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FORUM REVIEW ARTICLE

The Effects of Antioxidant Nutraceuticals on Cellular Sulfur Metabolism and Signaling

Kenneth R. Olson,[1,2] Paul J. Derry,[3] Thomas A. Kent,[3–5] and Karl D. Straub[6,7]

Abstract

Significance: Nutraceuticals are ingested for health benefits, in addition to their general nutritional value. These dietary supplements have become increasingly popular since the late 20th century and they are a rapidly expanding global industry approaching a half-trillion U.S. dollars annually. Many nutraceuticals are promulgated as potent antioxidants.

Recent Advances: Experimental support for the efficacy of nutraceuticals has lagged behind anecdotal exuberance. However, accumulating epidemiological evidence and recent, well-controlled clinical trials are beginning to support earlier animal and *in vitro* studies. Although still somewhat limited, encouraging results have been suggested in essentially all organ systems and against a wide range of pathophysiological conditions.

Critical Issues: Health benefits of ''antioxidant'' nutraceuticals are largely attributed to their ability to scavenge oxidants. This has been criticized based on several factors, including limited bioavailability, short tissue retention time, and the preponderance of endogenous antioxidants. Recent attention has turned to nutraceutical activation of downstream antioxidant systems, especially the Keap1/Nrf2 (Kelch like ECH associated protein 1/nuclear factor erythroid 2-related factor 2) axis. The question now becomes, how do nutraceuticals activate this axis?

Future Directions: Reactive sulfur species (RSS), including hydrogen sulfide (H_2S) and its metabolites, are potent activators of the Keap1/Nrf2 axis and avid scavengers of reactive oxygen species. Evidence is beginning to accumulate that a variety of nutraceuticals increase cellular RSS by directly providing RSS in the diet, or through a number of catalytic mechanisms that increase endogenous RSS production. We propose that nutraceutical-specific targeting of RSS metabolism will lead to the design and development of even more efficacious antioxidant therapeutic strategies. *Antioxid. Redox Signal.* 38, 68–94.

Keywords: ROS, RSS, oxidative stress, sulfur metabolism, Nrf2, garlic, lipoic acid, polyphenols

Introduction

We live in an oxidative environment. It rusts our automobiles, browns our apples, destroys our forests, and is associated with a myriad of pathophysiological conditions. It is also essential for our very existence. Maintaining a reduced cellular homeostasis, as described in the ''redox code'' as ''a set of principles that defines the positioning of the nicotinamide adenine dinucleotide (NAD, NADP) and thiol/disulfide and other redox systems as well as the thiol redox proteome in space and time'' (Jones and Sies, 2015), in the face of this unrelenting pressure is a constant challenge.

[1]Department of Physiology, Indiana University School of Medicine—South Bend, South Bend, Indiana, USA.
[2]Department of Biological Sciences, University of Notre Dame, Notre Dame, Indiana, USA.
[3]Center for Genomics and Precision Medicine, Institute of Biosciences and Technology, Texas A&M Health Science Center, Houston, Texas, USA.
[4]Department of Chemistry, Rice University, Houston, Texas, USA.
[5]Stanley H. Appel Department of Neurology, Houston Methodist Hospital and Research Institute, Houston, Texas, USA.
[6]Central Arkansas Veteran's Healthcare System, Little Rock, Arkansas, USA.
[7]Department of Medicine and Biochemistry, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA.

Failure to do so results in oxidative ''stress,'' initially defined as ''an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage.'' It is now known that oxidative stress is far more reaching, and terms such as oxidative eustress and oxidative distress are used to span the gamut between normal regulatory redox-mediated signaling processes and catastrophic pathophysiological events (for a historical context, see Sies, 2018).

The redox code has been further expanded to include additional species and a variety of regulatory processes in the ''redox interactome.'' This is defined as ''a primeval multilevel redox regulatory system whose architecture, together with the physiochemical characteristics of its constituents, allows efficient sensing and rapid adaptation to environmental changes and various other stressors to enhance fitness and resilience at the local and whole-organism level'' (Cortese-Krott et al, 2017). Central to this concept are selective classes of molecules known as ''reactive species.''

Although all biomolecules are technically ''reactive species,'' this term is now more or less restricted and used in the context of a few specific redox molecules, the reactive oxygen species (ROS), reactive nitrogen species, reactive sulfur species (RSS), and more recently, the reactive carbonyl species (RCS) (Cortese-Krott et al, 2017; Malard et al, 2021). Hydrogen peroxide (H_2O_2) and, to a somewhat lesser extent, superoxide ($O_2^{\bullet -}$) are arguably the two most significant oxidants in terms of their involvement in both oxidative eustress and distress (Chouchani et al, 2016; Reczek and Chandel, 2015; Sies, 2017; Sies and Jones, 2020).

Articles citing ''ROS'' and ''oxidative stress'' have dominated the literature. According to PubMed.gov, articles with ''reactive oxygen species'' in them first appeared in 1945, with 308,992 listed between then and 2020. In 2020 alone, there were 20,574 citations, more than one every half hour. ''Hydrogen peroxide'' first appeared in 1882 with 102,857 references through 2020. Articles citing ''oxidative stress'' have been cited 305,246 times since 1960, and ''reductive stress,'' which is also a recognized pathophysiological condition (Bellezza et al, 2020; Ma et al, 2020; Manford et al, 2021; Perez-Torres et al, 2017; Xiao and Loscalzo, 2020; Zhang and Tew, 2021), has been cited 8453 times between 1970 and 2020.

Articles with ''reactive sulfur species'' first appeared in 1966 with only 2832 listed between then and 2020 and it took until 1992 for more than 10 articles to be published in a single year. In 2020, there was less than one (0.7) published per day. ''Hydrogen persulfide'' did not appear in the literature until 1986 and to date, there have been only 292 references.

It has recently been pointed out that ROS are strikingly similar to RSS, and there are a number of reasons why ROS may be over-emphasized whereas RSS are under-appreciated (Olson, 2020). We propose that this may also influence our concept of the mechanisms of action of antioxidants. In this review, we will summarize the similarities and differences between ROS and RSS and we will illustrate how the effects of a variety nutraceutical antioxidants and related compounds can be attributed to RSS instead of ROS. It is hoped that this will further the design and development of even more specific antioxidant therapeutic strategies.

Is Distinguishing Between ROS or RSS the Key to Further Understanding Antioxidant Mechanisms?

It is clear that a number of factors have, justifiably or not, biased our understanding of oxidants and directed our views on antioxidant therapeutics. Our surroundings are clearly oxidative, and the detrimental effects of oxidants on organisms are easily demonstrated. However, we propose that in our exuberance to pursue oxidant stress we have neglected or overlooked other factors that may be as or more relevant, especially relative to RSS. These are considered in the following sections.

Chemical and biochemical similarities between ROS and RSS

There are a number of similarities between oxygen and sulfur, as both are chalcogens with six valence electrons. However, sulfur is a larger atom, which makes it less electronegative and the bonds between two sulfur atoms are more stable than those between two oxygen atoms. Sulfur's electrons are also more readily exchanged, which favors electron transfer reactions and allows sulfur atoms to participate in reversible oxidant/antioxidant redox reactions, a point germane to the present review.

There are also numerous similarities in the metabolism and signaling pathways of ROS and RSS, and this often creates confusion in distinguishing between them (Olson, 2020). Stepwise single-electron reduction of molecular oxygen produces superoxide, H_2O_2, hydroxyl radical, and water [Eq. (1)]:

$$\begin{aligned} O_2(+e^-) &\rightarrow O_2^{\bullet -}(+e^- + 2H^+) \rightarrow H_2O_2(+2e^-) \\ &\rightarrow 2HO^{\bullet}(+2e^- + 2H^+) \rightarrow 2H_2O \end{aligned} \quad (1)$$

whereas single-electron oxidations of hydrogen sulfide (H_2S) produce the thiyl radical, hydrogen persulfide (H_2S_2), ''supersulfide,'' and molecular sulfur, with the latter usually cyclizing to elemental sulfur (S_8) [Eq. (2)]:

$$\begin{aligned} 2H_2S(-2e^- - 2H^+) &\rightarrow 2HS^{\bullet}(-2e^-) \rightarrow H_2S_2 \\ (-e^- - 2H^+) &\rightarrow S_2^{\bullet -}(-e^-) \rightarrow S_2(S_8) \end{aligned} \quad (2)$$

The intermediates, H_2O_2 and H_2S_2, are the basis for ROS and RSS signaling and this occurs through common cysteines on regulatory proteins (cysteine-based regulatory protein [PSH]) [Eqs. (3) and (4)]:

$$H_2O_2 + PSH \rightarrow PSOH + H_2O \quad (3)$$

$$H_2S_2 + PSH \rightarrow PSSH + H_2S \quad (4)$$

Further, unlike H_2O, H_2S can reduce select protein disulfide bonds (Vasas et al, 2015), which adds another level of complexity to RSS signaling.

Aspects of a number of these downstream effectors regulated by H_2O_2, H_2S, and H_2S_2 are considered in greater detail in subsequent sections.

Factors that contribute to confusion between ROS and RSS

A number of factors have contributed to the confusion between the identity and properties of ROS and RSS (Olson,

2020). (1) Some assays designed to detect ROS, such as the redox-sensitive green fluorescent protein (roGFP), arguably the ''gold standard'' for ROS measurements (Schwarzlander et al, 2015), are 200 times more sensitive to RSS than they are to ROS and amperometric H_2O_2 electrodes are 24 times more sensitive to RSS (DeLeon et al, 2016a).

(2) The vast majority of biochemical and cell-culture experiments are performed in room air. In this environment, the dissolved oxygen concentration in typical buffers is at least 200 μM (Boutilier et al, 1984) and in standard tissue incubators it is $\sim$175 μM (Keeley and Mann, 2019). A few cells, with the exception of the upper airways and corneal epithelium, ever experience these oxygen concentrations and, in fact, in most cells it is 50 μM or less and $\sim$5 μM oxygen in the mitochondrion (summarized in Olson, 2020). As reduced sulfur and oxygen do not coexist, it is easy to see why ROS predominate in the elevated oxygen tensions used in most experiments.

(3) The rate of oxygen consumption of mice and rats, the most common animal models, is 8.5 and 4.4 times that of a human (Olson, 2020). These high rates of oxygen turnover would be expected to produce considerably more ROS than that of human tissue. Collectively, it is little wonder that more emphasis has been placed on ROS.

Several points regarding ROS signaling mechanisms further confound the issue. First is the source of signaling H_2O_2. The mitochondrion is presumed to be one of the major sources of superoxide and H_2O_2, especially in response to hypoxia (Chouchani et al, 2016; Sylvester et al, 2012), but neither ROS rapidly diffuses across membranes. Aquaporins have been proposed to serve as conduits for a mitochondrial-to-cytosolic transfer of H_2O_2 (Bienert and Chaumont, 2014), but to date, there has not been any direct evidence of H_2O_2 release from the mitochondrion to the cytosol (Sies and Jones, 2020). Does this effectively eliminate mitochondrial H_2O_2 in extra-mitochondrial signaling and relegate the latter to the NADPH oxidases (NOX) (Vermot et al, 2021)? Conversely, H_2S readily diffuses across membranes.

The second point is how efficient and specific is H_2O_2 in activating specific targets? Peroxiredoxins are far more abundant in the cytosol than putative target proteins and their cysteines more avidly react with H_2O_2 (Stocker et al, 2018). It has been proposed that very restricted microdomains are necessary to produce H_2O_2 and transmission of the redox signal to the peroxiredoxins and then to the effector protein (Stocker et al, 2018; Winterbourn, 2020). These issues, and the efficacy and production of RSS in microdomains as well as intracellular diffusion may help resolve these questions.

Importance of the evolutionary legacies of ROS and RSS

Despite the prevalence of ROS in the literature, RSS have dominated evolution (Olson, 2019; Olson and Straub, 2016). There is strong evidence that life began around hydrothermal vents in the anoxic seas $\sim$3.8 billion years ago (bya) and that nearly 85% of evolution occurred in this anoxic, or at best, extremely hypoxic environment before the Earth became oxidized to its present level around 0.6 bya. Sulfur, especially H_2S, undoubtedly played a central role; it served as a catalyst (pro-enzyme), mineral (pro-membrane), precursor to organic compounds, and most importantly, it was a constant and dependable source of energy delivering reducing equivalents to the relatively more oxidized ocean.

Earth's oxidation was believed to be a critical juncture in evolution (Kurland and Andersson, 2000; Ulrich and Jakob, 2019); organisms had to either develop mechanisms to deal with the oxidants, retreat to anoxic environments, or die. The ox-tox hypothesis (Andersson and Kurland, 1999; Kurland and Andersson, 2000) posited that this oxic environment led to the development of the sophisticated antioxidant mechanisms in the redox code that have persisted to the present (Jones and Sies, 2015). However, it is well known that essentially all these antioxidant mechanisms appeared 2 bya, long before the Earth became oxidized (Olson, 2019).

