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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- κ B) 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- κ B 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- κ B 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- κ B 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- κ B 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- κ B 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- κ B 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- κ B 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
Ferulic acid	Antioxidant response pathway	Nrf-2	HO-1↑	[31, 32]
	NFκB inflammatory pathway	NFκB	NO↓, iNOS↓	[33]
	Heat shock response pathway	HSF-1	Hsp70↑	[35]
	Autophagic response pathway	—	mTOR inhibition	[36]
Curcumin	Antioxidant response pathway	Nrf2	Glutathione, GR, GST, HO-1, NQO1	[43, 44]
	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]
Resveratrol	Antioxidant response pathway	Nrf2	Glutathione↑, HO-1↑	[49, 50]
	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]
EGCG	Sirtuin response pathway	—	SIRT1↑	[47, 48]
	Antioxidant response pathway	Nrf2	GST↑, NQO1↑, HO-1↑	[59, 60, 62, 64]
	NFκB inflammatory pathway	NFκB	IL-12p40↓, IL-6↓	[65–67]
	Heat shock response pathway	HSF-1	Overexpressed Hsp90↓	[58]
Luteolin	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]
	NFκB inflammatory pathway	NFκB	TNF-α↓, NO↓	[73–75, 81]
	Autophagic response pathway	—	HIF-1α inhibition	[82]
Quercetin	Sirtuin response pathway	—	SIRT1↑	[81]
	Antioxidant response pathway	Nrf2	GSH↑, GPx↑, GR↑, GST↑, GCLC↑, GCLM↑, HO-1↑	[89–95]
	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
Sulforaphane	Autophagic response pathway	—	HIF-1, mTOR inhibition	[88, 96–101]
	Antioxidant response pathway	Nrf2	HO-1↑, SOD-1↑,NQO1↑	[104–111]
	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 rotenone-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- κ B pathway [54]. In another study, resveratrol showed anti-inflammatory effect by suppressing the NF- κ B 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 ($\leq 2.5 \mu\text{m}$ in aerodynamic diameter PM_{2.5}) [64]. EGCG dose-dependently suppresses endothelial inflammation through NF- κ B inhibition in high glucose-induced HUVECs [65]. It can also suppress NF- κ B activation in cardiac fibroblasts and can show a protective effect against cardiac fibrosis [66]. EGCG inhibited lipopolysaccharide-induced inflammation with NF- κ B 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-1 α 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 IKB α /NF- κ B pathway in HUVECs [74]. In psoriatic skin, luteolin inhibited keratinocyte activation by decreasing NF- κ B, 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-1 α 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- κ B 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- κ B 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- κ B 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- κ B 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- κ B 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-1 α 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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