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Chapter 9

Role Phytochemicals Play in the Activation of Antioxidant Response Elements (AREs) and Phase II Enzymes and Their Relation to Cancer Progression and Prevention

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Chapter Outline

INTRODUCTION

Cancer comprises a large group of diseases that can affect different organs or tissues of the body. It is characterized by rapid uncontrolled growth and spread of abnormal cells. These abnormal cells can grow beyond their usual boundaries, invading neighbor cells, tissues of other organs, and metastases, and are the major causes of death from cancer.

Worldwide, cancer is one of the leading causes of morbidity and mortality, being the second leading cause of death in most developed countries (after cardiovascular disease) and the third leading cause of death in low- and middle-income countries (after cardiovascular disease and infectious diseases) [1]. Approximately 14 million new cases were diagnosed in 2012 [2]. Deaths from the disease totaled 8.8 million in 2015 [3]. During the last decade lung cancer was the main cause of deaths (1.69 million) followed by liver cancer (788,000), colorectal cancer (774,000), stomach cancer (754,000), and breast cancer (571,000).

The estimated number of newly diagnosed cases of cancer each year is likely to reach 16 million by 2020. This has steadily increased from 11 million in 2002. More than half of these cases occur in developing countries. Cancer incidence in the Eastern Mediterranean region is predicted to rise 1.8-fold in the next decade [1].

CAUSES AND MAJOR RISK FACTORS FOR INCREASE IN GLOBAL CANCER INCIDENCE

The transformation of normal cells into cancer cells is a multistage process that ends in a malignant tumor. These changes are the result of genetic factors interacting with three classes of carcinogens [3]. According to the World Health Organization (WHO) through its agency the International Agency for Research on Cancer (IARC), cancer-causing agents include physical carcinogens, such as UV light and nuclear radiation; chemical carcinogens, such as asbestos, components of aflatoxin (food poisoning), tobacco smoke, and heavy metals from drinking water (arsenic); and infectious carcinogens, such as certain viruses, bacteria, or parasites, which are estimated to be responsible for 16% of cancers globally. Aging is another important factor for the development of cancer. The increase in incidence of a specific type of cancer is related to age, which may be due to defects in the cellular repair mechanisms of older people [4].

The WHO Global Status Report on noncommunicable diseases (NCDs) addressed several risk factors for cancer, including tobacco use, alcohol consumption, little physical activity, and unhealthy diet. Tobacco smoking is one of the major risk factors for cancer and is responsible for approximately 22% of deaths, mainly from lung cancer [5]. Obesity is a major cause of colorectal, esophageal, breast (postmenopausal), endometrium, kidney, and pancreatic cancers. Alcohol is associated with liver, upper aerodigestive tract, breast, and colorectal cancers [6].

Major consumption of red processed meats and a low-fiber diet have been associated with colorectal cancer. Little physical activity is a major risk factor for colon, breast, and endometrial cancers that are indirectly brought about through its effect on body mass index (BMI) [7].

CANCER CHEMOPREVENTION

The cancer burden could be reduced by 30%–50% by lowering risk factors, establishing evidence-based prevention strategies, and reducing its induction by early detection and diagnosis of cancer and management of cancer patients [3,8].

Several behavioral and environmental factors show a lot of potential for cancer prevention, such as tobacco control, promotion of healthy diet, and physical activity. This can be brought about by reducing the harmful use of alcohol and changing lifestyles. In less developed countries (LDCs) 26% of cancers are due to infection [8,9], highlighting the need for protection against infectious diseases by putting in place a strategy to protect against cancer. Reduction in the incidence of new cancer cases can be achieved by vaccination against hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), human papillomavirus (HPV), and *Helicobacter pylori*.

Another approach to decreasing the global cancer burden (GCB) is by raising awareness, which is a very important and effective strategy to prevent cancer at the personal level, especially in LDCs where literacy skills are not high and the majority of the population lives in rural areas far from any health care units. Raising awareness results in early detection and diagnosis, promotes healthy behavior, and discourages unhealthy practices at the individual level. Raising awareness of the importance of avoiding excessive exposure to ultraviolet light and reducing occupational exposure to carcinogens can make all the difference.

MECHANISMS OF ACTION OF NATURAL PRODUCTS INVOLVED IN CANCER CHEMOPREVENTION

Current knowledge of the molecular mechanisms by which natural products elicit their cancer chemopreventive effects has massively grown in recent few decades. Extensive research work has shown that phytochemicals act on the three known steps of carcinogenesis: initiation, promotion, and progression (Fig. 9.1). Cancer chemoprevention can be defined as the ability of phytochemicals to inhibit the initiation of cancer cells.

Antioxidant Phytochemicals That Inhibit Cancer Initiation

During normal metabolism, homeostasis is maintained via the release of small amounts of free radicals, reactive oxygen species (ROS), and/or reactive nitrogen species (RNS) [10]. Other external stressors may lead to the production of
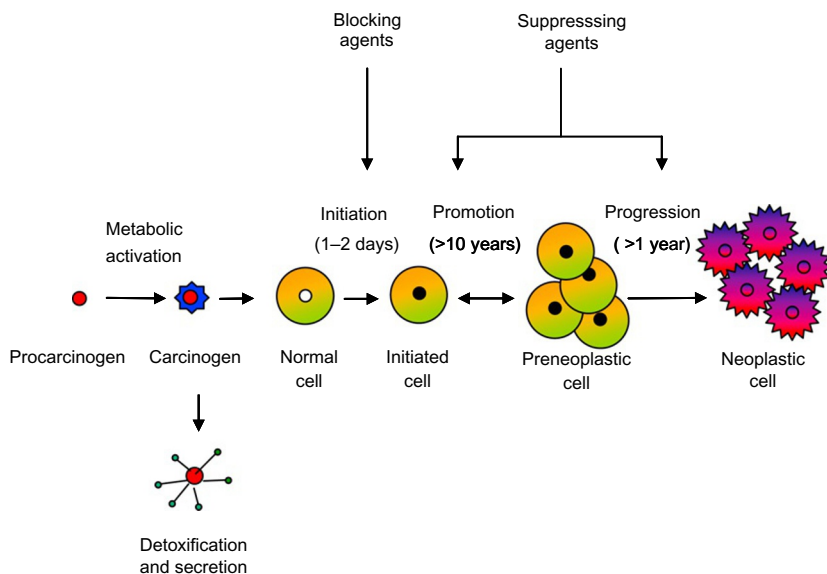
FIG. 9.1 Multistep carcinogenesis and sites of action of phytochemicals.

ROS and RNS, such as air pollution, ionizing radiation, and cigarette smoke [11]. An endogenous antioxidant defense system, such as catalases that catalyze the detoxification of hydrogen peroxide into water and molecular oxygen, may help to improve these conditions [12]. Perturbing cellular homeostasis, which is normally maintained by the balance between the free radicals produced and their detoxification by cellular antioxidant systems, is termed oxidative stress. The inability to reverse this imbalance may lead to the tissue injury observed in many diseases, such as liver cirrhosis and fibrosis [13]. If the production of free radicals and reactive metabolites is prolonged, this will lead to excessive oxidation of cellular macromolecules, such as DNA, RNA, and proteins, and the cell becomes initiated [14]. The consumption of dietary phytochemicals therefore interferes with the undesirable initiation of normal cells into initiated cells.

Role of Nrf2 in Cancer Chemoprevention by Phytochemicals

Nrf2 plays a principal role in the induction of cytoprotection and chemoprevention of cancer by phytochemical inducers. Under basal conditions Nrf2 is retained in the cytoplasm by interacting with its repressor protein Kelch-like ECH-associating protein 1 (Keap1), a substrate adaptor protein for cullin-3 ubiquitin ligases, and thus mediates ubiquitination and proteasomal degradation of the transcription factor. Keap1 represents a cysteine-based sensor with sulfhydryl groups that are susceptible to reaction with endogenous and exogenous molecules (inducers), such as the potent cancer chemopreventives isothiocyanate and sulforaphane [15,16].

