



Review

The Role of Organosulfur Compounds as Nrf2 Activators and Their Antioxidant Effects

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Abstract: Nuclear factor erythroid 2-related factor 2 (Nrf2) signaling has become a key pathway for cellular regulation against oxidative stress and inflammation, and therefore an attractive therapeutic target. Several organosulfur compounds are reportedly activators of the Nrf2 pathway. Organosulfur compounds constitute an important class of therapeutic agents in medicinal chemistry due to their ability to participate in biosynthesis, metabolism, cellular functions, and protection of cells from oxidative damage. Sulfur has distinctive chemical properties such as a large number of oxidation states and versatility of reactions that promote fundamental biological reactions and redox biochemistry. The presence of sulfur is responsible for the peculiar features of organosulfur compounds which have been utilized against oxidative stress-mediated diseases. Nrf2 activation being a key therapeutic strategy for oxidative stress is closely tied to sulfur-based chemistry since the ability of compounds to react with sulfhydryl (-SH) groups is a common property of Nrf2 inducers. Although some individual organosulfur compounds have been reported as Nrf2 activators, there are no papers with a collective analysis of these Nrf2-activating organosulfur compounds which may help to broaden the knowledge of their therapeutic potentials and motivate further research. In line with this fact, for the first time, this review article provides collective and comprehensive information on Nrf2-activating organosulfur compounds and their therapeutic effects against oxidative stress, thereby enriching the chemical and pharmacological diversity of Nrf2 activators.

Keywords: organosulfur compounds; Nrf2; antioxidant; anti-inflammation

Citation: Egbujor, M.C.; Petrosino, M.; Zuhra, K.; Saso, L. The Role of Organosulfur Compounds as Nrf2 Activators and Their Antioxidant Effects. *Antioxidants* **2022**, *11*, 1255. <https://doi.org/10.3390/antiox11071255>

Academic Editor: Kenneth R. Olson

Received: 24 May 2022

Accepted: 23 June 2022

Published: 26 June 2022

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1. Introduction

The biological role of small sulfhydryl (-SH) molecules has been widely recognized due to their ability to maintain cellular redox homeostasis [1]. Among them, thioredoxin (Trx), glutathione (GSH) and glutaredoxin are endogenous sulfur-containing molecules that have been described to play a key role in maintaining the redox balance of biological systems via multiple mechanisms, including activation of the Nrf2 pathway [2]. The participation of organosulfur compounds in redox biochemistry, combined with low toxicological profiles and therapeutic effects, make them promising molecules for pharmacological applications [3]. In the last few decades, the relevance of the employment of Nrf2 activators as a potential approach for the treatment of various chronic diseases has been highlighted [4]. The mechanism of action of many Nrf2 activating compounds relies on their ability to interact with Keap1 (Kelch-like ECH associated protein 1), which is a negative modulator of Nrf2. Once activated, Nrf2 mediates the transcription of a wide range of genes involved in maintaining the cellular redox balance, reducing inflammation and promoting mitochondrial respiration and biogenesis [4]. Therefore, drugs able to interfere with Nrf2–Keap1 interaction are of great interest for the treatment of such diseases. Despite the advancement

in research for the discovery of Nrf2 activators, only a few approved Nrf2 activators are available [5–8], such as sulforaphane, oltipraz, ergothioneine, and L-carbocysteine [2,9–15].

The present review explores recent studies on the activities of organosulfur compounds as activators of the Nrf2 signaling pathway and their potency in preventing or attenuating oxidative stress-mediated diseases.

1.1. Role of Nrf2 in Human (Patho)Physiology

Nrf2 is a critical transcription factor discovered in 1994 as a member of the human cap 'n' collar basic-region leucine zipper (bZip) family. It contains: (i) a highly conserved C-terminal basic zipper domain, which is required for protein–protein interactions as well as for binding to DNA; (ii) a small N-terminal negative regulatory domain, named Neh2, responsible for the interaction of Nrf2 with the Keap1 protein; and (iii) a large transcriptional activation domain which promotes the recruitment of transcriptional co-activators to an enhancer sequence in the promoter region of genes known as antioxidant response element (ARE) (Figure 1) [16–20].

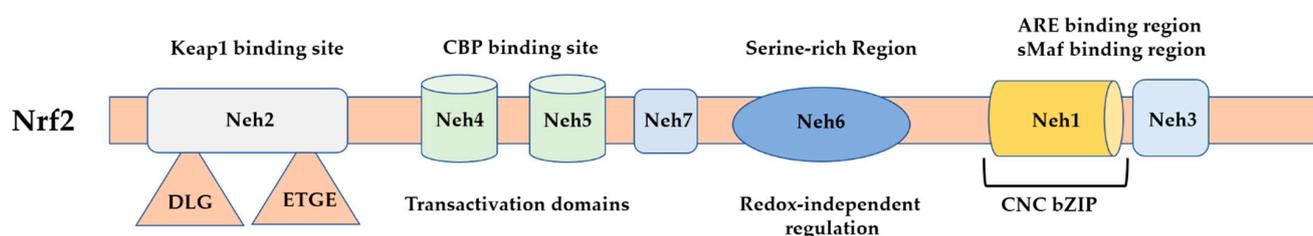


Figure 1. Domain organization of the transcription factor Nrf2. Nrf2 is characterized by seven highly conserved regions, Neh1 to Neh7. Neh1, Neh3, and Neh6 are located at the C-terminus of Nrf2, while Neh2, Neh4, and Neh5 are located in the N-terminal region. Neh1 contains a CNC-bZIP domain responsible for dimerization with small musculoaponeurotic fibrosarcoma (Maf) proteins and required for binding to ARE sequences in DNA. Neh2 domain controls the interaction with the cytoplasmic protein Keap1 via DLG and ETGE motifs. The Neh3 domain is required for the activation of transcription, along with the Neh4 and Neh5 domains that enhance Nrf2-mediated reporter gene transcription in an ATP-dependent manner. Neh4 and Neh5 domains are known as transactivation domains and are involved in the binding to the kinase-inducible domain interacting (KIX) and cysteine/histidine-rich domain 3 (CH3) domains of CBP (CREB (cAMP Responsive Element Binding protein)-binding protein). The Neh6 domain contains a serine-rich conserved region which is involved in degradation of Nrf2. This domain contains two binding sites (DSGIS and DSAPGS motifs) for the β -transducin repeat-containing protein (β -TrCP). Finally, the Neh7 domain interacts with the retinoic X receptor α , an Nrf2 repressor, and represses Nrf2 target gene transcription.

Follow-up studies in Nrf2-KO mice established that Nrf2 takes part in the regulation of about 250 genes containing ARE. These genes encode enzymes involved in the antioxidant response, thus playing a crucial role in attenuating oxidative stress, inflammation, and apoptosis [21–27]. Nrf2 is now widely accepted as the master regulator of stress response [28,29] and the cellular defence system and overall it has a key role in maintaining cellular homeostasis [30–32]. For instance, Nrf2 has been shown to support the Trx/GSH system, a major defence against ROS generation and redox imbalance in cell and tissues. Indeed, it has been established that Nrf2 induces increased expression levels of thioredoxin, thioredoxin reductase, and peroxiredoxin, involved in the reduction of oxidized cysteines of target proteins and redox signal transduction [33]. Moreover, Nrf2 stimulates GSH *de novo* biosynthesis and GSH recycling by increasing the expression levels of glutamate–cysteine ligase (GCL) and glutathione reductase [33–35]. Activation of the Nrf2/ARE pathway has been shown to increase the generation levels of NADPH, an important source of reducing equivalents involved in many redox reactions [1]. Nrf2 has been reported to promote the expression of enzymes involved in quinone redox cycling such as NADPH quinone oxidoreductase 1 (NQO1) [36–38]. The activation of the Nrf2/ARE

signaling pathway correlates with increased expression levels of heme oxygenase-1 (HO-1), which contributes to the elimination of ROS by generating the antioxidant biliverdin and catalysing the degradation of “free” heme, which has prooxidant properties [39]. Nrf2 attenuates the inflammatory response by inhibiting the transcriptional activity of NF- κ B and by suppressing pro-inflammatory cytokines [40,41]. Moreover, Nrf2 regulates the expression levels of cystathionine β -synthase (CBS) and cystathionine γ -lyase (CSE), the major enzymatic source of hydrogen sulfide (H₂S), as well as sulfide:quinone oxidoreductase (SQR), involved in its catabolism [42].

Nrf2 has also been shown to have cytoprotective effects by playing pivotal roles in preventing xenobiotics-induced toxicity and carcinogen-related tumorigenesis. These protective effects are mainly attributed to the activation of genes that encode for enzymes acting in detoxification and/or in the transport of various toxic xenobiotics, thus leading to their excretion from the body [43–46]. Indeed, a cross-talk between Nrf2/ARE dependent signaling and Ahr-XRE signaling has been recently demonstrated [47,48]. The Nrf2 promoter has three xenobiotic response element (XRE)-like element (XREL) regions, XREL1, XREL2, and XREL3, to which the aryl hydrocarbon receptor–xenobiotic response element (AhR) binds and causes transactivation of the AhR–XRE signaling pathway. AhR is a transcription factor that regulates gene expression of crucial xenobiotic-metabolizing enzymes in response to various chemicals; when activated it induces the transcription of its dependent genes including various cytochrome P450s (CYPs) [49] and drives their transcription [50] thus leading to a protective response against a wide range of xenobiotics.

The broad-spectrum effect of the activation of the Nrf2/ARE pathway on redox metabolism and its “multi-target” cytoprotective effect can be exploited for the treatment of chronic multifactorial disorders characterized by the lack of a unique aetiology. As extensively reviewed by Cuadrado et al. [4], pharmacological activators of the Nrf2 pathway may prove beneficial for treatment of respiratory, metabolic, cardiovascular, and neurodegenerative diseases. However, in cancer the role of Nrf2 is controversial. On the one hand, it has been shown that Nrf2 activation induces a transcriptional response which is responsible for maintaining low ROS levels and repairing oxidative damage, thus preventing tumorigenesis. On the other hand, several lines of evidence suggest that constitutive increased levels of Nrf2 promotes cancer progression, metastasis, and chemoresistance [51]. To date, the role of Nrf2 in cancer biology has not been clarified, as Nrf2 can act both as a tumour suppressor and an oncogenic protein. Therefore, from the pharmacological point of view, Nrf2 activators can be employed only in cancer prevention, whereas the development of Nrf2 inhibitors is under evaluation as a strategy for cancer treatment.

1.2. Nrf2 Regulation

Nrf2 is constitutively expressed in cells and tissues under homeostatic conditions, thus providing basal expression levels of its target genes. It displays a half-life of less than 10 min due to permanent degradation by the ubiquitin proteasome system. However, under stress conditions, Nrf2 degradation slows down, thus leading to its accumulation in the nucleus [52] (Figure 2A). This adaptive system ensures higher Nrf2 levels under stressing conditions, providing enhanced expression levels of ARE-dependent antioxidant genes and attenuating oxidative stress and inflammation. Nrf2 turnover is regulated by Keap1 (Figure 2A). Keap1 is a cytosolic protein consisting of three domains, the BTB domain (Broad complex, tramtrack and bric-à-brac domain), an intervening region (IVR), and a C-terminal Kelch domain. The Kelch domain of Keap1 folds up into a six-bladed β -propeller structure [53], which is a disc-like structure assembled by circularly arranged structural modules (named blades) with a small channel that runs through the center. Each blade is a twisted β -sheet composed of four antiparallel β -strands (A–D): strand A is positioned in line with the central channel and runs almost parallel with the six-fold axis of the propeller, while strands B–D progressively acquire more distance from the central axis and exhibit more twist until almost complete perpendicularity to the six-fold axis is reached with strand D that lies outside the edge of the protein (Figure 2B) [54,55].

A stable interface between blade I and VI allows the formation of an arrangement that closes the ring of the blades in the propeller, known as C-terminal strand mechanism of closure. Keap1 dimerization is required for Keap1–Nrf2 association, thus dimeric Keap1 combines with Nrf2 with a 2:1 stoichiometry [56,57] to form a Nrf2–Keap1 complex which, under normal conditions, undergoes ubiquitination and proteasomal degradation in the cytoplasm. This association occurs through the recognition of the Neh2-domain in the Nrf2 protein. The Neh2 domain of Nrf2 is a small N-terminal negative regulatory domain of the transcription factor which mediates binding of Nrf2 to the cytoplasmic Keap1 protein. Indeed, Neh2 is stretched between two Kelch domains in the Keap1 homodimer and binds Kelch via two different binding motifs, one with low affinity (the DLG domain) and one with high affinity (the ETGE domain) (Figures 1 and 2A), which is composed of an evolutionarily conserved amino acid sequence motif [57,58]. The DLG motif is characterized by three helices that weakly bind to the double glycine domain of Keap1. By contrast, the ETGE motif, characterized by a single β -hairpin structure, is able to bind the double glycine domain of Keap1 in a key-and-lock manner [58–60]. The binding of these two motifs of Nrf2 to the Keap1 homodimer allows the lysine residues in Neh2-domain to be ubiquitinated by Cullin3 (Cul3) ligase and thus leading Nrf2 labeled for proteasomal degradation. Keap1 activity is regulated by redox-sensitive cysteine residues exposed to the solvent, which, under oxidative stress, are modified by electrophiles, thus leading to the release of Nrf2 [61,62] (Figure 2A). The most common pharmacological approach to activate Nrf2 is to prevent its Keap1-dependent degradation. Indeed, many Nrf2 activators are actually Keap1 inhibitors by targeting the redox-sensitive cysteines [63,64]. Among them, Cys151 plays a central role in the regulation of the Keap1 pathway by (i) mediating the dimerization of Keap1 to its biologically active homodimer and (ii) stabilizing the Keap1–Cul3 complex. Consistently, compounds reactive towards Cys151 of Keap1 (also referred as Nrf2 activators of Class I, Figure 2C) elicit a powerful Nrf2-activator effect by preventing Keap1 dimerization and promoting detachment of Cul3. In turn, Cys151-mediated regulation of Keap1 has been demonstrated to have a pivotal role in the process leading to Nrf2 ubiquitination and eventually to its degradation. Endogenous signaling molecules such as nitric oxide (NO) and hydrogen sulfide (H₂S) have been shown to react with Cys151, hence mediating the activation of the Nrf2/ARE pathway [65]. Mechanistic details on the control of Nrf2 by H₂S and possible effects of sulfane sulfur-containing species (per-/polysulfides) will be discussed. Moreover, although it is commonly accepted that organosulfur compounds lower ROS levels through activation of the Nrf2/ARE pathway, some lines of evidence suggested that this mechanism may be mediated by ROS themselves. For instance, homocysteine, a classical organosulfur compound, exerts controversial effects on the antioxidant defense system. As extensively reviewed in [66], on the one hand homocysteine mediates antioxidant effects through the activation of the Nrf2/ARE pathway (as further discussed in Section 3.2.3), on the other hand elevated homocysteine levels are often associated with ROS-mediated cytotoxicity. This discrepancy could be related to the multiple metabolic pathways through which homocysteine influences cell functions in different conditions and tissues. To add a further grade of complexity, it is also conceivable that homocysteine-derived ROS are able, to a certain extent, to mediate the activation of the antioxidant response. Moreover, it has been shown that garlic-derived organosulfur compounds, such as diallyl sulfide, rapidly increase (after 15–30 min from the treatment) the generation of H₂O₂ [67,68], a known activator of Nrf2. This is in apparent contrast with the noxious effect exerted by ROS, but reconciled by the finding that pre-conditioning cells with low levels of H₂O₂ confers resistance to oxidative stress [69]. From the mechanistic point of view, the H₂O₂-mediated activation of the Nrf2/ARE pathway seems to be Cys151, Cys273, or Cys288 independent (Nrf2 activators of Class IV, Figure 2C). Accordingly, in mouse embryonic fibroblasts (MEFs) harboring triple cysteine sensor mutation on Keap1, in which the three cysteines Cys151, Cys273 and Cys288 were substituted with serine, tryptophan, and glutamic acid, respectively, activation of the Nrf2 pathway in response to Class IV activators (but not Class I–III) was observed [62]. This may suggest that other

cysteines than Cys151, Cys273, and Cys288 are involved in the H₂O₂-mediated activation of Nrf2. As previously reviewed by Suzuki et al. [70], Cys226, Cys434, and Cys613 may play a role in H₂O₂ sensing, although this needs to be further validated.

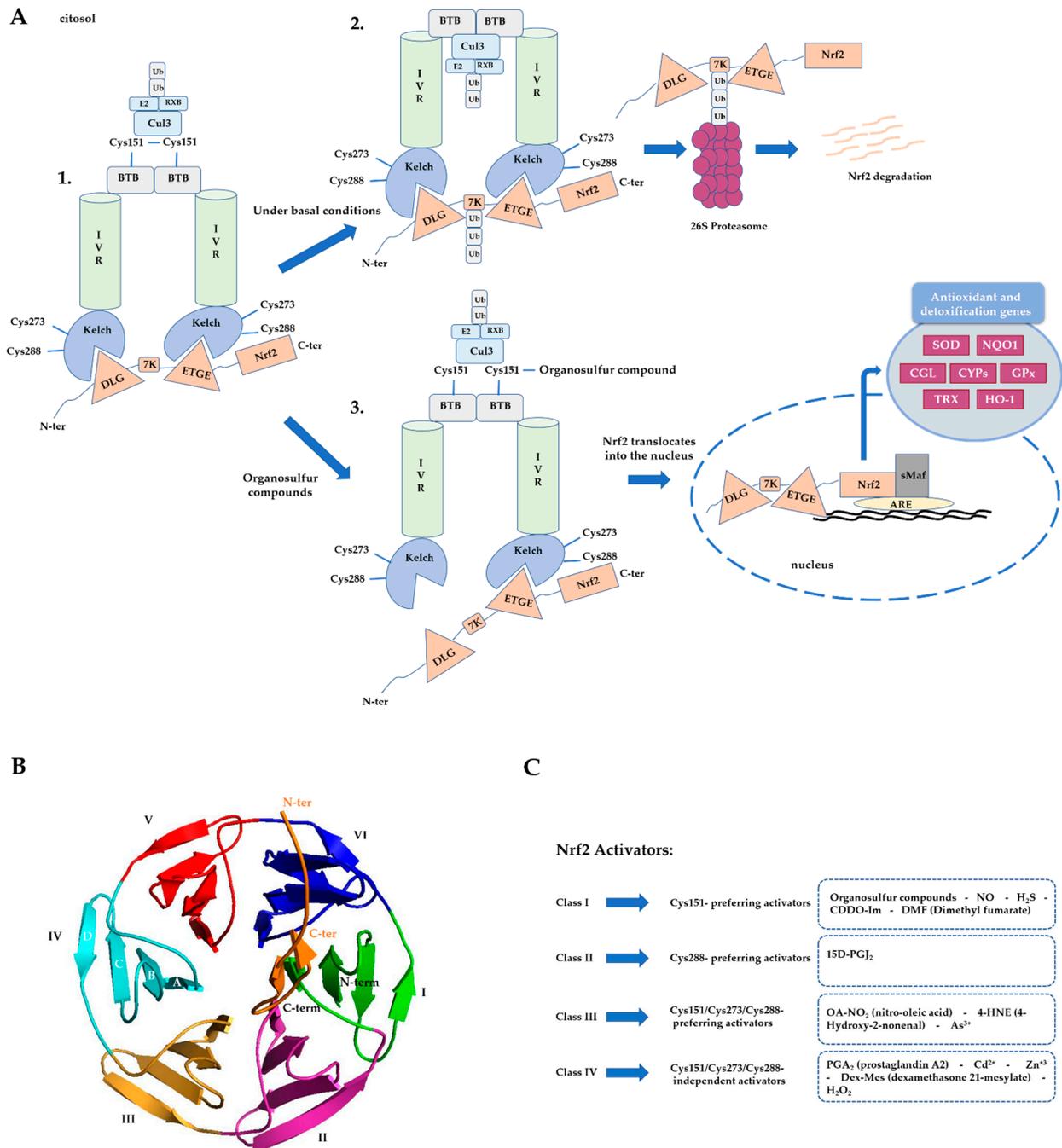


Figure 2. (A) Regulation of Nrf2 activity by Keap1. (1.) Keap1 in dimeric form, complexed with Nrf2. **(2.)** Under basal conditions, Nrf2 interacts with Keap1 homodimer through ETGE and DLG motifs. This interaction allows the ubiquitination of Nrf2 at its Lys-rich (7K) region and the following proteasomal degradation of the protein by the 26S proteasome. **(3.)** The presence of Nrf2 activators (such as organosulfur compounds) promotes the release of Nrf2 thus leading to its nuclear translocation. Particularly, activators react with specific cysteine residues in Keap1 (Cys151, Cys273, or Cys288). In the nucleus, Nrf2 heterodimerizes with small Maf (sMaf) proteins and binds to the antioxidant response element (ARE), activating the expression of a battery of cytoprotective genes. **(B) Structure of the Kelch domain of human Keap1 in complex with Nrf2 peptide (pdb #4IFL).**

The Kelch domain of Keap1 is characterized by a six-bladed β -propeller structure. Each blade, shown in a different color and numbered I–VI, is composed of four β -strands labeled A–D (as shown in white font on blade IV). The N and C termini are both located in blade I. The N and C termini of Nrf2 peptide are also indicated in figure. **(C) Scheme of chemical Nrf2 activators including some organosulfur compounds.** Four different classes of Nrf2 activators and representative chemicals for each class are reported. Class I contains the Cys151-preferring activators, class II the Cys288-preferring activators, class III the Cys151/Cys273/Cys288-preferring activators, and class IV the Cys151/Cys273/Cys288-independent activators.

