Contents lists available at ScienceDirect

Engineering

journal homepage: www.elsevier.com/locate/eng

Research
Animal Nutrition and Feed Science—Review

植物化学物质的生物功能及其在家畜中的应用研究——以 Nrf2/Keap1 系统为目标

覃思[a,b], 侯德兴[a,b,c,*]

[a] Key Laboratory for Food Science and Biotechnology of Hunan Province, College of Food Science and Technology, Hunan Agricultural University, Changsha 410128, China
[b] Hunan Co-Innovation Center for Utilization of Botanical Functional Ingredients, Hunan Agricultural University, Changsha 410128, China
[c] The United Graduate School of Agricultural Sciences, Faculty of Agriculture, Kagoshima University, Korimoto, Kagoshima 890-0065, Japan

ARTICLE INFO

Article history:
Received 5 April 2017
Revised 21 April 2017
Accepted 18 May 2017
Available online 24 July 2017

关键词
植物化学物质
生物功能
Nrf2/Keap1 系统
生长性能
肉质
肠道菌群

摘要

活性氧（ROS）对人类和其他动物健康的负面影响非常值得关注。ROS 可能由机械伤害、热刺激、感染和化学刺激产生。核转录相关因子（Nrf2）及其伴侣蛋白 Keap1 组成的 Nrf2/Keap1 系统在抗氧化作用中扮演着重要角色。Nrf2/Keap1 系统通过与抗氧化反应元件（ARE）相互作用，调控一系列解毒酶和抗氧化酶基因的表达来维持机体氧化还原的平衡状态。膳食植物化学物质在蔬菜、水果、谷物和草药中普遍存在，研究发现其有益健康，还可通过多种途径调节 Nrf2 介导的 II 相酶来提高家畜的生长性能和肉质。然而，关于植物化学物质作用效果的大量数据有些混乱，需要根据植物化学物质的功能和作用机制进行相应的分类。在本文中，我们首先介绍了植物化学物质的抗氧化性及其与 Nrf2/Keap1 系统的关系，并总结了植物化学物质通过靶向 Nrf2/Keap1 系统，对家畜生长性能、肉质和肠道菌群的影响。这些详尽的数据有助于阐述植物化学物质在家畜中潜在的生物功能特性。

1. 膳食植物化学物质调控 Nrf2/Keap1 系统的生物功能

1.1. 膳食植物化学物质

植物化学物质由植物通过初级或次级代谢产生，存在于各种水果、蔬菜、谷物和中草药中，并赋予植物颜色、味道、气味等感官特性[1]，它们可以帮助植物茁壮成长或抵御竞争者、捕食者和病原体的威胁。在过去20年里，人们已经发现了膳食植物化学物质的生物学功能与人类健康和疾病紧密相关[2,3]。根据其化学结构差异，已经有超过10 000种的膳食植物化学物质被分为类胡萝卜素、异硫氰酸酯类和多酚类物质。其中，研究最为详细的是多酚类物质，主要包括酚酸类、黄酮类和芪类化合物/木脂素。许多流行病学研究和实验室研究都证明了大多数多酚有利于预防几种慢性疾病，如糖尿病、心血管疾病、神经退行性疾病、癌症和其他炎性疾病[4]。

1.2. 植物化学物质对 Nrf2/Keap1 系统的调控

当植物化学物质被人类和其他动物摄入后，会被机体认为是外源物质，并刺激机体内一系列抗氧化酶和解毒酶（ADEs）基因的表达。大部分抗氧化酶和解毒酶基因的启动子中包含一段特定的保守核苷酸序列 5′-TA/CANNA/GTGAC/TNNNGCA/G-3′，命名为抗氧

* Corresponding author.
E-mail address: hou@chem.agri.kagoshima-u.ac.jp

英文原文: Engineering 2017, 3(5): 738–752
引用本文: Si Qin, De-Xing Hou. The Biofunctions of Phytochemicals and Their Applications in Farm Animals: The Nrf2/Keap1 System as a Target. *Engineering*, http://dx.doi.org/10.1016/J.ENG.2017.03.011

化反应元件（ARE）/亲电反应元件（EpRE）[5]。研究已经证实，Nrf2对ARE/EpRE有强烈的激活作用，可增强一系列ADEs基因的表达[6]，如NAD（P）H醌脱氢酶1（NQO1）、谷胱甘肽还原酶（GSR）和溶质载体家族7成员11（SLC7A11）[7]。转录因子Nrf2在人体中由*NFE2L2*基因控制转录，它含有一个碱性的亮氨酸拉链（bZIP）蛋白，可诱导II相抗氧化酶和解毒酶基因的表达，以防止慢性炎症和受伤引起的氧化损伤[2]。Kelch样ECH相关蛋白1（KEAP1）作为Nrf2的关键抑制因子，可介导相应蛋白酶降解Nrf2，以保持细胞质内Nrf2的动态平衡[8]。

