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EXPERT REVIEW

Hormetics: Dietary Triggers of an Adaptive Stress Response

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ABSTRACT A series of dietary ingredients and metabolites are able to induce an adaptive stress response either by generation of reactive oxygen species (ROS) and/or *via* activation of the Nrf2/Keap1 stress response network. Most of the molecules belong to activated Michael acceptors, electrophiles capable to S-alkylate redox sensitive cysteine thiols. This review summarizes recent advances in the (re) search of these compounds and classifies them into distinct groups. More than 60 molecules are described that induce the Nrf2 network, most of them found in our daily diet. Although known as typical antioxidants, a closer look reveals that these molecules induce an initial mitochondrial or cytosolic ROS formation and thereby trigger an adaptive stress response and hormesis, respectively. This, however, leads to higher levels of intracellular glutathione and increased expression levels of antioxidant enzymes such as glutathione peroxidase, thioredoxin reductase, and superoxide dismutase. According to this principle, the author suggests the term *hormetics* to describe these indirect antioxidants.

KEY WORDS adaptive response · hormesis · hormetics · Nrf2 · nutrition · oxidative stress · ROS

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INTRODUCTION

Since the introduction of the "Free Radical Theory of Ageing" by Denham Harman in 1956, reactive oxygen species (ROS) were considered one of the main reasons for the ageing process, including the development of age-related diseases (1). The desire to cure cancer, cardiovascular diseases, or *diabetes mellitus* by the use of antioxidants was nothing more than wishful thinking. Today, more than 50 years later, current meta-analyses of intervention studies with antioxidants reveal a devastating picture (2–4). Antioxidant supplementation has no beneficial effect on age-related diseases; it furthermore may cause side effects and even increase mortality (4). How can the discrepancies between Harman's hypothesis and clinical outcomes be explained, since the amount of ROS positively correlates with the incidence of neurodegeneration, cardiovascular events, *diabetes mellitus*, and cancer? Whether the appearance of increased ROS levels is a consequence of or a reason for the disease is the question to be answered. Nowadays, ROS change their attributes, and a more differentiated view is advisable to answer this question.

The main sources of ROS are mitochondria which evolve as a side product of the oxidative phosphorylation. Approximately 2–3% of the oxygen molecules that are needed for substrate oxidation are transferred into the highly reactive superoxide radical $\left(O_2^{-\cdot}\right)$. It can be transformed into a series of other oxidants, such as hydrogen peroxide (H_2O_2) or peroxynitrite ($ONOO^-$), that also react with macromolecules within the cell to build up non-functional proteins, lipids, or nucleic acids. As a consequence, oxidized molecules accumulate during life and contribute to a reduction of lifespan.

Beside harmful properties, ROS evolved as important signaling molecules in the redox homeostasis of cells. The production of superoxide from NADPH oxidase plays an important role in the immune system. The oxidative burst has a crucial role in phagocytes to degrade internalized particles and bacteria (5).

Other sources of ROS are xanthine oxidase, cyclo-oxygenases, and lipoxygenase. ROS are necessary for lifespan extension during the process of glucose restriction in the nematode *C. elegans* (6) and are involved during calorie restriction, the only way to extend lifespan in mammals (7). During physical exercise, ROS are responsible for the improvement of insulin sensitivity, an inverse predictor of *diabetes mellitus* (8). Last but not least, ROS mediate the adaptive stress response of cells. This concept, often termed as *hormesis*, was addressed recently by excellent reviews in a comprehensive manner (9–14). This review will give a brief introduction into small molecules within our diet that induce an adaptive stress response and thereby act as indirect antioxidants.

HORMESIS: AN ADAPTIVE STRESS RESPONSE

Oxidative stress is defined as an imbalance of anti-oxidative and pro-oxidative reactions in favor of the pro-oxidant. The term is commonly used in connection with age-associated diseases and ageing in general. When stress levels exceed defense capacity, they may cause oxidative damage in macromolecules, whereas low levels of stress can stimulate endogenous defense systems. Different terms are currently used to describe this stimulation. *Adaptive response*, *hormesis*, and *eustress* are discussed as important factors in the control of life expectancy. The phenomenon of a stress response was first described by Schulz in 1888 (15), and later the term *hormesis* (from Greek *hórmēsis* "rapid motion, eagerness") was used by Southam and Ehrlich in 1943 to define the induction of cellular stress response by a low-dosed sub-lethal stressor (16). As a consequence, an overcompensation reaction of the cell takes place that even resists lethal doses of the stressor (17). Instead of a linear dose response, hormesis is characterized by a biphasic J-shaped dose response curve. Hormetic stress response was observed with a series of stressors such as gamma radiation, heavy metals, oxidative stress, heat shock, and, most interestingly, physical exercise (8,18–20). In addition, dietary ingredients were discussed as stimulating hormesis (21,22). In a recent review, Calabrese defines *hormesis* as a biphasic dose response phenomenon that is generally described by a low-dose stimulation and a high-dose inhibition (10).

Several species benefit from a hormetic stress response. Live extension *via* hormesis was described in yeast (*Saccharomyces cerevisiae*) (23), fruit flies (*Drosophila melanogaster*) (24), nematodes (*Caenorhabditis elegans*) (25), and mice (26). Cellular stress signals may induce defense mechanisms such as DNA-repair, heat shock chaperons, and phase II enzymes.

A more specific view of hormesis refers to ROS originated from mitochondria (mtROS), capable of inducing an adaptive response. The term *mitochondrial hormesis* or *mitohormesis* (MH) was introduced several years ago by Tapia (20) and later proved by different groups (6,8,27,28). Mitohormesis is used in reference to physical exercise and calorie restriction but not phytochemicals or drugs, yet.

