ACCSCIENCE PUBLISHING

INNOSC Theranostics and Pharmacological Sciences

REVIEW ARTICLE

Therapeutic role of Nrf2/ARE pathway activation in chronic atrophic gastritis: Mechanisms, progress, and future perspectives

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Abstract

Chronic atrophic gastritis (CAG) is a prevalent and progressive gastric disorder that can lead to significant gastric dysfunction and an increased risk of gastric cancer. Oxidative stress plays a central role in the pathogenesis of CAG, contributing to cellular damage and inflammation. The nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway is crucial in cellular defense against oxidative stress by regulating the expression of antioxidant and cytoprotective genes. Activation of this pathway has shown promise in mitigating oxidative damage and promoting mucosal healing in CAG. This review aims to explore the therapeutic potential of Nrf2/ARE pathway activation in the context of CAG. We discuss the mechanisms underlying the activation of Nrf2, its role in regulating antioxidant genes, and its impact on oxidative stress management in the gastric mucosa. Recent advancements in pharmacological agents that activate the Nrf2 pathway, such as rhein and certain traditional Chinese medicines, are also highlighted. These interventions have demonstrated protective effects against oxidative stress, reduced inflammation, and promoted gastric mucosal healing. We, further, explore the potential clinical applications of Nrf2 activators in CAG treatment and the challenges in translating these findings into clinical practice. In addition, we outline future research directions aimed at optimizing Nrf2 activation strategies and exploring combination therapies to enhance therapeutic outcomes in CAG patients. The findings underscore the importance of targeting the Nrf2/ARE pathway as a promising strategy for managing oxidative stress-related gastric diseases.

Keywords: Nrf2/ARE pathway; Chronic atrophic gastritis; Antioxidant genes; Oxidative stress

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Citation: Wu W, Chen S, Su Y, Chen Y, Lin T, Liu Y. Therapeutic role of Nrf2/ARE pathway activation in chronic atrophic gastritis: Mechanisms, progress, and future perspectives. *INNOSC Theranostics and Pharmacological Sciences.* 2025;8(4):16-24.
doi: 10.36922/ITPS025130016

Received: March 30, 2025

1st revised: September 4, 2025

2nd revised: September 15, 2025

Accepted: September 19, 2025

Published online: October 22, 2025

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1. Introduction

Chronic atrophic gastritis (CAG) is an inflammatory gastric disorder involving progressive loss of gastric glandular cells, leading to mucosal atrophy and an increased

risk of gastric cancer. Key contributing factors include persistent *Helicobacter pylori* infection, autoimmune responses, and environmental influences. A central mechanism in CAG pathogenesis is oxidative stress, caused by an imbalance between reactive oxygen species (ROS) production and antioxidant defense. This imbalance promotes cellular damage, inflammation, and atrophy.

The nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway plays a critical role in combating oxidative stress. It regulates the expression of antioxidant and cytoprotective genes by binding to antioxidant response elements (AREs) in DNA. On activation, the Nrf2 proteins translocate to the nucleus and initiate the transcription of genes encoding enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, which collectively reduce oxidative damage and inflammation. Consequently, targeting the Nrf2/ARE pathway has emerged as a promising therapeutic strategy for CAG.

Compounds such as rhein have demonstrated protective effects in experimental models by activating Nrf2, reducing oxidative stress, and promoting mucosal healing.[1] Moreover, traditional Chinese medicine has also been explored for its efficacy in treating CAG, with various herbal formulations demonstrating potential in modulating the Nrf2/ARE pathway and improving clinical outcomes. This review aims to elucidate the latest research advancements regarding the involvement of the Nrf2/ARE signaling pathway in CAG, emphasizing its role in oxidative stress management and potential therapeutic strategies. By understanding the intricate relationship between oxidative stress, Nrf2 activation, and gastric mucosal integrity, we can better appreciate the therapeutic implications of targeting this pathway in the prevention and treatment of CAG and its associated complications.

