Natural product-derived pharmacological modulators of Nrf2/ARE pathway for chronic diseases

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Natural product-derived pharmacological modulators of Nrf2/ARE pathway for chronic diseases

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Oxidative stress is the central component of chronic diseases. The nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) pathway is vital in the up-regulation of cytoprotective genes and enzymes in response to oxidative stress and treatment with certain dietary phytochemicals. Herein, we classify bioactive compounds derived from natural products that are Nrf2/ARE pathway activators and recapitulate the molecular mechanisms for inducing Nrf2 to provide favorable effects in experimental models of chronic diseases. Moreover, pharmacological inhibition of Nrf2 signalling has emerged as promising strategy against multi-drug resistance thereby improving the treatment efficacy. We have also enlisted natural product-derived inhibitors of Nrf2/ARE pathway.

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1 Introduction

Oxidative stress plays a key role in several diseases including cancers,[1–3] cardiovascular diseases,[4–6] Alzheimer's disease (AD),[7–9] Parkinson's disease (PD),[10–12] Huntington's disease (HD),[13,14] amyotrophic lateral sclerosis (ALS),[15,16] atherosclerosis,[17,18] chronic kidney diseases,[19,20] and diabetes.[21] Oxidative stress is caused by an imbalance in reactive species and the antioxidative stress defense systems in cells.[10] These reactive species can be reactive oxygen species (ROS), reactive nitrogen species, or reactive electrophilic species. To counteract environmental stress caused by these reactive species, cells have developed adaptive, dynamic programs to maintain cellular redox homeostasis and reduce oxidative damage through a series of antioxidant molecules and detoxifying enzymes that can provide control over these reactive species either by quickly removing or detoxifying them.

The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway plays an imperative role in cellular redox homeostasis and

activating this pathway is one of the main defense mechanisms against oxidative or electrophilic stress.[22–26] The protective responses and induction of cytoprotective enzymes require at least three essential components: (a) *cis*-elements called antioxidant response elements (AREs) or electrophile-response elements (EpREs) with the core consensus sequence 5′-TGABnnnGC-3′ (where B = C, or G, or T, and the letter "n" represents any nucleotide) in their promoter regions which upstream regulatory sequences present on each gene in either single or multiple copies;[26–28] (b) Nrf2, the redox-sensitive and principal transcription factor that heterodimerizes with members of the small musculoaponeurotic fibrosarcoma (Maf) family of transcription factors and recruits the general transcriptional machinery for expression of ARE-related genes;[26,29,30] and (c) Kelch ECH association protein 1 (Keap1), a cytosolic repressor protein that binds to Nrf2, retaining it in cytoplasm, and promoting its proteasomal degradation.[31]

Natural products have contributed significantly to drug discovery, and several candidates have emerged either directly or through modification of the basic ring.[32,33] Many epidemiological studies have shown that phytochemicals in vegetables and fruits reduce the risk of different kinds of cancers, age-related pathological conditions, and prevent or mitigate chronic diseases in humans.[34–38] In the last few decades several studies have demonstrated the benefits of natural products counteracting oxidative stress by modulating the Nrf2/ARE pathway.[34,39–49] Nrf2 activation in the animal model of neurodegenerative diseases such as AD,[50] PD,[51] HD,[13,14] and ALS[15,16] have been demonstrated to extend survival. Furthermore, clinical application of Nrf2 activation has been utilised against stress-induced disease[52,53] including multiple sclerosis.[54]

Herein, we review the molecular mechanism of the Nrf2/ARE pathway under physiological and pathological conditions and highlight the protective role of this pathway in several chronic diseases. Furthermore, we summarize and classify >100 bioactive compounds derived from natural products that are activators of the Nrf2/ARE pathway and recapitulate molecular mechanisms for inducing Nrf2 levels to provide favorable effects in chronic diseases. Moreover, pharmacological inhibition of Nrf2 signalling has emerged as a promising strategy against multi-drug resistance thereby improving the treatment efficacy. We have also enlisted natural product-derived Nrf2 inhibitors.

Dong-Kug Choi received his Ph.D. from the University of Tokyo in 1999 and did his post-doctoral training at Columbia University, New York. He started his faculty career at Cornell University, New York in 2002. He is currently Vice-President for Industry and Academic Research affairs and President for Industry and Academic Collaboration foundation at GLOCAL campus, and professor at the Department of Biotechnology, Konkuk University, Korea. His research mainly focuses on investigating the molecular aspects in neurodegeneration and development of novel neuroprotective agents from natural and synthetic agents.

2 The Nrf2/ARE signalling

The Nrf2/ARE pathway is the major pathway that responds to reactive species and redox potentials by activating phase II detoxification enzymes at the transcriptional level.[55,56] Nrf2 belongs to the cap 'n' collar family of transcription factors with a distinct basic leucine-zipper motif.[30] Nrf2 is composed of six functional domains known as Nrf2-ECH homologies (Neh) designated as Neh1–6, respectively.[57] Until recently, a model of the dissociation of the cytoplasmic Nrf2/ARE complex *via* oxidative modification and conformational changes in a repressor protein was considered the conventional mechanism of activating the Nrf2/ARE signalling pathway. According to this model, under basal conditions, repressor Keap1 holds Nrf2 in the cytoplasm and promotes its ubiquitination,[55,58–60] followed by 26S proteasomal degradation in a constitutive manner.[61] In agreement with this, Nrf2 constitutively accumulates in nuclei in Keap1-knockout mice.[62] Moreover, Nrf2 is released from Keap1 in the presence of Nrf2-inducing chemicals/electrophilic and/or oxidative stimulus and is translocated to the nucleus where it binds with ARE in the promoter region of its target genes thereby inducing a battery of cytoprotective genes and anti-oxidative enzymes (Fig. 1).[26,29,63–67]

A distinguishing feature of Keap1 is its high cysteine content, which makes it an excellent candidate as an induction sensor. Stress generated from chemicals or radiation modifies reactive cysteines of Keap1 (C151, C273, and C288), followed by protein kinase C (PKC)-mediated phosphorylation at Ser 40, which leads to dissociation of Nrf2 from Keap1 and increased translocation and transcription of Nrf2 dependent genes.[60,68] Interestingly, some reports suggest that Keap1 shuttles between the nucleus and the cytoplasm *via* the Crm1-dependent nuclear export mechanism,[69] or that Keap1 transiently enters the nucleus and targets Nrf2 for ubiquitylation; thus, indicating that both ubiquitylation and degradation occur in the nucleus.[55]

Another recently proposed mechanism for regulation of the Nrf2/ARE pathway by Keap1 is the "hinge and latch model".[70] In this model, a Keap1 homodimer recruits its substrate, Nrf2, by binding to conserved DLG and ETGE motifs within the regulatory Neh2 domain of Nrf2.[71,72] Although the DLG and ETGE peptides bind to Keap1–DC in a similar manner, the DLG motif works as a latch to correctly position the lysines within the Nrf2 Neh2 domain for efficient ubiquitination by selectively locking and unlocking.[73] Binding *via* the high-affinity ETGE motif and the lower-affinity DLG motif of Nrf2 provides the hinge and latch, which facilitates optimal positioning of the lysine residues for conjugation with ubiquitin. As a result, Keap1 is able to efficiently target Nrf2 for proteasomal degradation.[73]

Apart from the cytosolic inhibitor Keap1, several mechanisms are involved in the regulation of the Nrf2/ARE pathway. Proteins such as p62[74] and p21[75] compete with Keap1–Nrf2

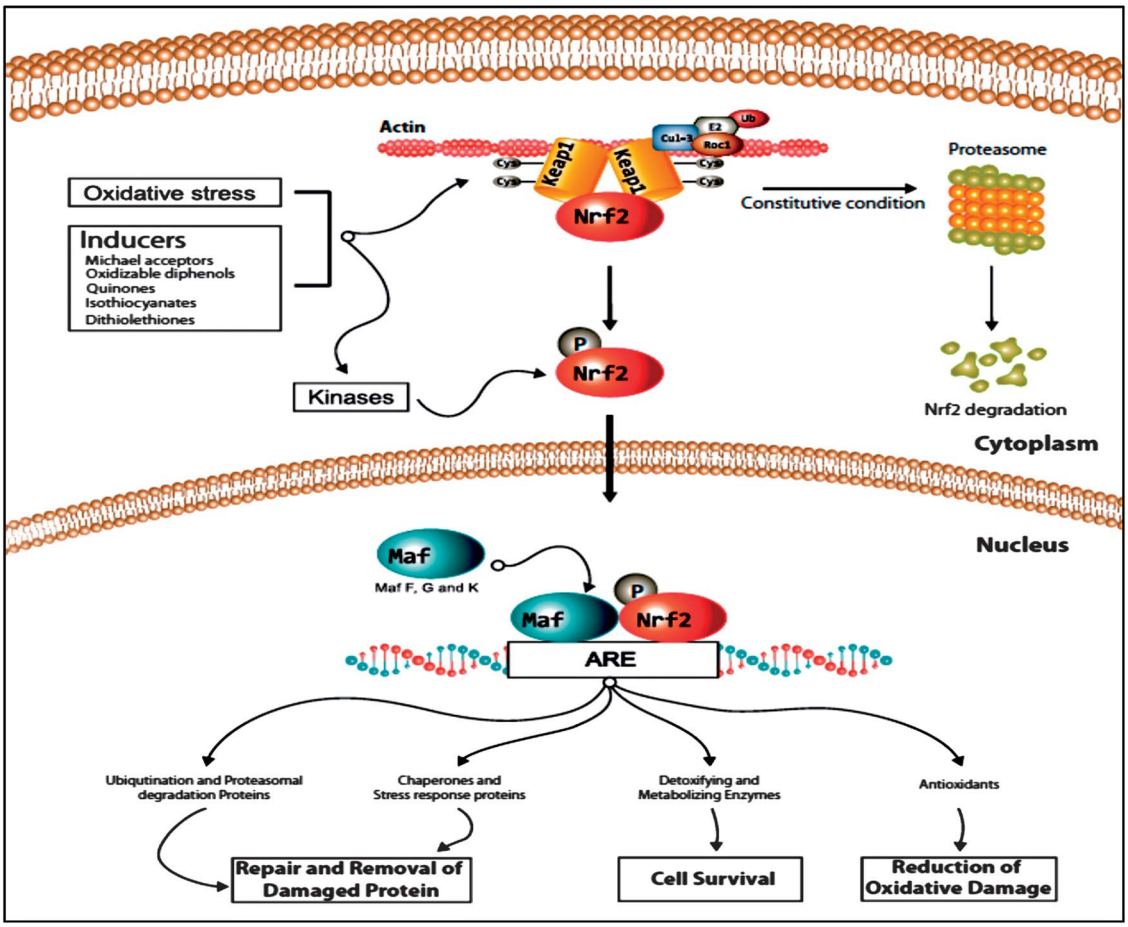


Fig. 1 Schematic illustration of regulation of the Nrf2 pathway under constitutive and stress conditions. Nrf2 continuously undergoes proteasomal degradation in constitutive conditions. The modification of Keap1 cysteine residues results in the inhibition of the ubiquitin E3 ligase activity of the Keap1–Cul3 complex. Disruption of the Nrf2–Keap1 association is mediated by electrophiles, free radicals, or inducers of Nrf2, and leads to a diminished rate of proteolysis, thereby enhancing nuclear accumulation of Nrf2 in the nucleus. Nrf2 binds with AREs in the promoter region of its target genes and induces a battery of cytoprotective genes and anti-oxidative enzymes resulting in an adaptive response (repair and removal of damaged protein, cell survival and reduction of oxidative damage). In addition, phosphorylation of Nrf2 at serine and threonine residues by kinases is assumed to facilitate dissociation of Nrf2 from Keap1 and subsequent translocation to the nucleus.