The induction of an adaptive stress response requires redox sensitive sensors within the cellular matrix that differentially influence transcription. These proteins contain

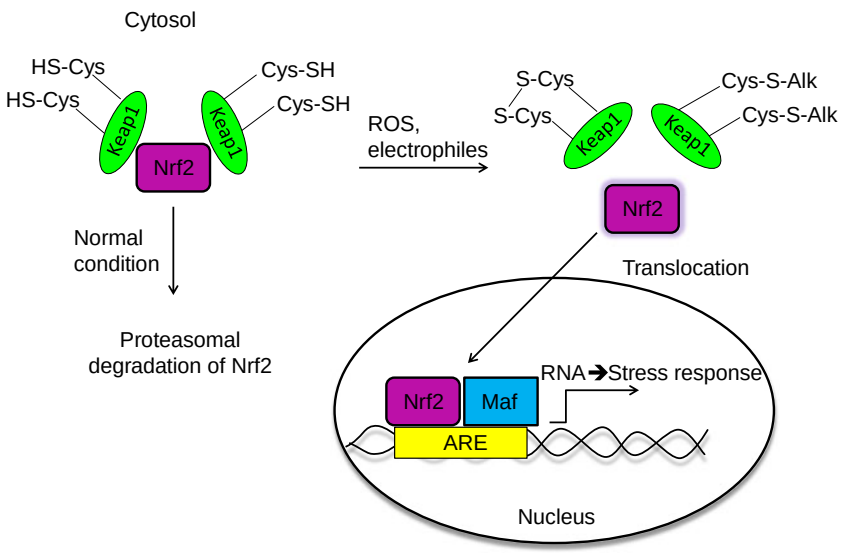

Fig. 1 Scheme for the regulation of the Nrf2/Keap1-signalling network via hormetics. Nrf2 is rapidly degraded under conditions of a normal redox balance. Since Keap1 is a cysteine-rich protein, chemical modifications induce conformational changes and the release of Nrf2. After its translocation into the nucleus, Nrf2 binds to antioxidant response elements (AREs), thereby affecting the expression of detoxifying and antioxidant enzymes (Table I).

Table I Target Genes Regulated by Nrf2

	Genes	Function	Reference
Antioxidant enzymes			
Glutathione peroxidase	GPX1-2	Elimination of hydrogen peroxide	(67)
Superoxide dismutase	SOD1-3	Elimination of superoxide radical	(68)
Catalase	CAT	Elimination of hydrogen peroxide	(68)
Thioredoxin reductase	TXNRD	Reduction of oxidants and oxidized thiols	(69)
Thioredoxin	TXN	Cysteine thiol-disulfide exchange	(69)
Peroxiredoxin	PRDX1 and PRDX6	Reduction of oxidized cysteines (sulfenic acids)	(70)
NAD(P)H dehydrogenase	NQO1	Reduction of quinones to hydroquinones	(69)
Aldo-keto reductase	AKR1A and AKR1B8	NADPH-dependent oxidoreductase	(71)
γ-Glutamylcysteine ligase regulatory subunit	GCLR	Glutathione biosynthesis and recycling	(69)
γ-Glutamylcysteine catalytic subunit	GCLC		
Glutathione reductase	GR		
Detoxifying enzymes and related			
Glutathione S-transferase	GST1-4, GSTM1-6, MGST2-3	Phase II enzyme (glutathionylation)	(68)
UDP-glucuronosyl transferase	UGT1-2	Phase II enzyme (glucuronidation)	(68)
Sulfotransferase	SULT1	Phase II enzyme (sulfonation)	(72)
Multidrug resistance related proteines	MRP2-3	Detoxification	(68)
Heme oxygenase-1	HMOX1	Heme catabolism, stress response	(69)
Ferritin	FTL, FTH	Iron metabolism, stress response	(71)

Table II Hormetics with an α-,β-unsaturated Carbonyl Unit

Compound	Nutritional source	Mode of action/pathway	Reference
Flavokawain B	Kava kava	ROS formation, GSH depletion/NF-κB	(73,74)
Isoliquiritigenin	Licorice	GSH depletion, $\Delta\Psi_m$ drop, Keap1-alkylation/Nrf2	(75,44)
Caffeic acid phenylester	Propolis, honey	ROS formation, GSH depletion/Nrf2 and NF-κB	(76–78)
Rosmarinic acid	Rosemary	*/*	–
Curcumin	Turmeric	mtROS formation/Nrf2	(79–81)
Piperine	Black pepper	*/Nrf2	(82)
Shogaol	Ginger	ROS formation, GSH depletion, $\Delta\Psi_m$ drop, Keap1-alkylation/Nrf2	(44,83)
Zerumbone	Ginger	ROS formation, GSH depletion/Nrf2	(84,85)
Xanthohumol	Hop, beer	O_2^{-*} formation, GSH depletion, Keap1-alkylation/Nrf2	(42,44,86,87)
15 d-PGJ_2	Arachidonic acid metabolite	ROS formation, Keap1-alkylation/Nrf2	(88–90)
Astaxanthin	Salmon, trout, shrimp	ROS reduction, GSH depletion/Nrf2	(91,92)
Cinnamaldehyde	Cinnamon oil	ROS formation, GSH depletion/Nrf2 and NF-κB	(93–95)
Safranal	Perilla, saffron	*/Nrf2	(45)
Perillaldehyde	Perilla	*/Nrf2	(45)
Citral	Perilla, lemongrass	*/Nrf2	(45)
2,4-Octadienal	Perilla	*/Nrf2	(45)
trans-2-Hexenal	Perilla	*/Nrf2	(45)
trans-2,cis-6-Nonenal	Perilla	*/Nrf2	(45)
4-Hydroxynonenal (4-HNE)	Product of lipidperoxidation	ROS formation, protein thiol-alkylation/Nrf2	(48,96)
Acrolein	Product of lipidperoxidation	ROS formation, GSH depletion/Nrf2	(97)
Malondialdehyde (MDA)	Product of lipidperoxidation	*/*	-
Crotonaldehyde	Product of lipidperoxidation	*/Nrf2	(98)