Of pharmacological relevance, dimethyl fumarate (DMF), an approved drug for treatment of multiple sclerosis and psoriasis, has been shown to induce Keap1 inactivation through electrophilic modification of Cys151 [71]. Similarly, other organosulfur compounds such as sulforaphane (SFN) and oltipraz or the synthetic terpenoid 1-[2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl] imidazole (CDDO-Im) induce a chemical modification of Cys151, thus resulting in the detachment of Cul3 ligase and in the stabilization of Nrf2 (Figure 2A,C) [62,63,72,73]. Furthermore, modification of other redox-active cysteine residues in Keap1, such as Cys288, induces conformational changes leading to the dissociation of Keap1–DLG interaction [63,74]. This mechanism may give reason of the functional consequences of the modification of Cys288 induced by 15d-PGJ2 (15-deoxy- Δ 12,14-prostaglandin J2), which has been reported to induce the break of the dimeric structure of Keap1 and the release of Nrf2 (Figure 2C) [62].

It is worthy to note that antioxidant response element (ARE) is the key player in the Keap1/Nrf2/ARE signaling system and essential to the Nrf2-mediated transcription of genes involved in the defense mechanisms of organisms. ARE can be described as a *cis*-acting element or enhancer sequence normally located in the promoter region of series of genes encoding detoxification enzymes. It mediates the transcriptional activation of genes, encoding proteins that control redox homeostasis and prevent oxidative damage [75]. Several transcriptional factors, especially Nrf2, depend on AREs for the regulation of cytoprotective genes [76]. The activation of the Nrf2/ARE pathway has been found to protect endothelial cells from oxidative damage [77]. Under oxidative stress conditions, Nrf2 undergoes dissociation from Keap1 and translocation into the nucleus where it forms heterodimer with small musculoaponeurotic fibrosarcoma (Maf) proteins and binds to ARE in order to effect transcriptional activation of antioxidant genes [78].

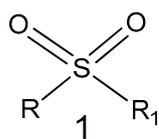
2. Nrf2-Activating Synthetic Organosulfur Compounds

2.1. Sulfonyl Group-Containing Compounds

Sulfonyl group-containing compounds, especially sulfones and sulfonamides, have been widely studied because of their significant therapeutic roles for a number of diseases. Their tense chemical structure and functionality enable them to form hydrogen bonding interaction with active site residues of biochemical targets. Their usual incorporation into a core ring structure gives them specific conformations which fit the active sites [79]. Sulfonyl group-containing compounds exhibit therapeutic effects against bacterial infections [80–86], tumors [87,88], Alzheimer's disease [89], oxidative stress-related diseases [90–93], and diabetes [79]. Moreover, sulfonyl-containing compounds have been found to activate the Nrf2 pathway and inhibit Keap1–Nrf2 protein–protein interaction, thereby alleviating oxidative stress and inflammatory conditions [94].

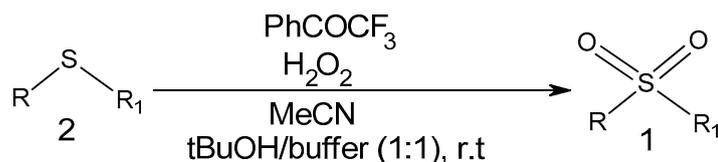
2.1.1. Sulfone Derivatives

Sulfone is an organic sulfur compound in which the sulfonyl functional group is bonded to two carbon atoms (Scheme 1). The central sulfur is hexavalent, doubly-bonded to two oxygen atoms and singly-bonded to two carbon atoms [95].



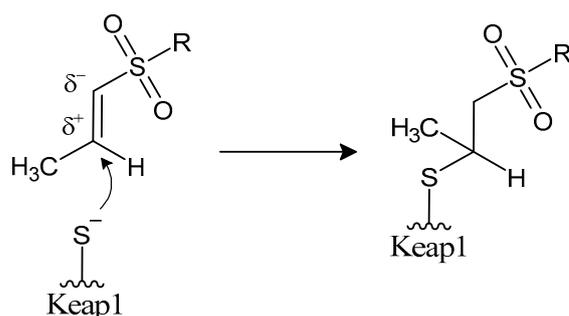
Scheme 1. Structure of sulfone.

Sulfones (1) are synthesized by organocatalytic oxidation of sulfides (Scheme 2), which remains a common method [95,96].



Scheme 2. Synthesis of sulfones.

With the aim of implementing the specificity and lowering off-targets, within the category of sulfones there have been designed molecules sufficiently electrophilic to react with redox sensitive cysteine residues of target proteins, but still unreactive towards low-molecular weight thiols such as glutathione (GSH) (in which case this would lead to depletion of GSH). This is the case, for instance, with electrophilic double-bond bearing vinyl sulfone scaffold: when the substituent R is a vinyl group, the polarized double bond C=C is highly reactive towards protein nucleophilic sulfhydryls [97] (Scheme 3). Vinyl sulfones have been extensively studied as a novel class of neuroprotective agents for Parkinson's disease therapy due to their significant Nrf2 activation [98–100]. The tuning of the electrophilicity and steric hindrance of vinyl sulfones can be harnessed for the development of new potent Nrf2 activators for neuroprotection [32]. From the molecular point of view, the target of this class of compounds has been shown to be Keap1. The direct binding to one of the solvent exposed cysteines of Keap1 prevents complexation with Nrf2 and its consequent degradation [97] (Scheme 3). This has been shown, for instance, with (E)-1-chloro-2-(2-((2-methoxyphenyl)sulfonyl)vinyl)benzene, here referred to as compound 4 (Table 1).



Scheme 3. Binding of Keap1 to Vinyl Sulfones.

Vinyl sulfones exhibit anti-inflammatory activities [101] and act as modulators of Nrf2 activity [98]. As shown in BV2-microglia cells activated with LPS, Lee et al. [98] reported that vinyl sulfone derivative (4) (Table 1) induces Nrf2 transcriptional activity, increases nuclear Nrf2 levels, up-regulates the expression of the Nrf2-dependent antioxidant enzyme genes and down-regulates the production of NO. Particularly, in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease (PD), oral administration of compound 4 decreased the number of activated microglia in the substantia nigra. This relies on the activation of the Nrf2 pathway, thereby exploiting antioxidant and anti-inflammatory properties, consistent with reduced neuroinflammation [98]. In a similar study, Woo et al. [99] reported that compound 4 activates Nrf2 and induces

the expression of the Nrf2-dependent antioxidant enzymes in DAergic neuronal cells at both mRNA and protein levels. Compound **4** exerts a protective effect against cytotoxic damage of DAergic neurons and attenuates Parkinson's disease-related motor deficits in MPTP-induced mice [99]. Vinyl sulfone is reportedly more potent than chalcone and vinyl sulfoxide in up-regulating the expression of the Nrf2-dependent HO-1 gene [99]. Carlstrom et al. [100] reported that compound **4**, while activating the Nrf2 pathway with a similar potency to DMF, displayed lower off-target effects on NF- κ B and Hypoxia-inducible factor 1 (HIF1). Choi et al. [102] reported that compound **4** activates Nrf2 and subsequently induces the Nrf2-dependent antioxidant enzyme expression in a dose-dependent manner. In the MPTP-induced Parkinson's disease model, compound **4** was found to exhibit significant efficacy but displayed poor drug-like properties, such as low solubility, metabolic stability, and permeability through the blood-brain barrier (BBB) [91]. In a follow-up study, Choi and co-workers [102] implemented the Nrf2 activation potency and the ADME/tox profile of compound **4** by incorporating pyridine and morpholine moieties to afford compound **5**. Reportedly, **5** ($EC_{50} = 346$ nM) is a more potent Nrf2 activator than compound **4** ($EC_{50} = 530$ nM). Moreover, **5** displayed excellent drug-like properties, showing low toxicity, high microsomal stability, low inhibitory effect on CYP, and good BBB permeability [102]. Compound **5** has been shown also to improve motility in acute MPTP-induced Parkinson's disease-infected mice, alleviate loss of DAergic neurons, and attenuate microglial activation [102].

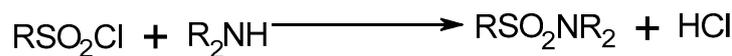
Song et al. [32] reported that vinyl sulfone derivatives (compounds **6** and **7**) (Table 1) activate the cellular response system at translational and transcriptional levels. As shown in PC12 cells, compounds **6** and **7** exert cytoprotective effects against oxidative stress via Nrf2 activation and consequent nuclear translocation of Nrf2. The Nrf2-mediated up-regulation of antioxidant species such as HO-1, TrxR, GSH, and NQO1 induced by compounds **6** and **7** protects PC12 cells from H_2O_2 -mediated damage [32].

Choi and co-workers [102] reported that the introduction of *o*-pyridine as a heterocycle into the ring B of compound **4** (Table 1) reduces Nrf2 activation by 17-fold while the addition of Cl- group to the *o*-pyridine improves the Nrf2 activation of compound **4**. It was observed that the addition of a Cl- group to the ortho position induces the highest Nrf2 activity while substituting the Cl- group with F- results to a six-fold decrease in Nrf2 activation. It was also reported that the introduction of methoxy groups at the 2-, 3-, and 4- positions of ring A exerts a remarkable Nrf2 activation effect on compound **4** in the order 3-OMe > 2-OMe > 4-OMe. However, 2-methoxy derivatives exhibit the highest HO-1 induction activity and suppression of NO production [98,99]. Although the addition of *o*-, *m*- or *p*-pyridine to the ring B enhances the Nrf2 activation of compound **4** in the order *p*-pyridine > *o*-pyridine > *m*-pyridine, the *p*-pyridine derivatives are more cytotoxic than *m*- and *o*-pyridine derivatives of compound **4** [102].

2.1.2. Sulfonamide Derivatives

The importance of finding novel pharmacological approaches in activating the Keap1-Nrf2 pathway is witnessed by the still growing number of studies reporting high-throughput screening campaigns employing orthogonal methods ranging from biophysical and bioinformatic approaches, complemented with x-ray crystallography. For instance, in PubChem Bioassay database are reported 528 compounds obtained from high-throughput screens of hundreds of thousands of compounds. Among the confirmed hits, some sulfonamide compounds showed in vitro potency below 100 nM, thus representing valuable pharmacological tools for inducing the activation of the Nrf2/Keap1 pathway [103].

Sulfonamides are a group of synthetic medicinal compounds in which a sulfonyl group is bound to an amine group. They have the functional group $-S(=O)_2-NH_2$ and general formula RSO_2NH_2 [104]. Sulfonamides can be prepared using several laboratory methods but the reaction of sulfonyl chlorides with amines or ammonia remains the classic synthetic method [105] (Scheme 4).



Scheme 4. Synthesis of sulfonamides.

Sulfonamides exhibit a broad spectrum of biological effects such as antioxidant [106], anticancer [107] and anti-inflammatory [108] activities. Sulfonamide derivatives have been found to activate Nrf2 and inhibit Keap1-Nrf2 protein-protein interaction thereby antagonizing oxidative stress. This results in the elimination of reactive oxygen species (ROS), alteration of glutathione homeostasis, up-regulation of the expression of antioxidant response element dependent genes and enhancement of antioxidant defence mechanism [1,109,110]. Peng and co-workers [111] reported that caffeic acid sulfonamide derivatives (8, 9, 10) (Table 1), when used in the treatment of H₂O₂-stimulated A549 cells, enhance mRNA expression of Nrf2 and its target genes. Naphthalene sulphonamide derivatives compound are notable Nrf2 activators. Compound 11 activates Nrf2 pathway by inhibiting the Keap1-Nrf2 protein-protein interaction [94]. Compound 12 stimulates Nrf2 protein expression, enhances the anti-oxidative mechanism in macrophage-like RAW264.7 cells and activates Nrf2/ARE pathway in HepG2-ARE-C8 cells [94]. Compound 13 and 14 are potent Keap1-Nrf2 inhibitors which displace the Nrf2 ETGE peptide, enhance the transcription of the Nrf2 targeting genes and activate the Nrf2/ARE signaling pathway [59,94,112,113]. In particular, both inhibit the Keap1-Nrf2 interaction via competing with Helix-2 of DLG for binding to Keap1 [94,113]. As shown in the crystal structure of human Keap1 Kelch domain complexed with compound 14 (Figure 3), this compound binds aminoacidic residues (Ser508, Arg415, Asn414 and Ser602) of the Keap1 Kelch domain, thus seating at the interface between Keap1 and Helix-2 of Nrf2 [59,94]. Naphthalene-based sulfonamides have proven to be promising Nrf2 activators and medicinal chemistry studies have been carried out. Interestingly, it has been shown that compound 13 when substituted with R = OH displays a K_D of 3.6 nM, thus being among the most powerful compounds found to inhibit protein-protein interaction between Keap1 and Nrf2 [94,103]. Instead, substitution with R = NH₂ lowers the binding affinity by about 10-fold.

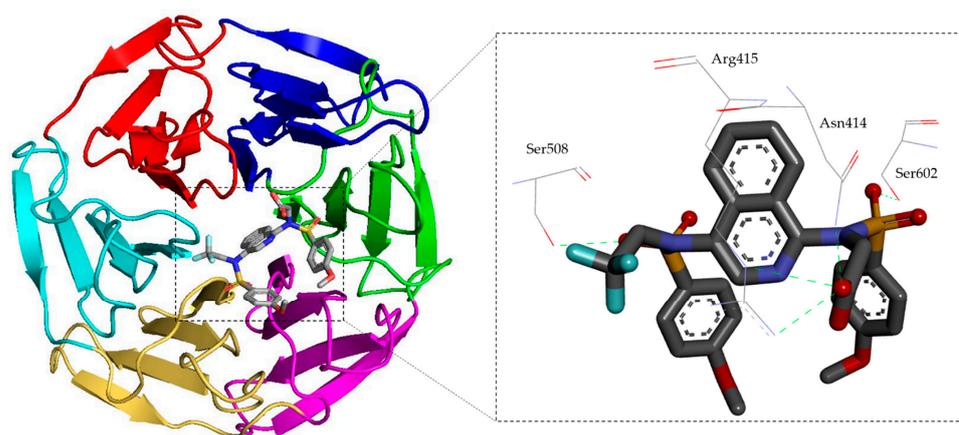


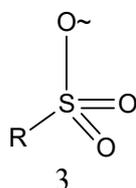
Figure 3. Crystal structure of compound 14 in complex with human Keap1 Kelch domain (pdb #6UF0). Overall structure of Keap1 Kelch domain in complex with compound 14 and details of interaction (inset).

Lu and co-workers [94] reported that the addition of a hydrophobic benzene ring to naphthalene sulfonamide derivatives (compound 15) (Table 1) enhances the Nrf2 activating efficiency. The presence of a methoxy group enhances the Keap1-Nrf2 protein-protein interaction (PPI) inhibition and the induction of the Nrf2/ARE pathway, while the absence of methoxy group in sulfonamide substituted phenyl ring decreases the biological effect [94]. *P*-methoxy groups confers higher Nrf2-activation potency than both *m*-methoxy group and *p*-methyl group. The addition of *o*-methyl group increases hydrophobic interactions and

hydrophobic groups improve the Keap1–Nrf2 protein–protein interaction (PPI) inhibitory effect of sulfonamide derivatives [94]. Recently, Georgakopoulos et al. [114] reported a non-electrophilic phenyl bis-sulfonamide (**16**) as an effective inhibitor of Keap1–Nrf2 protein–protein interaction having an alternative binding mode. Compound **16** binds and interacts with Keap1 cells and improves the expression of Nrf2-mediated genes such as NQO1, HO-1, and GST. Vinyl sulfonamides, another class of Nrf2 activators, have been reported to act as Keap1–Nrf2 PPI inhibitors and can be utilized as preventive and therapeutic agents for oxidative stress and inflammation (compound **17**). Choi et al. [115] reported that the addition of a methoxy group and chloride to the 2-position of the ring A and 2-position of the ring B increases the Nrf2 activation of vinyl sulfonamides (compound **18**).

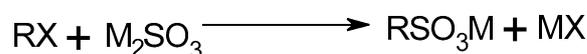
2.1.3. Sulfonate Derivatives

Sulfonate is a salt of a sulfonic acid with the functional group $R-SO_3^-$ [116] (Scheme 5). Sulfonates are colorless non-oxidizing salts that are generally stable in water [116], they are found in many useful biochemicals and dietary sugars such as sulfoquinovose [117].



Scheme 5. Sulfonate ion.

Sulfonates are synthesized by the reaction of alkyl halides with sulfites usually sodium sulfite (Scheme 6) [117].



Scheme 6. Synthesis of sulfonates.

Sulfonate derivatives exhibit significant antioxidant [118] and anti-inflammatory effects [119,120]. Vinyl sulfonates (compounds **19**, **20**, and **21**) (Table 1) have been reported as excellent Nrf2 activators with therapeutic potentials for the treatment of Parkinson's disease [115]. These compounds have been confirmed as potent antioxidant, anti-inflammatory, and neuroprotective agents via both in vivo and in vitro studies [115]. For instance, compound **19** activates the Nrf2/ARE signaling pathway in SH-SY5Y and BV-2 cells and significantly increases the NQO1, GCL, and GCLM protein levels. Compound **19** also attenuates LPS-induced inflammation in BV-2 cells, suppresses the up-regulation of iNOS and COX-2 and decreases the LPS-induced NO production [115]. Moreover, the expression of Nrf2-dependent antioxidant enzymes induced by compound **19** has been shown to prevent motor deficits in MPTP-induced Parkinson's disease and production of inflammatory mediators. In the same study, the Nrf2-activating efficacy of different classes of organosulfur compounds was compared, with compound **19** ($EC_{50} = 76$ nM) exhibiting higher Nrf2 activation than vinyl sulfone ($EC_{50} = 530$ nM) and sulforaphane ($EC_{50} = 580$ nM) [115]. Structure activity relationship of sulfonates, especially vinyl sulfonates, showed that they exhibit the highest Nrf2 activation when 2-Ome (2-Ome > 3-Ome > 4-Ome) is introduced to ring A and 2-Cl (2-Cl > 3-Cl > 4-Cl) to ring B [115]. An interesting organosulfur compound is sodium tanshinone IIA sulfonate (**22**), a major component of the traditional Chinese herb Danshen (*Salvia miltiorrhiza*). Due to its beneficial properties, this compound has been used for the treatment of oxidative stress-related diseases. Zhu and co-workers [121], in an in vitro model of silicosis, have shown that the beneficial effects of compound **22** are associated, at least in part, with the activation of the Nrf2 pathway. Particularly, in a coculture of macrophages Raw 264.7 with lung fibroblasts MRC-5, it has been shown that compound **22** inhibited the H_2O_2 - and silica-induced MRC-5 cell proliferation, thus showing anti-fibrotic properties. Moreover, compound **22** suppressed

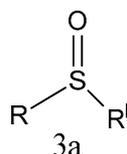
silica-induced ROS production, decreased the expression of collagen I and collagen III, and increased the thioredoxin and thioredoxin reductase protein expression in MRC-5 cells. Interestingly, all these events correlated with increased nuclear translocation of Nrf2, increased Nrf2 expression levels and up-regulation of the ARE genes [121].

2.2. Sulfinyl Group-Containing Compounds

The sulfinyl group refers to the SO group present in several organic compounds. This group is a strong electron-withdrawing substituent with a high configurational stability and biological activity [122,123]. The sulfinyl group is found in various biologically active compounds such as sulfoxide and sulforaphane with significant Nrf2 activation [124–126]. Sulfinyl moiety has been linked to anticancer and chemopreventive action of sulforaphane [127,128].

2.2.1. Sulfoxide Derivatives

Sulfoxides are chemical compounds in which a sulfinyl (SO) group is bonded to two carbon atoms (Scheme 7) [129]. They exhibit anti-inflammatory and antioxidant activities [130,131]. Dimethyl sulfoxide and alliin are good examples of sulfoxides with Nrf2 activation ability [125–129].



Scheme 7. Structure of sulfoxide.

Dimethyl sulfoxide (DMSO) is an organosulfur compound in which a sulfinyl group is bonded to two methyl groups [132]. DMSO is usually synthesized by the oxidation of dimethyl sulfide (Scheme 8) [133].



Scheme 8. Synthesis of dimethyl sulfoxide.

Due to its amphiphilic properties, comprising its high miscibility with water and its ability to dissolve lipophilic compound, DMSO is widely employed as a vehicle for drugs [125]. One essential feature of a good vehicle is being pharmacologically inert, a condition generally achieved when low DMSO concentrations are used (commonly DMSO 0.1% *v/v* is considered a safe concentration in cell biology). Expectedly, the effect of higher concentrations of DMSO (in the range of 1–20 % *v/v*) is not negligible anymore. At these concentrations DMSO has been shown to display antioxidant and anti-inflammatory effects [130,131].

Particularly, Liang and co-workers [125] reported that DMSO (**23**) (Table 1) stimulates the activation of Nrf2 and enhances its DNA binding in human umbilical vein endothelial cells (HUVEC). DMSO was found to be non-toxic to HUVEC even at very high concentrations [134]. DMSO-dependent HO-1 induction is mediated by Nrf2 pathway activation and DMSO also induces HO-1 expression and activity in a dose and time-dependent pattern in the cells. Furthermore, DMSO (**23**) has been reported to activate HO-1 protein expression via cJun-N-terminal kinase (JNKs)-dependent pathways, increase the nuclear translocation of Nrf2, and promote the antioxidant response element (ARE) binding of Nrf2 [125].