2. Mechanistic basis of the Nrf2/ARE pathway

2.1. Activation sources and mechanisms of Nrf2

The Nrf2 protein is a pivotal transcription factor that orchestrates the cellular response to oxidative stress and electrophilic insults. Its activation is primarily regulated by the Kelch-like ECH-associated protein 1 (Keap1) complex, which serves as a sensor for oxidative stress. Under normal conditions, Nrf2 is maintained in the cytoplasm through its interaction with Keap1, leading to its ubiquitination and subsequent proteasomal degradation. However, on exposure to oxidative stressors, such as ROS and electrophiles, specific cysteine residues on Keap1 are modified, resulting in the dissociation of Nrf2 from Keap1. This release allows Nrf2 to translocate into the nucleus, where it binds to the ARE in the promoter regions of target genes, initiating the transcription of various cytoprotective and detoxifying enzymes, such as heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1). This classical activation mechanism and the interaction between Nrf2 and Keap1 are summarized in Figure 1. Recent studies have highlighted the role of additional regulatory proteins, such as p62, which can further enhance Nrf2 activation by promoting the degradation of Keap1 through selective autophagy, thereby establishing a positive feedback loop that amplifies the antioxidant response during prolonged oxidative stress exposure.[2,3]

2.2. Interaction between Nrf2 and ARE

The interaction between Nrf2 and ARE is crucial for the transcriptional activation of genes involved in cellular defense mechanisms. Nrf2 forms a heterodimer with small musculoaponeurotic fibrosarcoma proteins, which facilitates its binding to ARE sequences located in the promoter regions of target genes. This binding is essential for the recruitment of co-activators and the assembly of the transcriptional machinery necessary for gene expression. Once activated, Nrf2 not only promotes the expression of antioxidant enzymes but also regulates genes involved in cellular metabolism and inflammation, thus playing a comprehensive role in maintaining redox homeostasis. Furthermore, the Nrf2/ARE signaling pathway has been implicated in various pathophysiological conditions, including neurodegenerative diseases, where dysregulation of this pathway can lead to increased oxidative stress and neuronal damage.[3,4]

2.3. Regulation and expression of antioxidant genes

The Nrf2/ARE pathway serves as a central regulator of antioxidant gene expression, critical for cellular defense against oxidative stress. On activation, the Nrf2 proteins translocate to the nucleus and bind to AREs, initiating the transcription of key enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase. These enzymes act synergistically to neutralize ROS and limit oxidative damage. Beyond enzymatic antioxidants, Nrf2 also upregulates phase II detoxifying enzymes that promote xenobiotic clearance. The regulation of this pathway is modulated through epigenetic mechanisms, including histone acetylation and methylation, as well as post-translational modifications of Nrf2, which fine-tune its transcriptional activity. This intricate regulation highlights the importance of the Nrf2/ARE system in redox homeostasis and its potential as a therapeutic target in oxidative stress-related diseases.[4-6]