图1中对Nrf2-ARE活化的分子机制进行了总结。如图1所示，对Nrf2/Keap1系统的调控机制可分为偶联机制和解偶联机制。在正常情况下，Keap1具有E3泛素连接酶功能，可抑制Nrf2与Cullin 3-RING盒蛋白1（Cul3-Rbx1）系统连接，使Nrf2发生不断的泛素化和蛋白酶体降解。处于诱导状态时，亲电试剂、氧化剂或植物化学物质作用于Keap1结构或残基，使其发生半胱氨酸修饰、泛素化、磷酸化和琥珀酰化，导致Nrf2脱离Keap1偶联泛素化系统[9]。另外，压力诱因可刺激特定蛋白激酶[如丝裂原活化蛋白激酶（MAPKs）、磷脂酰肌醇3-激酶（PI3K）、蛋白激酶C（PKC）、PKR样内质网激酶（PERK）、糖原合成酶激酶3（GSK3）或Nrf2]发生磷酸化，从而调节一系列转录因子或某些核蛋白的活性，如正调节的Brahma相关基因1（BRG1）、乳腺癌激活因子1（AIB1）和Maf，以及负调节的p53、p65和cFos[6,8]。此外，植物化学物质还可以引起表观遗传修饰，如DNA甲基化、组蛋白修饰和microRNA调谐，从而影响*NFE2L2*或*Keap1*基因的mRNA转录。上述情况可引起Nrf2在细胞核内积累，并与小Maf或CREB结合蛋白（CBP）形成异二聚体，然后结合到ARE上，最终激活其下游的ADEs基因表达[6,10]。

1.3. 膳食植物化学物质调控 Nrf2 的潜在分子机制

大量的体外和体内研究表明，许多膳食植物化学物质具有强大的调控Nrf2/Keap1系统的能力[2–4]。然而，

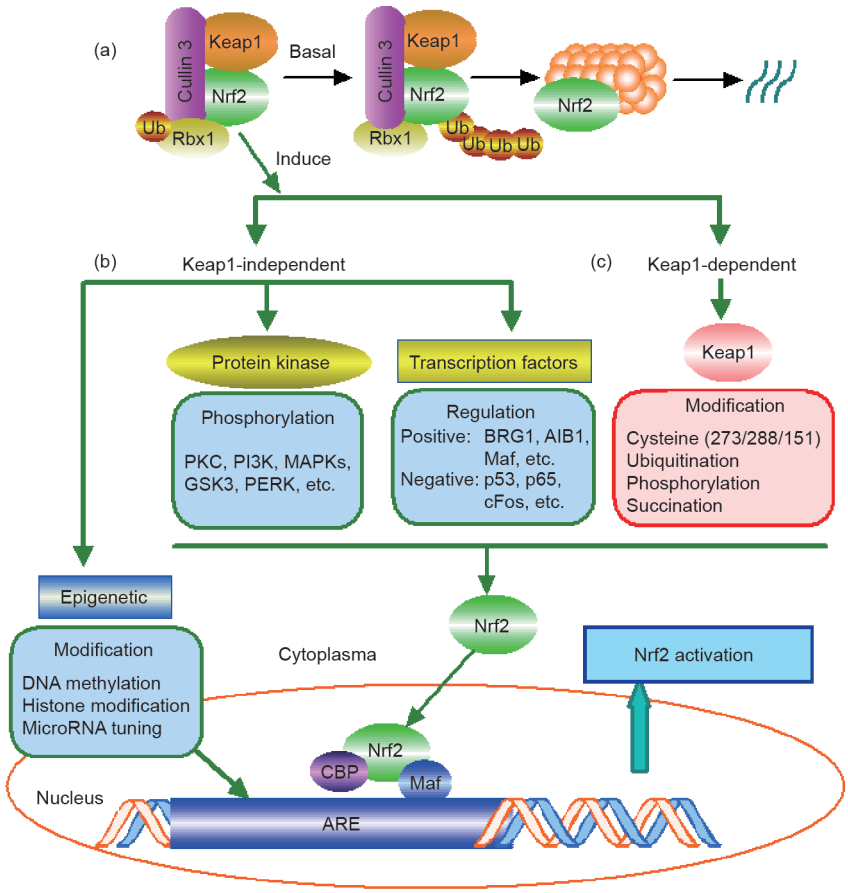


图1. Keap1/Nrf2信号通路调控的分子机制示意图。（a）在正常/基础条件下，Nrf2被Keap1介导的Cul3-Rbx1泛素化系统抑制，用于蛋白酶体降解。在诱导状态/刺激下，Nrf2被Keap1解偶联或偶联Nrf2途径激活。（b）Keap1解偶联通路。蛋白激酶（PKC、PI3K、MAPKs、GSK3和PERK）可以磷酸化Nfr2，一些转录因子与ARE结合以正向或负向调节Nrf2 / ARE介导的基因的表达（正调控因子包括BRG1、AIB1和Maf，负调控因子包括p53、p65和cFos）。表观遗传修饰包括启动子的DNA甲基化，组蛋白修饰如乙酰化或甲基化，以及通过转录调控对microRNA的调谐。（c）Keap1偶联通路。最低限度地涉及了Keap1在半胱氨酸273、288和151位置的半胱氨酸修饰、泛素化、磷酸化和琥珀化。

