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The Biofunctions of Phytochemicals and Their Applications in Farm Animals: The Nrf2/Keap1 System as a Target

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ABSTRACT

Reactive oxygen species (ROS) can be caused by mechanical, thermal, infectious, and chemical stimuli, and their negative effects on the health of humans and other animals are of considerable concern. The nuclear factor (erythroid-derived 2)-like 2/Kelch-like ECH-associated protein 1 (Nrf2/Keap1) system plays a major role in maintaining the balance between the production and elimination of ROS via the regulation of a series of detoxifying and antioxidant enzyme gene expressions by means of the antioxidant response element (ARE). Dietary phytochemicals, which are generally found in vegetables, fruits, grains, and herbs, have been reported to have health benefits and to improve the growth performance and meat quality of farm animals through the regulation of Nrf2-mediated phase II enzymes in a variety of ways. However, the enormous quantity of somewhat chaotic data that is available on the effects of phytochemicals needs to be properly classified according to the functions or mechanisms of phytochemicals. In this review, we first introduce the antioxidant properties of phytochemicals and their relation to the Nrf2/Keap1 system. We then summarize the effects of phytochemicals on the growth performance, meat quality, and intestinal microbiota of farm animals via targeting the Nrf2/Keap1 system. These exhaustive data contribute to better illuminate the underlying biofunctional properties of phytochemicals in farm animals.

1. Biofunctions of dietary phytochemicals in modulating the Nrf2/Keap1 system

1.1. Dietary phytochemicals

Phytochemicals are produced via primary or secondary plant metabolisms and originate in various kinds of fruits, vegetables, grains, and herbs, endowing them with the color, taste, smell, and other organoleptic properties of the plants [1]. They are produced to help plants thrive or to thwart competitors, predators, or pathogens. During the last two decades, dietary phytochemicals have been found to be strongly associated with human health and diseases through their biological functions [2,3]. More than 10 000 kinds of dietary phytochemicals have been classified into carotenoids, isothiocyanates, and polyphenols based on their chemical structure. Among these, the best-investigated category is that of polyphenols, which mainly include phenolic acids, flavonoids, and stilbenes/lignans. Many epidemiological investigations and lab-based studies have demonstrated that most polyphenols are conducive to the chemoprevention of several chronic diseases, including diabetes, cardiovascular diseases, neurodegenerative diseases, cancer, and other inflammatory diseases [4].

1.2. Phytochemicals as modulators for the Nrf2/Keap1 system

When phytochemicals are ingested by humans and other animals, they are recognized as xenobiotics. As a result, they stimulate the genes of a series of antioxidant and detoxifying enzymes (ADEs)

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to express. Most of these genes contain a specific conserved nucleotide sequence of 5′-TA/CANNA/GTGAC/TNNNGCA/G-3′ in their promoters, named antioxidant response element (ARE)/electrophile-responsive element (EpRE) [5]. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) has been demonstrated to strongly activate ARE/EpRE to enhance the gene expressions of a series of ADEs [6], such as NAD(P)H quinone dehydrogenase 1 (NQO1), glutathione reductase (GSR), and solute carrier family 7 member 11 (SLC7A11) [7]. Nrf2 is a transcription factor (TF) transcribed by the *NFE2L2* gene in humans, with a basic leucine zipper (bZIP) protein that induces the gene expressions of phase II antioxidant proteins and detoxifying enzymes in order to protect against oxidative damage triggered by chronic inflammation and injury [2]. The crucial negative regulator of Nrf2 is Kelch-like ECH-associated protein 1 (Keap1), which maintains the dynamic balance of cytoplasmic Nrf2 by proteasomal degradation [8].

The molecular mechanisms of Nrf2-ARE activation are summarized in the schematic diagram in Fig. 1. As shown in this diagram, the mechanisms of the regulating Nrf2/Keap1 system can be divided into Keap1-dependent and Keap1-independent mechanisms. Under basal conditions, Keap1 inhibits Nrf2 by functioning as an E3 ubiquitin ligase with the cullin 3-RING box protein 1 (Cul3-Rbx1) system for the constant ubiquitination and proteasomal degradation of Nrf2. Under induced status, electrophiles, oxidants, or phytochemicals can influence the Keap1 structure/residues, in the forms of cysteine modification, ubiquitination, phosphorylation, and succination, causing Nrf2 to escape from the Keap1-dependent ubiquitination system [9]. Alternatively, stress inducement may stimulate the phosphorylation of certain protein kinases, such as mitogen-activated protein kinases (MAPKs), phosphoinositide 3-kinase (PI3K), protein kinase C (PKC), PKR-like endoplasmic reticulum kinase (PERK), glycogen synthase kinase 3 (GSK3), or Nrf2 itself, thus regulating the activity of a series of TFs or certain nuclear proteins such as positive Brahma-related gene 1 (BRG1), nuclear receptor coactivator amplified in breast cancer 1 (AIB1), and Maf, as well as negative p53, p65, and cFos [6,8]. Moreover, phytochemicals may cause epigenetic modifications to affect the mRNA transcription of *NFE2L2* or *Keap1*, such as DNA methylation, histone modification, and microRNA tuning. All of the above result in the accumulation of Nrf2 in the nucleus to heterodimerize with small Maf or CREB-binding protein (CBP) and to bind to ARE, which finally activates the expression of its downstream ADEs genes [6,10].

1.3. Molecular mechanism underlying Nrf2 regulation by dietary phytochemicals

An extremely large number of studies performed *in vitro* and *in vivo* have revealed that many dietary phytochemicals have powerful abilities in regulating the Nrf2/Keap1 system [2–4]. However, the molecular mechanisms underlying this huge quantity of data are not well classified. Here, based on the current research status, we

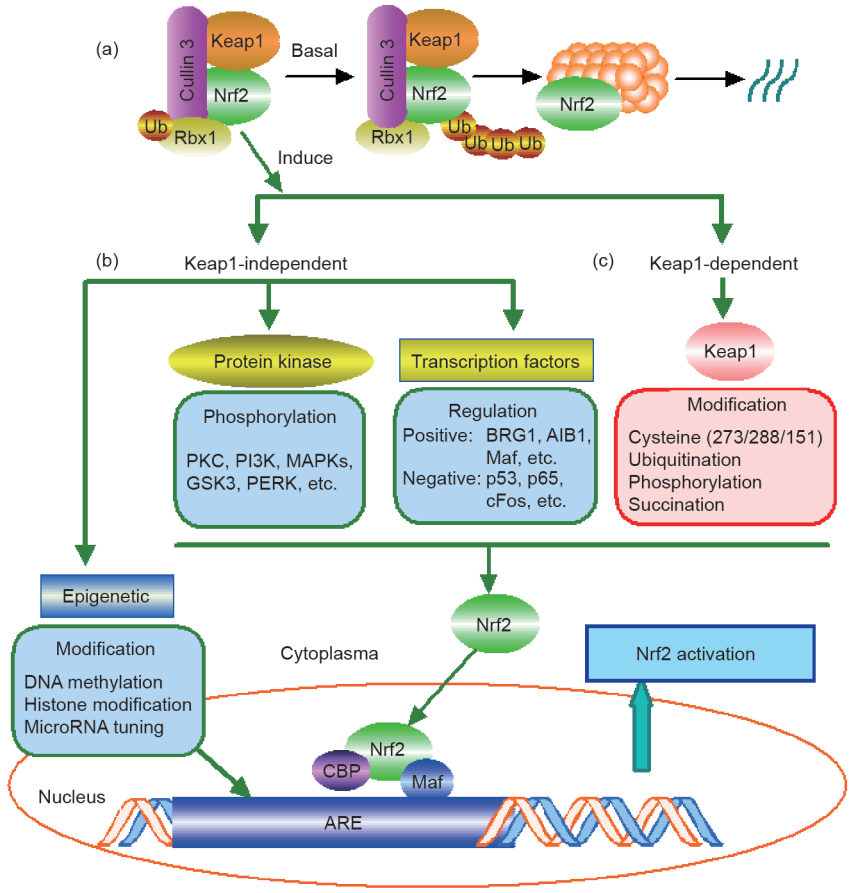


Fig. 1. Schematic diagram of the molecular mechanisms underlying the modulation of the Keap1/Nrf2 pathway. (a) Under normal/basal conditions, Nrf2 is inhibited by the Keap1-mediated Cul3-Rbx1 ubiquitination system for general proteasomal degradation. Under an induced state/stimulation, Nrf2 is activated by the Keap1-independent or Keap1-dependent Nrf2 pathway. (b) The Keap1-independent pathway. The protein kinases (PKC, PI3K, MAPKs, GSK3, and PERK) can phosphorylate Nrf2, and some transcription factors bind to ARE in order to positively or negatively regulate the expressions of Nrf2/ARE-mediated genes (positive regulators include BRG1, AIB1, and Maf, and negative regulators include p53, p65, and cFos). Epigenetic modifications include DNA methylations of promoters, histone modifications such as acetylations or methylations, and microRNA tuning by transcriptional regulations. (c) Keap1-dependent pathway. The cysteine modifications in the locations of Cysteine 273, 288, and 151, ubiquitination, phosphorylation, and succination of Keap1 are minimally involved.

review the molecular mechanisms of Nrf2 regulation by dietary phytochemicals and classify them into Keap1-dependent and Keap1-independent mechanisms.

1.3.1. Keap1-dependent pathway

Several models have been suggested to explain the inhibitory regulation of Nrf2 by Keap1. Most of the ARE inducers can target and modify the cysteines of Keap1 to affect Nrf2-ARE signaling. It is interesting that the location of the Keap1 cysteine that is targeted differs, depending on the type of the inducer [9,10]. The essential cysteine residues generally involve C288, C273, and C151 [11]. After the discovery of Keap1 as an E3 ligase substrate adaptor of the Cul3-Rbx1-containing ubiquitination system, the "Keap1 dissociation and Cul3-Rbx1 ubiquitination" model was developed to explain the major Nrf2 regulation mechanism [12]. Moreover, several other important models such as the "Keap1 hinge-and-latch," "Keap1 phosphorylation," "Keap1 ubiquitination," and "Keap1 succination" models reveal that modifications of Keap1 caused by a variety of stimuli constitute a primary mechanism in the modulation of the Nrf2/Keap1 system [13–17].

An enormous number of dietary phytochemicals have been found to modify the cysteines of Keap1 to regulate the Nrf2/Keap1 system. As displayed in Table 1 [18–80], sulforaphane, resveratrol, catechol estrogens, quercetin, carnosic acid, baicalein, glyceollins, oridonin, falcarindiol, piceatannol, xanthohumol, and 6-(methylsulfinyl)hexyl isothiocyanate were reported to activate the Nrf2/Keap1 system. Of these, quercetin works in the "Keap1 dissociation" model [18] and baicalein works in the "Keap1 ubiquitination" model; it is noteworthy that baicalein also works in the "Keap1 hinge-and-latch" model [26]. In addition, sulforaphane works in the "Keap1 hinge-and-latch" model in human Keap1, whereas it works in the "Keap1 dissociation" model in animal Keap1 [56–59]. These data suggest that Keap1 modification by phytochemicals varies, and that the cell model used is an important factor.

Table 1
The molecular mechanisms of Nrf2 regulation by phytochemicals.