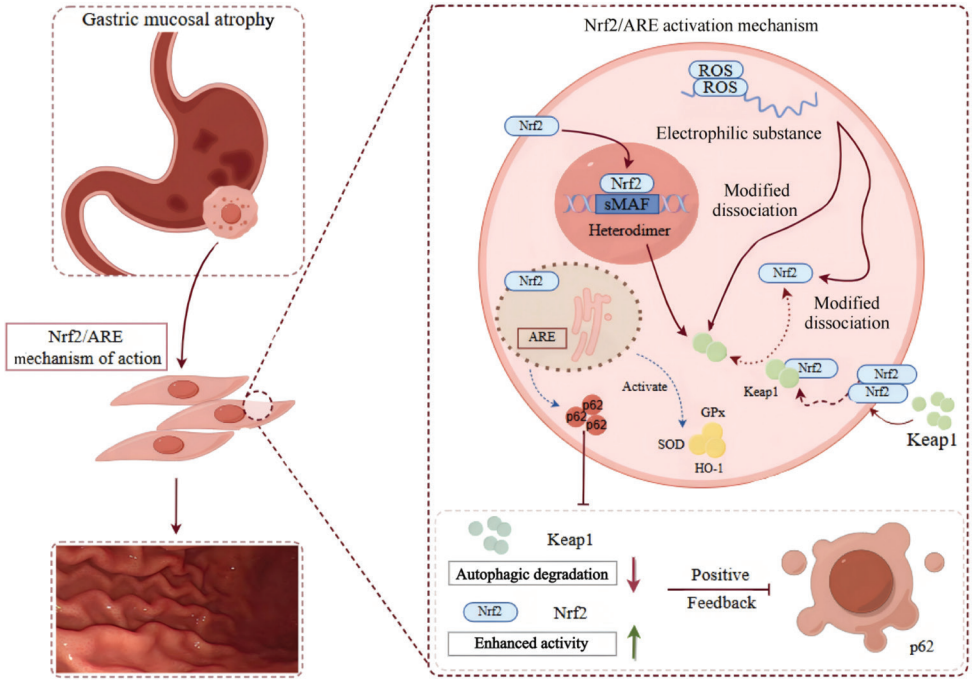


Figure 1. Schematic diagram illustrating the activation mechanism of the Nrf2/ARE pathway. Image created by the authors using Figdraw.com.
Abbreviations: ARE: Antioxidant response element; GPx: Glutathione peroxidase; HO-1: Heme oxygenase-1; Keap1: Kelch-like ECH-associated protein 1; Nrf2: Nuclear factor erythroid 2-related factor 2; ROS: Reactive oxygen species; sMAF: Small musculoaponeurotic fibrosarcoma; SOD: Superoxide dismutase.

3. The impact of acute oxidative stress on the gastric mucosa

3.1. Sources and mechanisms of oxidative stress

Acute oxidative stress in the gastric mucosa can arise from various sources, including exogenous factors such as alcohol consumption, non-steroidal anti-inflammatory drugs (NSAIDs), and infections like *H. pylori* infection. These factors lead to the generation of ROS, which can overwhelm the antioxidant defenses of gastric epithelial cells. For example, ethanol exposure has been shown to induce oxidative stress by increasing the production of malondialdehyde and decreasing antioxidant enzyme activities, such as those of superoxide dismutase and glutathione peroxidase, in gastric tissues.[7] Furthermore, *H. pylori* infection is associated with a cascade of inflammatory responses that exacerbate oxidative stress, resulting in cellular apoptosis and impaired regeneration of the gastric mucosa.[8] The mechanisms through which oxidative stress affects gastric tissues include the activation of pro-inflammatory signaling pathways, such as the nuclear factor-kappa B (NF-κB) pathway, which leads to the upregulation of inflammatory cytokines, including tumor necrosis factor-alpha and interleukin 6, contributing to mucosal injury.[9] In addition, oxidative stress can trigger endoplasmic reticulum stress, further promoting apoptosis in gastric epithelial cells.[10] The central role of oxidative stress in gastric mucosal injury and its interplay with the Nrf2 pathway is summarized in Figure 2. Understanding these sources and mechanisms is crucial for developing therapeutic strategies to mitigate oxidative stress-related gastric injuries.

3.2. Cellular responses to oxidative stress exposure

When gastric epithelial cells are exposed to acute oxidative stress, they exhibit a range of cellular responses aimed at counteracting the damaging effects of ROS. These responses include the activation of antioxidant defense mechanisms and the initiation of repair pathways. For example, studies have demonstrated that treatment with protective agents, such as rebamipide, can significantly reduce apoptosis in gastric epithelial cells exposed to ethanol, primarily by inhibiting endoplasmic reticulum stress and enhancing autophagy-related pathways.[11] In addition, polysaccharides derived from natural sources, such as *Lachnum*, have been shown to improve oxidative stress responses by enhancing the activities of antioxidant enzymes and reducing levels of pro-inflammatory cytokines.[11] Moreover, the application of dietary antioxidants, such as those found in apple leaves, has been linked to decreased oxidative stress and enhanced