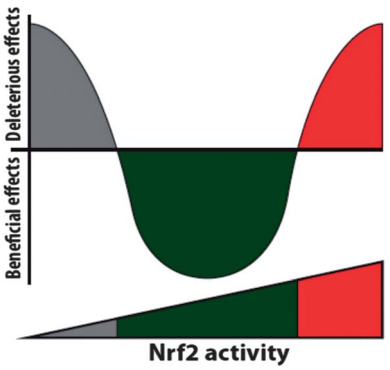


Fig. 2 Nrf2 in the hormetic pathway. Low levels of Nrf2 (shown in grey) in conditions such as aging lead to reduced levels of cytoprotective genes and enzymes. Inducing Nrf2 using the dietary chemicals present in fruits and vegetables provides protection against various diseases (shown in green). Sustained stimulation and high levels of Nrf2 (shown in red) lead to deleterious effects such as multi-drug resistance and atherosclerosis.

binding, promote stabilization of Nrf2 and up-regulation of Nrf2 target genes in autophagy-deficient and oxidative conditions, respectively. CR6-interacting factor 1, is another recently discovered negative regulator of ARE-dependent gene expression that acts at the stage of Nrf2 post-translational modification.[76]

2.1 Protein kinase(s) in Nrf2/ARE activation

Besides direct oxidation or covalent modification of Keap1 cysteine groups, Nrf2/ARE signalling can be modulated by post-transcriptional modification of Nrf2 by kinases. Phosphorylation is one of the key steps to activate the Nrf2 pathway, but the role of individual protein kinases and phosphatases in the Nrf2/ARE signal system mainly depends on cell type. Phosphorylation of Nrf2 at serine and threonine residues by kinases such as phosphatidylinositol 3-kinase (PI3K), PKC, c-Jun N-terminal kinase (JNK) and extracellular signal-regulated protein kinase (ERK) is assumed to facilitate the release of Nrf2 from Keap1 and subsequent translocation.[77–79] PKC directly phosphorylates

Table 1 Natural product-derived flavanoids and chalcones as inducers of the Nrf2/ARE pathway[a]

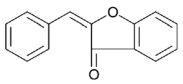
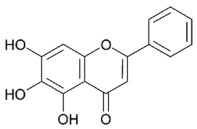
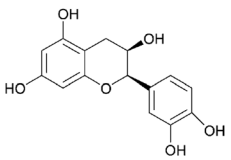
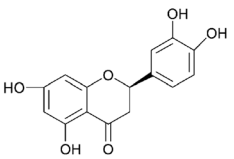
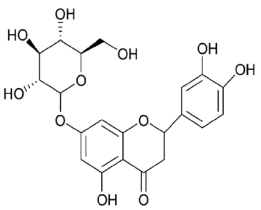
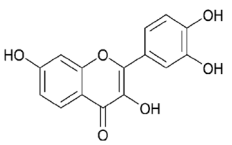
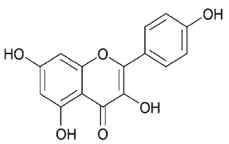
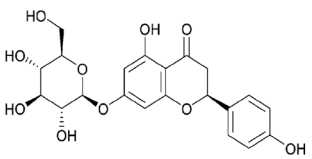
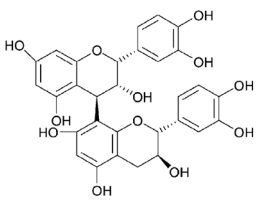
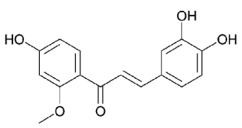
Structure no.		Bioactive compound	Class	Source	Therapeutic indication through Nrf2 activation	Ref.
3		Aurones	Flavonoid	*Dipteryx odorata*	Chemopreventive[*]	280
4		Baicalein	Flavonoid	*Scutellaria baicalensis*	Parkinson's disease[*,$]	131
5		Epicatechin	Flavonoid	Cocoa and tea	Stroke[*]	281
6		Eriodictyol	Flavonoid	*Dracocephalum rupestre*	Chemopreventive[*]	282
7		Eriodictyol-7-*O*-glucoside	Flavonoid	*D. rupestre*	Protection against cisplatin toxicity[#]	283
8		Fisetin	Flavonoid	Fruits and vegetables	Cytoprotective[*]	284
9		Kaempferol	Flavonoid	Green tea, broccoli, apple and berries	Chemoprotective[$]	285
10		Naringenin-7-*O*-glucoside	Flavonoid	*D. rupestre*	Doxorubicin-induced toxicity[*,$]	286
11		Procyanidin B2	Flavonoid	Cocoa, red wine and grape juice	Chemopreventive[*,$]	102
12		Sappanchalcone	Flavonoid	*Caesalpinia sappan*	Anti-inflammatory[*,$]	287

Table 1 (*Contd.*)

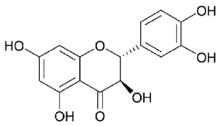
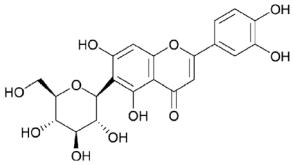
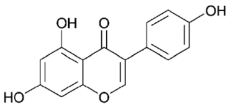
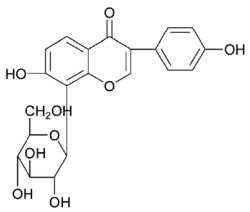
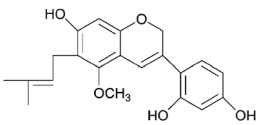
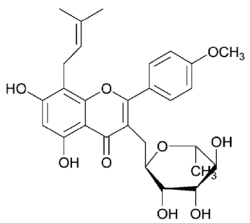
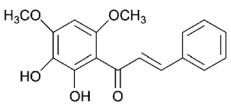
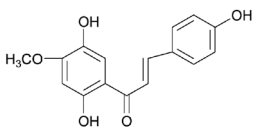
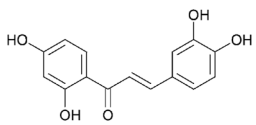
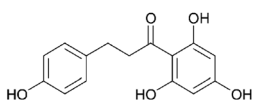
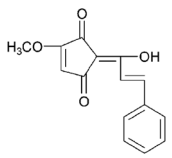
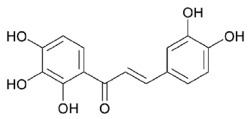
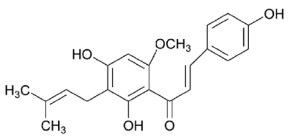
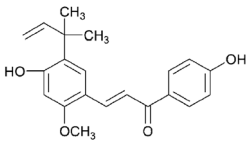
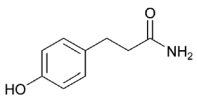
Structure no.	Bioactive compound	Class	Source	Therapeutic indication through Nrf2 activation	Ref.
13 	Taxifolin	Flavanone	*Larix sibirica*	Chemopreventive*	288
14 	Isoorientin	Flavone	*Sasa borealis*	Oxidative stress*,$	289
15 	Genistein	Isoflavones	Soybean	Neuroprotective*	290–292
16 	Puerarin	Isoflavone glycoside	*Pueraria lobata*	Cytoprotective$	293
17 	Dehydroglyasperin C	Prenylflavonoids	*Glycyrrhiza uralensis*	Neuroprotection*,$	294
18 	Icariside I	Prenylflavonoids	*Epimedium koreanum*	Cytoprotective*,$	295
19 	2′,3′-Dihydroxy-4′,6′-dimethoxychalcone	Chalcone	*Perilla frutescens*	Neuroprotection*	296
20 	4,2′,5′-Trihydroxy-4′-methoxychalcone	Chalcone	*Dalbergia odorifera*	Anti-inflammatory*	297
21 	Butein and phloretin	Chalcones	Fruits, vegetables, nuts, tea, coffee, and red wine	Hepatoprotective$	298
22 					
23 	Lucidone	Chalcone	*Lindera erythrocarpa*	Inhibition of HCV replication*	299

Table 1 (*Contd.*)

Structure no.	Bioactive compound	Class	Source	Therapeutic indication through Nrf2 activation	Ref.
24 	Okanin	Chalcone	*Bidens pilosa*	Anti-inflammatory*	300
25 	Xanthohumol	Chalcone	*Humulus lupulus*	Anti-inflammatory*	301
26 	Licochalcone E	Retrochalcone	*Glycyrrhiza inflata*	Parkinson's disease*	142
27 	Phloretamide	Dihydrochalcone	Apples	Chemopreventive*	302

[a] Nrf2 activators increase phase II cytoprotective genes and enzymes either through increased nuclear localization and transcriptional activity of Nrf2 (*), inhibition/delay of ubiquitination and degradation of Nrf2 (#), and/or activation of kinases ($).