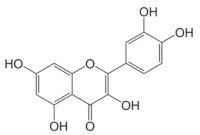
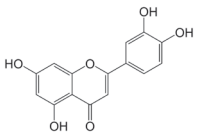
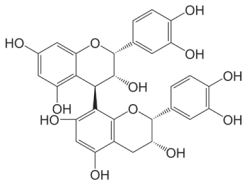
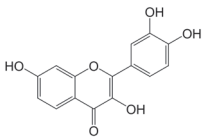
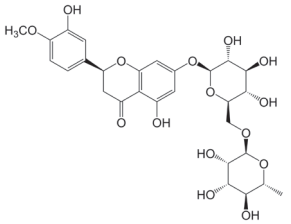
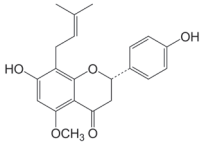
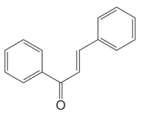
Classification	Origin	Compound	Structure	Dose	Time	Mechanism	Model	Refs.
Activation of Nrf2-ARE pathway								
Flavonoid-type polyphenols	Apple, tea, caper, lovage, onion	Quercetin		0–40 μmol·L^{-1}	6 h	↑ Keap1 modification, Nrf2 stability	HepG2 cells	[18]
				100–200 μmol·L^{-1}	24 h, 48 h	↑ p38 MAPK and ERK	Human hepatocytes epithelial cells	[19]
	Celery, green pepper	Luteolin		0–20 μmol·L^{-1}	24 h, 72 h	↑ ERK1/2, HO-1, ARE binding	PC12 cells	[20]
	Cocoa, red wine	Procyanidin B2		10 μmol·L^{-1}	20 h	↑ ERKs and p38 MAPK	Human colonic cells	[21]
	Strawberry	Fisetin		0–25 μmol·L^{-1}	NM	↑ PKC-δ and p38 MAPK	Human umbilical vein endothelial cells	[22]
	Citrus fruits	Hesperidin		0–80 μmol·L^{-1}	24 h	↑ ERK1/2	Human hepatic L02 cells	[23]
	Hops	Xanthohumol		4 μmol·L^{-1}	24 h	↑ Modification of Keap1 cysteine	Murine Hepa1c1c7 cells	[24]
	Plant phenols	Chalcone		10–25 μmol·L^{-1}	NM	↑ Nrf2, HO-1	Endothelial cells	[25]

Table 1 (*continued*)

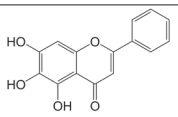
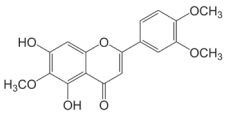
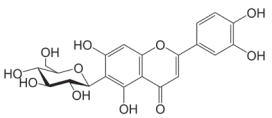
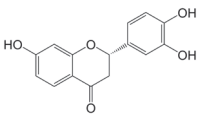
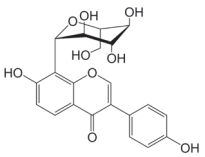
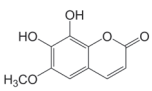
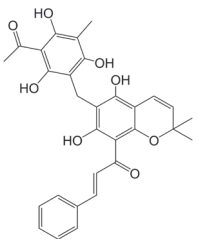
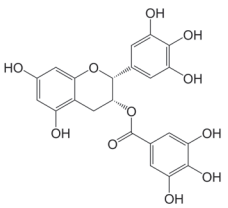
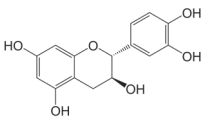
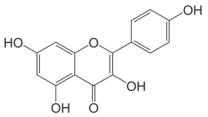
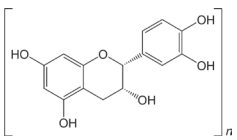
Classification	Origin	Compound	Structure	Dose	Time	Mechanism	Model	Refs.
	Scutellaria baicalensis	Baicalein		0–40 μmol·L^{-1}	9 h, 24 h	↑ Nrf2, HO-1	HepG2 cells	[26]
	Artemisia	Eupatilin		0–150 μmol·L^{-1}	16 h	↑ ERK	Feline ileal smooth muscle cells	[27]
	Sasa borealis	Isoorientin		5 μg·mL^{-1}	0–6 h	↑ PI3K/Akt	HepG2 cells	[28]
	Vernonia anthelmintica, Dalbergia odorifera	Butin		10 μg·mL^{-1}	12 h, 24 h	↑ PI3K/Akt	Chinese hamster lung fibroblast (V79-4)	[29]
	Inula helenium	Phytoestrogen puerarin		0–100 μmol·L^{-1}	2–18 h	↑ PI3K/Akt	Hepa1c1c7 cells	[30]
	Fraxinus rhinchophylla	Fraxetin		30–100 μmol·L^{-1}	24 h	↑ Nrf2, HO-1	Vascular smooth muscle cells	[31]
	Mallotus philippinensis	Rottlerin		1–10 μmol·$^{L-}$1	9 h	↑ ERK and p38 MAPK	HT29 cells	[32]
	Tea	EGCG		20 μmol·L^{-1}	48 h	↑ p38 MAPK and Akt	B lymphoblasts	[33]
				50 μmol·L^{-1}	6 h	↑ ERK and PI3K/Akt	Bovine aortic endothelial cells	[34]
	Cocoa, tea	Epicatechin		5–30 mg·kg^{-1} BW	1 h, 6 h, 18 h	↑ ERK and PI3K/Akt	Ischemic damaged mice	[35]
	Tea, broccoli	Kaempferol		0–10 μmol·L^{-1}	18 h	↑ JNK, HO-1, GCLC	Organ of Corti 1 (HEI-OC1) cells	[36]
	Wild grape	Procyanidins		25 μg·mL^{-1}	1 h	↑ p38 MAPK, PI3K/Akt	HepG2 cells	[37]

Table 1 (*continued*)

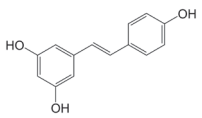
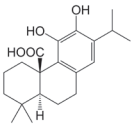
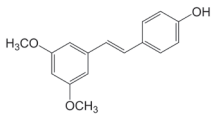
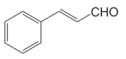
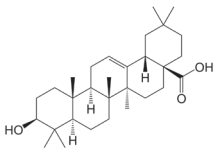
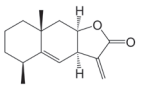
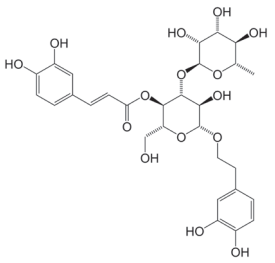
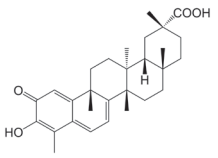
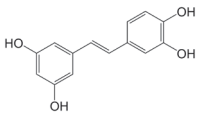
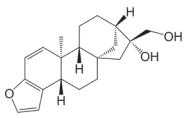
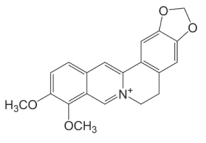
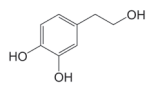
Classification	Origin	Compound	Structure	Dose	Time	Mechanism	Model	Refs.
Non-flavonoid-type polyphenols	Red grape	Resveratrol		10 μmol·L^{-1}	24 h	↑ Modification of Nrf2 and Keap1	A549 cells	[38]
				15 μmol·L^{-1}	0–6 h	↑ ERK and PI3K	PC12 cells	[39]
	Rosemary, common sage	Carnosic acid		1–20 μmol·L^{-1}	0–1 h	↑ p38 MAPK		[40]
				10 μmol·L^{-1}	1 h	↑ S-alkylation of Keap1		[41]
	Blueberries, grapes	Pterostilbene		5 mg·kg^{-1} BW	6 weeks	↑ Nrf2, HO-1	Male BALB/c mice	[42]
	Cinnamomum cassia Presl	Cinnamaldehyde		50–100 μmol·L^{-1}	0–12 h	↑ Nrf2, HO-1	Endothelial cells	[43]
	American pokeweed, garlic	Oleanolic acid		10–50 μmol·L^{-1}	0–2 h	↑ Akt and ERK	Primary rat vascular smooth muscle cells	[44]
	Inula helenium	Alantolactone		0–10 μmol·L^{-1}	NM	↑ PI3K and JNK	Hepa1c1c7 mouse hepatoma cells	[45]
	Scrophulariaceae	Acteoside		30 μmol·L^{-1}	0–12 h, 6 h	↑ ERK and PI3K/Akt	PC12 cells	[46]
	Tripterygium wilfordii	Celastrol		0–1 μg·mL^{-1}	0.5 h	↑ ERK and p38 MAPK	HaCaT cells	[47]
	Euphorbia lagascae	Piceatannol		30 μmol·L^{-1}	0–12 h	↑ Akt and modification of Keap1	MCF10A cells	[48]
	Coffee	Kahweol		0–10 μmol·L^{-1}	0–2 h	↑ Akt and p38 MAPK	SH-SY5Y cells	[49]
	Rhizoma coptidis	Berberine		1–10 μmol·L^{-1}	0–2 h	↑ PI3K/Akt, phosphorylation of Nrf2	Rat brain astrocyte cell line (RBA-1)	[50]
	Olive	Hydroxytyrosol		50 μmol·L^{-1}	0–1 h	↑ PI3K/Akt, MEK1/2-ERK1/2	Vascular endothelial cells	[51]
				0–200 μmol·L^{-1}	2–24 h	↑ JNK	Human retinal pigment	[52]

Table 1 (*continued*)

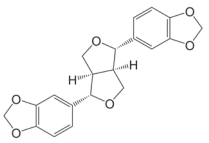
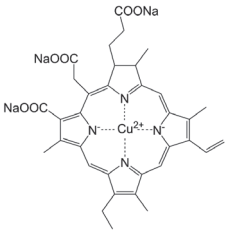
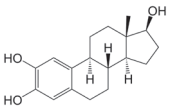
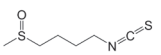
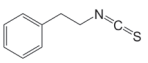
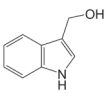
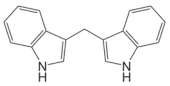
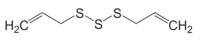
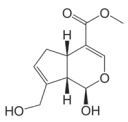
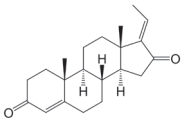
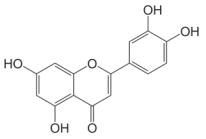
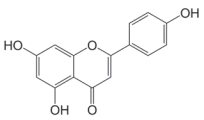
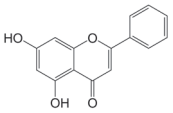
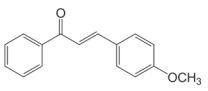
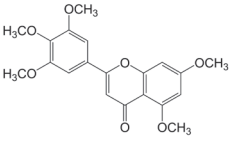
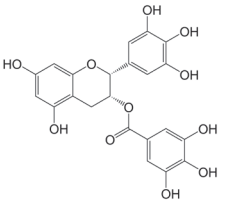
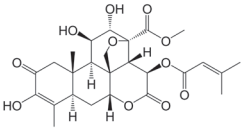
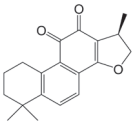
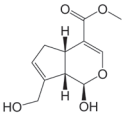
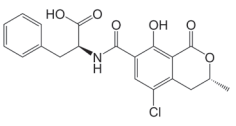
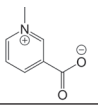
Classification	Origin	Compound	Structure	Dose	Time	Mechanism	Model	Refs.
	Sesame seeds	Sesamin and episesamin		0–10 μmol·L^{-1}	0–2 h	↑ p38 MAPK	Rat pheochromocytoma PC12 cells	[53]
	Spinach, green leafy vegetables	Chlorophyllin		50 μmol·L^{-1}	0–2 h	↑ PI3K/Akt	Human umbilical vein endothelial cells	[54]
	Soybean	Catechol estrogens		10 μmol·L^{-1}	3 h	↑ Modification of Keap1	RAW264.7 cells	[55]
Isothiocyanates and other phytochemicals	Cruciferous vegetables	Sulforaphane		0–200 μmol·L^{-1}	2 h	↑ Cysteine thioacetylation of Keap1	Human Keap-1-transfected HEK293 cells	[56]
				20 μmol·L^{-1}	24 h	↑ p38 MAPK isoforms	HepG2 cells	[57]
				20 μmol·L^{-1}	1 h	↑ ERK and PI3K	Caco-2 cells	[58]
				0–2.5 μmol·L^{-1}	5 d	↑ CpGs, demethylation of Nrf2 promoter, Nrf2, NQO1; ↓ DNMT1/3a, HDAC1/4/5/7	TRAMP C1 cells	[59]
	Cruciferous vegetables	PEITC		5 μmol·L^{-1}	12 h	↑ ERK and JNK	PC-3 cells	[60]
	Cruciferous vegetables	I3C		6.25 μmol·L^{-1}	24 h	↑ JNK	HepG2-C8 cells	[61]
	Cruciferous vegetables	DIM		0–5 μmol·L^{-1}	NM	↑ CpGs, demethylation of Nrf2 promoter, Nrf2, NQO1, JNK	TRAMP-C1 cells, TRAMP prostate tumors	[62]
	Garlic, onion	Diallyl trisulfide		100 μmol·L^{-1}	1 h	↑ Calcium-dependent signaling, ERK, p38 MAPK	HepG2 cells	[63]
	Gardenia jasminoides	Genipin		0–100 μmol·L^{-1}	24 h	↑ PI3K-JNK1/2	RAW264.7 macrophages	[64]
	Commiphora mukul	Guggulsterone		25 μmol·L^{-1}	0–2 h, 6 h	↑ PI3K/Akt	Human mammary epithelial cells	[65]
Inhibition of Nrf2-ARE pathway								
Flavonoid	Celery, green pepper	Luteolin (Lut)[a]		20 μmol·L^{-1}	24 h, 48 h	↑ Nrf2 mRNA degradation	A549, HCT116-OX, SW620OX, MDA-MB 231 cells	[66,67]