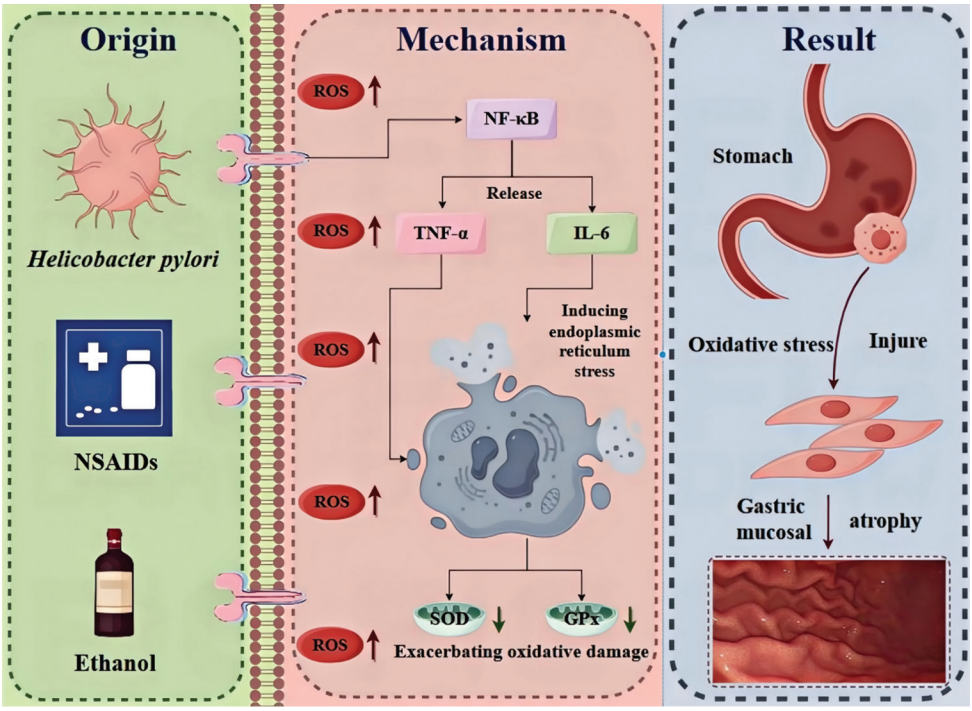


Figure 2. Relationship between oxidative stress and the Nrf2/ARE pathway in CAG. Image created by the authors using Figdraw.com.
Abbreviations: GPx: Glutathione peroxidase; IL-6: Interleukin 6; NF-κB: Nuclear factor-kappa B; NSAID: Non-steroidal anti-inflammatory drug; ROS: Reactive oxygen species; SOD: Superoxide dismutase; TNF-α: Tumor necrosis factor-alpha.

healing of gastric mucosa following injury.[12] These cellular responses highlight the potential for pharmacological interventions to bolster the gastric mucosa's resilience against oxidative stress, thereby promoting mucosal integrity and healing. Furthermore, the interplay between oxidative stress and cellular signaling pathways, including the mitogen-activated protein kinase and NF-κB pathways, underscores the complexity of the gastric mucosal response to oxidative challenges.[13]

4. The role of the Nrf2/ARE pathway in CAG

4.1. The relationship between Nrf2 expression levels and disease progression

The Nrf2 protein is a pivotal transcription factor that regulates the expression of antioxidant and cytoprotective genes in response to oxidative stress. In CAG, the expression levels of Nrf2 can be indicative of disease progression. Studies suggest that reduced Nrf2 activity is associated with increased oxidative stress and inflammation, both of which are key contributors to the pathogenesis of CAG. For example, the activation of the Nrf2/ARE pathway has been shown to counteract oxidative damage and promote cell survival in various tissues, including the gastric mucosa. In patients with CAG, diminished Nrf2 levels correlate with heightened oxidative stress markers and inflammatory cytokines, suggesting a potential link between Nrf2 downregulation and disease severity. Furthermore, specific genetic or epigenetic modifications affecting the Nrf2 pathway may exacerbate the progression of gastritis by impairing the protective mechanisms normally conferred by Nrf2 activation.