We proposed that and this was most likely concurrent with the need to regulate RSS metabolism (Olson and Straub, 2016). Further, anoxygenic photosynthesis, most likely based on the oxidation of H_2S and reduction of CO_2 [Eq. (5)], predated oxygenic photosynthesis [Eq. (6)] by more than a billion years.

$$2H_2S + 2CO_2 + \text{light} \rightarrow S_2 + CH_3CO_2H \quad (5)$$

$$2H_2O + 2CO_2 + \text{light} \rightarrow O_2 + CH_3CO_2H \quad (6)$$

These observations suggest that many of the metabolic pathways in extant organisms, including the ''antioxidant'' defenses, were established long before ROS were relevant oxidants. This caveat has let us to re-evaluate the ability of endogenous antioxidant mechanisms to affect sulfur metabolism.

Importance of Sulfur Metabolism in Understanding Antioxidant Mechanisms

Endogenous sulfur metabolism

Endogenous sulfur metabolism has become an increasingly complicated topic with the advent of new methodological approaches. Here, it is briefly summarized with emphasis on H_2S and polysulfide production as this appears to be where nutraceuticals exhibit their main effects. Additional details can be found in recent reviews (Doka et al, 2020; Fukuto and Hobbs, 2021; Fukuto et al, 2020; Kharma et al, 2019; Nagy et al, 2019; Olson, 2018; Pedre and Dick, 2021; Sawa et al, 2021; Sawa et al, 2020; Sbodio et al, 2019).

H_2S production. Six or more enzymes in at least 17 pathways, in addition to non-enzymatic mechanisms, contribute to H_2S production (Fig. 1A) and more will, undoubtedly, be identified (Olson, 2018). In the more or less canonical pathways, H_2S is produced from L-cysteine (L-Cys**S**), where **S** in this section indicates reactive sulfur atom, or to a lesser extent from L-methionine (L-Met**S**) by the enzymes cystathionine γ-lyase (CSE) and cystathionine β-synthase (CBS) or by the sequential action of cysteine aminotransferase (CAT) and 3-mercaptopyruvate sulfur transferase (3-MST**S**).

In the latter pathway, CAT transfers the sulfur from L-Cys**S** to pyruvate producing 3-mercaptopyruvate (3-MP**S**), which then binds to a sulfur on 3-MST**S** forming the persulfide, 3-MST**SS**. H_2S can then be released from 3-MST**SS**

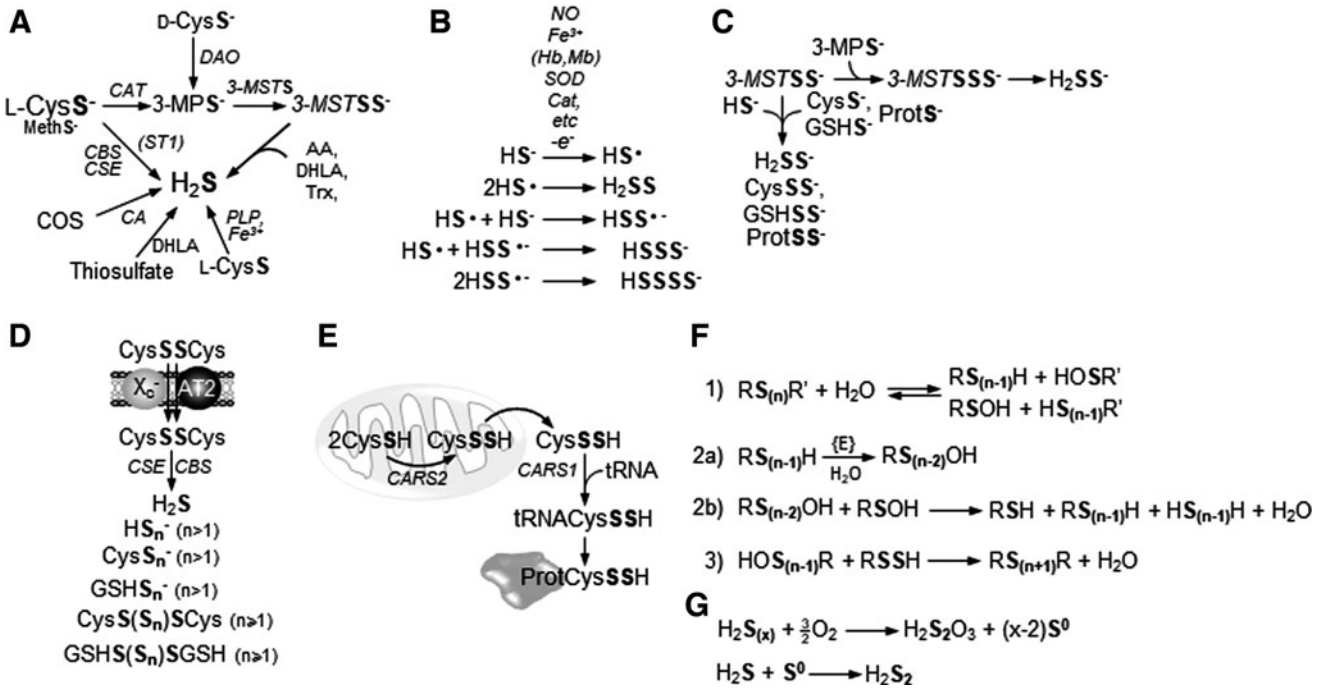

FIG. 1. Pathways for H_2S and per- polysulfide production in cells. (A) H_2S is primarily derived from L-Cys**S** (**S** indicates reactive sulfur atoms) or to a lesser extent from L-Met**S** by the enzymes CSE, CBS, CAT, and 3-MST**S**. CAT transfers the sulfur from L-Cys**S** to pyruvate producing 3-MP**S**, which then forms 3-MST**SS**, 3-MP**S** can also be produced from D-Cys**S** by DAO. H_2S is released from 3-MST**S**S by AA, DHLA, or Trx. H_2S can also be produced from COS by CA (although see Steiger et al, 2018), from thiosulfate by Trx or DHLA, from L-Cys**S** by ST1, or by PLP plus free or heme-bound iron (Fe^{3+}). H_2S can also be released from a variety of persulfides by numerous nucleophiles. **(B)** Per- and polysulfides are produced by direct reaction with NO, from $Fe3^+$, Hb, Mb, SOD, and Cat, often with initial formation of a thiyl radical ($HS^{\bullet}$). **(C)** Per- and polysulfides produced by exchange reactions with 3-MST**SS**. **(D)** Per- and polysulfides produced by CBS and CSE metabolism of cystine transported into cells by X_{c-} and AT2. **(E)** Mitochondrial CARS2 produces Cys**SS** that is translocated to the cytosol, where CARS1 affixes it to tRNA for incorporation into a protein (Prot). CARS 1 may also form additional Cys persulfides. **(F)** Hydrolysis equilibrium of polysulfides forms both neutrophilic and electrophilic compounds that may rearrange to form a variety of other compounds. Electrophiles {E}, required for these reactions shift the equilibrium to the right. **(G)** Polysulfide oxidation produces $H_2S_2O_3$ and S^0, and the latter can react with H_2S to produce other polysulfides. 3-MP**S**, 3-mercaptopyruvate; 3-MST**S**, 3-mercaptopyruvate sulfur transferase; AA, ascorbate; AT2, sodium-coupled neutral amino acid transporter; CA, carbonic anhydrase; CARS1, cytosolic cysteinyl-tRNA synthetase; CARS2, mitochondrial cysteinyl-tRNA synthetase; CAT, cysteine aminotransferase; Cat, catalase; CBS, cystathionine β-synthase; COS, carbonyl sulfide; CSE, cystathionine γ-lyase; CysSSCys, cystine; DAO, D-amino acid oxidase; D-Cys**S**, D-cysteine; DHLA, dihydrolipoic acid; GSH**S**, glutathione; H_2S, hydrogen sulfide; $H_2S_2O_3$, thiosulfate; Hb, methemoglobin; L-Cys**S**, L-cysteine; L-Met**S**, L-methionine; Mb, metmyoglobin; NO, nitric oxide; PLP, pyridoxyl phosphate; Prot**S**, protein reactive sulfur; S^0, elemental sulfur; SOD, superoxide dismutase; ST1, sulfur transferase 1, tRNA, transfer RNA; Trx, thioredoxin; X_{c-}, cystine/glutamate antiporter. Bold **S** indicates reactive sulfur.

by reductants such as ascorbate (AA), dihydrolipoic acid (DHLA), or thioredoxin (Trx). CSE and CBS are primarily cytosolic enzymes but can be translocated to the mitochondrion by hypoxia or other stressors, CAT and 3-MST**S** are found in both the cytosol and the mitochondrion, being more prevalent in the latter.

In arguably lesser reactions, H_2S can be generated in the brain and kidney in a reaction in which D-amino acid oxidase (DAO) transfers sulfur from D-cysteine (D-Cys**S**) to 3-MP**S** in peroxisomes for delivery to the mitochondrion (Seki et al, 2018; Shibuya et al, 2013). D-Cys**S** is found in particularly high concentrations, 65 and 4.2 μM in white and gray matter, respectively (Semenza et al, 2021). H_2S may be produced from carbonyl sulfide (COS) in the cytosol in a reaction catalyzed by carbonic anhydrase (CA), although the exact mechanism(s) for COS production in mammalian tissues remain to be identified (Steiger et al, 2018).

H_2S may also be produced from thiosulfate in the mitochondrion catalyzed by Trx or non-enzymatically by DHLA and by sulfur transferase 1 (ST1), a subunit of yeast mitochondrial complex I that may release H_2S directly from L-Cys**S**. A recent study has also shown that H_2S can be generated nonenzymatically from either D- or L-Cys**S** by pyridoxyl phosphate (PLP) and free or heme-bound iron (Fe^{3+}), and this has been purported to contribute to much of the basal H_2S production in most tissues except the liver and kidney (Yang et al, 2019). H_2S can also be released from a variety of persulfides by numerous nucleophiles.

Per- and polysulfide production. Oxidized sulfur (−1, 0) readily undergoes catenation reactions that produce relatively stable inorganic and organic per- and polysulfides with low-molecular-weight thiols, for example, Cys, glutathione (GSH), and DHLA, some of which may be found in low to

high micromolar concentrations in cells. These sulfur molecules can undergo exchange reactions with other thiols and per- polysulfides as well as with sulfur transferring enzymes Trx and Mocs3 and protein Cys.

Polysulfides (RS_nR', $n>1$) are also readily hydrolyzed to both nucleophilic (RS_{n-1}^-) and electrophilic sulfenic acid ($R'SO^-$) species. Per- and polysulfides may contain from two to six or more sulfur-sulfur bound atoms, all of which may be reactive, adding to the complexity.

Per- and polysulfides may be produced *de novo* from low-molecular-weight thiols or derived through a variety of exchange mechanisms. H_2S, or more likely the hydrosulfide anion (HS^-), may undergo a one-electron oxidization catalyzed by Fe^{3+}, methemoglobin, metmyoglobin, or other oxidants, to a thiyl radical ($HS^\bullet$), which may combine with different sulfur molecules to produce a variety of compounds (Fig. 1B). Sulfur in 3-MST**SS** (described above) can also be transferred to Cys, GSH, or protein-Cys (Fig. 1C).

H_2S also forms a persulfide with sulfide:quinone oxidoreductase (SQR), a complex II associated enzyme that catalyzes the initial oxidation step in H_2S catabolism, and this may be also transferred to GSH. There is a report that cysteine hydropersulfides and persulfides may be produced by either CSE or CBS from cystine (Cys**SS**Cys) transported into cells by either a cystine/glutamate antiporter (system X_c^-) or a sodium-coupled neutral amino acid transporter (AT2) and these can undergo further exchange reactions (Fig. 1D), although a number of studies have argued against this (Kimura et al, 2017b; Shibuya et al, 2009; Yadav et al, 2016).

Mitochondrial cysteinyl-tRNA synthetase (CARS2) transfers sulfur from one Cys to another to form Cys hydropersulfide (Cys**SS**H) that is then translocated to the cytosol where cytoplasmic cytosolic cysteinyl-tRNA synthetase (CARS1) may either transfer it to transfer RNA (tRNA; tRNA-Cy**SS**H) or add a second Cys sulfur before transfer (tRNA-Cys**SSS**H) (Fig. 1E). In this way, a per- or polyhydrosulfide is directly incorporated into a protein and it is estimated that this may be as much as 70%–80% of the Cys in proteins.

It has recently been reported that polysulfide species (RS_nR with $n>2$) are in a hydrolysis equilibrium that forms both neutrophilic and electrophilic compounds and that electrophiles shift this equilibrium to the right (Sawa et al, 2021). These may subsequently rearrange to form a variety of other compounds, a few of which are shown in Figure 1F. However, the physiological significance of these reactions remains to be determined. In addition, polysulfides may react with oxygen to produce thiosulfate and elemental sulfur (S^0) (Kleinjan et al, 2005) and S^0 can react with H_2S to produce other polysulfides (Fig. 1G). Collectively, these reactions lead to a complex and dynamic sulfur biome that is only beginning to be understood.

Metabolism of RSS by endogenous antioxidants

There is considerable literature on the mechanisms employed by eukaryotic cells to either remove superoxide and H_2O_2 or regulate their signaling capabilities. The majority of these endogenous antioxidant pathways either catalytically dismute ROS or reduce ROS by NADPH-fed thiol-switch mechanisms. However, recent evidence suggests that these pathways are also involved in RSS metabolism. The following paragraphs briefly compare ROS (mainly H_2O_2) and RSS (mainly hydrogen polysulfide [H_2S_n]) metabolism by these systems. These points raise the question, to what extent are endogenous ''antioxidant'' pathways involved in RSS homeostasis?