Table 1 (*continued*)

Classification	Origin	Compound	Structure	Dose	Time	Mechanism	Model	Refs.
	Parsley, celery, celeriac	Apigenin (Api) [a]		20 μmol·L^{-1}	14 d	↓ p-Akt	Tumor of mice	[68]
	Passiflora incarnata	Chrysin (Chry) [a]		10–20 μmol·L^{-1}	24 h	↓ p-Akt, p-ERK1/2, Nrf2 protein levels	BEL-7402/ADM cells	[69]
		4-methoxychalcone [a]		5 μg·mL^{-1}	3–24 h	↓ p-Akt (Thr308)	A549 cells	[70]
	Tangerine peel	3',4',5',5,7-pentamethoxyflavone [a]		10–25 μmol·L^{-1}	24 h	↓ p-ERK	A549 cells	[71]
	Tea	(EGCG) [a]		100 μmol·L^{-1}, 200 μmol·L^{-1}	24 h	↓ Nrf2 protein level; ↑ apoptosis	A549 cells	[72]
	Brucea	Brusatol (Bru)		10–300 nmol·L^{-1}	2 h	↓ Nrf2 mRNA translation	A549, Hepa1c1c7 cells	[73]
	Salvia	Cryptotanshinone		5–10 μmol·L^{-1}	24 h	NM	H1299 cells	[74]
		Metformin (Met)		1–5 mmol·L^{-1}	24 h	↓ pRaf, p-ERK1/2; ↑ microRNA-34a; ↓ Nrf2	HepG2, HeLa, A549, MCF-7 cells	[75,76]
		Mycotoxin ochratoxin A		5 μmol·L^{-1}	1 d, 3 d	↓ Nuclear import of Nrf2; ↓ DNA binding; ↑ microRNA-32; ↓ Nrf2	Human primary proximal tubule cells	[77,78]
	Leguminosae extract of fenugreek	Trigonelline (Trig)		0.0001–1 mmol·L^{-1}	3 h	↓ Nuclear import of Nrf2	Panc1, Colo357, MiaPaca2 cells	[79,80]

CpG: 5′-C-phosphate-G-3′; DIM: 3,3′-diindolylmethane; DNMT: DNA methyltransferase; EGCG: epigallocatechin-3-gallate; ERK: extracellular signal-regulated kinase; GCLC: glutamate-cysteine ligase catalytic subunit; HDAC: histone deacetylase; HO-1: heme oxygenase 1; I3C: indole-3-carbinol; JNK: c-Jun N-terminal kinase; MEK: mitogen-activated protein kinase kinase; PEITC: phenethyl isothiocyanate; BW: body weight; NM: not mentioned in the reference.

[a] indicates that the compound has a dual role in the regulation of the Nrf2-ARE pathway, including activation and inhibition.

1.3.2. Keap1-independent pathway

Aside from Keap1, a large number of other factors have been proven to play significant roles in the regulation of the Nrf2/Keap1 system. As shown in Fig. 1, these factors can be mainly classified into epigenetic modifications, the phosphorylation of protein kinases, and the regulation of TFs.

As shown in Table 1, the phosphorylation of extracellular signal-regulated kinase (ERK) can be promoted by quercetin [19], sulforaphane/phenethyl isothiocyanate (PEITC) [58,60], hydroxytyrosol [51], resveratrol [39], luteolin [20], procyanidin B2 [21], hesperidin [23], oleanolic acid [44], epigallocatechin-3-gallate (EGCG) [34], epicatechin [35], eupatilin [27], rottlerin [32], acteoside [46], and celastrol [47]. The activation of p38 MAPK can occur from treatments of quercetin [19], procyanidins [37], sulforaphane [57], procyanidin B2 [21], fisetin [22], rottlerin [32], carnosic acid [40], celastrol [47], sesamin/episesamin [53], EGCG [33], and kahweol [49]. The activity of c-Jun

N-terminal kinase (JNK) has been reported to be induced by treatments of alantolactone [45], hydroxytyrosol [52], PEITC [60], kaempferol [36], genipin [64], and indole-3-carbinol/3,3′-diindolylmethane [61,62]. The activity of PI3K can be stimulated by procyanidins [37], sulforaphane [58], hydroxytyrosol [51], resveratrol [39], chlorophyllin [54], genipin [64], isoorientin [28], butin [29], guggulsterone [65], alantolactone [45], phytoestrogen puerarin [30], berberine [50], acteoside [46], EGCG [34], and epicatechin [35].

Several lines of research have found that the Nrf2/Keap1 system can be regulated by dietary phytochemicals through modulation of other transcriptional factors or nuclear proteins. Jun dimerization protein 2 (JDP2) was found to be strongly associated with sulforaphane-induced Nrf2 activation, and it was shown that JDP2 positively promotes Nrf2-ARE activation caused by sulforaphane [81]. Another study reported that sulforaphane inhibited the Nrf2 signaling pathway at the transcription level via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); NF-κB promotes histone deacetylase 3 (HDAC3) to cause local hypoacetylation and competes against Nrf2 transactivation with CBP to inhibit Nrf2 signaling [82].

Some dietary phytochemicals are considered to be potent epigenetic modifiers, including isothiocyanates, tea polyphenols, genistein, and curcumin [83]. Sulforaphane, 3,3′-diindolylmethane, curcumin, and Z-ligustilide were shown to inhibit the expressions of DNA methyltransferase (DNMT) and HDAC, resulting in the demethylation of Nrf2 promoter and the reactivation of Nrf2 signaling in the prostate of TRAMP mice or in TRAMP C1 cells [59,62,84,85]. Moreover, apigenin, sulforaphane, and tanshinone IIA were reported to demethylate excessively methylated 5′-C-phosphate-G-3′ (CpG) sites in the Nrf2 promoter region in mouse skin epidermal JB6 P+ cells, which was associated with the reactivation of Nrf2 signaling, the expression of Nrf2 target genes, the suppression of TPA-induced transformation, and the inhibition of protein expression of DNMTs and HDACs [86–88]. These findings suggest that phytochemicals can regulate Nrf2 expression epigenetically; however, the exact effects of these special Nrf2 modulators on cancer and other chronic diseases need to be clarified by further study.

It is interesting that several lines of study reported that some flavonoids work as inhibitors of the Nrf2/Keap1 system in certain cancer cell lines and play an important role in overcoming cancer drug resistance (Table 1) [66–80]. For example, luteolin, apigenin, chrysin, 4-methoxychalcone, pentamethoxyflavone, and EGCG have been found to play different roles in Nrf2-ARE regulation in normal cells and in cancer cells. In normal cells, they work as activators for Nrf2-ARE regulation to prevent chronic diseases, whereas in cancer cells, they work as inhibitors for Nrf2-ARE regulation to overcome cancer drug resistance. This dual action of phytochemicals on the Nrf2/Keap1 system in normal and cancer cells is attracting considerable attention regarding its health benefits [89].

2. The effects of phytochemicals on the growth performances, meat quality, and intestinal microbiota of farm animals by targeting the Nrf2/Keap1 system

The source of phytochemicals for farm animals is generally agroindustrial byproducts, such as skins, stems, seeds, pomace, nuts, hulls, and waste from the production of juice, wine, or beer, in order to reduce feed cost [90]. Table 2 summarizes the effects of phytochemicals on the growth performances, meat quality, and intestinal microbiota of farm animals [91–135].

Table 2
The effects of phytochemicals on the growth performances, meat quality, and intestinal microbiota of farm animals.

Function classification	Phytochemical	Concentration	Animal/meat tested	Effect	Refs.
Growth performances					
	Resveratrol and resveratrol-rich grape extract	100 mg·(kg·d)$^{-1}$	Pigs	Lower fat deposition, improve myocardial function or glucose metabolism, prevent development of atherosclerotic lesions and coronary heart disease	[91–93]
	Polyphenol-rich grape seed and grape marc meal		Pigs	No change in Nrf2/Keap1 pathway	[94,95]
	Grape seed proanthocyanidin extract		Broilers	Improve weight gain and lower mortality of broilers infected with *Eimeria tenella*	[96]
	Thymol, tannic acid, or gallic acid	200 mg, 5 g·kg^{-1} diet	Broilers	Improve the feed utilization and final BW	[97]
	Grape pomace	60 g·kg^{-1} diet	Broilers	Improve feed efficiency	[98]
	Green tea polyphenols		Broilers	Improve the feed conversion ratio and impair feed efficiency without corticosterone treatment	[99]
	Resveratrol	1% of diet	Broilers	Impair body weight gain and feed conversion ratio	[100]
	Quercetin	0.2–0.6 g·kg^{-1} diet	Hens	Increase laying rate, decrease feed-to-egg ratio	[101]
	Tea polyphenols	5–15 mg·kg^{-1} diet	Laying hens	Prevent the adverse effect of vanadium on egg quality	[102]
	Pomegranate-extract polyphenols	5–10 g·d^{-1}	Dairy cows	Decreased the digestibility of protein and fat	[103]
	Polyphenol-rich grape seed and grape marc meal extract		Dairy cows	Improve milk performance	[104]
	Green tea and curcuma extract		Dairy cows	Cause a reduction of fat content in the liver and an increase in milk performance	[105]
Meat quality					
Antioxidant	Quercetin, a flavonoid; ampelopsin, isoflavones, a polyphenols mix	10 mg·(kg·d)$^{-1}$, 1 g·kg^{-1} diet	Pigs	Reduce plasma lipid peroxidation and lower MDA level	[94,106,107]
	Tea polyphenols, grape seed proanthocyanidin extract	1000 mg·kg^{-1} diet	Broilers and laying hens	Reduction of MDA and TBARS concentrations, induction of GPx activity	[96,98,102]
	Extracts of rosemary, grape skin, green tea, and coffee	50–200 ppm	Pork patties	Reduce lipid oxidation, reduce values of TBARS and hexanal	[108]

Table 2 (*continued*)