Beyond the expression of Nrf2, the activity of the Nrf2 signaling pathway and the expression of its downstream target genes, such as *NQO1* and *HMOX1*, have emerged as promising biomarkers for assessing the risk of CAG progression and predicting therapeutic response. Research indicates that the expression levels of NQO1 and HO-1 are significantly correlated with patient prognosis. For example, in gastric cancer tissues, high expression of NQO1 serves as an independent risk factor predicting shorter overall survival and poorer progression-free survival.[14] In terms of treatment prediction, hyperactivation of Nrf2 signaling is closely associated with resistance to chemotherapeutic agents such as 5-fluorouracil.[15] This suggests that detecting Nrf2 signaling activity in tissues could help identify chemotherapy-insensitive populations and provides a rationale for combining Nrf2 inhibitors to reverse drug resistance.

This relationship underscores the importance of Nrf2 as a potential biomarker for assessing the severity of CAG

and highlights the need for therapeutic strategies aimed at enhancing Nrf2 signaling to mitigate disease progression and improve patient outcomes.

4.2. The impact of Nrf2-mediated antioxidant effects on gastric mucosal repair

The Nrf2/ARE signaling plays a key role in gastric mucosal repair, particularly in CAG. Activation of Nrf2 enhances the expression of cytoprotective genes, including *HMOX1*, glutathione S-transferases, and *NQO1*, which collectively alleviate oxidative damage and support mucosal healing. In experimental models of gastric injury, Nrf2 activation has been shown to reduce ROS levels, enhance mucosal integrity, and accelerate repair processes. Furthermore, several natural compounds that activate Nrf2 have demonstrated therapeutic potential in promoting gastric mucosal regeneration in CAG. Thus, targeting the Nrf2/ARE pathway represents a promising strategy for treating gastric mucosal injury and facilitating repair in conditions such as CAG.[16,17]

4.3. The dual-edged sword effect and potential risks of Nrf2 activation

Although Nrf2 activation plays a key role in the antioxidant protection in CAG, it must be recognized that its effects are not entirely beneficial. Extensive studies have shown that sustained and excessive activation of Nrf2 may promote tumor cell survival, proliferation, and drug resistance, acting as a "tumor-promoting factor." In gastric tissue, the Nrf2 pathway normally exerts cytoprotective effects by regulating antioxidant gene expression. However, during gastric carcinogenesis, persistent activation of this pathway, often due to Keap1 mutations or epigenetic alterations, instead enhances tumor cell survival, invasion, and chemoresistance by inhibiting apoptosis, promoting angiogenesis, and upregulating multidrug resistance proteins, highlighting the distinct dual-edged sword nature of Nrf2 in gastric cancer.[18,19] It is noteworthy that sustained activation of Nrf2 may promote tumorigenesis in certain contexts, particularly against a background of pre-existing immune-mediated damage in the gastric mucosa. For example, in autoimmune gastritis, chronic inflammation and epithelial remodeling create a microenvironment conducive to gastric carcinogenesis, and aberrant activation of Nrf2 could potentially exacerbate this process.[20]

5. Experimental and clinical research progress

5.1. Research on Nrf2 activation in animal models

The Nrf2 protein has emerged as a critical transcription factor in mediating cellular responses to oxidative stress. Research utilizing animal models has demonstrated the significant role of Nrf2 activation in various pathological conditions. For example, research has shown that Nrf2 activation can alleviate neuroinflammation and reduce tissue injury in neurological conditions, attenuate oxidative and inflammatory damages following acute injury, and protect against ischemia-reperfusion injury in transplantation models by inhibiting NF-κB activation.[21,22] These findings collectively underscore the importance of Nrf2 as a modulator of oxidative stress and inflammation across various experimental models, providing a robust foundation for its exploration in clinical settings.