The reaction of inducers with Keap1 leads to conformational changes and inhibition of the Nrf2–keap1 protein complex with translocation of Nrf2 to the nucleus. At the nucleus, Nrf2 combines with transcription cofactors (small musculoaponeurotic fibrosarcoma, Maf, proteins) forming a heterodimer that binds to antioxidant response elements (AREs). The binding of Nrf2 to AREs occurs in the promoter region of genes encoding cytoprotective phase II proteins, such as NAD(P)H:quinone oxidoreductase 1 (NQO1), glutathione S transferases (GSTs), and heme oxygenase-1 (HO-1) (Fig. 9.2). This therefore reduces the endogenous levels of toxic reactive species, including carcinogens [17–20].

Nrf2, Inflammation, and Cancer Chemoprevention

Chronic inflammation underpins the development of many chronic diseases, including cancer, whereas acute inflammation is the pathophysiological response to injury and subsequent oxidative stress that makes the cell initiate the production of proteins, enzymes, and other compounds, including a number of proinflammatory cytokines, to restore homeostasis. The redox-dependent activity of the potent nuclear factor-kappa (NFκB) is fundamental in orchestrating the inflammatory response. On the other hand, at the center of the day-to-day biological response to oxidative stress is the Keap1/Nrf2/ARE pathway, which regulates the transcription of many antioxidant genes that preserve cellular homeostasis and detoxification genes that process and eliminate carcinogens and toxins before they can cause damage. Nrf2- and NFκB-dependent pathways interact to control the transcription or activity of downstream target proteins [21].

The Keap1/Nrf2/ARE pathway plays a major role in health and resilience. It can be made more robust and responsive by certain dietary factors. Transient activation of Nrf2 by dietary electrophilic phytochemicals can upregulate antioxidant and chemopreventive enzymes in the absence of actual oxidative stress inducers [22]. Priming the Keap1/Nrf2/ARE pathway by upregulating these enzymes prior to an injury, oxidative stress, or xenobiotic encounter increases cellular fitness such that the cell can respond more robustly to oxidative assaults without activating more intense inflammatory NFκB-mediated responses. Nevertheless, Nrf2 has been recognized as a hormetically regulated pathway in that it reflects a biphasic dose response [23]. Electrophilic phytochemicals at low to moderate dietary levels induce the activation of Nrf2 with a cell survival-promoting effect, while high pharmacological doses have the opposite effect, abrogating Nrf2- and ARE-responsive genes and upregulating NFκB or AP-1 [23].

NQO1 has been proven to catalyze the reduction of quinones like menadione to hydroquinones, providing a protection against quinone-mediated oxidative damage [24]. As an obligatory two-electron reductase, NQO1 is associated with chemopreventive and anticarcinogenic activity [20]. In this way the induction of NQO1 is expected to become a strategy for cytoprotection. NQO1 is
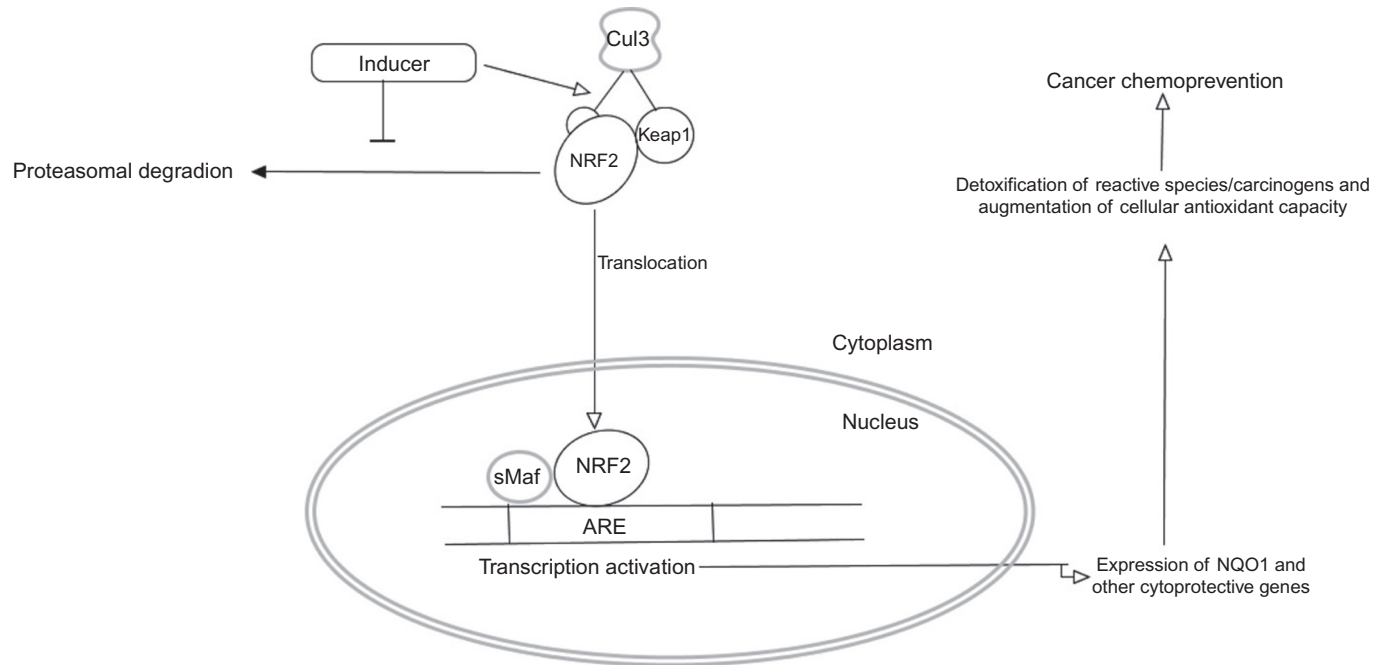
FIG. 9.2 Mechanism behind Nrf2-mediated activation of cytoprotective gene transcription by phytochemical inducers.

regulated by the Keap1/Nrf2/ARE pathway in which Keap1 binding to Nrf2 is involved in the ubiquitination and degradation of Nrf2. Electrophiles like chalcones (with an α,β-unsaturated ketone moiety) that bind to Keap1 in thiol groups by Michael addition prevents the conjugation of Keap1 with Nrf2 and upregulates the level of NQO1 as a consequence [20]. Glutathione (GSH) is a small molecule that contains thiol groups. It is thought that compounds that can react with GSH by Michael addition present good NQO1 induction activity [25].

There is an incredible diversity of electrophilic dietary phytochemicals that interact with the Keap1/Nrf2/ARE pathway. Consuming a wide variety of fresh fruits and vegetables helps to optimize the collective role of Nrf2-regulated proteins: to restore homeostasis from a state of oxidative stress and xenobiotic insult and to protect the integrity of DNA, proteins, membranes, and other lipids. Organic sulfides are among the most potent Nrf2-activating phytochemicals. Plants in the *Brassica* genus (broccoli, cabbage, Brussels sprouts, turnip, and collard greens) are a particularly rich source of organic sulfides, primarily glucosinolates and their isothiocyanate derivatives [22].

Adequate dietary intake of sulfur and trace minerals, such as zinc and selenium, provides the building block necessary to optimize Nrf2-mediated resilience to oxidative stress. Management of inflammatory and oxidative homeostasis of the body through proper diet may help to slow disease progression or prevent the development of chronic disorders altogether [26].

THE ROLE OF PLANTS AND THEIR PHYTOCHEMICALS IN RELATION TO CANCER PROGRESSION AND PREVENTION

The data accumulated from traditional healing and experimental and epidemiological evidences revealed the significance of phytochemicals in chemoprevention, which suggests that their daily intake may be a promising approach to the prevention of cancer.