Glutathione. GSH is typically found in millimolar concentrations in cells and serves as the first-line buffer for ROS. GSH readily reacts with H_2O_2 to form a GSH cysteine sulfenyl (GSOH) and/or oxidized glutathione dimer (GSSG). GSH also reacts with persulfide to form glutathione hydroper- or hydropolysulfides (GSS_nH, $n=1$–5) or diglutathione per- or polysulfides (GSS_nSG, $n=1$–5). Although GSH reacts with only one peroxide, it may react with multiple persulfides to form longer sulfur chains and these reactions are readily reversible (Fig. 2A).

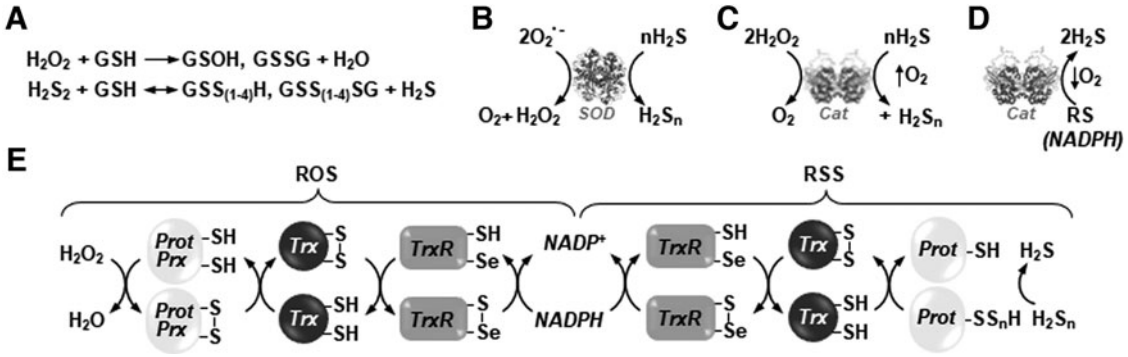

FIG. 2. Metabolism of ROS (H_2O_2) and RSS (H_2S_n) by endogenous antioxidants. (A) GSH is sulfenylated by H_2O_2 to form GSOH or GSSG. **(B)** SOD dismutes $O_2^{\bullet-}$ to H_2O_2 and O_2 whereas it oxidizes H_2S to polysulfides (H_2S_n; $n=2$–5). **(C)** Catalase dismutes H_2O_2 to H_2O and O_2; in the presence of O_2, it oxidizes H_2S to H_2S_n **(C)**, whereas in hypoxia **(D)** it uses NADPH to produce H_2S from select sulfur-containing substrates (RS). **(E)** Thiol switch pathways, such as the Trx/TrxR pathway, transfer electrons from NADPH to reduce H_2O_2 or sulfenylated proteins (Prot) or Prx or to produce H_2S from inorganic or organic per and polysulfides (H_2S_n, Prot-S_n). GSH, glutathione; GSSG, oxidized glutathione dimer; H_2O_2, hydrogen peroxide; H_2S_n, hydrogen polysulfide; $O_2^{\bullet-}$, superoxide; Prx, peroxiredoxin; ROS, reactive oxygen species; RSS, reactive sulfur species; TrxR, thioredoxin reductase.

Dismutation catalysts. Cytosolic and soluble (extracellular) copper-zinc superoxide dismutase (Cu-ZnSOD; SOD1 and SOD3, respectively) and mitochondrial manganese-SOD (MnSOD; SOD2) dismute superoxide to H_2O_2 and oxygen (Sheng et al, 2014). Both SOD1 and SOD2 also oxidize H_2S to persulfide (H_2S_2), which subsequently forms longer chain polysulfides (H_2S_{2-5}) (Olson et al, 2017a; Searcy, 1996; Searcy et al, 1995) (Fig. 2B). H_2S oxidation requires molecular oxygen but does not appear to utilize other possible electron donors such as nitrate, nitrite, sulfite, sulfate, thiosulfate, or metabisulfite, nor does it require superoxide or peroxide. High levels of H_2S (or possibly the persulfide product) also inhibit the reaction, probably through persulfidation of one of superoxide dismutase (SOD)'s three reactive cysteines, suggesting that H_2S oxidation may be subjected to negative feedback.

Catalase is the next antioxidant step dismuting peroxide to oxygen and water. Catalase is also a sulfide oxido:reductase (Olson et al, 2017b). In the presence of oxygen, catalase oxidizes H_2S to polysulfides (Fig. 2C), whereas in oxygen's absence it produces H_2S from sulfur-containing substances (Fig. 2D) including garlic oil, diallyltrisulfide (one of the active components of garlic), Trx, and sulfur dioxide, but not from sulfite, metabisulfite, COS, cysteine, cystine, glutathione, or oxidized glutathione, indicative of substrate specificity.

Interestingly, the oxygen tension at which catalase switches from a sulfur oxidase to a reductase tracks the same curve between 0 and 100 mmHg as the oxyhemoglobin saturation curve (Olson et al, 2017b), suggestive of a physiological function releasing vasodilating H_2S to the vasculature in hypoxic tissues.

Thiol switches. Although GSH is often perceived as the main first-line antioxidant, its main antioxidant function is more likely to serve as a buffer and to provide reducing equivalents for the antioxidant thiol-switch pathways (reviewed in: Lu and Holmgren, 2014; Ulrich and Jakob, 2019). These pathways deliver electrons from NADPH *via* redox-active vicinal cysteines or selenocysteines in Trx/thioredoxin reductase (TrxR) or glutaredoxin/glutaredoxin reductase (Grx/GrxR) to reduce sulfenylated protein cysteines, peroxide, or oxidized peroxiredoxins (Fig. 2E). These switches can also affect RSS metabolism by reducing both inorganic and organic per- and polysulfides (Doka et al, 2016; Ju et al, 2016; Wedmann et al, 2016) (Fig. 2E).

However, RSS metabolism by thiol-switch pathways is more versatile and extensive than ROS metabolism by these pathways. Excess H_2O_2 initially sufinylates proteins (ProtSO_2H) and then further oxidizes them to sulfonylated proteins (ProtSO_3H). Sulfinylated proteins are difficult to reduce back to native proteins, and sulfonylated proteins are destined for degradation (Lo Conte and Carroll, 2013). Per- or polysulfidation of proteins (ProtSS_nH) is believed to help protect proteins from excessive oxidative stress (Millikin et al, 2016; Nagahara et al, 2012; Ono et al, 2014).

Per- polysulfidated proteins can also be oxidized to the sulfenyl, sulfinyl, and sulfonyl forms (sulfinylated protein [ProtSSOH], ProtSSO_2H, and ProtSSO_3H, respectively); sulfenyl persulfidated proteins are readily identified in cells and are believed to contribute to intracellular signaling (Heppner et al, 2018). These can all be reduced back to the native persulfidated form by the Trx/TrxR and Grx/GrxR pathways (Doka et al, 2020).

A variety of inhibitors have been employed to block specific steps in these thiol-switch pathways with the general intent to increase cellular oxidant stress, generally H_2O_2 (de Souza et al, 2017; Glasauer and Chandel., 2014; Graczyk-Jarzynka et al, 2017; Hall et al, 2014; May et al, 2018; Reshetnikov et al, 2018; Rodman et al, 2016; Seefeldt et al, 2009; Zhao et al, 2009a; Zhao et al, 2009b). We observed that these same inhibitors also affected cellular RSS (Olson and Gao, 2019). However, they did not uniformly affect RSS: Some decreased H_2S, others increased it, and the change in H_2S did not consistently correlate with the change in polysulfides. Clearly, more work needs to be done to identify the downstream pathways affected by these RSS and to compare them with those putatively regulated by ROS.

It is recently becoming evident that certain cellular proteins also function as redox-based thiol switches that convert to reversible ATP-independent protein chaperones in response to H_2O_2 (Ulrich et al, 2021). To our knowledge, the effects of RSS on these switch mechanisms have not yet been examined.

Transcriptionally activated antioxidants, the Kelch like ECH associated protein 1-nuclear factor erythroid 2-related factor 2 pathway. The Nrf2 (Nuclear factor erythroid 2-related factor 2) pathway is the master regulator of antioxidant systems and is regulated at multiple levels through factors that affect transcription, post-transcription, and protein stability (Li et al, 2019). Regulation of protein stability through affecting its interaction with Keap1 (Kelch Like ECH associated Protein 1) is the most predominant. Keap1 serves as a linker protein between Cul3/Rbx1-based E3-ubiquitin ligase complex and Nrf2, which continuously targets the latter for ubiquitination.

Electrophilic stress or chemical inducers dissociate Keap1 from Nrf2 and allow Nrf2 to translocate from the cytosol to the nucleus where it binds to the antioxidant response elements (ARE), leading to the transcription of antioxidant genes. It is generally accepted that the most common factors causing Keap1 dissociation from Nrf2 are oxidation, especially sulfenylation, of cysteine residues Cys151, Cys273, and Cys288 in Keap1, or binding of p62 (sequestosome 1) to Keap1, which increases Keap1 degradation, thereby stabilizing Nrf2. Other factors, including protein kinase C (PKC), phosphorylate Nrf2, thereby dissociating it from Keap1, and $p21^{Cip/WAF1}$, DJ-1, PALB2 (partner and localizer of BRCA2), and tumor suppressor BRCA1 that also interrupt the Keap-Nrf2 interaction.

In addition, there are a number of Keap1 independent mechanisms. The phosphatidylinositol 3-kinase (PI3K)/Ak strain transforming (Akt) pathway activates Nrf2 by phosphorylating glycogen synthase kinase-3beta (GSK-3β), which, in turn, prevents GSK-3β from phosphorylating Nrf2 and marking it for ubiquitination. The Hrd1 (3-hydroxy-3-methylglutaryl reductase degradation 1) pathway is a negative regulator of Nrf2 by targeting it for ubiquitination.

At the level of transcription, Nrf2 is increased by the aryl hydrocarbon receptor (AhR), nuclear factor kappa-light-chain-enhancer of activated B cells (NfκB), and by Nrf2 itself, although Nrf2 also activates Keap1 transcription, which may, in turn, exert negative feedback. Both the tumor

suppressor p53 and retinoic acid receptor alpha indirectly suppress Nrf2-dependent transcription of antioxidant genes whereas p300/CBP histone acetyltransferases directly bind and acetylate Nrf2 in the nuclei, leading to enhanced promoter-specific DNA binding.

In the canonical ROS-activated pathway, cytoplasmic H_2O_2 sulfenylates Cys151 of Keap1, causing it to dissociate from Nrf2 and enabling the latter to translocate to the nucleus (Rachakonda et al, 2008). There it activates ARE in the nucleus that initiate the production of a variety of antioxidant proteins (Deshmukh et al, 2017; Motohashi and Yamamoto, 2004; Villavicencio Tejo and Quintanilla, 2021; Yamamoto et al, 2018). Understandably, the Keap1/Nrf2 pathway is often a therapeutic target (Alpha-Tocopherol and Beta Carotene Cancer Prevention Study Group, 1994; Cuadrado et al, 2019; Telkoparan-Akillilar et al, 2021).

Regulation of Nrf2 is also the focus of a wide variety of natural compounds (reviewed in Gugliandolo et al, 2020; Jayasuriya et al, 2021; Ooi et al, 2018). In all but a few instances (*e.g.*, sulforophane described below), the mechanism of action of the nutraceuticals is either unknown or attributed to ROS-type oxidants. However, Keap1 can also be persulfidated, thereby liberating Nrf2 and culminating in identical effector responses (Guo et al, 2014; Hourihan et al, 2013; Yang et al, 2013). In addition, RSS are implicated in persulfidating a variety of other molecules, including p66shc, p65, protein-tyrosine phosphatase 1B (PTP1B), mitogen-activated protein kinase/ERK (extracellular signal-regulated kinase) kinase 1 (MEk1), and phosphatase and tensin homolog (PTEN) (Meng et al, 2018), many of which may directly or indirectly affect Nrf2.

So, one must question how much of the Nrf2-Keap1 and related antioxidant mechanisms in cells are regulated by ROS and how much they are regulated by RSS? Or the alternative question is how much of the Keap1/Nrf2 pathway is involved in RSS homeostasis? This conundrum is further confounded by a number of observations described next that show that a variety of ''antioxidants'' effectively metabolize RSS.

Nutraceuticals and Related Compounds Are Inefficient Antioxidants

Nutraceuticals and related compounds are reported, often anecdotally, to have positive effects on virtually every organ system and exert protective effects or curative responses against a wide variety of diseases. Given such a broad interest in these compounds, it is not surprising that the global nutraceutical market was estimated at more than 417 billion U.S. dollars in 2020 and it is expected to grow at an annual compound growth rate of nearly 9% from 2020 to 2028 (www.grandviewresearch.com). Much of the academic and anecdotal interest in these compounds has focused on their purported antioxidant activity through their ability to scavenge ROS.

However, Forman and Zhang (2021) questioned the ability of these compounds to directly scavenge ROS or related radicals because these reaction rates are orders of magnitude slower than reactions that activate antioxidant defense mechanisms, especially the Nrf2/ARE axis. Although Gebicki and Nauser (2021) provide evidence that direct radical scavenging by polyphenols is kinetically feasible, the limited bioavailability of many of these compounds (discussed in section uptake and bioavailability) and rapid clearance from tissues that could precede any antioxidant effect supports the predominance of other, downstream effector antioxidant responses. The RSS metabolism by nutraceuticals, especially to produce hydropersulfides, appears to resolve these issues.