*unknown

cysteine thiols that are susceptible to thiol oxidation, thiol/disulfide exchange, and S-alkylation. The latter reaction occurs due to a dissociation of the thiol into a nucleophilic sulfide anion, which may react with electrophiles to form a covalent bond.

A large variety of electrophiles are described in the literature (29) and are the subject of excellent review articles (30,31). This review gives an update of these and additional compounds and briefly summarizes the target, crucial for a hormetic response.

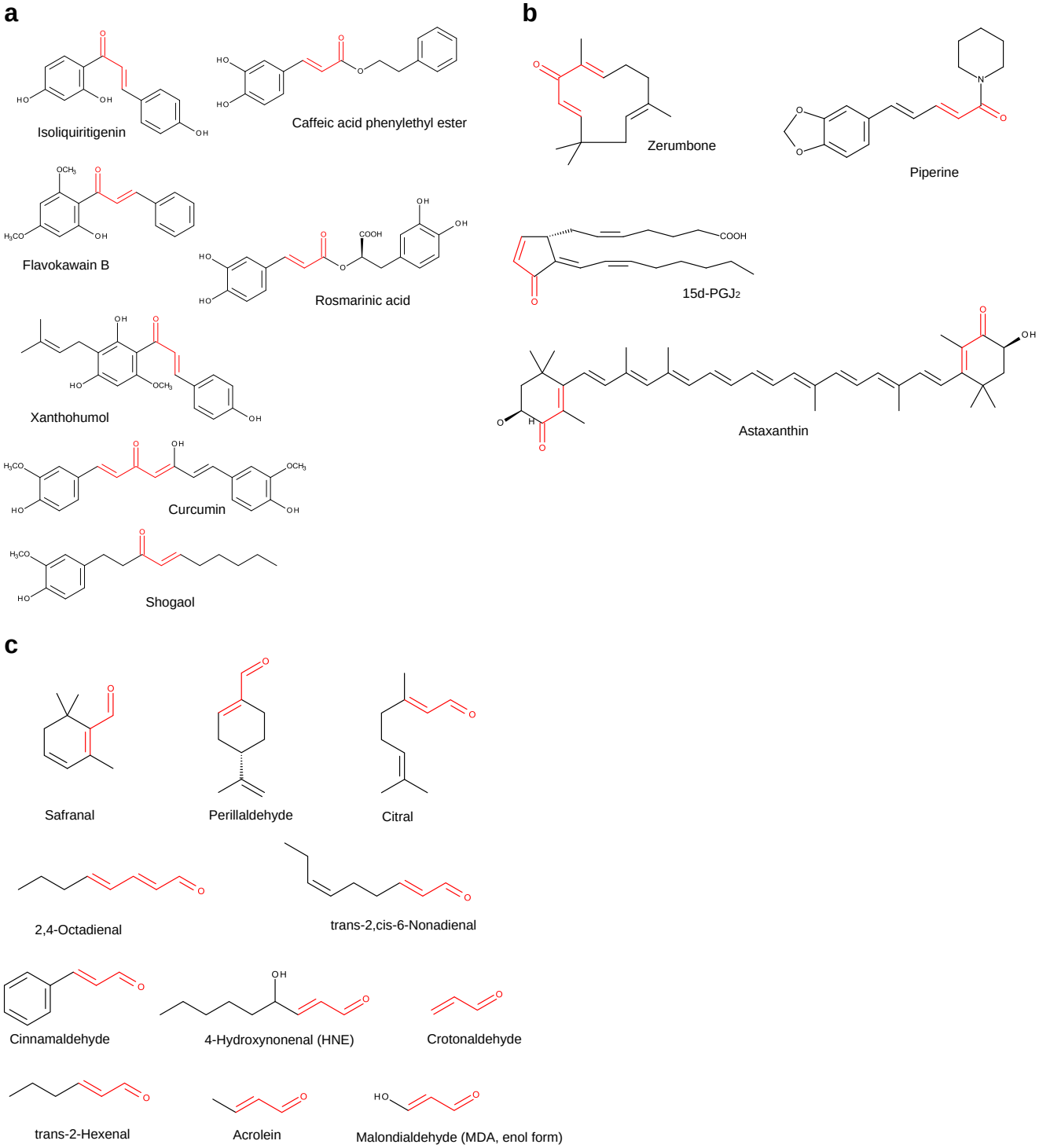

Fig. 2 (**a**) Chemical structures of α-β-unsaturated carbonyls. (**b**) Chemical structures of α-β-unsaturated carbonyls. (**c**) Chemical structures of α-β-unsaturated carbonyls.

