Chapter 1

Stress Response of Dietary Phytochemicals in a Hormetic Manner for Health and Longevity

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Additional information is available at the end of the chapter

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Abstract

The stress responses observed in mammalian cells can be classified as heat shock response, unfolded protein response, autophagic response, deoxyribonucleic acid damage response, antioxidant response, and sirtuin response at the intracellular and molecular levels. Factors that strengthen the hemodynamic structure causing low-level molecular damage and activating one or several stress response pathways are called hormetins. Hormetins can be categorized as physical, physiological, biological, and nutritional hormetins. Nutritional hormetins provide an interesting, comprehensive research topic because of their effects on health and lifespan. Dietary phytochemicals, with their low-level stress-inducing effects, are potential nutritional hormetins. Resveratrol, curcumin, epicatechin, isothiocyanates, ferulic acid, and certain vitamin-minerals can induce a heat shock response, unfolded protein response, autophagic response, deoxyribonucleic acid damage response, antioxidant response, and sirtuin response causing the stimulation of kinases and transcription factors. Studies have shown that these phytochemicals are related to nuclear factor-erythroid 2, sirtuins, nuclear factor-kappa B, and heat shock response pathways. In this chapter, the stress response of dietary phytochemicals will be systematically examined in a hormetic manner for delay of age-related diseases, healthy aging, and longevity based on current data.

Keywords: aging, longevity, health, stress response, hormesis, nutritional hormetin, phytochemical

1. Introduction

The term hormesis, based on toxicology, is described as a biphasic dose response in which environmental factors show a stimulant effect at low doses and a toxic effect at higher doses [1]. A comprehensive current definition of “hormesis” is "chemical and environmental factors

having a beneficial effect to cells in an organism at low doses, whereas they are damaging at high doses" [2]. Hemodynamic is the ability of live systems to provide protection against stress, and to maintain adaptation, survival, and continuity of health. Hemodynamic impairment, increased molecular heterogeneity, altered cellular function, and decreased adaptive stress responses are some factors that determine health status and lifespan [3, 4]. The development of adaptive stress response with mild and periodic stress is hormetically related to the strengthening of the hemodynamic structure, the reduction of disease risks, and healthy aging. Hormesis in aging implies that mild stress produces biologically beneficial effects by inducing protective mechanisms in the cells and the organism [5]. Stress response can be defined as the response of cells, tissues, and organisms to physical, chemical, or biological factor(s) affecting adaptation and lifespan by initiating a series of biological events. In terms of hormetic level, stressors at a mild level activate various signaling pathways, maintaining intrinsic changes leading to a high level of stress-adaptive response. Stress response in mammalian cells can be classified into seven basic pathways at the intracellular and molecular levels: (1) heat shock response; (2) unfolded protein response; (3) autophagic response; (4) deoxyribonucleic acid (DNA) repair response; (5) antioxidant response; (6) sirtuin response; and (7) nuclear factor-kappa B (NF-κB) inflammatory response. The conditions and factors identified as hormetic activate the pathway of one or more stress responses by mild molecular impairment and strengthen the hemodynamic structure. Hormetins can be grouped under three categories: (1) physical hormetins (exercise, thermal shock, and irrigation); (2) physiological hormetins (mental interrogation and focusing); (3) biological and nutritional hormetins (infections, micronutrients, phytochemicals, and energy restriction) [4, 6, 7].

Dietary phytochemicals are potential nutritional hormetins with mild stress-inducing effects. In the Greek language “phyto” means plant, so phytochemical means “plant chemical.” Phytochemicals are non-nutrient biologically active compounds produced to protect plants against microbial infections that occur because of environmental factors damaging the plant. Therefore, phytochemicals, which are secondary plant metabolites found primarily to protect their structures and properties in vegetables, fruits, grains, and various plants, may have positive effects on human health when taken in the diet. Phytochemicals are generally classified according to their chemical structure. The main groups with bioactive properties from these groups are phenolic compounds [8, 9]. Ferulic acid, resveratrol, epigallocatechin gallate (EGCG), luteolin, quercetin, and curcumin as phenolic compounds are dose-dependently responsible for the stimulation of kinases and transcription factors and produce a heat shock response, unfolded protein response, autophagic response, DNA repair response, antioxidant response, and sirtuin response [6, 10–13]. In this chapter, the stress response of dietary phytochemicals will be systematically examined in a hormetic manner for delay of age-related diseases, healthy aging, and longevity based on current data.

2. Dietary Phytochemicals as Nutritional Hormetins

When dietary phytochemicals are invoked in relation to neurodegenerative diseases, cardiovascular diseases, cancer, aging, and longevity, especially in the heat shock response, antioxidant

response, NF-κB inflammatory response, and autophagic response were emphasized regarding their hormetic adaptive stress response pathways. The characteristics and importance of these stress response pathways are summarized in what follows.

The major effectors involved in heat shock response are heat shock proteins (HSPs), which are cytoprotective proteins that facilitate cellular protein folding, prevent protein aggregation, and provide protein degradation activation. They also affect the cell survival by interacting with various molecules in the regulation of apoptosis and mitochondrial activities. HSPs are divided into five main groups: the Hsp100 family, Hsp90 family, Hsp70 family, Hsp60 family, and the small Hsp family. Hsp70 regulates protein homeostasis, thereby, it can provide protection against cancer, neurodegeneration, and infections [14, 15]. Hsp90 regulates the stability and intracellular sorting of client proteins found in many oncogenic processes. Thus, Hsp90 inhibition may prevent cancer progression [16]. Hsp27 can protect against neurodegenerative diseases by controlling apoptosis, cytoskeleton regulation, oxidative stress, and protein folding [17]. In general, HSPs provide the survival of cancer cells by overexpression in cancer cells. Thus, the inhibition of Hsp27, Hsp70, and Hsp90 can be targeted in the treatment of cancers in which HSPs are known to be over-expressed [18]. The nuclear factor-erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) is the main effective pathway in the formation of antioxidant stress responses. Under basal conditions, Nrf-2 is present in the cell cytoplasm bound to Keap1 protein. However, when combined with oxidative stress and chemo-blocking factors, Nrf2 is released from Keap-1 into the nucleus; it activates the ARE and induces the expression of the antioxidant enzymes including glutathione peroxidase (GPx), catalase, hemoxygenase (HO)-1, and the phase II detoxification enzymes, including glutathione S-transferase (GST). Extracellular signaling protein kinases are responsible for the release of Nrf2 from Keap-1 by phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2), protein kinase C (PKC), and c-Jun N-terminal kinase (JKN). Thus, Nrf2 associated with the cell defense mechanism, may have protective effects against oxidative stress-induced tissue degeneration, premature aging, cancer, neurodegenerative diseases, cardiovascular diseases, acute and chronic lung diseases, and autoimmune and inflammatory diseases [19–22]. Among the factors that induce Nrf2 in the formation of antioxidant stress responses are isothiocyanates and Michael acceptors. Michael acceptors are susceptible to flavonoids, chalkones, terpenoids, curcumin, cinnamic acid derivatives, and thiophenes, and interact with these phytochemicals to modulate the Nrf-2 pathway [23, 24]. The effector NF-κB protein complex action regulates the expression of genes involved in innate and adaptive immunity, inflammation, cellular stress response, cell survival, and proliferation. Therefore, this pathway can be effective in pathogenesis of inflammatory and autoimmune diseases, septic shock, viral infections, tumorigenesis, and neurodegenerative diseases. Various dietary phytochemicals such as curcumin and resveratrol can suppress NF-κB activation and protect against immunological and inflammatory diseases, cancer, and neurodegenerative diseases [12]. In an autophagic response, hypoxia-inducible factor (HIF)-1 and the activated mammalian target of rapamycin (mTOR) are important. mTOR is involved in cell proliferation and protein synthesis via insulin and insulin-like growth factor (IGF)-1 signaling. It can also cause the suppression of autophagy, and reduced autophagy is associated with decreased longevity. Thus, the increase in autophagy is associated with an increase in inflammatory

response, cellular senescence, decreased proteotoxic protein aggregation, and the removal of intracellular pathogens, cumulatively resulting in an increased innate immune response that leads to longevity [25]. HIF-1 regulates genes related to angiogenesis, iron and glucose metabolism, cell proliferation and cell survival. Various dietary phytochemicals, with HIF-1 inhibition, have protective effects against neurodegenerative diseases, cancer, cardiovascular diseases [12, 26]. In this section, hormetic effects of phenolic compounds predominantly expressed as hormetin including ferulic acid, curcumin, resveratrol, EGCG, luteolin, quercetin, and sulforaphane will be discussed in relation to these stress response pathways. The stress pathways, transcription factors, and biological outcomes of these phytochemicals have been summarized in **Table 1**.