Antioxidant Attributes of Hydropersulfides

It is quite likely that much of the biological activity of RSS is due to hydropersulfides (RS_nH; $n>1$, R = H, Cys, GSH, proteins). These can be produced through a variety of pathways as described in the Importance of Sulfur Metabolism in Understanding Antioxidant Mechanisms section. In a seminal review, Fukuto and Hobbs (2021) examine the antioxidant properties of these hydropersulfides and compare them with other thiols and polysulfides and with the major intracellular antioxidants, GSH, ascorbate, and tocopherols. The following paragraphs briefly summarize these effects; the reader is referred to their review and references therein for further details.

H_2S is a relatively weak reductant, but when the sulfur is oxidized, ultimately to a hydropersulfide, it becomes a much stronger reductant. Paradoxically the hydropersulfide may also be an oxidant. The pKa's for hydropersulfides are typically in the range of intracellular pH, or lower, whereas those for GSH and Cys are around 8. Therefore, under physiological conditions hydropersulfides may exist as either RSS^- or RSSH. RSS^- are far better reductants than RS^-, and RSSH are better hydrogen donors than RSH.

Oxidation of RS^-/RSH to RSS^-/RSSH, which would be expected to increase under oxidative stress, will produce better intracellular reductants (RSS^-) to deal with the stress, and the electrophilic RSSH will oxidize Keap1 and activate Nrf2 (see Transcriptionally Activated Antioxidants, the Kelch like ECH Associated Protein 1-Nuclear Factor Erythroid 2-Related Factor 2 Pathway section). Further, protein hydropersulfides are also far more resistant to damage from peroxide than their thiol counterparts (see the Thiol Switches section).

Glutathione is viewed as one of the most important intracellular antioxidants, in part because it is present in millimolar concentrations and, in part, because it provides reducing equivalents to reductive reactions catalyzed by glutathione S-transferase (GST), glutathione peroxidase (Gpx), and Grx. However, as pointed out by Fukuto and Hobbs (2021), only 10% GSH is found as GS^-, that is, 100–200 μM if GSH is 1–2 mM, whereas essentially all glutathione hydropersulfide (>100 μM) exists as GSS^-. With the concentrations of GSS^- and GS^- being nearly equal, but with GSS^- being a far superior nucleophile, GSS^- would be expected to exert more direct antioxidant activity than GSH. Further, GSH does not react directly with oxidized protein sulfenyls, whereas GSS^- directly reduces them, thereby obviating the need for Grx-catalyzed reactions.

Ascorbate and tocopherols are one-electron reductants, as are RSSH/RSS^-, and can terminate oxidizing chain reactions. But RSS^- are also potent nucleophiles, which allows them to scavenge other oxidants (H_2O_2, ROOH, OHOOH, *etc.*) and reactive electrophiles, which ascorbate and tocopherols cannot, of if they do, it is a very slow reaction. In addition, in the presence of Fe or Cu, ascorbate will react with H_2O_2 to produce other potent oxidants.

RSS-Mediated Actions of Nutraceuticals

It is evident that RSS exert a variety of antioxidant functions in cells. Recent evidence, although limited to date, has also shown that many antioxidant nutraceuticals may affect RSS, either by increasing intracellular H_2S as a precursor to reactive per- and polysulfides, or by oxidizing endogenous H_2S to produce them. The following sections examine RSS metabolism by three types of nutraceuticals: sulfur-donating, sulfur containing catalysts and non-sulfur containing catalysts. Although there is extensive literature on the effects of nutraceuticals on ROS metabolism, our focus will be on their contributions to RSS metabolism.

Sulfur donating nutraceuticals

Allium and *Brassica*. *Allium* species include garlic, onions, leeks, shallots, scallions, chives, and ramp; *Brassica* species, the cruciferous vegetables, include bok choy, broccoli, Brussels sprouts, cabbage, canola oil, cauliflower, collard greens, kale, mustards, and turnips. Organosulfur plants have been consumed by humans for medicinal purposes for more than 6000 years (Majewski, 2014). Research in garlic (*Allium sativum*) and onions (*Allium cepa*) has grown exponentially since the early 1980s; the word ''garlic'' was mentioned in more than 491 articles and ''onion'' in 527 articles in 2020 alone (https://pubmed.ncbi.nlm.nih.gov).

Garlic is consumed fresh, powdered, cooked in a variety of ways, aged, after organic solvent extraction, or after prolonged fermenting at 60°C–90°C under 80%–90% humidity (80%–90%) for up to 90 days. The latter produces ''black garlic,'' which is known for beneficial modification of the nutrients and sensory attributes and improved bioactivity (Miraghajani et al, 2018). Onions are mostly eaten raw or cooked. Flowers, leaves, roots, seeds, and stalks of various *Brassica* may be eaten raw or cooked or extracted for oil.

Positive health benefits of these foods have been reported to occur in virtually all organ systems, both in experimental animals and in controlled studies and anecdotal reports in humans. Most of the benefits are attributed to their antioxidative, anti-inflammatory, immunomodulatory, and antiobesity actions and they are reported to have anti-cancer activities as well as cytoprotective properties. These nutraceuticals are the subject of more than 30 reviews annually (for recent reviews see: Abe et al, 2020; Ahmed and Wang, 2021; Bastaki et al, 2021; Beigoli et al, 2021; Borlinghaus et al, 2021; Cao et al, 2021; Farhat et al, 2021; Garcia-Ibanez et al, 2020; Guillamon et al, 2021; Kianian et al, 2021; Kimura et al, 2017a; Kurnia et al, 2021; Le et al, 2020; Luo et al, 2021; Nohara et al, 2021; Sun et al, 2021; Uuh-Narvaez and Segura-Campos, 2021).

Many of the health benefits of *Allium* and *Brassica* have been attributed to sulfur-rich compounds, of which dozens have been identified. Especially notable are the diallyl mono-, di-, and tri-sulfides (DAS, DADS, and DATS, respectively) and ajoene in *Allium* and isothiocyanates, for example, sulforophane in *Brassica* (Fig. 3). When garlic cells are damaged, the enzyme alliinase is released and it catalyzes the formation of allicin from the endogenous precursor alliin (*S*-allyl-L-cysteine sulfoxide). Allicin then rapidly decomposes into DAS, DADS, and DATS (Fig. 3A), with essentially all the biological activity being attributed to the latter.

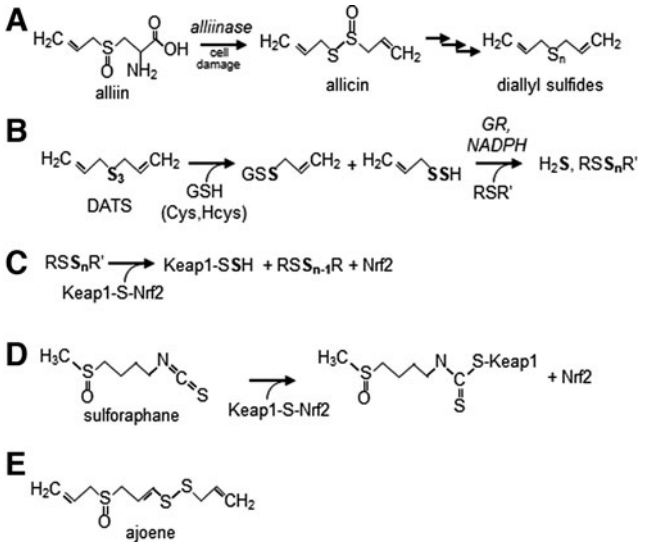

FIG. 3. Reactive sulfur and signaling by *Allium* and *Brassica* species. (A) Alliinase is released by damaged garlic cells and catalyzes the formation of allicin from alliin. Allicin then decomposes into mono-, di-, and tri-diallyl sulfides (DAS, DADS, and DATS, respectively). **(B)** DATS may react with low-molecular-weight thiols (GSH, Cys) to produce a variety of glutathione and cysteine allylsulfides and allylpersulfides, and these may then be reduced by glutathione reductase and NADPH to produce H_2S, or they may exchange the sulfane sulfur with other thiols (R and R′ signifying H, GSH or Cys) to produce a variety of polysulfides. **(C)** Persulfidation of Keap1 disassociates it from Nrf2, and the latter initiates the ARE. **(D)** Sulforaphane from *Brassica* also binds to Keap1 and liberates Nrf2. **(E)** Ajoene, another sulfur molecule found in *Allium*. ARE, antioxidant response elements; DADS, diallyl disulfide; DAS, diallyl sulfide; DATS, diallyl trisulfide; Keap1, Kelch like ECH associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2.

H_2S can be released from DATS in buffer by m*M* concentrations of GSH, Cys, homocysteine (Hcys) and in red blood cells, a reaction requiring glucose, which presumably provides NADPH for a glutathione reductase-catalyzed reaction (Fig. 3B) (Benavides et al, 2007). DATS has also been reported to release H_2S from myocardial cells (Predmore et al, 2012).

Polysulfides are also formed from DATS (DeLeon et al, 2016b), and this may account for much of the biological action of *Allium*-derived sulfur species as H_2S cannot directly persulfidate cysteine on regulatory proteins. This would better explain the ability of DATS to relax arteriolar smooth muscle by activating ATP-sensitive potassium (K_{ATP}) channels (Benavides et al, 2007). Polysulfides can also liberate Nrf2 from Keap1, as described earlier (see also Fig. 3C). A variety of garlic compounds, including DADS, DATS, S-allylmercaptocysteine, S-allyl-L-cysteine sulfoxide, S-1-propenylcysteine, and ajoene, also increase Nrf2 in a number of cell and animal models (Cho et al, 2019; Hassanein et al, 2021; Kay et al, 2010; Khalaf et al, 2022; Kim et al, 2014; Miltonprabu et al, 2017; Mo et al, 2020; Shan et al, 2016; Shi et al, 2015; Tsai et al, 2013; Tsuneyoshi et al, 2019; Uto-Kondo et al, 2018; Wang et al, 2021; Wang et al, 2020; Yang et al, 2020).

There is less known about the specific mechanism of Nrf2 activation, but the Cys moieties of Keap1 are a likely target. Using human gastric epithelial cell lines, Kim et al (2014) found that Cys288 on Keap1 was essential for DATS activation of Nrf2, whereas neither Cys151 nor Cys273 appeared to be involved. Further, they observed that there was an increase in mass of the peptide fragment containing Cys288 that was consistent with mono-allyl mono-sulfide binding to Keap1. However, this is somewhat in contrast to the observations of Hu et al (2011), who showed that sulforaphane reacted with four of the Keap1 Cys and covalently bound to the Keap1 Cys151 freeing it from Nrf2. Nevertheless, these studies point to the importance of the sulfur in these nutraceuticals whose actions are independent of ROS.

Allium and *Brassica* also are rich in polyphenols, in addition to sulfur compounds (Ahmed et al, 2021; Cao et al, 2021; Kurnia et al, 2021). Some vegetables, especially broccoli, are also rich in lipoic acid (LA) (Theodosis-Nobelos et al, 2021). The effects of these compounds on sulfur metabolism will be considered in their respective sections later.

Sulfur containing catalytic nutraceuticals

Similar to the sulfur-donating nutraceuticals in *Allium* and *Brassica*, interest in the health benefits of the sulfur-cycling LA has grown exponentially since the mid-1980s with 378 articles in 2020 alone and 30–50 reviews yearly since 2013 (Pubmed.gov). LA, termed the ''universal antioxidant'' (Kagan et al, 1992), is endogenously synthesized and employed as a cofactor in a variety of mitochondrial metabolic activities (Solmonson and DeBerardinis, 2018). As endogenous synthesis does not substantially contribute to circulating levels of LA, most purported health benefits are derived from LA supplements (Theodosis-Nobelos et al, 2021).

The LA supplements are widely used, at times with equivocal results, to treat a variety of conditions, including cancer (Attia et al, 2020; Dorsam and Fahrer, 2016; Farhat and Lincet, 2020), cardiovascular and renal diseases (Jalilpiran et al, 2021; Skibska and Goraca, 2015; Zhang and McCullough, 2016), diabetes and metabolic syndrome (Akbari et al, 2018; Jeffrey et al, 2021; Mahmoudi-Nezhad et al, 2021; Pashaj et al, 2015), inflammation (Moura et al, 2015; Zygmunt et al, 2013), a variety of neurological diseases (Holmquist et al, 2007; Kaur et al, 2021; Molz et al, 2017; Toth et al, 2021; Waslo et al, 2019), and other situations associated with excessive oxidant production (Ambrosi et al, 2018; Sheikholeslami et al, 2021; Solmonson and DeBerardinis, 2018). In general, animal and *in vitro* studies are more convincing, but controlled, clinical studies on the benefits to humans are gaining more support.

LA appears to be relatively non-toxic; it is soluble in lipids and somewhat soluble in water. This allows relatively high doses to be administered for extended periods, and up to 1200–2400 mg/day have been used in clinical trials (Loy et al, 2018; Theodosis-Nobelos et al, 2021; Yadav et al, 2010), although prooxidant and excess metal chelation (especially selenium) has been reported (Theodosis-Nobelos et al, 2021). A pair of vicinal sulfur atoms form an intramolecular disulfide bridge in LA that is readily reduced by cellular reductants, especially Trx/TrxR, which consumes NADPH and forms DHLA, the predominant form in cells (Arner et al, 1996).