5.2. Clinical cases and the efficacy of Nrf2 regulation

Clinical research has increasingly focused on the therapeutic implications of Nrf2 modulation in various diseases. In patients with coronary heart disease, studies have shown that treatment with nicorandil combined with trimetazidine resulted in decreased levels of serum miR-223-3p and Nrf2, correlating with improved clinical outcomes.[23] In addition, in the context of autoimmune diseases, the activation of the Nrf2 pathway has been associated with reduced inflammation and oxidative stress, suggesting that Nrf2 activators may serve as potential therapeutic agents.[24] In the realm of cancer, particularly hepatocellular carcinoma, overexpression of Nrf2 has been linked to poor prognosis, indicating that while Nrf2 activation can confer protective effects against oxidative stress, its dysregulation may facilitate tumor progression.[25] Moreover, recent insights into the role of Nrf2 in modulating the immune response during COVID-19 highlight its potential as a therapeutic target in managing hyperinflammation associated with the disease.[26]

Although Nrf2 activators show promise in monotherapy, their interactions in combination therapies, which are particularly significant for patients with CAG who often require polypharmacy, remain unclear. For example, NSAIDs are common triggers of gastric mucosal injury. Although Nrf2 activators could theoretically mitigate such damage, their metabolic interactions with NSAIDs and the long-term safety of combination therapy require further investigation.[27] On the other hand, Nrf2-mediated HO-1 induction enhances the protective effect of proton-pump inhibitors against NSAID-induced gastric injury, extending beyond acid suppression alone.[28] However, the hypoacidic environment caused by proton-pump inhibitors may also affect the bioavailability of certain Nrf2 activators, potentially leading to a conflict with their mucosal protective goals, a matter warranting further exploration. Risk–benefit assessment is especially critical for CAG patients who require long-term NSAID use due to cardiovascular disease or arthritis. Future studies should employ more sophisticated preclinical models and well-designed clinical trials to thoroughly investigate

the pharmacokinetic and pharmacodynamic interactions between Nrf2 activators and commonly used drugs, thereby facilitating the development of safe and effective individualized treatment strategies.

Collectively, these clinical findings illustrate the dual nature of Nrf2 regulation, emphasizing the need for a nuanced approach in targeting this pathway for therapeutic interventions across a spectrum of diseases.

5.3. Challenges and limitations in translational medicine

There exists a significant "translational gap" in current research. Translating the remarkable efficacy observed in animal models into clinical benefits for human patients faces multiple challenges. First, the complexity and heterogeneity of human diseases are far greater than those of experimental animal models. Second, natural compounds, such as sulforaphane and curcumin, generally suffer from low bioavailability.[29,30] Determining their optimal effective dosage, administration routes, and therapeutic windows in humans is crucial, yet remains insufficiently studied. Finally, the dual role of Nrf2 necessitates long-term and rigorous safety evaluations of its activators, especially in populations at risk for gastric cancer. Most existing clinical studies are small-scale and short-term observations, lacking large-scale, randomized, double-blind, and placebo-controlled clinical trials to confirm their efficacy and safety.

6. Future research directions

6.1. Development and application of Nrf2 agonists

The Nrf2 pathway is a pivotal regulator of cellular defense against oxidative stress, making it a promising therapeutic target for conditions driven by such mechanisms, including CAG. Recent studies have highlighted the potential of both natural and synthetic Nrf2 agonists to enhance antioxidant responses and mitigate cellular damage. For example, compounds such as sulforaphane and bardoxolone methyl have shown efficacy in activating Nrf2, increasing the expression of downstream antioxidant enzymes, and improving cellular resilience against oxidative stress.[31,32] Critically, despite a strong mechanistic rationale, robust clinical evidence supporting the use of Nrf2-targeting therapies in CAG patients is still lacking. This highlights a significant gap in translational medicine. Future efforts must prioritize the development of highly specific and safe Nrf2 agonists and rigorously evaluate their efficacy in dedicated *in vivo* models of CAG and early-phase clinical trials. Particular attention should be paid to optimizing dosing regimens and developing novel delivery systems, such as nanoparticle-based systems, thereby enhancing the bioavailability and effectiveness of Nrf2 activators in clinical settings.[33] Furthermore, given the context-dependent role of Nrf2, especially its ambiguous function in carcinogenesis,[34] future studies must carefully assess the long-term safety and disease-stage-specific therapeutic window of these agents in the context of CAG and its progression to gastric cancer.

