CHEMICAL ENGINEERING TRANSACTIONS
VOL. 113, 2024
A publication of AIDIC
The Italian Association of Chemical Engineering
Online at www.cetjournal.it
Guest Editors: Jeng Shiun Lim, Bohong Wang, Guo Ren Mong, Petar S. Varbanov

ISBN 979-12-81206-14-4; **ISSN** 2283-9216
DOI: 10.3303/CET24113059

Unleashing Nature's Epigenetic Warriors: Bioactive Compounds and the Nrf2/Keap1 System

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Oxidative stress results from an imbalance between reactive oxygen species (ROS) and endogenous antioxidant defenses, contributing to various diseases. The Nrf2/ARE signaling pathway represents a promising therapeutic target against oxidative stress-mediated disorders, including diabetes, fibrosis, neurotoxicity, and cancer. Dietary phytochemicals derived from herbs and spices have gained attention for their potential health benefits, particularly in relation to Nrf2/ARE system and epigenetic regulation. Some important phytochemicals include: curcumine, quercetin, and sulforaphane. Curcumine obtained from turmeric, curcumin exhibits anti-inflammatory and neuroprotective properties. Curcumin demethylates specific CpG loci within the Nrf2 promoter, enhancing Nrf2 expression. Its epigenetic effects have been observed in various tumor types. Quercetin, resveratrol, and epigallocatechin Gallate (EGCG), these polyphenols modulate Nrf2 signaling by inhibiting Keap1 or activating Nrf2 expression. They enhance the expression of downstream antioxidant enzymes (e.g., HO-1, SOD, CAT). Sulforaphane: Abundant in cruciferous vegetables, sulforaphane activates Nrf2 expression. It also regulates Nrf2 signaling via various kinases (e.g., GSK3beta, PI3/AKT, and MAPK). While existing literature supports the protective effects of dietary phytochemicals against oxidative stress-related diseases, further investigations are required. Future studies should explore additional upstream signaling molecules beyond Nrf2 and elucidate the full impact of phytochemicals on epigenetic regulation. Understanding these mechanisms will pave the way for innovative therapeutic strategies aimed at combating oxidative stress and promoting overall health.

1. Introduction

The environment can expose reproductive cells to stress from things like high temperatures and xenobiotics. This can cause oxidative stress and apoptosis, which can harm the cells. Normally, the body has its own ways to deal with harmful reactive oxygen species (ROS) and keep cells healthy. But when there's too much ROS for too long, it can damage cells and disrupt normal processes. To help with this, taking external antioxidants can improve the body's ability to handle ROS and influence important biochemical pathways. This can help protect reproductive cells from oxidative damage and apoptosis by activating the Nrf2 signaling pathway.

The Nrf2 protein regulates antioxidant gene expression, protecting cells from oxidative damage. Under normal conditions, it is bound to Keap1 and Cullin 3 proteins, but when cells are stressed, Nrf2 moves into the nucleus to activate detoxification genes (He et al., 2020). The Nrf2/ARE pathway regulates antioxidant-inducible and detoxification genes like heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), glutathione S-transferase (GST), and glutamate-cysteine ligase (GCS), which protect cells from oxidative stress and support essential metabolic reactions, especially in liver cells.

In Alzheimer's disease, impairment of the Nrf2 pathway may be related to disease progression. Research suggests that enhancing Nrf2 activity can protect cells from Aβ (beta-amyloid) accumulation and prevent nerve cell death. The Nrf2 pathway also plays a protective role against vascular dementia, a condition characterized by cognitive decline due to reduced blood oxygen levels (Liao et al., 2023). Maintaining proper redox balance ensures that cells remain stable and function optimally. Therefore, imbalances can lead to cellular damage and contribute to various diseases (Piccirillo et al., 2022).

Paper Received: 30 June 2024; Revised: 4 August 2024; Accepted: 27 October 2024
Please cite this article as: Truc T.T., 2024, Unleashing Nature's Epigenetic Warriors: Bioactive Compounds and the Nrf2/Keap1 System, Chemical Engineering Transactions, 113, 349-354 DOI:10.3303/CET24113059

The strategies to combat oxidative stress are antioxidant-rich diet, physical activity, and antioxidant supplements. Nrf2 activation by natural compounds offers a multifaceted approach to maintaining health, from antioxidant defense to inflammation control and detoxification. Natural compound (sulforaphane from broccoli, curcumin from turmeric, allicin from garlic) can benefit health by enhancing antioxidant defense by neutralize free radicals and preventing cellular damage (Subba et al., 2022). These compound played the protective against neurodenenerative diseases by reducing oxidative stress associated with conditions like Alzheimer's and Parkinson's diseases (Cordaro et al., 2022).
In this comprehensive review, our objective was to elucidate the mechanisms by which natural compounds activate the Nrf2/ARE pathway for the prevention and treatment of diseases, drawing insights from a diverse range of studies.

