Approaches

Emerging gene therapy strategies aim to enhance Nrf2 expression or inhibit Keap1 using viral vectors or CRISPR/Cas9-mediated genome editing. These approaches have shown promise in preclinical studies but require further evaluation for safety and efficacy in humans [27].

6.4 Challenges in Therapeutic Targeting of Nrf2

While Nrf2 activation offers significant therapeutic potential, several challenges remain: [27].

- **Chronic activation risks:** Long-term, uncontrolled activation of Nrf2 may lead to altered metabolic regulation and potential oncogenic effects.
- **Tissue specificity:** Systemic activation could affect multiple organs, raising concerns about unintended effects.
- **Pharmacokinetics and bioavailability:** Many natural compounds suffer from poor absorption and rapid metabolism, limiting clinical utility.

7. Challenges and Future Perspectives

Although pharmacological activation of Nrf2 shows promise, several challenges remain. Chronic activation of Nrf2 may lead to adverse effects, including altered metabolism and potential promotion of tumorigenesis. Another challenge is achieving cell-specific activation, as indiscriminate Nrf2 stimulation could disrupt normal cellular signaling. Future research should focus on developing selective modulators and understanding the long-term consequences of Nrf2 activation. Clinical trials are needed to validate the efficacy and safety of Nrf2-based therapies in various CNS disorders.

8. CONCLUSION

The Nrf2 pathway plays a central role in maintaining redox homeostasis and protecting the CNS from oxidative and electrophilic stress. Dysregulation of Nrf2 signaling contributes to the pathogenesis of numerous neurodegenerative and acute neurological disorders. Therapeutic strategies that activate Nrf2 hold great potential for neuroprotection and disease modification. Continued research into the molecular regulation of Nrf2 and the development of selective activators may provide new avenues for the treatment of CNS diseases.

DECLARATIONS

Funding

Partially funded by Department of Prosthodontics, Faculty of Dentistry, Cairo University, Egypt.

Competing and conflicting Interests

The authors declare that they have no competing interests.

Ethical approval

The study protocol gained approval by the Committee of Ethics and Scientific Research, Faculty of Dentistry, Cairo University.

Informed consent

Informed consent was obtained from all participants.

REFERENCES

1.Ahmed T. Galal, Sayed A. Sayed, Hazem M.M .Abd-El-Gaffarb, Abd-El-Raheem Abd Rabo Sadk, Bothyna Z. Elsayed .(2024). Prenatal Ultrasonography in the Diagnosis of Neurological Fetal Anomalies with Postnatal Confirmation. SVU-InternationalJournal of Medical Sciences. Vol.7, Issue 2, pp: 273-289.

2.Heurtaux, T., Bouvier, D. S., Benani, A., Helgueta Romero, S., Frauenknecht, K. B., Mittelbronn, M., & Sinkkonen, L. (2022). Normal and pathological NRF2 signalling in the central nervous system. *Antioxidants*, *11*(8), 1426.

3.Silvestro, S., & Mazzon, E. (2022). Nrf2 activation: involvement in central nervous system traumatic injuries. A promising therapeutic target of natural compounds. *International journal of molecular sciences*, *24*(1), 199.

4.Zgorzynska, E., Dziedzic, B., & Walczewska, A. (2021). An overview of the Nrf2/ARE pathway and its role in neurodegenerative diseases. *International Journal of Molecular Sciences*, *22*(17), 9592.

5.Johnson, J. A., Johnson, D. A., Kraft, A. D., Calkins, M. J., Jakel, R. J., Vargas, M. R., & Chen, P. C. (2008). The Nrf2–ARE pathway: an indicator and modulator of oxidative stress in neurodegeneration. *Annals of the new York Academy of Sciences*, *1147*(1), 61-69.

6.Vargas, M. R., & Johnson, J. A. (2009). The Nrf2–ARE cytoprotective pathway in astrocytes. *Expert reviews in molecular medicine*, *11*, e17.

7.Yan, W., Wang, H. D., Hu, Z. G., Wang, Q. F., & Yin, H. X. (2008). Activation of Nrf2–ARE pathway in brain after traumatic brain injury. *Neuroscience letters*, *431*(2), 150-154.

8.Yang, Y., Jiang, S., Yan, J., Li, Y., Xin, Z., Lin, Y., & Qu, Y. (2015). An overview of the molecular mechanisms and novel roles of Nrf2 in neurodegenerative disorders. *Cytokine & growth factor reviews*, *26*(1), 47-57.

9.Tastan, B., Arioz, B. I., & Genc, S. (2022). Targeting NLRP3 inflammasome with Nrf2 inducers in central nervous system disorders. *Frontiers in immunology*, *13*, 865772.

10.Scannevin, R. H., Chollate, S., Jung, M. Y., Shackett, M., Patel, H., Bista, P., ... & Rhodes, K. J. (2012). Fumarates promote cytoprotection of central nervous system cells against oxidative stress via the nuclear factor (erythroid-derived 2)-like 2 pathway. *The Journal of pharmacology and experimental therapeutics*, *341*(1), 274-284.