Although LA/DHLA can act as either a pro- or an antioxidant in cells (Moini et al, 2002), with a redox potential of –0.32 V, the latter function is generally considered to be predominant. The antioxidant functions of LA/DHLA have been long been attributed to scavenging free radicals and chelating divalent transition metals, acting as an SOD mimetic, recycling oxidized vitamin E and as a redox regulator of proteins such as myoglobin, prolactin, Trx, and NF-KB transcription factor (Packer et al, 1995). However, it has been pointed out that LA/DHLA does not accumulate *in vivo* and is rapidly catabolized (Theodosis-Nobelos et al, 2021).

This essentially reinforces the hypothesis that the effects of LA/DHLA are more likely due to the initiation of downstream effectors, for example, Cu^{+2} and Fe^{+3} chelation to reduce free radical production (Theodosis-Nobelos et al, 2021) and, probably more importantly, Nrf2 production rather than any direct radical or ROS scavenging ability (Forman and Zhang, 2021).

Although there are a few reports that LA/DHLA may decrease Nrf2 (Yue et al, 2021; Zhang et al, 2021b) or have no effect (Taniai et al, 2014; Wu et al, 2021), the vast majority of studies show that LA/DHLA increases Nrf2 expression, decreases protein turnover, and promotes translocation into the nucleus (cf. Bian et al, 2020; Fayez et al, 2018; Fratantonio et al, 2018; Hossain et al, 2021; Kyung et al, 2019; Lee et al, 2019; Liu et al, 2021; Mohammed et al, 2021; Shay et al, 2012; Wang et al, 2016).

Most of these studies implicate the dissociation of Keap1 from Nrf2, but there is scant evidence on how this achieved. Fratantonio et al (2018) exposed human umbilical vein endothelial cells (HUVECs) to either LA or DHLA and observed that only the former increased nuclear accumulation of Nrf2 and free Keap1 in the cytosol. They proposed that LA acted as an oxidant by alkylating Cys on Keap1. However, Fratantonio et al (2018) only exposed HUVECs to LA/DHLA for 2 h and it is unclear whether other factors might contribute to this response over longer periods.

Polysulfide production catalyzed by LA/DHLA may be a likely candidate. H_2S cannot be directly released from LA except by exposure to light (Bilska-Wilkosz et al, 2017), whereas DHLA can contribute to H_2S and polysufide production by a number of mechanisms. In one mechanism, CAT transfers the amine group from a cysteine molecule to α-ketoglutarate, which forms 3-mercaptopyruvate (3-MP**S**). The sulfur in 3-MP**S** is then transferred to the enzyme 3-mercaptopyruvate sulfur transferase (3-MST**S**), forming a persulfide on the enzyme (Nagahara et al, 2018; Olson, 2018). H_2S can then be released from 3-MST**S** persulfide by DHLA (Mikami et al, 2011) or the sulfur transferred to small thiols to form persulfides (Kimura et al, 2017b; Nagahara et al, 2018). We (Olson et al, 2020b) have shown that H_2S is produced in HEK293 cells treated with LA and that this appears to require intracellular conversion of LA to DHLA, as the effect becomes progressively more pronounced over 24 h.

H_2S production is augmented in these experiments by thiosulfate, and as DHLA, but not LA, directly produces H_2S from thiosulfate in buffer (Olson et al, 2013); this suggests that DHLA is required for H_2S production in cells as well. Subsequent oxidation of H_2S to polysulfides could then augment Keap-1 dissociation from Nrf2 and prolong the antioxidant response. The possible mechanisms for LA/DHLA antioxidant activity are shown in Figure 4.

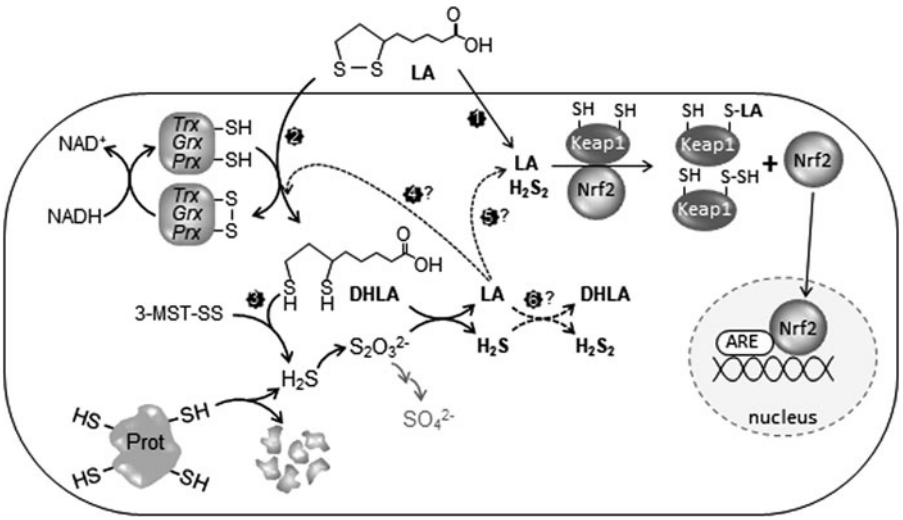

FIG. 4. Possible mechanisms of antioxidant activity by LA and DHLA. (1) LA taken up by cells (on *right*) can oxidize cysteine on Keap1, thereby liberating Nrf2 and allowing it to activate ARE in the cell nucleus. (2) LA taken up by cells can be reduced by Trx, Grx, and Prx to DHLA. DHLA can release H_2S from thiosulfate ($S_2O_3^{2-}$) produced during the course of protein (Prot) catabolism and cysteine degradation to sulfate (SO_4^{2-}). The H_2S can then be oxidized to persulfide (H_2S_2), which will oxidize Keap1 cysteine and liberate NrF2. (3) DHLA can also liberate H_2S from 3-MST-**SS**. Other possible, but yet to be identified mechanisms include intracellular recycling of LA to DHLA (4), or oxidation of Keap1 (5), or oxidation of H_2S to persulfide (H_2S_2) (6), which will also liberate Nrf2 from Keap1. 3-MST-**SS**, 3-mercaptopyruvate sulfur transferase persulfide; Grx, glutaredoxin; H_2S_2, hydrogen persulfide; LA, lipoic acid.

Non-sulfur containing catalytic nutraceuticals

Non-sulfur containing nutraceuticals comprise the broadest category of natural compounds that can be ingested to potentially affect cellular sulfur metabolism. Interest in phytochemicals began in earnest in the late 1990s and has grown exponentially with 1273 publications citing ''phytochemicals'' in 2021 and ''polyphenols,'' the largest group of phytochemicals cited 995 times and featured in nearly 200 review titles (PubMed.gov), although Zhang et al (2021a) have identified the topic ''polyphenol'' in nearly 7500 articles in the web of science in 2019.

Polyphenolic nutraceuticals have been reported to exert positive benefits in essentially all organ systems. Of late, there has been considerable interest in polyphenols and enteric microbiota (Diotallevi et al, 2020; Man et al, 2020; Piwowarski et al, 2021; Rodriguez-Daza et al, 2021), but assorted reviews are also available on polyphenols and cancer (Al-Harbi et al, 2021; Benvenuto et al, 2020; Hazafa et al, 2020), cardiovascular and renal diseases (Bao and Peng, 2016; Ditano-Vazquez et al, 2019; Godos et al, 2019; Marunaka et al, 2017; Marx et al, 2017; Poti et al, 2019), diabetes and metabolic syndrome (Boccellino and D'Angelo, 2020; Cheng et al, 2020; Chiva-Blanch and Badimon, 2017; Den Hartogh and Tsiani, 2019; Diotallevi et al, 2020), neurological diseases (Ammar et al, 2020), inflammation (Medina-Remon et al, 2017), and other systems (Bowtell and Kelly, 2019; Chisari et al, 2019; Chodari et al, 2021; Torre, 2017). The present discussion is limited to those compounds that have been shown to metabolize sulfur in a way that suggests a possible contribution to their antioxidant activities.

More than 8000 phenolic nutrients have been identified (Tsao, 2010). There are a number of different methods of classification of nutraceutical polyphenols, source of origin, biological function, and chemical structure; the latter is used in this discussion. Tsao (2010) identified 4 broad categories: flavonoids (of which there are 4000), polyphenolic amides, phenolic acids, and other non-flavonoid polyphenols. Each category has multiple subgroups, and many of these can be further divided.

Sulfur metabolism by polyphenols and related nutraceuticals. Flavonoids consist of anthocyanins, flavan-3-ols, flavones, flavanones, and flavonols. They have two phenolic rings (A and B) connected by ring C, and most have the B ring attached to the C2 position of ring C (Fig. 5A). A detailed compilation of foods rich in flavonoids can be found in the USDA Database for the Flavonoid Content of Selected Foods, Release 3.3, 2018, https://www.ars.usda.gov/ARSUserFiles/80400535/Data/Flav/Flav3.3.pdf

Anthocyanidins and the glycolysated anthocyanins are responsible for the red, purple, and blue colors in fruits and vegetables and in some *Allium* and *Brassica* (Khoo et al, 2017). Cyanidin is one common example (Fig. 5B). Over-the-counter extracts of blueberries, bilberries, cranberries, as well as pure cyanidin oxidize H_2S to polysulfides and thiosulfate in buffer (Olson et al, 2021a). This process requires O_2 and appears to involve redox cycling of the polyphenol in which the polyphenol is autoxidized by O_2 to a semiquinone radical, which then oxidizes H_2S to a thiyl radical and two thiyl radicals will combine to produce the persulfide, H_2S_2.

When added to HEK293 cells, these extracts and cyanidin also decrease H_2S and increase polysulfide, suggesting that their effects are the same in cells as they are in buffer. The flavonol, quercetin (Fig. 5C), found in numerous fruits, spices, seeds, and vegetables as well as chocolate, and the non-flavonoid polyphenol stilbenoid, resveratrol (Fig. 5D), most

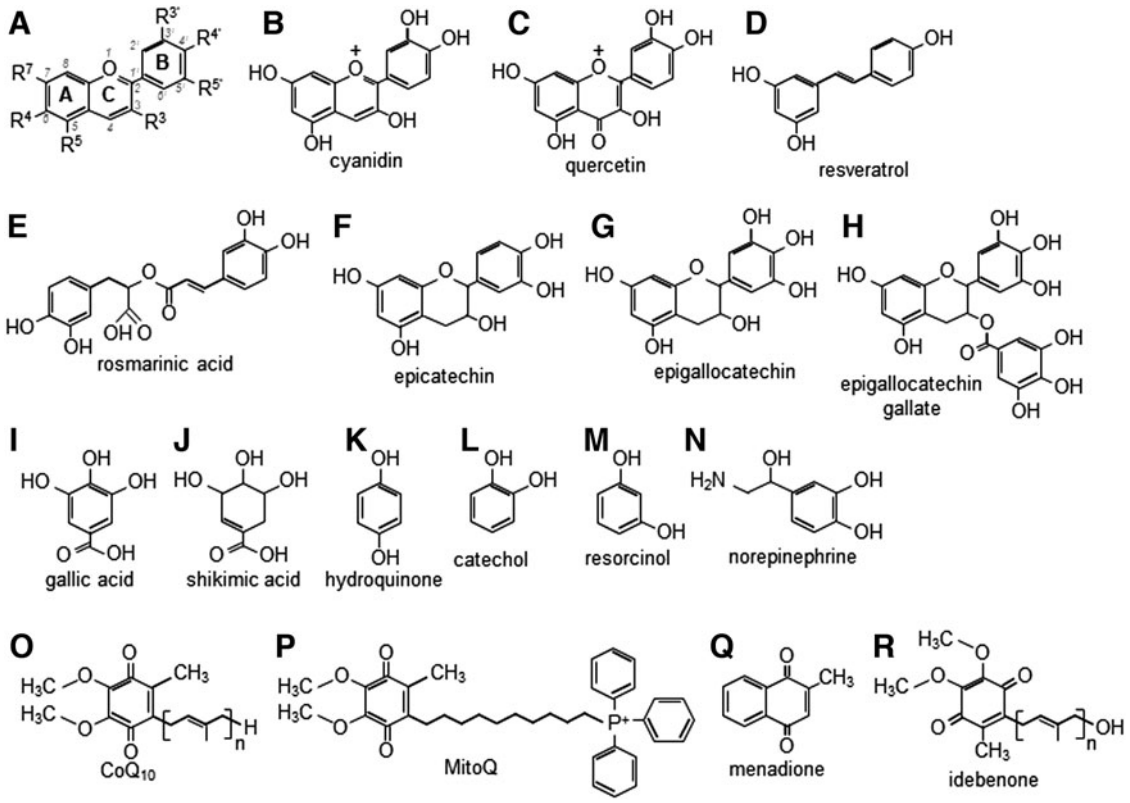

FIG. 5. (A–R) Nutraceutical polyphenols and quinones described in this review. Panel **A** shows the basic structure of the flavonoid and the three rings, A, B and C; R indicates substitution sites for H, OH, or OCH_3.

often associated with grapes and red wine, also oxidize H_2S to polysulfides in buffer and decrease cellular H_2S and increase polysulfides (Olson et al, 2021a).