2. Review discussion

2.1 Bioactive Compounds and the Nrf2/Keap1 System

2.1.1 The impact of allicin on the Nrf2 system

Allicin has the capability to activate the Nrf2 system by virtue of its chemical property that enables it to bind to specific sulfhydryl protein groups on Keap1. This binding alters the structure of Keap1, resulting in the release and accumulation of Nrf2 in the nucleus. Subsequently, Nrf2 orchestrates the expression of crucial antioxidants and detoxification enzymes such as HO-1, NQO1, Glutathione Peroxidase, and Glutathione-S-Transferase (Nadeem et al., 2021). This process aids in the cleansing of reactive oxygen species (ROS), mitigating oxidative stress, and safeguarding cells from damage caused by free radicals (Gao et al., 2019).
Numerous studies have been conducted to explore the potential impact of allicin on various diseases, particularly in relation to the Nrf2 system. These diseases encompass chronic kidney disease (CKD), cardiovascular disease, neurological disease, and colon cancer (Garcia-Trejo et al., 2016). For instance, a study by Kong et al. 2023 demonstrated the potential of allicin in preventing the progression of hypertrophic cardiomyopathy, a condition associated with heart failure. Compared to the model group, the artemisinin, allicin, and combined groups showed improvements in pathological patterns. They had more intact muscle fibers, a neater arrangement, and more normal cell morphology. Artemisinin and allicin alleviated cardiac dysfunction and decreased myocardial fibrosis in diabetic cardiomyopathy rats by inactivating the NF-κB signaling cascade (Kong et al., 2023). There is a growing body of evidence indicating that allicin's protective effects on the heart are attributed to its ability to activate the Nrf2 system, leading to the expression of antioxidant enzymes and the prevention of angiotensin II formation. Allicin attenuated LPS-induced injury by increasing cell viability, reducing inflammatory cytokines, and modulating Nrf2 and HO-1 expressions. It also inhibited the NLRP3 inflammasome, protecting against cardiac damage (Sun et al., 2023). Moreover, studies have indicated allicin's potential in protecting nerves in conditions such as spinal cord injury and neurological degeneration. Additionally, allicin has been found to induce apoptosis in human colon cancer cells by activating the Nrf2 transcription factor.

2.1.2 [6]-Shogaol

Ginger possesses antioxidant, anti-inflammatory, antibacterial, and anti-cancer properties. The natural compounds in ginger can be categorized into two groups. The volatile compounds, such as sesquiterpenes and monoterpenoid hydrocarbons, contribute to the flavor of ginger (Ajanaku et al., 2022). On the other hand, the non-volatile pungent compounds include gingerol, shogaol, paradol, and zinger. The most biologically active compounds are gingerol and shogaol, which are derived from phenylpropanoids. Gingerol is a spicy compound found in fresh roots, with 6-gingerol being the most common type. Shogaol is a type of water-dehydrated gingerol, found in small amounts in fresh roots and mainly in dry roots, with 6-shogaol being the most common form. Recent studies have indicated that 6-shogaol exhibits stronger antioxidant and anti-inflammatory properties than 6-gingerol. Furthermore, evidence from both in vivo and in vitro studies suggests that ginger and its main bioactive compounds (zingerone, 6-shogaol, and 6-gingerol) have been found to potentially have neuroprotective effects in Parkinson's disease (Huh et al., 2023). These effects are primarily attributed to the potential regulation of neuroinflammation, oxidative stress, intestinal permeability, dopamine synaptic transmission, and possibly mitochondrial dysfunction. *Z. officinale* extracts were the most investigated for their in vitro, in vivo, and clinical effects on the immune system. Among the bioactive metabolites, 6-, 8-, and 10-gingerols, 6-shogaol, and zerumbone from *Zingiber* species have demonstrated strong immunomodulating effects (Yuandani et al, 2023).
The compound 6-shogaol exhibits antioxidant, anti-inflammatory, and potential anti-cancer properties due to its structure, which contains methoxyphenol and α, β-carbonyl groups. These components are believed to impact the Keap1 structure, weakening the link between Keap1 and Nrf2 (Gan et al., 2013). This enables Nrf2 to translocate into the nucleus and activate the transcription of antioxidant and detoxifying enzymes such as HO-1, NQO1, GClC, and GCLM. Hur et al. (2020) demonstrated that 6-shogaol enhances the translocation of Nrf2

into the nucleus and reduces the levels of ROS in muscle cells. Additionally, Park et al. (2016) suggested that 6-shogaol could potentially serve as a therapy for allergic dermatitis by activating the Nrf2 system. Furthermore, research by Mak et al. (2023) indicated that 6-shogaol may protect the liver by activating Nrf2 and reducing the levels of harmful agents such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and peroxide lipid.