Function classification	Phytochemical	Concentration	Animal/meat tested	Effect	Refs.
	Extracts of white peony, red peony, moutan peony, sappan wood, rehmannia, and angelica	0.5%–2.0%	Raw and cooked goat meat patties	Reduce lipid oxidation	[109]
	Extracts of olive leaf, date pits, and rosemary leaf		Raw beef patties, ground beef, and buffalo meat patties	Reduce TBARS value, lipid oxidation, and oxymyoglobin oxidation	[110–112]
	Adzuki bean extract and grape seed extract		Pork and beef sausages	Reduce lipid oxidation and TBARS values	[113,114]
	Garlic juice	1% and 3%	Emulsified sausage	Decrease peroxide value, TBARS, and residual nitrite	[115]
	Sage essential oil	3%	Raw pork	Decrease the TBARS value	[116]
	Oregano essential oil	3%	Pork and beef	Lower levels of oxidation	[116]
Anti-inflammatory	Grape seed and grape marc meal extract or hop extract		Growing pigs	Downregulation of various pro-inflammatory genes	[95]
	Cocoa powder	2.5 g, 10 g, 20 g	Pigs	Decrease gene expression of TNF-α and Toll-like receptors	[117]
	Tea polyphenols	0.03–0.09 g·kg^{-1} BW	Broilers	Downregulation of the genes of IL-1β, IL-4, IL-10, TNF-α, and IFN-γ	[118]
	Pomegranate-extract polyphenols	5–10 g·d^{-1}	Pigs	Increase the secretion of IFN-γ and IL-4, improve total IgG response	[119]
	Grape seed and grape marc meal extract		Dairy cows	Downregulation of the marker of endoplasmic reticulum stress, FGF-21, and fat accumulation in the liver	[104]
Sensory	White peony extract	0.5%–2.0%	Raw and cooked meat patties	Increase the redness value (a^* value)	[109]
	Rosemary extract	300–500 ppm	Raw frozen sausage	Maintain the red color	[120]
	Green tea extract	300 mg·kg^{-1} meat	Raw patties	Decrease a^* value	[121]
			Cooked patties	Delay rancid flavor development	[122]
	Grape seed extract	0.01%–0.02%	Beef patties	Reduce visual green discoloration	[123]
	Myrtle extract	10%	Beef patties	Prevent color changes	[124]
	Eleutherine americana extract	2.7–10.8 mg·(100 g)$^{-1}$	Cooked pork	Increase a^* value	[125]
	Adzuki bean extract	0.2%	Cured and uncured cooked pork sausages	Increase a^* value but decrease lightness (L^* value) and yellowness (b^* value)	[126]
	Green tea extract	500–6000 ppm	Raw and cooked goat meat	Increase a^* value	[127]
	Grape seed extract			Decrease a^* value	[128]
	Pepper extract		Cooked pork	Maintain a^* value	[128]
	Curry leaf extract	5 mL·(500 g)$^{-1}$ meat	Raw ground pork	Decrease L^* value and a^* value while increasing b^* value	[129]
	Rosemary leaf extract	130 ppm	Raw and cooked ground buffalo meat patties	Stabilized color	[130]
	Plum products		Variety of meat and poultry products	Minor effect on flavor but caused color change	[131,132]
	Grape seed extract		Meat products	Significant change in color	[133]
Intestinal microbiota					
	Cocoa powder		Pigs	Increase the abundance of *Lactobacillus*, *Bifidobacterium* spp., *Bacteroides-Prevotella*, and *Faecalibacterium prausnitzii*	[117,134]
	Grape pomace concentrate		Broilers	Increase the abundance of *Enterococcus* and decrease that of *Clostridium*	[98]
	Quercetin		Laying hens	Decrease the total aerobes and coliforms and increase the abundance of *Bifidobacterium*	[101]
	Tea polyphenols		Pigs	Increase the amount of lactobacilli and decrease that of the total bacteria, Bacteroidaceae, and *Clostridium perfringens*	[102]
			Calves	Decrease *Bifidobacterium* spp., *Lactobacillus* spp., and *Clostridium perfringens*	[135]

FGF: fibroblast growth factor; GPx: glutathione peroxidase; IFN: interferon; IgG: immunoglobulin G; IL: interleukin; MDA: malondialdehyde; TBARS: thiobarbituric acid reactive substance; TNF: tumor necrosis factor; BW: body weight.

2.1. Growth performances

Several lines of study have reported the effects of phytochemicals on the growth performances of farm animals including pigs, poultry, and cattle.

In pigs, stilbenoid resveratrol and grape extract with a rich concentration of resveratrol were found to lower fat deposition, improve glucose metabolism and myocardial function, and prevent the progression of atherosclerotic lesions and coronary heart disease [91–93]. Although an improvement in growth performance was found in pig feed based on polyphenol-rich grape seed and marc meal, the activity of TF Nrf2 and the expressions of ARE-associated antioxidant genes or detoxifying enzymes showed no significant change [94,95].

In broilers and laying hens, phytochemicals were found to have a significant effect on improving growth performances. The supplementation of proanthocyanidin extract from grape seed was reported to lower the mortality of broilers infected with *Eimeria tenella* and improve their weight gain [96]. The broiler diet, which contained thymol (200 mg·kg^{-1} diet), gallic acid (5 g·kg^{-1} diet), and tannic acid (5 g·kg^{-1} diet), was found to improve the feed utilization and final body weight [97]. Grape pomace concentrate (60 g·kg^{-1} diet) was found to improve feed efficiency [98]. Green tea polyphenols in the broiler diet improved the feed conversion ratio in liver and muscle treated with corticosterone, but impaired the feed efficiency without corticosterone treatment [99]. Resveratrol (1% of diet) impaired the body weight gains of broiler birds as well as their feed conversion ratios [100]. Dietary quercetin (0.2–0.6 g·kg^{-1} diet) was found to increase the laying rate and decrease the feed-to-egg ratio [101]. Tea polyphenols (5–15 mg·kg^{-1} diet) were reported to prevent the adverse effect of vanadium on egg quality [102].

In dairy cows, pomegranate-extracted polyphenols decreased the digestibility of protein and fat due to the suppression of these nutrients by high tannins content [103]. The supplementation of dairy cow feed with polyphenol-rich grape seed and marc extract was found to improve milk performance [104]. Plant products were shown to cause a reduction of fatty liver formation and an improvement in milk performance in cows [105].

Although direct proof of the link between phytochemical-caused improvements on the growth performance of farm animals and the Nrf2/Keap1 system has not yet been fully established, significant improvements in antioxidant and anti-inflammatory properties caused by phytochemicals-based feedings have been extensively observed in many studies, and may be strongly associated with the Nrf2/Keap1 system.

2.2. Meat quality

A very large number of studies were performed to study the effects of phytochemicals on meat quality, with a focus on antioxidant properties, anti-inflammatory properties, and sensory performances such as color, texture, and flavor [106–133].

2.2.1. Antioxidant properties

The antioxidant properties of phytochemicals in farm animals, meat, and meat products have been extensively studied, forming a basis for an understanding of other functions of phytochemicals.

Phytochemicals supplementation was reported to improve the redox status and reduce excessive oxidative stress in pigs treated by peroxidation, by reducing plasma lipid peroxidation and lowering malondialdehyde (MDA) level. However, phytochemicals had no such effects in the case of non-pro-oxidative treatment [94,106,107]. Plant phytochemicals in the diet also moderately improved the antioxidant status in broilers and laying hens through the reduction of MDA and thiobarbituric acid reactive substance (TBARS) concentrations, and the induction of glutathione peroxidase (GPx) activity [96,98,102]. However, the antioxidant status was found to be less influenced in dairy cattle by phytochemicals supplementation, although the activity of superoxide dismutase (SOD) increased occasionally [104,105].

In meat and meat products, lipid oxidation is found to be the primary cause of quality loss. During the digestion–absorption–metabolism process, a number of oxidative compounds and stresses emerge and accumulate in the organism or tissues, adversely limiting the shelf-life and affecting the quality of the meat or meat products, including texture, color, flavor, nutritive value, and safety [136]. The toxic effects of synthetic antioxidants and consumers' interest in natural products have accelerated the development of natural phytochemicals as better choices than additives [137]. For example, the addition to pork patties of phytochemicals, such as extracts of grape skin, green tea, rosemary, and coffee, was observed to reduce lipid oxidation and the values of TBARS and hexanal at doses of 50–200 ppm [108]. In raw or cooked goat meat patties, extracts of red peony, white peony, moutan peony, rehmannia, sappan wood, and angelica were found to reduce lipid oxidation, at doses of 0.5%–2.0% [109]. In raw beef patties, ground beef, and buffalo meat patties, extracts of olive leaf, date pits, and rosemary leaf were found to reduce TBARS value, lipid oxidation, and oxymyoglobin oxidation, respectively [110–112]. In pork and beef sausages, adzuki bean extract and grape seed extract were found to reduce lipid oxidation and TBARS values [113,114]. The antioxidant properties of green tea extract, rosemary extract, and grape seed extract are well studied and their application in meat and meat products has been reviewed in a report [130].

2.2.2. Anti-inflammatory properties

Diets containing grape seed, marc extract, and hop extract were found to downregulate the expressions of various pro-inflammatory genes in the small intestine of growing pigs [95]. Cocoa powder in pig feed also decreased the gene expressions of Toll-like receptors and tumor necrosis factor (TNF)-α [117].

The anti-inflammatory effect of tea polyphenols on poultry was reported by investigating the expressions of a series of pro-inflammatory cytokines in the intestine of broilers. The results showed that tea polyphenols (0.03–0.09 g·kg^{-1} body weight) caused a downregulation of the gene expressions of TNF-α, interleukin (IL)-4, IL-10, IL-1β, and interferon (IFN)-γ [118].

Feeding cattle with pomegranate-extract polyphenols (5–10 g·d^{-1}) increased the secretion of IL-4 and IFN-γ in peripheral blood mononuclear cells and improved the total immunoglobulin G (IgG) responses to the vaccination of ovalbumin [119]. Feeding dairy cows grape seed and marc extract stimulated a significant downregulation of the marker of endoplasmic reticulum stress, fibroblast growth factor (FGF)-21, as well as decreasing fat accumulation in the liver [104].

2.2.3. Sensory performance

Sensory performance is generally used to evaluate the color, flavor, and taste of meat or meat products. Phytochemicals have been found to affect the sensory performance of meat significantly.

For example, 0.5%–2.0% of white peony extract increased the redness value (a^* value) in raw and cooked meat patties [109]; 300–500 ppm of rosemary extract maintained the red color of raw frozen sausage [120]; 300 mg·kg^{-1} meat of green tea extract decreased the a^* value in raw patties and eliminated rancid flavor in cooked patties [121,122]; 0.01%–0.02% of grape seed extract reduced visual green discoloration of beef patties [123]; 10% of myrtle extract prevented color changes in beef patties [124]; 2.7–10.8 mg·(100 g)$^{-1}$ of *Eleutherine americana* extract increased a^* value in cooked pork [125]; 0.2% of adzuki bean extract increased a^* value but decreased lightness (L^*

value) and yellowness (b^* value) in cured or uncured cooked pork sausages [126]; 500–6000 ppm of green tea extract increased a^* value whereas grape seed extract decreased a^* value in raw and cooked goat meat, and pepper extract was helpful in maintaining a^* value in cooked pork [127,128]; 5 mL·(500 g)$^{-1}$ meat of curry leaf extract decreased the L^* value and a^* value while increasing the b^* value in raw ground pork [129]; and 130 ppm of rosemary leaf extract stabilized the color in raw and cooked ground buffalo meat patties [130].

In addition, plum products exhibited minor effect on flavor but caused color change in many meat and poultry products, and grape seed extract led to a significant change in color in meat products [137].