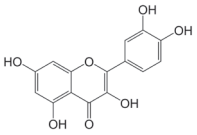
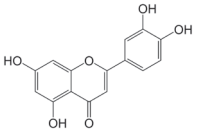
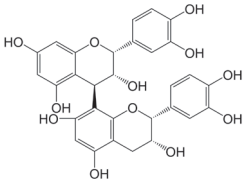
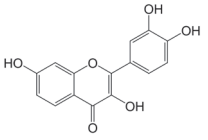
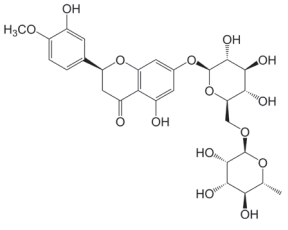
这些数据所揭示的分子机制分类并不清晰。在此，我们基于目前的研究现状，回顾了膳食植物化学物质调控Nrf2的分子机制，并划分为Keap1偶联机制和Keap1解偶联机制。

1.3.1. Keap1 偶联通路

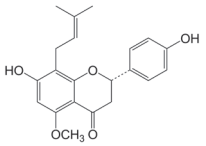
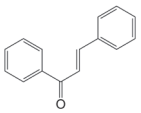
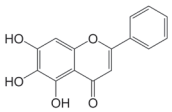
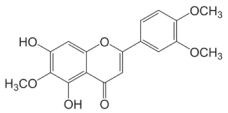
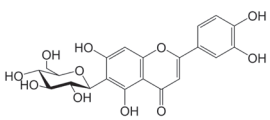
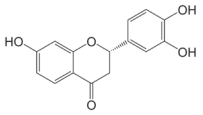
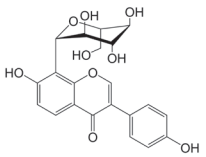
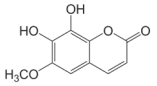
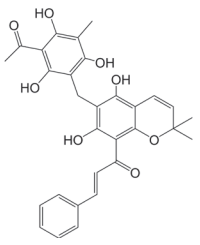
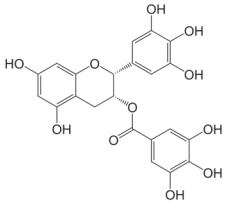
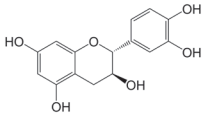
人们已经提出几种模型来解释Keap1对Nrf2活性的抑制作用。大多数ARE诱导剂可以定位和修改Keap1的半胱氨酸位点，从而影响Nrf2-ARE信号通路。有趣的是，诱导剂类型不同，其靶向定位的Keap1半胱氨酸位点也不同[9,10]。通常必需的半胱氨酸残基位点为C288、C273和C151[11]。在Cul3-Rbx1-内含泛素化系统中发现Keap1可以作为E3连接酶底物适配物之后，“Keap1解离和Cul3-Rbx1泛素化”模型就用来解释主要的Nrf2调控机制[12]。此外，其他几个重要的模型，如“Keap1铰链和闩锁”“Keap1磷酸化”“Keap1泛素化”和“Keap1琥珀酸酯化”模型表明，由各种刺激引起的Keap1修饰构成了调控Nrf2/Keap1系统的主要机制[13–17]。

研究发现，大量的膳食植物化学物质可通过修饰Keap1中的半胱氨酸位点来调控Nrf2/Keap1系统。如表1所示[18–80]，莱菔硫烷、白藜芦醇、儿茶酚雌激素、槲皮素、鼠尾草酸、黄芩素、大豆抗毒素、冬凌草甲素、发卡二醇、白皮杉醇、黄腐酚和6-（甲基亚磺酰基）己基异硫氰酸酯已被报道均可激活Nrf2/Keap1系统。其中，槲皮素作用于“Keap1解离”模型[18]，黄芩素在“Keap1泛素化”模型起作用，值得注意的是，黄芩素也可作用于“Keap1铰链和闩锁”模型[26]。此外，莱菔硫烷在人体内作用于“Keap1铰链和闩锁”模型，而在动物体内则作用于“Keap1解离”模型[56–59]。这些数据表明，植物化学物质引起的Keap1的变化之所以不同，其研究使用的细胞模型是一个重要因素。