2.1. Ferulic acid

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is a cinnamic acid derivative phenolic compound. It is also the preliminary metabolite for curcumin and lignins. Grain bran, whole grains, artichoke, eggplant, banana, cabbage, and coffee are rich in ferulic acid. Ferulic acid has a positive effect on diseases such as cancer, Alzheimer's disease, Parkinson disease, and diabetes through various pathways. Among the mechanisms of action of ferulic acid are the antioxidant response, heat shock response, and NF-κB inflammatory response, especially in the adaptive stress response pathways [27–29]. Ferulic acid showed a protective effect against heat stress-induced intestinal epithelial barrier dysfunction in IEC-6 intestinal epithelial cells in a dose-dependent manner in male Sprague-Dawley rats *in vitro* and *in vivo* [30]. In a study conducted on the human neuroblastoma cell line SH-SY5Y, ferulic acid increased dose-dependent HO-1 expression through Nrf2 [31]. In a study on PC12 cells, ferulic acid increased HO-1 expression through ERK1/2-Nrf2 signaling pathway and protected against lead acetate-induced neurite outgrowth inhibition [32]. On the other hand, 1-feruloyl glycerol and 1-feruloyl diglycerol predominate in water-soluble forms of ferulic acid in rat primordial astrocytes, suppressing nitric oxide (NO) synthesis and inducible nitric oxide synthase (iNOS) expression by suppressing the NF-κB pathway. Accordingly, these ferulic acid forms may provide a protective effect against neurodegenerative diseases [33]. The tumor necrosis factor (TNF)-α induces endothelial dysfunction by reducing NO bioavailability. Ferulic acid increased tyrosine-dependent NO production and suppressed the NF-κB pathway in TNF-α-stimulated inflammatory human umbilical vein endothelial cells (HUVECs) [34]. Another study showed that ferulic acid demonstrated a cardioprotective effect by increasing Hsp70 through the NO-ERK1/2 pathway in mice cardiomyocytes and suppressing the NF-κB pathway [35]. In another study, HeLa and mouse primary hepatocyte cells activated basal autophagy with an mTOR inhibition almost equivalent to that of rapamycin [36]. As a result, ferulic acid can exert a protective effect against neurodegenerative diseases, cardiovascular diseases, and cancer inflammatory diseases by acting on stress pathways and thus can positively affect longevity.

2.2. Curcumin

Curcumin (1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), also known as diferuloylmethane, is a yellow phenolic compound, found in *Curcuma longa* (turmeric) a

Phytochemicals	Stress pathways	Transcription factors	Biological outcomes	References
	Antioxidant response pathway	Nrf-2	HO-1↑	[31, 32]
Ferulic acid	NFκB inflammatory pathway	NFκB	NO↓, iNOS↓	[33]
	Heat shock response pathway	HSF-1	Hsp70↑	[35]
	Autophagic response pathway	—	mTOR inhibition	[36]
	Antioxidant response pathway	Nrf2	Glutathione, GR, GST, HO-1, NQO1	[43, 44]
Curcumin	NFκB inflammatory pathway	NFκB	SOD-2↑, Hsp60↑	[42, 45]
	Heat shock response pathway	HSF-1	Overexpressed Hsp27↓, Hsp70↓, Hsp90↓ Hsp27↑, Hsp70↑	[39, 40] [41, 42]
	Sirtuin response pathway	—	SIRT3↑	[42]
	Antioxidant response pathway	Nrf2	Glutathione↑, HO-1↑	[49, 50]
Resveratrol	NFκB inflammatory pathway	NFκB	iNOS↓, IL-6↓, TNF-α↓	[54, 55]
	Heat shock response pathway	HSF-1	Hsp25↑, Hsp70↑	[47, 48]
	Autophagic response pathway	—	mTOR inhibition	[52, 53]
	Sirtuin response pathway	—	SIRT1↑	[47, 48]
	Antioxidant response pathway	Nrf2	GST↑, NQO1↑, HO-1↑	[59, 60, 62, 64]
EGCG	NFκB inflammatory pathway	NFκB	IL-12p40↓, IL-6↓	[65–67]
	Heat shock response pathway	HSF-1	Overexpressed Hsp90↓	[58]
	Autophagic response pathway	—	HIF-1α, mTOR inhibition	[68, 69]
	Antioxidant response pathway	Nrf2	HO-1↑, CYP1A1↑, NQO1↑, GST-P1↑, GCLC↑, GCLM↑	[76–78, 80, 81, 83]
Luteolin	NFκB inflammatory pathway	NFκB	TNF-α↓, NO↓	[73–75, 81]
	Autophagic response pathway	—	HIF-1α inhibition	[82]
	Sirtuin response pathway	—	SIRT1↑	[81]
	Antioxidant response pathway	Nrf2	GSH↑, GPx↑, GR↑, GST↑, GCLC↑, GCLM↑, HO-1↑	[89–95]
Quercetin	NFκB inflammatory pathway	NFκB	COX-2↓	[90, 94]
	Heat shock response pathway	HSF-1	Overexpressed Hsp27↓, Hsp70↓	[85–87]

Phytochemicals	Stress pathways	Transcription factors	Biological outcomes	References
	Autophagic response pathway	—	HIF-1, mTOR inhibition	[88, 96–101]
	Antioxidant response pathway	Nrf2	HO-1↑, SOD-1↑,NQO1↑	[104–111]
Sulforaphane	NFκB inflammatory pathway	NFκB	TNF- α↓, IL-6↓	[109]
	Autophagic response pathway	—	HIF-1α inhibition	[114]

↑: increased; ↓: decreased.

Table 1. Summary of stress pathways, transcription factors, and biological outcomes of phytochemicals

plant of the ginger family. Curcumin is the compound responsible for the chemical and biological properties of this spice, as well as its color and taste. Numerous studies have shown that curcumin is associated with antioxidant, anti-inflammatory, antimutagenic, antimicrobial, and anticancer effects, mitigating chronic diseases and increasing longevity [37, 38]. HSPs, HSF1, and histone deacetylase (HDAC) 6 are upregulated in cancer. Expression of Hsp 27, Hsp70, Hsp90, HSF1, and HDAC-6, which are overexpressed in K-562 and HL-60 leukemia cells, was reduced when curcumin was administered [39]. Also, curcumin appeared to reverse the inhibition on Hsp70 induced by the gp120 V3 loop peptide and increased the expression of Hsp70 in primary rat cortical neuronal apoptosis [40]. In addition, curcumin can protect against endosulfan toxicity by decreasing endosulfan-induced apoptosis through increased Hsp 27 expression in human peripheral blood mononuclear cells (PBMCs) [41]. In hyperglycemic HepG2 human hepatoma cells, curcumin increased the expression of NF-κB and Hsp70, sirtuin (SIRT)-3, glutathione peroxidase (GPx)-1, and superoxide dismutase (SOD)-2 in a dose-dependent manner [42]. On the other hand, curcumin may act as an antioxidant in the stress-response pathway. Primary cell cultures of cerebellar granule neurons of rats increased the expression of HO-1, glutathione, glutathione reductase (GR), GST, and SOD through Nrf-2 depending on the dose and duration and thereby protected against hemin-induced toxicity [43]. In mice liver cells with T-cell lymphoma, the expression of GST, GR, and NAD(P)H:quinine oxidoreductase (NQO1) enzymes was increased by activation of curcumin Nrf-2 [44]. Lipopolysaccharide (LPS)-stimulated BV2 mouse microglia cells also inhibited microglial activation by inhibiting the curcumin Hsp60/TLR4/MyD88/NF-κB pathways [45]. As a result, curcumin can show protective effects against cancer, neurodegeneration, and inflammation by acting on stress-response pathways.