Nrf2 at Ser 40[80] thereby promoting its dissociation from Keap1.[77,81] However, certain protein kinases participate in the negative regulation of Nrf2/ARE.[82,83] The Nrf2 pathway appears to be regulated positively by ERK and JNK whereas p38 MAPK confers both positive and negative regulation.[84–86]

2.2 Genes regulated by the Nrf2/ARE pathway

The Nrf2/ARE pathway modulates the expression of more than 500 genes.[87] The target genes regulated by ARE include phase I and II detoxification enzymes, transport proteins, proteasome subunits, chaperones, growth factors and their receptors, as well as some other transcription factors (Fig. 1).[31,61,88,89]

These enzymes are expressed in various isoforms and are distributed in various organelles and subcellular compartments and cooperatively participate in metabolic reactions that eliminate reactive species at their sites of origin. Glutathione (GSH) is the most abundant small-molecule antioxidant that scavenges ROS and neutralizes electrophiles.[90] Large-molecule antioxidant and detoxifying enzymes such as superoxide dismutase (SOD), glutathione peroxidase, catalase, glutathione reductase (GR), glutamate cysteine ligase (GCL), NAD(P)H:quinone oxidoreductase 1 (NQO1), heme oxygenase-1 (HO-1), γ-glutamyl cysteine synthetase catalytic subunit (GCLC), γ-glutamyl cysteine synthetase modifier subunit (GCLM), glutathione *S*-transferase (GST), UDP-glucuronyl transferase, thioredoxin reductase, peroxiredoxin and sulfotransferase are of prime importance in protecting against oxidative stress at the cellular level.[26,91,92]

These expressed cytoprotective proteins are referred to as the "ultimate antioxidants," as they are not consumed during their antioxidant actions, can catalyze a wide variety of detoxification reactions and have relatively long half-lives. Moreover, these enzymes detoxify many harmful substances by converting them to hydrophilic metabolites that can be excreted readily from the body.[93] Phase II enzymes, such as NQO1 and GCS, are highly inducible in animals and humans,[94] and a strong inverse relationship exists between their tissue levels and susceptibility to chemical carcinogenesis.[95] Furthermore, loss of Nrf2 signalling increases susceptibility to acute toxicity, inflammation, carcinogenesis, and several chronic diseases. Nrf2 inducers exhibit their antioxidant/neuroprotective effects by up-regulating various cytoprotective enzymes and proteins. Moreover, several genes that have not been classified as antioxidants or detoxification enzymes are regulated by Nrf2. Thus, the Nrf2-downstream target genes have been expanded beyond known functions such as antioxidant, detoxification, xenobiotic-metabolizing, ubiquitin-mediated proteasomal degradation systems, intracellular redox-regulating, genes encoding transporters and genes controlling cell growth.[96–98]

3 The Nrf2/ARE pathway as a multiprotector

Nrf2 protects various cell types by coordinately up-regulating not only classic ARE-driven genes but also cell type-specific protective genes essential for the basic defense system of each cell type.[99] The generation of Nrf2-knockout mice confirmed that Nrf2 is the major orchestrator of the cellular stress response to oxidants and electrophiles.[100] Nrf2-null animals

Table 2 Natural product-derived terpenoids as inducers of Nrf2/ARE pathway[a]

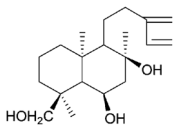
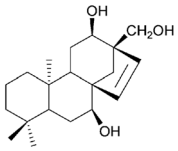
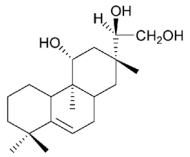
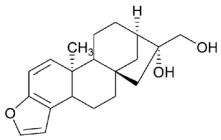
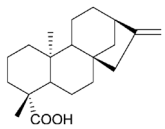
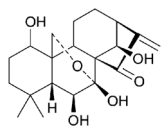
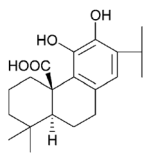
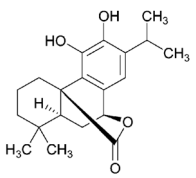
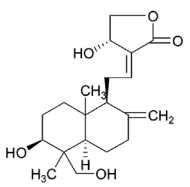
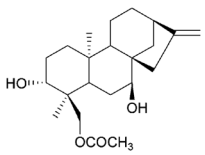
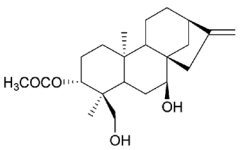
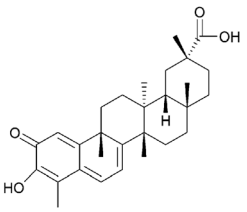
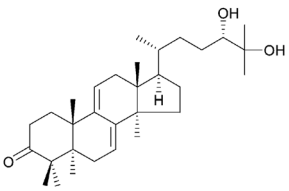
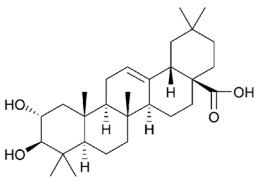
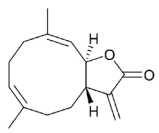
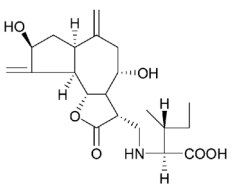
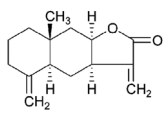
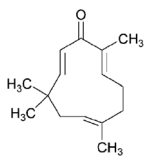
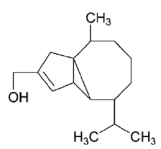
Structure no.	Bioactive compound	Class	Source	Therapeutic indication through Nrf2 activation	Ref.
34 	Andalusol	Diterpenoids	*Sideritis* spp.	Neuroprotection[*]	313
35 	Conchitriol	Diterpenoids	*Sideritis* spp.	Neuroprotection[*]	313
36 	Lagascatriol	Diterpenoids	*Sideritis* spp.	Neuroprotection[*]	313
37 	Kahweol	Diterpene	Coffee	Parkinson's disease[$]	314
38 	Kaurenoic acid	Diterpenoid	*Aralia continentalis*	Anti-inflammatory[*]	315
39 	Oridonin	Diterpenoid	*Rabdosia rubescens*	Arsenic-induced toxicity[#]	316
40 	Carnosic acid	Diterpene	*Rosmarinus officinalis*	Neuroprotection[*]	317
41 	Carnosol	Diterpene	*R. officinalis*	Neuroprotection[$]	318
42 	Andrographolide	Labdane diterpenoid	*Andrographis paniculata*	Chronic obstructive pulmonary disease[*]	319
43 	Linearol	Kaurane diterpenes	*Sideritis* spp.	Cytoprotective and astroprotective[*]	320,321

Table 2 (*Contd.*)

Structure no.		Bioactive compound	Class	Source	Therapeutic indication through Nrf2 activation	Ref.
44		Sidol	Kaurane diterpenes	*Sideritis* spp.	Cytoprotective and astroprotective*	320,321
45		Celastrol	Triterpenoid	*Tripterygium wilfordii*	Anti-inflammatory$	322
46		Ganodermanondiol	Triterpene	*Ganoderma lucidum*	Hepatoprotective*	323
47		Maslinic acid	Triterpene	*Coleus tuberosus*	Cytoprotective*	324
48		Costunolide	Sesquiterpene lactones	*Saussurea lappa*	Anti-inflammatory*	325
49		Pulchellamin G	Sesquiterpene lactone	*Saussurea pulchella*	Anti-inflammatory*	326
50		Isoalantolactone	Sesquiterpene lactone	*Inula helenium*	Chemoprevention*	327
51		Zerumbone	Sesquiterpene	*Zingiber zerumbet*	Chemopreventive*	328
52		α-Iso-cubebenol	Sesquiterpene	*Schisandra chinensis*	Anti-inflammatory$	329

[a] Nrf2 activators increase phase II cytoprotective genes and enzymes either through increased nuclear localization and transcriptional activity of Nrf2 (*), inhibition/delay of ubiquitination and degradation of Nrf2 (#), and/or activation of kinases ($).

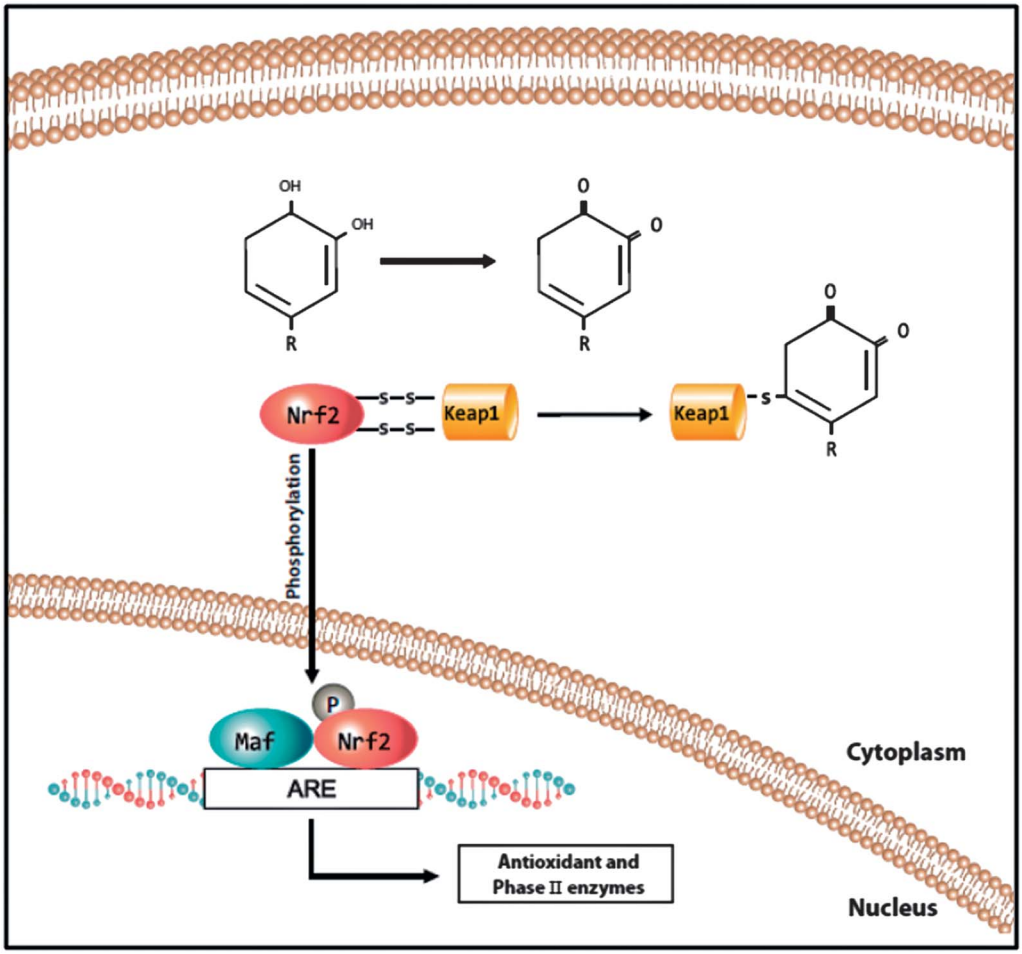


Fig. 3 Diphenol is oxidized to its quinone derivative and then reacts with Keap1 in a Michael addition reaction with the corresponding ortho-quinone (or paraquinone) form. Nrf2 is released from Keap1 and translocated into the nucleus to express phase II cytoprotective genes and enzymes. Phosphorylation of Nrf2 also plays a critical role in the transactivation of antioxidant enzymes.

display low basal and/or inducible expression of cytoprotective genes in a variety of tissues, including liver,[25,101,102] lung,[98,103,104] gastrointestinal tract,[102,105,106] brain,[96,107,108] skin,[109] and bladder.[110,111] Indeed, Nrf2-knockout mice are prone to the acute damage induced by acetaminophen,[112,113] ovalbumin,[114] diesel exhaust,[115] cigarette smoke,[98,116] pentachlorophenol,[117] and 4-vinylcyclohexene diepoxide[118] in comparison to their wild-type counterparts. In addition, the Nrf2-knockout mice show increased tumor formation when they are exposed to carcinogens such as benzo[*a*]pyrene,[102] diesel exhaust,[115] and *N*-nitrosobutyl(4-hydroxybutyl)amine.[110] Conversely, pharmacological or genetic activation of Nrf2 has protective effects in numerous models of chronic disease, including cancer.[34,39–49,61,119] Hence, the Nrf2/ARE pathway has emerged as multiprotector at the cellular and molecular levels. Moreover, the chances of contracting a disease increase drastically with age, whereas Nrf2 activity and expression of Nrf2 downstream targets declines with age.[120–123] Interestingly, most diseases have different compensatory levels of Nrf2 at the earlier and later stages. This might be because of adaptation due to increased oxidative stress, cell death and some other factors.