A review of the literature shows that natural products and phytochemicals provide humanity with a great number of chemopreventive agents (CPAs) against a wide range of commonly occurring cancers. These CPAs are present in vegetables, fruits, medicinal plants, or their extracts. Although the mechanism behind the protective effect is unclear in most cases the consumption of fruits, vegetables, or dietary supplements containing minerals, vitamins, or/and plant extracts lower the incidence of cancer [27].

Plant Extracts

There is increasing interest in studying the chemopreventive potential of natural compounds against cancer, due to the reduced cancer risk in people consuming high dietary phytochemicals. Chemoprevention may involve the interruption or reversion of the initiation and progression of the disease by setting various targets with the goal of preventing end-stage invasive disease

and impeding or delaying the development of cancer. To stop the initiation stage the metabolic activation of carcinogens should be prevented and thereby suppress their interaction with cellular macromolecular targets, such as DNA, RNA, and proteins. This can be achieved by inducing of a set of phase II detoxifying enzymes and antioxidant enzymes, such as the chemopreventive markers NQO1and HO-1.

Chrysanthemum zawadskii *and* Glycyrrhiza uralensis

In Wu et al. [28], investigating the extracts of *Chrysanthemum zawadskii* (CZ) and *Glycyrrhiza uralensis* (GU), Nrf2-deficient mice (Nrf2−/−; KO) and Nrf2 wild-type mice (Nrf2+/+; WT) were used to assess whether the in vivo phase II DM/detoxifying/antioxidative properties exerted by both extracts were mediated by Nrf2.

To investigate the ability of CZ and GU to regulate Nrf2 target genes and induce Nrf2-mediated ARE-luciferase activity, quantitative polymerase chain reaction (qPCR) analysis and ARE-luciferase assay were applied to HepG2C8 cells. It was found that CZ and GU induced ARE-luciferase activity by four-fold ($P < 0.001$) and threefold ($P < 0.01$), respectively, compared with the control group. Moreover, CZ and GU significantly induced expression of the endogenous Nrf2 target gene and NQO-1. CZ and GU induced the expression of phase II UDP-glucuronosyltransferase 1A1 (UGT1A1) by 2.50-fold and 1.51-fold, respectively.

To discover whether the extracts bring about phase II detoxifying/antioxidant gene activation through the Nrf2-signaling pathway or not the expression level of these genes was measured using qPCR in the liver of Nrf2-deficient mice (Nrf2−/−; KO) and Nrf2–wild-type mice (Nrf2+/+; WT) treated in vivo with different doses of CZ and GU (150 and 300 mg/kg). The results showed that NQO-1 and UGT1A1 mRNA were induced (especially in the Nrf2 WT mice). Meanwhile, NQO-1 and UGT1A1 gene expression was induced by GU in both wild-type (WT) and Nrf2 KO mice, the extract of CZ only inducing NQO-1 in the Nrf2 WT mice. In contrast, CZ induced expression of the UGT1A1 gene in Nrf2 KO mice only at the higher dose. As expected, Nrf2 expression was only observed in Nrf2 WT mice and induced by both CZ and GU, while this was not observed in Nrf2 KO mice by CZ or by GU.

Microarray data have shown that detoxifying and antioxidant genes, such as aldehyde oxidase-1 (AOX1), glutathione *S*-transferase Mu 3 (GSTm3), UGT1A1, UDP glucuronosyltransferase—two families, polypeptide B5 (UGT2B5), and NQO-1, which were induced by GU and CZ extracts, are highly Nrf2 dependent. Although AOX1 gene expression has also occurred in Nrf2 KO mice the expression intensities were lower than those detected in Nrf2 WT mice. Induction of such gene expression by CZ and GU extracts was observed in the liver of Nrf2 WT mice but not that of Nrf2 KO mice. In vivo study has revealed a greater degree of induction of Nrf2-mediated genes by CZ and GU than that observed in in vitro cell culture study. The reasons for these discrepancies

are not clear, but may be attributable to the production of active metabolites in CZ and GU [29,30], such as licochalcone, β-glycyrrhetinic acid, and isoliquiritigenin, as a result of exciting luteolin-7-glucoside, luteolin, and acacetin-7-rhamnoglucoside from CZ extracts [31]. Such active metabolites, together with the parent compounds, may contribute to the increased expression of Nrf2-mediated genes, especially in WT mice in vivo.

The Nrf2-signaling pathway plays a crucial role in downregulating and defending against acute inflammation, in addition to bringing about detoxification and antioxidation [32,33]. NFκB is a redox-sensitive transcription factor that could be regulated by intracellular redox status. It also mediates the inflammatory-signaling pathway [34]. Wu et al. [28] proved that CZ extracts had significant antioxidative stress, antiinflammatory, and detoxification effects. The antiinflammatory and antioxidative stress capabilities of GU and CZ can be potentially utilized for cancer chemoprevention in humans, since chronic inflammation is related to 20% of human cancers.

Camellia sinensis

Tea is the most popular natural beverage in the world and has been gaining more and more attention as a result of its beneficial properties for health. Oolong tea is a traditional Chinese tea (*Camellia sinensis* (L.) Kuntze) produced through a process that allows the plant to wither and dry under strong sun and radiative conditions, before curling and twisting.

Many studies have shown the diverse biological activities of black tea and its polyphenolic compounds, which have antioxidant, anticancer, antiinflammatory, and metabolic regulatory effects. Tea polyphenols, such as theaflavins and catechins, are considered multifunctional compounds effective in the prevention and treatment of different types of cancer [35].

Drinking black tea reduces the incidence and number of skin papillomas in mice treated with 7,12-dimethylbenz[*a*]anthracene (DMBA) by activating detoxification enzymes and decreasing lipid peroxidation [36]. Oral administration of black tea polyphenols delayed tumorigenesis and reduced tumor number and volume in DMBA-induced mouse skin carcinogenesis by inducing apoptosis in tumor cells [37].

Topical application of black tea polyphenols combined with resveratrol synergistically inhibited DMBA/12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced skin carcinogenesis by reducing tumor incidence, number, and volume. Mechanistic study showed that this combination downregulated mitogen-activated protein kinases (MAPKs) and increased tumor suppressor gene *p53* and apoptosis [38]. Consistent with the results in a skin cancer model, oral intake of black tea polyphenols or extract also suppressed DMBA-induced mammary tumors and oral tumors by scavenging reactive oxygen species (ROS), thus reducing oxidative stress [39] and downregulating cyclooxygenase-2 (COX-2), NFκB, and protein kinase B (Akt) [39]. It also interfered with the activity of carcinogen-metabolizing enzymes [40].

In a 1,2-dimethylhydrazine (DMH)-induced colorectal tumor model, consumption of tea with a high content of polymeric black tea polyphenols inhibited tumorigenesis by downregulating the Wnt/β-catenin pathway and proliferative gene expression [41]. Oral administration of black tea polyphenols was also effective against arsenic-induced formation of 8-hydroxy-2′-deoxyguanosine (8-OHdG) by upregulating DNA repair enzymes in Swiss albino mice [42].

The activation of detoxification enzymes is the most common feature the effect of black tea has on antagonizing various chemical-induced carcinogens. The detoxifying enzyme system plays an important role in determining the final fate of carcinogens/procarcinogens and their subsequent impact on carcinogenesis [43]. Regulation of many detoxifying enzymes is mediated by nuclear factor E2-related factor 2 (Nrf2), a transcription factor that binds to AREs/electrophile response elements (EpREs), which is located in the promoter region of related genes where it initiates gene expression. Ingredients in black tea, including epigallocatechin gallate (EGCG), activate Nrf2 and upregulate protective enzymes [43,44].

