

Review

Redox Homeostasis and Natural Dietary Compounds: Focusing on Antioxidants of Rice (*Oryza sativa* L.)

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Abstract: Redox homeostasis may be defined as the dynamic equilibrium between electrophiles and nucleophiles to maintain the optimum redox steady state. This mechanism involves complex reactions, including nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, activated by oxidative stress in order to restore the redox balance. The ability to maintain the optimal redox homeostasis is fundamental for preserving physiological functions and preventing phenotypic shift toward pathological conditions. Here, we reviewed mechanisms involved in redox homeostasis and how certain natural compounds regulate the nucleophilic tone. In addition, we focused on the antioxidant properties of rice and particularly on its bioactive compound, γ -oryzanol. It is well known that γ -oryzanol exerts a variety of beneficial effects mediated by its antioxidant properties. Recently, γ -oryzanol was also found as a Nrf2 inducer, resulting in nucleophilic tone regulation and making rice a para-hormetic food.

Keywords: natural compound; phytochemical; rice; *Oryza sativa* L.; γ -oryzanol; redox homeostasis; Nrf2; oxidative stress; ROS; antioxidant

1. Introduction

Redox homeostasis may be defined as the internal dynamic equilibrium with respect to the continuous alterations of electrophilic and nucleophilic tone in order to maintain the optimum redox steady state [1–3]. The maintenance of redox homeostasis is crucial for preserving physiological functions since reactive oxygen and nitrogen species (ROS/RNS) are constantly generated in the normal metabolism of aerobic cells [4]. In fact, redox homeostasis alterations, as the result of the inability to maintain the optimal redox steady state, are associated with a phenotypic shift toward pathological conditions [5,6]. According with the Harman theory of aging, an imbalance between the efficiency of antioxidant systems and the production of free radicals, derived from mitochondrial respiration and/or external environmental stressors, is at the base of aging process alterations and the development of age-related diseases. Following this concept, scavenging free radicals from a cellular environment might be the right approach for a beneficial effect. Indeed, ROS/RNS are not intrinsically harmful, and the Harman theory today could be too simplistic [7]. The fine regulation of the dynamic equilibrium between electrophilic and nucleophilic tone is at the base of redox homeostasis. When electrophilic tone increases, nucleophilic feedback reactions will be activated through the engagement of redox signaling in order to restore the system back to the initial steady state [5,8]. These reactions involve the antioxidant response element (ARE or also known as electrophile response element, EpRE)-regulated phase II enzymes such as NAD(P)H: quinone oxidoreductase 1 (NQO1), heme oxygenase-1 (HO-1), and glutathione S-transferase (GST), which transcriptional activation requires a basic leucine zipper transcription factor called nuclear factor erythroid 2-related factor 2 (Nrf2) [9–11].

Natural antioxidants have recently obtained great attention in preventing lifestyle and age-related diseases. They contain phytochemicals that help the body to counteract oxidative stress by directly scavenging free radicals or activating antioxidant pathways [12–15]. Recently, new evidence has shown that certain natural compounds are able to induce ARE-regulated phase II enzymes, thus participating in the maintenance of redox homeostasis [16–30]. A good understanding of the mechanisms by which certain natural compounds preserve nucleophilic tone is of great interest in the field of the public health prevention, especially in the aging population.

Thus, the aim of this review is to summarize the mechanisms involved in redox homeostasis and how certain natural compounds regulate the nucleophilic tone. In addition, we discussed on the antioxidant properties of rice focusing on γ -oryzanol, underlining the relationship between chemical structures and biological effects. Besides, based on our recent finding, we emphasized a possible role of γ -oryzanol as a para-hormetic natural compound.

2. Oxidants and the Electrophilic Tone Regulation

Since 1985, the concept of oxidative stress has been introduced to redox biological research [31]. In general, the term of oxidative stress is referred to an imbalance between the efficiency of antioxidant capacity and free radical production. Several types of reactive species are generated in the body in the form of free radicals or non-radicals as the result of normal metabolic reactions or the exposure to exogenous toxins and pathological events. These species include oxygen derivatives (i.e., $O_2^{\cdot-}$, OH^{\cdot} , $OH_2^{\cdot-}$, H_2O_2) and nitrogen derivatives (i.e., NO , NO_2 , N_2O_3 , $ONOO^-$) [32–36]. Besides the mitochondria [37,38], ROS can be formed by enzymes using molecular oxygen such as cytochrome P450, xanthine oxidase, and plasma membrane-bound NADPH oxidase [39,40]. RNS are synthesized by nitric oxide synthase generating nitric oxide, which can react with superoxide forming a potent oxidant peroxynitrite. This peroxynitrite can further react with other molecules to produce more RNS such as nitrogen dioxide and dinitrogen trioxide [39,40].