3.1 Role of the Nrf2/ARE pathway in neurodegenerative diseases

Neurodegenerative diseases including AD, PD, HD and ALS occur as a result of neurodegenerative processes. The Nrf2/ARE pathway has emerged as a therapeutic target for neuroprotection from neurodegenerative diseases.[22,124] Patients with AD exhibit a dramatic reduction in nuclear Nrf2 within hippocampal neurons.[125] Similarly, a decline in Nrf2 activity and overexpressing Nrf2 through adenovirus or increasing Nrf2 using an inducer confers neuroprotection in experimental model of AD.[126,127] PD differs from AD in that Nrf2 is expressed at higher levels in neurons of PD patients,[125] and experimental models of PD show greater loss of dopaminergic neurons in Nrf2-knockout mice.[128,129] Furthermore, overexpression of Nrf2 or down-regulating Keap1 or Nrf2 inducers shows protective effects in animal models of PD.[42,130,131]

HD is an autosomal, dominantly inherited neurodegenerative disease. Similar to AD, transgenic HD mice show a decline in Nrf2 activity,[132–134] and Nrf2-knockout mice are more sensitive to the detrimental effects of 3-nitropropionic acid or malonate, which causes degeneration similar to HD.[135] In addition, Nrf2

Table 3 Natural product-derived polyphenols and quinones as inducers of Nrf2/ARE pathway[a]

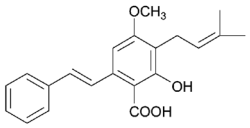
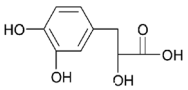
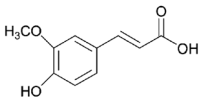
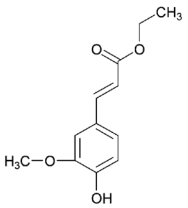
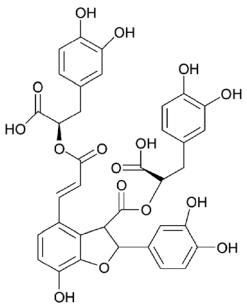
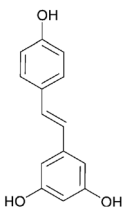
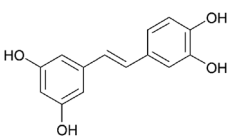
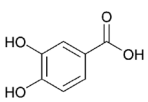
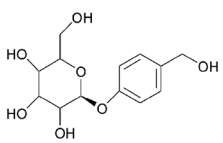
Structure no.		Bioactive compound	Class	Source	Therapeutic indication through Nrf2 activation	Ref.
64		Cajaninstilbene acid	Polyphenol	*Cajanus cajan*	Cytoprotective[*,$]	349
65		Danshensu	Polyphenol	*Salvia miltiorrhiza*	Parkinson's disease[$]	350
66		Ferulic acid	Polyphenol		Cytoprotective[*,$]	351
67		Ethyl ferulate	Polyphenol	Fruits and vegetables such as tomatoes, sweetcorn and rice	Neuroprotective[*]	352
68		Lithospermic acid B	Polyphenol	*S. miltiorrhiza*	Diabetes[*]	353
69		Resveratrol	Polyphenol	Peanuts, grapes and red wines	Hepatoprotective[*]	44
70		Piceatannol	Polyphenol	*Euphorbia lagascae*	Chemopreventive[*] and neuroprotective[*]	354,355
71		Protocatechuic acid	Polyphenol	Green tea	Oxidative stress[$]	356
72		Gastrodin	Polyphenol	*Gastrodia elata*	Alzheimer's disease[*,$]	141

Table 3 (*Contd.*)

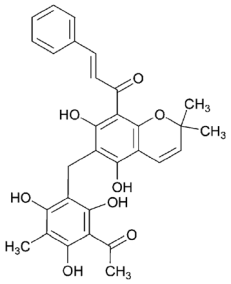
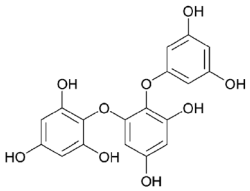
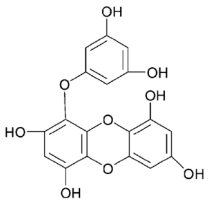
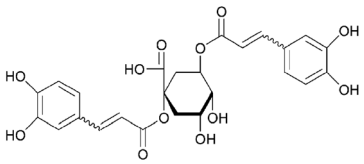
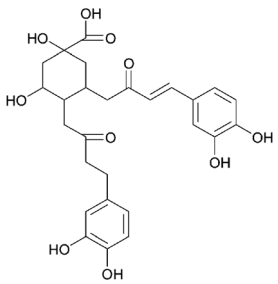
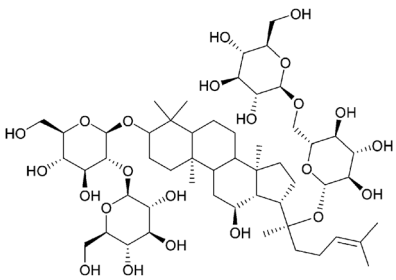
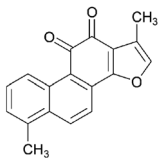
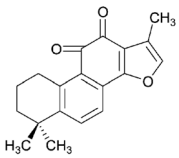
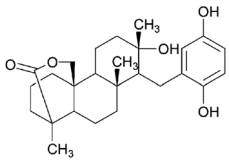
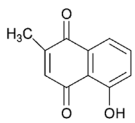
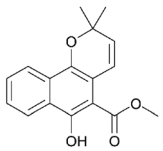
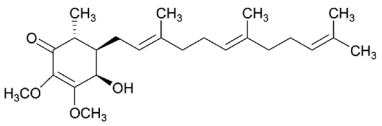
Structure no.	Bioactive compound	Class	Source	Therapeutic indication through Nrf2 activation	Ref.
73 	Rottlerin	Polyphenol	*Mallotus philippinensis*	Chemopreventive[$]	357
74 	Triphlorethol-A	Phlorotannin	*Ecklonia cava*	Cytoprotective[*,$]	358
75 	Eckol	Phlorotannin	*E. cava*	Cytoprotective[$]	359
76 	1,5-Dicaffeoylquinic acid	A caffeoylquinic acid derivative	Traditional medicinal herbs	Cerebral ischemia[*]	360
77 	3-Caffeoyl, 4-dihydrocaffeoyl quinic acid	Chlorogenic acid derivative	*Salicornia herbacea*	Hepatoprotective[*,$]	361
78 	Ginsenoside Rb1	Phytoestrogen	*Panax ginseng*	Parkinson's disease[*,$]	362

Table 3 (*Contd.*)

Structure no.	Bioactive compound	Class	Source	Therapeutic indication through Nrf2 activation	Ref.
79 	Tanshinone I	Phenanthrene-quinone	*S. miltiorrhiza*	Anti-inflammatory[#]	363
80 	Tanshinone IIA	Phenanthrene-quinone	*S. miltiorrhiza*	Cytoprotective[$]	364
81 	Strongylophorine-8	Para-hydroquinone	*Petrosia corticata*	Neuroprotection[*]	365
82 	Plumbagin	Naphthoquinone	*Plumbago zeylanica*	Cerebral ischemia[*]	366
83 	Mollugin	Naphthohydroquine	*Rubia cordifolia*	Chemotherapeutic[*,$]	367
84 	Antroquinonol	Ubiquinone derivative	*Antrodia camphorata*	Nephroprotective[*]	368,369

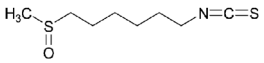
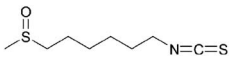
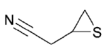
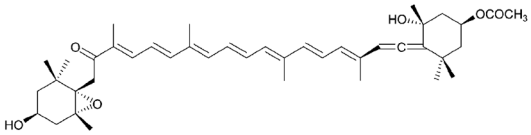
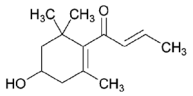
[a] Nrf2 activators increase phase II cytoprotective genes and enzymes either through increased nuclear localization and transcriptional activity of Nrf2 (*), inhibition/delay of ubiquitination and degradation of Nrf2 (#), and/or activation of kinases ($).

inducers promote recovery of transgenic HD mice.[136] ALS is caused by degeneration of motor neurons in the spinal cord, brain stem, and motor cortex. Post-mortem studies of patients with ALS show a decline in Nrf2 activity in the motor cortex and spinal cord and increased Keap1 mRNA in the motor cortex.[137] Similarly, Nrf2 activity is repressed in experimental models of ALS,[138,139] and increasing Nrf2 activity prevents degeneration of motor neurons.[15,140] Collectively, targeting Nrf2/ARE and its downstream gene is a promising therapeutic target for neurodegenerative diseases. Several Nrf2 inducers from natural products have proven efficacy in both *in vivo* and *in vitro* models of neurological disorders.[131,141–143]

3.2 Role of the Nrf2/ARE pathway in chemoprotection/chemoresistance

Nrf2 is overexpressed in several types of human cancer, including cancer of the lung, oesophagus, ovary, head and neck squamous cell carcinoma, gallbladder, and skin.[119,144–149] One of the probable approaches for preventing cancers is using natural products to induce cytoprotective enzymes including phase II and anti-oxidative enzymes that detoxify and eliminate harmful reactive intermediates formed from carcinogens. A variety of natural compounds exert their chemopreventive activities against a wide spectrum of cancer types by evoking the Nrf2/ARE signalling pathway.[150–153] Nevertheless, the cytoprotective properties of the Nrf2/ARE pathway can be exploited by tumor cells to promote their survival. Mutational activation of Nrf2 might cause malignancy and increase chemoresistance.[154–156] Chemoresistance is a major problem during the successful treatment of many cancers. Increased levels of cellular thiols, facilitated detoxification of drugs, and rapid DNA repair are associated with chemoresistance.[157–159] Consistent with this notion, suppression of Nrf2 activity inhibits tumor growth and enhances the efficacy of cancer chemotherapeutic agents.[160–162] Thus, Nrf2/ARE is somewhat of a double-edged sword in cancer

Table 4 Natural product-derived organosulfur compounds and polyenes as inducers of Nrf2/ARE pathway[a]

Structure no.		Bioactive compound	Class	Source	Therapeutic indication through Nrf2 activation	Ref.
92		6-(Methylsulfinyl)hexyl isothiocyanate	Isothiocyanate	*Wasabia japonica*	Detoxification*	399
93		6-Methylthiohexyl isothiocyanate	Isothiocyanate	*W. japonica*	Cytoprotective*	46
94		1-Cyano-2,3-epithiopropane	Epithionitriles	Cruciferous vegetables	Chemopreventive@	400
97		Fucoxanthin	Carotenoid	*Undaria pinnatifida*	Chemopreventive$	401
98		3-Hydroxy-β-damascone	Carotenoid	Apple	Chemopreventive*	402

[a] Nrf2 activators increase phase II cytoprotective genes and enzymes either through increased nuclear localization and transcriptional activity of Nrf2 (*), inhibition of Keap1 (@), and/or activation of kinases ($).

biology with regard to the benefits and risks to cells.[155,163–165] Activating Nrf2 is important for cancer chemoprevention in normal and premalignant tissues; however, Nrf2 activity provides a growth advantage by increasing the cancer chemoresistance and enhancing the tumor cell growth in fully malignant cells.[166] Temporally inhibiting Nrf2-dependent cytoprotection using Nrf2 inhibitors is important to enhance a patient's response to anticancer drugs.[156] Thus, Nrf2 activity could be targeted for cancer treatment as well as chemoprevention, although in different patient populations.