2.3. Resveratrol

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a phenolic compound found in some plants such as grapes, berries, peanuts, and Japanese knotweed, with purported medical uses. Several studies have shown that resveratrol affects chronic diseases and longevity through anti-carcinogenic, anti-inflammatory, and antioxidant properties [46]. Resveratrol dose-dependently increased expression of Hsp70 and SIRT-1 in human neuroblastoma SH-SY5Y

cells induced by neurotoxicity with high-dose homocysteine [47]. It has been reported that resveratrol induced Hsp25 and Hsp70 proteins in G93A-SOD1 mutant mice cells and can prevent motor neuron losses [48]. Resveratrol dose-dependently increased glutathione expression through the Nrf2 pathway in normal human keratocytes [49]. In the human neuroblastoma cell line SH-SY5Y, resveratrol dose-dependently increased HO-1 expression and HO-1-dependent autophagic flux and prevented rotatone-induced apoptosis [50]. It has been determined that resveratrol dose-dependently reduced the vascular endothelial growth factor (VEGF), leptin, interleukin (IL)-6, and IL-8 expression in hypoxia-induced human adipocytes and prevented adipokine-induced inflammation and angiogenesis [51]. In addition, resveratrol induced autophagy by directly inhibiting mTOR in HeLa cells [52]. Prostate cancer cells induced autophagy through inhibition of the Akt/mTOR pathway in PC3 and DU145 cells [53]. In murine RAW 264.7 macrophages and microglial BV-2 cells, resveratrol also inhibited microglial activation by suppressing the NF-κB pathway [54]. In another study, resveratrol showed anti-inflammatory effect by suppressing the NF-κB pathway in RAW 264.7 murine macrophages in a dose-dependent manner [55]. These studies suggest that resveratrol has anti-inflammatory, antioxidant, anti-carcinogenic effects and can strengthen hemodynamic structure, which in turn can positively affect the aging process and longevity.

2.4. Epigallocatechin gallate

The major catechin EGCG, which is found in green tea at a level of 48–55%, has protective effects against chronic diseases such as neurodegenerative diseases, metabolic syndrome, and cancer by its anti-inflammatory and antioxidant effects [56, 57]. EGCG, with Hsp90 inhibition, showed a protective effect against cancer in a novel human prostate cancer progression model [58]. In primary vascular endothelial cells, GST and NQO1 enzymes were increased dose-dependently by Nrf2 [59]. In another study, EGCG increased the level of HO-1 expression by Nrf-2 activation in endothelial cells, resulting in the passage of caveolin-1 from the plasma membrane to the cytosol, accumulating in the caveolae-regulating signaling pathways associated with vascular disease pathology [60]. Accordingly, EGCG may reduce endothelial inflammation and protect against atherosclerosis [61]. EGCG also showed a protective effect against oxidative stress-induced cerebral ischemia through Nrf2/ARE activation [62]. EGCG suppressed the Nrf-2 pathway in a lethal dose with biphasic dose-response effect in mice hepatocytes [63]. EGCG has been shown to inhibit oxidative stress damage induced by HO-1 through Nrf2 in HUVECs with ambient fine particulate matter (≤2.5 μm in aerodynamic diameter PM2.5) [64]. EGCG dose-dependently suppresses endothelial inflammation through NF-κB inhibition in high glucose-induced HUVECs [65]. It can also suppress NF-κB activation in cardiac fibroblasts and can show a protective effect against cardiac fibrosis [66]. EGCG inhibited lipopolysaccharide-induced inflammation with NF-κB suppression in bone marrow-derived macrophages (BMMs) isolated from ICR mice [67]. EGCG also showed a protective effect against human papillomavirus-16 oncoprotein-induced lung cancer and IGF-1 stimulated lung cancer angiogenesis through HIF-1α inhibition [68, 69]. In addition, primary bovine aortic endothelial cells stimulate autophagy in cells, leading to degradation of lipid droplets. In this way, EGCG may be effective in the prevention of cardiovascular diseases [70]. EGCG regulates ultraviolet B (UVB)-mediated autophagy through the mTOR signaling pathway

and significantly alleviates the toxic effects of UVB irradiation in macular retinal pigment epithelial cells. Thus, it may also have a protective effect against macular degeneration [71]. As a result, EGCG can be effective in the prevention of neurodegeneration, cancer, cardiovascular diseases, inflammatory diseases, and macular degeneration through stress pathways.

2.5. Luteolin

Luteolin (3′,4′,5,7-tetrahydroxy flavone) is a phenolic compound found in broccoli, pepper, thyme, celery, lettuce, oregano, artichoke, and carrots; it has antioxidant, anticancer, anti-inflammatory, and neuroprotective effects [72]. Luteolin destabilized the Hsp90 client protein c-Jun and Akt and inhibited LPS-induced production of TNF-α and NO dose-dependently in macrophages [73]. In addition, luteolin prevented TNF-α-induced endolytic monocyte adhesion in mice by suppressing vascular inflammation and the IKBα/NF-κB pathway in HUVECs [74]. In psoriatic skin, luteolin inhibited keratinocyte activation by decreasing NF-κB, which increased dose-dependently [75]. Luteolin and luteolin-7-*O*-glucoside modulated Nrf2/mitogen-activated protein kinase (MAPK) mediated the HO-1 signaling cascade in RAW 264.7 cells [76]. In wild-type mouse traumatic brain injury models, luteolin showed neuroprotective action by Nrf2/ARE pathway activation [77]. Luteolin inhibited tBHP-induced oxidative stress by increasing ERK2/Nrf2/ARE signaling pathway activation and HO-1, glutamate cysteine ligase catalytic (GCLC), and glutamate cysteine ligase modifier (GCLM) subunit transcription in rat primary hepatocytes [78]. In addition, in HepG2, Hepa1c1c7, and RL-34 HepG2 hepatocytes, it dose-dependently inhibited the expression of phase I enzyme cytochrome P450 1A1 (CYP1A1), and phase II enzymes NQO1 and GST-P1 through an aryl hydrocarbon receptor (AhR) and Nrf2 pathways [79]. In HepG2 human hepatocytes, luteolin also dose-dependently activated the PI3K/Nrf2/ARE system, increased HO-1 expression, and reduced the expression of lipopolysaccharide-induced NO, iNOS, and cytosolic phospholipase A2 (cPLA2) in hepatocytes [80]. Luteolin also reduced acute mercuric chloride-induced hepatotoxicity by anti-inflammatory and antioxidant responses by regulating the SIRT1/Nrf2/TNF-α pathways [81]. The induction of VEGF by oxidative stress has an important role in the pathogenesis of premature retinopathy. Luteolin has shown a protective effect against retinal neovascularization by reducing hypoxia-induced VEGF expression through decreasing HIF-1α expression in human retinal microvascular endothelial cells (HRMECs) [82]. Luteolin reduced 4-hydroxy-2-nonenal-induced cell death of neuronal-like catecholaminergic PC12 cells by regulating unfolded protein response and the MAPK, Nrf2/ARE pathways [83]. As a result, luteolin also affects neurodegeneration, endothelial function, and liver function through stress-response pathways as do other hormetic phytochemicals.

2.6. Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is found in many vegetables and fruits. It has anti-inflammatory, anticarcinogenic, and antioxidant effects on cardiovascular diseases, cancer, neurodegenerative diseases, and can reduce aging and positively increase the life span [84]. Quercetin inhibited the growth of A549 and H460 cancer cells with Hsp70 inhibition in lung cancer cells and increased sensitivity to chemotherapy [85]. Quercetin inhibited the t-AUCB-induced autophagy by inhibiting Hsp 27 and Atg 72 in glioblastoma cells [86]. In addition,