Rubus fruticosus

Cho et al. [45] found that 1% HCl in the ethanol extract of blackberry (*Rubus fruticosus* L.) fruits (BFs) reduced lipid peroxidation that was elevated in CCl_4-treated rats. BFs have also been shown to be highly effective at retaining the activity of antioxidant enzymes that had been reduced by CCl_4, such as glutathione reductase (GR), superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT).

Cho et al.'s study suggested that the antioxidant activity of BFs may be related to enhanced expression of antioxidant enzymes as a result of Nrf2 activation. Nrf2 plays a crucial role in the activation of antioxidant and detoxifying enzymes, such as glutamate cysteine ligase (GCL), GPx, SOD, CAT, HO-1, NQO-1, and GR by regulating their transcription [46,47]. Nrf2 expression was much less in the CCl_4-treated group than the control group. The expression of antioxidant enzymes by manganese superoxide dismutase (MnSOD), CuZnSOD, HO-1, and GPx-1/2 also decreased, but not that of catalase. On the other hand, BFs could elevate the expression of Nrf2, GPx-1, MnSOD, and CuZnSOD in CCl_4-treated rats in a dose-dependent manner. An increase of HO-1 expression was also observed in BF-treated groups in a dose-dependent manner.

Acanthopanax senticosus

Aqueous extract from Siberian ginseng (*Acanthopanax senticosus* Harms, ASE) attenuated liver injury induced by *tert*-butyl hydroperoxide-treated mice and increased the activity of antioxidant enzymes and the ratio of GSH/GSSG in serum and in liver homogenates. ASE also increased Nrf2 gene expression,

but not CuZnSOD, MnSOD, CAT, GPx, and GCLC. Protein expression results showed that Nrf2 and antioxidant enzymes were all increased significantly by ASE. The results also indicated that ASE protects against oxidative stress. Such protection may be generated by the induction of Nrf2 and related antioxidant enzymes [48].

Phyllanthus emblica

Many reports have shown that protein kinase C (PKC) and extracellular signal-regulated kinase (ERK) can upregulate Nrf2 by increasing Nrf2 transcriptional activity, with subsequent upregulation of glutathione synthetase (γ-GCS) expression (glutathione synthetase is a phase II enzyme) [49]. It was also found that administration of p38 mitogen-activated protein kinase (p38MAPK) and ERK pathway inhibitor, respectively, could downregulate HO-1 expression in lungs of endotoxin-shocked rats [50]. ERK signaling pathway inhibitor PD98059 (2′-amino-3′-methoxyflavone) was also found to inhibit the nuclear translocation of Nrf2 and significantly reduce the intranuclear protein level of Nrf2 [7,51].

The effects extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (p38MAPK), and other kinase pathways have on activating the Nrf2-signaling pathway have been investigated using *Phyllanthus emblica* L. ethanol extract (PEE) [52]. In the study HepG2 cell lines were pretreated with different protease inhibitors for 2 h and the cells were treated with PEE for 24 h. mRNA expressions of Nrf2 and downstream target genes HO-1, NQO1, P-glycoprotein-1 (P-gp), multidrug resistance-associated protein 2 (MRP2) were detected by real-time PCR (RT-PCR). The protein level and nuclear translocation of Nrf2 were detected by Western blotting. RT-PCR results showed that treatment with PD98059, SB203580, and rottlerin suppressed HO-1, NQO1, P-gp, and MRP2 mRNA induction by PEE, but only treatment with SB203580 and rottlerin could inhibit Nrf2 mRNA expression by the extract. Western blotting showed that treatment with PD98059, SB203580, and rottlerin suppressed HO-1 and P-gp protein, which bring about the PEE effect. The study found that treatment with various inhibitors could induce cytoplasmic expression of the Nrf2 protein and that only treatment with PD98059 and SB203580 could inhibit nuclear translocation of Nrf2. The Nrf2 pathway-activating mechanisms of PEE may be associated with the roles ERK and p38MAPK play in directly phosphorylating Nrf2 and promoting Nrf2 nuclear import to increase its nuclear accumulation.

Phytochemicals

Several phytochemicals have been investigated for their capacity to induce Nrf2-based NQO1 or their effects on Nrf2-induced phase II antioxidant enzyme gene expression. Most of these compounds are flavonoids and related compounds, such as flavonolignans and stilbenes; terpenoids, such as diterpenes, sesquiterpenes, and triterpenes; sulfur-containing compounds, such as

sulforaphanes and glucosinolates; and other phenolics, such as curcuminoids and mangeferin. Most of these compounds were reported to be active as a result of the presence of such moieties as Michael acceptors, olefinic compounds conjugated to electron-withdrawing groups, oxidizable phenolic groups, quinones, isothiocyanates, thiocarbamates, and polyenes [53,54].

Flavonoids and Related Compounds

Flavonoids (Fig. 9.3) are a major class of plant constituents that includes flavonols, flavones, isoflavonoids, and chalcones. Several flavonoids and their related derivatives like flavonolignans have been investigated for their effects on the Nrf2/ARE pathway and induction of phase 2 antioxidant enzymes like NQO1.
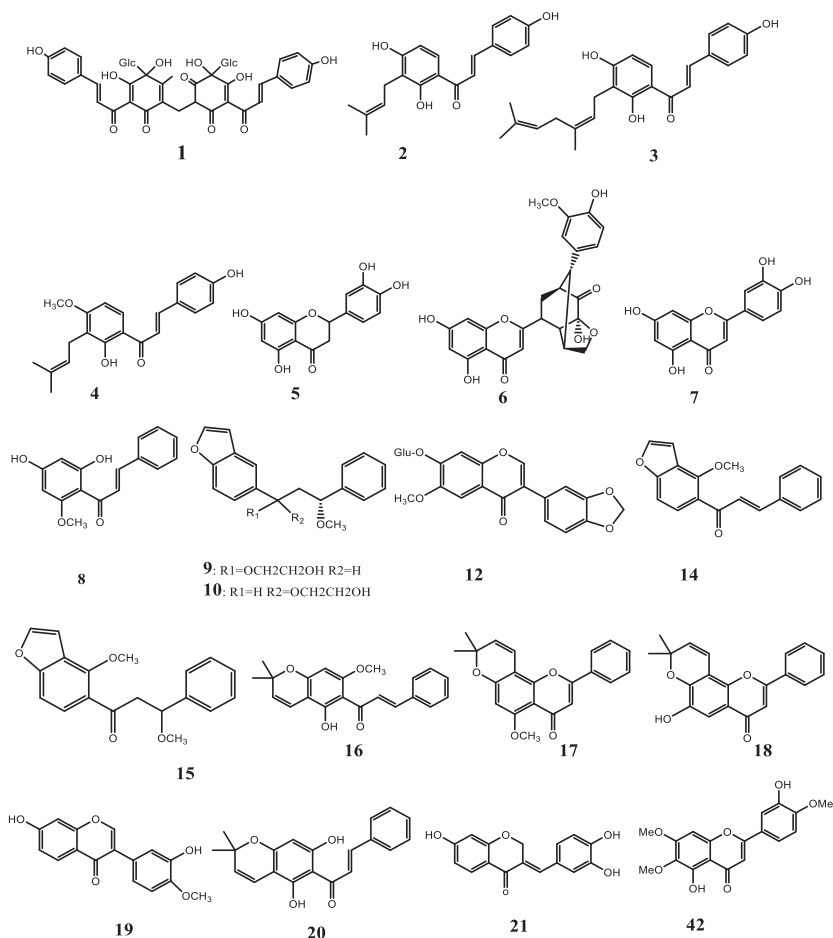

FIG. 9.3 Flavonoids with antioxidant activity through the Nrf2/ARE pathway.