Although it is widely believed that these free radicals and oxidized products can cause cellular and tissue damage, it is also true that the nature has selected ROS/RNS as a signal transduction mechanism responsive to the effects of nutrients and oxidative environment. Only in the past two decades, it has become apparent that ROS serve as signaling molecules to regulate biological and physiological processes [32–34,40–43]. Their roles as harmful compounds or signal molecules depend on the types of ROS/RNS, duration of the stimulus, and their local concentrations [35,44]. Redox signaling involves specific electrophiles that react with specific protein thiolates, and this redox shift is rapidly reverted by feedback reactions. In this context, redox post-translational modifications (rPTMs) of cysteine residues, reminiscent of phosphorylation and ubiquitination of critical amino acids, regulate a broad spectrum of protein activities [45]. For example, in redox signaling pathway, thiolate anion (Cys-S) of cysteine residues can be oxidized by H_2O_2 to sulfenic (Cys-SOH), modulating protein functions. This reaction can be reverted by thioredoxin and glutaredoxin, thus ensuring the fine regulation of signal transduction. On the other hand, accumulation of H_2O_2 can further oxidize sulfenic (Cys-SOH) to sulfinic (Cys-SO₂H) and sulfonic (Cys-SO₃H) species, both of which are irreversible mechanisms and permanently damage protein structures and functions [46,47]. RNS are also involved in redox signaling pathway through S-nitrosylation, generating S-nitrosoproteins [48]. S-nitrosylation is the reversible reaction of nitric oxide-derived species with thiols of cysteine residues through oxidation or transnitrosylation, a transferring of NO [45,49]. The relevance of S-nitrosylation role as a pleiotropic player of protein rPTMs is underlined by the specificity of target substrates and the enzymatic mechanisms involved in S-nitrosylation/denitrosylation [45,49]. S-nitrosylation regulates diverse pathways such as G-protein-coupled receptor signaling [50], glutamate-dependent neurotransmission [51], vesicular trafficking [52], death receptor-mediated apoptosis [53], and stimulation of prostaglandin synthesis [54]. On the other hand, aberrant S-nitrosylation affects protein functions, and it is related to the development of various diseases including cancer, diabetes type 1 and 2, cardiovascular (CVD), Parkinson's (PD), and Alzheimer's (AD) diseases [55]. Another example is

the lipid peroxidation, the reaction of oxidative chain degradation in lipid cell membrane. This reaction is activated by free radicals in polyunsaturated fatty acids of lipid membrane, producing lipid hydroperoxides (LOOH) and their derivatives [56,57]. LOOH are further catalyzed by lipoxygenases enzyme, which also requires the activation of hydroperoxide, resulting in cellular damage [58,59]. However, this chain reaction of lipid peroxidation also produces one of α , β -unsaturated aldehydes called 4-hydroxynonenal (HNE). HNE is mainly generated from the reaction between n-6 fatty acids and hydroperoxide, and functions as a signal transduction molecule for redox homeostasis [59–62]. In normal state, HNE is produced in the proper amount to maintain redox steady state modulating the mRNA expression of antioxidant enzymes [63]. While in the presence of oxidative stress, the production of HNE is substantially increased and able to act as a signaling species for nucleophilic feedback to counteract oxidative stress and maintain the original steady state [64,65]

3. Antioxidants and the Maintenance of Neutrophilic Tone

To counteract the effects of electrophiles and oxidants, the body is endowed with a category of compounds called antioxidants. These antioxidants are produced endogenously (i.e., enzymes: superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx)) or received from exogenous sources (i.e., vitamins: vitamin C and E; minerals: zinc (Zn), manganese (Mn), and selenium (Se); and phenolic compounds). They represent the first defense against a burst of ROS/RNS to restore nucleophilic tone. Antioxidant enzyme cascade reacts sequentially to neutralize free radicals. SOD catalyzes the dismutation of superoxide anion producing H_2O_2 , which is in turn decomposed by CAT or GPx to water [66–69]. Vitamins, phenolic compounds, and minerals are not endogenously produced, thus they have to be integrated from diet. Vitamin C is a hydrosoluble, while vitamin E is a liposoluble antioxidants [70–72]. Also, phenolic compounds are one of the most common antioxidants found in food [73–75]. Thanks to their chemical structures, these vitamins and phenolic compounds can neutralize free radicals by donating hydrogen atoms and become stable resonance structures, thereby protecting cell membranes and proteins from oxidative damage [75–81]. Dietary minerals are known as essential cofactors of antioxidant enzymes involved in redox homeostasis. For example, Zn, Mn, and Se function in various classes of enzymes. Zn is present in cytosolic SOD (SOD1). Mn is well-known for mitochondrial SOD (SOD2), while Se is a co-enzyme of GPx [82–84].