6.2. Exploration of combination therapy strategies

The complexity of many diseases, particularly chronic conditions such as metabolic syndromes, cancers, and neurodegenerative diseases, has prompted increasing interest in combination therapy strategies. These strategies aim to enhance therapeutic efficacy by targeting multiple pathways simultaneously, thus overcoming limitations associated with monotherapy, such as drug resistance and insufficient treatment response.[32,35] For example, combining Nrf2 agonists (Table 1) with other pharmacological agents

Table 1. Summary of Nrf2 activators and potential therapeutic applications

Nrf2 activator	Source	Potential therapeutic applications	Mechanism of action	Stage of development	Limitations/ considerations
Sulforaphane	Natural compound (cruciferous vegetables)	• Cardiovascular diseases • Neurodegenerative disorders • Cancer prevention	• Direct activation of Nrf2 • Increases antioxidant enzyme expression	Clinical trials	Dosage and bioavailability challenges
Bardoxolone methyl	Synthetic compound	• Chronic kidney disease • Inflammatory conditions	• Potent Nrf2 pathway activation • Reduces oxidative stress	Approved	Potential pro-inflammatory effects in some contexts
Rhein	Natural compound (traditional Chinese medicine)	• Chronic atrophic gastritis • Anti-inflammatory treatments	• Modulates Nrf2 pathway • Reduces oxidative stress in the gastric mucosa	Preclinical	Limited long-term safety data
Curcumin	Natural compound (turmeric)	• Neurological disorders • Metabolic syndrome • Cancer prevention	• Indirect Nrf2 activation • Suppresses inflammatory pathways	Preclinical	Poor bioavailability
Polysaccharides	Natural compounds	• Gastric mucosal protection • Antioxidant therapy	• Enhances antioxidant enzyme activities • Reduces pro-inflammatory cytokines	Preclinical	Variability in extraction and potency

Abbreviation: Nrf2: Nuclear factor erythroid 2-related factor 2.

has shown promise in preclinical studies, particularly in enhancing antioxidant defenses and reducing inflammation in various models of disease.[33,34] Moreover, the integration of Nrf2 agonists with immunotherapies has the potential to improve outcomes in cancer treatment by modulating the tumor microenvironment and enhancing immune responses.[31] Future research should prioritize the identification of synergistic drug combinations through rigorous preclinical and clinical trials, focusing on understanding the underlying mechanisms of action and the potential for adverse interactions among combined therapies. The development of personalized medicine approaches, which tailor combination strategies based on individual patient profiles and disease characteristics, represents a promising avenue for improving treatment outcomes and minimizing side effects.

7. Conclusion

The Nrf2/ARE signaling pathway has gained considerable interest as a promising therapeutic target for CAG. Activation of this pathway enhances the expression of antioxidant genes, thereby alleviating oxidative stress and its damaging effects on the gastric mucosa. While the protective role of Nrf2 activators against oxidative damage is well-established, existing studies present variability in the choice of agents, dosages, and clinical applications. These inconsistencies underline the need for more standardized research approaches to better evaluate their therapeutic potential. Future efforts should focus on translating promising preclinical results into clinical practice, addressing not only efficacy but also safety, side effects, and drug interactions. Research is also needed to clarify the mechanisms behind Nrf2-mediated protection and to identify predictive biomarkers for patient response. Such insights will help in developing personalized treatments for CAG. The therapeutic potential of the Nrf2/ARE pathway in CAG is evident, yet it requires further exploration to fully realize its clinical benefits. By addressing the gaps in current research and fostering collaboration among scientists, clinicians, and pharmaceutical developers, we can pave the way for innovative treatments that significantly improve patient outcomes in this challenging condition.

Acknowledgments

None.

Funding

This study was funded by the Nanhai Xinxing Medical and Health Talent Platform Project of Hainan Province (NHXX-WJW-2023030) and the Hainan Province Science and Technology Special Fund of China (ZDYF2022SHFZ304).

Conflict of interest

The authors declare that they have no competing interests.

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Writing–original draft: Weiyan Wu, Yuting Chen
Writing–review & editing: Yan Su, Tiandong Lin, Yangyang Liu

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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