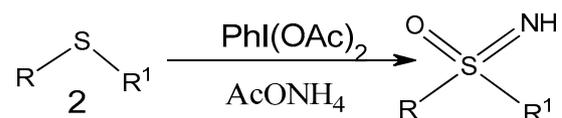
2.2.2. Vinyl Sulfoxide Derivatives

Shim et al. [135] reported that vinyl sulfoxide derivatives (compound **24** and **25**) (Table 1) exhibit moderate HO-1 inducing activities (69.8 and 62.4% respectively) as a measure of Nrf2 activation but do not inhibit NO production. Woo et al. [99] also reported that vinyl sulfoxide derivative (**26**) displays a moderate HO-1 inducing activity (133.5%)

and Nrf2 activation when compared with vinyl sulfone (257.5%) and chalcone (164.4%) analogues. Shim and co-workers [135] reported that the addition of OH-, Ome-, and F-groups affects the HO-1 induction of compounds **24** and **25**, and the presence of hydroxyl and keto forms produces the same effect on HO-1 induction.

2.2.3. Sulfoximine Derivatives

Sulfoximines are aza-analogues of sulfones in which the sulfinyl group is bonded to a nitrogen. They possess several biological activities, as extensively reviewed in [136,137]. Sulfoximine is synthesized from sulfides via one-pot O- and N-transfers (Scheme 9) [138].



Scheme 9. Synthesis of sulfoximine.

Carlstrom et al. [100] reported that vinyl sulfoximine derivatives (compounds **27** and **28**) (Table 1) activate transcriptional factors such as Nrf2, HIF1, and NFkB via the pTRAF platform in comparison with dimethyl fumarate. Compounds **27** and **28** activate Nrf2 and downstream transcripts in vitro with a very minimal off-target effect on HIF1 and NFkB. In HEK293 cells, GCLM, GSTA4, and NQO1 which are known Nrf2-activated transcripts display similar regulation with both compound **28** and dimethyl fumarate. Microglia exhibits a diverse Nrf2-pattern, while oligodendrocytes show a more overlapping response to compound **28** and dimethyl fumarate. Compound **28** exhibits very high Nrf2-activation potency upon evaluation in pTRAF-transfected HEK293 cells. When compared with dimethyl fumarate, compound **28** possesses a better Nrf2-specific activating profile and the oligodendrocyte phenotype in terms of the proliferation of pre-myelinating cells is influenced by this factor. Moreover, the off-target effects of compound **28** are more limited when compared to dimethyl fumarate in HEK293 cells. Compound **28** exhibits improved Nrf2 activation when co-stimulated with tumor necrosis factor [100]. Treatment with a sulfoximine derivative L-buthionine-S-R-sulfoxime reportedly upregulated γ -glutamylcysteine ligase mRNA and L-cys/L-cys2 transporter via the activation of Nrf2 and other pathways in the striatum [139].

2.3. Oltipraz

Oltipraz (**29**) (Table 1) is an organosulfur compound that belongs to the class of synthetic dithiolethiones [140]. Being a chemopreventive and anti-angiogenic agent, it protects the body from several carcinogenic insults via the induction of detoxification enzymes [141]. It is synthesized by the reaction of methyl2-methyl-3-(pyrazine-2-yl)-3-oxopropionate with phosphorus pentasulfide in a mixed solvent of xylene and toluene [142]. Oltipraz (**29**) has been reported as an effective activator of the Nrf2 signaling pathway, being a soft electrophile, it activates Nrf2 and stimulates the production of many phase II detoxification enzymes [141]. It induces the expression of antioxidant genes such as quinone oxidoreductase (NQO1) via the activation of Nrf2 and constitutive androstane receptor (CAR) [143]. Oltipraz (**29**) also hinders fat-induced insulin resistance and obesity via the upregulation of Nrf2 in C57BL/6J mice [144] and prevents high glucose-induced apoptosis and oxidative stress via activation of the Nrf2/NQO1 pathway in RSC96 cells [145]. Atilano-Roque et al. [146] observed the effect of Nrf2 activation by oltipraz in the amelioration of injury in the human kidney cells. It was discovered that oltipraz could be a potential therapy for the enhancement of nephroprotectant effects for cisplatin-exposed kidney injury patients. Ramos-Gomez et al. [147] reported that the effects of oltipraz and Nrf2 genotype on benzo[a]pyrene-DNA adducts and tumor yield are interactive. This suggests that the anticarcinogenic activity of oltipraz in mice depends on its ability to modulate the Nrf2-regulated genes since the loss of Nrf2 in nrf2-deficient mice abrogates its chemopreventive effects. Iida et al. [148] corroborated the fact that activation of Nrf2 is pivotal to the chemopreventive potency of oltipraz (**29**) against the carcinogenesis of urinary bladder and enhancement of the detoxification of carcinogens.

Table 1. Synthetic organosulfur compounds and their Nrf2 activation.

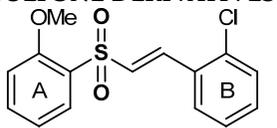
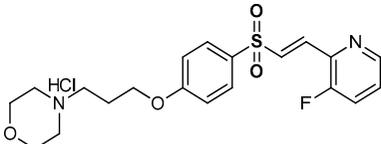
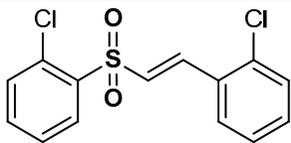
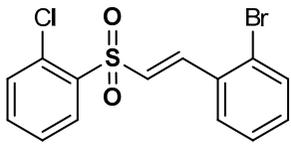
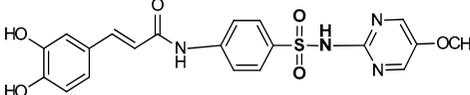
Entry	Compounds	Effective Concentration/Dose	Biological Activity	Study Model	Targeted Diseases	Ref
4	<p>SULFONE DERIVATIVES</p>  <p>(E)-1-chloro-2-((2-methoxyphenyl)sulfonyl)vinylbenzene</p>	1–5 μ M	Antioxidant, anti-inflammatory	Microglia, Parkinson's disease animal model	Parkinson's disease	[98]
		1–10 μ M	Antioxidant, neuroprotection	MPTP-induced Parkinson's disease mouse model	Parkinson's disease	[99]
		10 μ M	Neuroprotection	HEK293 cells	Traumatic brain injury	[100]
5	 <p>(E)-4-(3-(4-((2-(3-fluoropyridin-2-yl)vinyl)sulfonyl)phenoxy)propyl)morpholine hydrochloride</p>	10 μ M	Antioxidant, neuroprotection	MPTP-induced Parkinson's disease mouse model	Parkinson's disease	[102]
6	 <p>(E)-1-chloro-2-((2-chlorophenyl)sulfonyl)vinylbenzene</p>	0.5–1 μ M	Antioxidant, neuroprotection	PC12 Cells	Oxidative stress	[32]
7	 <p>(E)-1-bromo-2-((2-chlorophenyl)sulfonyl)vinylbenzene</p>	0.5–1 μ M	Antioxidant, neuroprotection	PC12 Cells	Oxidative stress	[32]
8	<p>SULFONAMIDE DERIVATIVES</p>  <p>(E)-3-(3,4-dihydroxyphenyl)-N-(4-(N-(5-methoxypyridin-2-yl)sulfamoyl)phenyl)acrylamide</p>	50–200 μ M	Antioxidant	A549 Cells	Oxidative stress	[111]

Table 1. Cont.

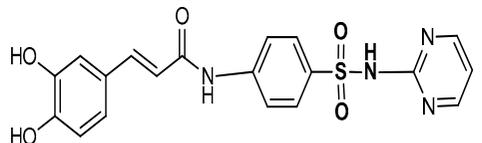
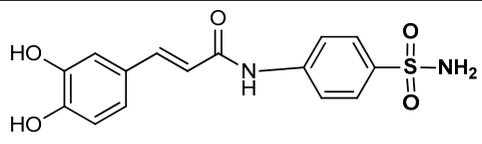
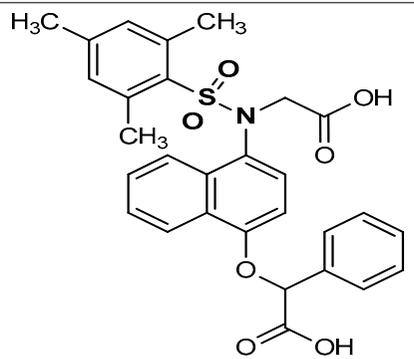
Entry	Compounds	Effective Concentration/Dose	Biological Activity	Study Model	Targeted Diseases	Ref
9	 <p>(E)-3-(3,4-dihydroxyphenyl)-N-(4-(N-pyrimidin-2-yl)sulfamoylphenyl)acrylamide</p>	50–200 μ M	Antioxidant	A549 Cells	Oxidative stress	[111]
10	 <p>(E)-3-(3,4-dihydroxyphenyl)-N-(4-sulfamoylphenyl)acrylamide</p>	50–200 μ M	Antioxidant	A549 Cells	Oxidative stress	[111]
11	 <p>2-((4-(N-(carboxymethyl)-2,4,6-trimethylphenyl)sulfonamido)naphthalen-1-yl)oxy)-2-phenylacetic acid</p>	0.58 μ M	Antioxidant, Keap1–Nrf2 PPI inhibition	RAW264.7 Cells	Inflammation	[94]

Table 1. Cont.

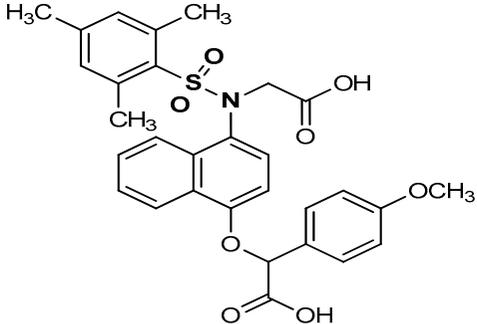
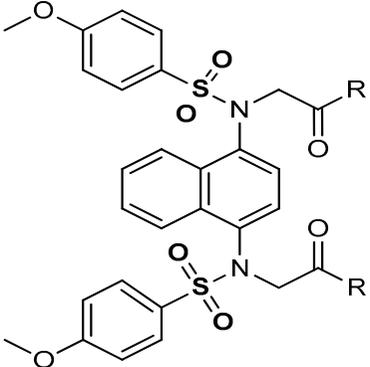
Entry	Compounds	Effective Concentration/Dose	Biological Activity	Study Model	Targeted Diseases	Ref
12	 <p data-bbox="255 715 853 799">2-((4-(N-(carboxymethyl)-2,4,6-trimethylphenylsulfonamido)naphthalen-1-yl)oxy)-2-(4-methoxyphenyl)acetic acid</p>	≥500 μL	Antioxidant, Keap1–Nrf2 PPI inhibition	RAW264.7 Cells. HepG2 Cells, mice, rat	Inflammation	[94]
13	 <p data-bbox="293 1193 815 1278">2,2'-(naphthalene-1,4-diylbis((4-methoxyphenyl)sulfonyl)azanediyl))diacetic acid (R=OH)</p>	≥500 μL	Antioxidant, Keap1–Nrf2 PPI inhibition	RAW264.7 Cells. HepG2 Cells, mice, rat	Inflammation	[94]

Table 1. Cont.

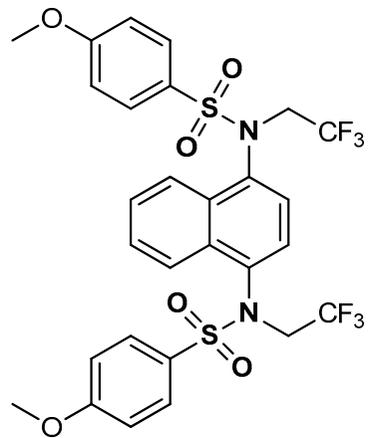
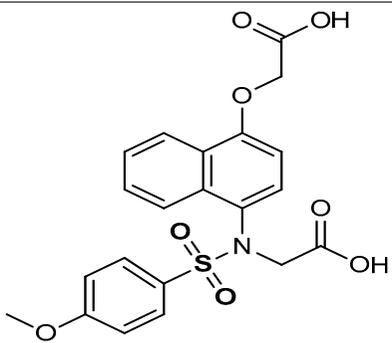
Entry	Compounds	Effective Concentration/Dose	Biological Activity	Study Model	Targeted Diseases	Ref
14	 <p data-bbox="235 821 873 917">N-(4-((4-methoxy-N-(2,2,2-trifluoroethyl)phenyl)sulfonamido)isoquinolin-1-yl)-N-((4-methoxyphenyl)sulfonyl)glycine</p>	$\geq 500 \mu\text{L}$	Antioxidant, Keap1-Nrf2 PPI inhibition	RAW264.7 Cells. HepG2 Cells, mice, rat	Inflammation,	[94]
15	 <p data-bbox="302 1268 806 1332">2-(N-(4-(carboxymethoxy)naphthalen-1-yl)-4-methoxyphenylsulfonamido)acetic acid</p>	8.19 μM	Antioxidant, Keap1-Nrf2 PPI inhibition	RAW264.7 Cells	Inflammation	[94]

Table 1. Cont.

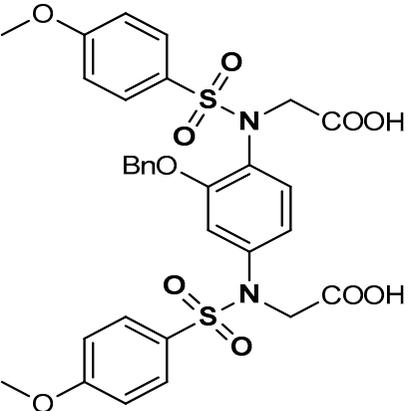
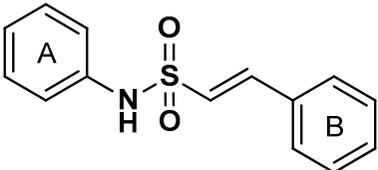
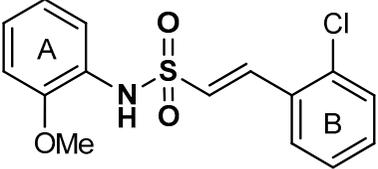
Entry	Compounds	Effective Concentration/Dose	Biological Activity	Study Model	Targeted Diseases	Ref
16	 <p>2,2'-(2-(Benzyloxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl)diacetic acid</p>	10–100 μM	Keap1–Nrf2 PPI inhibition, Antioxidant,	Hepa1c1c7 mouse hepatic cells	Cytotoxicity	[114]
17	 <p>(E)-N,2-diphenylethanesulfonamide</p>	>10 μM	Antioxidant, anti-inflammatory, neuroprotection	MPTP-induced PD mouse model	Parkinson's disease	[115]
18	 <p>(E)-2-(2-chlorophenyl)-N-(2-methoxyphenyl)ethanesulfonamide</p>	6.35 μM	Antioxidant, anti-inflammatory, neuroprotection	MPTP-induced PD mouse model	Parkinson's disease	[115]

Table 1. Cont.

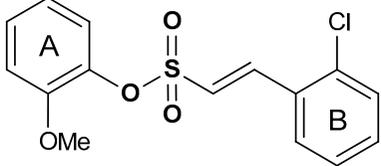
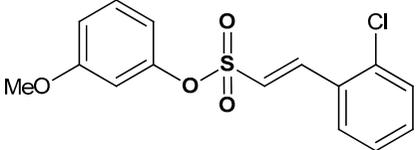
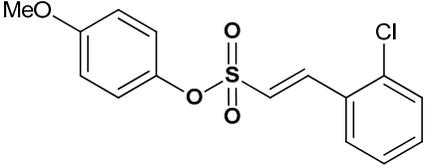
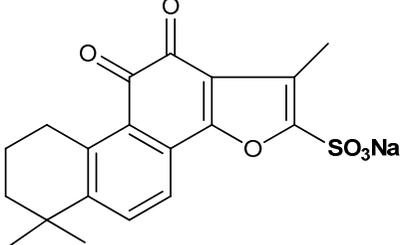
Entry	Compounds	Effective Concentration/Dose	Biological Activity	Study Model	Targeted Diseases	Ref
	SULFONATE DERIVATIVES					
19	 <p>(E)-2-methoxyphenyl 2-(2-chlorophenyl)ethenesulfonate</p>	0.076 μ M	Antioxidant, anti-inflammatory, neuroprotection	MPTP-induced PD mouse model	Parkinson's disease	[115]
20	 <p>(E)-3-methoxyphenyl 2-(2-chlorophenyl)ethenesulfonate</p>	0.165 μ M	Antioxidant, anti-inflammatory, neuroprotection	MPTP-induced PD mouse model	Parkinson's disease	[115]
21	 <p>(E)-4-methoxyphenyl 2-(2-chlorophenyl)ethenesulfonate</p>	0.237 μ M	Antioxidant, anti-inflammatory, neuroprotection	MPTP-induced PD mouse model	Parkinson's disease	[115]
22	 <p>sodium 1,6,6-trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro [1,2-b]furan-2-sulfonate</p>	10 μ g/mL	Antioxidant	RAW 264.7 Cells, MRC-5 Cells	Silicosis	[121]

Table 1. Cont.

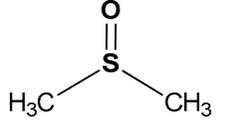
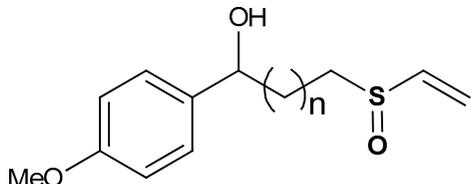
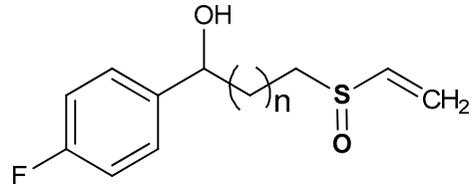
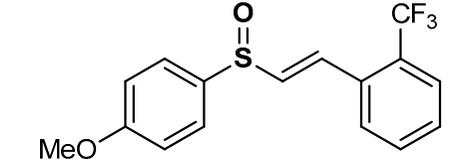
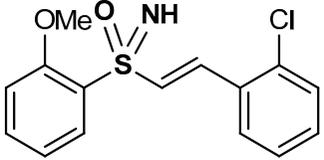
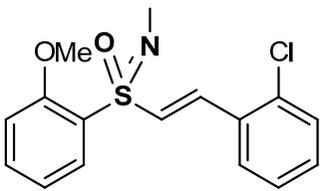
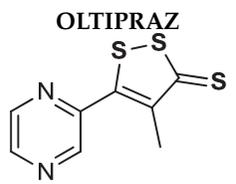
Entry	Compounds	Effective Concentration/Dose	Biological Activity	Study Model	Targeted Diseases	Ref
	SULFOXIDE DERIVATIVES					
23	 (methylsulfinyl)methane	0.1–0.8%	Antioxidant, anti-inflammatory	Human umbilical vein endothelial cells (HUVECs)	Oxidative stress	[125]
24	 1-(4-methoxyphenyl)-3-(vinylsulfinyl)propan-1-ol	20 μ M	Antioxidant, Nrf2 activation, HO-1 induction	BV-2 Cells	Parkinson's disease	[135]
25	 1-(4-fluorophenyl)-3-(vinylsulfinyl)propan-1-ol	20 μ M	Antioxidant, Nrf2 activation, HO-1 induction	BV-2 Cells	Parkinson's disease	[135]
26	 (E)-1-(2-((4-methoxyphenyl)sulfinyl)vinyl)-2-(trifluoromethyl)benzene	20 μ M	Neuroprotection, Antioxidant	BV-2 Cells	Parkinson's disease	[99]

Table 1. Cont.

Entry	Compounds	Effective Concentration/Dose	Biological Activity	Study Model	Targeted Diseases	Ref
SULFOXIMINE DERIVATIVES						
27	 <p>(E)-1-chloro-2-(2-(2-methoxyphenyl)sulfonimidoyl)vinyl)benzene</p>	10 μ M	Nrf2 activation, Antioxidant	HEK293 Cells	Traumatic brain injury (TBI)	[100]
28	 <p>1-chloro-2-((E)-2-[S-(2-methoxyphenyl)-N-methylsulfonimidoyl]ethenyl)benzene</p>	10 μ M	Nrf2 activation, Antioxidant	HEK293 Cells	Traumatic brain injury (TBI)	[100]
29	 <p>4-methyl-5-(pyrazin-2-yl)-3H-1,2-dithiole-3-thione</p>	150 mg/kg	Antioxidant, Nrf2 activation	HepG2 cells and C57BL/6 mouse liver	oxidative stress	[143]
		0.75 g/kg	Antioxidant	C57BL/6J mice	Obesity, insulin resistance, Oxidative stress	[144]
		20 μ M	Antioxidant	RSC96 cells	Oxidative stress, Apoptosis	[145]
		12 μ M	Antioxidant, Nrf2 activation	HEK293 cells	Kidney cell injury	[146]
		500 mg/kg	Antioxidant, Chemoprevention	Mice	Cancer	[147]
		250 mg/kg	Anticancer, Antioxidant	Mouse urothelial cells	Urinary bladder carcinogenesis	[148]

3. Nrf2-Activating Natural Organosulfur Compounds

3.1. Isothiocyanates

Isothiocyanates (ITCs) are organosulfur compounds majorly obtained as hydrolysis products of glucosinolates from cruciferous vegetables. However, their synthetic derivatives can be obtained by the substitution of the oxygen atom in the isocyanate moiety with a sulfur atom. Owing to their chemical diversity and biological activities, ITCs have been widely studied in food science and medical research [149,150]. Naturally occurring ITCs such as benzyl isothiocyanate (BITC), allyl isothiocyanate (AITC), phenylethyl isothiocyanate (PEITC), and sulforaphane (SFN) activate the Nrf2/Keap1 signaling pathway. Cheng et al. [151] reported that moringa isothiocyanate (30) (Table 2) suppresses oxidative stress and inflammation in high glucose induced renal cells via the activation of Nrf2/ARE signaling and upregulation of Nrf2 target genes.