quercetin inhibited Hsp70 in U937 human monoblastic leukemia cell line [87]. Quercetin inhibited hypoxia-induced AMPK by dramatically inducing apoptosis in hypoxia and reducing the activity of HIF-1 in HCT116 cancer cells [88]. Quercetin dose-dependently increased glutathione, glutamylcysteine synthetase (GSH), GPx, GR, and GST expression in liver HepG2 cells through p38/MAPK and Nrf-2 activation [89]. Quercetin protected against toxicity and inflammation by increasing Nrf-2 expression and decreasing NF-kB and cyclooxygenase (Cox)-2 expression in a time-dependent manner in mycotoxin ochratoxin A-induced liver HepG2 cells [90]. Furthermore, dose-dependently, through p62 and Nrf2-ARE activation, quercetin increased HO-1, GCLC, and GCLM subunit expression and showed a protective effect against hepatotoxicity [91]. Quercetin, depending on the dose, inhibited the production of LPS-induced NO production in BV2 microglial cells, suppressed the NF-κB pathway, and activated the Nrf2-dependent HO-1 pathway [92, 93]. Quercetin showed a protective effect against indomethacin-induced gastrointestinal oxidative stress and inflammation through Nrf-2 activation and NF-kB inhibition in human intestinal Caco-2 cells [94]. In malignant mesothelioma MSTO-211H and H2452 cells, quercetin also inhibited cell growth and showed cytoprotective effect with Nrf-2 activation [95]. In a study on porcine renal proximal tubule cell line LLC-PK1 cells and C57BL/6j mice, quercetin inhibited renal ischemia/reperfusion injury by increasing AMP phosphorylase, inhibiting mTOR phosphorylation, and activating autophagy [96]. A combination of quercetin, resveratrol, and catechin was administered to human metastatic cancer cell lines MDA-MB-231 and MDA-MB-435; quercetin was shown to be the most effective compound for Akt/mTOR inhibition and can prevent breast cancer growth and metastasis [97]. Quercetin inhibited mTOR by expressing SESTIN 2, p53, and activating AMPK in a dose-dependent manner and induced apoptosis via increased intracellular ROS in HCT116 colon cancer cells [98]. The mTOR complex has an important role in cell growth, protein synthesis, and autophagy, with the inhibition of quercetin mTOR/PI3K/Akt in cancer and other diseases where excessive mTOR complex activity is observed [99]. In addition, quercetin, by affecting autophagy with the inhibition of proteasome and mTOR activity, can be both protective and therapeutic against cancer with the death of human breast cancer cell lines MCF7 and MDA-MB-453, the cervical adenocarcinoma cell line HeLa, the ovarian cancer cell line OVCAR3, and the human B-lymphoblastoid cell line IM-9 [100]. Quercetin inhibited tumor growth and angiogenesis by inhibiting VEGF regulated by AKT/mTOR in HUVECs [101]. As a result, quercetin may exert a protective effect against cancer, especially by acting on stress-response pathways.

2.7. Sulforaphane

Sulforaphane (SulR-1-isothiocyanato-4-methylsulfinyl butane) is an isothiocyanate found extensively in cruciferous vegetables. Studies have shown that sulforaphane has a protective effect against cancer, diabetes, cardiovascular diseases, neurodegenerative diseases, and kidney diseases, and is mostly influenced by an Nrf-2-mediated antioxidant response [102, 103]. Sulforaphane may prevent diabetic auric damage and cardiomyopathy by increasing Nrf2 activation in mice [104, 105]. Sulforaphane showed protective effect against ethanol-induced oxidative stresses and apoptosis in neural crest cells by generating an antioxidant response with Nrf2 activation [106]. Sulforaphane activates the Nrf2/ARE pathway and inhibits 3-nitropropionic acid-induced toxicity in striatal cells by inhibiting MAPKs and NF-κB pathways [107]. In MSTO-211H

cells administered with sulforaphane, Nrf2-mediated HO-1 expression was regulated by the PI3K/Akt pathway [108]. Sulforaphane inhibited muscle inflammation by inhibiting Nrf-2 and NF-kB in dystrophin-deficient mdx mice [109]. Sulforaphane showed a protective effect against acute alcohol-induced liver steatosis by activation of Nrf2 and synthesis of antioxidant proteins in HepG2 E47 liver cells [110]. Sulforaphane increased Nrf2 expression in TRAMP C1 prostate cancer cells and affected epigenetic regulation [111]. Sulforaphane induced autophagy through ERK activation in immortalized mouse CN1.4 cortical and human SHSY5Y neuronal cells [112]. Huntington's disease, a neurodegenerative disease, involves damage to the ubiquitin proteasome system. In a mouse study, sulfate inhibited proteasomal and autophagic activation and cytotoxicity resulting from proteasomal impairment [113]. Sulforaphane inhibited HIF-1α expression in HCT116 human colon cancer cells and AGS human gastric cancer cells, but inhibited hypoxia-induced VEGF expression only in HCT116 cells [114]. Sulforaphane affects the stress-response pathways and can show protective effects, especially against neurodegeneration and cancer.

3. Conclusion

Dietary phytochemicals can exert a protective effect against cancer, neurodegenerative diseases, cardiovascular diseases, inflammatory and immune diseases by acting on multiple stress-response pathways. Therefore, healthy aging and longevity can be achieved by preventing the deterioration of hemodynamics. In addition, it is necessary to emphasize that the hormetic stress pathways of each dietary phytochemical is a very wide ranging subject. Therefore, the mechanisms of action of important phytochemicals and stress response pathways in this chapter have been summarized in the light of data obtained in recent years; this may lead to a broader outlook on this subject and to new studies.

Abbreviations

AhR:	aryl hydrocarbon receptor
ARE:	antioxidant response element
BMMs:	bone marrow-derived macrophages
Cox-2:	cyclooxygenase-2
cPLA2:	cytosolic phospholipase A2
DNA:	deoxyribonucleic acid
EGCG:	epigallocatechin gallate
ERK:	extracellular signal-regulated kinase
GCLC:	glutamate cysteine ligase catalytic
GCLM:	glutamate cysteine ligase modifier

GPx: glutathione peroxidase

GST: glutathione-S-transferase

HDAC: histone deacetylase

HO-1: hemeoxygenase-1

HRMECs: human retinal microvascular endothelial cells

HSP: heat shock protein

HIF-1: hypoxia-inducible factor-1

HUVECs: human umbilical vein endothelial

IGF-1: insulin-like growth factor

iNOS: inducible nitric oxide synthase

JKN: c-Jun N-terminal kinase

LPS: lipopolysaccharide

MAPK: mitogen-activated protein kinase

mTOR: mammalian target of rapamycin

NFκB: nuclear factor kappa B

NO: nitric oxide

Nrf2: nuclear factor-erythroid 2-related factor 2

NQO1: NAD(P)H:quinine oxidoreductase

PBMCs: human peripheral blood mononuclear cells

PKC: protein kinase C

SOD: superoxide dismutase

TNF-α: tumor necrosis factor-α

UVB: ultraviolet B

VEGF: vascular endothelial growth factor

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References

[1] Mattson MP. Hormesis defined. Ageing Research Reviews. 2008;**7**(1):1-7. DOI: 10.1016/j.arr.2007.08.007

[2] Mattson MP, Calabrese EJ. Hormesis: What it is and why it matters? In: Mattson MP, Calabrese EJ, editors. Hormesis a Revolution in Biology, Toxicology and Medicine. 1st ed. New York: Humana Press; 2010. pp. 1-13. DOI: 10.1007/978-1-60761-495-1_1

[3] Rattan SIS. Biogerontology: From here to where? The Lord Cohen medal Lecture-2011. Biogerontology. 2012;**13**(1):83-91. DOI: 10.1007/s10522-011-9354-3

[4] Rattan SIS. Rationale and methods of discovering hormetins as drugs for healthy ageing. Expert Opinion on Drug Discovery. 2012;**7**(5):439-448. DOI: 10.1517/17460441.2012.677430

[5] Rattan SIS. Hormesis in ageing. Ageing Research Reviews. 2008;**7**(1):63-78. DOI: 10.1016/j.arr.2007.03.002

[6] Son TG, Camandola S, Mattson MP. Hormetic dietary phytochemicals. NeuroMolecular Medicine. 2008;**10**(4):236-246. DOI: 10.1007/s12017-008-8037-y

[7] Demirovic D, Rattan SIS. Establishing cellular stress response profiles as biomarkers of homeodynamics, health and hormesis. Experimental Gerontology. 2013;**48**(1):98-98. DOI: 10.1016/j.exger.2012.02.005

[8] Somani SJ, Modi KP, Majumdar AS, Sadarani BN. Phytochemicals and their potential usefulness in inflammatory bowel disease. Phytotherapy Research. 2015;**29**(3):339-350. DOI: 10.1002/ptr.5271

[9] Doughari JH. Phytochemicals: Extraction methods, basic structures and mode of action as potential chemotherapeutic agents, phytochemicals. In: Rao V, editor. A Global Perspective of Their Role in Nutrition and Health. 1st ed. Rijeka: InTech; 2012. pp. 1-32. DOI: 10.5772/26052

[10] Hayes DP. Nutritional hormesis. European Journal of Clinical Nutrition. 2007;**61**:147-159. DOI: 10.1038/sj.ejcn.1602507