2.1.3 Sulforaphane

Sulforaphane is a molecule belonging to the isothiocyanate group of organosulfur compounds. It is formed through the enzymatic conversion of glucoraphanin, a glucosinolate present in cruciferous vegetables like broccoli and cauliflower (Roman et al., 2018). Research suggests that sulforaphane exhibits promising anti-cancer and antibacterial properties in experimental models. Furthermore, preliminary studies indicate potential cardiovascular benefits, including anti-atherosclerotic and heart-protective effects (Liu et al., 2023).

The compound sulforaphane exhibits a notable reactivity owing to the electronic properties of the isothiocyanate group (Figure1). This group readily interacts with sulfur, nitrogen, or central oxygen, influencing the Keap1 protein and subsequently releasing Nrf2. Once inside the nucleus, Nrf2 binds to specific areas, activating the expression of enzymes that play a role in antioxidant and detoxification processes, contributing to the body's defense against inflammation.

According to Bhandari et al. (2016), sulforaphane has been observed to impact nerve cells by activating the Nrf2 system and influencing gene expression. These findings suggest potential benefits of sulforaphane as a supplement for addressing neuritis and age-related oxidative stress.

Oxidative stress is a significant factor in the development of cardiovascular disease and consumption of sulforaphane-rich foods has been associated with the activation of the Nrf2 system and subsequent secretion of antioxidant and detoxification enzymes (Figure 1). The activation of sulforaphane's Nrf2 system can impede the adhesion of inflammatory cells on endothelial surfaces, potentially slowing down the progression of plaque and atherosclerosis (Liu et al., 2017). By activating Nrf2, sulforaphane and other isothiocyanate compounds found in vegetables have been shown to inhibit the expression of inflammatory genes and oxidative imbalances in endothelial cells, contributing to the maintenance of the cerebral vascular system and the blood-brain barrier, both vital for the proper functioning of brain tissue (Choi et al., 2011).

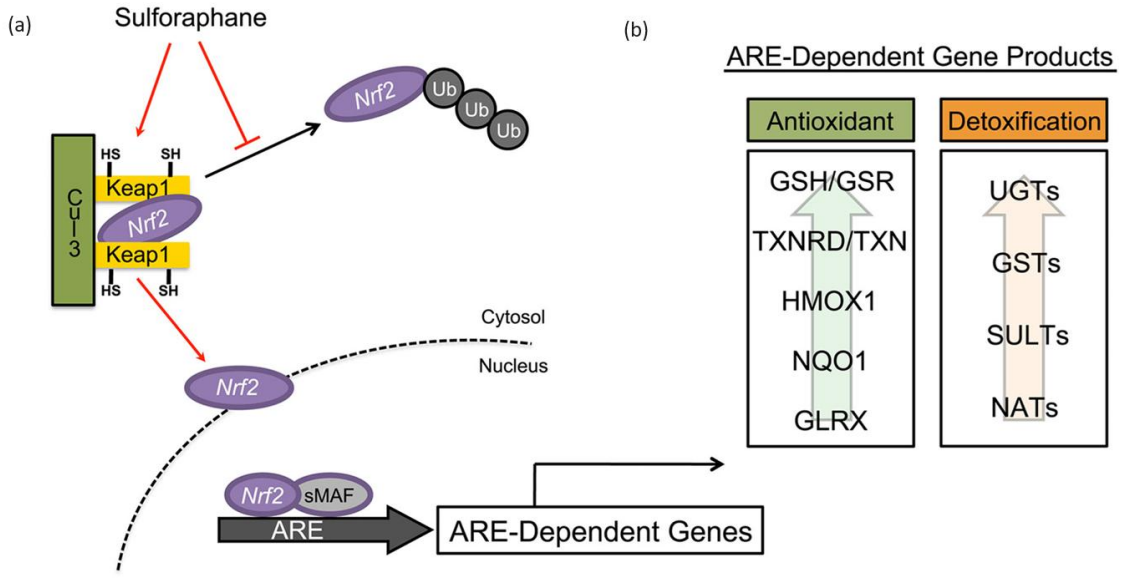

Figure 1: Mechanism of Sulforaphane-Induced Activation of ARE-Dependent Genes. (a) This diagram illustrates how sulforaphane, a dietary compound found in broccoli and other cruciferous vegetables, (b) influences gene expression related to antioxidant defense and detoxification pathways.(Bopduballi et al., 2012)