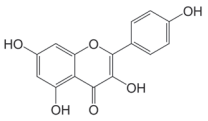
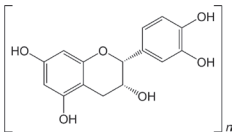
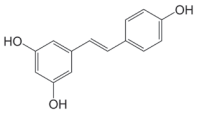
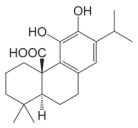
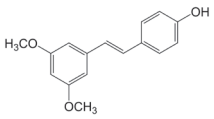
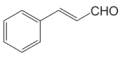
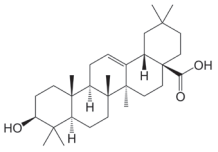
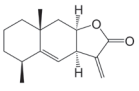
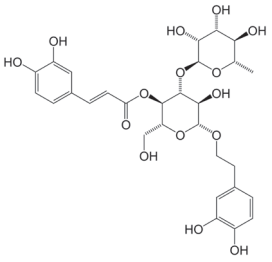
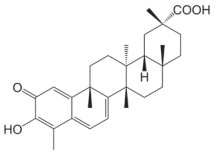
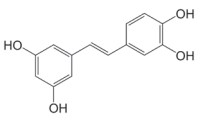
表1 植物化学物质调控Nrf2的分子机制

Classification	Origin	Compound	Structure	Dose	Time	Mechanism	Model	Refs.
Activation of Nrf2-ARE pathway								
Flavo-noid-type polyphenols	Apple, tea, caper, lovage, onion	Quercetin		0–40 μmol·L^{-1}	6 h	↑ Keap1 mod-ification, 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 colon-ic 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]

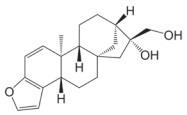
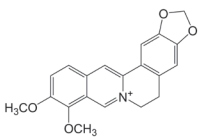
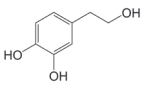
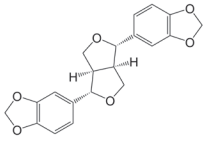
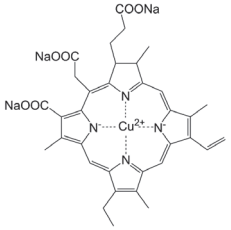
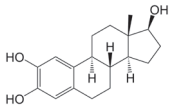
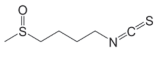
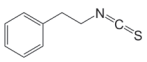
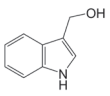
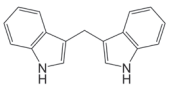
（续表）

Classification	Origin	Compound	Structure	Dose	Time	Mechanism	Model	Refs.
	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]
	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]

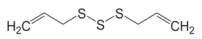
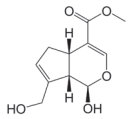
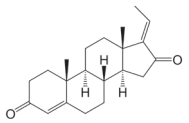
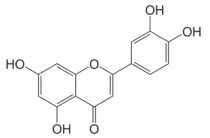
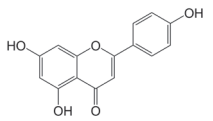
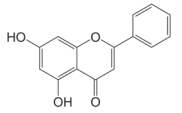
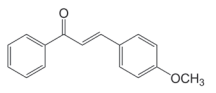
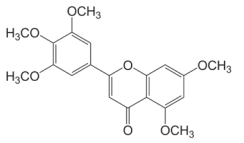
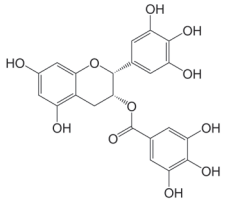
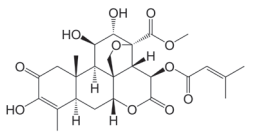
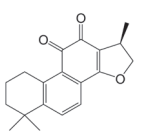
（续表）

Classification	Origin	Compound	Structure	Dose	Time	Mechanism	Model	Refs.
	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]
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]

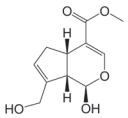
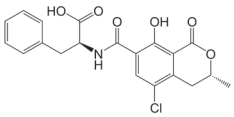
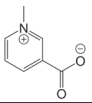
（续表）

Classification	Origin	Compound	Structure	Dose	Time	Mechanism	Model	Refs.
	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]
	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]

（续表）

Classification	Origin	Compound	Structure	Dose	Time	Mechanism	Model	Refs.
	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]
	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]

（续表）

Classification	Origin	Compound	Structure	Dose	Time	Mechanism	Model	Refs.
		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 解偶联通路

除了Keap1，大量的其他因素也被证实在Nrf2/Keap1系统的调控中起着相当大的作用。如图1所示，这些因素主要分为表观遗传修饰、蛋白激酶磷酸化和转录因子的调节。