Catechins, (flavan-3-ols), are especially notable for their presence in tea, although they are found in a wide variety of other foods, especially fruits, wine, and cocoa. Catechins are different from most flavonoids in that in the C ring there is no double bond between C2 and C3, and no C4 carbonyl (Fig. 5E). After water, tea is the second most consumed beverage (Yang et al, 2009) and its origins date back nearly 5000 years ago to the Tang Dynasty in China (Lu, 1995). In the sixth century AD., it was brought to Japan by Buddhist monks; matcha green tea is extensively used in the Japanese tea ceremony.

We (Olson et al, 2020a) observed that matcha and other green teas, Sencha, Gyokuro, and Hung Chan, all containing catechins but prepared slightly differently, effectively oxidized H_2S to polysulfides in buffer. Addition of these teas to H_2S produced a rapid decrease in H_2S and an increase in polysulfides, especially H_2S_2 followed by lesser amounts of H_2S_3 and H_4S_5. There was also a transient increase in sulfite and a steady, prolonged increase in thiosulfate. Surprisingly, there was also some H_2S in these freshly brewed teas.

We also examined the effects of three catechins, epicatechin (EC) (Fig. 5E), epigallocatechin (EGC) (Fig. 5F), and epigallocatechin gallate (EGCG) (Fig. 5G), on H_2S metabolism and all oxidized it to H_2S_{2-4} with EGC showing somewhat greater potency. These reactions were dependent on O_2, and they consumed O_2 as well. EC, EGC, and EGCG decreased H_2S in HEK293 cells and increased polysulfides, consistent with their effects in buffer.

Phenolic acids are non-flavonoids, mainly as benzoic and cinnamic acids. They are found in grain, seeds, and tea mainly in bound forms that are liberated by enzymes or alkaline hydrolysis (Tsao, 2010). Gallic acid (Fig. 5I), a trihydroxybenzoic acid, readily oxidizes H_2S to polysulfides in buffer and in HEK293 cells (Olson et al, 2021b). Shikimic acid (Fig. 5J) is a cyclohexene, but not a quinone, that is otherwise identical to gallic acid. Shikimic acid does not oxidize H_2S (Olson et al, 2021b). This illustrates the importance of the benzene moiety in sulfur metabolism, and it suggests that quinones are key catalysts in sulfur metabolism.

Sulfur metabolism by quinones. Much of the chemical and biological activity of polyphenols appears to be associated with the B ring. The presence of two or more hydroxyl groups makes polyphenols electron rich and imparts much of the antioxidant function that increases as the number of hydroxyl groups increases (Akagawa et al, 2003; Lambert and Elias, 2010; Xing et al, 2019; Yang et al, 2009). This suggests that H_2S can be oxidized by quinones and, indeed, this is the case. The ability of various quinones to oxidize H_2S to polysulfides and thiosulfate in buffer and in HEK293 cells depends on the position of the OH groups; 1,4 dihydroxybenzene (hydroquinone) (Fig. 5K) is more efficacious than 1,2 dihydroxybenzene (catechol) (Fig. 5L), whereas 1,3-dihydroxybenzene (resorcinol) (Fig. 5M) is ineffective, and the 1,2,3 trihydroxybenzene, pyrogallol also effectively oxidizes H_2S (Olson et al, 2021a). All these reactions required O_2.

However, we also observed that both epinephrine and norepinephrine (Fig. 5N) oxidized H_2S, unlike either dopamine

or tyrosine, the mono-hydroxy precursor of biogenic amines. This shows that the ability of quinones to oxidize H_2S can be further affected by specific modification of the side chains, suggesting that the actual ability of quinones to oxidize H_2S needs to be confirmed case by case.

The efficacy of 1,4 quinones points to a potential role for ubiquinone in sulfur metabolism. Ubiquinone (Coenzyme Q10) (Fig. 5O) is found in all eukaryote cells and is best known for its role in the mitochondrial electron transport chain (ETC), where it conducts electrons from complex I and II to complex III (Wang and Hekimi et al, 2016). CoQ_{10} is also present in many other cell membranes; it is especially plentiful in Golgi membranes where it is believed to function as an antioxidant (Mugoni et al, 2013). CoQ_{10} also suppresses ferroptosis in plasma membranes. Here, oxidized CoQ_{10} is reduced by electrons from NADH, in a reaction catalyzed by ferroptosis suppressor protein 1 (FSP1), and the reduced CoQ_{10} acts as a lipophilic radical-trapping antioxidant to prevent the propagation of lipid peroxides (Bersuker et al, 2019; Doll et al, 2019).

CoQ_{10} is one of the most widely used supplements and in clinical trials has shown some efficacy in treating statin associated muscle symptoms, congestive heart failure, and other diseases associated with oxidative stress (Gutierrez-Mariscal et al, 2020; Raizner, 2019). Like many nutraceuticals, research interest in CoQ_{10} as a supplement began in the 1980s and has increased exponentially since then with more than 900 articles on ''CoQ_{10}'' and nearly 100 articles on ''CoQ_{10} supplements'' in 2020 (Pubmed.gov).

We (Olson et al, 2022) recently observed that CoQ_{10}, and its more water-soluble analogs CoQ_1 and CoQ_0, readily oxidize H_2S to polysulfides, namely H_2S_2 and thiosulfate in buffer and in both HEK293 and HT29 cells they decrease cellular H_2S, which suggests that polysulfides and thiosulfate are produced from endogenous sulfide. Consistent with reactions between H_2S and polyphenols and other quinones, H_2S oxidation by CoQ compounds requires and consumes O_2.

A number of related quinones have demonstrated a similar ability to oxidize H_2S to polysulfides in buffer and in cells. These include MitoQ (CoQ_{10} linked to triphenylphosphonium) to increase mitochondrial (Fig. 5P) uptake and enhance antioxidant activity (Smith and Murphy, 2010), menadione (Vitamin K_3) (Fig. 5Q), a fat-soluble vitamin precursor similar to CoQ_{10} but lacking the 2,3 methoxy groups, and idebenone (Fig. 5R), a more water-soluble analog of CoQ_{10} with ten methylene molecules and a terminal hydroxyl replacing the isoprenyl groups of CoQ_{10} (Gueven et al, 2021).

Numerous studies have demonstrated antioxidant activities of MitoQ (cf. Escribano-Lopez et al, 2019; Hamed et al, 2021; Ning et al, 2021; Pak et al, 2018). A mitochondrial localization of MitoQ would also position it to metabolize H_2S. Conversely, menadione is better known as an oxidant that at low levels mediates oxidant signaling and initiates Nrf2-type antioxidant responses, whereas at higher levels menadione triggers oxidative distress (Loor et al, 2010). Menadione activation of the antioxidant responses would be consistent with polysulfide's actions on Keap1, although this has not been examined.

Idebenone was long thought to be a direct antioxidant that scavenged ROS, but this has recently been questioned and it is more likely to also activate antioxidant defenses, especially Nrf2 (Gueven et al, 2021). Interestingly, idebenone is considerably more efficacious in hypoxic cells and tissues (Gueven et al, 2021). It is now fairly well established that hypoxia also increases intracellular H_2S (Olson, 2021) and this could increase polysulfide production by providing more substrate for idebenone.

The actual therapeutic benefits of CoQ_{10} and related quinones, as they pertain to sulfur metabolism and signaling, are yet to be elucidated. They may augment H_2S catabolism, produce signaling persulfides or persulfides that act as radical scavengers and/or they may help ''store'' H_2S as thiosulfate. These compounds may also function as ''alternative oxidases'' by oxidizing H_2S without feeding electrons into the ETC. Collectively, these studies suggest that CoQ_{10} and related supplements may provide therapeutic options to affect cellular H_2S. A more pressing issue is how polyphenols and quinones oxidize H_2S.

Although there is much that needs to be resolved, the propensity of quinones to engage in redox-cycling reactions suggests a common mechanism for H^2S oxidation by polyphenols, phenolic acids and quinones. Single-electron oxidation-reduction reactions between a quinol, semiquinone, and quinone provide one possibility (Fig. 6A). Many simple as well as complex polyphenolic quinones are readily autoxidized (Abrash et al, 1989; Eyer, 1991; Kalyanaraman et al, 1984; Kobayashi et al, 2004; Misra and Fridovich, 1972; Mochizuki et al, 2002; Polewski, 2000; Prysyazhna et al, 2019; Roginsky and Alegria, 2005; Song et al, 2008; Stegmann et al, 1981; Szewczuk et al, 2005).

One possible reaction would be the autoxidation of the quinol to a semiquinone, which would then oxidize H_2S to a thiyl radical and reduce the semiquinone back to the quinol. Alternatively, the semiquinone may undergo a second autoxidation and this could oxidize another H_2S to the thiyl radical. It is also possible that a quinone undergoes a two-electron oxidation of H_2S to produce elemental sulfur, although this has not been demonstrated. Single-electron autoxidation of a quinol will also produce superoxide, which could potentially oxidize H_2S (Wedmann et al, 2014).

However, a role for superoxide unlikely because it has been shown that removing superoxide with SOD promotes autoxidation, which is otherwise kinetically unfavorable (Song et al, 2008), and we have observed similar results with a variety of polyphenols and quinones (Olson et al, 2021a; Olson et al, 2021b; Olson et al, 2020a).

Conversely, Abiko et al (2019) have shown that oxidized CoQ_{10}, menadione, and other quinone-related electron acceptors do not react with H_2S, but will accept an electron from at least two hydropersulfides, H_2S_2 and H_2S_4, thereby producing persulfide and semiquinone radicals (Fig. 6B). These results contrast with our observations described earlier and point to the need for additional studies in this area.

It is also known that a number of quinones/hydroquinones comproportionate in buffers under physiological conditions (Fig. 6C) and that the resultant semiquinones are relatively stable (Alegria et al, 1996; Roginsky et al, 1999). This affords another mechanism for RSS metabolism. Some of the possible products of quinone-mediated H_2S oxidation are shown in Figure 6D.

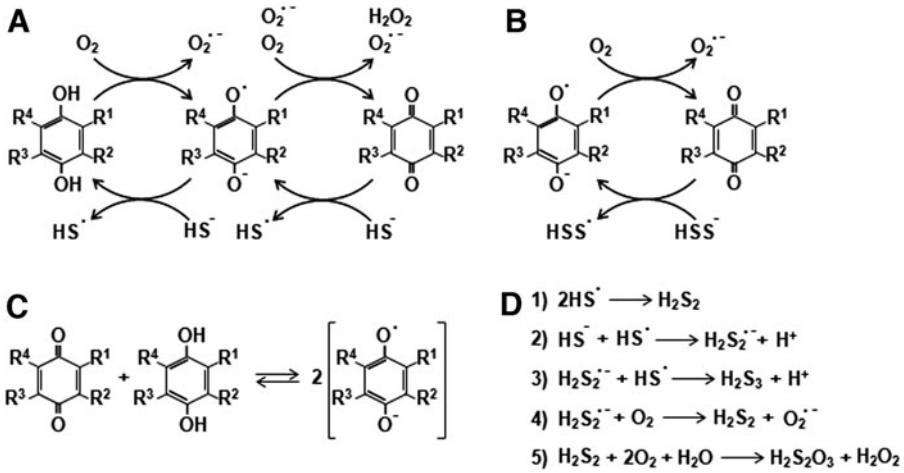

FIG. 6. Suggested mechanisms for H_2S oxidation by polyphenols and quinones and formation of various polysulfides and thiosulfate from thiyl radicals and superoxide. (A) A quinol is autoxidized to a semiquinone, which then oxidizes H_2S to a thiyl radical, reducing the semiquinone back to the quinol. The semiquinone may also undergo a second autoxidation to the quinone, and this could oxidize another H_2S. It is also possible that the quinone undergoes a two-electron oxidation of H_2S to produce elemental sulfur. Single-electron autoxidation of the quinol and semiquinone will also produce superoxide. **(B)** A quinone is reduced by a hydropersulfide-forming persulfide and semiquinone radicals, and the semiquinone is reoxidized by oxygen-producing superoxide. **(C)** Two semiquinones can be formed by comproportionation of a quinone and hydroquinone in buffer under physiological conditions. **(D)** A few of the possible reactions catalyzed by quinones. Two thiyl radicals can combine to form persulfide (1); a thiyl radical can combine with a hydrosulfide anion to produce a persulfide radical (2), which can then combine with another thiyl radical to produce a 3-sulfur polysulfide (3). The persulfide radical can also react with oxygen to produce persulfide and superoxide (4) or persulfide can react with oxygen to produce thiosulfate and water (5).

Issues of Bioavailability and Uptake

Polyphenol nutraceuticals are not ideally suited as drugs because they are often poorly absorbed, and when taken up, they are highly susceptible to the protective schemes posed by the digestive tract and liver (Scalbert et al, 2002). The structural features that make polyphenols potentially beneficial antioxidants are also exploited by the liver and gastrointestinal tract through Phase I and Phase II metabolism to either decrease uptake or expedite clearance from the body (Deng et al, 2006; Liu and Hu, 2007; van Duynhoven et al, 2011). Each phase has a specific set of reactions to achieve these goals.