[11] Mattson MP. Dietary factors, hormesis and health. Ageing Research Reviews. 2008;**7**(1):43-48. DOI: 10.1016/j.arr.2007.08.004

[12] Lee J, Jo DG, Park D, Chung HY, Mattson MP. Adaptive cellular stress pathways as therapeutic targets of dietary phytochemicals: Focus on the nervous system. Pharmacological Reviews. 2014;**66**(3):815-868. DOI: 10.1124/pr.113.007757

[13] Demirovic D, Rattan SIS. Curcumin induces stress response and hormetically modulates wound healing ability of human skin fibroblasts undergoing ageing in vitro. Biogerontology. 2011;**12**(5):437-444. DOI: 10.1007/s10522-011-9326-7

[14] Evans CG, Chang L, Gestwicki JE. Heat shock protein 70 (Hsp70) as an emerging drug target. Journal of Medicinal Chemistry. 2010;**53**:4585-4602. DOI: 10.1021/jm100054f

[15] Gupta SC, Sharma A, Mishra M, Mishra MK, Chowdhuri DK. Heat shock proteins in toxicology: How close and how far? Life Sciences. 2010;**86**:377-384. DOI: 10.1016/j.lfs.2009.12.015

[16] Hong DS, Banerji U, Tavana B, George GC, Aaron J, Kurzrock R. Targeting the molecular chaperone heat shock protein 90 (HSP90): Lessons learned and future directions. Cancer Treatment Reviews. 2013;**39**:375-387. DOI: 10.1016/j.ctrv.2012.10.001

[17] Mymrikov EV, Seit-Nebi AS, Gusev NB. Large potentials of small heat shock proteins. Physiological Reviews. 2011;**91**:1123-1159. DOI: 10.1152/physrev.00023.2010

[18] Jego G, Hazoume A, Seigneuric R, Garrido C. Targeting heat shock proteins in cancer. Cancer Letters. 2013;**332**(2):275-285. DOI: 10.1016/j.canlet.2010.10.014

[19] Hine CM, Mitchell JR. NRF2 and the phase II response in acute stress resistance induced by dietary restriction. Journal of Clinical and Experimental Pathology. 2012;**Suppl 4**(4):7329-7362. DOI: 10.4172/2161-0681.S4-004

[20] Jung KA, Kwak MK. The Nrf2 system as a potential target for the development of indirect antioxidants. Molecules. 2010;**15**(10):7266-7291. DOI: 10.3390/molecules15107266

[21] Kaspar JW, Niture SK, Jaiswal AK. Nrf2:INrf2(Keap1) signaling in oxidative stress. Free Radical Biology & Medicine. 2009;**47**(9):1304-1309. DOI: 10.1016/j.freeradbiomed.2009.07.035

[22] Zhang DD. Mechanistic studies of the Nrf2-Keap1 signaling pathway. Drug Metabolism Reviews. 2006;**38**(4):769-789. DOI: 10.1080/03602530600971974

[23] Birringer M. Hormetics: Dietary triggers of an adaptive stress response. Pharmaceutical Research. 2011;**28**:2680-2694. DOI: 10.1007/s11095-011-0551-1

[24] Kumar H, Kim IS, More SV, Kim BW, Choi DK. Natural product-derived pharmacological modulators of Nrf2/ARE pathway for chronic diseases. Natural Prodcut Reports. 2014;**31**(1):109-139. DOI: 10.1039/c3np70065h

[25] Madeo F, Tavernarakis N, Kroemer G. Can autophagy promote longevity? Nature Cell Biology. 2010;**12**(9):842-846. DOI: 10.1038/ncb0910-842

[26] Xia Y, Choi HK, Lee K. Recent advances in hypoxia-inducible factor (HIF)-1 inhibitors. European Journal of Medicinal Chemistry. 2012;**49**:24-40. DOI: 10.1016/j.ejmech.2012.01.033

[27] Barone E, Calabrese V, Mancuso C. Ferulic acid and its therapeutic potential as a hormetin for age related diseases. Biogerontology. 2009;**10**:97-108. DOI: 10.1007/s10522-008-9160-8

[28] Mancuso C, Santangelo R. Ferulic acid: Pharmacological and toxicological aspects. Food and Chemical Toxicology. 2014;**65**:185-195. DOI: 10.1016/j.fct.2013.12.024

[29] Ghosh S, Basak P, Dutta S, Chowdhury S, Sil PC. New insights into the ameliorative effects of ferulic acid in pathophysiological conditions. Food and Chemical Toxicology. 2017;**103**:41-55. DOI: 10.1016/j.fct.2017.02.028

[30] He S, Liu F, Xu L, Yin P, Li D, Mei C, Jiang L, Ma Y, Xu J. Protective effects of ferulic acid against heat stress-induced intestinal epithelial barrier dysfunction in vitro and in vivo. PLoS One. 2016;**11**(2):e0145236. DOI: 10.1371/journal.pone.0145236

[31] Catino S, Paciello F, Micell F, Rolesi R, Troiani D, Calabrese V, Santangelo R, Mancuso C. Ferulic acid regulates the Nrf2/Heme oxygenase-1 system and counteracts trimethyltin-induced neuronal damage in the human neuroblastoma cell line SH-SY5Y. Frontiers in Pharmacology. 2016;**6**(305):1-12. DOI: 10.3389/fphar.2015.00305

[32] Yu CL, Zhao XM, Niu YC. Ferulic acid protects against lead acetate-induced inhibition of neurite outgrowth by upregulating HO-1 in PC12 cells: Involvement of ERK1/2-Nrf2 pathway. Molecular Neurobiology. 2016;**53**(9):6589-6500. DOI: 10.1007/s12035-015-9555-x

[33] Kikugawa M, Ida T, Ihara H, Sakamoto T. Ferulic acid and its water-soluble derivatives inhibit nitric oxide production and inducible nitric oxide synthase expression in rat primary astrocytes. Bioscience, Biotechnology, and Biochemistry. 2017;**81**(8):1607-1611. DOI: 10.1080/09168451.2017.1336925

[34] Zhao J, Suyama A, Chung H, Fukuda T, Tanaka M, Matsui T. Ferulic acid enhances nitric oxide production through up-regulation of argininosuccinate synthase in inflammatory human endothelial cells. Life Sciences. 2016;**145**:224-232. DOI: 10.1016/j.lfs.2015.12.044

[35] Liao Z, He H, Zeng G, Liu D, Tang L, Yin D, Chen D, He M. Delayed protection of ferulic acid in isolated hearts and cardiomyocytes: Upregulation of heat-shock protein 70 via NO-ERK1/2 pathway. Journal of Functional Foods. 2017;**34**:18-27. DOI: 10.1016/j.jff.2017.04.012

[36] Bian Z, Furuya N, Zheng DM, Trejo JAO, Tada N, Ezaki J, Ueno T. Ferulic acid induces mammalian target of rapamycin inactivation in cultured mammalian cells. Biological & Pharmaceutical Bulletin. 2013;**36**(1):120-124. DOI: 10.1248/bpb.b12-00695

[37] Pulido-Moran M, Moreno-Fernandez J, Ramirez-Tortosa C, Ramires-Tortosa MC. Curcumin and health. Molecules. 2016;**21**(3):264-286. DOI: 10.3390/molecules21030264

[38] Salem M, Rohani S, Gillies ER. Curcumin, a promising anti-cancer therapeutic: A review of its chemical properties, bioactivity and approaches to cancer cell delivery. RSC Advances. 2014;**4**:10815-10829. DOI: 10.1039/c3ra46396f

[39] Sarkar R, Mukherjee S, Biswas J. Curcumin augments the efficiency of antitumor drugs used in leukemia by modulation of heat shock proteins via HDAC6. Journal of Enviromental Patology, Toxicology and Oncology. 2014;**33**(3):247-263. DOI: 10.1615/JEnvironPatholToxicolOncol.2014010913

[40] Xia C, Cai Y, Li S, Yang J, Xiao G. Curcumin increases HSP70 expression in primary rat cortical neuronal apoptosis induced by gp120 V3 loop peptide. Neurochemical Research. 2015;**40**:1996-2005. DOI: 10.1007/s11064-015-1695-x