如表1所示，槲皮素[19]、莱菔硫烷/苯乙基异硫氰酸酯（PEITC）[58,60]、羟基酪醇[51]、白藜芦醇[39]、木犀草素[20]、原花青素B2[21]、橙皮苷[23]、齐墩果酸[44]、表没食子儿茶素-3-没食子酸酯（EGCG）[34]、表儿茶素[35]、异泽兰黄素[27]、卡马拉[32]、麦角甾苷[46]和雷公藤红素[47]均可以促进细胞外信号调节激酶（ERK）的磷酸化。槲皮素[19]、原花青素[37]、莱菔硫烷[57]、原花青素B2[21]、漆黄素[22]、咖马林[32]、鼠尾草酸[40]、雷公藤红素[47]、芝麻素/细辛脂素[53]、EGCG[33]和咖啡豆醇[49]可激活p38 MAPK。据报道，土木香内酯[45]、羟基酪醇[52]、PEITC[60]、山奈酚[36]、京尼平[64]和吲哚甲醇/3,3′-二吲哚甲烷[61,62]可诱导c-Jun氨基末端激酶（JNK）的活性。原花青素[37]、莱菔硫烷[58]、羟基酪醇[51]、白藜芦醇[39]、叶绿素[54]、京尼平[64]、异荭草素[28]、紫铆素[29]、没药甾酮[65]、土木香内酯[45]、植物雌激素葛根素[30]、黄连素[50]、麦角甾苷[46]、EGCG[34]和表儿茶酸[35]可刺激PI3K的活性。

许多研究已经发现，植物化学物质可通过调控其他转录因子和核蛋白，进而调控Nrf2/Keap1系统。例如，Jun二聚蛋白2（JDP2）被认为是与莱菔硫烷诱导Nrf2活化密切相关的物质，结果表明，JDP2可促进莱菔硫烷介导的Nrf2-ARE的活化[81]。另一项研究报道称，莱菔硫烷可通过NF-κB在转录水平抑制Nrf2信号通路，一方面NF-κB提高组蛋白脱乙酰化酶3（HDAC3）活性造成局部低乙酰化，另一方面NF-κB与Nrf2竞争结合CBP，抵抗Nrf2的反式激活从而抑制Nrf2信号通路[82]。

一些膳食植物化学物质如异硫氰酸盐、茶多酚、染料木素和姜黄素，被认为是有效的表观遗传改性剂[83]。莱菔硫烷、3,3′-二吲哚甲烷、姜黄素和Z-藁本内酯能够抑制DNA甲基转移酶（DNMT）和HDAC的表达，从而导致Nrf2启动子的甲基化并再激活TRAMP小鼠前列腺或TRAMP C1细胞中的Nrf2信号通路[59,62,84,85]。此外，芹菜素、莱菔硫烷和丹参酮IIA可作用于小鼠表皮细胞JB6 P+的Nrf2基因启动子区域，引起甲基化5′-C-磷酸盐-G-3′（CPG）位点去甲基化。这与Nrf2信号通路再激活、Nrf2靶基因的表达、TPA诱导的转型抑制以及DNMTs和HDACs蛋白表达的抑制作用相关[86–88]。这些研究结果表明，植物化学物质可以通过表观遗传来调节Nrf2的表达；然而，作为特定的Nrf2调节剂，它们在癌症及其他慢性疾病中的确切效果有待进一步研究阐明。

有趣的是，几个系列研究表明，在某些癌细胞系中，黄酮类化合物可作为Nrf2/Keap1系统的抑制剂，并在克服恶性肿瘤耐药性中起重要作用（表1）[66–80]。例如，研究发现在正常细胞和癌细胞中，木犀草素、芹菜素、白杨素、4-甲氧基查耳酮、五甲氧基黄酮和EGCG在Nrf2-ARE调控中发挥着不同的作用。在正常细胞中，它们作为Nrf2-ARE调控的激活剂，可预防慢性疾病。

而在癌细胞中，它们作为Nrf2-ARE调控的抑制剂，可克服恶性肿瘤的耐药性。鉴于植物化学物质对正常和癌细胞中Nrf2/Keap1系统的双重作用，其有益健康方面引起了相当大的关注[89]。

2. 通过靶向 Nrf2/Keap1 系统，植物化学物质对家畜生长性能、肉质和肠道菌群的影响

为了减少饲料成本，家畜的植物化学物质来源通常是农业和工业副产物，如果皮、茎、种子、果渣、坚果、外壳和生产果汁、葡萄酒或啤酒的废弃物[90]。表2总结了植物化学物质对家畜生长性能、肉质和肠道菌群的影响[91–135]。

2.1. 生长性能

几个系列研究报道了植物化学物质对猪、禽、牛等家畜生长性能的影响。

在对猪的研究中，发现白藜芦醇和含有较高浓度白藜芦醇的葡萄提取物，可降低脂肪沉积，改善葡萄糖代谢和心肌功能，预防动脉粥样硬化病变和冠心病的发展[91–93]。虽然富含多酚的葡萄籽和果渣的猪饲料对猪的生长性能有所改善，但对转录因子Nrf2的活性和ARE相关抗氧化基因或解毒酶的表达没有显著影响[94,95]。