Phase I

In Phase I, a nutraceutical can be oxidized, reduced, or hydrolyzed. The most common modifications of polyphenols tend to be oxidation or hydroxylation, and these are generally limited to resveratrol (Fig. 5D) and rosmarinic acid (Fig. 5E), the most hydrophobic of the compounds discussed here (Kim et al, 2019). Because polyphenols are highly reduced and hydrophilic (Yang and Pan, 2012), further reduction is not likely to occur nor is hydroxylation, and the only compounds discussed herein that are susceptible to hydrolysis are rosmarinic acid (Fig. 5E) and EGCG (Fig. 5H) at their ester moiety.

Oxidation of polyphenols is, in part, facilitated by the cytochrome P450 monooxygenase system. Most active in the liver, the cytochrome P450 enzymes attach oxygen groups (oxidation or hydroxylation) to xenobiotics to prepare them for Phase II modification and excretion (Phang-Lyn and Llerena, 2022). As a specific example of this reaction, resveratrol is hydroxylated in the liver through oxidation by CYP1A2, a CYP450 isozyme that oxidizes polyaromatic hydrocarbons and unsaturated fatty acids. CYP1A2 hydroxylates the 3-position of the phenol ring to form piceatannol, a 1,2-hydroquinone with antioxidant properties (Fig. 7A) (Bolton and Dunlap, 2017; Piotrowska et al, 2012).

Hydroxylation can also be catalyzed by tyrosinase and peroxidase as part of Phase I metabolism. EC (Fig. 5F) is a substrate for hepatic microsomal tyrosinase and peroxidase. Tyrosinase can convert EC to EGC (Fig. 5G), and the combination of both enzymes leads to the EC quinone (Moridani et al, 2001) that later undergoes the Phase II transformation glutathionylation. Finally, hydrolysis of EGCG produces two more hydrophilic compounds than EGCG itself: gallate and EGC. Monoamine oxidases are not involved in the metabolism of these polyphenols except for norepinephrine (Fig. 5N) because no amine groups are present. Likewise, neither peptidases nor amidases participate.

Phase II

The nutraceuticals described in this review contain phenols or alkyl alcohols that are susceptible to Phase II conjugations by methylation, glucuronidation, and sulfation (Fig. 7). The same rules apply for the more prototypical hydroquinones: hydroquinone, catechol, and resorcinol (Fig. 5K–M). The specific sites that are conjugated vary by enzyme and by species. This may affect their clearance, prevent redox cycling, or both.

Methylation by methyltransferases such as catechol-O-methyltransferase (COMT) converts hydroxyls into ethers. COMT in the liver, the kidneys, and the intestines methylates

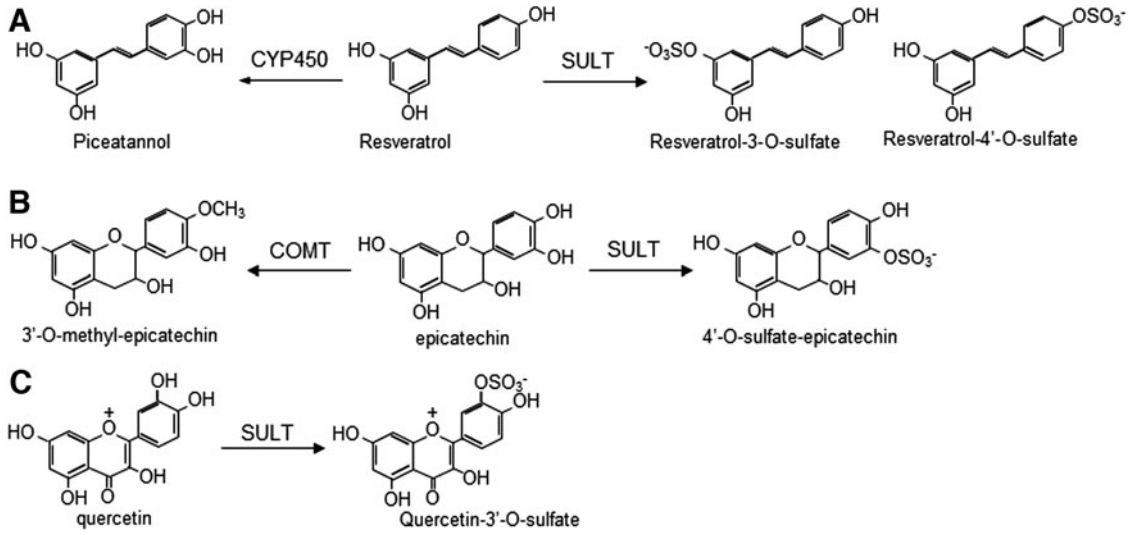

FIG. 7. Phase I and II transformations of resveratrol, epicatechin ,and quercetin. (A) In Phase I biotransformation, resveratrol can be hydroxylated at the 3′ position by CYP450 to form the hydroquinone piceatannol or in a Phase II biotransformation it may be sulfated by SULT to 3- and 4′-sulfated isomers. **(B)** Epicatechin undergoes Phase II transformations of both methylation by COMT and sulfation by SULT on the B-ring. **(C)** In Phase II biotransformation, quercetin can be sulfated by SULT on the 3′ position of the B-ring. COMT, catechol-O-methyltransferase; SULT, sulfate transferase.

catechols to produce catechol ethers (Ma et al, 2014). Not all phenolic groups on polyphenols are methylated by COMT. For instance, in humans, the gall(-ol,-ate) groups on EGC (n′) and EGCG (n″) are partially methylated in the 3′, 3″, 4′, and 4″ positions, whereas the EC B ring is fully methylated by COMT. In rats, the hydroxyl on position 7 is methylated but not in humans (Fig. 7).

Rosmarinic acid but not resveratrol is susceptible to methylation by COMT (Springer and Moco, 2019). Methylation of catechol and gallyl groups prevents their oxidation to semiquinones and quinones (Sang et al, 2011), but it also nearly eliminates the direct antioxidant capacity, though indirect effects still exist (Deng et al, 2006). In this set of compounds, the 1,2- and 1,4-hydroquinones have an open carbon in the beta position to the nearest carbonyl. When oxidized to a quinone, these compounds become Michael Acceptors with an electrophilic carbon in the beta position from the nearest carbonyl.

Nucleophiles such as amines or thiols can attack the beta carbon to produce a more water-soluble, or inert product. However, quinones can redox cycle and in the process reduce oxygen to superoxide, which can lead to a variety of adverse effects. A key example of this biotransformation is quercetin, which can function as a 1-electron donor to produce a quercetin ortho-quinone product with pro-oxidant properties (Colunga Biancatelli et al, 2020).

Glucuronidation increases the molecular weight of the substrate molecule by covalently binding a hexose moiety that is rich in hydrogen bond donating capacity. Hepatocytes import compounds from the hepatic portal vein and glucuronidate them for export into the bile duct. Glucuronidation enhances the solubility of the compound and limits its ability to reenter circulation *via* the intestines. Compounds that undergo Phase I biotransformations in the liver can also become glucuronidated in the kidneys for renal excretion.

Multiple isoforms of UDP-glucuronosyltransferases (UGT) in the liver glucuronidate phenol-like compounds at specific sites. An example compound is EGCG, which can undergo ester hydrolysis, glucuronidation, and methylation as Phase I and Phase II modifications (Fig. 8). Glucuronidation occurs at different sites in different species; in humans, catechins are modified at the hydroxyl groups on the 3′ and 3″, and 4″ carbons (Lu et al, 2003), whereas in rats, the 7 position is also glucuronidated (or methylated) because of differences in isozyme expression (Lu et al, 2003).

Sulfation appends a sulfite to a hydroxyl group in a reaction catalyzed by sulfate transferase 1 (SULT1). This applies a negative charge to the molecule, which decreases its lipophilicity, making it less likely to be taken up by cells and more readily excreted by the kidneys. Several of the polyphenols in this review are susceptible to sulfation, including quercetin (3′-OH), resveratrol (4′-OH), and EC (4′-OH), for example (Fig. 7). Notably, the conjugation sites for each modification overlap and it is possible to produce a blend of metabolites.

Uptake and bioavailability

The uptake of polyphenols is highly variable, but the bioavailability is generally poor compared with other compounds such as vitamin C with an oral bioavailability of 30% (Yung et al, 1982) and vitamin E, 10%–30% (Reboul, 2017). Polyphenolic bioavailability is often below 10%–15% (Bertelli et al, 2021), that is, anthocyanidins (1%–2%) (Tena et al, 2020), quercetin (<1%) (Li et al, 2016), resveratrol (<1%), and flavan-3-ols (2%–15% range) (Jaramillo Flores, 2019; Tenore et al, 2015). The depot of unavailable polyphenol varies as do their metabolic steps. The reasons for this low bioavailability are important and solving them may spur the development of new polyphenol-like drugs that specifically metabolize RSS and offer novel therapies.

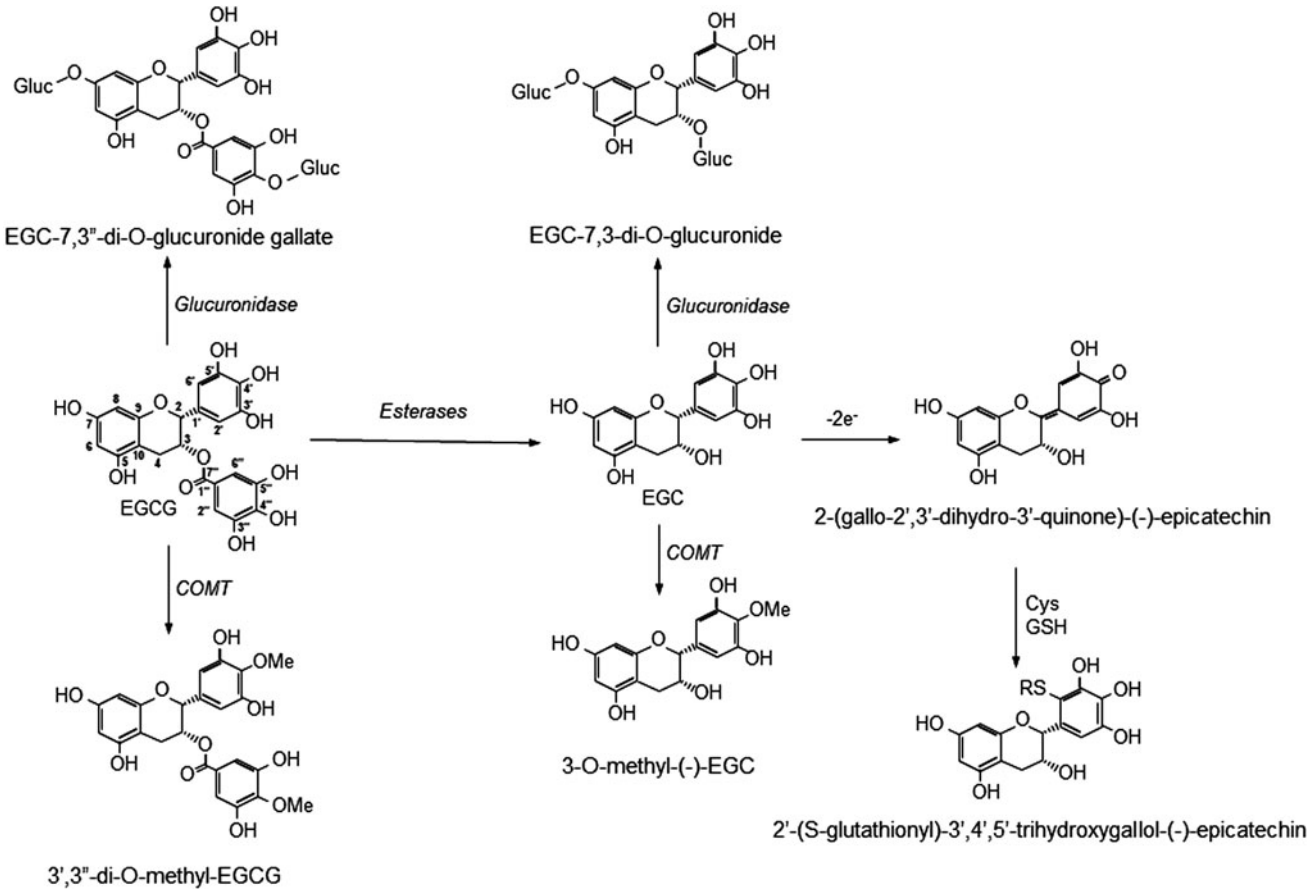

FIG. 8. EGCG is susceptible to a wide variety of Phase I and II biotransformations. The gallate ester is cleaved by esterases to form EGC. Both EGCG and EGC can be glucuronidated or methylated. EGC is also susceptible to oxidation, which forms a Michael acceptor that reacts with Michael donors such as glutathione or cysteine (RS). EGC, epigallocatechin; EGCG, epigallocatechin gallate.

Before entering the plasma, orally administered drugs must pass through enterocytes that line the intestines. It is here where they undergo a substantial amount of Phase II modification before they are either recirculated into the intestinal lumen or transported to the liver (Donovan et al, 2001). Crespy et al (1999) showed that 52% of quercetin is recirculated into the intestinal lumen of rats. By directly exposing dissected rat jejunum and ileum to quercetin, they found that 64% was glucuronated and methylated and 36% was sulfated, indicative of substantial intestinal modification.