Table III Hormetic 1,4-naphthoquinones

Compound	Nutritional source	Mode of action/pathway	Reference
Juglone	Walnut	ROS formation, GSH depletion, $\Delta\Psi_m$ drop/SKN1[a], EGFR signaling	(50,99–101)
Vitamin K_2	Meat, eggs, diary, natto	O_2^{-*} formation, $\Delta\Psi_m$ drop/*	(102)
Menadione	–[b]	Keap1-alkylation, ROS formation, GSH depletion/Nrf2, EGFR signaling	(35,50)
Plumbagin	Leadwort	ROS formation, GSH depletion/Nrf2, EGFR signaling	(50,103)
Lawsone	–[c]	ROS formation, GSH depletion/EGFR signaling	(50)
Lapachol	Lapacho tea	ROS formation, GSH depletion/EGFR signaling	(50)

[a] SKN1 is the Nrf2 homologue in *C. elegans*

[b] synthetic vitamin K analogue

[c] henna colorant

*unknown

KEAP1/NRF2: SENSOR FOR HORMETIC RESPONSE

Post-transcriptional modifications mainly occur with the help of enzymes with transferase activity. Electrophiles and molecules with a high redox potential may non-enzymatically interact with redox sensitive protein thiols. A most prominent sensor is the Keap1-Nrf2-ARE signaling network, which was recently reviewed in detail (13,31–33) (Fig. 1). In brief, under conditions of a normal redox balance, the cytosolic transcription factor NF-E2-related factor 2 (Nrf2) is associated with its suppressor protein Kelchlike ECH-associated protein 1 (Keap1) and maintained at low expression levels via proteasomal degradation (34). Since Keap1 is a cysteine-rich protein (27 cysteines), its role as a redox sensor is obvious. Conformational changes of Keap1 during chemical modifications of cysteines led to dissociation and translocation of Nrf2 into the nucleus. Several cysteine residues, such as Cys273, Cys288 and Cys151, were identified by mass spectroscopic methods as particularly sensitive to redox modifications (35,36).

Nrf2 is a basic leucine zipper that stimulates stress-inducible gene expression via binding to the antioxidant response element (ARE). Nrf2 induces phase II enzymes such as glutathione S-transferases (GST) and UDP-glucuronosyl transferase (UGT), antioxidant enzymes like glutathione peroxidases (GPx), superoxide dismutase (SOD) and peroxiredoxin. In addition, Nrf2 activation involves genes from cellular redox regulation including glutathione synthetase, thioredoxin, thioredoxin reductase and NAD(P)H: quinone oxidoreductase 1 (NQO1). Table I summarizes genes that are controlled by Nrf2.

Most interestingly, phosphorylation of Nrf2 by protein kinases, such as extracellular signal-regulated protein kinase (ERK1/2), protein kinase C (PKC), c-Jun N-terminal kinase (JKN) and others, enables the dissociation of Nrf2

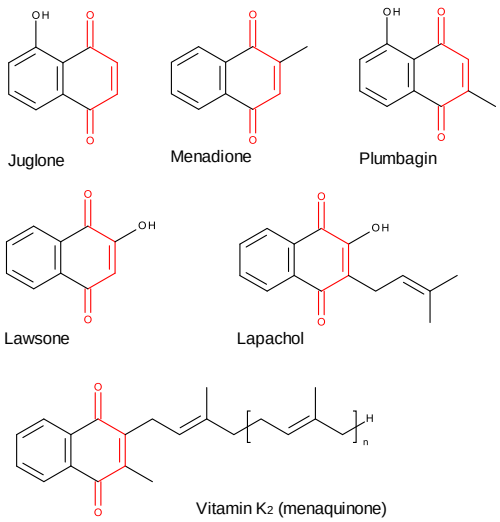

Fig. 3 Chemical structures of 1-4-naphthoquinones.

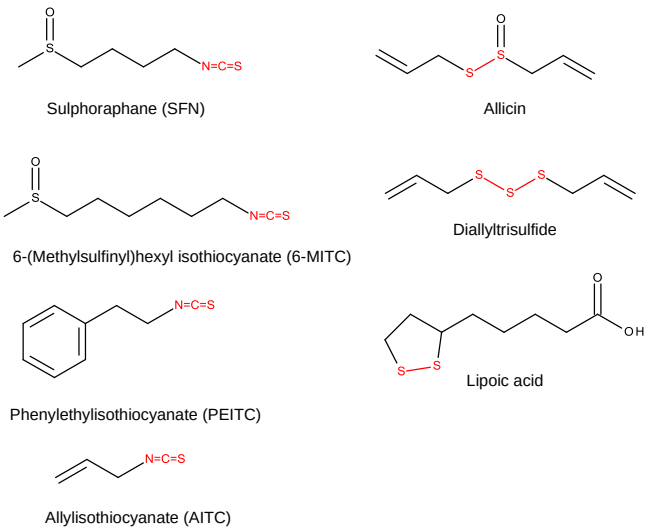

Fig. 4 Chemical structures of sulfur-containing hormetics.

Table IV Sulfur-Containing Hormetics

Compound	Nutritional source	Mode of action/pathway	Reference
Allicin	Fresh garlic	Induction of apoptosis/Nrf2	(104)
Diallyltrisulfide	Aged garlic	ROS formation/Nrf2	(51,105,106)
Lipoic acid	Meat, spinach, broccoli	ROS formation/Nrf2	(107–109)
Sulphoraphane	Broccoli, cauliflower, brassicas, kale	ROS formation, GSH-alkylation[a]/Nrf2	(109–112)
6-(Methylsulfinyl)hexylisothiocyanate	Wasabi	GSH depletion, NAC-alkylation[a]/Nrf2	(113–115)
Phenylethylisothiocyanate	Watercress, garden cress	ROS formation/Nrf2	(116)
Allylisothiocyanate	Cabbage, mustard, horseradish	ROS formation/Nrf2	(116)

[a] reversible, * unknown

from its repressor Keap1 (31). Since many kinases have redox-active cysteine sides, this alternative activation route must be considered for some molecules.