[41] Ahmed T, Banerjee BD. HSP27 modulates survival signaling in endosulfan-exposed human peripheral blood mononuclear cells treated with curcumin. Human & Experimental Toxicology. 2016;**35**(7):695-704. DOI: 10.1177/0960327115597986

[42] Gounden S, Chuturgoon A. Curcumin upregulates antioxidant defense, lon protease, and heat-shock protein 70 under hyperglycemic conditions in human hepatoma cells. Journal of Medicinal Food. 2017;**20**(5):465-473. DOI: 10.1089/jmf.2016.0146

[43] González-Reyes S, Guzmán-Beltrán S, Medina-Campos ON, Pedraza-Chaverri J. Curcumin pretreatment induces Nrf2 and an antioxidant response and prevents hemin-induced toxicity in primary cultures of cerebellar granule neurons of rats. Oxidative Medicine and Cellular Longevity. 2013;**2013**:801418. DOI: 10.1155/2013/801418

[44] Das V, Vinayak M. Long term effect of curcumin in restoration of tumour suppressor p53 and phase-II antioxidant enzymes via activation of Nrf2 signalling and modulation of inflammation in prevention of cancer. PLoS One. 2015;**10**(4):e0124000. DOI: 10.1371/journal.pone.0124000

[45] Ding F, Li F, Li Y, Hou X, Ma Y, Zhang N, Ma J, Zhang R, Lang B, Wang H, Wang Y. HSP60 mediates the neuroprotective effects of curcumin by suppressing microglial activation. Experimental and Therapeutic Medicine. 2016;**12**:823-828. DOI: 10.3892/etm.2016.3413

[46] Smoliga JM, Baur JA, Hausenblas HA. Resveratrol and health—A comprehensive review of human clinical trials. Molecular Nutrition & Food Research. 2011;**55**:1129-1141. DOI: 10.1002/mnfr.201100143

[47] Curro M, Trovato-Salinaro A, Gugliandolo A, Koverech G, Lodato F, Caccamo D, Calabrese V, Ientile R. Resveratrol protects against homocysteine-induced cell damage via cell stress response in neuroblastoma cells. Journal of Neuroscience Research. 2015;**93**:149-156. DOI: 10.1002/jnr.23453

[48] Han S, Choi JR, Shin KS, Kang SJ. Resveratrol upregulated heat shock proteins and extended the surviva lof G93A-SOD1 mice. Brain Research. 2012;**1483**:112-117. DOI: 10.1016/j.brainres.2012.09.022

[49] Soueur J, Eilstein J, Léreaux G, Jones C, Marrot L. Skin resistance to oxidative stress induced by resveratrol: From Nrf2 activation to GSH biosynthesis. Free Radical Biology & Medicine. 2015;**78**:213-223. DOI: 10.1016/j.freeradbiomed.2014.10.510

[50] Lin TK, Chen SD, Chuang YC, Lin HY, Huang CR, Chuang JH, Wang PW, Huang ST, Tiao MM, Chen JB, Liou CW. Resveratrol partially prevents rotenone-induced neurotoxicity in dopaminergic SH-SY5Y cells through induction of heme oxygenase-1 dependent autophagy. International Journal of Molecular Sciences. 2014;**15**:1625-1646. DOI: 10.3390/ijms15011625

[51] Cullberg KB, Olholm J, Paulsen SK, Foldager CB, Lind M, Richelsen B, Pedersen SB. Resveratrol has inhibitory effects on the hypoxia-induced inflammation and angiogenesis in human adipose tissue in vitro. European Journal of Pharmaceutical Sciences. 2013;**49**:251-257. DOI: 10.1016/j.ejps.2013.02.014

[52] Park D, Jeong H, Lee NM, Koh A, Kwon O, Yang YR, Noh J, Suh PG, Park H, Ryu SH. Resveratrol induces autophagy by directly inhibiting mTOR through ATP competition. Scientific Reports. 2016;**6**:21772. DOI: 10.1038/srep21772

[53] Selvaraj S, Sun Y, Sukumaran P, Singh BB. Resveratrol activates autophagic cell death in prostate cancer cells via downregulation of STIM1 and the mTOR pathway. Molecular Carcinogenesis. 2016;**55**:818-831. DOI: 10.1002/mc.22324

[54] Capiralla H, Vingtdeux V, Zhao H, Sankowski R, Al-Abed Y, Davies P, Marambaud P. Resveratrol mitigates lipopolysaccharide- and Aβ-mediated microglial inflammation by inhibiting the TLR4/NF-κB/STAT signaling cascade. Journal of Neurochemistry. 2012;**120**:461-472. DOI: 10.1111/j.1471-4159.2011.07594.x

[55] Ma C, Wang Y, Dong L, Li M, Cai W. Anti-inflammatory effect of resveratrol through the suppression of NF-κB and JAK/STAT signaling pathways. Acta Biochimica et Biophysica Sinica. 2015;**47**(3):207-213. DOI: 10.1093/abbs/gmu135

[56] Braicu C, Ladomery MR, Chedea VS, Irimie A, Berindan-Neagoe I. The relationship between the structure and biological actions of green tea catechins. Food Chemistry. 2013;**141**(3):3282-3289. DOI: 10.1016/j.foodchem.2013.05.122

[57] Legeay S, Rodier M, Fillon L, Faure S, Clere N. Epigallocatechin gallate: A review of its beneficial properties to prevent metabolic syndrome. Nutrients. 2015;**7**:5443-5468. DOI: 10.3390/nu7075230

[58] Moses MA, Henry EC, Ricke WA, Gasiewicz TA. The heat shock protein 90 inhibitor, (−)-epigallocatechin gallate, has anticancer activity in a novel human prostate cancer progression model. Cancer Prevention Research. 2015;**8**(3):249-257. DOI: 10.1158/1940-6207.CAPR-14-0224

[59] Han SG, Han SS, Toborek M, Hennig B. EGCG protects endothelial cells against PCB 126-induced inflammation through inhibition of AhR and induction of Nrf2-regulated genes. Toxicology and Applied Pharmacology. 2012;**261**:181-188. DOI: 10.1016/j.taap.2012.03.024

[60] Pullikotil B, Chen H, Muniyappa R, Greenberg CC, Yang S, Reiter CEN, Lee JW, Chung JH, Quon MJ. Epigallocatechin gallate induces expression of heme oxygenase-1 in endothelial cells via p38 MAPK and Nrf-2 that suppresses pro-inflammatory actions of TNF-α. The Journal of Nutritional Biochemistry. 2012;**23**(9):1134-1145. DOI: 10.1016/j.jnutbio.2011.06.007

[61] Zheng Y, Morris A, Sunkara M, Layne J, Toborek M, Hennig B. Epigallocatechin gallate stimulates NF-E2-related factor and heme oxygenase-1 via calveolin-1 displacement. The Journal of Nutritional Biochemistry. 2012;**23**:163-168. DOI: 10.1016/j.jnutbio.2010.12.002

[62] Han J, Wang M, Jing X, Shi H, Ren M, Lou H. (−)-Epigallocatechin gallate protects against cerebral ischemia-induced oxidative stress via Nrf2/ARE signaling. Neurochemical Research. 2014;**39**(7):1292-1299. DOI: 10.1007/s11064-014-1311-5

[63] Wang D, Wang Y, Wan X, Yang CS, Zhang J. Green tea polyphenol (−)-epigallocatechin-3-gallate triggered hepatotoxicity inmice: Responses ofmajor antioxidant enzymes and the Nrf2 rescue pathway. Toxicology and Applied Pharmacology. 2015;**283**:65-74. DOI: 10.1016/j.taap.2014.12.018

[64] Yang GZ, Wang ZJ, Bai F, Qin XJ, Cao J, Lv JY, Zhang MS. Epigallocatechin-3-gallate protects HUVECs from PM2.5-induced oxidative stress injury by activating critical antioxidant pathways. Molecules. 2015;**20**:6626-6639. DOI: 10.3390/molecules20046626

[65] Yang J, Han Y, Chen C, Sun H, He D, Guo J, Jiang B, Zhou L, Zeng C. EGCG attenuates high glucose-induced endothelial cell inflammation by suppression of PKC and NF-κB signaling in human umbilical vein endothelial cells. Life Sciences. 2013;**92**:589-597. DOI: 10.1016/j.lfs.2013.01.025