Carthamus red or carthamin (CR) (**1**) is a flavonoid compound isolated from *Carthamus tinctorius* (safflower). Safflower and CR have been used extensively as a natural color additive for food and cosmetics and as a nutraceutical in China [55]. Wu et al. [56] designed a study to assess whether the regulation of Nrf2, NQO1, and GSTα by CR accounted for its hepatoprotective effect. This study showed that CR increases antioxidant enzyme activities via the Nrf2 pathway. The study further showed that the protein levels of Nrf2, GSTα, and NQO1 were noticeably decreased in CCl$_4$-induced liver injury in rats, indicating that CCl$_4$-caused hepatotoxicity triggered oxidative damage. After CR intervention, the endogenous Nrf2, GSTα, and NQO1 levels in hepatic tissue were effactually increased compared with the model control group. The study noted that CR provided a beneficial effect through activation of the Nrf2 pathway and induction of cytoprotective enzymes.

Luo and coworkers reported 23 compounds from *Angelica keiskei* that had a notable NQO1 induction effect. The chalcones isobavachalcone (**2**), xanthangelol (**3**), and 4-hydroxyderricin (**4**) were found to be the most potent NQO1 inducers [57].

Dihydroquercetin (DHQ) (**5**), a naturally occurring flavanol, has been proven to induce phase II antioxidant enzymes through the Nrf2/ARE-mediated pathway. In addition to its direct scavenging activity of DPPH, inhibition of lipid peroxidation, and inhibition of xanthine oxidase, DHQ showed remarkable protective properties against DNA oxidative damage. DHQ has also been observed to increase the transcriptional activity of Nrf2 by binding to AREs. An increase in nuclear translocation of Nrf2 and upregulation of Nrf2-related genes, such as NQO1 and HO-1, have also been reported [58].

The activity of flavonolignans from milk thistle (*Silybum marianum*) and their dehydroderivatives has been reported by Roubalová et al. [59]. 2,3-Dehydrosilydianin (**6**) significantly increased the activity of NQO1 in murine hepatoma (Hepa1c1c7) cells at concentrations of 25 μM. It was found to significantly increase the accumulation of Nrf2 and expression of the NQO1 gene. Other flavonolignans, such as silybin, silydianin, and silychrysin, showed no or negligible activity.

Quercetin (**7**) and vitamin C have been found to decrease the expression of Nrf2 mRNA in breast cancer cells. After treatment with vitamin C and quercetin the nuclear/cytosolic Nrf2 ratio was found to have reduced 1.7-fold in epithelial, human breast cancer cell line MDA-MB 231 cells, 2-fold in MDA-MB 468 cells, 1.4-fold in the human breast adenocarcinoma cell line (MCF-7), and 1.2-fold in adenocarcinomic human alveolar basal epithelial cells (A549). The results suggest the use of quercetin as an adjuvant in cancer therapy for patients overexpressing Nrf2 [60].

Cardamonin (**8**), a chalcone isolated from *Alpinia katsumadai*, has been shown to reveal upregulation of phase II antioxidant enzymes in PC12 cells, a cell line derived from pheochromocytoma of the rat adrenal medulla. The cytoprotective effect of this compound is thought to be mediated

through transcription of Nrf2. Cardamonin is suggested by the authors to be a promising small molecule for stress-based neurodegenerative disorders [61].

Chalcanes and flavonoids can be isolated from the leaves of *Millettia pulchra* (Benth.) Kurz var. laxior (Dunn) Z. Wei, a Chinese traditional medicine. The compounds included ($\alpha'R,\beta R$)-2′,β-dimethoxy-α′-hydroxyethoxy-furano-[4″,5″:3′,4′] chalcane (**9**), ($\alpha'S,\beta R$)-2′,β-dimethoxy-α′-hydroxyethoxy-furano-[4″,5″:3′,4′]- chalcane (**10**), quercetin (**5**), methyl 2-*O*-β-D-glucopyranosylbenzoate (**11**), 6,7- dimethoxy-3′,4′-methylenedioxyisoflavone (**12**), and lyoniresinol (**13**), were directly capable of inducing NQO1, suggesting their chemopreventive properties [62]. Other compounds isolated from *M. pulchra* have been proven to be good Michael acceptors by their reaction with GSH. As the expression of NQO1 is regulated in part by Michael reaction acceptors, compounds with such properties are suggested to be good candidates as NQO1 inducers. Further study investigating NQO-1 induction of isolated compounds using in vitro cell-based (Hepa 1c1c7 cells) assay revealed that ovalitenin A (**14**), (*R*)-ovalitenin B (**15**), pongachalconel (**16**), 5-methoxy-2,2-dimethylpyrano-[5,6:8,7]flavones (**17**), and 6-hydroxy-2,2- dimethylpyrano-[5,6:8,7]flavones (**18**) were the most active [63].

Calycosin (**19**), an isoflavonoid isolated from *Astragalus membranaceus*, has been investigated for its suppressive effect on the expression of proinflammatory cytokines in rheumatoid arthritis synovial fibroblasts (RASFs). Calycosin, in addition to inhibiting the expression of interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-25 (IL-25), interleukin-33 (IL-33), and cyclooxygenase 2 (COX-2), activated the antioxidant enzymes HO-1, NQO1, and Nrf2. Furthermore, it increased the accumulation of sequestosome 1 (SQSTM1, p62) and the degradation of Keap1, thus increasing the nuclear translocation of Nrf2 [64].

Lonchocarpine (**20**), a chalcone isolated from *Abrus precatorius*, has been shown to have antibacterial, antiinflammatory, and antiproliferative properties. It was investigated for its capacity to induce phase II antioxidant enzymes in brain astrocytes by Jeong et al. [65]. Lonchocarpine directly inhibited the reactive ROS in astrocytes in hydrogen peroxide-treated cells. In addition, it stimulated the production of phase II antioxidant enzymes (HO-1 and NQO1), manganese superoxide dismutase (MnSOD), and the nuclear translocation of Nrf2 and its binding to AREs and ARE transcriptional activation in astrocytes. Further mechanistic study revealed that lonchocarpine stimulated the phosphorylation of AMP-activated protein kinase (AMPK), which has been identified to be involved in the induction of HO-1 expression by the compound. These results suggest the use of lonchocarpine as a chemopreventive agent and in neurodegenerative diseases [65].

Sapanone A (SPNA) (**21**), a homoisoflavonoid, showed it had an antiinflammatory effect by modulating the Nrf2 pathway in murine macrophages. Treating the cells with SPNA induced the production of HO-1 and translocation of Nrf2 to the nucleus. In addition, the knockdown of Nrf2 by siRNA blocked SPNA-mediated HO-1 induction. The MAPK inhibitor

SB203580 reversed this effect of SPNA, suggesting that the induction of Nrf2-based HO-1 is through the MAPK pathway [66].

More than 20 other flavonoids and related compounds were covered in a review paper by Kumar et al. [54]. The chemopreventive mechanism of these compounds through the Nrf2 pathway and their possible antiinflammatory and neuroprotective effects were discussed.