3.1.1. Benzyl Isothiocyanate

Benzyl isothiocyanate (BITC) (31) (Table 2) attenuates obesity-induced hyperglycemia via the enhancement of Nrf2-mediated antioxidant IRS-1/AKT/TBC1D1 signaling in muscles [152]. EL Badawy et al. [153] reported that BITC modulates oxidative stress, inflammation and apoptosis via the activation of Nrf2/HO-1 and NF- κ B signaling pathways in gastric injury in rats. BITC inhibits the production of excessive superoxide in inflammatory leukocytes and also exhibits significant chemo preventive effects via the activation of the Nrf2/Keap1 signaling pathway [154,155].

3.1.2. Allyl Isothiocyanate

Allyl isothiocyanate (AITC) (32) (Table 2) exhibits chemopreventive actions via Nrf2/Keap1 signaling and induces phase II cytoprotective and detoxifying enzymes [155]. AITC attenuates inflammation and oxidative stress via the modulation of Nrf2/HO-1 and NF- κ B pathways, thereby ameliorating traumatic brain injury in mice [156]. Zhang et al. [157] reported that AITC elevates the expression of multidrug resistance-related protein 1 (MRP1) in cigarette smoke extract-stimulated human bronchial epithelial cells via the activation of the JNK/Nrf2 pathway. It also reduces spontaneous degradation in hepatocyte and attenuates acetaminophen-induced liver injury via the activation of Nrf2, thereby making it a potential drug for liver-related injuries [158].

3.1.3. Phenylethyl Isothiocyanate

Phenylethyl Isothiocyanate (PITC) (33) (Table 2) is an effective activator of cytoprotective pathways such as Nrf2 and heat shock factor 1 (HSF1). However, it helps the accumulation of reactive oxygen species at high concentration resulting in cytotoxicity [159]. PITC activates Nrf2 and significantly upregulates mRNA and protein levels of the HO-1, NQO1 and γ -glutamyl cysteine synthetase (γ GCS) in cultured fibroblast [160]. Nrf2 plays an essential role in the antioxidant and anti-inflammatory effect of PEITC as Nrf2 knockout reportedly attenuated its anti-inflammatory activities [161]. Moreover, the chemopreventive actions of PITC have been linked to the activation of Nrf2/ARE signaling. It also activates ARE-mediated phase II drug metabolism expressions via the Nrf2 and C-Jun N-terminal Kinase 1 (JNK1) pathways [162].

3.1.4. Sulforaphane

Sulforaphane (SFN) (34) (Table 2) is a sulfinyl group-containing aliphatic lipophilic organosulfur compound, it is a broccoli-derived phytochemical with several biological activities, especially Nrf2 activation and chemopreventive abilities. Sulforaphane (1-isothiocyanato-(4R)-(methylsulfinyl)butane: $\text{CH}_3\text{S}(\text{O})(\text{CH}_2)_4\text{N}=\text{C}=\text{S}$) being a phytochemical-based supplement, is by comparison a more potent Nrf2 activator than resveratrol, curcumin, and silymarin [163]. Its lipophilicity and lower molecular weight (MW = 177.29) are responsible for its higher bioavailability compared to the polyphenol-based dietary supplements with Nrf2-activating ability [163]. SFN exhibits antioxidant and anti-inflammatory activities via Nrf2/GSH system [164,165]. SFN

induces Nrf2 by covalently binding to Keap1 [166,167]. Kubo et al. reported [168] that, via the induction of Nrf2/ARE/Prdx6 activity, sulforaphane reactivates cellular antioxidant defense during oxidative stress and aging. SFN in a dose-dependent fashion augments the expression of peroxiredoxin-6 (Prdx6), glutathione S-transferase (GST) and catalase (CAT) and halts their Nrf2 dysregulation [168]. It strengthens Nrf2/DNA binding and enhances promoter activities by increasing the expression and nuclear translocation of Nrf2. SFN in a dose-dependent manner also protects cells from UVB-induced toxicity, attenuates H₂O₂ loss of Prdx6 due to dysregulation of Nrf2/ARE and therefore combats aging-related diseases [168]. Clarke et al. [169] reported that SFN is easily metabolized and distributed to target tissues in both wild-type and Nrf2^{-/-} Mice. It is majorly present in tissues as N-acetylcysteine, glutathione and cysteinyl conjugates not as free molecule. Although SFN activates the Nrf2 pathway, Nrf2 is not essential for the metabolism and tissue distribution of SFN. Based on a quantitative LC-MS/MS analysis, SFN was recommended as an effective dietary chemopreventive agent for colon and prostate cancer [169]. Thimmulappa et al. [170] reported that SFN exerts its chemopreventive effect via activation of the Nrf2 pathway and consequent induction of phase II enzymes, thus providing protection against a broad spectrum of exogenous and endogenous toxicants. SFN attenuates the formation of colonic aberrant crypt foci in carcinogen-treated rats [171]. Using oligonucleotides, Thimmulappa and co-workers [170] observed that SFN induces Nrf2-regulation of genes encoding antioxidant enzymes such as GST, UDP-glucuronosyltransferases (UGT), γ -glutamylcysteine synthetase (GCS), NQO1, genes encoding cellular NADPH regenerating enzymes, xenobiotic metabolizing enzymes, and antioxidants. Recently, Xiong and co-workers [172] reported that SFN attenuates methamphetamine (METH)-induced apoptosis and oxidative damage by exerting a neuroprotective effect via the activation of the Nrf2-mediated pathway in neuronal cells. It also significantly increases cell viability in PC12 cells post-METH exposure via the activation of the Nrf2/HO-1/GCS pathway. SFN is an essential and functional food-derived supplement for ameliorating neuronal oxidative damage due to METH-induced neurotoxicity [172]. Morimitsu et al. [173] reported that 6-methylsulfinylhexyl isothiocyanate (6-HITC) (35) (Table 2), a broccoli isolate and an analogue of sulforaphane, activates the Nrf2-dependent detoxification pathway. The isolate 6-HITC (35) activates antioxidant response element (ARE), and induces nuclear localization of Nrf2 and the gene expression of the phase II enzymes. It also induces π GSTP1 and α GSTA1 isozymes in RL34 cells and hepatic phase II detoxification enzymes in the body more potently than SFN [173].

3.2. Sulfur-Containing Amino Acids and Derivatives

Sulfur-containing amino acids such as methionine, taurine, homocysteine, and cysteine are abundant in plants and animals with numerous biological activities [174]. They exhibit significant antioxidant and anti-inflammatory effects [174,175]. Sulfur-containing amino acids are metabolically interconnected, therefore a clear discrimination of their actual contribution to a biological effect cannot always be achieved. For instance, homocysteine is a product of the methionine cycle. Homocysteine undergoes two possible fates: it can i) be re-methylated to methionine, thus closing the methionine cycle; or ii) enter the transsulfuration pathway and be sequentially processed by cystathionine β -synthase (CBS) and cystathionine γ -lyase (CSE), thus leading to the generation of cysteine. In turn, cysteine is the precursor for other physiologically relevant thiols, such as taurine and glutathione. Another possible fate of cysteine is to be catabolized to 3-mercaptopyruvate (3-MP) by cysteine aminotransferase. The 3-MP is then bio-converted to pyruvate by 3-mercaptopyruvate sulfur transferase (3MST), in a reaction that leads to the formation of persulfides (R-SSH) as co-products, such as glutathione persulfide (GSSH) and cysteine persulfide [176]. Interestingly, persulfides are potent electrophiles, which have been shown to exert an antioxidant effect on mouse neuroblastoma cells, by directly targeting Keap1 and thereby inducing Nrf2 translocation into the nucleus [177]. Hence, the effect of sulfur-containing amino acids on the activation of the Nrf2 pathway is, at least in part, mediated by persulfides, which through S-sulfhydration of Keap1 induce activation of Nrf2 and consequent activation of the antioxidant response.

3.2.1. Methionine

L-Methionine (2-amino-4-(methylthio)butanoic acid) (36) (Table 2) is an essential sulfur-containing amino acid which helps in the stimulation of glutathione synthesis and depression of ROS accumulation [178,179]. It is an essential amino acid and through the transsulfuration pathway, a branch of the methionine cycle, leads to the biogenesis of cysteine and taurine. In turn, cysteine is a building block for the synthesis of GSH, the most abundant antioxidant species in the cell [180]. Given its key role in the bio-generation of endogenous sulfur species, it is not surprising that methionine has been appreciated for its antioxidant and anti-inflammatory effects [181,182]. Wang et al. [183] reported that the cytoprotective effect of methionine can be associated with the activation of the Nrf2/ARE pathway, as shown working in the Wistar rat model. Particularly, the activation of the Nrf2/ARE pathway by methionine normally occurs within 14 days of oral administration and induces endogenous antioxidant activity that depresses ROS-mediated oxidative damages [183]. An increased methionine intake affects the mRNA level and protein expression of Keap1 and increases the translocation of Nrf2 into the nucleus as well as its expression in the cytosol [183]. Feeding growing rats with methionine induces an effective regulation of the expression of hepatic enzymes involved in the metabolism of GSH via Nrf2/ARE pathway activation. Methionine stimulates the expression of ARE-dependent antioxidants such as CAT, HO-1, SOD, and NQO1 via Nrf2 activation [183]. It has been observed that increasing the oral administration of methionine enhances the activities of these ARE-dependent antioxidants, and this implies that the induction of endogenous antioxidant response depends on the quantity of methionine available. Methionine also stimulates both the synthesis of GSH and the expression of methionine sulfoxide reductase through the Nrf2/ARE pathway [183]. In a similar study aiming to elucidate the role of methionine on the antioxidant effect of rice protein (RP) when orally administered, adult rats were fed with RP and methionine-supplemented RP. Herein, the authors corroborated that methionine activates the Nrf2/ARE pathway through which it augments the endogenous antioxidant capacity of RP [184]. Moreover, the activation of the Nrf2/ARE pathway by methionine stimulates the expression of methionine reductase and enhances glutathione synthesis which accounts for the augmentation of endogenous antioxidant activity of RP. Methionine activates Nrf2 by inhibiting Keap1 and Cul3 which results in the up-regulation of ARE-driven antioxidant genes [184]. This notwithstanding, an entire line of research supports the hypothesis that lower methionine intake reduces ROS generation and increases overall animal longevity. For instance, Liu et al. [185] recently reported that dietary restriction of methionine in lambs affects the redox system, changes the content of methionine and its metabolites in the liver and plasma, and, eventually, induces Nrf2 signaling pathway activation. This apparent discrepancy in the role of methionine on the regulation or redox balance is reconciled by the observation that reduced GSH levels, consequent to methionine restriction, induce the activation of the antioxidant response through Nrf2 as a compensatory mechanism. This mechanism of methionine restriction to induce its biological effects through decreasing GSH levels was shown in a study, in which cysteine was added to the methionine restriction diet [186].

3.2.2. Taurine

Taurine (2-aminoethanesulfonic acid) (37) (Table 2) is a sulfur-containing amino acid commonly found in animal tissues, bile, and large intestines [187]. For industrial purposes taurine is synthesized by the ammonolysis of isethionic acid [188]. In humans, the bio-synthesis of taurine is strictly interconnected with the transsulfuration pathway (see above), which eventually leads to the production of cysteine. Among the possible metabolic fates, cysteine can undergo oxidation to its sulfinic acid by cysteine dioxygenase. The subsequent decarboxylation to hypotaurine and oxidation by hypotaurine dehydrogenase leads to taurine [189]. Similarly to other sulfur-containing compounds, taurine has also been shown to display antioxidant and anti-inflammatory activities. For instance, taurine supplementation attenuates oxidative stress and inflammation in patients with type 2 diabetes and reduces cardiovascular risk [190–192].

Yang and co-workers [193] demonstrated that taurine, via the activation of the Nrf2/HO-1 pathway, decreases ROS generation and attenuates ionizing radiation-induced GC-2 cell damage [193]. Agca et al. [194] reported that taurine attenuates the severity of oxidative stress through enhancement of the expression levels of Nrf2 and HO-1, thus leading to the activation of the Nrf2/HO-1 signaling pathway in diabetic rats [194].

3.2.3. Homocysteine

Homocysteine (38) (Table 2) is a sulfur-containing amino acid and is the end-product of the methionine cycle in the liver [195,196]. The possible fates of homocysteine are: (i) re-entering in the methionine cycle, thus undergoing re-methylation to methionine; or (ii) contributing to the generation of cysteine through the transsulfuration pathway. The transsulfuration pathway plays a pivotal role in the regulation of sulfur metabolism and has a tight connection with the antioxidant response [197]. It consists in a double-step reaction in which homocysteine is enzymatically condensed with serine (or cysteine) by CBS, thus producing cystathionine. The latter, in turn, is bio-converted to cysteine by CSE. Both CBS and CSE produce hydrogen sulfide (H₂S) as side-product, a gaseous signaling molecule (also referred as a gasotransmitter) mediating cell protection against oxidative stress through stabilization of Nrf2 via Keap1 inhibition [42,71]. Hourihan et al. [42] reported that MEF cells exposed to NaHS, an H₂S donor, correlated with increased Nrf2 half-life and increased expression levels of Nrf2 target genes. Most interestingly, CBS and CSE (but not 3MST) are among the genes controlled by Nrf2, thus establishing a feedback loop in which the homocysteine-derived H₂S activates Nrf2 which in turn induces the expression of H₂S-synthesizing enzymes [42]. The induction of CSE and CBS by Nrf2 is not surprising as they regulate the transsulfuration pathway, which is the major source of the two main physiological antioxidants, cysteine and GSH, along with H₂S which activates antioxidant stress response via the sulfhydrylation of target proteins [198]. CBS and CSE enzymatic activity have also been associated with the production of reactive sulfur species, such as persulfides (R-SSH) [199]. Differently from their thiol cognate which can be only nucleophilic, persulfide can be either nucleophilic or electrophilic, according to the protonation state. Persulfides owe their reactivity to the presence of an electron lone pair on the atom adjacent to the nucleophilic atom (α -effect) [200]. Consistently, persulfides have been shown to be much stronger antioxidants as compared to their corresponding thiols, by direct scavenging ROS and by activating antioxidant response, similarly to the Nrf2 pathway [201]. Persulfidation of Keap1 has been shown to promote the dissociation of Nrf2 from the Nrf2–Keap1 complex, thus inducing the expression of the downstream Nrf2-targeted genes [71,202,203]. Regardless the actual mediator of the effect of homocysteine, its role in cellular redox homeostasis and regulation of inflammation is controversial. For instance, in a study investigating the effect of chronic administration of homocysteine in a hypercholesterolemic rat model, it was shown that homocysteine treatment prevented cholesterol-induced inflammation and partly counteracted the cortical blood–brain barrier disruptions [204]. On the other hand, chronic hyperhomocysteinemia has been shown to induce long-term memory deficits in the rat model [205]. Indeed, as shown in HepG2 cells, homocysteine treatment induces oxidative stress which is responsible for the activation of the Nrf2 pathway, with consequent increased levels of ARE-associated proteins, such as HO-1 and GCL [206–208]. Navneet et al. [209] reported that excess of homocysteine (50 μ M–10 mM) activates the Nrf2 pathway in retinal Muller glial cells, increases Nrf2 expression, and decreases oxidative stress and ROS levels [209].

3.2.4. N-Acetylcysteine

N-acetylcysteine (NAC) (39) (Table 2) is a stable and supplement form of cysteine used for the treatment of paracetamol overdoses [210]. It possesses significant antioxidant and anti-inflammatory properties [211,212]. Jannatifar et al., in a clinical trial study, reported that oral supplementation of NAC enhances the quality of semen in asthenoteratozoospermia men by improving the expression level of Nrf2 genes and antioxidant enzymes [213].

NAC also decreases the production of malondialdehyde (MDA) and protects the sperm cells against oxidative stress via Nrf2 activation [213]. Zhou and co-workers reported that *N*-acetylcysteine amide (NACA) (40) (Table 2) attenuates brain injury, and increases the nuclear import of Nrf2 and the expression of Nrf2 downstream factors in mRNA and protein levels of mice at one day after traumatic brain injury [214]. NACA is antiapoptotic and attenuates oxidative stress and neuronal damage [214]. It is not clear whether NAC-mediated activation of the Nrf2 pathway is due to direct interaction with one of the redox-sensitive cysteines of Keap1. Most probably, given the poor electrophilicity of this compound, its effect is mediated by other molecular mediators. Indeed, Ezerina et al. have shown that NAC stimulates the production of persulfides, which were proposed as the actual mediators of the immediate antioxidants and cytoprotective effect of NAC [215]. Consistently, NAC has been reported to boost 3-MST activity both in isolated enzyme and SW480 cell models, increasing the production of H₂S, likely through the formation of NAC-persulfide intermediate [216].

3.2.5. Carbocysteine

Carbocysteine ([®]-2-amino-3-(carboxymethylsulfanyl)propanoic acid) (41) (Table 2) is a mucolytic agent with significant antioxidant and anti-inflammatory activities [217]. Pace et al. reported that carbocysteine reduces the production of ROS, increases HO-1, GSH, Nrf2, and HDAC-2 nuclear expression and activity in cigarette smoke extract-stimulated cells [218].

3.2.6. Ergothioneine

Ergothioneine (42) (Table 2) is a sulfur-containing amino acid with potent antioxidant activities. It is a metabolite of histidine commonly found in high concentration in mushrooms amongst other foods [219]. They are produced by biosynthesis in certain species of fungi and bacteria [220]. Salama et al. [221] reported that Ergothioneine (42) ameliorates cisplatin-induced nephrotoxicity via the activation of Nrf2, p53 and NF-κB signaling and upregulation of antioxidant genes such as NQO1 and HO-1 in rats. Hseu and co-workers [222] reported that ergothioneine (42) attenuates UVB-induced skin damage even at nanomolar concentration by exhibiting dermato-protective activity via the induction of Nrf2/ARE-mediated antioxidant genes. In a similar development, ergothioneine reportedly alleviated inflammation, ROS production, apoptosis and senescence of fibroblast due to UVB-induced keratinocytes damage through the activation of the Nrf2/HO-1 signaling pathway [223].

3.3. Allicin

Allicin (43) (Table 2) is an organosulfur compound obtained from garlic bulbs, its taste and odor are typical of freshly crushed garlic [224]. Allicin (diallyl thiosulfinate) inhibits lipids peroxidation and exhibits antioxidant, radical scavenging, chemopreventive, and anti-inflammatory activities [225–227]. Bat-Chen et al. reported that allicin induces the apoptotic death of HCT-116 a colon cancer cell line via Nrf2 activation [228]. Allicin stimulates the release of cyt C, increases Bax-protein levels and decreases Bcl-2 level. It also stimulates the accumulation, translocation, and transactivation of Nrf2 to the nucleus. Interestingly, Nrf2 siRNA-transfected HCT-116 cells resist to allicin-induced inhibition of proliferation [228]. Zhang and co-workers reported that allicin exerts antioxidative and anti-inflammatory effects that prevent lipopolysaccharide (LPS)-associated injury in human umbilical vein endothelial cells (HUVEC) by regulating the endogenous antioxidant system and inflammation via activation of Nrf2 and suppression of mitochondrial dysfunction [229]. Moreover, allicin hinders LPS-decreased cell viability, LPS-induced apoptosis, and adhesion of neutrophils to LPS-exposed HUVECs. It reduces LPS-induced oxidative stress and NF-κB binding activity in HUVECs. Allicin increases LPS-suppressed Nrf2 activity and regulates the expression of mitochondrial proteins and anti-inflammatory response. It modulates Nrf2 activation and increases the expression of LXRα in a dose-dependent manner [229].

Table 2. Natural organosulfur compounds and their Nrf2 activation.