2.3. Intestinal microbiota

Studies focusing on the effect of phytochemicals on the intestinal microbiota *in vivo* have increased markedly in recent years. It is considered that intestinal microbiota are the first targets of dietary phytochemicals, and that they show many links to health. Thus, many health-promoting effects of phytochemicals may be attributed to their modulation of the intestinal microbiota [138]. For example, only 5%–10% of polyphenols can be absorbed in the small intestine; 90%–95% enter the colon and are bio-transformed with the aid of the enzymatic colon microbiota into a series of polyphenolic metabolites [90]. The polyphenolic metabolites are able to partially re-absorb into the systematic circulation after conjugation once again in the liver and the enterocyte, and partially serve as antimicrobial substances or growth-promoting substrates. On the other hand, polyphenols or their metabolites can affect the composition and density of the colon microbiota in a profitable manner, including promotion of the growth of beneficial bacteria in a prebiotic-like manner and inhibition of certain pathogenic bacteria [139,140].

Limited studies were performed to specifically investigate the effects of polyphenols on the intestinal microbiota in farm animals. Cocoa powder feeding was found to increase the abundance of several bacterial strains in pigs, including *Lactobacillus*, *Bifidobacterium* spp., *Bacteroides-Prevotella*, and *Faecalibacterium prausnitzii* [117,134]. A few studies revealed that polyphenols may exhibit favorable effects in the intestine of broilers. Grape pomace concentrate supplementation in broiler feed was found to have a beneficial effect on the intestinal microbial population by increasing the abundance of *Enterococcus* and decreasing that of *Clostridium* [98]. Quercetin feeding in laying hens was reported to improve the caecal microflora status by decreasing the total number of aerobes and coliforms and increasing that of *Bifidobacterium* [101]. Tea polyphenols were found to increase the amount of lactobacilli and decrease that of the total bacteria, Bacteroidaceae, and *Clostridium* (*C.*) *perfringens* in pigs; however, they decreased *Bifidobacterium* spp., *Lactobacillus* spp., and *C. perfringens* in calves [102,135].

A recent review summarized the impact of polyphenols on the intestinal microbiota in rat and human models, and revealed that polyphenols or polyphenol-rich sources are able to affect the relative abundance of different bacterial groups by reducing the abundances of the potential pathogens *C. perfringens* and *C. histolyticum*, as well as that of Gram-negative *Bacteroides* spp., and by increasing the populations of certain beneficial strains, such as clostridia, bifidobacteria, and lactobacilli [108].

Based on the effects of phytochemicals on bacterial strains in several lines of studies, the antioxidant and anti-inflammatory properties of phytochemicals may be linked to improvements in gut health [141,142].

2.4. Detrimental effects of phytochemicals in farm animals

Although the biofunctional properties of phytochemicals are powerful and promising for farm animals, detrimental effects of phytochemicals have also been reported in some cases. For example, high consumption of polyphenols can inhibit the absorption of nutrients [143,144] and cause toxic effects. Moreover, a high dose of quercetin was observed to be related to chronic nephropathy in rats and to reduce the life expectancy in mice [145]. Excess administration of green tea polyphenols was reported to disrupt kidney function in mice [146] and enhance tumor development in the colon of male rats [147]. Excess intake of caffeic acid caused kidney and gastrointestinal tumors in mice and rats [148]. Although these data were obtained from experimental animals, they suggest that the administration of a high dose of phytochemicals should be avoided in farm animals.

Although the anti-inflammatory, antioxidative, and cytoprotective properties of phytochemicals have been less studied in farm animals, an extremely large number of such studies have been done using human and experimental animal models. Thus, the biofunctions of phytochemicals in farm animals are also considered to occur through modulating the Nrf2/Keap1 system, which is a central modulator in combating oxidative stress and chronic inflammation [90].

3. Future perspectives

Several lines of studies have reported that the Nrf2/Keap1 system can regulate the general energy metabolism system by inhibiting gluconeogenesis [149]; modulate the activities of several lipases involved in the degradation of triglycerides/phospholipids [150] as well as enzymes involved in fatty acid oxidation, lipid biosynthesis, fatty acid desaturation, and fatty acid transport [150]; affect redox-sensitive metabolic systems such as the AMP-activated protein kinase pathway [151]; and adjust mitochondrial metabolism processes such as glucose oxidation and substrate entry, and ATP production [152,153]. EGCG has been shown to affect the general energy metabolism system in rats and in humans [154]. However, no data are available regarding farm animals, and the underlying molecular mechanism remains unclear. Thus, further studies are required to clarify the impact of phytochemicals on the energy metabolism system in farm animals.

Although extensive data have been accumulated on the biofunctions of phytochemicals in humans and in experimental animals, most of these data focus on the chemopreventive effects of phytochemicals on chronic diseases such as cancer, cardiovascular disease, and metabolic syndrome. The molecular data have been deeply mined to clarify how dietary phytochemicals modulate signaling pathways and gene expressions for homeostasis. On the other hand, the biofunctions of phytochemicals in farm animals have been paid a great deal of attention regarding growth performance, meat quality, and the use of phytochemicals as an antibiotic replacer or substituter, although the molecular data on mechanisms that have been obtained from farm animals are fewer than those obtained from humans and experimental animals. It appears to be difficult to compare the differences in the mechanisms of phytochemicals in farm animal nutrition and in human nutrition. However, the results from studies on the antioxidant properties and mechanisms of phytochemicals in farm animals are almost the same as the results of similar studies in humans, with the Nrf2/Keap1 system acting as an axis. Therefore, it is possible to take advantage of the phytochemical data from humans and experimental animals and apply them to farm animals.

Phytochemicals have multiple biofunctions for human and other animal health. The modulation of the Nrf2/Keap1 system by phytochemicals may play a central role in their multiple biofunctions because the Nrf2/Keap1 system is linked to antioxidant functions, anti-inflammation functions, and many other functions. The relatively low absorption ratio of most phytochemicals in the small intestine

shifts the research field from a focus on direct antioxidant properties to a focus on indirect pro-oxidant properties, biotransformation, signaling transduction, and gene expression regulation. Although the limited studies on the effects of phytochemicals on the intestinal microbiota of farm animals are currently insufficient to show the significant improvements in growth performance, antioxidant parameters, and inflammatory parameters, these findings will pave the way for further studies to understand the health-promoting effects of dietary phytochemicals.

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Compliance with ethics guidelines

Si Qin and De-Xing Hou declare that they have no conflict of interest or financial conflicts to disclose.