研究发现，植物化学物质可显著提高肉鸡和产蛋鸡的生长性能。据报道，在饲料中添加来自葡萄籽的原花青素提取物，降低了肉鸡感染艾美球虫的死亡率，并提高了其体重增加量[96]。在饮食中添加百里酚

表2 植物化学物质对家畜生长性能、肉质和肠道菌群的影响

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]

（续表）

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 $g \cdot kg^{-1}$ BW	Broilers	Downregulation of the genes of IL-1β, IL-4, IL-10, TNF-α, and IFN-γ	[118]
	Pomegranate-extract polyphenols	5–10 $g \cdot d^{-1}$	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 $mg \cdot kg^{-1}$ 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 $mg \cdot (100\ g)^{-1}$	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 $mL \cdot (500\ g)^{-1}$ 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]

（续表）

Function classification	Phytochemical	Concentration	Animal/meat tested	Effect	Refs.
	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.

（200 mg·kg^{-1}）、没食子酸（5 g·kg^{-1}）和单宁酸（5 g·kg^{-1}），可提高肉鸡的饲料利用率和最终体重[97]。饲料中添加葡萄果渣浓缩物（60 g·kg^{-1}）可提高饲料利用率[98]。肉鸡饮食中添加绿茶多酚，改善了用皮质酮处理的肝脏和肌肉中的饲料转化率，但是在没有皮质酮处理的情况下反而会使饲料转化率受损[99]。饮食中添加1%白藜芦醇，削弱了肉仔鸡的体重增加以及饲料转化率[100]。膳食中添加槲皮素（0.2~0.6 g·kg^{-1}）可增加产蛋率，降低料蛋比[101]。据报道，膳食中添加茶多酚（5~15 mg·kg^{-1}）可防止钒对蛋品质的不利影响[102]。

对奶牛的研究中发现，从石榴中提取的多酚降低了奶牛对蛋白质和脂肪的消化率，因为高单宁含量会抑制这些营养物质的吸收[103]。饲料中添加富含多酚的葡萄籽和果渣提取物可以提高奶牛的产奶性能[104]。研究表明，植物产品可减少奶牛脂肪肝的形成，并改善泌乳性能[105]。

尽管目前还没有充分的证据能够证明植物化学物质提高家畜生长性能与Nrf2/Keap1系统有直接关系，但是许多研究已经发现，含有植物化学物质的饲料可显著改善家畜的抗氧化和抗炎性能，而这可能与Nrf2/Keap1系统密切相关。

2.2. 肉质

研究人员在植物化学物质对肉质的影响方面进行了大量研究，其重点是抗氧化性能、抗炎性能和感官性能，如颜色、质地和风味[106–133]。

2.2.1. 抗氧化性能

研究人员广泛研究了植物化学物质在家畜、肉类和肉制品中的抗氧化性质，为理解植物化学物质的其他功能奠定了基础。

据报道，植物化学物质补充剂可减少血浆脂质过氧化物和降低丙二醛（MDA）水平，从而改善氧化还原状态，减少过氧化反应对猪的过度氧化应激。然而在非促氧化处理的情况下，植物化学物质却没有这种效果[94,106,107]。饮食中的植物植物化学物质可通过降低MDA和硫代巴比妥酸反应物（TBARS）的浓度以及诱导谷胱甘肽过氧化物酶（GPx）的活性，来适当地改善肉鸡和产蛋鸡的抗氧化能力[96,98,102]。在奶牛中发现，尽管超氧化物歧化酶（SOD）的活性偶尔增加，但植物化学成分的添加对奶牛抗氧化状态的影响却很小[104,105]。

研究发现，脂质氧化是导致肉类和肉类产品质量下降的主要原因。在消化-吸收-代谢过程中，大量氧化物和氧化应激在机体或组织中出现并累积，不利于限定保质期，并对肉或肉制品的质量（如质地、颜色、风味、营养价值和食品安全）造成不良影响[136]。合成抗氧化剂的毒副作用和消费者对天然产物的兴趣，加速了天然植物化学物质在添加剂替代物领域的发展[137]。例如，将植物化学物质如葡萄皮、绿茶、迷迭香和咖啡的提取物添加到猪肉馅饼中，当添加剂量为50~200 ppm时，可以减少脂质氧化，还可以降低TBARS和己醛的值[108]。在生的或熟的山羊肉馅饼中，添加红牡丹、白牡丹、牡丹、地黄、苏木和当归的提取物，剂量为0.5%~2.0%时可以减少脂质氧化[109]。在生牛肉饼、碎牛肉和水牛肉馅饼中，添加橄榄叶、枣核和迷迭香叶提取物可降低TBARS值，并减少脂质氧化和氧合肌红蛋白氧化[110–112]。在猪肉和牛肉香肠中，添加红豆提取物和葡萄籽提取物均可减少脂质氧化并降低TBARS值[113,114]。文献[130]对绿茶提取物、迷迭香提取物和