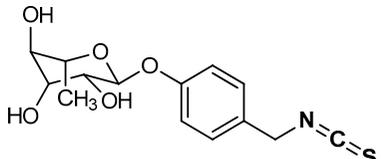
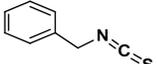
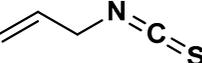
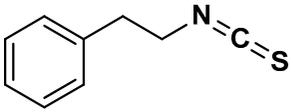
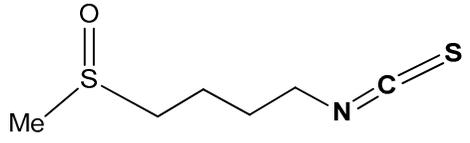
Entry	Compounds	Effective Concentration/Dose	Biological Activity	Study Model	Targeted Diseases	Ref
	ISOTHIOCYANATES					
30	 (2S,3R,4R,5R,6S)-2-(4-(isothiocyanatomethyl)phenoxy)-6-methyltetrahydro-2H-pyran-3,4,5-triol	0.4–100 μ M	Antioxidant, anti-inflammatory	HepG2-C8 cells	Diabetic nephropathy, oxidative stress	[151]
31	 (isothiocyanatomethyl)benzene	5 μ M	Antioxidant	Mice	Hyperglycemia, oxidative stress	[152]
		0.7 and 1.5 mg/kg	Antioxidant, anti-inflammatory	Rat	Gastric injury	[153]
32	 3-isothiocyanatoprop-1-ene	10 mg/kg	Antioxidant, anti-inflammatory	C57BL/6J mice	Traumatic brain injury	[156]
		40 μ M	Antioxidant	16HBE14o-cells	COPD	[157]
		25 or 50 mg/kg	Hepatotoxicity, antioxidant	HepG2 and AML12 cells	Acetaminophen-induced liver injury	[158]
33	 (2-isothiocianoethyl)benzene	1–100 μ M	Antioxidant, cytoprotection	NIH3T3 cells	cytotoxicity	[160]
		5 and 10 μ M	Antioxidant, anti-inflammatory	C57BL/6J mouse strain	Inflammation	[161]
		20 and 50 μ M	Chemoprevention, antioxidant	HeLa cells	cancer	[162]
34	 1-isothiocyanato-4-(methylsulfinyl)butane	3–8 μ M	Antioxidant	Human or rat epithelial cells	Oxidative stress	[168]
		110–440 μ mol/kg	Anticancer, chemoprevention	Wild-type mice	Cancer	[169]
		9 μ mol/day	Anticancer, chemoprevention	Mice	Cancer	[170]
		1–10 μ M	Antioxidant, neuroprotection	PC12 Cells	Oxidative stress, apoptosis	[172]

Table 2. Cont.

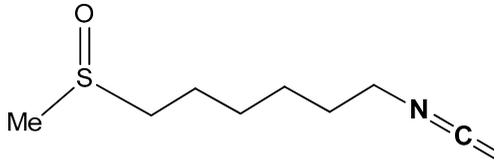
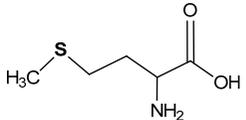
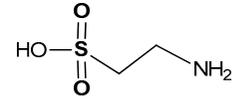
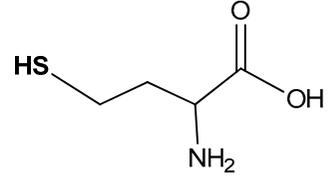
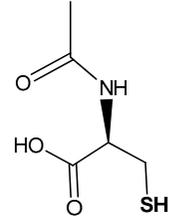
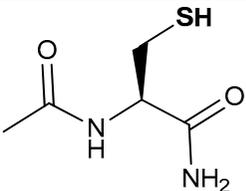
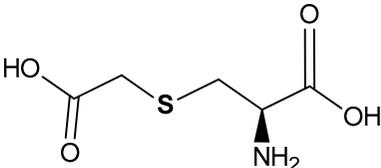
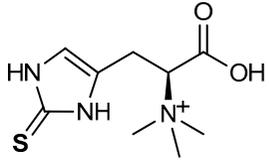
Entry	Compounds	Effective Concentration/Dose	Biological Activity	Study Model	Targeted Diseases	Ref
35	 <p>6-Methylsulfinylhexyl isothiocyanate</p>	5 μ M	Anticancer, chemoprevention	RL34 Cells	Cancer	[173]
36	<p>SULFUR-CONTAINING AMINO ACIDS AND DERIVATIVES</p>  <p>2-amino-4-(methylthio)butanoic acid</p>	21.50–43.00 mg, 100 g ⁻¹ body wt	Antioxidant	Growing rats	Oxidative stress	[183]
		21.2 mg/g	Antioxidant	Growing and adult rats	Oxidative stress	[184]
		0.4–0.91%	Hepatic antioxidant	Lambs	Oxidative stress	[185]
37	 <p>2-aminoethanesulfonic acid</p>	10–80 mM	Antioxidant	Mouse spermatocytes (GC-2 Cells)	Oxidative stress	[193]
		2% w/v	Antioxidant	Diabetic rats	Diabetic neuropathy	[194]
38	 <p>2-amino-4-mercaptobutanoic acid</p>	50 μ MD/L	Antioxidant	Hepatoma cell line (HepG2 Cells)	Oxidative stress	[206]
		50 μ M	Antioxidant	Hepatoma cell line (HepG2 Cells)	Oxidative stress	[207]
		0–100 μ M	Antioxidant	Hepatoma cell line (HepG2 Cells)	Oxidative stress	[208]
		50 μ M–1 mM	Antioxidant	Muller glial cells	Oxidative stress	[209]
39	 <p>(R)-2-acetamido-3-mercaptopropanoic acid</p>	600 mg	Antioxidant	Infertile men with asthenoteratozoospermia	Oxidative stress	[213]

Table 2. Cont.

Entry	Compounds	Effective Concentration/Dose	Biological Activity	Study Model	Targeted Diseases	Ref
40	 <p>(R)-2-acetamido-3-mercapto-propanamide</p>	100 mg/kg	Antioxidant, neuroprotection	Mouse model of TBI	Oxidative stress, TBI	[214]
41	 <p>(R)-2-amino-3-((carboxymethyl)thio)propanoic acid</p>	10 ⁻⁴ M	Antioxidant, Cytoprotection	Bronchial epithelial cells (16-HBE)	Chronic obstructive pulmonary disease (COPD)	[218]
42	 <p>(2S)-3-(2-Sulfanylidene-2,3-dihydro-1H-imidazol-4-yl)-2-(trimethylazaniumyl)propanoate</p>	70 mg/kg	Antioxidant, Anti-inflammatory	Rat	Nephrotoxicity	[221]
		125–500b nM	Antioxidant, Dermato-protection	Human keratinocytes	Skin damage, Oxidative stress	[222]
		0.1–10 mM	Antioxidant, Anti-inflammatory	Human keratinocytes	Skin damage, Oxidative stress, Inflammation	[223]
43	<p>ALLICIN</p>  <p>S-allyl prop-2-ene-1-sulfinothioate</p>	10 µg/mL	Apoptosis	Colon cancer cells (HCT-116)	Colon cancer	[228]
		40 µg/mL	Antioxidant, Anti-inflammatory	HUVECs	Oxidative stress, Inflammation	[229]

4. Conclusions

Nrf2 maintains redox homeostasis, regulates phase II antioxidant response, controls neuroinflammation, and remains a fascinating therapeutic target for several chronic diseases. Despite extensive research on the discovery of Nrf2 activators, only a few are approved for oxidative stress and inflammation-mediated diseases. A large body of scientific evidence shows that several organosulfur compounds are potent Nrf2 activators essential for antioxidative and anti-inflammatory purposes. This review has therefore comprehensively explored the Nrf2-activating potentials of organosulfur compounds, with particular focus on their antioxidant and anti-inflammatory effect. The ability to react with sulfhydryl (SH) groups is common amongst Nrf2 activators, and thus connects Nrf2 activation to sulfur-based chemistry, thereby creating opportunities for the discovery of novel Nrf2-activating organosulfur compounds. This review will therefore stimulate innovative research in this crucial area of medicinal chemistry.

Author Contributions: Conceptualization: L.S.; literature searches and manuscript writing: M.C.E., M.P., K.Z. and L.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: The authors thank Alessandro Giuffrè for his support and precious advice.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

α GSTA1	Glutathione S-transferase A1
ADME/tox	Absorption, Distribution, Metabolism, and Elimination/Toxicity
ARE	Antioxidant response element
BAX	BCL2 Associated X, Apoptosis Regulator
BBB	Blood-brain barrier
Bcl-2	B-cell lymphoma 2
BTB domain	Broad complex, tramtrack and bric-à-brac domain
β -TrCP	β -transducin repeat-containing protein
CAT	Catalase
CBP	CREB-binding protein
CBS	Cystathionine β -synthase
CDDO-Im	1-[2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl] imidazole
CH3	Cysteine/histidine-rich domain 3
JNKs	c-Jun N-terminal kinases
COX-	2-Cyclooxygenase-2
CREB	cAMP Responsive Element Binding protein
CSE	Cystathionine γ -lyase
Cul3	Cullin3 ligase
CYP	Cytochrome P450
Cyt c	Cytochrome c
15d-	PGJ2-15-deoxy- Δ 12,14-prostaglandin J2
DA	Dopaminergic
DMF	Dimethyl fumarate
DMSO	Dimethyl sulfoxide
EC ₅₀	Half maximal effective concentration
GCL	Glutamate-cysteine ligase
GCLM	Glutamate-cysteine ligase regulatory subunit
GCS	Gamma-glutamylcysteine synthetase
GSH	Glutathione
GSSH	Glutathione persulfide
GST	Glutathione S-transferase
GSTA4	Glutathione S-transferase Alpha 4
π GSTP1	Glutathione S-transferase π
HDAC-2	Histone Deacetylase 2

HEK293	Human embryonic kidney 293 cells
6-HITC	6-methylsulfinylhexyl isothiocyanate
HIF1	Hypoxia-inducible factor 1
H ₂ O ₂	Hydrogen peroxide
H ₂ S	Hydrogen sulfide
HO-1	Heme oxygenase-1
HUVEC	Human umbilical vein endothelial cells
iNOS	Inducible nitric oxide synthase
IVR	Intervening region
K _D	Dissociation constant
Keap1	Kelch-like ECH associated protein 1
KIX	Kinase-inducible domain interacting
LC-MS/MS	High performance liquid chromatography-mass spectrometry
LPS	Lipopolysaccharides
LXR α	Liver X receptor
MAD	Malondialdehyde
3-MP	3-mercaptopyruvate
3MST	3-mercaptopyruvate sulfur transferase
Maf	Musculoaponeurotic fibrosarcoma
METH	Methamphetamine
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MW	Molecular weight
NAC	N-acetylcysteine
NACA	N-acetylcysteine amide
NADPH	Nicotinamide adenine dinucleotide phosphate
NaHS	Sodium hydrosulfide
NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
NQO1	NADPH dehydrogenase 1
Nrf2	Nuclear factor erythroid 2-related factor 2
PD	Parkinson's disease
PPI	Protein-protein interaction
Prdx6	Peroxiredoxin 6
pTRAF	Plasmid for transcription factor reporter activation based upon fluorescence
ROS	Reactive oxygen species
RP	Rice protein
SFN	Sulforaphane
SH	Sulfhydryl group
siRNA	Small interfering RNA
SO	Sulfinyl group
SOD	Superoxide dismutase
Trx	Thioredoxin
TrxR	Thioredoxin reductase
UGT	UDP-glucuronosyltransferase
UVB	Ultraviolet B radiation

References

1. Cuadrado, A.; Manda, G.; Hassan, A.; Alcaraz, M.J.; Barbas, C.; Daiber, A.; Ghezzi, P.; Leon, R.; Lopez, M.G.; Oliva, B.; et al. Transcription factor Nrf2 as a therapeutic target for chronic diseases: A system medicine approach. *Pharmacol. Rev.* **2018**, *70*, 348–382. [[CrossRef](#)] [[PubMed](#)]
2. Mukwevho, E.; Ferreira, Z.; Ayeleso, A. Potential role of sulfur-containing antioxidant systems in highly oxidative environments. *Molecules* **2014**, *19*, 19376–19389. [[CrossRef](#)] [[PubMed](#)]
3. Parcell, S.; Cand, N.D. Sulfur in human nutrition and applications in medicine. *Altern. Med. Rev.* **2002**, *7*, 22–44. [[PubMed](#)]
4. Cuadrado, A.; Rojo, A.I.; Wells, G.; Hayes, J.D.; Cousin, S.P.; Rumsey, W.L.; Attucks, O.C.; Franklin, K.S.; Levonen, A.; Kensler, T.W.; et al. Therapeutic targeting of the Nrf2 and Keap1 partnership in chronic diseases. *Nat. Rev. Drug Discov.* **2019**, *18*, 295–317. [[CrossRef](#)]
5. Egbujor, M.C.; Saha, S.; Buttari, B.; Profumo, E.; Saso, L. Activation of Nrf2 signaling pathway by natural and synthetic chalcones: A therapeutic road map for oxidative stress. *Expert Rev. Clin. Pharmacol.* **2021**, *14*, 465–480. [[CrossRef](#)]

6. Saha, S.; Buttari, B.; Panieri, E.; Profumo, E.; Saso, L. An overview of Nrf2 signaling pathway and its role in inflammation. *Molecules* **2020**, *25*, 5474. [[CrossRef](#)]
7. He, Y.; Jiang, J.; He, B.; Shi, Z. Chemical activators of the Nrf2 signalling pathway in nonalcoholic fatty liver disease. *Nat. Prod. Commun.* **2021**, *16*, 1934578X20987095.
8. Imai, T.; Matsubara, H.; Hara, H. Potential therapeutic effects of Nrf2 activators on intracranial hemorrhage. *J. Cereb. Blood Flow Metab.* **2021**, *41*, 1483–1500. [[CrossRef](#)]
9. Liebman, S.E.; Le, T.H. Eat your Broccoli: Oxidative stress, Nrf2, and sulforaphane in chronic kidney disease. *Nutrients* **2021**, *13*, 266. [[CrossRef](#)]
10. Russo, M.; Spagnuolo, C.; Russo, G.L.; Skalicka-Woźniak, K.; Daglia, M.; Sobarzo-Sánchez, E.; Nabavi, S.F.; Nabavi, S.M. Nrf2 targeting by sulforaphane: A potential therapy for cancer treatment. *Crit. Rev. Food Sci. Nutr.* **2018**, *58*, 1391–1405. [[CrossRef](#)]
11. Sun, Q.; Shen, X.; Ma, J.; Lou, H.; Zhang, Q. Activation of Nrf2 signaling by oltipraz inhibits death of human macrophages with mycobacterium tuberculosis infection. *Biochem. Biophys. Res. Commun.* **2020**, *531*, 312–319. [[CrossRef](#)] [[PubMed](#)]
12. Hseu, Y.-C.; Yang, H.-L. Use of ergothioneine for inducing activity of nuclear factor erythroid 2-related factor-2 (Nrf2) in cell: EP2992882A1. In *Inventors*; Taiwan Assignee; China Medical University: Taiwan, China, 2016. Available online: <https://patents.google.com/patent/EP2992882A1/en> (accessed on 22 June 2022).
13. Abdelhamid, A.M.; Youssef, M.E.; Cavalu, S.; Mostafa-Hedeab, G.; Youssef, A.; Elazab, S.T.; Ibrahim, S.; Allam, S.; Elgharabawy, R.M.; El-Ahwany, E.; et al. Carbocysteine as a Modulator of Nrf2/HO-1 and NFκB Interplay in Rats: New Inspiration for the Revival of an Old Drug for Treating Ulcerative Colitis. *Front. Pharmacol.* **2022**, *13*, 887233. [[CrossRef](#)]
14. Mahn, A.; Castillo, A. Potential of sulforaphane as a natural immune system enhancer: A review. *Molecules* **2021**, *26*, 752. [[CrossRef](#)] [[PubMed](#)]
15. Clifford, T.; Acton, J.P.; Cocksedge, S.P.; Davis, K.A.B.; Balley, S.J. The effect of dietary phytochemicals on nuclear factor erythroid 2-related factor 2 (Nrf2) activation: A systemic review of human intervention trials. *Mol. Biol. Rep.* **2021**, *48*, 1745–1761. [[CrossRef](#)] [[PubMed](#)]
16. Motohashi, H.; O'Connor, T.; Katsuoka, F.; Engel, J.D.; Yamamoto, M. Integration and diversity of the regulatory network composed of Maf and CNC families of transcription factors. *Gene* **2002**, *294*, 1–12. [[CrossRef](#)]
17. Itoh, K.; Wakabayashi, N.; Katoh, Y.; Ishii, T.; Igarashi, K.; Engel, J.D.; Yamamoto, M. Keap1 represses nuclear activation of antioxidant responsive elements by Nrf2 through binding to the amino terminal Neh2 domain. *Genes Dev.* **1999**, *13*, 76–86. [[CrossRef](#)]
18. Katoh, Y.; Itoh, K.; Yoshida, E.; Miyagishi, M.; Fukamizu, A.; Yamamoto, M. Two domains of Nrf2 cooperatively bind CBP, a CREB binding protein, and synergistically activate transcription. *Genes Cells* **2001**, *6*, 857–868. [[CrossRef](#)]
19. Jaramillo, M.C.; Zhang, D.D. The emerging role of the Nrf2-Keap1 signaling pathway in cancer. *Genes Dev.* **2013**, *27*, 2179–2191. [[CrossRef](#)]
20. Wang, H.; Liu, K.; Geng, M.; Gao, P.; Wu, X.; Hai, Y.; Li, Y.; Li, Y.; Luo, L.; Hayes, J.D.; et al. RXRα inhibits the NRF2-ARE signaling pathway through a direct interaction with the Neh7 domain of NRF2. *Cancer Res.* **2013**, *73*, 3097–3108. [[CrossRef](#)]
21. Hayashi, M.; Kuga, A.; Suzuki, M.; Panda, P.; Kitamura, H.; Motohashi, H.; Yamamoto, M. Microenvironmental Activation of Nrf2 Restricts the Progression of Nrf2-Activated Malignant Tumors Nrf2-High Microenvironment Restricts Nrf2-Activated Tumors. *Cancer Res.* **2020**, *80*, 3331–3344. [[CrossRef](#)]
22. Singh, S.; Nagalakshmi, D.; Sharma, K.K.; Ravichandiran, V. Natural antioxidants for neuroinflammatory disorders and possible involvement of Nrf2 pathway: A review. *Heliyon* **2021**, *7*, e06216. [[CrossRef](#)]
23. Yao, W.; Lin, S.; Su, J.; Cao, Q.; Chen, Y.; Chen, J.; Zhang, Z.; Hashimoto, K.; Qi, Q.; Zhang, J. Activation of BDNF by transcription factor Nrf2 contributes to antidepressant-like actions in rodent. *Transl. Psychiatry* **2021**, *11*, 140. [[CrossRef](#)] [[PubMed](#)]
24. Dhaliwal, N.; Dhaliwal, J.; Singh, A.; Chopra, K. Dimethyl fumarate attenuates 2-vo-induced vascular dementia via activating the Nrf2 signaling pathway in rats. *Inflammopharmacology* **2021**, *29*, 537–547. [[CrossRef](#)] [[PubMed](#)]
25. Li, Y.; Shao, J.P.; Zhao, F.-Q.; Liu, H. Nrf2-ARE signalling partially attenuates lipopolysaccharide-induced mammary lesions via regulation of oxidative and organelle stresses but not inflammatory response in mice. *Oxid. Med. Cell. Longev.* **2021**, *2021*, 8821833.
26. Zhang, W.-B.; Lai, X.; Guo, X.-F. Activation of Nrf2 by miR-152 inhibits doxorubicin-induced cardiotoxicity via attenuation of oxidative stress, inflammation and apoptosis. *Oxid. Med. Cell. Longev.* **2021**, *2021*, 8860883. [[PubMed](#)]
27. KO, E.; Kim, D.; Min, D.W.; Kwon, S.H.; Lee, J.-Y. Nrf2 regulates cell motility through RhoA-Rock1 signaling in non-small-cell lung cancer cells. *Sci. Rep.* **2021**, *11*, 1247. [[CrossRef](#)] [[PubMed](#)]
28. Moi, P.; Chan, K.; Aunis, I.; Cao, A.; Kan, Y.W. Isolation of NF-E2-related factor 2 (Nrf2), a NF-E2-like basic leucine zipper transcriptional activator that binds to the tandem NF-E2/API repeat of the beta-globin locus control region. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 9926–9930. [[CrossRef](#)]
29. Chan, K.; Li, R.; Chang, J.C.; Kan, Y.W. Nrf2 a member of the NFE2 family of transcription factors, is not essential for murine erythropoiesis, growth, and development. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 13943–13948. [[CrossRef](#)]
30. Kerins, M.J.; Ooi, A. The Roles of NRF2 in Modulating Cellular Iron Homeostasis. *Antioxid. Redox Signal.* **2018**, *29*, 1756–1773. [[CrossRef](#)]
31. Sun, H.; Zhu, J.L.; In, H.; Gu, K.; Feng, F. Recent progress in the development of small molecule Nrf2 modulators: A patent review (2012–2016). *Expert Opin. Ther. Pat.* **2017**, *27*, 763–785. [[CrossRef](#)]