[66] Cai Y, Yu SS, Chen TT, Gao S, Geng B, Yu Y, Ye JT, Liu PQ. EGCG inhibits CTGF expression via blocking NF-κB activation in cardiac fibroblast. Phytomedicine. 2013;**20**:106-113. DOI: 10.1016/j.phymed.2012.10.002

[67] Joo SY, Song Y, Park YL, Myung E, Chung CY, Park KJ, Cho SB, Lee WS, Kim HS, Rew JS, Kim NS, Joo YE. Epigallocatechin-3-gallate inhibits LPS-induced NF-κB and MAPK signaling pathways in bone marrow-derived macrophages. Gut and Liver. 2012;**6**(2):188-196. DOI: 10.5009/gnl.2012.6.2.188

[68] He L, Zhang E, Shi J, Li X, Zhou K, Zhang Q, Lee AD, Tang X. (2)-Epigallocatechin-3-gallate inhibits human papillomavirus (HPV)-16 oncoprotein-induced angiogenesis in non-small cell lung cancer cells by targeting HIF-1a. Cancer Chemotherapy and Pharmacology. 2013;**71**:713-725. DOI: 10.1007/s00280-012-2063-z

[69] Li X, Feng Y, Liu J, Feng X, Zhou K, Tang X. Epigallocatechin-3-gallate inhibits IGF-1-stimulated lung cancer angiogenesis through downregulation of HIF-1α and VEGF expression. Journal of Nutrigenetica and Nutrigenomics. 2013;**6**:169-178. DOI: 10.1159/000354402

[70] Kim HS, Montana V, Jang HJ, Parpura V, Kim J. Epigallocatechin gallate (EGCG) stimulates autophagy in vascular endothelial cells. The Journal of Biological Chemistry. 2013;**288**(31):22693-22705. DOI: 10.1074/jbc.M113.477505

[71] Li CP, Yao J, Tao ZF, Li XM, Jiang Q, Yan B. Epigallocatechin gallate (EGCG) regulates autophagy in human retinal pigment epithelial cells: A potential role for reducing UVB light-induced retinal damage. Biochemical and Biophysical Research Communications. 2013;**438**:739-745. DOI: 10.1016/j.bbrc.2013.07.097

[72] Nabavi SF, Braidy N, Gortzi O, Sobarzo-Sanchez E, Daglia M, Skalicka-Wozniak K, Nabavi SM. Luteolin as an anti-inflammatory and neuroprotective agent: A brief review. Brain Research Bulletin. 2015;**119**(Pt A):1-11. DOI: 10.1016/j.brainresbull.2015.09.002

[73] Chen D, Bi A, Dong X, Jiang Y, Rui B, Lıı J, Yin Z, Luo L. Luteolin exhibits anti-inflammatory effects by blocking the activity of heat shock protein 90 in macrophages. Biochemical and Biophysical Research Communications. 2014;**443**:326-332. DOI: 10.1016/j.bbrc.2013.11.122

[74] Jia Z, Nallasamy P, Liu D, Shah H, Li JZ, Rojin C, Si H, McCormickJ ZH, Zhen W, Li Y. Luteolin protects against vascular inflammation in mice and TNF-alpha-induced monocyte

adhesion to endothelial cells via suppressing IKBα/NF-κB signaling pathway. Journal of Nutritional Biohemistry. 2015;**26**(3):293-302. DOI: 10.1016/j.jnutbio.2014.11.008

[75] Weng Z, Patel AB, Vasiadi M, Therianou A, Theoharides TC. Luteolin inhibits human keratinocyte activation and decreases NF-kB induction that is increased in psoriatic skin. PLoS One. 2014;**9**(2):e90739. DOI: 10.1371/journal.pone.0090739

[76] Song YS, Park CM. Luteolin and luteolin-7-O-glucoside strengthen antioxidative. Food and Chemical Toxicology. 2013;**65**:70-75. DOI: 10.1016/j.fct.2013.12.017

[77] Xu J, Wang H, Ding K, Zhang L, Wang C, Li T, Wei W, Lu X. Luteolin provides neuroprotection in models of traumatic brain injury via the Nrf2–ARE pathway. Free Radical Biology & Medicine. 2014;**71**:186-195. DOI: 10.1016/j.freeradbiomed.2014.03.009

[78] Huang CS, Lii CK, Lin AH, Yeh YW, Yao HT, Li CC, Wang TS, Chen HW. Protection by chrysin, apigenin, and luteolin against oxidative stress is mediated by the Nrf2-dependent up-regulation of heme oxygenase 1 and glutamate cysteine ligase in rat primary hepatocytes. Archives of Toxicology. 2013;**87**:167-178. DOI: 10.1007/s00204-012-0913-4

[79] Zhang T, Kimura Y, Jiang S, Harada K, Yamashita Y, Ashida H. Luteolin modulates expression of drug-metabolizing enzymes through the AhR and Nrf2 pathways in hepatic cells. Archives of Biochemistry and Biophysics. 2014;**557**:36-46. DOI: 10.1016/j.abb.2014.05.023

[80] Paredes-Gonzalez X, Fuentes F, Jeffery S, Saw CLL, Shu L, ZY S, Kong ANT. Induction of NRF2-mediated gene expression by dietary phytochemical flavones apigenin and luteolin. Biopharmaceutics & Drug Disposition. 2015;**36**:440-451. DOI: 10.1002/bdd.1956

[81] Yang D, Tan X, Lv Z, Liu B, Baiyun B, Lu J, Zhang Z. Regulation of SIRT1/Nrf2/TNF-α signaling pathway by luteolin is critical to attenuate acute mercuric chloride exposure induced hepatotoxicity. Scientific Reports. 2016;**6**:37157. DOI: 10.1038/srep37157

[82] Park SW, Cho CS, Jun HO, Ryu NH, Kim JH, YS Y, Kim JS, Kim JH. Anti-angiogenic effect of luteolin on retinal neovascularization via blockade of reactive oxygen species production. Investigative Ophthalmology & Visual Science. 2012;**53**:7718-7726. DOI: 10.1167/iovs.11-8790

[83] Wu PS, Yen JH, Kou MC, Wu MJ. Luteolin and apigenin attenuate 4-hydroxy-2-nonenal-mediated cell death through modulation of UPR, Nrf2-ARE and MAPK pathways in PC12 cells. PLoS One. 2015;**10**(6):e0130599. DOI: 10.1371/journal.pone.0130599

[84] Russo M, Spagnuolo C, Tedesco I, Bilotto S, Russo GL. The flavonoid quercetin in disease prevention and therapy: Facts and fancies. Biochemical Pharmacology. 2012;**83**:6-15. DOI: 10.1016/j.bcp.2011.08.010

[85] Lee SH, Lee EJ, Min KH, Hur GY, Lee SH, Lee SY, Kim JH, Shin C, Shim JJ, In KH, Kang KH, Lee SY. Quercetin enhances chemosensitivity to gemcitabine in lung cancer cells by inhibiting heat shock protein 70 expression. Clinical Lung Cancer. 2015;**16**(6):e235-e243. DOI: 10.1016/j.cllc.2015.05.006

[86] Li J, Tang C, Li L, Li R, Fan Y. Quercetin blocks t-AUCB-induced autophagy by Hsp27 and Atg7 inhibition in glioblastoma cells in vitro. Journal of Neuro-Oncology. 2016;**129**(1):39-45. DOI: 10.1007/s11060-016-2149-2

[87] Storniolo A, Raciti M, Cucina A, Bizzarri M, Di Renzo L. Quercetin affects Hsp70/IRE1α mediated protection from death induced by endoplasmic reticulum stress. Oxidative Medicine and Cellular Longevity. 2015;**2015**:645157. DOI: 10.1155/2015/645157

[88] Kim HS, Wannatung T, Lee S, Yang WK, Chung SH, Lim JS, Choe W, Kang I, Kim SS, Ha J. Quercetin enhances hypoxia-mediated apoptosis via direct inhibition of AMPK activity in HCT116 colon cancer. Apoptosis. 2012;**17**:938-949. DOI: 10.1007/s10495-012-0719-0

[89] Granado-Serrano AB, Martín MA, Bravo L, Goya L, Ramos S. Quercetin modulates Nrf2 and glutathione-related defenses in HepG2 cells: Involvement of p38. Chemico-Biological Interactions. 2012;**195**:154-164. DOI: 10.1016/j.cbi.2011.12.005