葡萄籽提取物的抗氧化性能进行了研究，并对这些提取物在肉和肉制品中的应用进行了综述。

2.2.2. 抗炎性能

研究发现，含有葡萄籽、果渣和啤酒花提取物的日粮可抑制生长猪小肠中各种促炎因子基因的表达[95]。猪饲料中的可可粉也降低了Toll样受体和肿瘤坏死因子（TNF）-α的基因表达[117]。

通过对肉鸡肠道内一系列促炎细胞因子表达的研究，探讨了茶多酚对家禽的抗炎作用。结果表明，每千克肉鸡体重茶多酚添加量为0.03~0.09 g时，可下调TNF-α、白细胞介素（IL）-4、IL-10、IL-1β和干扰素（IFN）-γ等基因的表达[118]。

用石榴多酚提取物（5~10 g·d^{-1}）喂牛，既增加了其外周血单核细胞中IL-4和IFN-γ的分泌量，又提高了其接种卵清蛋白疫苗后产生的免疫球蛋白G（IgG）的总量[119]。奶牛饲料中添加葡萄籽和果渣提取物，可显著下调内质网应激标记物——成纤维细胞生长因子（FGF）-21的表达，同时可减少肝脏中脂肪的堆积[104]。

2.2.3. 感官性能

感官性能通常用于评估肉类或肉制品的颜色、风味和口感。已经发现植物化学物质显著影响肉品质的感官性能。

例如，0.5%~2.0%的白牡丹提取物可增加生肉和熟肉馅饼的红度（a^*值）[109]。300~500 ppm的迷迭香提取物可维持生的冷冻香肠的红色[120]。300 mg·kg^{-1}的绿茶提取物可降低生肉饼的a^*值，并可消除熟肉饼中酸败的风味[121,122]。0.01%~0.02%的葡萄籽提取物可减少牛肉的视觉绿色变色[123]。10%番石榴提取物可预防牛肉馅饼变色[124]。100 g肉品中添加2.7~10.8 mg的红葱提取物可增加熟猪肉的a^*值[125]。在熏制或未熏制的猪肉香肠中，添加0.2%的红豆提取物可增加a^*值，但会降低亮度（L^*值）和黄度（b^*值）[126]。在生的和熟的山羊肉中添加500~6000 ppm的绿茶提取物可增加肉品a^*值，而添加葡萄籽提取物却降低肉品a^*值，同时辣椒提取物有助于保持熟猪肉的a^*值[127,128]。500 g生猪肉糜中添加5 mL的咖喱叶提取物可降低其L^*值和a^*值，同时增加b^*值[129]。在生的和熟的水牛肉饼中添加130 ppm的迷迭香叶提取物可维持肉色的稳定[130]。

此外，李子制品对许多肉类和家禽产品的风味影响较小，但会引起其颜色变化，而葡萄籽提取物则会导致肉类产品颜色发生显著变化[137]。

2.3. 肠道菌群

近年来，关注植物化学物质对体内肠道菌群影响的研究显著增加。这是因为肠道菌群被认为是膳食植物化学物质的首要作用目标，并表现出许多与健康有关的关系。因此，许多植物化学物质促进健康的作用可能归因于它们对肠道菌群的调节[138]。例如，只有5%~10%的多酚在小肠中被吸收，其余90%~95%多酚进入结肠，并借助于结肠菌群的酶促作用转化为一系列多酚代谢物[90]。在肝脏和肠细胞中多酚代谢物再次结合，一部分被再次吸收到系统循环中，一部分用作抗菌底物或生长促进底物。另外，多酚或其代谢物有益于结肠菌群的组成和密度，如以益生元的方式促进有益菌的生长并抑制某些病原菌的生长[139,140]。

专门研究多酚对家畜肠道菌群影响的课题开展得还很有限。已发现饲料中添加可可粉可增加猪肠道中几种菌株的丰度，如乳杆菌属、双歧杆菌属、拟杆菌属-普雷沃氏菌属和柔嫩梭菌群-普拉梭菌[117,134]。一些研究表明，多酚可能在肉鸡的肠道中表现出良好的效果。饲料中添加葡萄渣浓缩物可增加肉鸡肠道中肠球菌的丰度，而降低梭菌属的丰度，从而有益于肠道菌群总量[98]。据报道，用槲皮素饲喂产蛋鸡，可减少肠道需氧菌和大肠杆菌总数，并增加双歧杆菌的数量，从而改善盲肠微生物群落状态[101]。在猪的肠道中，茶多酚可增加乳杆菌的数量，并减少总细菌、拟杆菌科和产气荚膜梭菌的数量。然而，茶多酚却降低了犊牛肠道中双歧杆菌、乳杆菌属和产气荚膜梭菌的数量[102,135]。