32. Song, Z.-L.; Hou, Y.; Bai, F.; Fang, J. Generation of potent Nrf2 activators via tuning the electrophilicity and steric hinderance of vinyl sulfones for neuroprotection. *Bioorg. Chem.* **2020**, *107*, 104520. [[CrossRef](#)] [[PubMed](#)]
33. Jaganjac, M.; Milkovic, L.; Sunjic, S.B.; Zarkovic, N. The NRF2, thioredoxin, and glutathione system in tumorigenesis and anticancer therapies. *Antioxidants* **2020**, *9*, 1151. [[CrossRef](#)] [[PubMed](#)]
34. Harvey, C.J.; Thimmulappa, R.K.; Singh, A.; Blake, D.J.; Ling, G.; Wakabayashi, N.; Fujii, J.; Myers, A.; Biswal, S. Nrf2-regulated glutathione recycling independent of biosynthesis is critical for cell survival during oxidative stress. *Free Radic. Biol. Med.* **2009**, *46*, 443–453. [[CrossRef](#)]
35. Kensler, T.W.; Wakabayashi, N.; Biswal, S. Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. *Annu. Rev. Pharmacol. Toxicol.* **2007**, *47*, 89–116. [[CrossRef](#)] [[PubMed](#)]
36. Barid, L.; Dinkova-Kostova, A.T. The cytoprotective role of the Keap1-Nrf2 pathway. *Arch. Toxicol.* **2011**, *85*, 241–272. [[CrossRef](#)]
37. Magesh, S.; Chen, Y.; Hu, L. Small molecule modulators of Keap1-Nrf2 ARE pathway as potential preventive and therapeutic agents. *Med. Res. Rev.* **2012**, *32*, 687–726. [[CrossRef](#)]
38. Done, A.J.; Traustadottir, T. Nrf2 mediates redox adaptations to exercise. *Redox Biol.* **2016**, *10*, 191–199. [[CrossRef](#)]
39. Bauer, M.; Bauer, I. Heme oxygenase-1: Redox regulation and role in the hepatic response to oxidative stress. *Antioxid. Redox Signal.* **2002**, *4*, 749–758. [[CrossRef](#)]
40. Bellezza, I.; Tucci, A.; Galli, F.; Grottelli, S.; Mieria, A.L.; Piloll, F.; Minelti, A. Inhibition of NF- κ B nuclear translocation via HO-1 activation underlies α -tocopheryl succinate toxicity. *J. Nutr. Biochem.* **2012**, *23*, 1585. [[CrossRef](#)]
41. Yerra, V.G.; Negi, G.; Sharma, S.S.; Kumar, A. Potential therapeutic effect of the simultaneous targeting of the Nrf2 and NF-KB pathways in dietary neuropathy. *Redox Biol.* **2013**, *1*, 394–397. [[CrossRef](#)]
42. Hourihan, J.M.; Kenna, J.G.; Hayes, J.D. The gasotransmitter hydrogen sulfide induces Nrf2-target genes by inactivating the Keap1 ubiquitin ligase substrate adaptor through formation of a disulphide bond between cys-226 and cys-613. *Antioxid. Redox Signal.* **2013**, *19*, 465–481. [[CrossRef](#)] [[PubMed](#)]
43. Hayes, J.D.; Dinkova-Kostova, A.T. The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. *Trends Biochem. Sci.* **2014**, *39*, 199–218. [[CrossRef](#)] [[PubMed](#)]
44. Wu, K.C.; Liu, J.J.; Klaassen, C.D. Nrf2 activation prevents cadmium-induced acute liver injury. *Toxicol. Appl. Pharmacol.* **2012**, *263*, 14–20. [[CrossRef](#)]
45. Sears, M.E. Chelation: Harnessing and enhancing heavy metal detoxification—A review. *Sci. World J.* **2013**, *2013*, 219840. [[CrossRef](#)]
46. Shen, G.; Kong, A.N. Nrf2 plays an important role in coordinated regulation of Phase II drug metabolism enzymes and Phase III drug transporters. *Biopharm. Drug Dispos.* **2009**, *30*, 345–355. [[CrossRef](#)] [[PubMed](#)]
47. Hayes, J.D.; Dinkova-Kostova, A.T.; McMahon, M. Cross-talk between Transcription Factors AhR and Nrf2: Lessons for Cancer Chemoprevention from Dioxin. *Toxicol. Sci.* **2009**, *111*, 199–201. [[CrossRef](#)]
48. Shaw, P.; Mondal, P.; Bandyopadhyay, A.; Chattopadhyay, A. Environmentally relevant concentration of chromium activates Nrf2 and alters transcription of related XME genes in liver of zebrafish. *Chemosphere* **2019**, *214*, 35–46. [[CrossRef](#)]
49. Kawajiri, K.; Fujii-Kuriyama, Y. The aryl hydrocarbon receptor: A multifunctional chemical sensor for host defense and homeostatic maintenance. *Exp. Anim.* **2017**, *66*, 75–89. [[CrossRef](#)]
50. Ooi, B.K.; Chan, K.G.; Goh, B.H.; Yap, W.H. The Role of Natural Products in Targeting Cardiovascular Diseases via Nrf2 Pathway: Novel Molecular Mechanisms and Therapeutic Approaches. *Front. Pharmacol.* **2018**, *9*, 1308. [[CrossRef](#)]
51. Rojo de la Vega, M.; Chapman, E.; Zhang, D.D. NRF2 and the Hallmarks of Cancer. *Cancer Cell* **2018**, *34*, 21–43. [[CrossRef](#)]
52. McMahon, M.; Thomas, N.; Itoh, K.; Yamamoto, M.; Hayes, J.D. Redox-regulated turnover of Nrf2 is determined by at least two separate protein domains, the redox-sensitive Neh2 degron and the redox-insensitive Neh6 degron. *J. Biol. Chem.* **2004**, *279*, 31556–31567. [[CrossRef](#)] [[PubMed](#)]
53. Chen, C.K.M.; Chen, N.L.; Chan, A.; Wang, H.J. The many blades of the β -propeller proteins: Conserved but versatile. *Trends Biochem. Sci.* **2011**, *36*, 553–561. [[CrossRef](#)] [[PubMed](#)]
54. Li, X.; Zhang, D.; Hannink, M.; Beamer, L.J. Crystal structure of the Kelch domain of human Keap1. *J. Biol. Chem.* **2004**, *279*, 54750–54758. [[CrossRef](#)] [[PubMed](#)]
55. Lo, S.C.; Li, X.; Henzl, M.T.; Beamer, L.J.; Hannink, M. Structure of the Keap1:Nrf2 interface provides mechanistic insight into Nrf2 signaling. *EMBO J.* **2006**, *25*, 3605–3617. [[CrossRef](#)]
56. Egger, A.L.; Liu, G.; Pezzuto, J.M.; Van Breemen, R.B.; Mesecar, A.D. Modifying specific cysteines of the electrophile-sensing human Keap1 protein is insufficient to disrupt binding to the Nrf2 domain Neh2. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 10070–10075. [[CrossRef](#)] [[PubMed](#)]
57. Tong, K.I.; Katoh, Y.; Kusunoki, H.; Itoh, K.; Tanaka, T.; Yamamoto, M. Keap1 recruits Neh2 through binding to ETGE and DLG motifs: Characterization of the two-site molecular recognition model. *Mol. Cell. Biol.* **2006**, *26*, 2887–2900. [[CrossRef](#)]
58. Fukutomi, T.; Takagi, K.; Mizushima, T.; Ohuchi, N.; Yamamoto, M. Kinetic, thermodynamic, and structural characterizations of the association between Nrf2-DLGex degron and Keap1. *Mol. Cell. Biol.* **2014**, *34*, 832–846. [[CrossRef](#)]
59. Horie, Y.; Sazuki, T.; Inoue, J.; Iso, T.; Wells, G.; Moore, T.W.; Mizushima, T.; Dinkova-Kostova, A.T.; Kasai, T.; Kamei, T.; et al. Molecular basis for the disruption of Keap1–Nrf2 interaction via Hinge & Latch mechanism. *Commun. Biol.* **2021**, *4*, 576.

60. Padmanabhan, B.; Tong, K.I.; Ohta, T.; Nakamura, Y.; Scharlock, M.; Ohtsuji, M.; Kang, M.I.; Kobayashi, A.; Yokoyama, S.; Yamamoto, M. Structural basis for defects of Keap1 activity provoked by its point mutations in lung cancer. *Mol. Cell* **2006**, *21*, 689–700. [[CrossRef](#)]
61. Yamamoto, T.; Suzuki, T.; Kobayashi, A.; Wakabayashi, J.; Maher, J.; Motohashi, H.; Yamamoto, M. Physiological significance of reactive cysteine residues of Keap1 in determining Nrf2 activity. *Mol. Cell. Biol.* **2008**, *28*, 2758–2770. [[CrossRef](#)]
62. Saito, R.; Suzuki, T.; Hiramoto, K.; Asami, S.; Naganuma, E.; Suda, H.; Iso, T.; Yamamoto, H.; Morita, M.; Baird, L.; et al. Characterizations of Three Major Cysteine Sensors of Keap1 in Stress Response. *Mol. Cell. Biol.* **2015**, *36*, 271–284. [[CrossRef](#)] [[PubMed](#)]
63. Robledinos-Antón, N.; Fernández-Ginés, R.; Manda, G.; Cuadrado, A. Activators and Inhibitors of NRF2: A Review of Their Potential for Clinical Development. *Oxid. Med. Cell. Longev.* **2019**, *2019*, 9372182. [[CrossRef](#)] [[PubMed](#)]
64. Tran, K.T.; Pallesen, J.S.; Solbak, S.M.Ø.; Narayanan, D.; Baig, A.; Zang, J.; Aguayo-Orozco, A.; Carmona, R.M.C.; Garcia, A.D.; Bach, A. A Comparative Assessment Study of Known Small-Molecule Keap1-Nrf2 Protein-Protein Interaction Inhibitors: Chemical Synthesis, Binding Properties, and Cellular Activity. *J. Med. Chem.* **2019**, *62*, 8028–8052. [[CrossRef](#)]
65. McMahan, M.; Lamont, D.J.; Beattie, K.A.; Hayes, J.D. Keap1 perceives stress via three sensors for the endogenous signaling molecules nitric oxide, zinc, and alkenals. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 18838–18843. [[CrossRef](#)] [[PubMed](#)]
66. Kaplan, P.; Tatarkova, Z.; Sivonova, M.K.; Racay, P.; Lehotsky, J. Homocysteine and mitochondria in cardiovascular and cerebrovascular systems. *Int. J. Mol. Sci.* **2020**, *21*, 7698. [[CrossRef](#)] [[PubMed](#)]
67. Kwon, K.-B.; Yoo, S.-J.; Ryu, D.-G.; Yang, J.-Y.; Rho, H.-W.; Kim, J.-S.; Park, J.-W.; Kim, H.R.; Park, B.H. Induction of apoptosis by diallyl disulfide through activation of caspase-3 in human leukemia HL-60 cells. *Biochem. Pharmacol.* **2002**, *63*, 41–47. [[CrossRef](#)]
68. Filomeni, G.; Aquilano, K.; Rotilio, G.; Ciriolo, M.R. Reactive oxygen species-dependent c-Jun NH2-terminal kinase/c-Jun signaling cascade mediates neuroblastoma cell death induced by diallyl disulfide. *Cancer Res.* **2003**, *63*, 5940–5949.
69. Haskew-Layton, R.E.; Payappilly, J.B.; Smirnova, N.A.; Maa, T.C.; Chana, K.K.; Murphy, T.H.; Guoa, H.; Langley, B.; Sultana, R.; Butterfield, D.A.; et al. Controlled enzymatic production of astrocytic hydrogen peroxide protects neurons from oxidative stress via an Nrf2-independent pathway. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 17385–17390. [[CrossRef](#)]
70. Suzuki, T.; Masayuki, Y. Stress-sensing mechanisms and the physiological roles of the Keap1–Nrf2 system during cellular stress. *J. Biol. Chem.* **2017**, *292*, 16817–16824. [[CrossRef](#)]
71. Brennan, M.S.; Matos, M.F.; Li, B.; Hronowski, X.; Gao, B.; Juhasz, P.; Rhodes, K.J.; Scannevin, R.H. Dimethyl fumarate and monoethyl fumarate exhibit differential effects on KEAP1, NRF2 activation, and glutathione depletion in vitro. *PLoS ONE* **2015**, *10*, e0120254. [[CrossRef](#)]
72. Takaya, K.; Suzuki, T.; Motohashi, H.; Onodera, K.; Satomi, S.; Kensler, T.W.; Yamamoto, M. Validation of the multiple sensor mechanism of the Keap1-Nrf2 system. *Free Radic. Biol. Med.* **2012**, *53*, 817–827. [[CrossRef](#)]
73. Dayalan, N.S.; Muramatsu, A.; Saito, R.; Asami, S.; Honda, T.; Hosoya, T.; Itoh, K.; Yamamoto, M.; Suzuki, T.; Dinkova-Kostova, A.T. C151 in KEAP1 is the main cysteine sensor for the cyanoenone class of NRF2 activators, irrespective of molecular size or shape. *Sci. Rep.* **2018**, *8*, 8037. [[CrossRef](#)] [[PubMed](#)]
74. Baird, L.; Yamamoto, M. The molecular mechanisms regulating the KEAP1-NRF2 pathway. *Mol. Cell. Biol.* **2020**, *40*, e00099-20. [[CrossRef](#)] [[PubMed](#)]
75. Nguyen, T.; Sherratt, P.J.; Pickett, C.B. Regulatory mechanisms controlling gene expression mediated by the antioxidant response element. *Annu. Rev. Pharmacol. Toxicol.* **2003**, *43*, 233–260. [[CrossRef](#)]
76. Raghunath, A.; Sundarraj, K.; Nagarajan, R.; Arfuso, F.; Bian, J.; Kumar, A.P.; Sethi, G.; Perumal, E. Antioxidant response elements: Discovery, classes, regulation and potential applications. *Redox Biol.* **2018**, *17*, 297–314. [[CrossRef](#)] [[PubMed](#)]
77. Chen, X.L.; Dodd, G.; Thomas, S.; Zhang, X.; Wasserman, M.A.; Rovin, B.H.; Kunsch, C. Activation of Nrf2/ARE pathway protects endothelial cells from oxidant injury and inhibits inflammatory gene expression. *Am. J. Physiol. Heart Circ. Physiol.* **2006**, *290*, H1862-70. [[CrossRef](#)]
78. Itoh, K.; Chiba, T.; Takahashi, S.; Ishii, T.; Igarashi, K.; Katoh, Y.; Oyake, T.; Hayashi, N.; Satoh, K.; Hatayama, T.; et al. An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. *Biochem. Biophys. Res. Commun.* **1997**, *236*, 313–322. [[CrossRef](#)] [[PubMed](#)]
79. Chen, X.; Hussain, S.; Parveen, S.; Zhang, S.; Yang, Y.; Zhu, C. Sulfonyl group-containing compounds in the design of potential drugs for the treatment of diabetes and its complications. *Curr. Med. Chem.* **2012**, *19*, 3578–3604. [[CrossRef](#)] [[PubMed](#)]
80. Egbujor, M.C.; Okoro, U.C.; Okafor, S. Design, synthesis, molecular docking, antimicrobial and antioxidant activities of new phenylsulfamoyl carboxylic acids of pharmacological interest. *Med. Chem. Res.* **2019**, *28*, 2118–2127. [[CrossRef](#)]
81. Egbujor, M.C.; Okoro, U.C. New methionine-based p-toluenesulphonamoyl carboxamide derivatives as antimicrobial and antioxidant agents: Design, synthesis. *J. Pharm. Res. Int.* **2019**, *28*, 1–12. [[CrossRef](#)]
82. Egbujor, M.C.; Okoro, U.C.; Okafor, S.; Nwankwo, N.E. Design, synthesis and molecular docking of novel serine-based sulphonamide bioactive compounds as potential antioxidant and antimicrobial agents. *Indo Am. J. Pharm. Sci.* **2019**, *6*, 12232–12240.
83. Egbujor, M.C.; Nwobodo, D.C.; Ekwuatu, P.I.; Abu, I.P.; Ezeagu, C.U. Sulphonamide drugs and *Pseudomonas aeruginosa* resistance: A review. *Int. J. Mod. Pharm. Res.* **2020**, *4*, 78–83.
84. Egbujor, M.C.; Okoro, U.C.; Okafor, S. Novel alanine-based antimicrobial and antioxidant agents: Synthesis and molecular docking. *Indian J. Sci. Technol.* **2020**, *13*, 1003–1014. [[CrossRef](#)]

85. Egbujor, M.C.; Okoro, U.C.; Nwobodo, D.C.; Ezeagu, C.U.; Amadi, U.B.; Okenwa-Ani, C.G.; Ugwu, J.I.; Okoye, I.G.; Abu, I.P.; Egwuatu, P.I. Design, synthesis, antimicrobial and antioxidant activities of novel threonine-based sulfonamide derivatives. *J. Pharm. Res. Int.* **2020**, *32*, 51–61. [[CrossRef](#)]
86. Humljan, J.; Kotnik, M.; Constreras-Martel, C.; Blanot, D.; Urleb, U.; Dessen, A.; Olmajer, T.; Gobec, S. Novel naphthalene-N-Sulfonyl-D-glutamic acid derivatives as inhibitors of MurD, a Key peptidoglycan biosynthesis enzyme. *J. Med. Chem.* **2008**, *51*, 7486–7494. [[CrossRef](#)] [[PubMed](#)]
87. Bachovchin, D.A.; Zuhl, A.M.; Speers, A.E.; Wolfe, M.R.; Weerapana, E.; Brown, S.J.; Rosen, H.; Cravatt, B.F. Discovery and optimisation of sulfonyl acrylonitriles as selective, covalent inhibitors of protein phosphatase-methylesterase-1. *J. Med. Chem.* **2011**, *54*, 5229–5236. [[CrossRef](#)] [[PubMed](#)]
88. Alqasoumi, S.I.; Al-Taweel, A.M.; Alafeefy, A.M.; Ghorab, M.M.; Noaman, E. Discovering some novel tetrahydroquinoline derivatives bearing the biologically active sulphonamide moiety as a new class of antitumor agents. *Eur. J. Med. Chem.* **2010**, *45*, 1849–1853. [[CrossRef](#)] [[PubMed](#)]
89. Silvestri, R. Boom in the development of non-peptidic beta-secretase (BACE1) inhibitors for the treatment of Alzheimer's disease. *Med. Res. Rev.* **2009**, *29*, 295–338. [[CrossRef](#)] [[PubMed](#)]
90. Egbujor, M.C.; Okoro, U.C.; Okafor, S.; Nwankwo, N.E. Synthesis, characterization and in silico studies of novel alkanoylated 4-methylphenyl sulphonamoyl carboxylic acids as potential antimicrobial and antioxidant agents. *Int. J. Pharm. Phytopharm. Res.* **2019**, *9*, 89–97.
91. Egbujor, M.C.; Egu, S.A.; Okonkwo, V.I.; Jacob, A.D.; Egwuatu, P.I.; Amasiatu, I.S. Antioxidant drug design: Historical and recent developments. *J. Pharm. Res Int.* **2021**, *32*, 36–56. [[CrossRef](#)]
92. Egbujor, M.C.; Okoro, U.C.; Okafor, S.N.; Amasiatu, I.S.; Amadi, U.B.; Egwuatu, P.I. Synthesis, molecular docking and pharmacological evaluation of new 4-methylphenylsulphamoyl carboxylic acids analogs. *Int. J. Res. Pharm. Sci.* **2020**, *11*, 5357–5366. [[CrossRef](#)]
93. Egbujor, M.C.; Okoro, U.C.; Egu, S.A.; Egwuatu, P.I.; Eze, F.U.; Amasiatu, I.S. Design, synthesis and biological evaluation of alanine-based sulphonamide derivatives. *Int. J. Res. Pharm. Sci.* **2020**, *11*, 6449–6458. [[CrossRef](#)]
94. Lu, M.-C.; Shao, H.-L.; Liu, T.; You, Q.-D.; Jian, Z.-Y. Discovery of 2-oxy-2-phenylacetic acid substituted naphthalene sulphonamide derivatives as potent Keap1-Nrf2 protein-protein interaction inhibitors for inflammatory conditions. *Eur. Med. Chem.* **2020**, *207*, 112734. [[CrossRef](#)] [[PubMed](#)]
95. Voutyritsa, E.; Triandafillidi, I.; Kokotos, C.G. Green Organocatalytic Oxidation of Sulfides to Sulfoxides and Sulfones. *Synthesis* **2017**, *49*, 917–924.
96. Kirihara, M.; Itou, A.; Noguchi, T.; Yamamoto, J. Tantalum carbide or niobium carbide catalyzed oxidation of sulphides with hydrogen peroxide: High efficient and chemo selective syntheses of sulfoxides and sulfones. *Synlett* **2010**, *2010*, 57–1561. [[CrossRef](#)]
97. Palmer, J.T.; Rasnick, D.; Klaus, J.L.; Brömme, D. Vinyl sulfones as mechanism-based cysteine protease inhibitors. *J. Med. Chem.* **1995**, *38*, 3193–3196. [[CrossRef](#)]
98. Lee, J.A.; Kim, J.H.; Woo, S.Y.; Son, H.J.; Han, S.H.; Jang, B.K.; Choi, J.W.; Kim, D.J.; Park, K.D.; Hwang, O. A novel compound VSC2 has anti-inflammatory and antioxidant properties in microglia and in Parkinson's disease model. *Br. J. Pharmacol.* **2015**, *172*, 1087–1100. [[CrossRef](#)]
99. Woo, S.Y.; Kim, J.H.; Moon, M.K.; Han, S.-H.; Yeon, S.K.; Choi, J.W.; Jang, B.K.; Song, J.; Kang, Y.G.; Kim, J.W.; et al. Discovery of vinyl sulfones as a novel class of neuroprotective agents towards Parkinson's disease therapy. *J. Med. Chem.* **2014**, *57*, 1473–1487. [[CrossRef](#)]
100. Carlstrom, K.E.; Chinthakindi, P.K.; Espinosa, B.; Nimer, F.A.; Arner, E.S.J.; Arvidsson, P.I.; Piehl, F.; Johansson, K. Characterization of more selective central nervous system Nrf2- activating novel vinyl sulfoxime compounds compared to dimethyl fumarate. *Neurotherapeutics* **2020**, *17*, 1142–1152. [[CrossRef](#)] [[PubMed](#)]
101. Navarro, L.; Rosell, G.; Sanchez, S.; Boixareu, N.; Pors, K.; Pouplana, R.; Campanera, J.M.; Pujol, M.D. Synthesis and biological properties of aryl methyl sulfones. *Bioorg. Med. Chem.* **2018**, *26*, 4113–4126. [[CrossRef](#)]
102. Choi, J.W.; Kim, S.; Park, J.-H.; Kim, H.J.; Shin, S.J.; Kim, J.W.; Woo, S.Y.; Lee, C.; Han, S.M.; Lee, J.; et al. Optimization factor erythroid 2-related factor 2 (Nrf2) activators for Parkinson's disease therapy. *J. Med. Chem.* **2019**, *62*, 811–830. [[CrossRef](#)] [[PubMed](#)]
103. Begnini, F.; Geschwindner, S.; Johansson, P.; Wissler, L.; Lewis, R.J.; Danelius, E.; Lutten, A.; Matricon, P.; Carlsson, J.; Lenders, S.; et al. Importance of Binding Site Hydration and Flexibility Revealed When Optimizing a Macrocyclic Inhibitor of the Keap1-Nrf2 Protein-Protein Interaction. *J. Med. Chem.* **2022**, *65*, 3473–3517. [[CrossRef](#)]
104. Oving, A.; Bhattacharyya, J. Sulfonamide drugs: Structure, antibacterial property, toxicity, and biophysical interactions. *Biophys. Rev.* **2021**, *13*, 259–272. [[CrossRef](#)] [[PubMed](#)]
105. De Luca, L.; Giacomelli, G. An easy microwave-assisted synthesis of sulfonamides directly from sulfonic acids. *J. Org. Chem.* **2008**, *73*, 3967–3969. [[CrossRef](#)] [[PubMed](#)]
106. Eze, F.U.; Okoro, U.C.; Ugwu, D.I.; Okafor, S.N. New carboxamides bearing benzene sulfonamides: Synthesis, molecular docking and pharmacological properties. *Bioorg. Chem.* **2019**, *92*, 103265. [[CrossRef](#)]
107. Nadeem, R.A.; Qadir, M.A.; Ahmed, M.; Sajid, I. Cephalosporin conjugated sulphonamides: Synthesis, characterization and anticancer activities. *Letts. Drug Des. Discov.* **2020**, *17*, 264–270. [[CrossRef](#)]