11.Mazzuferi, M., Kumar, G., van Eyll, J., Danis, B., Foerch, P., & Kaminski, R. M. (2013). Nrf2 defense pathway: Experimental evidence for its protective role in epilepsy. *Annals of neurology*, *74*(4), 560-568.

12.Dai, W., Wang, H., Fang, J., Zhu, Y., Zhou, J., Wang, X., & Zhou, M. (2018). Curcumin provides neuroprotection in model of traumatic brain injury via the Nrf2-ARE signaling pathway. *Brain research bulletin*, *140*, 65-71.

13.van Muiswinkel, F. L., & Kuiperij, H. B. (2005). The Nrf2-ARE Signalling pathway: promising drug target to combat oxidative stress in neurodegenerative disorders. *Current Drug Targets-CNS & Neurological Disorders*, *4*(3), 267-281.

14.Paladino, S., Conte, A., Caggiano, R., Pierantoni, G. M., & Faraonio, R. (2018). Nrf2 pathway in age-related neurological disorders: insights into MicroRNAs. *Cellular Physiology and Biochemistry*, *47*(5), 1951-1976.

15.Wang, L., Zhang, X., Xiong, X., Zhu, H., Chen, R., Zhang, S., ... & Jian, Z. (2022). Nrf2 regulates oxidative stress and its role in cerebral ischemic stroke. *Antioxidants*, *11*(12), 2377.

16.Ayman Gamea, Hussein Bahey Eldeen Hussein, Fatma Gad Alkareem Ahmed,Tarek Desoky.(2024). Brain Volumetric Abnormalities, Cognitive and Psychological Profile of Patients with Conversion Neurological Symptoms. *SVU-International Journal of Medical Sciences*.Vol.7, Issue 2, pp: 724-732.

17. Islam Gadelrab Ahmed, Bassam Yahia Abd ELFattah Ewida,Mohamed Moslem Hefny , Ahmed Fathy Zaki. (2025). Cognitive Profile and Mood Disorders in Multiple Sclerosis patients in Upper Egypt. *SVU-International Journal of Medical Sciences*. Vol.8, Issue 1, pp: 1258-1275.

18.Tarek Desoky, Mohammed H. Hassan, Khaled Ahmed Elbeh, Mohamed Abdala Abbas ,Samer A. El-Sawy, Shimaa Fathy Sakr, Mahmoud Ahmed Bekiet, Reham Bakry Mohamed, Mohamed Moslem Hefny.(2024). Genetic polymorphisms of ACE2 G8790A (rs2285666) and Apo E (rs 121918398) in Alzheimer's disease among cohort of Egyptian patients: Relation to disease susceptibility and severity. *SVUInternational Journal of Medical Sciences*. Vol.7, Issue 2, : 325-339.

19.Tufekci, K. U., Civi Bayin, E., Genc, S., & Genc, K. (2011). The Nrf2/ARE pathway: a promising target to counteract mitochondrial dysfunction in Parkinson′ s disease. *Parkinson's disease*, *2011*(1), 314082.

20.Saha, S., Buttari, B., Panieri, E., Profumo, E., & Saso, L. (2020). An overview of Nrf2 signaling pathway and its role in inflammation. *Molecules*, *25*(22), 5474.

21.Sivandzade, F., Bhalerao, A., & Cucullo, L. Cerebrovascular and neurological disorders: protective role of NRF2. *International journal of molecular sciences*, 2019;*20*(14), 3433.

22.Joshi, G., & A. Johnson, J. The Nrf2-ARE pathway: a valuable therapeutic target for the treatment of neurodegenerative diseases. *Recent*

patents on CNS drug discovery.2012;*7*(3), 218-229.
23.Marini, P., Maccarrone, M., Saso, L., & Tucci, P. The Effect of Phytocannabinoids and Endocannabinoids on Nrf2 Activity in the Central Nervous System and Periphery. *Neurology international*;2024). *16*(4), 776-789.
24.Dinkova-Kostova, A. T., Kostov, R. V., & Kazantsev, A. G. The role of Nrf2 signaling in counteracting neurodegenerative diseases. *The FEBS journal*.2018;*285*(19), 3576-3590.
25.Gray, N. E., Farina, M., Tucci, P., & Saso, L. The role of the NRF2 pathway in maintaining and improving cognitive function. *Biomedicines*. 2022;*10*(8), 2043.
26.Ding, K., Wang, H., Xu, J., Li, T., Zhang, L., Ding, Y.,& Zhou, M. Melatonin stimulates antioxidant enzymes and reduces oxidative stress in experimental traumatic brain injury: the Nrf2–ARE signaling pathway as a potential mechanism. *Free Radical Biology and Medicine*.2014;*73*, 1-11.
.27Ahmed Fathi Zaki, Arwa Atef Abd Elfattah, Mohamed Moslem Hefny,Ayman Gamea. Post Stroke Fatigue; Frequency, Risk Factors, Radiological Topographic Localization and Impact on Quality of Life. *SVU-International Journal of Medical Sciences*. 2024; 7(2): 787-811.