In addition, cellular stress response-related enzymes, also called ARE-regulated phase II enzymes (HO-1, NQO1, and GST), are engaged in long-lasting maintenance of the redox homeostasis, supporting the nucleophilic tone [10,11]. These enzymes are transcriptionally under the control of Nrf2 through its binding to the consensus ARE within the 5'-flanking promoter region of these target genes. Nrf2 is considered as a sentinel of oxidative stress and protects the body by making it more resistant to oxidative insults [85]. For instance, Nrf2 knockout mice are substantially more susceptible to a broad range of chemical toxicity and disease conditions associated with oxidative pathology such as AD, PD, and amyotrophic lateral sclerosis (ALS) [86–93]. Activation of Nrf2-mediated gene transcription involves various complex processes [94,95]. Nrf2 generally binds to Kelch like ECH associated protein 1 (Keap1) in the cytoplasm. Keap1 is a protein regulator playing a key role in controlling the steady state of Nrf2 pathway based on redox conditions. In basal or unstressed conditions, Nrf2 is less activated and has rapid turnover rate with short half-life due to the formation of Nrf2-Keap1-Cul3 complex in the cytoplasm. Keap1, which interacts with Cul3-E3-ligase (an ubiquitin ligase), binds to Nrf2 and helps in promoting Nrf2 ubiquitination leading to rapid proteasomal degradation by 26 S proteasome [96–103]. This complex can be interrupted by various electrophiles resulting in the activation of Nrf2 signaling pathway. In the presence of oxidative stress, Keap1 further functions as a stress signal through the stress-induced oxidation of its key cysteine residues. The stimuli can oxidize or covalently modify disulfide bond (-S-S-) of cysteine residues causing conformational changes and interrupt the Keap1-Cul3 complex by inhibiting the ubiquitin E3 ligase activity. The reaction decreases the ability of Keap1 to bind Nrf2, thereby freeing Nrf2 and activating its nuclear translocation. Before its nuclear translocation, Nrf2 is phosphorylated by protein kinases

(protein kinase C- δ (PKC δ) and protein kinase B (Akt)), which are also induced by electrophiles and oxidants. When Nrf2 is translocated into the nucleus, it dimerizes with the small Maf heterodimer proteins and binds to a cis-acting element of ARE activating the transcription of ARE-dependent phase II enzymes such as HO-1, GST, and NQO1 [96,99,103–108]. In addition, this Nrf2-ARE activation is also found to control the expression of several cytoprotective genes such as thioredoxin 1, thioredoxin reductase 1, sulfiredoxin 1, NADPH-generating enzymes (glucose-6-phosphate dehydrogenase (*G6PD*), 6-phosphogluconate dehydrogenase (*PGD*), malic enzyme (*ME*)1, and isocitrate dehydrogenase (*IDH*)1), ferritin, and glutathione-based system (*GPx*, glutathione disulfide (*GSSG*), glutathione reductase (*GSR*)) [105,109–120].

Interestingly, several natural antioxidant compounds, thanks to their electrophilic properties, are Nrf2-ARE inducers. Most of them consist of oxidizable phenols, quinones, Michael acceptors (olefins), isothiocyanates, dithiolethiones, vicinal dimercaptans, or polyenes [121–127]. These antioxidant compounds and their oxidized derivatives have the ability to react (by oxidation, reduction, and alkylation) with sulfhydryl group of cysteine residues of Keap1, favoring Nrf2 nuclear translocation and activation of ARE signaling process [128–136]. It is noteworthy that chemical structure of HNE (α , β -unsaturated aldehyde), one of the most effective endogenous Nrf2 activator, is also a common functional group found in many natural antioxidants [137,138]. Thus, the antioxidant potential of natural products may stem from mimicking the signaling of endogenous electrophiles by activating Nrf2 to restore nucleophilic tone and maintain the equilibrium of redox homeostasis. This mechanism is called “para-hormesis” [96].