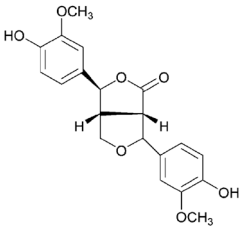
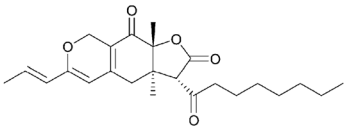
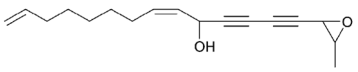
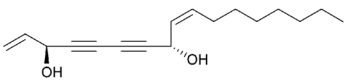
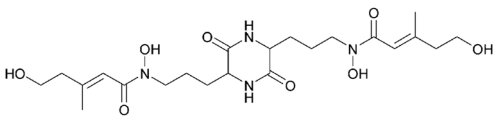
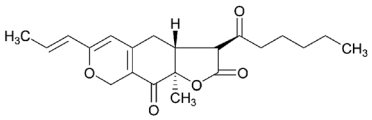
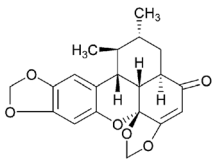
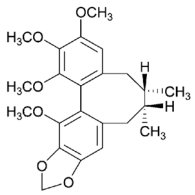
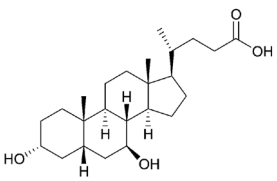
3.3 Role of the Nrf2/ARE pathway in liver diseases and detoxification

The liver is a multifunctional organ responsible for detoxification as well as metabolism. Nrf2 activation is observed in non-parenchymal cells including hepatic stellate cells, Kupffer cells and in parenchymal hepatocytes.[167,168] Nrf2-knockout mice show greater susceptibility to liver injuries and a reduced antioxidant response to 1-bromopropane,[169] chronic ethanol consumption,[170] a high fat diet,[171] and a methionine- and choline-deficient diet[172,173] compared to those in wild-type counterparts. Activating Nrf2 using a natural product-derived activator,[41] or through Keap1 knockdown and hepatocyte-specific knockout[174] prevents liver injury. Conversely, autophagy-deficient mice show aberrant accumulation of p62, and develop severe liver damage. The p62 accumulation disrupts the Keap1–Nrf2 association and provokes Nrf2 stabilization and accumulation. Thus, an overproduction of p62 or a deficiency in autophagy competes with the interaction between Nrf2 and Keap1, resulting in stabilization of Nrf2 and transcriptional activation of Nrf2 target genes. The pathological process associated with p62 accumulation results in hyperactivation of Nrf2 and delineates unexpected roles of selective autophagy in controlling the transcription of cellular genes.[74,175] Nrf2 is expressed ubiquitously, particularly in tissues associated with detoxification (liver and kidney) and those that are exposed to the external environment (skin, lung, and gastrointestinal tract).[176] Nrf2-knockout mice show exacerbated acetaminophen (APAP) hepatotoxicity and Nrf2-knockout mice die sooner and at lower doses of APAP.[112,113] Furthermore, the ability to eliminate APAP metabolites decreases in Nrf2-knockout mice and Keap1-knockdown enhances the efflux of APAP metabolites.[177] Interestingly, a high level of NQO1 is also observed in human liver tissues during APAP overdose.[178] Furthermore, natural compounds protect against APAP-induced hepatotoxicity by activating Nrf2.[179–181]

3.4 Role of the Nrf2/ARE pathway in inflammation and autoimmune diseases

The Nrf2 pathway plays an important role in acute[98,182] and chronic inflammation.[183] Disruption of this pathway increases susceptibility to various inflammatory conditions such as rheumatoid arthritis, asthma, emphysema, gastritis, colitis and atherosclerosis.[184] Unfortunately, long-term inflammatory signalling can result in decreased Nrf2 activity and decreased antioxidant and defense capacity.[185,186] Indeed, studies have demonstrated that Nrf2 responds to pro-inflammatory stimuli and rescues cells/tissues from inflammatory injury.[187–189] Among the enzymes up-regulated by Nrf2, HO-1 has pronounced anti-inflammatory as well as anti-oxidative properties. The HO-1 promoter contains AREs, and activating Nrf2 enhances HO-1 expression in several cell types.[24,190,191] Up-regulating HO-1 prevents the inflammatory response in various inflammatory conditions.[192–194] Nrf2-knockout mice display significant enhancement of inflammatory biomarkers as compared with those in their wild-type counterparts.[106,195,196]

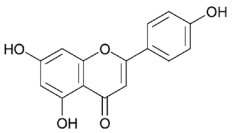
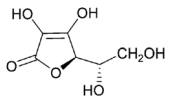
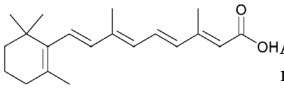
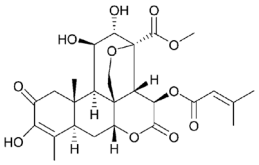
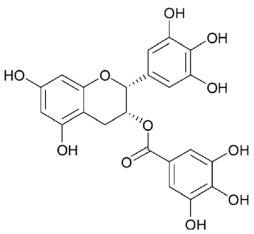
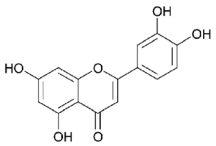
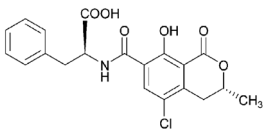
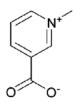
Table 5 Natural product-derived miscellaneous compounds as inducers of Nrf2/ARE pathway[a]

Structure no.	Bioactive compound	Class	Source	Therapeutic indication through Nrf2 activation	Ref.
100 	4-Ketopinoresinol	(α–γ) Double-cyclized type of lignan	*Coix lachryma-jobi*	Chemopreventive*,$	412
101 	Ankaflavin	Polyketide	*Monascus* species	Antidiabetic*	413
102 	Gymnasterkoreayne B	Polyacetylene compound	*Gymnaster koraiensis*	Chemoprevention*	414
103 	Falcarindiol	Diacetylene	*Notopterygium incisum*	Chemopreventive*	415,416
104 	Dimerumic acid	A degradation product of coprogen B	*Monascus anka*	Diabetes*	417
105 	Monascin	Azaphilonoid	Monascus spp.	Diabetes*	418
106 	Sauchinone	Lignan	*Saururus chinensis*	Hepatoprotective$	179
107 	Schisandrin B	Dibenzocyclooctadiene	*S. chinensis*	Cardioprotection*,$	419
108 	Ursodeoxycholic acid	Dehydrocostus lactone	*S. lappa*	Cytoprotective*	420

[a] Nrf2 activators increase phase II cytoprotective genes and enzymes either through increased nuclear localization and transcriptional activity of Nrf2 (*), inhibition/delay of ubiquitination and degradation of Nrf2 (#), and/or activation of kinases ($).

Conversely, Nrf2-activating agents inhibit inflammation in several experimental models.[197–199] It has been suggested that Nrf2 is a critical regulator of the innate immune response. Nrf2-deficient mice suffer from multi-organ autoimmune inflammation, enhanced lymphoproliferation, hemolytic anemia,[200,201] and develop nephritis that shares several key features with human lupus nephritis.[202] Interestingly, homozygous HO-1-knockout mice develop glomerulonephritis.[203] Nrf2

Table 6 Natural product-derived inhibitors of Nrf2/ARE pathway

Structure no.		Bioactive compound	Class	Source	Therapeutic indication through Nrf2 inhibition
109		Apigenin	Flavonoid	Fruits and vegetables	**109** dramatically reduced Nrf2 expression at both the mRNA and protein levels through down-regulation of the PI3K/Akt pathway, leading to a reduction of Nrf2-downstream genes. **109** significantly sensitizes doxorubicin-resistant cells to doxorubicin and increases its intracellular concentration.[437]
110		Ascorbic acid	Vitamin C	Citrus fruits	**110** resulted in a decrease in Nrf2–DNA binding and decreases in levels of γ-GCSl mRNA and GSH in imatinib-resistant KCL22/SR cells and partly restored imatinib sensitivity to KCL22/SR cells.[438]
111		All-*trans* retinoic acid	Vitamin A	From dietary β-carotene	**111** markedly reduced the ability of Nrf2 to mediate induction of ARE-driven genes by cancer chemopreventive agent tBHQ. **111** did not block the nuclear accumulation of Nrf2 but reduced the binding of Nrf2 to the ARE enhancer as a consequence of forming a complex with retinoic acid.[439]
112		Brusatol	Quassinoid	*Brucea javanica*	**112** selectively reduced the protein level of Nrf2 through enhanced ubiquitination and degradation of Nrf2.[160]
63		EGCG	Polyphenol	Green tea	**63** at high concentration induced apoptosis by suppressing expression of HO-1 protein and mRNA, and this effect correlated with a decrease in both Nrf2–ARE binding and HO-1–ARE–luciferase activity.[258]
113		Luteolin	Flavonoid	Celery, green pepper, parsley, perilla leaf, and chamomile tea	**113** elicited a dramatic reduction in Nrf2 at both the mRNA and the protein levels, leading to decreased Nrf2 binding to AREs, down-regulation of ARE-driven genes, and depletion of reduced glutathione in A549 cells and finally leading to sensitization to therapeutic drugs.[161]
114		Ochratoxin A	Mycotoxin	*Aspergillus* and *Penicillium* subspecies	**114** significantly lowered nuclear translocation and transactivation of Nrf2 and also lowered Nrf2 mRNA levels.[440]
115		Trigonelline	Alkaloid	Fenugreek seeds	**115** efficiently decreased basal and tBHQ-induced Nrf2 activity in pancreatic carcinoma cell lines and H6c7 pancreatic duct cells. **115** also blocks Nrf2-dependent expression of proteasomal genes and reduces proteasome activity in all cell lines tested.[441]

also plays a role in autoimmune diseases such as rheumatoid arthritis,[204] lupus-like autoimmune nephritis,[202] systemic lupus erythematosus,[205] and multiple sclerosis.[54,206]