Polyphenolic Compounds

Emodin (**22**) (Fig. 9.4), a well-known anthraquinone, has been reported to have an antiinflammatory effect. The possible involvement of the AMPK/ Nrf2 pathway in the antiinflammatory activity of emodin in lipopolysaccharide (LPS)-induced neuro-inflammation was studied by Park et al. [67].
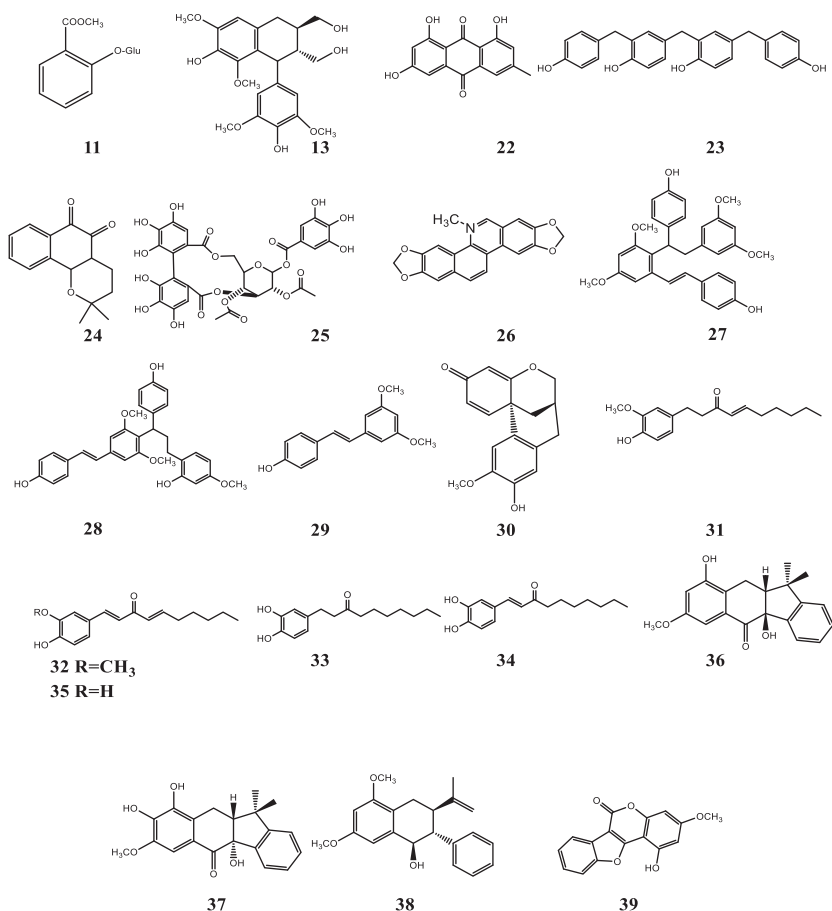

FIG. 9.4 Phenolics with antioxidant activity through the Nrf2/ARE pathway.

Emodin increased the expression of HO-1 and NQO1 and the translocation of Nrf2. In addition, AMPK inhibitors blocked the effect of emodin. Moreover, emodin inhibited the proinflammatory cytokines COX-2 and iNOS induced by LPS. Finally, the effect of emodin was decreased by the transfection of Nrf2 and HO-1 siRNA and AMPK inhibitors, confirming its activity through the Nrf2/AMPK pathway [67].

2-[4-Hydroxy-3-(4-hydroxybenzyl)benzyl]-4-(4-hydroxybenzyl)phenol (compound 20 C) (**23**), a bibenzyl compound isolated from *Gastrodia elata*, protected PC12 cells from rotenone-induced oxidative stress. The effect of the compound has been deduced to be through the Nrf2/ARE/HO-1-signaling pathway [68].

Lee et al. [69] investigated the mechanism underlying the potent antiinflammatory and antioxidant activities of the naturally occurring *O*-naphthoquinone β-lapachone (**24**). It showed a capacity to significantly inhibit iNOS, proinflammatory cytokines, and MMPs in LPS-treated microglia. Further mechanistic study of the antioxidant activity of β-lapachol revealed its action, which was by inducing HO-1 and NQO1 via the Nrf2/ARE pathway.

Geraniin (**25**) is a dehydroellagitannin isolated from *Geranium* species and known for its significant antioxidant activity in vitro. The antioxidant effect of geraniin in HepG2 cells has been found to be mediated by upregulation of Nrf2-induced antioxidant enzymes. The upregulation of Nrf2 is confirmed to be PI3K/AKT and extracellular signal-regulated protein kinase1/2 (ERK1/2) pathway dependent [70]. Sanguinarine (**26**) is an aromatic polycyclic quaternary ammonium compound isolated from roots of *Macleaya cordata* and *Macleaya microcarpa* and known for its antiinflammatory and antioxidant properties. It induced the production of HO-1 and NQO1 in mouse hippocampus-derived neuronal HT22 cells through the Nrf2 pathway leading to a neuroprotective response. In addition, it antagonized the neurotoxic and apoptotic effect of glutamate by attenuating mitochondrial function, membrane integrity, and inhibition of apoptosis [71].

Dragon's blood is a well-known Chinese medicine, known for its red resin, which can be obtained from many plants. Dichloromethane extract from the resin of *Dracaena cochinchinensis* S.C. Chen, known as Chinese dragon's blood, has been shown to exhibit promising NQO1-inducing activity. Cochinchinenene E (**27**), cochinchinenene F (**28**), pterostilbene (**29**), and 10-hydroxy-11-methoxydracaenone (**30**) showed the most potent NQO1-inducing activity [72].

Shogaol (**31**) is a well-known chemical constituent of many plants belonging to the Zingiberaceae family, such as ginger and alligator pepper. Shogaol has been reported to exhibit significant antioxidant and antiinflammatory activities. Zhu and coworkers [73] investigated the antioxidant activity of shogaol derivatives by activating the Nrf2 pathway. The derivatives that had an α,β-unsaturated carbonyl group and catechol moieties, compounds (**32–35**), showed the most potent activity. Moreover, the study authors reported that these

moieties were essential for conjugating the sulfohydryl group of cysteines in KAEP-1 leading to liberation and activation of Nrf2 from the Keap1–Nrf2 complex. In addition, they reported that 6-shogaol is more active than other shogaols with different chain lengths.

Caraxanes isolated from Mediterranean carex (*Carex distachya*) are a group of tetracyclic secondary metabolites biosynthetically derived from stilbenes by prenylation and successive cyclization. Three caraxanes have been isolated from the leaves of *C. distachya*: CXB (**36**), CXG (**37**), and CXI (**38**). CXI was the most potent of the three at reducing Kaep-1 gene expression and induction of Nrf2 [74].

Wedelolactone (**39**), a coumestan isolated from *Eclipta prostrata* L., has been shown to have to have an antiproliferative effect. The capability of this compound to protect normal human bronchial epithelial (NHBE) cells against inflammatory response due to smoking was studied. Pretreatment with the compound preserved the SOD and GSH in bronchial epithelial cells. Moreover, it was found to affect the expression of NQO-1 ad HO-1 by modulating expression of the Nrf2 pathway [75]. Other phenolics, such as ferulic acid, ethylferulate, protochatechuic acid, caffeoylquinic acid derivatives, and quinones (e.g., plumbagin and mollugin), were reviewed in Kumar et al. [54].

Terpenoids

The effect of betulinic acid (**40,** Fig. 9.5), a well-known triterpene isolated from many plants, on membranous nephropathy has been investigated. Betulinic acid was found to be effective in controlling the condition due to its antiinflammatory and antioxidant effects. The antioxidant effect of betulinic acid is mainly due to activation of Nrf2 and its related antioxidant enzymes HO-1 and NQO1. In addition, it attenuated the expression of NFκB [76].

Total methanolic extract of *Teucrium oliverianum* has been investigated for its NQO1-inducing properties. Of the compounds isolated from the chloroform-soluble fraction of the plant, teucrolivin B (**41**), a diterpene, was the most potent inducer. In addition, eupatorin (**42**), a flavonoid, and 8-*O*-acetylherpagide (**43**), an iridoid, were promising inducers of NQO1 [77].