2.1.4 Coriander cilantrum sativum L. (*C. sativum*)

Coriander (*Coriandrum sativum* L.), also known as cilantro, is an herbaceous plant from the Apiaceae family. It has its origins in the Mediterranean region but is widely cultivated in North Africa, Central Europe, and Asia. The seeds and fresh leaves are commonly utilized. Coriander seeds are esteemed as a popular spice in the Mediterranean region and are a fundamental component of curry powder in Indian cuisine. Additionally, coriander leaves are highly valued for their distinctive aroma and are extensively used in Thai and Vietnamese

culinary traditions. They are utilized as herbs and spices to enhance the flavor of dishes or to mitigate any unpleasant food odors. In traditional medicine, coriander leaves are prescribed for treating digestive disorders and stimulating appetite. Recent studies have indicated that coriander may possess hypoglycemic, antibiotic, antioxidant, analgesic, and anti-inflammatory properties (Sobhani et al., 2022).

The volatile essential oil derived from cilantro leaf extract contains a variety of non-cyclic compounds, including (E)-2-decenal (Santos et al., 2021). This particular non-cyclic compound, featuring an α, β-unsaturated aldehyde group, interacts with the thiol groups on Keap1, resulting in a structural change in Keap1. This activation of the Nrf2 system serves to safeguard cells by stimulating the production of antioxidant enzymes and detoxification mechanisms. According to the findings of Khayatan et al. (2011), glutathione and oxidative defense enzymes such as superoxide dismutase and catalase can effectively impede the generation of reactive oxygen species (ROS).

2.1.5 2′,3′-dihydroxy-4′,6′-dimethoxychalcone (DDC) from *Perilla frutescens.*

The plant known as Perilla frutescens L. is a short-term herbaceous tree originating from East Asia. It comes in two forms: the green leaf form (Green Perilla) and the purple leaf form (Red Perilla), which differ in anthocyanin content. Perilla has been traditionally used as a vegetable in China, Korea, and Vietnam, as well as a seasoning in Japanese cuisine. Additionally, perilla leaves are utilized in traditional medicine as an antioxidant and anti-inflammatory agent. Furthermore, 2', 3'-dihydroxy-4', 6'-dimethoxychalcone (DDC) is a derivative of Chalcone, a flavonoid compound found in plants. Chalcone derivatives exhibit a wide range of biological activities, including anti-inflammatory, antioxidant, anti-cancer, and immunosuppressive properties. Researchers, led by Yasuhiko Izumi, have successfully isolated DDC from green perilla leaves. It's worth noting that DDC is also present in the leaves of Uvaria Dulcis and Sarcandra Hainanensis.

The α, β - carbonyl unsaturated group in the structure of DDC is believed to play a crucial role in the interaction between DDC and the thiol groups on Keap1. This interaction is thought to lead to the modification of Keap1, weakening its association with Nrf2, and subsequently releasing Nrf2 to the nucleus (Figure2). This process stimulates the transcription of a set of genes involved in oxidative stress response and cellular protection. Recent research conducted by Sun et al. (2020) has demonstrated that DDC can activate the Nrf2 system, offering cellular protection against toxicity induced by 6-hydroxydopamine (6-OHDA) both in vitro and in vivo. 6-OHDA is a known neurotoxin. By activating the Nrf2 system, DDC promotes the expression of antioxidant enzymes such as γ-GCS, NQO1, and HO-1, while also reducing the formation of reactive oxygen species (ROS) (Takada-Takatori et al., 2019). In this study, DDC demonstrated suppressive effects on auricular thickening and scratching behavior in cCHS mice, and also led to an increase in the expression levels of antioxidative enzymes. These findings suggest a potential therapeutic approach for reducing neuronal cell death in neurodegenerative diseases such as Parkinson's disease.