As stated above, the repressor Keap1 is prone to cysteine modifications, and a variety of molecules with activated double bonds, such as α-,β-unsaturated carbonyls or isothiocyanates, are able to S-alkylate this protein. An indirect activation may occur when GSH is depleted *via* adduct formation with xenobiotics. As a consequence, increased ROS levels, in particular H_2O_2, lead to Keap1 protein thiol modifications. Finally, molecules may *in situ* generate H_2O_2 via redox cycling as shown for 1,4-naphthoquinones. It is worth noting that the activation of Nrf2 via Keap1 oxidation by hydrogen peroxide is controversially discussed (37,38).

HORMETICS

This review aims to classify a (still growing) list of dietary ingredients that initially act as oxidants and/or activators of the Nrf2-pathway and thereby inducing an adaptive stress response. Interestingly, many of these compounds were described as antioxidants and potential drugs against neurodegeneration or cancer. This discrepancy can be explained by the pharmacokinetic profile of molecules inducing hormesis. A most prominent example, resveratrol, was re-investigated by Calabrese *et al.* (39). The well-known antioxidant exhibits proliferative as well as pro-apoptotic properties depending on the concentrations used. The authors suggested several targets of action, such as the insulin growth factor-II (IGF-II), cathepsin D, and vitamin D receptor. Recently, it was shown that resveratrol may increase intracellular ROS, deplete glutathione (GSH) and stimulate the Nrf2-pathway (Table VI), thus adding an important mechanism to the target list (40,41). Resveratrol is one example of polyphenols capable of inducing oxidative stress response and thereby act as indirect antioxidants. The author suggests the term *hormetics* for molecules that follow this principle.

Structure-activity relationships (SAR) of inducers of an adaptive stress response were investigated in several studies. Paul Talalay, a pioneer in this field, classified Michael reaction acceptors (activated electrophiles) into different chemical groups (29) covering oxidizable diphenols, olefins or acetylenes conjugated to electron-withdrawing groups, isothiocyanates, thiocarbamates, trivalent arsenicals, dithiolethiones, hydroperoxides, vicinal dimercaptans, and others. A series of those structural determinants is found in phytochemicals and dietary ingredients and will be covered by this review.

Table V Potential Hormetic Linear or Branched Chain Fatty Acids and Derivatives

Compound	Nutritional source	Mode of action/pathway	Reference
α-13′-Carboxychromanol	Metabolite of vitamin E	mtROS formation, $\Delta\Psi_m$ drop/*	(55)
Apo-10′-lycopenoic acid	Metabolite of lycopene	Induction of apoptosis/Nrf2	(117,118)
Geranylgeranoic acid	Turmeric, schisandra, licorice	Induction of apoptosis, $\Delta\Psi_m$ drop/*	(119)
Crocetin	Saffron	*/Protection against oxidative stress (Nrf2?)	(56)
Phytanic acid	Metabolite of chlorophyll, dry lichen, walnuts	mtROS formation, $\Delta\Psi_m$ drop/Inhibition of PDH[a]	(54,120,121)
Pristanic acid	Metabolite of chlorophyll	ROS formation $\Delta\Psi_m$ drop/*	(54)
Palmitic acid	Free fatty acid	ROS formation, $\Delta\Psi_m$ drop/*	(122)
Linoleic acid	Free fatty acid	ROS formation, $\Delta\Psi_m$ drop/*	(123)

*unknown

[a] PDH: mitochondrial pyruvate dehydrogenase

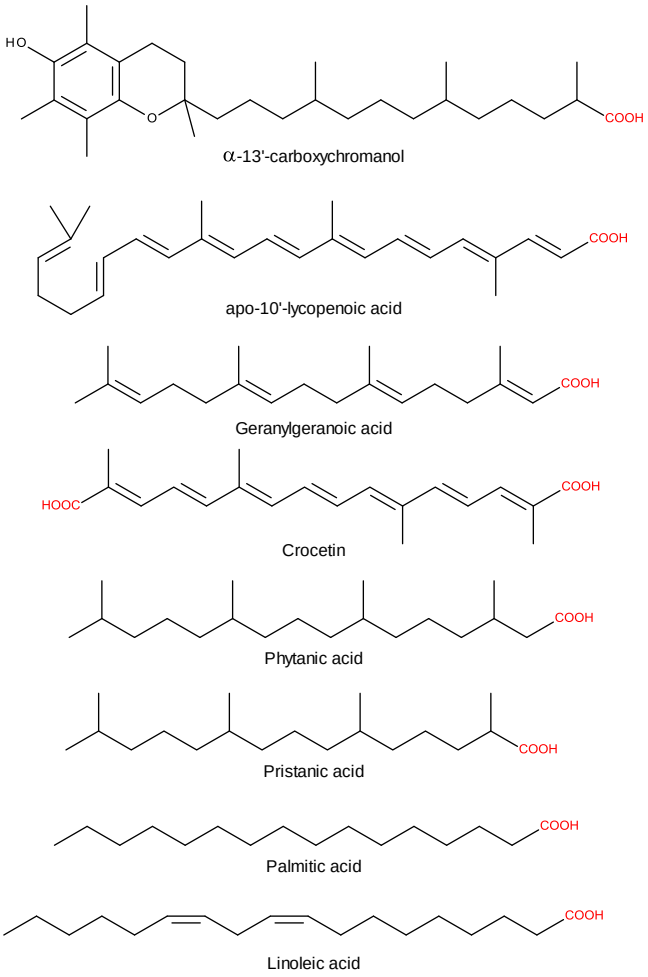

Fig. 5 Chemical structures of linear or branched chain fatty acids and derivatives with hormetic effects.