4. Rice Antioxidants

Rice has been a primary staple food for billions of people worldwide and also represents cultural identity and global unity for centuries [139,140]. Rice that is cultivated for consumption has two major species: *Oryza sativa* and *Oryza glaberrima*. *Oryza sativa* species are the varieties originated from South-East Asia and also found throughout Asia, America, and Europe. *Oryza glaberrima* species are originated from West Africa and only grown in this area [141]. Rice from all the varieties can be further categorized into two subspecies, *Japonica* and *Indica*, based on the degrees of spikelet and pollen sterility in F1 hybrids between them. Rice contains essential amino acids, dietary fibers, carotenoids, folate, lignin, and minerals, and it is rich in many bioactive phytochemicals: γ -oryzanol, vitamin E (tocopherols and tocotrienols), γ -aminobutyric acid (GABA), phenolics, flavones, and anthocyanins [142–145]. Studies in rice have shown that rice is not only important in terms of a staple food, but also play a role in promoting various health benefits such as anti-inflammation, anti-diabetic, anti-hyperlipidemic, anti-cancer, and antioxidant potential [146–154].

Some of the therapeutic effects of rice in preventing diabetes type 2 (T2D), CVD, obesity, different types of cancer, and inflammation are attributed to its antioxidant properties [155–158]. The antioxidant properties of rice have been first published in 1989, which some of its active compounds including flavonoids, α -tocopherols, and γ -oryzanol were identified [159,160]. Since 2000, research interest on rice has been improved and the number of research articles related to its antioxidant properties dramatically increased more than 15 times [161,162]. Today, it is known that rice contains about 100 kinds of antioxidants, which can be essentially classified into two major groups: vitamins and phenolic-based compounds [163–165]. The mechanisms by which these bioactive compounds exert antioxidant activity have been investigated [166,167]. For example, it is well known that vitamin E exerts its antioxidant effects by quenching free radicals. Vitamin E in rice includes tocopherols ($\alpha, \beta, \gamma, \delta$ forms) and tocotrienols ($\alpha, \beta, \gamma, \delta$ forms) [143]. Thanks to its structure of the chromanol ring connected with a free hydroxyl group, hydrogen atom of the hydroxyl group can be donated to a free radical resulting in the delocalized and stabilized unpaired electron, vitamin E radical (Figure 1). Since the reactivity of the vitamin E radical is much less than other radicals, it is relatively stable to break the radical chain cascade [168–171].

Vitamin E

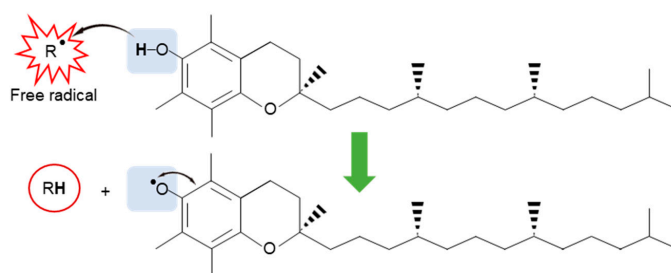


Figure 1. Antioxidants (vitamin E) in rice and structure-activity relationship. Vitamin E exerts its antioxidant effects by quenching free radicals. The hydroxyl group on chromanol ring can donate its hydrogen atom to a free radical resulting in a delocalized and stabilized unpaired electron, vitamin E radical.

Phenolic compounds consist of at least one aromatic ring and one hydroxyl group [172,173]. This chemical structure is present in many active compounds including ferulic, cinnamic, *p*-coumaric, caffeic, sinapic, chlorogenic, gallic, vanillic, *p*-hydroxybenzoic, protocatechuic, and syringic acids, flavonoids, and their derivatives [163–165]. Those found more in pigmented rice are anthocyanins (cyanidin-3-*O*-glucoside, cyanidin-3-*O*-galactoside, cyanidin-3-*O*-rutinoside, peonidin-3-*O*-glucoside, and pelargonidin-3-*O*-glucoside) and proanthocyanidins, which are responsible for purple to black color and reddish color respectively, while the ferulic acid esters are more abundant in rice bran layer [174–179]. The phenolic-based structure highly provides antioxidant properties as free radical scavengers. The hydroxyl group on the phenolic ring can transfer its hydrogen atom to a free radical forming a delocalized and stabilized unpaired electron, phenoxy radical, across the phenolic ring (Figure 2). The antioxidant capacity of phenolic-based compounds is in function of the numbers of hydroxyl groups, the location of hydroxyl group on aromatic ring (ortho, para, meta positions), and the presence of other functional groups on the molecule [180,181]. The antioxidant activities of these compounds are four times stronger than that of α -tocopherol [182–184]. In addition, some of these compounds such as anthocyanins and ferulic acid derivatives are also able to activate ARE-regulated phase II enzyme expression [185–189].