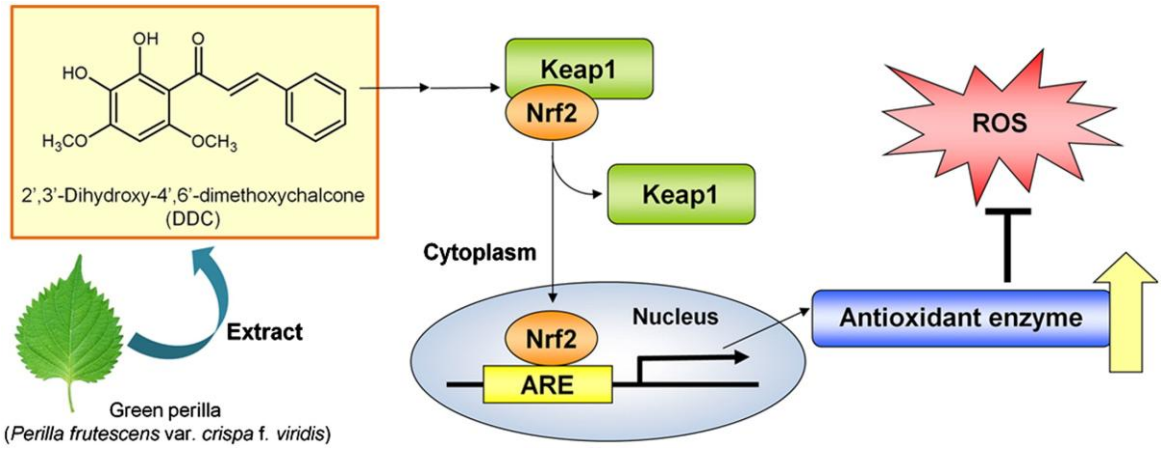

Figure 2: Mechanism of antioxidant enzyme activation by green Perilla extract. This diagram illustrates how an extract from the green perilla leaf, specifically identified as 2',3'-Dihydroxy-4',6'-dimethoxychalcone (DDC), interacts with cellular proteins to activate antioxidant enzymes.(Izumi et al., 2012)

2.2 Bioavailability, dose and duration, regulatory challenges

Many natural compounds (such as curcumin, quercetin, or resveratrol) have poor bioavailability. They are rapidly metabolized or poorly absorbed in the gastrointestinal tract. Clinical applications require effective delivery systems (nanoparticles, liposomes) or structural modifications to enhance bioavailability. Determining optimal

dosages and treatment durations is challenging. Too low a dose may be ineffective, while too high a dose could lead to adverse effects. Natural compounds often work synergistically and combining them may enhance Nrf2 activation. Chitosan is the polysaccharide most widely reported in recent years in the preparation of mucoadhesive biopolymer NPs for encapsulation of natural hydrophilic and hydrophobic compounds whose bioactive properties are compromised due to their poor aqueous solubility, low intestinal absorption, or rapid metabolism and elimination. Chuah et al. (2014) encapsulated curcumin in CS NPs (340 nm, with 77 % entrapment efficiency) to favor delivery to the colon and confer an anti-cancer effect. This work also suggested that curcumin could partially contribute to the mucoadhesion process, possibly via interaction with the mucus glycoproteins.

Liposomes have a phospholipids-containing lipid bilayer structure, including a hydrophilic head and a hydrophobic fatty acid tail. Firstly, nanoliposomes have a large dissolution area and can be rapidly absorbed, resulting in a large absorption concentration gradient. Secondly, nanoliposomes are small, which can increase the area of biological tissues and embedded compounds, increase the permeability of drugs, and prevent enzyme degradation, which provides the potential for improving oral bioavailability. Chuah et al. (2014) showed that nanoliposomes can be used for embedding garlic extract, which can protect their antioxidant activity and reduce the bad flavor.

3. Conclusion

Nrf2 is a pivotal transcription factor that plays a crucial role in initiating the transcription of cytoprotective genes when the body is under oxidative stress or exposed to xenobiotics. Some of the genes it triggers include HO-1, GCLM, NQO1, and UGT. The activation of Nrf2 is essential for protecting the body from various diseases, including neurodegeneration, aging, cardiovascular disease, inflammation, and cancer. The Nrf2/Keap1 signaling pathway is widely recognized as the primary defense mechanism within cells. Natural antioxidants found in certain foods, such as curcumin in turmeric, allicin in garlic, sulforaphane in broccoli, and shogaol and gingerol in ginger, have been shown to positively influence the Nrf2 system. These compounds can stimulate the Nrf2/Keap1 system, leading to the expression of phase II detoxification enzymes and antioxidant proteins. Coriander, known scientifically as Coriandrum sativum L., is commonly used as both a vegetable and a spice. Its leaves contain essential oils with a variety of (E)-2-alkenyl compounds. These compounds, known as acyclic electrophiles, have the potential to interact with thiol groups on Keap1, initiating covalent modifications that activate Nrf2 and encourage the expression of cytoprotective enzymes. As a result, Nrf2 complements the beneficial effects of nutrients found in coriander by activating the body's intrinsic antioxidant and detoxification systems.

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