3.5 Role of the Nrf2/ARE pathway in diabetes and cardiac diseases

Oxidative stress, driven by increased production of cellular ROS and concomitant depletion of antioxidant defenses plays a key role in the pathogenesis of late diabetic complications.[207,208] The Nrf2 pathway is dysregulated in diabetes through mechanisms that result in reduced Nrf2 levels and impaired Nrf2 translocation.[209–211] Dysregulation of Nrf2 accelerates the pathological effect of diabetes on the heart and kidney leading to cardiomyopathy and nephropathy.[212–214] Genetic activation of Nrf2 signalling by Keap1 gene hypomorphic knockdown (*Keap1*$^{flox/-}$) markedly suppresses the onset of diabetes. *Keap1*$^{flox/-}$ also prevents high-calorie diet-induced diabetes. Moreover, oral administration of the Nrf2 inducer also attenuates diabetes in mice. Inducing Nrf2 alters genes related to antioxidation, energy consumption, and gluconeogenesis in metabolic tissues.[215] Conversely, depleting Nrf2 and expression of its dependent genes compromises antioxidant capacity resulting in dysfunctional myogenic tone

in diabetes that is reversed by the natural product-derived Nrf2 activator.[216]

Oxidative stress is an important component in the pathogenesis of many cardiovascular disorders,[217] including atherosclerosis,[218] hypertension,[219] heart failure,[220] and ischemia/reperfusion injury.[221] Many of the Nrf2-regulated enzymes are essential in the pathogenesis of cardiovascular diseases.[222] However, reports indicate both beneficial and detrimental effects of activating Nrf2 in the cardiovascular system.[223,224] Nrf2 overexpression attenuates ROS production and hypertrophic growth in cardiomyocytes, and cardiac fibroblasts.[225] Acute activation of Nrf2 is cardioprotective,[226,227] but accumulating evidence suggests that chronic activation of Nrf2 may be harmful to cardiac function[228,229] leading to pathophysiological processes and heart failure. Adenoviral delivery of the Nrf2 gene to rat ventricular cardiomyocytes results in high-level expression of Nrf2 in both cytosol and the nucleus.[230] Clinically established fumarate derivatives activate the Nrf2 pathway and provide cardioprotection.[231] Nrf2-dependent transcriptional activation of AREs also confers cardioprotection.[232] Moreover, various polyphenols and flavonoids show a protective effect in cerebral ischemia.[233–235]

3.6 Role of the Nrf2/ARE pathway in airway and renal diseases

Nrf2 is expressed in relative abundance in tissues such as lung and kidney where detoxification reactions routinely occur.[176,236] The Nrf2/ARE pathway plays an important role in airway disorders[237] and renal disease.[238] Lung hyperpermeability, inflammation, and epithelial cell injury are enhanced in Nrf2-knockout mice compared to those in wild-type mice. Accordingly, antioxidant enzymes are markedly suppressed along with diminished cytoprotective GSH biosynthesis and disturbed redox balance in Nrf2-knockout mice.[239,240] Furthermore, Nrf2-knockout mice are more susceptible to butylated hydroxytoluene,[241] chronic exposure to cigarette smoke,[98] elastase,[103] bleomycin,[242] ovalbumin,[114] and diesel exhaust particles.[115] Moreover, Nrf2/ARE inducers have a protective effect in lung disorders.[196,243,244] Impaired Nrf2 activity and reduced expression of its target gene products occur in experimental models of chronic kidney disease.[245,246] Similarly, Nrf2-null mice are more susceptible to ferric nitrilotriacetate nephrotoxicity,[247,248] ischemia–reperfusion renal injury,[249] diabetic nephropathy,[212] cisplatin-induced nephrotoxicity,[250] accumulate renal lipid peroxides and develop lupus-like autoimmune glomerulonephritis.[202,205] Conversely, the renal protective role of Nrf2 is supported by the finding that dietary Nrf2 activators protect against renal oxidative damage.[251]

4 The Nrf2/ARE pathway as a hormetic signalling pathway

Hormesis has long been used to describe a phenomenon in which an environmental agent induces biologically contradictory effects at different doses; most commonly there is a stimulatory or beneficial effect at low doses and an inhibitory or toxic effect at high doses.[252,253] Major components of the hormetic response pathway include various stress resistance proteins such as heat-shock proteins, antioxidants, growth factors and transcription factors.[253,254] The Nrf2 pathway has evolved as a hormetic pathway.[255,256] Activating the Nrf2/ARE pathway plays an important role in protecting the body against oxidative stress-induced disease and drug toxicity. Moreover, the absence or low levels of Nrf2/ARE increase susceptibility to several diseases. In contrast, sustained activation leads to several diseases including multi-drug resistance, an increased chance of cancer survival and atherosclerosis (Fig. 2). Evolutionary considerations suggest that plants produce phytochemicals against insects, environmental challenges, exposure to radiation, toxins, and other infectious agents. These phytochemicals have biological activities (DNA repair, antioxidant activity, insect repellent, and many more).[257] Most of the phytochemicals produced are highly concentrated in the skin of fruits and buds of vegetables. Certain phytochemicals are also produced by symbiotic bacteria or fungi that live in the plants.[257] Interestingly, these fruits and vegetables normally consumed by humans fall within the low-dose stimulating range of concentrations and are beneficial for inducing cytoprotective genes and enzymes. Interestingly also, certain phytochemicals like epigallocatechin gallate (EGCG)[277,342,258] and luteolin[161,259] can act both as inducer and inhibitor of the Nrf2 pathway which might be explained by the hormetic mechanism.

5 Modulators of the Nrf2 pathway: derived from natural products

5.1 Nrf2 inducers

Inducers that increase the expression of cytoprotective genes are classified into 10 chemically distinct classes: (*i*) Michael acceptors (olefins or acetylenes conjugated to electron-withdrawing groups); (*ii*) oxidizable phenols and quinones; (*iii*) isothiocyanates; (*iv*) thiocarbamates; (*v*) trivalent arsenicals; (*vi*) dithiolethiones; (*vii*) hydroperoxides; (*viii*) vicinal dimercaptans; (*ix*) heavy metals; and (*x*) polyenes.[260,261]

The only common feature among these classes of compounds is their ability to react with sulfhydryl groups by alkylation, oxidation, or reduction.[262,263] Electrophilicity is a common property of most known ARE inducers due to their ability to become electrophilic quinones upon auto-oxidation. However, not all electrophiles regulate ARE activity. Most of the natural product-derived Nrf2 modulators are Michael acceptors, oxidizable phenols and quinones, isothiocyanates, dithiolethiones, polyenes or vicinal dimercaptans. The following section discusses the probable mechanism by which these classes of chemicals modulate Nrf2 activity.

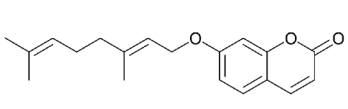
5.1.1 Michael acceptors. Michael acceptors (olefins or acetylenes conjugated with electron-withdrawing groups) are prominent among the chemically distinct classes of cytoprotective enzymes inducers.[262,264] They undergo Michael addition with critical nucleophilic amino acids, located in a subproteome of electrophile-sensitive proteins, such as cysteine, lysine, and serine.[265] They are susceptible to attack by nucleophiles and are typically found in various phytochemicals such as flavonoids, coumarins, chalcones, terpenoids, curcuminoids,

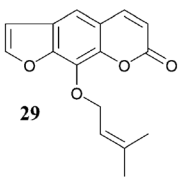
cinnamic acid derivatives, and thiophenes. Important nucleophiles that likely mediate the response are highly reactive sulfhydryl groups present on a potential cellular "sensor(s)" that reacts with the inducers (natural compounds), signalling up-regulation of phase II enzymes.[262] The presence of hydroxyl group(s) at the *ortho* position(s) on the aromatic ring(s) dramatically enhances inducer potencies.[266] Michael acceptors show a bell-shaped dose–response curve, with cellular toxicity at high dosages and light chemical stress at lower concentrations with the activation of physiological hormesis in cells (Fig. 2).[267]

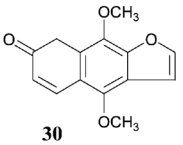
Flavonoids are composed of flavones, flavonols, flavanones, flavanols, chalcones, anthocyanins, and isoflavones. Flavonoids as such do not have electrophilic activity but are commonly known to have electron-donating antioxidant properties.[268] However, flavonoid metabolites do have electrophilic activity and can covalently bind to GSH and DNA.[269] Flavonoids induce the expression of NQO1 and GST *via* Nrf2, possibly involving upstream modulation of PKC.[270] Flavonoids, particularly those with a catechol moiety, have the potential to be oxidized to quinones or semiquinones, resulting in redox cycling and production of ROS, which react with the sulfhydryl group of GSH and the cysteine residues of Keap1.[270,271] Quercetin **1** is a typical polyphenol flavonoid antioxidant found in vegetables and fruits, particularly in onions, apples, tea, broccoli, red wine and grains.

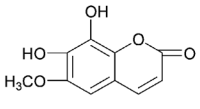
Chalcones are naturally-occurring substances ubiquitously present in plants, where they participate in defense strategies as antioxidants, antifungal and antimicrobial agents.[278] Chalcones possess a highly electrophilic α,β-unsaturated carbonyl moiety, which is necessary for Nrf2 activation and inducing phase II detoxifying enzyme expression.[279] Table 1 shows the list of flavanoids and chalcones as Nrf2 activators derived from natural products.