Phenolic compounds

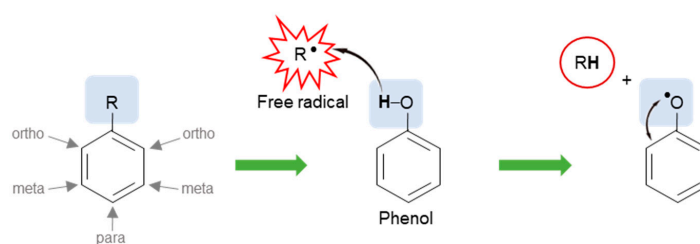


Figure 2. Antioxidants (phenolic compounds) in rice and structure-activity relationship. Phenolic compounds act as free radical scavengers since hydroxyl group on the phenolic ring can transfer its hydrogen atom to a free radical, forming a delocalized and stabilized unpaired electron, phenoxy radical, across the phenolic ring. The antioxidant capacity of phenolic compounds is in function of the numbers of hydroxyl groups, the location of hydroxyl group on aromatic ring (*ortho*, *para*, *meta* positions), and the presence of other functional groups on the molecule.

5. Γ -Oryzanol: Structure-Antioxidant Activity Relationship

Γ -Oryzanol is present in the highest amount in rice as a mixture of phytosteryl ferulates containing ferulic acid esters of phytosterols (sterols and triterpene alcohols) [55,190]. In γ -oryzanol, there are at least 10 different phytosteryl ferulates such as cycloartenyl ferulate, 24-methylenecycloartenyl ferulate, campesteryl ferulate, sitosteryl ferulate, stigamsteryl ferulate, campestanil ferulate, sitostanyl

ferulate, $\Delta 7$ -campestenyl ferulate, $\Delta 7$ -sitostenyl ferulate, and $\Delta 7$ -stigmastenyl ferulate [55,190–192]. Among these, the principal components accounting for approximately 80% are cycloartenyl, 24-methylenecycloartenyl, campesteryl, and sitosteryl ferulates [193–197].

Γ -Oryzanol has been proposed as a potent antioxidant compound [198]. A growing number of studies have demonstrated that γ -oryzanol acts as a free radical scavenger and improves the activity of endogenous antioxidant enzymes. Γ -Oryzanol major components (campesteryl ferulate, cycloartenyl ferulate, and 24-methylenecycloartenyl ferulate) are more potent antioxidants than all components of vitamin E, and 24-methylenecycloartenyl ferulate has the highest antioxidant activity [199]. The antioxidant properties of γ -oryzanol tested with different types of radicals—such as inorganic oxygen-derived radicals, DPPH radicals, lipid soluble organic radicals, 2,2'-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) free radicals, and linoleic acid peroxidation—revealed that γ -oryzanol acts as organic, lipophilic as well as hydrophilic radical scavengers [200,201]. Moreover, γ -oryzanol was found to possess SOD-like activity in inhibiting superoxide radical catalyzed pyrogallol autoxidation [202]. In *in vitro* cells, pretreatment with the main compounds of γ -oryzanol (sitosteryl ferulate, cycloartenyl ferulate, and 24-methylenecycloartenyl ferulate) prevented H_2O_2 -induced ROS production via scavenging free radicals [203]. Likewise, we recently demonstrated in HEK-293 cells that γ -oryzanol pretreatment prevents H_2O_2 -induced ROS generation by increasing the activity and protein expression of antioxidant enzymes such as SODs [204].