Michael Acceptors with α-,β-Unsaturated Carbonyl Function

This class of Michael acceptors includes α-,β-unsaturated ketones, aldehydes, and carboxylic acid and esters (Table II, Fig. 2a,b,c). The molecules listed in Table II were mainly tested in cell culture systems. Most of the molecules induce an initial ROS formation accompanied with GSH depletion, and some compounds are described to lower the mitochondrial membrane potential $\Delta\Psi_m$. The question arises whether the ROS formation is pivotal for Nrf2 activation or rather a secondary signal from apoptotic cells. Surviving cells, however, exhibit higher proliferation rates and increased GHS levels besides higher expression levels of antioxidant enzymes. Compounds with an enone-structure (flavokawain B, Isoliquiritigenin, zerumbone, xanthohumol, curcumin, shogaol, piperine, 15d-PGJ_2, astaxanthin) seem to generate ROS followed by Nrf2 activation. Mass spectroscopic methods revealed a direct S-alkylation of Keap1 with xanthohumol, shoagol, isoliquiritigenin and 15-deoxy-Δ12,14-prostaglandin J_2 (15d-PGJ_2), respectively (42–44).

Caffeic acid phenylethyl ester found in honeybee hives induces a strong hormetic response, but structural-related rosmarinic acid was not investigated so far. Nrf2 and NF-κB activation were described for cinnamaldehyde, the prototype of an α-,β-unsaturated aldehyde. Several aldehydes such as perillaldehyde from *perilla frutescence* were recently identified to induce the Nrf2/Keap1 system (45).

Interestingly, lipid oxidation products strongly induce Nrf2 activity and fit well within the list of phytochemicals assigned as neuroprotectors or anticarcinogens. For example, 4-hydroxy-2-nonenal (4-HNE), the final aldehyde derived from oxidation of ω-6 polyunsaturated fatty acids, such as linoleic acid, linolenic acid, and arachidonic acid, induces an adaptive response. It furthermore reacts with redox-sensitive cysteines of thioredoxin and thioredoxin reductase (46), glyceraldehyde-3-phosphate dehydrogenase (47), glutathione *S*-transferase (48), and actins (49). Similar results were obtained with crotonaldehyde and acrolein, whereas malondialdehyde was not investigated yet.

1,4-Naphthoquinones

1,4-Naphthoquinones are potent cytotoxic agents capable of producing H_2O_2 via redox cycling. In addition, they are strong Michael acceptors and thus prone to protein thiol S-alkylations. Several naturally occurring 1,4-naphthoquinone, such as plumbagin from leadwort, juglone from various types of walnut, lawsone from henna colorants, lapachol from lapacho tea, and vitamin K_2, induce ROS formation and GSH depletion (Table III, Fig. 3). Vitamin K_2-induced apoptosis is mediated by mitochondrial superoxide radical generation, and juglone, plumbagin, and the synthetic vitamin K analogue menadione activate the Nrf2 network. In addition, naphthoquinones stimulate ErB2 and EGFR signaling pathways (50) (Fig. 4).

Table VI Hormetic Acetylenes

Compound	Nutritional source	Mode of action/pathway	Reference
Falcarinol	Carrots, celery	Induction of hemoxygenase 1(HO1)/(Nrf2 ?)	(124)
Falcarindiol	Carrots, celery	Keap1-alkylation/Nrf2	(58,124)
Panaxydol	Red ginseng, carrots	ROS formation/JNK and p38 MAPK	(125)

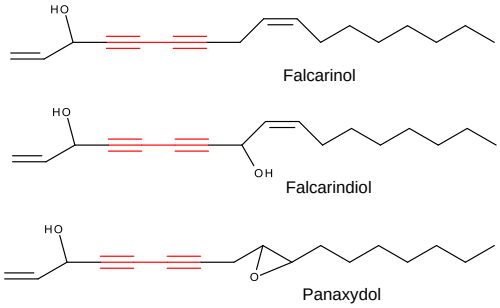

Fig. 6 Chemical structures of hormetic acetylenes.

Isothiocyanates and Disulfides

Isothiocyanates and disulfides are also Michael acceptors that react with protein thiols to form thiocarbamates or mixed disulfides, respectively. Compounds in Table IV induce ROS and activate the Nrf2 pathway. Beneficial health effects of sulfur-containing products from garlic have been described for many years. The chemical reactions of allicin and diallyltrisulfide lead to protein thiolation, decrease GSH, and increase ROS levels. The complex redox chemistry was reviewed recently by Filomeni *et al.* (51). Of the isothiocyanantes, sulforaphane from broccoli is probably the most intensively studied, also in respect to Nrf2 activation by phytochemicals. 6-(Methylsulfinyl)hexylisothiocyanate, allylisothiocyanate and phenylethylisothiocyanate exhibit similar chemical and biochemical properties. A reversible reaction of isothiocyanates with GSH and presumably with Keap1 forms thiocarbamates (52,53).