[90] Ramyaa P, Krishnaswamy R, Padma PP. Quercetin modulates OTA-induced oxidative stress and redox signalling in HepG2 cells—Up regulation of Nrf2 expression and down regulation of NF-κB and COX-2. Biochimica et Biophysica Acta. 2014;**1840**:681-692. DOI: 10.1016/j.bbagen.2013.10.024

[91] Ji LL, Sheng YC, Zheng ZY, Shi L, Wang ZT. The involvement of p62–Keap1–Nrf2 antioxidative signaling pathway and JNK in the protection of natural flavonoid quercetin against hepatotoxicity. Free Radical Biology & Medicine. 2015;**85**:12-23. DOI: 10.1016/j.freeradbiomed.2015.03.035

[92] Kang CH, Choi YH, Moon SK, Kim WJ, Ki GY. Quercetin inhibits lipopolysaccharide-induced nitric oxide production in BV2 microglial cells by suppressing the NF-κBpathway andactivating the Nrf2-dependent HO-1 pathway. International Immunopharmacology. 2013;**17**:808-813. DOI: 10.1016/j.intimp.2013.09.009

[93] Sun GY, Chen Z, Jasmer KJ, Chuang DY, Gu Z, Hannink M, Simonyi A. Quercetin attenuates inflammatory responses in BV-2 microglial cells: Role of MAPKs on the Nrf2 pathway and induction of heme oxygenase-1. PLoS One. 2015;**10**(10):e0141509. DOI: 10.1371/journal.pone.0141509

[94] Carrasco-Pozo C, Castillo RL, Beltrán C, Miranda A, Fuentes J, Gotteland M. Molecular mechanisms of gastrointestinal protection by quercetin against indomethacin-induced damage: Role of NF-κB and Nrf2. The Journal of Nutritional Biochemistry. 2016;**27**:289-298. DOI: 10.1016/j.jnutbio.2015.09.016

[95] Lee YJ, Lee DM, Lee SH. Nrf2 expression and apoptosis in quercetin-treated malignant mesothelioma cells. Molecules and Cells. 2015;**38**(5):416-425. DOI: 10.14348/molcells.2015.2268

[96] Chen BL, Wang LT, Huang KH, Wang CC, Chiang CK, Liu SH. Quercetin attenuates renal ischemia/reperfusion injury via an activation of AMP-activated protein kinase-regulated autophagy pathway. The Journal of Nutritional Biochemistry. 2014;**25**:1226-1234. DOI: 10.1016/j.jnutbio.2014.05.013

[97] Rivera AR, Castillo-Pichardo L, Gerena Y, Dharmawardhane S. Anti-breast cancer potential of quercetin via the Akt/AMPK/mammalian target of rapamycin (mTOR) signaling cascade. PLoS One. 2016;**11**(6):e0157251. DOI: 10.1371/journal.pone.0157251

[98] Kim GT, Lee SH, Kim YM. Quercetin regulates sestrin 2-AMPK-mTOR signaling pathway and induces apoptosis via increased intracellular ROS in HCT116 colon cancer cells. Journal of Cancer Prevention. 2013;**18**(3):264-270. DOI: 10.15430/JCP.2013.18.3.264

[99] Bruning A. Inhibition of mTOR signaling by quercetin in cancer treatment and prevention. Anti-Cancer Agents in Medical Chemistry. 2013;**13**(7):1025-1031

[100] Klappan AK, Hones S, Mylonas I, Bruning A. Proteasome inhibition by quercetin triggers macroautophagy and blocks mTOR activity. Histochemistry and Cell Biology. 2012;**137**:25-36. DOI: 10.1007/s00418-011-0869-0

[101] Pratheeshkumar P, Budhraja A, Son YO, Wang X, Zhang Z, Ding S, Wang L, Hitron A, Lee JC, Xu M, Chen G, Luo J, Shi X. Quercetin inhibits angiogenesis mediated human prostate tumor growth by targeting VEGFR- 2 regulated AKT/mTOR/P70S6K signaling pathways. PLoS One. 2012;**7**(10):e47516. DOI: 10.1371/journal.pone.0047516

[102] Elbarbry F, Elrody N. Potential health benefits of sulforaphane: A review of the experimental, clinical and epidemiological evidences and underlying mechanisms. Journal of Medicinal Plant Research. 2011;**5**(4):473-484

[103] Dinkova-Kostova AT, Kostov RV. Glucosinolates and isothiocyanates in health and disease. Trends in Molecular Medicine. 2012;**18**(6):337-347. DOI: 10.1016/j.molmed.2012.04.003

[104] Miao X, Bai Y, Sun W, Cui W, Xin Y, Wang Y, Tan Y, Miao L, Fu Y, Su G, Cai L. Sulforaphane prevention of diabetes-induced aortic damage was associated with the up-regulation of Nrf2 and its down-stream antioxidants. Nutrition and Metabolism. 2012;**9**(84):1-9. DOI: 10.1186/1743-7075-9-84

[105] Bai Y, Cui W, Xin Y, Miao X, Barati MT, Zhang C, Chen Q, Tan Y, Cui T, Zheng Y, Cai L. Prevention by sulforaphane of diabetic cardiomyopathy is associated with up-regulation of Nrf2 expression and transcription activation. Journal of Molecular and Cellular Cardiology. 2013;**57**:82-95. DOI: 10.1016/j.yjmcc.2013.01.008

[106] Chen X, Liu J, Chen SY. Sulforaphane protects against ethanol-induced oxidative stress and apoptosis in neural crest cells by the induction of Nrf2-mediated antioxidant response. British Journal of Pharmacology. 2013;**169**:437-448. DOI: 10.1111/bph.12133

[107] Jang M, Cho IH. Sulforaphane ameliorates 3-nitropropionic acid-induced striatal toxicity by activating the Keap1-Nrf2-ARE pathway and inhibiting the MAPKs and NF-κB pathways. Molecular Neurobiology. 2016;**53**:2619-2635. DOI: 10.1007/s12035-015-9230-2

[108] Lee YJ, Jeong HY, Kim YB, Lee YJ, Won SY, Shim JH, Cho MK, Nam HS, Lee SH. Reactive oxygen species and PI3K/Akt signaling play key roles in the induction of Nrf2-driven heme oxygenase-1 expression in sulforaphane-treated human mesothelioma MSTO-211H cells. Food and Chemical Toxicology. 2012;**50**:116-123. DOI: 10.1016/j.fct.2011.10.035

[109] Sun CC, Li SJ, Yang CL, Xue RL, Xi YY, Wang L, Zhao QL, Li DJ. Sulforaphane attenuates muscle inflammation in dystrophin-deficient mdx mice via NF-E2-related factor 2 (Nrf2)-mediated inhibition of NF-κB signaling pathway. The Journal of Biological Chemistry. 2015;**290**(29):17784-17795. DOI: 10.1074/jbc.M115.655019

[110] Zhou R, Lin J, Wu D. Sulforaphane induces Nrf2 and protects against CYP2E1-dependent binge alcohol-induced liver steatosis. Biochimica et Biophysica Acta. 2014;**1840**:209-218. DOI: 10.1016/j.bbagen.2013.09.018

[111] Zhang C, Su ZY, Khor TO, Shu L, Kong ANT. Sulforaphane enhances Nrf2 expression in prostate cancer TRAMP C1 cells through epigenetic regulation. Biochemical Pharmacology. 2013;**85**:1398-1404. DOI: 10.1016/j.bcp.2013.02.010

[112] Jo C, Kim S, Cho SJ, Choi KJ, Yun SM, Koh YH, Johnson YVW, Park SI. Sulforaphane induces autophagy through ERK activation in neuronal cells. FEBS Letters. 2014;**588**: 3081-3088. DOI: 10.1016/j.febslet.2014.06.036

[113] Liu H, Talalay P. Relevance of anti-inflammatory and antioxidant activities of exemestane and synergism with sulforaphane for disease prevention. Proceedings of the National Academy of Sciences of the United States of America. 2013;**110**(47):19065-19070. DOI: 10.1073/pnas.1318247110

[114] Kim DH, Sung B, Kang YJ, Hwang SY, Kim MJ, Yoon JH, Im E, Kim ND. Sulforaphane inhibits hypoxia-induced HIF-1α and VEGF expression and migration of human colon cancer cells. International Journal of Oncology. 2015;**47**:2226-2232. DOI: 10.3892/ijo.2015.3200

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