References

[1] Molyneux RJ, Lee ST, Gardner DR, Panter KE, James LF. Phytochemicals: The good, the bad and the ugly? Phytochemistry 2007;68(22–24):2973–85.
[2] Surh YJ. Cancer chemoprevention with dietary phytochemicals. Nat Rev Cancer 2003;3(10):768–80.
[3] Lampe JW. Spicing up a vegetarian diet: Chemopreventive effects of phytochemicals. Am J Clin Nutr 2003;78(3 Suppl):579S–83S.
[4] Fraser GE. Vegetarian diets: What do we know of their effects on common chronic diseases? Am J Clin Nutr 2009;89(5):1607S–12S.
[5] Wasserman WW, Fahl WE. Functional antioxidant responsive elements. Proc Natl Acad Sci USA 1997;94(10):5361–6.
[6] Hayes JD, McMahon M, Chowdhry S, Dinkova-Kostova AT. Cancer chemoprevention mechanisms mediated through the Keap1-Nrf2 pathway. Antioxid Redox Signal 2010;13(11):1713–48.
[7] Chorley BN, Campbell MR, Wang X, Karaca M, Sambandan D, Bangura F, et al. Identification of novel Nrf2-regulated genes by ChIP-Seq: Influence on retinoid X receptor alpha. Nucleic Acids Res 2012;40(15):7416–29.
[8] Baird L, Dinkova-Kostova AT. The cytoprotective role of the Keap1-Nrf2 pathway. Arch Toxicol 2011;85(4):241–72.
[9] Dinkova-Kostova AT, Massiah MA, Bozak RE, Hicks RJ, Talalay P. Potency of Michael reaction acceptors as inducers of enzymes that protect against carcinogenesis depends on their reactivity with sulfhydryl groups. Proc Natl Acad Sci USA 2001;98(6):3404–9.
[10] Kobayashi M, Li L, Iwamoto N, Nakajima-Takagi Y, Kaneko H, Nakayama Y, et al. The antioxidant defense system Keap1-Nrf2 comprises a multiple sensing mechanism for responding to a wide range of chemical compounds. Mol Cell Biol 2009;29(2):493–502.
[11] Zhang DD, Hannink M. Distinct cysteine residues in Keap1 are required for Keap1-dependent ubiquitination of Nrf2 and for stabilization of Nrf2 by chemopreventive agents and oxidative stress. Mol Cell Biol 2003;23(22):8137–51.
[12] Furukawa M, Xiong Y. BTB protein Keap1 targets antioxidant transcription factor Nrf2 for ubiquitination by the Cullin 3-Roc1 ligase. Mol Cell Biol 2005;25(1):162–71.
[13] Canning P, Sorrell FJ, Bullock AN. Structural basis of Keap1 interactions with Nrf2. Free Radic Biol Med 2015;88(Pt B):101–7.
[14] Tong KI, Katoh Y, Kusunoki H, Itoh K, Tanaka T, Yamamoto M. Keap1 recruits Neh2 through binding to ETGE and DLG motifs: Characterization of the two-site molecular recognition model. Mol Cell Biol 2006;26(8):2887–900.
[15] Komatsu M, Kurokawa H, Waguri S, Taguchi K, Kobayashi A, Ichimura Y, et al. The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1. Nat Cell Biol 2010;12(3):213–23.
[16] Adam J, Hatipoglu E, O'Flaherty L, Ternette N, Sahgal N, Lockstone H, et al. Renal cyst formation in Fh1-deficient mice is independent of the Hif/Phd pathway: Roles for fumarate in KEAP1 succination and Nrf2 signaling. Cancer Cell 2011;20(4):524–37.
[17] Jain AK, Mahajan S, Jaiswal AK. Phosphorylation and dephosphorylation of tyrosine 141 regulate stability and degradation of INrf2: A novel mechanism in Nrf2 activation. J Biol Chem 2008;283(25):17712–20.
[18] Tanigawa S, Fujii M, Hou DX. Action of Nrf2 and Keap1 in ARE-mediated NQO1 expression by quercetin. Free Radic Biol Med 2007;42(11):1690–703.
[19] Yao P, Nussler A, Liu L, Hao L, Song F, Schirmeier A, et al. Quercetin protects human hepatocytes from ethanol-derived oxidative stress by inducing heme oxygenase-1 via the MAPK/Nrf2 pathways. J Hepatol 2007;47(2):253–61.
[20] Lin CW, Wu MJ, Liu IY, Su JD, Yen JH. Neurotrophic and cytoprotective action of luteolin in PC12 cells through ERK-dependent induction of Nrf2-driven HO-1 expression. J Agric Food Chem 2010;58(7):4477–86.
[21] Rodríguez-Ramiro I, Ramos S, Bravo L, Goya L, Martín MÁ. Procyanidin B2 induces Nrf2 translocation and glutathione S-transferase P1 expression via ERKs and p38-MAPK pathways and protect human colonic cells against oxidative stress. Eur J Nutr 2012;51(7):881–92.
[22] Lee SE, Jeong SI, Yang H, Park CS, Jin YH, Park YS. Fisetin induces Nrf2-mediated HO-1 expression through PKC-δ and p38 in human umbilical vein endothelial cells. J Cell Biochem 2011;112(9):2352–60.
[23] Chen MC, Ye YY, Ji G, Liu JW. Hesperidin upregulates heme oxygenase-1 to attenuate hydrogen peroxide-induced cell damage in hepatic L02 cells. J Agric Food Chem 2010;58(6):3330–5.
[24] Dietz BM, Kang YH, Liu G, Eggler AL, Yao P, Chadwick LR, et al. Xanthohumol isolated from *Humulus lupulus* inhibits menadione-induced DNA damage through induction of quinone reductase. Chem Res Toxicol 2005;18(8):1296–305.
[25] Liu YC, Hsieh CW, Wu CC, Wung BS. Chalcone inhibits the activation of NF-κB and STAT3 in endothelial cells via endogenous electrophile. Life Sci 2007;80(15):1420–30.
[26] Qin S, Chen J, Tanigawa S, Hou DX. Gene expression profiling and pathway network analysis of hepatic metabolic enzymes targeted by baicalein. J Ethnopharmacol 2012;140(1):131–40.
[27] Song HJ, Shin CY, Oh TY, Sohn UD. The protective effect of eupatilin on indomethacin-induced cell damage in cultured feline ileal smooth muscle cells: Involvement of HO-1 and ERK. J Ethnopharmacol 2008;118(1):94–101.
[28] Lim JH, Park HS, Choi JK, Lee IS, Choi HJ. Isoorientin induces Nrf2 pathway-driven antioxidant response through phosphatidylinositol 3-kinase signaling. Arch Pharm Res 2007;30(12):1590–8.
[29] Zhang R, Chae S, Lee JH, Hyun JW. The cytoprotective effect of butin against oxidative stress is mediated by the up-regulation of manganese superoxide dismutase expression through a PI3K/Akt/Nrf2-dependent pathway. J Cell Biochem 2012;113(6):1987–97.
[30] Hwang YP, Jeong HG. Mechanism of phytoestrogen puerarin-mediated cytoprotection following oxidative injury: Estrogen receptor-dependent up-regulation of PI3K/Akt and HO-1. Toxicol Appl Pharmacol 2008;233(3):371–81.
[31] Thuong PT, Pokharel YR, Lee MY, Kim SK, Bae K, Su ND, et al. Dual anti-oxidative effects of fraxetin isolated from *Fraxinus rhinchophylla*. Biol Pharm Bull 2009;32(9):1527–32.
[32] Park EJ, Lim JH, Nam SI, Park JW, Kwon TK. Rottlerin induces heme oxygenase-1 (HO-1) up-regulation through reactive oxygen species (ROS) dependent and PKC δ-independent pathway in human colon cancer HT29 cells. Biochimie 2010;92(1):110–5.
[33] Andreadi CK, Howells LM, Atherfold PA, Manson MM. Involvement of Nrf2, p38, B-Raf, and nuclear factor-κB, but not phosphatidylinositol 3-kinase, in induction of hemeoxygenase-1 by dietary polyphenols. Mol Pharmacol 2006;69(3):1033–40.
[34] Wu CC, Hsu MC, Hsieh CW, Lin JB, Lai PH, Wung BS. Upregulation of heme oxygenase-1 by Epigallocatechin-3-gallate via the phosphatidylinositol 3-kinase/Akt and ERK pathways. Life Sci 2006;78(25):2889–97.
[35] Granado-Serrano AB, Martín MA, Haegeman G, Goya L, Bravo L, Ramos S. Epicatechin induces NF-κB, activator protein-1 (AP-1) and nuclear transcription factor erythroid 2p45-related factor-2 (Nrf2) via phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) and extracellular regulated kinase (ERK) signalling in HepG2 cells. Br J Nutr 2010;103(2):168–79.
[36] Gao SS, Choi BM, Chen XY, Zhu RZ, Kim Y, So H, et al. Kaempferol suppresses cisplatin-induced apoptosis via inductions of heme oxygenase-1 and glutamate-cysteine ligase catalytic subunit in HEI-OC1 cell. Pharm Res 2010;27(2):235–45.
[37] Bak MJ, Jun M, Jeong WS. Procyanidins from wild grape (*Vitis amurensis*) seeds regulate ARE-mediated enzyme expression via Nrf2 coupled with p38 and PI3K/Akt pathway in HepG2 cells. Int J Mol Sci 2012;13(1):801–18.
[38] Kode A, Rajendrasozhan S, Caito S, Yang SR, Megson IL, Rahman I. Resveratrol induces glutathione synthesis by activation of Nrf2 and protects against cigarette smoke-mediated oxidative stress in human lung epithelial cells. Am J Physiol Lung Cell Mol Physiol 2008;294(3):L478–88.
[39] Chen CY, Jang JH, Li MH, Surh YJ. Resveratrol upregulates heme oxygenase-1 expression via activation of NF-E2-related factor 2 in PC12 cells. Biochem Biophys Res Commun 2005;331(4):993–1000.
[40] Tsai CW, Lin CY, Wang YJ. Carnosic acid induces the NAD(P)H: Quinone oxidoreductase 1 expression in rat clone 9 cells through the p38/nuclear factor erythroid-2 related factor 2 pathway. J Nutr 2011;141(12):2119–25.
[41] Satoh T, Kosaka K, Itoh K, Kobayashi A, Yamamoto M, Shimojo Y, et al. Carnosic acid, a catechol-type electrophilic compound, protects neurons both *in vitro* and *in vivo* through activation of the Keap1/Nrf2 pathway via S-alkylation of targeted cysteines on Keap1. J Neurochem 2008;104(4):1116–31.
[42] Chiou YS, Tsai ML, Nagabhushanam K, Wang YJ, Wu CH, Ho CT. et al. Pterostilbene is more potent than resveratrol in preventing azoxymethane (AOM)-induced colon tumorigenesis via activation of the NF-E2-related factor 2 (Nrf2)-mediated antioxidant signaling pathway. J Agric Food Chem 2011;59(6):2725–33.
[43] Liao BC, Hsieh CW, Liu YC, Tzeng TT, Sun YW, Wung BS. Cinnamaldehyde inhibits the tumor necrosis factor-α-induced expression of cell adhesion molecules in endothelial cells by suppressing NF-κB activation: Effects upon IκB and Nrf2. Toxicol Appl Pharmacol 2008;229(2):161–71.
[44] Feng J, Zhang P, Chen X, He G. PI3K and ERK/Nrf2 pathways are involved in