108. Abdel-Aziz, A.A.; Angeli, A.; El-Azab, A.S.; Hammouda, M.E.A.; El-sherbeny, M.A.; Supuran, C.T. Synthesis and anti-inflammatory activity of sulphonamides and carboxygenase/carbonic anhydrase inhibitory actions. *Bioorg. Chem.* **2019**, *84*, 260–268. [[CrossRef](#)]
109. Dodson, M.; De la Vega, M.R.; Cholani, A.B.; Schmidlin, C.J.; Chapman, E.; Zhang, D.D. Modulating Nrf2 in disease: Timing is everything. *Annul. Rev. Pharmacol. Toxicol.* **2019**, *59*, 555–575. [[CrossRef](#)]
110. Egbujor, M.C.; Garrido, J.; Borges, F.; Saso, L. Sulfonamide a valid scaffold for antioxidant drug development. *Mini-Rev. Org. Chem.* **2022**, *19*. [[CrossRef](#)]
111. Peng, X.; Hu, T.; Zhang, Y.; Zhao, A.; Natarajan, B.; Wei, J.; Yan, H.; Chen, H.; Lin, C. Synthesis of caffeic acid sulphonamide derivatives and their protective effect against H₂O₂ induced oxidative damage in A549 cells. *RSC Adv.* **2020**, *10*, 9924–9933. [[CrossRef](#)] [[PubMed](#)]
112. Jiang, Z.-Y.; Lu, M.-C.; Xu, L.-L.; Yang, T.-T.; Xi, M.-Y.; Xu, X.-L.; Guo, X.-K.; Zhang, X.-J.; You, Q.-D.; Sun, H.-P. Discovery of potent Keap1-Nrf2 protein-protein interaction inhibitor based on molecular binding determinants analysis. *J. Med. Chem.* **2014**, *57*, 2736–2745. [[CrossRef](#)] [[PubMed](#)]
113. Naidu, S.D.; Suzuki, T.; Dikovskaya, D.; Knatko, E.V.; Higgins, M.; Sato, M.; Novak, M.; Villegas, J.A.; Moore, T.W.; Yamamoto, M.; et al. The isoquinoline PRL-295 increases the thermostability of Keap1 and disrupts its interaction with Nrf2. *iScience* **2021**, *25*, 103703. [[CrossRef](#)]
114. Georgakopoulos, N.; Torgakopoulos, N.; Talapatra, S.; Dikovskaya, D.; Naidu, S.D.; Higgins, M.; Gatliff, J.; Ayhan, A.; Nikoloudaki, R.; Schaap, F.; et al. Phenyl bis-sulfonamide keap1-Nrf2 protein-protein interaction inhibitors with an alternative binding mode. *J. Med. Chem.* **2022**, *65*, 7380–7398. [[CrossRef](#)]
115. Choi, J.W.; Shin, S.J.; Kim, H.J.; Park, J.H.; Kim, H.J.; Lee, E.H.; Pae, A.N.; Bahn, Y.S.; Park, K.D. Antioxidant, Anti-inflammatory, and Neuroprotective Effects of Novel Vinyl Sulfonate Compounds as Nrf2 Activator. *ACS Med. Chem. Lett.* **2019**, *10*, 1061–1067. [[CrossRef](#)]
116. Strecker, A. Ueber eine neue bildungsweise und die constitution der sulfosauren. *Ann. Chem. Pharm.* **1868**, *148*, 90–96.
117. Sacoman, J.L.; Badish, L.N.; Sharkey, T.D.; Hollingsworth, R.I. The metabolic and biochemical impact of glucose 6-sulfonate (sulfoquinovose), a dietary sugar, on carbohydrate metabolism. *Carbohydr. Res.* **2012**, *362*, 21–29. [[CrossRef](#)] [[PubMed](#)]
118. Luan, F.; Wei, L.; Zhang, J.; Mi, Y.; Dong, F.; Li, Q.; Guo, Z. Antioxidant activity and antifungal activity of chitosan derivatives with propane sulfonate groups. *Polymers* **2018**, *10*, 395. [[CrossRef](#)]
119. Arshia, A.J.; Faheem, A.; Khan, K.M.; Shah, S.; Perveen, S. Benzophenone esters and sulfonates: Synthesis and their potential as anti-inflammatory agents. *Med. Chem.* **2019**, *15*, 162–174. [[CrossRef](#)]
120. Jeelani, R.; Jahanbakhsh, S.; Kohan-Ghadr, H.-R.; Thakur, M.; Khan, S.; Aldaheri, S.R.; Yang, Z.; Andreana, P.; Morris, R.; Abu-soud, H.M. Mesna(2-mercaptoethane sodium sulfonate) functions as a regulator of myeloperoxidase. *Free Radic. Biol. Med.* **2017**, *110*, 54–62. [[CrossRef](#)]
121. Zhu, Z.; Wang, V.; Liang, D.; Yang, G.; Li, C.; Niu, P.; Tian, L. Sodium Tanshinone IIA sulfonate suppresses pulmonary fibroblasts proliferation and activation induced by silica: Role of the Nrf2/Trx pathway. *Toxicol. Res.* **2016**, *5*, 116. [[CrossRef](#)]
122. Gilchrist, T.L. *Comprehensive Organic Functional Group Transformations, Synthesis: Carbon with Three or Four Attached Heteroatoms*; Elsevier Science: Oxford, UK, 2017; Volume 6.
123. Otocka, S.; Kwiatkowska, M.; Madalinska, L.; Kielbasinski, P. Chiral organosulfur ligands/catalysts with a stereogenic sulfur atom: Applications in asymmetric synthesis. *Chem. Rev.* **2017**, *117*, 4147–4181. [[CrossRef](#)]
124. Kielbasinski, P.; Kwiatkowska, M.; Mikolajczyk, M. Organic Heteroatom-Containing compounds. In *Future Directions in Biocatalysis*, 2nd ed.; Matsuda, T., Ed.; Elsevier: Oxford, UK, 2017; Volume 1, pp. 191–250.
125. Liang, C.; Xue, Z.; Cang, J.; Wang, H.; Li, P. Dimethyl sulfoxide induces heme oxygenase-1 expression via JNKs and Nrf2 pathways in human umbilical vein endothelial cells. *Mol. Cell. Biochem.* **2011**, *355*, 109–115. [[CrossRef](#)]
126. Kensler, T.W.; Egner, P.A.; Agyeman, A.S.; Visvanathan, K.; Groopman, J.D.; Chen, J.-G.; Chen, T.-Y.; Fahey, J.W.; Talalay, P. Keap1-Nrf2 signaling: A target for cancer prevention by sulforaphane. *Top. Curr. Chem.* **2013**, *329*, 163–178. [[PubMed](#)]
127. Khair, N.; Werner, S.; Mallouk, S.; Lieder, F.; Alcudia, A.; Fernandez, I. Enantiopure sulforaphane analogues with various substituents at the sulfinyl sulfur: Asymmetric synthesis and biological activities. *J. Org. Chem.* **2009**, *74*, 6002–6009. [[CrossRef](#)] [[PubMed](#)]
128. Kielbasinski, P.; Kwiatkowska, M.; Cierpial, T.; Rachwalski, M.; Lesniak, S. The sulfinyl group: Biological activity. *Phosphorus Sulfur Silicon Relat. Elem.* **2019**, *194*, 649–653. [[CrossRef](#)]
129. Patai, S.; Rappoport, Z. (Eds.) *Syntheses of Sulphones, Sulphoxides and Cyclic Sulphides*; John Wiley & Sons: Hoboken, NJ, USA, 1995.
130. Sanmartin-Suarez, C.; Soto-Otero, R.; Sanchez-Sellero, I.; Mendez-Alvarez, E. Antioxidant properties of dimethyl sulfoxide and its viability as a solvent in the evaluation of neuroprotective antioxidants. *J. Pharmacol. Toxicol. Methods* **2011**, *63*, 209–215. [[CrossRef](#)] [[PubMed](#)]
131. Unnikrishna, M.K.; Rao, M.N.A. Anti-inflammatory activity of methionine, methionine sulfoxide and methionine sulfone. *Agents Actions* **1990**, *31*, 110–112. [[CrossRef](#)]
132. Novak, K.M. *Drug Facts and Comparisons*, 56th ed.; Wolters Kluwer Health: St. Louis, MO, USA, 2002; p. 619.
133. Gavrilin, M.V.; Sen' Chukova, G.V.; Kompantseva, E.V. Structure of Chemical compounds, methods of analysis and process control. Methods for the synthesis and analysis of dimethyl sulfoxide (a review). *Pharm. Chem. J.* **2000**, *34*, 35–38.

134. Steffel, J.; Hermann, M.; Greutert, H.; Gay, S.; Luscher, T.F.; Ruschitzka, F.; Tanner, F.C. Celecoxib decreases endothelial tissue factor expression through inhibition of c-Jun terminal NH2 Kinase phosphorylation. *Circulation* **2005**, *111*, 1685–1689. [[CrossRef](#)]
135. Shim, Y.S.; Hwangm, H.S.; Nam, G.; Choi, K. Synthesis and Nrf2 activating ability of thiourea and vinyl sulfoxide derivatives. *Bull. Korean Chem. Soc.* **2013**, *34*, 2317. [[CrossRef](#)]
136. Han, Y.; Xing, K.; Zhang, J.; Tong, T.; Shi, Y.; Cao, H.; Yu, H.; Zhang, Y.; Liu, D.; Zhao, L. Application of sulfoximines in medicinal chemistry from 2013 to 2020. *Eur. J. Med. Chem.* **2021**, *209*, 112885. [[CrossRef](#)] [[PubMed](#)]
137. Peters, T. Methionine Sulfoximine: A Novel Anti-Inflammatory Agent. Ph.D. Thesis, Wayne State University, Detroit, MI, USA, 2018; p. 2124.
138. Tota, A.; Zensola, M.; Chawner, S.J.; John-Acnpbell, S.; Carlucci, C.; Romanazzi, G.; Degennaro, L.; Bull, J.A.; Luisi, R. Synthesis of NH-sulfoximines from sulfides by chemoselective one-pot N- and O-transfers. *Chem. Commun.* **2017**, *53*, 348–351. [[CrossRef](#)] [[PubMed](#)]
139. Valdovinos-Flores, C.; Limon-Pacher, J.H.; Leon-Rodriguez, R.; Petrosyan, P.; Garza-Lombo, C.; Gonsebatt, M.E. Systemic L-buthionine-S-R-sulfoximine treatment increases plasma NGF and upregulates L-cys/L-cys2 transporter and γ -glutamylcysteine ligase mRNAs through the NGF/TrKA/Akt/Nrf2 pathway in the striatum. *Front. Cell. Neurosci.* **2019**, *13*, 325. [[CrossRef](#)]
140. Ansari, M.I.; Khan, M.M.; Saquib, M.; Khatoon, S.; Hussain, M.K. Dithiolethiones: A privileged pharmacophore for anticancer therapy and chemoprevention. *Future Med. Chem.* **2018**, *10*, 1241–1260. [[CrossRef](#)]
141. Tew, K.D. *Oltipraz*; Reference Module in Biomedical Sciences; Elsevier: Amsterdam, Switzerland, 2016.
142. Kim, J.W.; Choi, K.D.; Lim, J.W.; Lee, K.H.; Lee, S.H. Method for Preparing Oltipraz. U.S. Patent 7288652B2, 30 October 2007.
143. Merrelle, M.D.; Jackson, J.P.; Augustine, L.M.; Fisher, C.D.; Slitt, A.L.; Maher, J.M.; Huana, W.; Moore, D.D.; Zhang, Y.; Klaassen, C.D.; et al. the Nrf2 activator oltipraz also activates the constitutive androstane receptor. *Drug Metab. Dispos.* **2008**, *36*, 1716–1721. [[CrossRef](#)] [[PubMed](#)]
144. Yu, Z.; Shao, Z.; Ling, W.; Fantus, I.G.; Jin, T. Oltipraz upregulates the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) antioxidant system and prevents insulin resistance and obesity induced by a high-fat diet in C57BL/6J mice. *Diabetologia* **2011**, *D*, 922–934. [[CrossRef](#)]
145. Jiang, Z.; Bian, M.; Wu, J.; Li, D.; Ding, L.; Zeng, Q. Oltipraz prevents high glucose-induced oxidative stress and apoptosis in RSC96 cells through the Nrf2/NQO1 signaling pathway. *BioMed Res. Int.* **2020**, *2020*, 5939815. [[CrossRef](#)]
146. Antilano-Roque, A.; Wen, X.; Alekunes, L.M.; Joy, M.S. Nrf2 activators as potential modulators of injury in human kidney cells. *Toxicol. Rep.* **2016**, *3*, 153–159. [[CrossRef](#)] [[PubMed](#)]
147. Ramos-Gomez, M.; Dolan, P.M.; Itoh, K.; Yamamoto, M.; Kensler, T.W. Interactive effects of nrf2 genotype and oltipraz on benzo[a]pyrene-DNA adducts and tumor yield in mice. *Carcinogenesis* **2003**, *24*, 461–467. [[CrossRef](#)]
148. Iida, K.; Itoh, K.; Kumagai, Y.; Oyasu, R.; Hattori, K.; Kawai, K.; Shimazui, I.; Akaza, H.; Yamamoto, M. Nrf2 is essential for the chemopreventive efficacy of oltipraz against urinary bladder carcinogenesis. *Cancer Res.* **2004**, *64*, 6424–6431. [[CrossRef](#)]
149. Faley, J.W.; Zalcman, A.T.; Talalay, P. The chemical diversity and distribution of glucosinolates and isothiocyanates among plants. *Phytochemistry* **2001**, *56*, 5–51.
150. Dinkova-Kostova, A.T. Chemoprotection against cancer by isothiocyanate: A focus on the animal models and protective mechanisms. In *Natural Products in Cancer Prevention and Therapy*; Springer: Berlin/Heidelberg, Germany, 2012; pp. 179–201.
151. Cheng, D.; Gao, L.; Su, S.; Sargsyan, D.; Wu, R.; Raskin, H.; Koug, A.-N. Moringa isothiocyanate activates Nrf2: Potential role in diabetic nephropathy. *AAPs J.* **2019**, *21*, 31. [[CrossRef](#)] [[PubMed](#)]
152. Chuang, W.-T.; Yen, C.-C.; Huang, C.-S.; Chen, H.-W.; Lii, C.-K. Benzyl isothiocyanate ameliorates high-fat diet-induced hyperglycemia by enhancing Mrf2-dependant antioxidant defuse-mediated IRS-1/AKT/TBC1D1 signaling and GLUT4 expression in skeletal muscle. *J. Agric. Food Chem.* **2020**, *68*, 15228–15238. [[CrossRef](#)] [[PubMed](#)]
153. El Badawy, S.A.; Ogaly, H.A.; Abd-Elsalam, R.M.; Azouz, A.A. Benzyl isothiocyanates modulate inflammation, oxidative stress and apoptosis via Nrf2/ho-1 and NF-KB signaling pathways on indomethacin-induced gastric injury in rats. *Food Funct.* **2021**, *12*, 6001–6013. [[CrossRef](#)]
154. Miyoshi, N.; Takabayashi, S.; Osawa, T.; Nakamura, Y. Benzyl isothiocyanate inhibits excessive superoxide generation in inflammatory leukocytes. Implication for prevention against inflammation-related carcinogenesis. *Carcinogenesis* **2004**, *25*, 567–575. [[CrossRef](#)]
155. Das, B.N.; Kim, Y.-W.; Keum, Y.-S. Mechanisms of Nrf2/Keap1-Dependent phase II cytoprotective and detoxifying gene expression and potential cellular targets of chemo preventive isothiocyanates. *Oxid. Med. Cell. Longev.* **2013**, *2013*, 839409.
156. Caglayan, B.; Kilic, E.; Dalay, A.; Altunay, S.; Tuzcu, M.; Erten, F.; Orhan, C.; Gunal, M.Y.; Yulug, B.; Juturu, V.; et al. Allyl isothiocyanate attenuates oxidative stress and inflammation by modulating Nrf2/Ho-1 and NF-KB pathways in traumatic brain injury in mice. *Mol. Biol. Rep.* **2019**, *46*, 241–250. [[CrossRef](#)]
157. Zhang, M.; Wang, S.; Wang, X.; Xu, X.; Yao, Z.; Fang, W.; Wu, J.; Wu, Q.; Li, Z.; Wang, D. Allyl isothiocyanate increases MRP1 expression in cigarette extract-simulated human bronchial epithelial cells via the JNK/Nrf2 pathway. *Exp. Ther. Med.* **2021**, *4*, 409. [[CrossRef](#)]
158. Kim, M.W.; Kang, J.-H.; Jung, H.J.; Park, S.Y.; Lephant, T.H.; Namgung, J.-H.; Seo, S.-Y.; Yoon, Y.S.; Oh, S.H. Allyl isothiocyanate protects acetaminophen-induced liver injury via Nrf2 activation by decreasing spontaneous degradation in hepatocyte. *Nutrients* **2020**, *12*, 3585. [[CrossRef](#)]