α-Isocubebenol (**44**), which is isolated from *Schisandra chinensis*, is known for its antiinflammatory and antitumor properties. The protective effect of the compound on glutamate-induced neurotoxicity in mouse hippocampus-derived neuronal cells (HT22 cells) has been studied. α-Isocubebenol attenuated glutamate-induced intracellular accumulation of ROS. In addition, it increased the phosphorylation of cAMP response element-binding protein (CREB) and nuclear accumulation of Nrf2. Moreover, it induced the phase II detoxifying enzymes HO-1 and NQO1. Several compounds have been identified from the ethyl acetate extract of *Potamogeton crispus*. One of them crenulatoside A (**45**), a sesquiterpene, showed significant NQO-1 induction in human neuroblastoma SH-SY5Y cells [78].
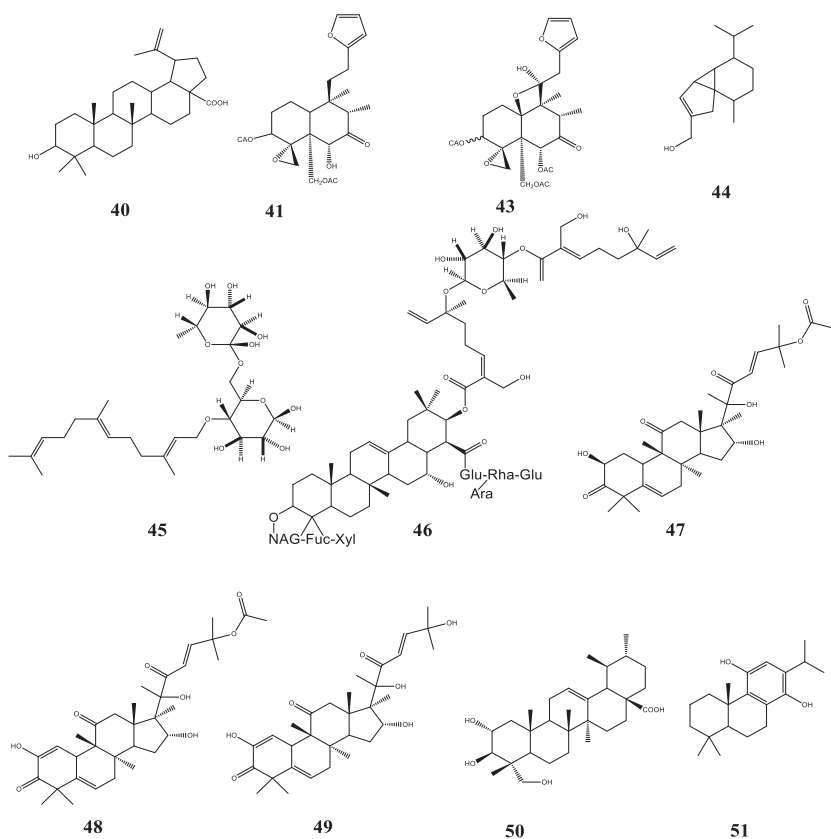
FIG. 9.5 Terpenoids with antioxidant activity through the Nrf2/ARE pathway.

The avicin D (**46**), a triterpenoidal saponin isolated from *Acacia victoria*, possesses an α,β-unsaturated carbonyl, known as the Michael acceptor, which makes it a candidate for induction of phase II antioxidant enzymes. Avicin D has been shown to be capable of increased nuclear translocation of Nrf2, in addition to the induction of NQO1 and HO-1. Moreover, it inhibited skin hyperplasia and p53 mutation in skin stressed by UV light in a mouse model [79].

Cucurbitacins are a group of triterpenoidal compounds from the Cucurbitaceae family that have a number of pharmacological effects. Cucurbitacin B (**47**), cucurbitacin E (**48**), and cucurbitacin I (**49**) have been investigated for their antineuroinflammatory effect. Cucurbitacin decreased proinflammatory cytokines and attenuated iNOS and COX-2 expression in Toll-like receptor TLR 2/4 agonist-stimulated microglia. In addition, it markedly activated the Nrf2/ARE pathway and its related factors NQO1 and HO-1 [80].

Asiatic acid (AA, **50**), a triterpene isolated from *Centella asiatica*, has been shown to have an antioxidative effect against oxidative stress in

tert-butyl hydroperoxide (*t*-BHP)-stimulated HepG2 cells. AA revealed its antioxidant potential in *t*-BHP-stimulated HepG2 cells in vitro. In addition, AA activated Nrf2 expression and its nuclear translocation and reduced the expression of Keap-1, resulting in the upregulation of AREs. Expression of phase II antioxidant genes was also upregulated by AA [81].

DA1 (**51**), a diterpene with a hydroquinone moiety reported to be a derivative of naturally occurring cryptoquinone, has been investigated because of the neuronal protective effect it has through the Nrf2 pathway. DA1 activated the Nrf2/ARE pathway, induced phase II antioxidant enzymes, and increased glutathione levels. DA1 also revealed a very broad safety zone, making it as a promising neuroprotective agent [82].

Sulfur-Containing Compounds

Dithiolethiones are a group of sulfur-containing, five-membered ring compounds found in many cruciferous plants, such as cabbage and Brussels sprouts. Many authors have reported the antioxidant and cytoprotective effects of these compounds (Fig. 9.6). Oltipraz (**52**), antholedithione (ADT) (**53**), and 1,2-dithiole-3-thione (D3T) (**54**) have been reported to induce NQO-1 in Hep1c1c7 cells. H_2O_2 was found to be the second messenger in the induction of antioxidant enzymes by these compounds [83]. D3T (**54**) was reported to be cytoprotective in cardiovascular cells. It acts by inducing phase II antioxidant enzymes in primary cardiomyocytes. Pretreatment of cells with D3T protected the cells against xanthine oxidase, doxorubicin, H_2O_2, 3-morpholinosydnonimine, and 4-hydroxy-2-nonenal [84].

Sulforaphane (**55**) is another cruciferous sulfur-containing compound that belongs to the isothiocyanate group. It has been reported to upregulate cytoprotective genes in liver cells. Incubation of sulforaphane with rat aortic smooth muscles induced phase II antioxidant enzymes, such as SOD, catalase,
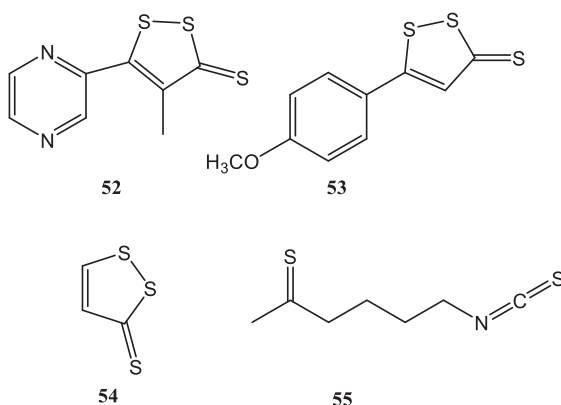

FIG. 9.6 Sulfur-containing compounds with antioxidant activity through the Nrf2/ARE pathway.

NQO-1, and GSH. In addition, it protected smooth muscle against electrophilic cytotoxicity induced by H_2O_2 and xanthine oxidase. Moreover, it protects against intracellular accumulation of ROS [85].

Miscellaneous Compounds and Compounds From Microbial and Marine Sources

Fig. 9.7 shows the chemical structures of the different phytochemical classes involved in cancer progression and prevention. *Morinda citrifolia* L. (Rubiaceae), known as noni, is a tropical fruit widely used in traditional