Linear and Branched Chain Fatty Acids and Derivatives

This class of compound comprises linear and branched chain fatty acids, mostly found as catabolic metabolites (Table V, Fig. 5). The lycopene metabolite apo-10′-lycopenic acid and geranylgeranoic acid from schisandra belong to the class of Michael acceptors, since they have a double bond conjugated to a carboxylic acid. Nrf2 activation was only described for apo-10′-lycopenic acid yet. It is questionable if these compounds directly interact with Keap1. The chlorophyll metabolite phytanic acid inhibits mitochondrial pyruvate dehydrogenase, leading to an increase of mtROS and the vitamin E metabolite α-13′-carboxychromanol induces mitochondrial ROS formation (54,55). Crocetin, the yellow color pigment of saffron, was shown to protect primary rat hepatocytes from oxidative stress (56), presumably via Nrf2 activation. Palmitic acid is discussed to uncouple mitochondria which lead to increased mtROS levels (57). Taken together, not much is known about this class of compounds, but it seems likely that they interact with the mitochondrial metabolism and thereby generate mtROS that likely induce an adaptive stress response. Further studies are needed to prove Nrf2 activation of this class of compounds.

Acetylenes

Although a rather small group of compounds, these naturally occurring acetylenes behave as typical Michael acceptors (Table VI, Fig. 6). Falcarinol, falcarindiol, and panaxydol present in carrots and celery induce ROS formation and, most importantly, induce the Nrf2 network. Keap1-alkylation of cysteine thiol Cys151 by falcarindiol was recently demonstrated by Ohnuma *et al.* (58).

Polyphenols

Classical polyphenols are antioxidants by definition; they are able to scavenge free radicals. This property was demonstrated in a series of *in vitro* studies but was scarcely

Table VII Classical Polyphenols as Hormetic Effectors

Compound	Nutritional source	Mode of action/pathway	Reference
Liquiritigenin	Licorice	ROS formation, GSH depletion, $\Delta\Psi_m$ drop/*	(126)
Naringenin-glucoside	Grapefruits, oranges, tomatoes	*/ERK and Nrf2	(127)
Kaempferol	Green tea, broccoli, apples	ROS formation, $\Delta\Psi_m$ drop/Nrf2	(128–130)
Jaceiosidin	*Artemisia* species	ROS formation/Nrf2 and NF-κB	(131,132)
Resveratrol	Grapes, blueberries, peanuts, red wine	ROS formation, GSH depletion/Nrf2	(40,41,133,134)
Quercetin	Vegetables, fruits, red wine	ROS formation, $\Delta\Psi_m$ drop/Nrf2	(135,136)
Epigallocatechin-3-gallate	Green tea	H_2O_2 formation, GSH depletion, $\Delta\Psi_m$ drop/Nrf2	(137–140)
Hesperidin	Citrus fruits	*/ERK and Nrf2	(141,142)
Carnosic acid	Rosemary	Keap1-alkylation/Nrf2	(60,143)
Cyanidine-3-rutinoside	Vegetables, fruits	ROS formation/Nrf2	(144,145)
Protocatechuic acid	Fruits, vegetables, teas, wine	*/Nrf2	(146)

*unknown

seen in living systems. An overall antioxidative benefit, however, was clearly demonstrated in cell culture and animal studies. A recent review by Siow and Mann propagates polyphenols as hormetic effectors (21,59). The polyphenols in Table VII are structurally related to polyphenols from Table II but are not Michael acceptors at first glance. But most interestingly, they induce ROS formation, GSH depletion, as well as Nrf2 activation. Less is known about how polyphenols increase intracellular ROS levels. Several studies suggest the conversion of diphenols to quinones. The mechanism involves a two electron auto-oxidation from a catechol-type to an electrophilic quinone-type molecule. The reaction easily occurs with catechols (1,2-diphenols) and hydroquinones (1,4-diphenols) but not with resorcinols (1,3-diphenols) (29). For example, carnosic acid is oxidized to a 1,2-quinone-type electrophile, which readily alkylates Keap1 resulting in the release of Nrf2 (Fig. 6b) (60). Nrf2 translocates into the nucleus and activates transcription of phase 2 enzymes via the ARE transcriptional element in the promotor region of the corresponding genes. By this mechanism, polyphenols may induce a hormetic response (Figs. 7 and 8).

Secondary metabolism may transfer flavones and flavanones into chalcones that belong to the group of Michael acceptors. This pathway would also explain some of the pro-oxidant properties. In addition, disruption of mitochondrial metabolism was described for the green tea polyphenol EGCG that accumulates at 90–95% within mitochondrial fraction rat liver cells (61). As a result, hydrogen peroxide formation was observed.