oleanolic acid-induced heme oxygenase-1 expression in rat vascular smooth muscle cells. J Cell Biochem 2011;112(6):1524–31.
[45] Seo JY, Lim SS, Kim JR, Lim JS, Ha YR, Lee IA, et al. Nrf2-mediated induction of detoxifying enzymes by alantolactone present in *Inula helenium*. Phytother Res 2008;22(11):1500–5.
[46] Wang HQ, Xu YX, Zhu CQ. Upregulation of heme oxygenase-1 by acteoside through ERK and PI3 K/Akt pathway confer neuroprotection against β-amyloid-induced neurotoxicity. Neurotox Res 2012;21(4):368–78.
[47] Seo WY, Goh AR, Ju SM, Song HY, Kwon DJ, Jun JG, et al. Celastrol induces expression of heme oxygenase-1 through ROS/Nrf2/ARE signaling in the HaCaT cells. Biochem Biophys Res Commun 2011;407(3):535–40.
[48] Lee HH, Park SA, Almazari I, Kim EH, Na HK, Surh YJ. Piceatannol induces heme oxygenase-1 expression in human mammary epithelial cells through activation of ARE-driven Nrf2 signaling. Arch Biochem Biophys 2010;501(1):142–50.
[49] Hwang YP, Jeong HG. The coffee diterpene kahweol induces heme oxygenase-1 via the PI3K and p38/Nrf2 pathway to protect human dopaminergic neurons from 6-hydroxydopamine-derived oxidative stress. FEBS Lett 2008;582(17):2655–62.
[50] Chen JH, Huang SM, Tan TW, Lin HY, Chen PY, Yeh WL, et al. Berberine induces heme oxygenase-1 up-regulation through phosphatidylinositol 3-kinase/AKT and NF-E2-related factor-2 signaling pathway in astrocytes. Int Immunopharmacol 2012;12(1):94–100.
[51] Zrelli H, Matsuoka M, Kitazaki S, Araki M, Kusunoki M, Zarrouk M, et al. Hydroxytyrosol induces proliferation and cytoprotection against oxidative injury in vascular endothelial cells: Role of Nrf2 activation and HO-1 induction. J Agric Food Chem 2011;59(9):4473–82.
[52] Zou X, Feng Z, Li Y, Wang Y, Wertz K, Weber P, et al. Stimulation of GSH synthesis to prevent oxidative stress-induced apoptosis by hydroxytyrosol in human retinal pigment epithelial cells: Activation of Nrf2 and JNK-p62/SQSTM1 pathways. J Nutr Biochem 2012;23(8):994–1006.
[53] Hamada N, Tanaka A, Fujita Y, Itoh T, Ono Y, Kitagawa Y, et al. Involvement of heme oxygenase-1 induction via Nrf2/ARE activation in protection against H_2O_2-induced PC12 cell death by a metabolite of sesamin contained in sesame seeds. Bioorg Med Chem 2011;19(6):1959–65.
[54] Zhang Y, Guan L, Wang X, Wen T, Xing J, Zhao J. Protection of chlorophyllin against oxidative damage by inducing HO-1 and NQO1 expression mediated by PI3K/Akt and Nrf2. Free Radic Res 2008;42(4):362–71.
[55] Sumi D, Numasawa Y, Endo A, Iwamoto N, Kumagai Y. Catechol estrogens mediated activation of Nrf2 through covalent modification of its quinone metabolite to Keap1. J Toxicol Sci 2009;34(6):627–35.
[56] Hong F, Freeman ML, Liebler DC. Identification of sensor cysteines in human Keap1 modified by the cancer chemopreventive agent sulforaphane. Chem Res Toxicol 2005;18(12):1917–26.
[57] Keum YS, Yu S, Chang PP, Yuan X, Kim JH, Xu C, et al. Mechanism of action of sulforaphane: Inhibition of p38 mitogen-activated protein kinase isoforms contributing to the induction of antioxidant response element-mediated heme oxygenase-1 in human hepatoma HepG2 cells. Cancer Res. 2006;66(17):8804–13.
[58] Jakubíková J, Sedlák J, Mithen R, Bao Y. Role of PI3K/Akt and MEK/ERK signaling pathways in sulforaphane- and erucin-induced phase II enzymes and MRP2 transcription, G2/M arrest and cell death in Caco-2 cells. Biochem Pharmacol 2005;69(11):1543–52.
[59] Zhang C, Su ZY, Khor TO, Shu L, Kong AN. Sulforaphane enhances Nrf2 expression in prostate cancer TRAMP C1 cells through epigenetic regulation. Biochem Pharmacol 2013;85(9):1398–404.
[60] Xu C, Yuan X, Pan Z, Shen G, Kim JH, Yu S, et al. Mechanism of action of isothiocyanates: The induction of ARE-regulated genes is associated with activation of ERK and JNK and the phosphorylation and nuclear translocation of Nrf2. Mol Cancer Ther 2006;5(8):1918–26.
[61] Saw CL, Cintrón M, Wu TY, Guo Y, Huang Y, Jeong WS, et al. Pharmacodynamics of dietary phytochemical indoles I3C and DIM: Induction of Nrf2-mediated phase II drug metabolizing and antioxidant genes and synergism with isothiocyanates. Biopharm Drug Dispos 2011;32(5):289–300.
[62] Wu TY, Khor TO, Su ZY, Saw CL, Shu L, Cheung KL, et al. Epigenetic modifications of Nrf2 by 3,3′-diindolylmethane *in vitro* in TRAMP C1 cell line and *in vivo* TRAMP prostate tumors. AAPS J 2013;15(3):864–74.
[63] Chen C, Pung D, Leong V, Hebbar V, Shen G, Nair S, et al. Induction of detoxifying enzymes by garlic organosulfur compounds through transcription factor Nrf2: Effect of chemical structure and stress signals. Free Radic Biol Med 2004;37(10):1578–90.
[64] Jeon WK, Hong HY, Kim BC. Genipin up-regulates heme oxygenase-1 via PI3-kinase-JNK1/2-Nrf2 signaling pathway to enhance the anti-inflammatory capacity in RAW264.7 macrophages. Arch Biochem Biophys 2011;512(2):119–25.
[65] Almazari I, Park JM, Park SA, Suh JY, Na HK, Cha YN, et al. Guggulsterone induces heme oxygenase-1 expression through activation of Nrf2 in human mammary epithelial cells: PTEN as a putative target. Carcinogenesis 2012;33(2):368–76.
[66] Tang X, Wang H, Fan L, Wu X, Xin A, Ren H, et al. Luteolin inhibits Nrf2 leading to negative regulation of the Nrf2/ARE pathway and sensitization of human lung carcinoma A549 cells to therapeutic drugs. Free Radic Biol Med 2011;50(11):1599–609.
[67] Chian S, Li YY, Wang XJ, Tang XW. Luteolin sensitizes two oxaliplatin-resistant colorectal cancer cell lines to chemotherapeutic drugs via inhibition of the Nrf2 pathway. Asian Pac J Cancer Prev 2014;15(6):2911–6.
[68] Gao AM, Ke ZP, Wang JN, Yang JY, Chen SY, Chen H. Apigenin sensitizes doxorubicin-resistant hepatocellular carcinoma BEL-7402/ADM cells to doxorubicin via inhibiting PI3K/Akt/Nrf2 pathway. Carcinogenesis 2013;34(8):1806–14.
[69] Gao AM, Ke ZP, Shi F, Sun GC, Chen H. Chrysin enhances sensitivity of BEL-7402/ADM cells to doxorubicin by suppressing PI3K/Akt/Nrf2 and ERK/Nrf2 pathway. Chem Biol Interact 2013;206(1):100–8.
[70] Lim J, Lee SH, Cho S, Lee IS, Kang BY, Choi HJ. 4-methoxychalcone enhances cisplatin-induced oxidative stress and cytotoxicity by inhibiting the Nrf2/ARE-mediated defense mechanism in A549 lung cancer cells. Mol Cells 2013;36(4):340–6.
[71] Hou X, Bai X, Gou X, Zeng H, Xia C, Zhuang W, et al. 3′,4′,5′,5,7-pentamethoxyflavone sensitizes cisplatin-resistant A549 cells to cisplatin by inhibition of Nrf2 pathway. Mol Cells 2015;38(5):396–401.
[72] Kweon MH, Adhami VM, Lee JS, Mukhtar H. Constitutive overexpression of Nrf2-dependent heme oxygenase-1 in A549 cells contributes to resistance to apoptosis induced by epigallocatechin 3-gallate. J Biol Chem 2006;281(44):33761–72.
[73] Ren D, Villeneuve NF, Jiang T, Wu T, Lau A, Toppin HA, et al. Brusatol enhances the efficacy of chemotherapy by inhibiting the Nrf2-mediated defense mechanism. Proc Natl Acad Sci USA 2011;108(4):1433–8.
[74] Xia C, Bai X, Hou X, Gou X, Wang Y, Zeng H, et al. Cryptotanshinone reverses cisplatin resistance of human lung carcinoma A549 cells through down-regulating Nrf2 pathway. Cell Physiol Biochem 2015;37(2):816–24. .
[75] Do MT, Kim HG, Khanal T, Choi JH, Kim DH, Jeong TC, et al. Metformin inhibits heme oxygenase-1 expression in cancer cells through inactivation of Raf-ERK-Nrf2 signaling and AMPK-independent pathways. Toxicol Appl Pharmacol 2013;271(2):229–38.
[76] Do MT, Kim HG, Choi JH, Jeong HG. Metformin induces microRNA-34a to down-regulate the Sirt1/Pgc-1α/Nrf2 pathway, leading to increased susceptibility of wild-type p53 cancer cells to oxidative stress and therapeutic agents. Free Radic Biol Med 2014;74:21–34.
[77] Cavin C, Delatour T, Marin-Kuan M, Fenaille F, Holzhäuser D, Guignard G, et al. Ochratoxin A-mediated DNA and protein damage: Roles of nitrosative and oxidative stresses. Toxicol Sci 2009;110(1):84–94.
[78] Boesch-Saadatmandi C, Wagner AE, Graeser AC, Hundhausen C, Wolffram S, Rimbach G. Ochratoxin A impairs Nrf2-dependent gene expression in porcine kidney tubulus cells. J Anim Physiol Anim Nutr (Berl) 2009;93(5):547–54.
[79] Arlt A, Sebens S, Krebs S, Geismann C, Grossmann M, Kruse ML, et al. Inhibition of the Nrf2 transcription factor by the alkaloid trigonelline renders pancreatic cancer cells more susceptible to apoptosis through decreased proteasomal gene expression and proteasome activity. Oncogene 2013;32(40):4825–35.
[80] Boettler U, Sommerfeld K, Volz N, Pahlke G, Teller N, Somoza V, et al. Coffee constituents as modulators of Nrf2 nuclear translocation and ARE (EpRE)-dependent gene expression. J Nutr Biochem 2011;22(5):426–40.
[81] Tanigawa S, Lee CH, Lin CS, Ku CC, Hasegawa H, Qin S, et al. Jun dimerization protein 2 is a critical component of the Nrf2/MafK complex regulating the response to ROS homeostasis. Cell Death Dis 2013;4:e921.
[82] Liu GH, Qu J, Shen X. NF-κB/p65 antagonizes Nrf2-ARE pathway by depriving CBP from Nrf2 and facilitating recruitment of HDAC3 to MafK. Biochim Biophys Acta 2008;1783(5):713–27.
[83] Shankar S, Kumar D, Srivastava RK. Epigenetic modifications by dietary phytochemicals: Implications for personalized nutrition. Pharmacol Ther 2013;138(1):1–17.
[84] Su ZY, Khor TO, Shu L, Lee JH, Saw CL, Wu TY, et al. Epigenetic reactivation of Nrf2 in murine prostate cancer TRAMP C1 cells by natural phytochemicals Z-ligustilide and *Radix angelica sinensis* via promoter CpG demethylation. Chem Res Toxicol 2013;26(3):477–85.
[85] Khor TO, Huang Y, Wu TY, Shu L, Lee J, Kong AN. Pharmacodynamics of curcumin as DNA hypomethylation agent in restoring the expression of Nrf2 via promoter CpGs demethylation. Biochem Pharmacol 2011;82(9):1073–8.
[86] Paredes-Gonzalez X, Fuentes F, Su ZY, Kong AN. Apigenin reactivates Nrf2 antioxidative stress signaling in mouse skin epidermal JB6 P+ cells through epigenetics modifications. AAPS J 2014;16(4):727–35.
[87] Su ZY, Zhang C, Lee JH, Shu L, Wu TY, Khor TO, et al. Requirement and epigenetics reprogramming of Nrf2 in suppression of tumor promoter TPA-induced mouse skin cell transformation by sulforaphane. Cancer Prev Res (Phila) 2014;7(3):319–29.
[88] Wang L, Zhang C, Guo Y, Su ZY, Yang Y, Shu L, et al. Blocking of JB6 cell transformation by tanshinone IIA: Epigenetic reactivation of Nrf2 antioxidative stress pathway. AAPS J 2014;16(6):1214–25.
[89] Zhu J, Wang H, Chen F, Fu J, Xu Y, Hou Y, et al. An overview of chemical inhibitors of the Nrf2-ARE signaling pathway and their potential applications in cancer therapy. Free Radic Biol Med 2016;99:544–56.
[90] Gessner DK, Ringseis R, Eder K. Potential of plant polyphenols to combat oxidative stress and inflammatory processes in farm animals. J Anim Physiol Anim Nutr (Berl). Epub 2016 Jul 25.
[91] Burgess TA, Robich MP, Chu LM, Bianchi C, Sellke FW. Improving glucose metabolism with resveratrol in a swine model of metabolic syndrome through alteration of signaling pathways in the liver and skeletal muscle. Arch Surg 2011;146(5):556–64.
[92] Azorín-Ortuño M, Yañéz-Gascón MJ, Pallarés FJ, Rivera J, González-Sarrías A, Larrosa M, et al. A dietary resveratrol-rich grape extract prevents the developing of atherosclerotic lesions in the aorta of pigs fed an atherogenic diet. J Agric Food Chem 2012;60(22):5609–20.
[93] Robich MP, Osipov RM, Nezafat R, Feng J, Clements RT, Bianchi C, et al. Resveratrol improves myocardial perfusion in a swine model of hypercholesterolemia and chronic myocardial ischemia. Circulation 2010;122(11 Suppl 1):S142–9.