159. Naidu, S.D.; Suzuki, T.; Yamamoto, M.; Fahey, J.W.; Dinkova-Kostova, A.T. Phenyl isothiocyanate, a dual activator of transcription factors Nrf2 and HSF1. *Mol. Nutr. Food Res.* **2018**, *62*, 1700908. [[CrossRef](#)]
160. Ernst, I.M.; Wagner, A.E.; Schuemann, C.J.; Storm, N.; Hoppner, W.; Doring, F.; Stocker, A.; Rimbach, G. Allyl-, butyl- and phenylethyl-isothiocyanate activate Nrf2 in cultured fibroblasts. *Pharmacol. Res.* **2011**, *63*, 233–240. [[CrossRef](#)] [[PubMed](#)]
161. Boyanapalli, S.S.S.; Paredes-Gonzalez, X.; Fuetes, F.; Zhang, C.; Guo, Y.; Pung, D.; Saw, C.L.L.; Kong, A.N.T. Nrf2 knockout attenuates the anti-inflammatory effects of phenylethyl isothiocyanates and curcumin. *Chem. Res. Toxicol.* **2014**, *27*, 2036–2043. [[CrossRef](#)] [[PubMed](#)]
162. Keum, Y.-S.; Owuor, E.D.; Kim, B.-R.; Hu, R.; Kong, A.N.T. Involvement of Nrf2 and JNK1 in the activation of antioxidant response element (ARE) by chemopreventive agent phenylethyl isothiocyanate (PEITC). *Pharm. Res.* **2003**, *20*, 1351–1356. [[CrossRef](#)] [[PubMed](#)]
163. Houghton, C.A.; Fassett, R.G.; Combes, J.S. Sulforaphane and other nutrigenomic Nrf2 activators: Can the clinician's expectation be matched by the reality? *Oxid. Med. Cell. Longev.* **2016**, *2016*, 7857186. [[CrossRef](#)]
164. Liu, P.; Wang, W.; Tang, J.; Bowater, R.P.; Bao, Y. Antioxidant effects of sulforaphane in human HepG2 cells and immortalised hepatocytes. *Food Chem. Toxicol.* **2019**, *128*, 129–136. [[CrossRef](#)]
165. Ruhee, R.T.; Suzuki, K. The integrative role of sulforaphane in preventing inflammation, oxidative stress and fatigue: A review of a potential protective phytochemical. *Antioxidants* **2020**, *9*, 521. [[CrossRef](#)]
166. Hua, D.; Luo, A.; Wu, Z.; Huang, C.; Li, S.; Xu, X.; Xu, J.; Yang, C.; Wang, D.; Liu, C. Sulforaphane improves cognitive dysfunction after surgery and anaesthesia in mice: The role of Keap1-Nrf2 signaling. *Brain Res. Bull.* **2022**, *181*, 1–11. [[CrossRef](#)]
167. Li, X.; Ying, H.; Zhang, Z.; Yang, Z.; You, C.; Cai, X.; Lin, Z.; Xiao, Y. Sulforaphane attenuates chronic intermittent hypoxia-induced brain damage in mice via augmenting Nrf2 nuclear translocation and autophagy. *Front. Cell. Neurosci.* **2022**, *16*, 827527. [[CrossRef](#)]
168. Kubo, E.; Chhunchha, B.; Singh, P.; Sasaki, H.; Singh, D.P. Sulforaphane reactivates cellular antioxidant defence by inducing Nrf2/ARE/Prdx6 activity during aging and oxidative stress. *Sci. Rep.* **2017**, *7*, 14130. [[CrossRef](#)]
169. Clarke, J.D.; Hsu, A.; Williams, D.E.; Dashwood, R.H.; Stevens, J.F.; Ho, E. Metabolism and tissue distribution of sulforaphane in Nrf2 knockout and wild-type mice. *Pharm. Res.* **2011**, *28*, 3171–3179. [[CrossRef](#)]
170. Thimmulappa, R.K.; Mai, K.H.; Srisuma, S.; Kensle, T.W.; Yamamoto, M.; Siswal, S. Identification of Nrf2-regulated genes induced by the chemopreventive agent sulforaphane by oligonucleotide microarray. *Cancer Res.* **2002**, *62*, 5196–5203. [[PubMed](#)]
171. Chung, F.L.; Conaway, C.C.; Rao, C.V.; Reddy, B.S. Chemoprevention of colonic aberrant crypt foci in Fischer rats by sulforaphane and phenethyl isothiocyanate. *Carcinogenesis* **2000**, *21*, 2287–2291. [[CrossRef](#)] [[PubMed](#)]
172. Xiong, Q.; Tian, X.; Li, W.; Chen, L.; Zhou, M.; Xu, C.; Ru, Q. Sulforaphane alleviates methamphetamine-induced oxidative damage and apoptosis via the Nrf2-mediated pathway in vitro and in vivo. *Food Agric. Immunol.* **2020**, *31*, 859–880. [[CrossRef](#)]
173. Morimitsu, Y.; Nakagawa, Y.; Hayashi, K.; Fujii, H.; Kumagai, T.; Nkamura, Y.; Osawa, T.; Horio, F.; Itoh, K.; Iida, K.; et al. A sulforaphane analogue that potently activates the Nrf2-dependent detoxification pathway. *J. Biol. Chem.* **2002**, *277*, 3456–3463. [[CrossRef](#)] [[PubMed](#)]
174. Kim, J.-H.; Jang, H.-J.; Cho, W.-Y.; Yeon, S.J.; Lee, C.-H. In vitro antioxidant actions of sulfur-containing amino acids. *Arab. J. Chem.* **2020**, *13*, 1678–1684. [[CrossRef](#)]
175. Guo, D.; Yang, J.; Ling, F.; Tu, L.; Li, J.; Chen, Y.; Zou, K.; Zhu, L.; Hou, X. Elemental diet enriched with amino acids alleviates mucosal inflammatory response and prevents colonic epithelial barrier dysfunction in mice with DSS-induced chronic colitis. *J. Immunol. Res.* **2020**, *2020*, 9430763. [[CrossRef](#)]
176. Kimura, Y.; Koike, S.; Shibuya, N.; Lefer, D.; Ogasawara, Y.; Kimura, H. 3-Mercaptopyruvate sulfurtransferase produces potential redox regulators cysteine- and glutathione-persulfide (Cys-SSH and GSSH) together with signaling molecules H₂S₂, H₂S₃ and H₂S. *Sci. Rep.* **2017**, *7*, 10459. [[CrossRef](#)]
177. Koike, S.; Ogasawara, Y.; Shibuya, N.; Kimura, H.; Ishii, K. Polysulfide exerts a protective effect against cytotoxicity caused by t-butylhydroperoxide through Nrf2 signaling in neuroblastoma cells. *FEBS Lett.* **2013**, *587*, 3548–3555. [[CrossRef](#)]
178. Tesseraud, S.; Coustrard, S.M.; Collin, A.; Seiliez, I. Role of sulfur amino acids in controlling nutrient metabolism and cell functions: Implications for nutrition. *Br. J. Nutr.* **2009**, *101*, 1132–1139. [[CrossRef](#)]
179. Lee, B.C.; Gladyshev, V.N. The biological significance of methionine sulfoxide stereochemistry. *Free Radic. Biol. Med.* **2011**, *50*, 271–277. [[CrossRef](#)]
180. Forman, H.J.; Zhang, H.; Rinna, A. Glutathione: Overview of its protective roles, measurement, and biosynthesis. *Mol. Asp. Med.* **2009**, *30*, 1–12. [[CrossRef](#)]
181. Yu, M.; Chen, H.; Liu, P.; Yang, M.; Zou, L.; Xiao, D. Antioxidant Function and Metabolomics Study in Mice after Dietary Supplementation with Methionine. *BioMed Res. Int.* **2020**, *2020*, 9494528. [[CrossRef](#)] [[PubMed](#)]
182. Dai, H.; Coleman, D.N.; Hu, L.; Martinez-cortes, I.; Wang, W.; Parys, C.; Shen, X.; Loo, J.J. Methionine and arginine supplementation alter inflammatory and oxidative stress responses during lipopolysaccharide challenge in bovine mammary epithelial cells in vitro. *J. Dairy Sci.* **2020**, *103*, 676–689. [[CrossRef](#)] [[PubMed](#)]
183. Wang, Z.; Liang, M.; Li, H.; Cai, L.; He, H.; Wu, Q.; Yang, L. L-methionine activates Nrf2-ARE pathway to induce endogenous antioxidant activity for depressing ROS- derived oxidative stress in growing rats. *J. Sci. Food Agric.* **2019**, *99*, 4849–4862. [[CrossRef](#)] [[PubMed](#)]

184. Li, H.; Cai, L.; Liang, M.; Wang, Z.; Zhang, Y.; Wu, Q.; Yang, L. Methionine augments endogenous antioxidant capacity of rice protein through stimulating MSR antioxidant system and activating Nrf2-ARE pathway in growing and adult rats. *Eur. Food Res. Technol.* **2020**, *246*, 1051–1063. [[CrossRef](#)]
185. Liu, R.; Diao, Q.; Cui, K. Effect of dietary methionine deficiency followed by a re-feeding phase on the hepatic antioxidants activities of lambs. *Animals* **2021**, *11*, 7. [[CrossRef](#)]
186. Wanders, D.; Stone, K.P.; Forney, L.A.; Cortez, C.C.; Dille, K.N.; Simon, J.; Xu, M.; Hotard, E.C.; Nikonorova, I.A.; Pettit, A.P.; et al. Role of GCN2-Independent Signaling Through a Noncanonical PERK/NRF2 Pathway in the Physiological Responses to Dietary Methionine Restriction. *Diabetes* **2016**, *65*, 1499–1510. [[CrossRef](#)]
187. Schuller-Levis, G.B.; Park, E. Taurine: New implications for an old amino acid. *FEMS Microbiol. Lett.* **2003**, *226*, 195–202. [[CrossRef](#)]
188. Kosswig, K. Sulfonic acids, aliphatic. In *Ullman's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, Germany, 2000.
189. Jurkowska, H.; Stipanuk, M.H.; Hirschberger, L.L.; Roman, H.B. Propargylglycine inhibits hypotaurine/taurine synthesis and elevates cystathionine and homocysteine concentrations in primary mouse hepatocytes. *Amino Acids* **2015**, *47*, 1215–1223. [[CrossRef](#)]
190. Maleki, V.; Mahdavi, R.; Hajzadeh-sharafabad, F.; Alizadeh, M. The effects of taurine supplementation on oxidative stress indices and inflammation biomarkers in patients with type 2 diabetes: A randomized, double blind, placebo-controlled trial. *Diabetol. Metab. Syndr.* **2020**, *12*, 9. [[CrossRef](#)]
191. Quaradaxhi, T.; Gadance, L.K.; McSweeney, K.R.; Abraham, J.R.; Apostolopoulos, V.; Zulli, A. The anti-inflammatory effect of taurine on cardiovascular disease. *Nutrients* **2020**, *12*, 2847. [[CrossRef](#)] [[PubMed](#)]
192. Ibrahim, M.A.; Eraqi, M.M.; Alfaiz, F. Therapeutic role of taurine as antioxidant in reducing hypertension risks in rats. *Heliyon* **2020**, *6*, e03209. [[CrossRef](#)]
193. Yang, W.; Huang, J.; Xiao, B.; Liu, Y.; Zhu, Y.; Wang, F.; Sun, S. Taurine protects mouse spermatocytes from ionizing radiation-induced damage through activation of Nrf2-HO-1 signaling. *Cell. Physiol. Biochem.* **2017**, *44*, 1629–1639. [[CrossRef](#)] [[PubMed](#)]
194. Agca, C.A.; Tuzcu, M.; Hayirli, A.; Sahin, K. Taurine ameliorates neuropathy via regulating NF- κ B and Nrf2/HO-1 signaling cascades in diabetic rats. *Food Chem. Toxicol.* **2014**, *711*, 116–121. [[CrossRef](#)] [[PubMed](#)]
195. Aparna, P.; Betigeri, A.M.; Pasupathi, P. Homocysteine and oxidative stress markers and inflammation in patients with coronary artery disease. *Int. J. Biol. Med. Res.* **2010**, *1*, 125–129.
196. Selhub, J. Homocysteine metabolism. *Annu. Rev. Nutr.* **1999**, *19*, 217–246. [[CrossRef](#)]
197. Sbodio, J.I.; Snyder, S.H.; Paul, B.D. Regulators of the transsulfuration pathway. *Br. J. Pharmacol.* **2019**, *176*, 583–593. [[CrossRef](#)] [[PubMed](#)]
198. Yang, G.; Zhao, K.; Ju, Y.; Mani, S.; Cao, Q.; Puukila, S.; Khaper, N.; Wu, L.; Wang, R. Hydrogen sulfide protects against cellular senescence via S-sulfhydration of Keap1 and activation of Nrf2. *Antioxid. Redox Signal.* **2013**, *18*, 1906–1919. [[CrossRef](#)] [[PubMed](#)]
199. Ida, T.; Sawa, T.; Ihara, H.; Tsuchiya, Y.; Watanabe, Y.; Kumagai, Y.; Suematsu, M.; Motohashi, H.; Fujii, S.; Matsunaga, T.; et al. Reactive cysteine persulfides and S-polythiolation regulate oxidative stress and redox signaling. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 7606–7611. [[CrossRef](#)]
200. Edwards, J.O.; Pearson, R.G. The factors determining nucleophilic reactivities. *J. Am. Chem. Soc.* **1962**, *84*, 16–24. [[CrossRef](#)]
201. Zuhra, K.; Tomé, C.S.; Forte, E.; Vicente, J.B.; Giuffrè, A. The multifaceted roles of sulfane sulfur species in cancer-associated processes. *Biochim. Biophys. Acta Bioenerg.* **2021**, *1862*, 148338. [[CrossRef](#)] [[PubMed](#)]
202. Xie, L.; Gu, Y.; Wen, M.; Zhao, S.; Wang, W.; Ma, Y.; Meng, G.; Han, Y.; Wang, Y.; Liu, G.; et al. Hydrogen Sulfide Induces Keap1 S-sulfhydration and Suppresses Diabetes-Accelerated Atherosclerosis via Nrf2 Activation. *Diabetes* **2016**, *65*, 3171–3184. [[CrossRef](#)] [[PubMed](#)]
203. Panieri, E.; Buha, A.; Telkoparan-Akillilar, P.; Cevik, D.; Kouretas, D.; Veskoukis, A.; Skaperda, Z.; Tsatsakis, A.; Wallace, D.; Suzen, S.; et al. Potential Applications of NRF2 Modulators in Cancer Therapy. *Antioxidants* **2020**, *9*, 193. [[CrossRef](#)]
204. Pirchl, M.; Ullrich, C.; Sperner-Unterweger, B.; Humpel, C. Homocysteine has anti-inflammatory properties in a hypercholesterolemic rat model in vivo. *Mol. Cell. Neurosci.* **2012**, *49*, 456–463. [[CrossRef](#)]
205. Pirchl, M.; Ullrich, C.; Humpel, C. Differential effects of short- and long-term hyperhomocysteinaemia on cholinergic neurons, spatial memory and microbleedings in vivo in rats. *Eur. J. Neurosci.* **2010**, *32*, 1516–1527. [[CrossRef](#)] [[PubMed](#)]
206. Mani, M.; Golmohammadi, T.; Khaghani, S.; Zamani, Z.; Azadmanesh, K.; Meshkani, R.; Pasalar, P. Homocysteine induces heme oxygenase-1 expression via transcription factor Nrf2 activation in HepG2 cells. *Iran. Biomed. J.* **2013**, *17*, 93–100.
207. Mani, M.; Khaghani, S.; Mohammadi, T.G.; Zamani, Z.; Azadmanesh, K.; Meshkani, R.; Pasalar, P.; Mostafavi, E. Activation of Nrf2-antioxidant response element mediated glutamate cysteine ligase expression in hepatoma cell line by homocysteine. *Hepat. Mon.* **2013**, *13*, e8394. [[CrossRef](#)] [[PubMed](#)]
208. Zhang, B.; Dong, J.-L.; Chen, Y.-L.; Liu, Y.; Huaug, S.-S.; Zhong, X.-L.; Cheng, Y.-H.; Wang, Z.-G. Nrf2 mediates the protective effects of homocysteine by increasing. *Mol. Med. Rep.* **2017**, *16*, 597–602. [[CrossRef](#)] [[PubMed](#)]
209. Navneet, S.; Cui, X.; Zhao, J.; Wang, J.; Kaidery, N.A.; Thomas, B.; Bollinger, K.E.; Yoon, Y.; Smith, S.B. Excess homocysteine upregulates the Nrf2-antioxidant pathway in retinal muller glial cells. *Exp. Eye Res.* **2019**, *178*, 228–237. [[CrossRef](#)] [[PubMed](#)]
210. Zed, P.J.; Krenzelok, E.P. Treatment of acetaminophen overdose. *Am. J. Health Syst. Pharm.* **1999**, *56*, 1081–1093. [[CrossRef](#)] [[PubMed](#)]

211. Shi, Z.; Puyo, C.A. N-Acetylcysteine to Combat COVID-19: An Evidence Review. *Ther. Clin. Risk Manag.* **2020**, *16*, 1047–1055. [[CrossRef](#)]
212. Cazzola, M.; Calzetta, L.; Facciolo, F.; Rogliani, P.; Matera, M.G. Pharmacological investigation on the antioxidant and anti-inflammatory activity of N-acetylcysteine in an ex vivo model of COPD exacerbation. *Respire Res.* **2017**, *18*, 26. [[CrossRef](#)] [[PubMed](#)]
213. Jannatifar, R.; Parivar, K.; Roodbari, N.H.; Nasr-Esfahani, M.H. The effect of N-acetyl- cysteine on Nrf2 antioxidant gene expression in asthenoteratozoo-spermia men. A clinical trial study. *Int. J. Fertil. Steril.* **2020**, *14*, 171–175.
214. Zhou, Y.; Wang, H.-D.; Zhou, X.-M.; Fang, J.; Zhu, L.; Ding, K. N-acetylcysteine amide provides. Neuroprotection via Nrf2-ARE pathway in a mouse model of traumatic brain injury. *Drug Des. Dev. Ther.* **2018**, *12*, 4117–4127. [[CrossRef](#)]
215. Ezeriņa, D.; Takano, Y.; Hanaoka, K.; Urano, Y.; Dick, T.P. N-Acetyl Cysteine Functions as a Fast-Acting Antioxidant by Triggering Intracellular H₂S and Sulfane Sulfur Production. *Cell Chem. Biol.* **2018**, *25*, 447–459. [[CrossRef](#)] [[PubMed](#)]
216. Zuhra, K.; Tomé, C.S.; Masi, L.; Giardina, G.; Paulini, G.; Malagrino, F.; Forte, E.; Vicente, J.B.; Giuffrè, A. N-Acetylcysteine Serves as Substrate of 3-Mercaptopyruvate Sulfurtransferase and Stimulates Sulfide Metabolism in Colon Cancer Cells. *Cells* **2019**, *8*, 828. [[CrossRef](#)] [[PubMed](#)]
217. Maccio, A.; Madeddu, C.; Panzone, F.; Mantovani, G. Carbocysteine: Clinical experience and new perspective in the treatment of chronic inflammatory diseases. *Expert Opin. Pharmacother.* **2009**, *10*, 693–703. [[CrossRef](#)] [[PubMed](#)]
218. Pace, E.; Ferraro, M.; Vincenzo, S.D.; Cipollina, C.; Gerbino, S.; Gjomarkaj, M. Comparative cytoprotective effects of carbocysteine and fluticasone propionate in cigarette smoke extract-stimulated bronchial epithelial cells. *Cell Stress Chaperones* **2013**, *18*, 733–743. [[CrossRef](#)]
219. Borodina, I.; Kenny, L.C.; McCarthy, C.M.; Paramasivan, K.; Pretorius, E.; Roberts, T.J.; Van der Hoek, S.A.; Kell, D.B. The Biology of Ergothioneine an antioxidant nutraceutical. *Nutr. Res. Rev.* **2020**, *33*, 190–217. [[CrossRef](#)] [[PubMed](#)]
220. Jones, G.W.; Doule, S.; Fitzpatrick, D.A. The evolutionary history of the genes involved in the biosynthesis of the antioxidant ergothioneine. *Gene* **2014**, *549*, 161–170. [[CrossRef](#)] [[PubMed](#)]
221. Salama, S.A.; Abd-Allah, G.M.; Mohamadin, A.M.; Elshafey, M.M.; Gad, H.S. Ergothioneine mitigates cisplatin-evoked nephrotoxicity via targeting Nrf2, NF- κ B, an apoptotic signaling and inhibiting γ -glutamyl transpeptidase. *Life Sci.* **2021**, *278*, 119572. [[CrossRef](#)] [[PubMed](#)]
222. Hseu, Y.C.; Lo, H.W.; Lorivi, M.; Tsai, Y.C.; Tang, M.J.; Yang, H.L. Dermato-protective properties of Ergothioneine through induction of Nrf2/ARE-mediated antioxidant genes in UVA-irradiated human keratinocytes. *Free Radic. Biomed.* **2015**, *86*, 102–117. [[CrossRef](#)] [[PubMed](#)]
223. Hyun, J.K.; Kim, J.; Ahn, M.; Kim, J.H.; Lee, G.S.; Shin, T. Ergothioneine alleviates senescence of fibroblasts induced by UVB damage of keratinocytes via activation of the Nrf2/H 0-1 pathway and HSP70 in keratinocytes. *Exp. Cell Res.* **2021**, *400*, 112516.
224. Borlinghaus, J.; Albrecht, F.; Gruhike, M.C.; Nwachukwu, I.D.; Slusarenko, A.J. Allicin: Chemistry and biological properties. *Molecules* **2014**, *19*, 12591–12618. [[CrossRef](#)]
225. Chan, J.Y.; Yuen, A.C.; Chan, R.Y.; Chan, S.W. A review of the cardiovascular benefits and antioxidant properties of allicin. *Phytother. Res.* **2013**, *27*, 637–646. [[CrossRef](#)] [[PubMed](#)]
226. Rabinkov, A.; Miron, T.; Konstantinovski, L.; Wilhek, M.; Mirelman, D.; Weiner, L. The mode of action of allicin: Trapping of radicals and interaction with thiol containing proteins. *Biochim. Biophys. Acta* **1998**, *1379*, 233–244. [[CrossRef](#)]
227. Metwally, D.M.; Al-Olayan, E.M.; Alanazi, M.; Alzahrany, S.B.; Semlali, A. Antischistosomal and anti-inflammatory activity of garlic and allicin compared with that of praziquantel in vivo. *BMC Complement. Altern. Med.* **2018**, *18*, 135. [[CrossRef](#)]
228. Bat-Chen, W.; Golan, T.; Peri, I.; Ludmer, Z.; Schwartz, B. Allicin purified from fresh garlic cloves induces apoptosis in colon cancer cells via Nrf2. *Nutr. Cancer* **2010**, *62*, 947–957. [[CrossRef](#)] [[PubMed](#)]
229. Zhang, M.; Pan, H.; Xu, Y.; Wnag, X.; Qiu, Z.; Jiang, L. Allicin decrease Lipopolysaccharide-induced oxidative stress and inflammation in human umbilical vein endothelial cells through suppression of mitochondrial dysfunction and activation of Nrf2. *Cell. Physiol. Biochem.* **2017**, *41*, 2255–2267. [[CrossRef](#)]