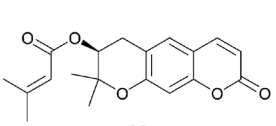
Coumarins represent a diverse class of phytochemicals that are ubiquitous in the human diet. They induce the activities of cytoprotective genes and enzymes such as GST and NQO1.[303–305] Auraptene **28**, imperatorin **29**, and isopimpinellin **30** are naturally-occurring coumarins found in citrus fruits. Auraptene and imperatorin induce murine liver cytosolic GST activities *via* the Nrf2/ARE mechanism and the effect was attenuated in Nrf2-knockout mice, whereas isopimpinellin induces GST and NQO1 *via* additional mechanisms.[306] Fraxetin **31** from *Fraxinus rhynchophylla* shows a protective effect in atherosclerosis by increasing the protein level of HO-1 which increases the level of Nrf2 and reporter activity with the induction of antioxidant enzymes.[307] Decursin **32**, another coumarin isolated from *Angelica gigas*, causes Nrf2 activation, and HO-1 induction through activation of MAPK signal pathways which protects PC12 cells from $A\beta_{25-35}$-induced oxidative cytotoxicity.[308]



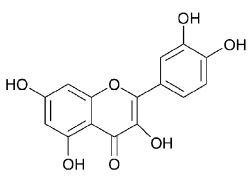


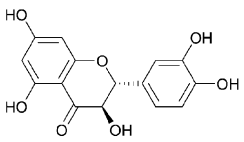




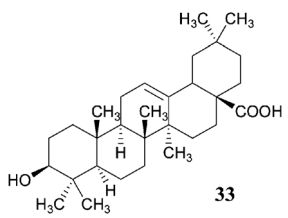


1 is a powerful radical scavenger able to prevent or delay conditions that favour cellular oxidative stress.[48,272] Consuming fruits and vegetables containing high amounts of **1** may be associated with a low risk of developing cancer.[273] **1** enhances the accumulation of Nrf2, thereby inducing anti-oxidative gene expression and interaction with cellular defense systems such as NQO1, inducible nitric oxide synthase, cyclo-oxygenase, xanthine oxidase, lipoxygenase and HO-1 to increase Nrf2 levels. **1** induced Nrf2 up-regulation and Keap1 induced down-regulation, required for activation of cytoprotective genes.[274–276] Dihydroquercetin **2**, a dihydrophenol from *Larix gmelinii* shows cytoprotective effects by up-regulating Nrf2 levels.[277]



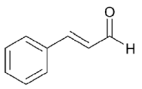


Terpenoids, including mono-, sesqui-, di-, and tri-terpenoids, are a large and diverse class of naturally-occurring organic chemicals derived from five-carbon isoprene units assembled and modified in thousands of ways. Terpenoids are ubiquitously found in the plant kingdom and provide an important scaffold for new drug development.[309] Two potent synthetic oleanane triterpenoids, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid and its methyl ester, are derived from oleanolic acid **33**. One of the possible mechanisms of these terpenoids as Nrf2 inducers is their involvement in the Michael reaction (enone) of reactive cysteine residues on the Keap1 protein.[310]



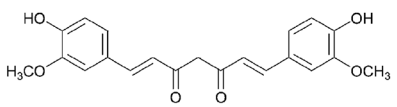
Oleanolic acid **33** is a pentacyclic triterpenoid compound with a widespread occurrence throughout the plant and it is a potent inducer of the Nrf2 pathway.[181] **33** confers an adaptive survival response in atherosclerosis by activation of Nrf2 followed by up-regulation of HO-1 expression.[311] **33** has its antioxidant activity through increasing the generation of antioxidant and the expression of Nrf2, and MAPK, mainly JNK and ERK.[312] Table 2 shows the list of terpenoids as Nrf2 activators derived from natural products.

Cinnamaldehyde **53**, isolated from *Cinnamomum cassia* is a reactive Michael acceptor due to the presence of an α,β-unsaturated aldehyde that spontaneously forms covalent adducts with thiols and activates Nrf2-regulated ARE-mediated gene expression.[330] **53** provides chemopreventive effects by enhancing Nrf2 nuclear translocation and up-regulating phase II enzymes in HepG2 cells[331] and human colon cancer cells (HCT116, HT29).[332] The target chemopreventive effect of **53** was due to up-regulation of HO-1 and γ-GCSC,[332] ERK1/2, Akt, and JNK pathways.[331]



53

Curcumin **54**, a yellow pigment found in turmeric has been used for cancer, lung diseases, renal diseases, neurological diseases, liver diseases, metabolic diseases, cardiovascular diseases, and various other inflammatory diseases.[333] Dibenzoylmethane **55**, a β-ketone analog of curcumin, increases mRNA expression of NQO1, GSTA2, and GCLC in mouse hepatoma cells and inhibits benzo[*a*]pyrene-induced DNA adducts by enhancing its detoxification in the lungs.[244] Caffeic acid and its derivative caffeic acid phenethyl ester **56** are produced in many kinds of plants. **54** and **56** induce HO-1 in endothelial cells,[334] astrocytes,[335] and renal cells.[43,336]



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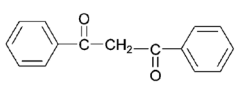

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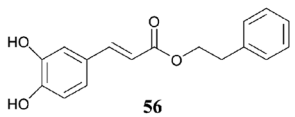

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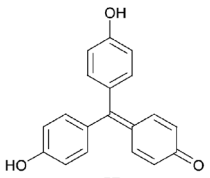
Interestingly, rosolic acid **57**, a triphenylmethane from *Plantago asiatica* with Michael reaction acceptor functionality, can affect HO-1 expression and induces a phase II response.[34,278] (*Z*)-Ligustilide **58**, a dihydrophthalide isolated from *Angelica sinensis*, has α, β, γ, and δ-unsaturated lactone moieties with a cross-conjugated alkene system required for multiple Michael addition. **58** alkylates important cysteine residues in Keap1, leading to the accumulation of Nrf2 in the nucleus where it enhances the transcription of ARE-dependent detoxification genes.[337] **58** promotes Nrf2 nuclear translocation, and remarkably increases Nrf2 and HO-1 protein expression and protects against cerebral ischemia progression remarkably in both *in vivo* and *in vitro*.[338] The kavalactones Methysticin **59**, Yangonin **60**, and Kavain **61** isolated from *Piper methysticum* are effective in protecting neurons against $A\beta_{(1-42)}$ toxicity *in vitro* by activating Nrf2 and elevating cytoprotective gene expression as exemplified by γ-GCS and HO-1 up-regulation in neural PC-12 and astroglial C6 cells.[143] Kavalactones contain the α,β-unsaturated carbonyl group in its lactone ring and may act as a Michael reaction acceptor. Thiophene isolated from *Echinops grijisii* are Michael addition acceptors.[339] 2-(Pro-1-ynyl)-5-(5,6-dihydroxypenta-1,3-diynyl)thiophene **62**, a novel phase II enzyme inducer, activates the Nrf2 pathway *via* depleting the cellular level of glutathione. **62** modifies Keap1 by *S*-glutathionylation, an important post-translational modification of protein cysteines with critical roles in oxidative stress and signal transduction.[340]



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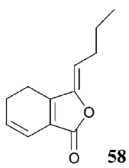

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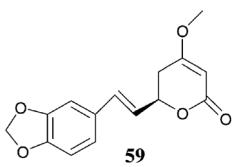

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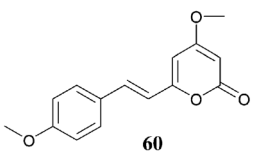

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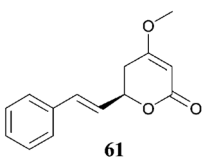

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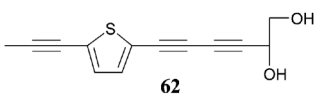
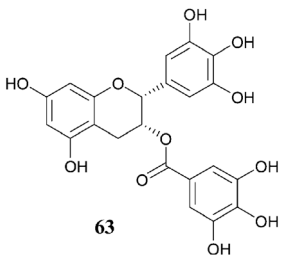


62

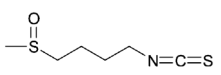
5.1.2 Oxidizable diphenols and quinones. Oxidizable diphenols and quinone belong to one of the earliest discovered classes of inducers. They were synthesized to understand the mechanism for induction of the cytoprotective enzymes GST and NQO1 long before the Nrf2/ARE pathway was identified.[341,342] Three types of diphenols such as catechol (1,2-diphenol), resorcinol (1,3-diphenol), and hydroquinone (1,4-diphenol) behave differently in reversible 1- or 2-electron oxidation reactions. Catechols and hydroquinones are active as NQO1 inducers, whereas resorcinols are inactive. Catechols and hydroquinones can give rise to quinones which, being electrophilic, are the ultimate inducers whereas resorcinols cannot participate in redox reactions and cannot give rise to quinones; it was also established that redox lability is clearly critical for the ability to induce enzymes.[264,342] Later it was established that induction of the Nrf2/ARE pathway by oxidizable diphenols involves the redox mechanism. The first step is oxidation of the diphenol to its quinone derivative that contains Michael acceptors, and then, secondly, reaction of the quinone with critical cysteine residues in Keap1 that are essential for its ubiquitin ligase substrate adaptor activity, and thus for repression of Nrf2. Diphenols undergo cytochrome P450-mediated oxidation *in vivo* to form quinones as the ultimate inducers (Fig. 3).[343]

Epigallocatechin gallate (EGCG) **63** is the most abundant and most active catechin polyphenol found in green tea. **63** has a pronounced ability to up-regulate Nrf2 and induce ARE-luciferase reporter gene transactivation.[279,344] **63** activates Nrf2-mediated HO-1 expression and stimulates the expression of many Nrf2-dependent genes in mice.[279,344,345] Interestingly, **63** induces the expression of HO-1, γ-glutamyltransferase 1, and GCLC in wild-type mice, but not in Nrf2-deficient mice.[346] Moreover, **63** inhibits lipopolysaccharide-induced pulmonary fibrosis by enhancing the activities of antioxidant and phase II enzymes such as GST and NQO1 mediated by Nrf2–Keap1 signalling.[347] Two principal mechanisms of action of **63** on Nrf2-mediated cytoprotective responses have been elucidated: first, **63** directly and/or indirectly interacts with cysteine residues present in Keap1, thereby inducing Nrf2 nuclear translocation;[348] second, **63** phosphorylates serine/threonine residues of Nrf2 *via* activation of protein kinases.[279,344,345] Table 3 shows the list of polyphenols and quinones as Nrf2 activators derived from natural products.