56 R_1=OH, R_2=αO-*n*-butyl, R_3=OH
57 R_1=OCH$_3$, R_2=βOH, R_3=OH

58

59 R_1=R_4= H, R_2=R_3=OH
60 R_1=R_3= OH, R_2=H, R_4= COOMe
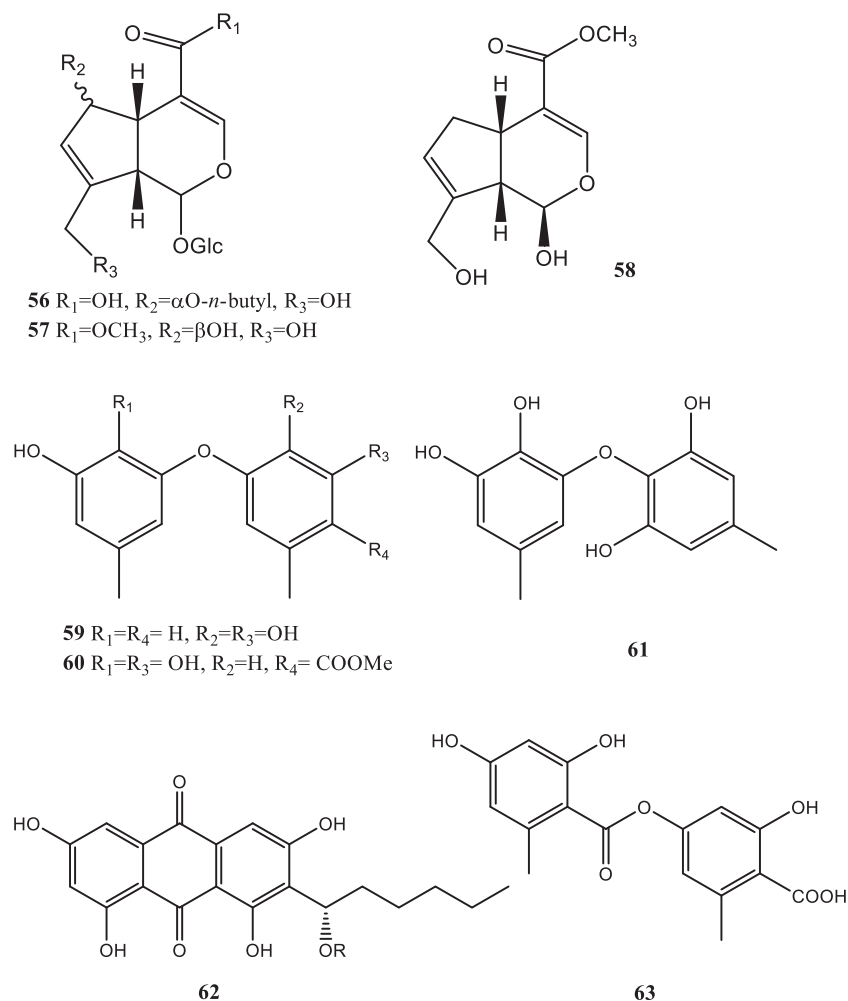
61

62

63

FIG. 9.7 Miscellaneous compounds derived from microbial sources with antioxidant activity through the Nrf2/ARE pathway.

medicine. Rhodolatouside (**56**) and scandoside (**57**), iridoid methyl esters isolated from fermented noni extract among other compounds, have been shown to be the most potent NQO-1 inducers [86].

Genipin (**58**) is an iridoid that has a known neuroprotective effect. Koriyama and coworkers investigated a long-acting derivative of genipin named (1*R*)-isopropyloxygenipin (IPRG001) for its potential as a neuroprotective agent for retinal ganglion cells, using in vitro and in vivo models. IPRG001 was found to induce Nrf2 translocation through S-nitrosylation of Keap-1 and subsequently induce phase II cytoprotective enzymes, such as NQO-1 and HO-1 [87].

The marine-derived fungus *Aspergillus versicolor* has been shown to yield several phenolic compounds that have significant antioxidant effects. Of these compounds, cordyol C (**59**), methylgerfelin (**60**), violaceol II (**61**), 1′-*O*-methylaverantin (**62**), and lecanoric acid (**63**) showed Nrf2-activated expression. The capability of these compounds to induce an ARE-dependent antioxidant effect was investigated using HepG2C8 cells [88].

CONCLUSIONS AND PROSPECTS

This chapter clearly demonstrated that many natural products with diverse chemical structures have the potential to activate the Nrf2/ARE pathway and prevent cancer chemically. Mother Nature remains a rich source of plants with promising phytochemicals that are awaiting investigation and characterization by investigators. However, for cancer therapy purposes a number of small molecules are being investigated for possible inhibition of Nrf2, which is overexpressed in many solid tumors. This overexpression of Nrf2 represents the "dark side" of Nrf2 because it confers resistance to cancer cells against chemotherapeutic agents. For example, the phytochemical brusatol isolated from *Brucea javanica* seeds downregulated Nrf2 protein/target genes in a variety of cancer cells and enhanced the cytotoxic effect of cisplatin [89]. Employing computer-based strategies to predict the bioactivity of compounds will open up new scope for the characterization and optimization of new phytochemical drug candidates. Recent identification of the crystal structure of the Keap1–Nrf2 complex [90] holds much promise for several exciting research areas to develop specific modulators of the Nrf2 pathway using chemo-informatic approaches.

ABBREVIATIONS

A549	adenocarcinomic human alveolar basal epithelial cells
AA	asiatic acid
Akt	protein kinase B
AOX1	aldehyde oxidase-1
AREs	antioxidant response elements

ASE	*Acanthopanax senticosus* Harms
BFs	blackberry fruits
BMI	body mass index
CAT	catalase
COX-2	cycloxygenase-2
CPAs	chemopreventive agents
CR	carthamus red or carthamin
CREB	cAMP response element-binding protein
CuZnSOD	copper–zinc superoxide dismutase
CZ	*Chrysanthemum zawadskii*
DHQ	dihydroquercetin
DMBA	7,12-dimethylbenz[*a*]anthracene
DMH	1,2-dimethylhydrazine
DNA	deoxyribonucleic acid
EGCG	epigallocatechin gallate
EMR	Eastern Mediterranean region
EpRE	electrophile response element
ERK	extracellular signal-regulated kinase
GCB	global cancer burden
GCL	glutamate cysteine ligase
GCLC	glutamate cysteine ligase catalytic
γ-GCS	glutathione synthetase
GPx	glutathione peroxidase
GR	glutathione reductase
GSH	glutathione
GSSG	glutathione disulfide-d10
GSTm3	glutathione *S*-transferase Mu 3
GSTs	glutathione *S*-transferases
GSTα	glutathione *S*-transferase alpha
GU	*Glycyrrhiza uralensis*
HBV	hepatitis B virus
HCV	hepatitis C
HIV	human immunodeficiency virus
HO-1	heme oxygenase
HPV	human papillomavirus
IARC	International Agency for Research on Cancer
IL-1β	interleukin-1β
iNOS	inducible nitric oxide synthase
IPRG001	(1*R*)-isopropyloxygenipin
Keap1	Nrf2/Kelch-like ECH-associated protein
KO	knockout mice
LDC	less developed countries
MAPKs	mitogen-activated protein kinases
MCF-7	human breast adenocarcinoma cell line

MDA-MB	epithelial, human breast cancer cell line
MnSOD	manganese superoxide dismutase
MRP2	multidrug resistance-associated protein 2
NCDs	noncommunicable diseases
NFκB	nuclear factor-kappa
NHBE	normal human bronchial epithelial
NQO1	NAD(P)H:quinone oxidoreductase 1
Nrf2+/+; WT	Nrf2 wild type
Nrf2−/−; KO	Nrf2-deficient mice
Nrf2	nuclear factor erythroid-derived related factor 2
8-OHdG	8-hydroxy-2′- deoxyguanosine
p38MAPK	P38 mitogen-activated protein kinase
PC12	cell line derived from pheochromocytoma of the rat adrenal medulla
PKC	protein kinase C
PD98059	flavonoid that binds to inactive forms of MEK1
PEE	*Phyllanthus emblica* L.
P-gp	P-glycoprotein 1
qPCR	quantitative polymerase chain reaction
RASFs	rheumatoid arthritis synovial fibroblasts
RNA	ribonucleic acid
RNS	reactive nitrogen species
ROS	reactive oxygen species
RT-PCR	real-time PCR
SB203580	4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole
SH-SY5Y	human neuroblastoma cell line
SOD	superoxide dismutase
SPNA	sapanone A
SQSTM1, p62	sequestosome 1
TLRs	Toll-like receptors
TPA	12-*O*-tetradecanoylphorbol-13-acetate
UGT1A1	UDP-glucuronosyltransferase 1A1
UGT2B5	UDP glucuronosyltransferase 2 family, polypeptide B5
WHO	World Health Organization
WT	wild-type mice

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