Both modifications enhance excretion. In addition, excretion of the compounds by the intestinal epithelium is facilitated by multidrug resistance associated proteins (MRPs) (Hong et al, 2003). These transporters may also be involved in poor response by cancer cells to chemotherapy, including catechins (Hong et al, 2002). Lastly, polyphenols that enter the circulation are also susceptible to being bound to plasma albumin, which can further reduce their bioavailability. For instance, the flavonoid quercetin has low plasma-albumin equilibrium constants (3×10^{-6}–4×10^{-5} *M*), which suggests that these compounds are mostly bound to serum albumin in solution (Bolli et al, 2010).

The size of naturally occurring polyphenols is another impediment to their bioavailability, as most of these are not found as free molecules (Rowland et al, 2018). Quercetin can be found in food as an adduct to a sugar moiety and is water soluble (Almeida et al, 2018). Depending on the sugar attached, an aglycone or glycoside, the quercetin has different metabolic fates. Quercetin aglycone is more hydrophobic than quercetin glycoside and can diffuse into enterocytes without glycosidic hydrolysis; however, quercetin glycosides must first be hydrolyzed by the intestinal brush border enzyme, lactase phlorizin hydrolase, to the aglycone before absorption because of its hydrophilicity (Almeida et al, 2018; Dabeek and Marra, 2019).

There is substantial variation in how individuals metabolize quercetin and its adducts, which suggests that additional factors such as the individual microbiome of an individual will also be important (Almeida et al, 2018; Graefe et al, 1999; Marin et al, 2015).

The gut flora also plays an important role in the uptake of polyphenols (Li et al, 2000; Sang et al, 2011). For instance, some bacteria cleave functional groups. *Escherichia coli* hydrolyzes the ester bond in phenolic acid esters such as rosmarinic acid and *Lactobacillus casei* deglycosylates anthocyanins (Correa et al, 2019). Other bacterial strains such as *Clostridium coccoides* perform ring fission operations on the carbon skeletons of catechins and break the planar aromatic structure of the C-B bicycle (Correa et al, 2019).

Chen et al (2020) identified 21 metabolites of EC, each with varied degrees of antioxidant capacity, when incubated with fecal bacteria. Within 8 h, less than 10% of the original catechin mass remained. However, it is important to note that the peak plasma concentration of these compounds is within 2 h, (Scholl et al, 2018) and although the role of bacterial metabolism may not be a major contributor to reduced bioavailability, it may reduce uptake. Conversely, polyphenol consumption has bidirectional effects on the gut flora with highly variable effects (Correa et al, 2019).

High uptake does not necessarily correlate to high bioavailability. For example, in a study of 6 human subjects ~70%–75% of an oral dose of C^{14}-labeled resveratrol was absorbed (Walle, 2011; Walle et al, 2004), and multiple metabolites carrying sulfate and glucuronate moieties, indicating Phase II modification, were present in the urine (Walle et al, 2004). However, resveratrol, detectable by UV-vis spectroscopy, was not observed in plasma samples, suggesting that only 0%–1% was bioavailable (Walle, 2011).

Gut microbes may also be responsible for reduced bioavailability, and ~50% of the metabolites from resveratrol were believed to originate from microbial modifications (Walle, 2011). Indeed, the presence of dihydroresveratrol in feces suggested bacterial modification rather than an endogenous Phase I process (Bode et al, 2013).

One challenge and question surrounding the use of polyphenols is whether artificial polyphenols can be prepared with similar activity but with higher bioavailability. Scheepens et al (2010) proposed systemic alterations, including altering the gut microbiome or reducing the activity of ABC transporters and Phase 1 and II enzymes. Liposomes have also been proposed as a means to carry polyphenols into cells, because they reduce the effects of solubility and they protect the cargo from enzymes (Enaru et al, 2021). A third possibility is the design of synthetic polyphenol-like compounds that are antioxidants but have a higher bioavailability (Galante et al, 2019).

Issues of Antioxidants as Therapeutics

Cited here are many studies that suggest therapeutic benefits of nutraceuticals. However, acceptance by the medical establishment has still tended to lag except in some specific circumstances (Bertelli et al, 2021). This lack of overall acceptance may be due to several factors, for example, evidence that their anti-ROS actions are slow, and their potential negative effects.

For example, higher mortality was suggested in long-term use of the antioxidant beta carotene in the Finnish Smokers' Study (Alpha-Tocopherol and Beta Carotene Cancer Prevention Study Group). Many clinical studies are either uncontrolled or have small numbers of subjects (Bertelli et al, 2021). High profile negative studies such as the DATAOP Parkinson Disease study, utilizing Vitamin E, showed no benefit despite evidence that oxidative stress is likely involved in the pathogenesis of this disease (Parkinson Study Group, 1993). Other issues related to nutraceutical trials include differences in preparations and wide ranges of bioavailability, as reviewed earlier. Clearly, the field needs these issues addressed on a consistent basis as critical to their clinical acceptance (Bertelli et al, 2021).

Many of the clinical studies cited in this review were designed to improve chronic conditions or overall health factors. Skepticism of antioxidant therapy is reinforced by their inability to demonstrate clinical effectiveness in acute injuries. There are mechanistic issues that favor disease prevention over acute disease therapy (Samuel et al, 2014). Once conditions induce the release of excess superoxide, for example, mitochondrial electron leakage, a cascade of reactions occur that can lead to formation of the hydroxyl radical (Liochev and Fridovich, 1994).

This can cause additional oxidative damage that is capable of acutely overwhelming endogenous antioxidant mechanisms. Because of the cascade of downstream injury, for example, lipid peroxidation (Radi et al, 1991), protein nitrosylation (Deng-Bryant et al, 2008), *etc.*, there is a strong challenge to the therapeutic capacity of any agent. Therefore, the antioxidant *capacity* is critical if it is to be used once the disease process has begun (Samuel et al, 2014). This need for a high-capacity antioxidant would favor those with catalytic ability to reduce radicals (Samuel et al, 2014).

Catalytic antioxidants such as NADPH:quinone oxidoreductase (NQO-1) and Gpx are two examples of enzymes conditionally transcribed by the oxidative stress sensitive Nrf2 axis (Ma, 2013). NQO-1 and Gpx utilize NADPH as a reducing substrate during their catalytic cycles (Gaber et al, 2001; Ross and Siegel, 2017). NADPH is a product of glycolysis and the electron transport chain, to continue their redox cycles as opposed to an exogenous agent because the reducing substrate is produced through normal metabolic processes.

The capacity of these enzymes is, therefore, dependent upon the availability of glycolytic substrates and not themselves. Ultimately, a catalytic antioxidant should prove to be more potent than one that can quench a near stoichiometric amount of radical.

Consistent with this notion, in pre-clinical models, traditional non-catalytic antioxidants appear to be much more effective when applied pre-injury, for example, ischemia reperfusion models in stroke (Kokubo et al, 2002); however, when translated to clinical therapy, this issue was mostly ignored and nearly all studies in which an antioxidant was administered after the injury have been negative (Slemmer et al, 2008).

One reason for this study design limitation is the logistic difficulty of getting consent in an acute trial, for example, in acute stroke, to administer a research drug before lifesaving resuscitation measures. Similarly, antioxidant therapy in chronic diseases has typically been initiated once symptoms have emerged, for example, Alzheimer Disease, diabetes, *etc.* Given there are a few available antioxidants that are catalytic for ROS (Delanty and Dichter, 2000), it is not surprising that there is little incontrovertible evidence that antioxidants are beneficial once a disease has commenced.

In contrast to the therapeutics addressing the ROS cascade, catabolism of H_2S to polysulfides and thiosulfate by polyphenols appear to have a high capacity and demonstrate behavior consistent with being catalytic as shown in our prior work with teas, berries, and pure polyphenols (Olson et al, 2021a; Olson et al, 2021b; Olson et al, 2020a). These studies have recently been extended to include H_2S oxidation to polysulfides by CoQ_n ($n = 0$, 1, 10) without a ceiling effect due to the catalytic properties of these compounds (Olson et al, 2022).

Importantly, with RSS, the products of H_2S catabolism are themselves therapeutic, for example, polysulfides having excellent antioxidant characteristics (Chauvin et al, 2019; Fukuto and Hobbs 2021), in contrast to the product of SOD, H_2O_2, which has a role in normal signaling, but in excess, can be converted to hydroxyl radical and consume peroxidases and alter downstream protein function (Fucci et al, 1983). The additional capacity and beneficial H_2S catabolites may explain, for example, the positive results with LA in diabetic neuropathy and multiple sclerosis where LA was administered even after symptoms have developed (Loy et al, 2018; Salehi et al, 2019).

LA's ability to increase Nrf2 signaling adds an additional, unique mechanism for cytoprotection that would be particularly useful in chronic conditions (Pilar Valdecantos et al, 2015). Upregulation of its antioxidant targets over time would be more beneficial than in an acute oxidative injury setting. Targeting RSS metabolism may, therefore, provide a treatment for a wider range of disorders of oxidative injury than currently available through a focus on ROS.

Concluding Comments

Commercialization of nutraceuticals is an exponentially expanding, multibillion dollar business whose benefits are being promulgated in virtually every medium. However, enthusiasm should begin to wane upon reading the fine print, ''These statements have not been evaluated by the Food and Drug Administration'' and ''This product is not intended to diagnose, treat, cure or prevent any disease.'' These caveats undoubtedly reflect the relative dearth of controlled clinical trials and uncertainties about the mechanism(s) of action, especially regarding their purported antioxidant activity.

Here, we propose an alternative mechanism for a variety of nutraceuticals based on their effects on RSS. The RSS are endogenously produced and metabolized in cells; they exhibit potent antioxidant activities, and a wide range of nutraceuticals appear to augment or affect RSS metabolism in a way that would potentiate a variety of antioxidant activities. It is hoped that this review will turn attention to RSS as a potential target for nutraceuticals and foster further evaluation of how they can best be used to maximize their health benefits.

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Authors' Contributions

K.R.O. conceptualized the project, and all authors contributed to writing the original draft, review, and editing.

Author Disclosure Statement

T.A.K., K.R.O., and P.J.D. have pending patents on the therapeutic use of polyphenols in regulating H_2S metabolism. The other author has no competing financial interests that exist.

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Address correspondence to:
Prof. Kenneth R. Olson
Department of Physiology
Indiana University School of Medicine—South Bend
Raclin Carmichael Hall
1234 Notre Dame Avenue
South Bend, IN 46617
USA

E-mail: kolson@nd.edu

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Abbreviations Used

3-MP**S** = 3-mercaptopyruvate
3-MST**S** = 3-mercaptopyruvate sulfur transferase
3-MST-**SS** = 3-mercaptopyruvate sulfur transferase persulfide
AA = ascorbate
ARE = antioxidant response elements
AT2 = sodium-coupled neutral amino acid transporter
bya = billion years ago
CA = carbonic anhydrase
CARS1 = cytosolic cysteinyl-tRNA synthetase
CARS2 = mitochondrial cysteinyl-tRNA synthetase
Cat = catalyase
CAT = cysteine aminotransferase
CBS = cystathionine β-synthase
COMT = catechol-O-methyltransferase
COS = carbonyl sulfide
CSE = cystathionine γ-lyase
CysSSCys = cystine
DADS = diallyl disulfide
DAO = D-amino acid oxidase
DAS = diallyl sulfide
DATS = diallyl trisulfide
D-Cys**S** = D-cysteine
DHLA = dihydrolipoic acid
EC = epicatechin
EGC = epigallocatechin
EGCG = epigallocatechin gallate
ETC = mitochondrial electron transport chain
Gpx = glutathione peroxidase
Grx = glutaredoxin
GrxR = glutaredoxin reductase
GSH**S** = glutathione
GSK-3β = glycogen synthase kinase-3beta
GSSG = oxidized glutathione dimer
H_2O_2 = hydrogen peroxide

Abbreviations Used (Cont.)

H_2S = hydrogen sulfide
H_2S_2 = hydrogen persulfide
$H_2S_2O_3$ = thiosulfate
H_2S_n = hydrogen polysulfide
Hb = methemoglobin
HUVECs = human umbilical vein endothelial cells
Keap1 = Kelch like ECH associated protein 1
LA = lipoic acid
L-Cys**S** = L-cysteine
L-Met**S** = L-methionine
Mb = metmyoglobin
MitoQ = CoQ_{10} linked to triphenylphosphonium
NO = nitric oxide
NQO-1 = NADPH:quinone oxidoreductase
Nrf2 = Nuclear factor erythroid 2-related factor 2
$O_2^{\bullet-}$ = superoxide
PLP = pyridoxyl phosphate
Prot**S** = protein reactive sulfur
Prx = peroxiredoxins
PSH = cysteine-based regulatory protein
ROS = reactive oxygen species
RSS = reactive sulfur species
S^0 = elemental sulfur
SOD = superoxide dismutase
SOD1 = cytosolic Cu-Zn-superoxide dismutase
SOD2 = mitochondrial manganese-superoxide dismutase
SOD3 = soluble (extracellular) Cu-Zn-superoxide dismutase
ST1 = sulfur transferase 1
SULT1 = sulfate transferase 1
tRNA = transfer RNA
Trx = thioredoxin
TrxR = thioredoxin reductase
X_{c-} = cystine/glutamate antiporter