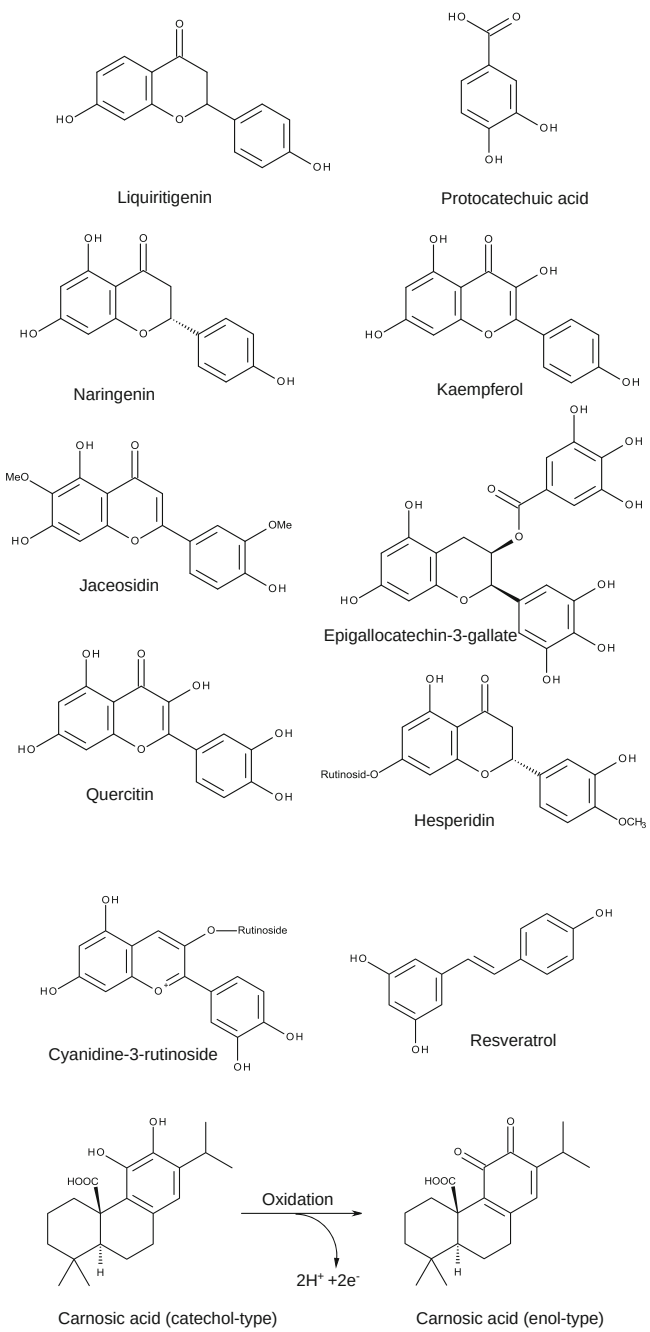

Fig. 7 Chemical structures of polyphenols with hormetic effects.

Miscellaneous

Table VIII covers the molecules which could not be assigned to the classifications made before. However, all molecules behave like hormetics and are worth investigating in further studies.

CONCLUSION

The aim of this review is the description of a series of electrophilic natural compounds from edible plants. Most of them are known for their antioxidant properties *in vitro*

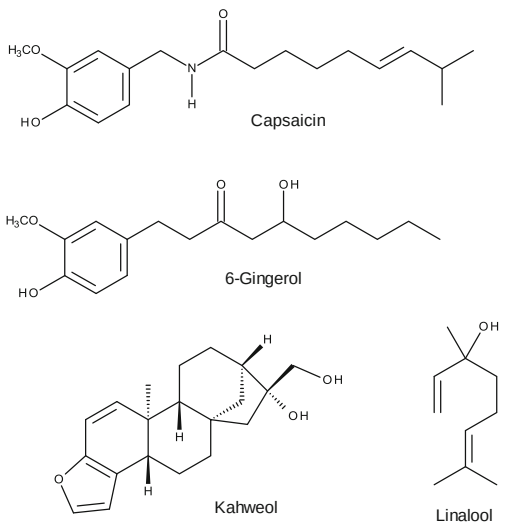

Fig. 8 Chemical structures of hormetics with unclear structure-function-relationship.

Table VIII Potential Hormetics with Unclear Structure-Function Relationship

Compound	Nutritional source	Mode of action/pathway	Reference
6-Gingerol	Ginger	ROS formation, GSH depletion, $\Delta\Psi_m$ drop/NF-κB	(147–149)
Capsaicin	Chili peppers	ROS formation, $\Delta\Psi_m$ drop/Nrf2	(150–153)
Linalool	Coriander	ROS formation, GSH depletion/Complex I and II inhibition	(154)
Kahweol	Coffee	*/Nrf2	(155)

and *in vivo*. The review does not reflect the numerous ways of modulating signaling networks, the endocrine system, or inflammatory events.

Only recently, classical antioxidants were investigated for a biphasic redox behavior. A hormetic stress response is often observed, depending on the administered concentration and duration of treatment. The concept of hormesis will probably change our view of many antioxidants. The Nrf2/Keap1 network plays a crucial role in the mediation of an adaptive response. The number of publications addressing Nrf2 is growing dramatically. A simple PubMed database search found 216 hits during the years 2000–2005 and increased to 1,059 hits from 2005 to 2010. Since 2010, more than 800 publications refer to Nrf2.

Studies with antioxidant supplements failed to improve overall age-related health (see Introduction); however, nearly all meta-analyses assigned health benefits to the consumption of fruit and vegetables (62–65). Two possible reasons might explain these results. First, supplementation with high doses of antioxidants may suppress an adaptive stress signaling as shown with volunteers taking a combination of vitamin C (1,000 mg/day) and vitamin E (400 IU/day) during a 4-week intervention of physical exercise. Physical exercise is known to improve markers for age-related disease such as *diabetes mellitus* and also triggers potentially harmful ROS formation. Compared to controls, the intervention group did not improve insulin sensitivity or ROS defense capacity as shown by muscular superoxide dismutase and glutathione peroxidase expression, suggesting an adaptive stress response that was blocked by antioxidants (8). Second, prospective cohort studies found that dietary consumption of at least 400 g/day vegetables and fruits was sufficient to achieve the recommended daily allowance for vitamins and minerals. Moreover, the quantity of phytochemicals consumed may induce a hormetic response that could be responsible for the beneficial health effect of fruits and vegetables.

Future research will identify more hormetics in our diet, and "electrophile" profiling of food and plant extracts may accelerate this research field. One elegant approach was described recently when different spices and herbs, including coffee, were investigated for their ability to activate a luciferase-based reporter gene construct for ARE (66). Finally, simple biomarkers will be needed to estimate the potency of a hormetic stress response in human trials.

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