63

5.1.3 Isothiocyanates (ITCs). ITCs are widely consumed in the form of their glucosinolate precursors which are abundant within cruciferous plants. The glucosinolates are hydrolyzed to ITCs, the active inducers, by the coexisting plant enzyme myrosinase or by the microflora of the mammalian gastrointestinal tract.[370,371] ITCs from broccoli sprouts are found to be six times more bioavailable than the precursor glucosinolates.[371] The natural ITCs sulforaphane (SFN) **85** and phenethyl isothiocyanate **86** are the most studied in this group. **85** induces phase II gene expression *in vitro* and *in vivo*[372,373] and up-regulates the expression of NQO1, GST and GCL in wild-type mice compared with those in Nrf2-null mice.[97] **85** also increases the expression of phase II gene expression at mRNA and protein levels in a number of cell lines,[49,374,375] and increases GST and NQO1 activities in rats.[376] Interestingly, a dose-escalation safety study of **85** in healthy subjects showed a dose-dependent increase in NQO1 in skin tissues.[377] In a recent clinical study, oral administrations of **85** increased phase II antioxidant enzymes such as GSTM1, GSTP1, NQO1, and HO-1 in the upper airway.[378] **86** activates ARE-mediated phase II drug metabolism gene expressions *via* the JNK1- and Nrf2-dependent pathways and confers chemoprevention.[379]



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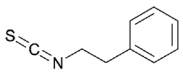
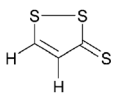


86

Interrupting Nrf2–Keap1 and activating MAPK have been proposed as the main mechanisms for the induction of phase II enzymes by ITCs.[23,78,380] Another possible **85** mechanism involves the formation of an SFN–Keap1 thionoacyl adduct, which modifies the tertiary structure of Keap1 most readily at the cysteine residues localized at the Kelch domain, thereby stabilizing Nrf2.[381] Clinical studies have evaluated the safety, tolerance, and metabolism of broccoli sprouts.[382,383]

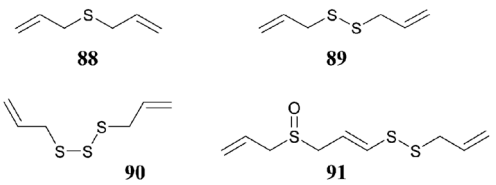
5.1.4 Dithiolethiones and diallyl sulfides. Dithiolethiones are five-membered cyclic sulfur-containing compounds that have emerged as potent cytoprotective agents. The cytoprotective role of dithiolethiones is strengthened by a report showing elevated transcript levels, protein levels and activities of phase II genes in wild-type mice, but not in homozygous Nrf2-mutant mice.[384] 3*H*-1,2-Dithiole-3-thione **87** is the simplest and most potent dithiolethione isolated from cruciferous vegetables such as cabbage and brussel sprouts. **87** induces phase II enzymes in hepatic and cardiovascular tissues/cells,[384–386] and enhances both nuclear translocation and *de novo* synthesis of Nrf2 in murine keratinocytes.[387] Interestingly, hepatic gene expression profiles examined by oligonucleotide microarray analysis in vehicle or **87**-treated wild-type mice as well as in Nrf2 single- and Keap1–Nrf2 double-knockout mice were used to identify those genes regulated by the Keap1–Nrf2 pathway. Transcript levels of 292 genes (detoxification and anti-oxidative enzymes) were elevated in wild-type mice 24 h after treatment with **87** but not in Nrf2-deficient mice.[388] **87** contains the 1,2-dithiol-3-thione moiety, which undergoes thioldisulfide exchange with sulfhydryl groups.[389] Interestingly, its regioisomer 1,3-dithiole-2-thione is ineffective even at much higher concentrations, indicating that the 1,2-dithiol-3-thione moiety is essential for inducing phase II enzyme activity.[390] The possible mechanism of accumulation of Nrf2 and transactivation of its target genes by dithiolethiones is either *via* activation of kinases[391] or thioldisulfide exchange with sulfhydryl groups.[389]



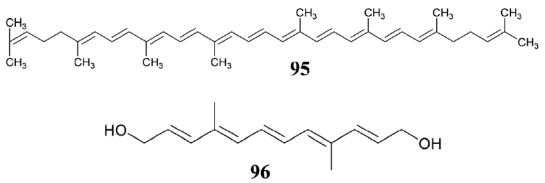
87

Diallyl sulfides (diallyl sulfide **88**, diallyl disulfide **89**, and diallyl trisulfide **90**) are lipophilic thioesters derived from a class of organosulfur compounds found in *Allium* vegetables (including garlic and onion). **88**, **89**, and **90** differentially up-regulate the protein or gene expression of phase II detoxifying enzymes with strength in the order of **90** > **89** > **88**;[392] however, some reports suggest that **88** causes a striking increase in the greatest number of genes.[393] High intake of raw or cooked garlic provided a protective effect against stomach and colorectal cancers in a site-specific case-control study.[394] Ajoene **91**, a stable garlic byproduct increases PKCδ-dependent Nrf2 activation, GCL induction, and the cellular GSH concentration, which may contribute to protecting cells from oxidative stress.[395] Several hypotheses have been proposed[396,397] but the exact mechanism underlying the ARE-inducing activity by diallyl sulfides remains poorly understood.[392,397,398] Table 4 shows the

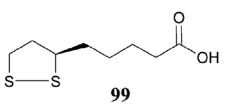
list of polyphenols and quinones as Nrf2 activators derived from natural products.



5.1.5 Polyenes. Compounds with an extensive system of conjugated double bonds are referred as polyenes. They readily undergo biotransformation to electrophilic metabolites that can react with free sulfhydryl groups. Carotenoids, a class of polyenes, are colorful plant pigments that induce phase II enzymes.[403,404] Lycopene **95**, a carotenoid pigment mainly found in tomatoes, is a more potent inducer of AREs than phytotene, astaxanthin and β-carotene.[405] Carotenoid derivatives having aldehyde end groups are more active in ARE induction than the corresponding acids. Interestingly, 10,10′-diapocarotene-10,10′-dial **96**, a metabolite of lycopene, is a more potent inducer of AREs than lycopene.[406] It has been proposed that carotenoids are metabolized to reactive electrophilic metabolites *in vivo* containing Michael acceptors that covalently modify Keap1, resulting in the activation of Nrf2 and elevated expression of ARE genes.[406]



5.1.6 Vicinal dimercaptans. Vicinal dimercaptans (mercaptans with two adjacent thiol groups) are transformed into the electrophilic disulfide bonds *in vivo*. α-Lipoic acid **99** is a naturally-occurring dietary thiol-antioxidant found almost in all vegetables and fruits, and is also produced endogenously. It has potential therapy for chronic diseases associated with oxidative stress.[407] The mechanism is not been established but some reports suggests that **99** activates ERK1/2, p38 MAPK, PI3K and Akt[408–410] and induces HO-1 expression in THP-1 monocytic cells *via* Nrf2 and p38.[411] **99** may increase Nrf2-dependent transcriptional activity by forming lipoyl-cysteinyl mixed disulfides on Keap1.[278]



5.1.7 Miscellaneous. Apart from the above-mentioned compounds some other natural product-derived compounds are activators of the Nrf2/ARE pathway, as listed in Table 5.

5.2 Negative regulation of the Nrf2/ARE pathway

Several mechanisms are involved in negative regulation of the Nrf2/ARE pathway. Overexpression of Cadherins, proteins responsible for cell–cell adhesion at the adherens junction, inhibits nuclear accumulation of Nrf2 and prevents Nrf2-dependent gene induction.[421] Estrogen-related receptor β by acting as a repressor of Nrf2 inhibits Nrf2 transcriptional activity and has been useful as a therapeutic target in cancer chemoprevention studies.[422] The plasma membrane resident protein caveolin-1 inhibits the expression of antioxidant enzymes by directly interacting with Nrf2 and subsequently suppressing its transcriptional activity in lung epithelial Beas-2B cells.[423] Another mode of Nrf2 regulation has been proposed in which glycogen synthase kinase-3 β (GSK-3 β) mediates phosphorylation of Nrf2 and prevents Nrf2 nuclear localization. Co-expression of active GSK-3 β prevents binding and activation of AREs located in phase II gene promoters.[424] GSK-3 β promotes cytosolic localization of Nrf2, inhibits transcriptional activity and blocks the antioxidant and cytoprotective functions of Nrf2.[84] Activated GSK-3 β phosphorylates Fyn at threonine residues, leading to nuclear localization of Fyn.[425] Interestingly, once Fyn is localized inside the nucleus, it phosphorylates tyrosine residue 568 of Nrf2, which leads to a Crm-1-mediated nuclear export and degradation of Nrf2.[426] Another transcription factor Bach1 is ubiquitously expressed and competes with Nrf2, leading to negative regulation of the AREs, and the balance of Nrf2 *versus* Bach1 inside the nucleus influences up- or down-regulation of ARE-mediated gene expression.[427] Interestingly, retinoid X receptor alpha (RXRα) RNAi-mediated knockdown increases basal ARE-driven gene expression and induction of ARE-driven genes. Conversely, overexpression of RXRα decreases ARE-driven gene expression. RXRα diminishes Nrf2 cytoprotection by binding directly to the newly defined Neh7 domain in Nrf2.[428]

5.2.1 Nrf2 inhibitors. As discussed previously, activating Nrf2 has therapeutic potential and activating the Nrf2/ARE pathway is a cell response to defend cells against oxidative stress. However, some concerns have been proposed with increasing Nrf2 signalling. Keap1-knockout mice indicate that constitutively activating Nrf2 can result in serious adverse effects such as hyperkeratosis of the upper digestive tract.[429,430] Furthermore, high Nrf2 levels and somatic mutations have been detected in various cancer tissues and Nrf2 plays an important role in the development of chemoresistance.[119,166,431,432] Moreover, Nrf2 has also been found to promote atherosclerosis[224,433–435] and liver damage in autophagy-deficient mice.[74,175] Interestingly, RNAi-mediated decrease of Nrf2 expression in lung cancer cells induces the generation of ROS, suppresses tumor growth, and results in increased sensitivity to chemotherapeutic drug-induced cell death *in vitro* and *in vivo*.[436] Thus, inhibition of the Nrf2/ARE pathway might provide a beneficial approach against multi-drug resistance. Table 6 summarizes the list of inhibitors for the Nrf2/ARE pathway.

6 Concluding remarks

Oxidative stress is the central component of almost all chronic diseases. The Nrf2/ARE pathway was primarily thought to be a regulator of antioxidant enzymes but recent studies have proved its role in the regulation of many genes for stress-generated

diseases. Both oxidative stress and Nrf2 inducers are able to transcriptionally activate Nrf2 target genes to trigger a cytoprotective response. Indeed, several studies have shown the importance of Nrf2 in therapeutic approaches using Nrf2 overexpression or Nrf2 knockdown. It is now clear that inducing the Nrf2-dependent response represents the cell's attempt to defend itself from stressful conditions. Therefore, the Nrf2/ARE pathway is currently considered a cell-survival pathway and is becoming of clinical therapeutic interest for treating multiple sclerosis and diabetic nephropathy. However, sustained activation of the Nrf2/ARE pathway favours some deleterious effects such as multi-drug resistance, and atherosclerosis. Moreover, free radical production increases with ageing which is root cause of neurodegenerative diseases, diabetes, cancer and cardiovascular diseases. Contrary Nrf2 production appears to decline with ageing. It is still unclear which target gene in the Nrf2 pathway contributes to these detrimental effects; hence, it is mandatory to evaluate the role of activating Nrf2 in *in-vitro* and *in-vivo* experimental models with the use of available Nrf2 inducers, Nrf2 overexpression, or Keap1 down-regulation. Epidemiological studies have shown that natural products provide beneficial effects by regulating Nrf2 levels. Inducers and inhibitors provide a more valuable and direct pharmacological approach to extrapolate the desired outcomes in a clinical setting.

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