近期的一篇综述总结了多酚在大鼠和人类模型中对肠道菌群的影响，并且发现多酚或富含多酚的外源物可减少潜在病原菌（如产气荚膜梭菌、溶组织梭菌和G$^-$拟杆菌属的某些菌株）的丰度和增加某些益生菌（如梭菌、双歧杆菌和乳酸菌）的丰度，从而影响不同细菌种群的相对丰度[108]。

基于以上植物化学物质对肠道微生物菌株的影响的系列研究，植物化学物质的抗氧化和抗炎性能可能与肠道健康的改善有关[141,142]。

2.4. 植物化学物质对家畜的不利影响

虽然植物化学物质的生物功能特性对家畜而言是强大的、有应用价值的，但在某些研究中也发现了植物化学物质对机体的不利影响。例如，过多的摄入多酚物质会抑制营养物质的吸收[143,144]并引起毒副作用。此外，研究发现高剂量的槲皮素与大鼠的慢性肾病有关，并降低了小鼠的预期寿命[145]。据报道，过量的施用

绿茶多酚可破坏小鼠的肾脏[146]，并促进雄性大鼠结肠肿瘤的形成[147]。过量摄取咖啡酸会引起小鼠和大鼠的肾脏和胃肠道肿瘤[148]。虽然这些数据是从实验动物获得的，但也表明在家畜中应该避免给予高剂量的植物化学物质。

虽然植物化学物质的抗炎、抗氧化和细胞保护性能在家畜中的研究较少，但是在人体和实验动物模型已经进行了大量的类似研究。因此，植物化学物质在动物体内的生物功能也被认为是通过调节Nrf2/Keap1系统（作为抗氧化应激和抗慢性炎症的中枢调节系统）而实现的[90]。

3. 展望

一系列研究已经证实，Nrf2/Keap1系统可以通过抑制糖异生作用来调节一般能量代谢系统[149]；可以调节参与甘油三酯/磷脂降解的脂肪酶的活性[150]，同时还调节脂肪酸氧化、脂质生物合成、脂肪酸去饱和及脂肪酸转运酶的活性[150]；可以影响氧化还原代谢系统，如AMP激活蛋白激酶通路[151]；并可以调整线粒体代谢过程，如葡萄糖氧化和底物进入、ATP的生成[152,153]。EGCG已被证明会影响大鼠和人类的一般能量代谢系统[154]。然而，植物化学物质作用于家畜的试验数据并不充分，而且其深层次分子机制仍不清楚。因此，需要进一步的研究来阐明植物化学物质对家畜能量代谢系统的影响。

尽管在人体和实验动物的研究中积累了大量关于植物化学物质生物功能的数据，但大部分数据都集中在植物化学物质对慢性疾病（如癌症、心血管疾病和代谢综合征）的化学预防作用方面。因此，分子数据还需要深入研究，以阐明膳食植物化学物质是如何通过调节信号通路和基因表达来维持体内平衡的。另外，植物化学物质的作用机制数据主要来自于人体和实验动物，来自家畜的研究数据较少，而且以家畜为对象研究植物化学物质生物功能的数据也很少，但植物化学物质可改善家畜生长性能和肉质以及植物化学物质可用作抗生素替代物已经引起了人们的极大关注。比较家畜营养和人类营养中植物化学物质作用机制的差异似乎很难，但在与Nrf2/Keap1系统相关的研究中发现，植物化学物质在家畜体内的抗氧化特性和作用机制与人体类似研究的结果几乎一致。因此，可以将植物化学物质在人体和实验动物中的研究数据利用起来，并将其应用于家畜。

植物化学物质对人类和其他动物健康具有多重生物功能。由于Nrf2/Keap1系统与抗氧化功能、抗炎功能以及许多其他功能相关，因此植物化学物质对Nrf2/Keap1系统的调节可能在其多重生物功能中起核心作用。大多数植物化学物质在小肠中的吸收比相对较低，所以人们将研究领域从直接抗氧化剂特性转移到侧重于间接促氧化特性、生物转化、信号转导和基因表达调控。虽然植物化学物质影响家畜肠道菌群的研究还很有限，不足以表明其能显著改善生长性能、抗氧化参数和炎症因子，但这些发现为揭示膳食植物化学物质促进健康的进一步研究奠定了基础。

致谢

本项工作得到了湖南农业大学核心研究计划“1515”、国家自然科学基金（31101268）和鹿儿岛大学学者研究（De-Xing Hou）项目的支持。

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 downregulate 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, sesa-

mol, 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′-dihydroxy-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.