[94] Gessner DK, Ringseis R, Siebers M, Keller J, Kloster J, Wen G, et al. Inhibition of the pro-inflammatory NF-κB pathway by a grape seed and grape marc meal extract in intestinal epithelial cells. J Anim Physiol Anim Nutr (Berl) 2012;96(6):1074–83.
[95] Gessner DK, Fiesel A, Most E, Dinges J, Wen G, Ringseis R, et al. Supplementation of a grape seed and grape marc meal extract decreases activities of the oxidative stress-responsive transcription factors NF-κB and Nrf2 in the duodenal mucosa of pigs. Acta Vet Scand 2013;55:18.
[96] Wang ML, Suo X, Gu JH, Zhang WW, Fang Q, Wang X. Influence of grape seed proanthocyanidin extract in broiler chickens: Effect on chicken coccidiosis and antioxidant status. Poult Sci 2008;87(11):2273–80.
[97] Starčević K, Krstulović L, Brozić D, Maurić M, Stojević Z, Mikulec Ž, et al. Production performance, meat composition and oxidative susceptibility in broiler chicken fed with different phenolic compounds. J Sci Food Agric 2015;95(6):1172–8.
[98] Viveros A, Chamorro S, Pizarro M, Arija I, Centeno C, Brenes A. Effects of dietary polyphenol-rich grape products on intestinal microflora and gut morphology in broiler chicks. Poult Sci 2011;90(3):566–78.
[99] Eid YZ, Ohtsuka A, Hayashi K. Tea polyphenols reduce glucocorticoid-induced growth inhibition and oxidative stress in broiler chickens. Br Poult Sci 2003;44(1):127–32.
[100] Sridhar M, Suganthi RU, Thammiaha V. Effect of dietary resveratrol in ameliorating aflatoxin B1-induced changes in broiler birds. J Anim Physiol Anim Nutr (Berl) 2015;99(6):1094–104.
[101] Liu HN, Liu Y, Hu LL, Suo YL, Zhang L, Jin F, et al. Effects of dietary supplementation of quercetin on performance, egg quality, cecal microflora populations, and antioxidant status in laying hens. Poult Sci 2014;93(2):347–53.
[102] Yuan ZH, Zhang KY, Ding XM, Luo YH, Bai SP, Zeng QF, et al. Effect of tea polyphenols on production performance, egg quality, and hepatic antioxidant status of laying hens in vanadium-containing diets. Poult Sci 2016;95(7):1709–17.
[103] Oliveira RA, Narciso CD, Bisinotto RS, Perdomo MC, Ballou MA, Dreher M, et al. Effects of feeding polyphenols from pomegranate extract on health, growth, nutrient digestion, and immunocompetence of calves. J Dairy Sci 2010;93(9):4280–91.
[104] Gessner DK, Gröne B, Couturier A, Rosenbaum S, Hillen S, Becker S, et al. Dietary fish oil inhibits pro-inflammatory and ER stress signalling pathways in the liver of sows during lactation. PLoS One 2015;10(9):e0137684.
[105] Winkler A, Gessner DK, Koch C, Romberg FJ, Dusel G, Herzog E, et al. Effects of a plant product consisting of green tea and curcuma extract on milk production and the expression of hepatic genes involved in endoplasmic stress response and inflammation in dairy cows. Arch Anim Nutr 2015;69(6):425–41.
[106] Luehring M, Blank R, Wolffram S. Vitamin E-sparing and vitamin E-independent antioxidative effects of the flavonol quercetin in growing pigs. Anim Feed Sci Tech 2011;169(3–4):199–207. .
[107] Hou X, Zhang J, Ahmad H, Zhang H, Xu Z, Wang T. Evaluation of antioxidant activities of ampelopsin and its protective effect in lipopolysaccharide-induced oxidative stress piglets. PLoS One 2014;9(9):e108314.
[108] Nissen LR, Byrne DV, Bertelsen G, Skibsted LH. The antioxidative activity of plant extracts in cooked pork patties as evaluated by descriptive sensory profiling and chemical analysis. Meat Sci 2004;68(3):485–95.
[109] Hayes JE, Stepanyan V, O'Grady MN, Allen P, Kerry JP. Evaluation of the effects of selected phytochemicals on quality indices and sensorial properties of raw and cooked pork stored in different packaging systems. Meat Sci 2010;85(2):289–96.
[110] Hayes JE, Stepanyan V, Allen P, O'Grady MN, Kerry JP. Effect of lutein, sesamol, ellagic acid and olive leaf extract on the quality and shelf-life stability of packaged raw minced beef patties. Meat Sci 2010;84(4):613–20.
[111] Krah DL. A simplified multiwell plate assay for the measurement of hepatitis A virus infectivity. Biologicals 1991;19(3):223–7.
[112] Naveena BM, Vaithiyanathan S, Muthukumar M, Sen AR, Kumar YP, Kiran M, et al. Relationship between the solubility, dosage and antioxidant capacity of carnosic acid in raw and cooked ground buffalo meat patties and chicken patties. Meat Sci 2013;95(2):195–202.
[113] Jayawardana BC, Hirano T, Han KH, Ishii H, Okada T, Shibayama S, et al. Utilization of adzuki bean extract as a natural antioxidant in cured and uncured cooked pork sausages. Meat Sci 2011;89(2):150–3.
[114] Kulkarni S, DeSantos FA, Kattamuri S, Rossi SJ, Brewer MS. Effect of grape seed extract on oxidative, color and sensory stability of a pre-cooked, frozen, re-heated beef sausage model system. Meat Sci 2011;88(1):139–44.
[115] Choi SH, Kwon HC, An DJ, Park JR, Oh DH. Nitrite contents and storage properties of sausage added with green tea powder. Kor J Food Sci Ani Resour 2003;23(4):299–308.
[116] Fasseas MK, Mountzouris KC, Tarantilis PA, Polissiou M, Zervas G. Antioxidant activity in meat treated with oregano and sage essential oils. Food Chem 2008;106(3):1188–94.
[117] Jang S, Sun J, Chen P, Lakshman S, Molokin A, Harnly JM, et al. Flavanol-enriched cocoa powder alters the intestinal microbiota, tissue and fluid metabolite profiles, and intestinal gene expression in pigs. J Nutr 2016;146(4):673–80.
[118] Li HL, Li ZJ, Wei ZS, Liu T, Zou XZ, Liao Y, et al. Long-term effects of oral tea polyphenols and *Lactobacillus brevis* M8 on biochemical parameters, digestive enzymes, and cytokines expression in broilers. J Zhejiang Univ Sci B 2015;16(2):1019–26.
[119] Oliveira RA, Narciso CD, Bisinotto RS, Perdomo MC, Ballou MA, Dreher M, et al. Effects of feeding polyphenols from pomegranate extract on health, growth, nutrient digestion, and immunocompetence of calves. J Dairy Sci 2010;93(9):4280–91.
[120] Aksu MI, ÖZER H. Effects of lyophilized water extract of *Satureja hortensis* on the shelf life and quality properties of ground beef. J Food Process Pres 2013;37(5):777–83.
[121] Han J, Rhee KS. Antioxidant properties of selected Oriental non-culinary/nutraceutical herb extracts as evaluated in raw and cooked meat. Meat Sci 2005;70(1):25–33.
[122] Bañón S, Díaz P, Rodríguez M, Garrido MD, Price A. Ascorbate, green tea and grape seed extracts increase the shelf life of low sulphite beef patties. Meat Sci 2007;77(4):626–33.
[123] Rojas MC, Brewer MS. Effect of natural antioxidants on oxidative stability of cooked, refrigerated beef and pork. J Food Sci 2007;72(4):S282–8.
[124] Akarpat A, Turhan S, Ustun NS. Effects of hot-water extracts from myrtle, rosemary, nettle and lemon balm leaves on lipid oxidation and color of beef patties during frozen storage. J Food Process Pres 2008;32(1):117–32. .
[125] Ifesan BO, Siripongvutikorn S, Hutadilok-Towatana N, Voravuthikunchai SP. Evaluation of the ability of *Eleutherine americana* crude extract as natural food additive in cooked pork. J Food Sci 2009;74(7):M352–7.
[126] Jayathilakan K, Sharma GK, Radhakrishna K, Bawa AS. Antioxidant potential of synthetic and natural antioxidants and its effect on warmed-over-flavour in different species of meat. Food Chem 2007;105(3):908–16. .
[127] Rababah TM, Ereifej KI, Alhamad MN, Al-Qudah KM, Rousan LM, Al-Mahasneh MA, et al. Effects of green tea and grape seed and TBHQ on physicochemical properties of Baladi goat meats. Int J Food Prop 2011;14(6):1208–16. .
[128] Wójciak KM, Dolatowski ZJ, Okoń A. The effect of water plant extracts addition on the oxidative stability of meat products. Acta Sci Pol Technol Aliment 2011;10(2):175–88.
[129] Biswas AK, Chatli MK, Sahoo J. Antioxidant potential of curry (*Murraya koenigii* L.) and mint (*Mentha spicata*) leaf extracts and their effect on colour and oxidative stability of raw ground pork meat during refrigeration storage. Food Chem 2012;133(2):467–72.
[130] Shah MA, Bosco SJ, Mir SA. Plant extracts as natural antioxidants in meat and meat products. Meat Sci 2014;98(1):21–33.
[131] Nuñez de Gonzalez MT, Boleman RM, Miller RK, Keeton JT, Rhee KS. Antioxidant properties of dried plum ingredients in raw and precooked pork sausage. J Food Sci 2008;73(5):H63–71.
[132] Nuñez de Gonzalez MT, Hafley BS, Boleman RM, Miller RM, Rhee KS, Keeton JT. Qualitative effects of fresh and dried plum ingredients on vacuum-packaged, sliced hams. Meat Sci 2009;83(1):74–81.
[133] Ahn J, Grün IU, Fernando LN. Antioxidant properties of natural plant extracts containing polyphenolic compounds in cooked ground beef. J Food Sci 2002;67(4):1364–9. .
[134] Magistrelli D, Zanchi R, Malagutti L, Galassi G, Canzi E, Rosi F. Effects of cocoa husk feeding on the composition of swine intestinal microbiota. J Agric Food Chem 2016;64(10):2046–52.
[135] Ishihara N, Chu DC, Akachi S, Juneja LR. Improvement of intestinal microflora balance and prevention of digestive and respiratory organ diseases in calves by green tea extracts. Livest Prod Sci 2001;68(2–3):217–29. .
[136] Lahucky R, Nuernberg K, Kovac L, Bucko O, Nuernberg G. Assessment of the antioxidant potential of selected plant extracts—*In vitro* and *in vivo* experiments on pork. Meat Sci 2010;85(4):779–84.
[137] Karre L, Lopez K, Getty KJ. Natural antioxidants in meat and poultry products. Meat Sci 2013;94(2):220–7.
[138] Surai PF. Polyphenol compounds in the chicken/animal diet: From the past to the future. J Anim Physiol Anim Nutr (Berl) 2014;98(1):19–31.
[139] Moreno-Indias I, Sánchez-Alcoholado L, Pérez-Martínez P, Andrés-Lacueva C, Cardona F, Tinahones F, et al. Red wine polyphenols modulate fecal microbiota and reduce markers of the metabolic syndrome in obese patients. Food Funct 2016;7(4):1775–87.
[140] Etxeberria U, Fernández-Quintela A, Milagro FI, Aguirre L, Martínez JA, Portillo MP. Impact of polyphenols and polyphenol-rich dietary sources on gut microbiota composition. J Agric Food Chem 2013;61(40):9517–33.
[141] Patra AK, Saxena J. The effect and mode of action of saponins on the microbial populations and fermentation in the rumen and ruminant production. Nutr Res Rev 2009;22(2):204–19.
[142] Neyrinck AM, Etxeberria U, Taminiau B, Daube G, Van Hul M, Everard A, et al. Rhubarb extract prevents hepatic inflammation induced by acute alcohol intake, an effect related to the modulation of the gut microbiota. Mol Nutr Food Res 2017;61(1). Epub 2016 Jun 1.
[143] You Q, Chen F, Wang X, Luo PG, Jiang Y. Inhibitory effects of muscadine anthocyanins on α-glucosidase and pancreatic lipase activities. J Agric Food Chem 2011;59(17):9506–11.
[144] Yilmazer-Musa M, Griffith AM, Michels AJ, Schneider E, Frei B. Grape seed and tea extracts and catechin 3-gallates are potent inhibitors of α-amylase and α-glucosidase activity. J Agric Food Chem 2012;60(36):8924–9.
[145] Dunnick JK, Hailey JR. Toxicity and carcinogenicity studies of quercetin, a natural component of foods. Fundam Appl Toxicol 1992;19(3):423–31.
[146] Inoue H, Akiyama S, Maeda-Yamamoto M, Nesumi A, Tanaka T, Murakami A. High-dose green tea polyphenols induce nephrotoxicity in dextran sulfate sodium-induced colitis mice by down-regulation of antioxidant enzymes and heat-shock protein expressions. Cell Stress Chaperones 2011;16(6):653–62.
[147] Hirose M, Hoshiya T, Mizoguchi Y, Nakamura A, Akagi K, Shirai T. Green tea catechins enhance tumor development in the colon without effects in the lung or thyroid after pretreatment with 1,2-dimethylhydrazine or 2,2′-dihy-

droxy-di-*n*-propylnitrosamine in male F344 rats. Cancer Lett 2001;168(1):23–9.
[148] Hagiwara A, Hirose M, Takahashi S, Ogawa K, Shirai T, Ito N. Forestomach and kidney carcinogenicity of caffeic acid in F344 rats and C57BL/6N × C3H/HeN F1 mice. Cancer Res 1991;51(20):5655–60.
[149] Uruno A, Furusawa Y, Yagishita Y, Fukutomi T, Muramatsu H, Negishi T, et al. The Keap1-Nrf2 system prevents onset of diabetes mellitus. Mol Cell Biol 2013;33(15):2996–3010.
[150] Hayes JD, Dinkova-Kostova AT. The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. Trends Biochem Sci 2014;39(4):199–218.
[151] Cardaci S, Filomeni G, Ciriolo MR. Redox implications of AMPK-mediated signal transduction beyond energetic clues. J Cell Sci 2012;125(Pt 9):2115–25.
[152] Singh A, Happel C, Manna SK, Acquaah-Mensah G, Carrerero J, Kumar S, et al. Transcription factor Nrf2 regulates miR-1 and miR-206 to drive tumorigenesis. J Clin Invest 2013;123(7):2921–34.
[153] Dinkova-Kostova AT, Abramov AY. The emerging role of Nrf2 in mitochondrial function. Free Radic Biol Med 2015;88(Pt B):179–88.
[154] Yang CS, Zhang J, Zhang L, Huang J, Wang Y. Mechanisms of body weight reduction and metabolic syndrome alleviation by tea. Mol Nutr Food Res 2016;60(1):160–74.