The antioxidant properties of γ -oryzanol have also been shown in *in vivo* models. In *Drosophila melanogaster* model, γ -oryzanol enhanced antioxidant defense by significantly improving the antioxidant enzymes such as SOD, CAT, and GST, and decreasing the malondialdehyde (MDA) and ROS production [205]. In streptozotocin-induced oxidative stress, γ -oryzanol also effectively increased the levels of SOD and reduced glutathione in rats [206]. In mice model of ethanol-induced liver injury, γ -oryzanol was able to prevent increased hepatic lipid hydroperoxide, TBARS levels as well as plasma aspartate and alanine aminotransferase activities. Moreover, in the same study, γ -oryzanol also improved SOD activity, suggesting that its effects in preventing ethanol-induced hepatic injury could be mediated by its antioxidant properties [207]. Interestingly, the effects of γ -oryzanol were also evaluated in animals fed with high fat diet (HFD). What the authors found was a significant increase of antioxidant enzyme activities and decrease of free radicals in those mice fed with HFD supplemented with γ -oryzanol compared with control HFD animals. Furthermore, in these mice, γ -oryzanol decreased hepatic lipogenesis and suppressed plasma triglyceride and total cholesterol levels with an increase of HDL cholesterol concentrations [208]. The effects on lipid metabolism of γ -oryzanol were also investigated in dyslipidemic patients, where its beneficial effects were compared with other different dietary supplements including vitamin E and polyunsaturated fatty acids (PUFA) n-3. Among these, the group consuming γ -oryzanol expressed a greater lowering of oxidative stress via regulation of ROS levels, total antioxidant capacity, and inflammatory biomarkers—i.e., tumor necrosis factor (TNF- α), interleukin-1 β (IL-1 β), and thromboxane B2 (TXB2)—supporting the notion that the anti-hyperlipidemic effects of γ -oryzanol are mediated by its antioxidant properties [209].

The peculiar beneficial properties of γ -oryzanol lay also on its ability to regulate the transcriptional expression of genes related to redox homeostasis and cell survival. For example, in SH-SY5Y cells challenged with H_2O_2 , γ -oryzanol decreased oxidative stress and prevented neurotoxicity by upregulating antioxidant genes (SODs) and anti-apoptotic genes (NF- κ B and Bcl-2) and by downregulating pro-apoptotic genes (TNF, BAX, and caspase-9) [13]. Recently, we further demonstrated that γ -oryzanol activated Nrf2 nuclear translocation and Nrf2-ARE pathway, with an increase of mRNA and protein expression of ARE-response phase II enzymes such as HO-1, NQO1 [204]. The activation of Nrf2 pathway seems to be central in the biological effects of γ -oryzanol. In fact, various of those aforementioned genes are found to be directly or indirectly regulated by Nrf2. For example, Niture and Jaiswal [210], by using band/supershift and ChIP assays, showed a direct interaction between Nrf2 and Bcl-2 antioxidant response element leading to activation of Bcl-2 gene expression. NF- κ B and TNF are not directly under the control of Nrf2, but it could be modulated by

target genes of Nrf2 such as *HO-1* and *NQO1* [211,212]. Likewise, Nrf2 was found also to regulate the expression of *BAX* and caspase-9 in human glioblastoma cells [213].

Therefore, from a structure-activity point of view, (Figure 3) γ -oryzanol could possess free radical scavenging properties due to the transfer of hydrogen atom of 4-hydroxyl group on the phenolic ring of ferulic acid moiety, forming a phenoxy radical. This phenoxy radical is highly stabilized by the delocalization of the unpaired electron across the phenolic ring, unsaturated side chain, and carbonyl group (α , β -unsaturated carbonyl moiety) [214–217]. On the other hand, γ -oryzanol might activate Nrf2 pathway through at least two possible mechanisms: (1) the formation of more stable oxygen species including H_2O_2 during the transferring of hydrogen atoms to free radical species, which could be a signaling molecule for Nrf2 activation [182,218–220]; (2) the presence of α , β -unsaturated carbonyl moiety is responsible for its electrophilicity, a main common property of Keap1-Nrf2-ARE pathway inducers. α , β -Unsaturated carbonyl moiety, a Michael acceptor, is a carbon–carbon double bond (olefin) conjugated with an electron-withdrawal carbonyl group [123,221]. This carbonyl group can delocalize an electron across the oxygen to the olefin inducing a partial cation (positive charge) at the (olefin) carbon atom, thereby providing this carbon atom an electrophilicity. Thus, α , β -unsaturated carbonyl moiety becomes an electrophilic moiety to attract electrons and nucleophiles, particularly cysteine residues of Keap1 leading to oxidation of Keap1, Nrf2 nuclear translocation, and in turn Nrf2-ARE activation [222,223]. Interestingly, the α , β -unsaturated carbonyl moiety in γ -oryzanol is structurally similar to α , β -unsaturated aldehyde of HNE, an endogenous electrophile signaling molecule known as a Nrf2 inducer [123,221]. Therefore, γ -oryzanol possesses peculiar chemical properties, from both ferulic acid moiety and phytosterols, to counteract oxidative stress and mimic body electrophiles to activate nucleophilic feedback reactions, restoring redox homeostasis.

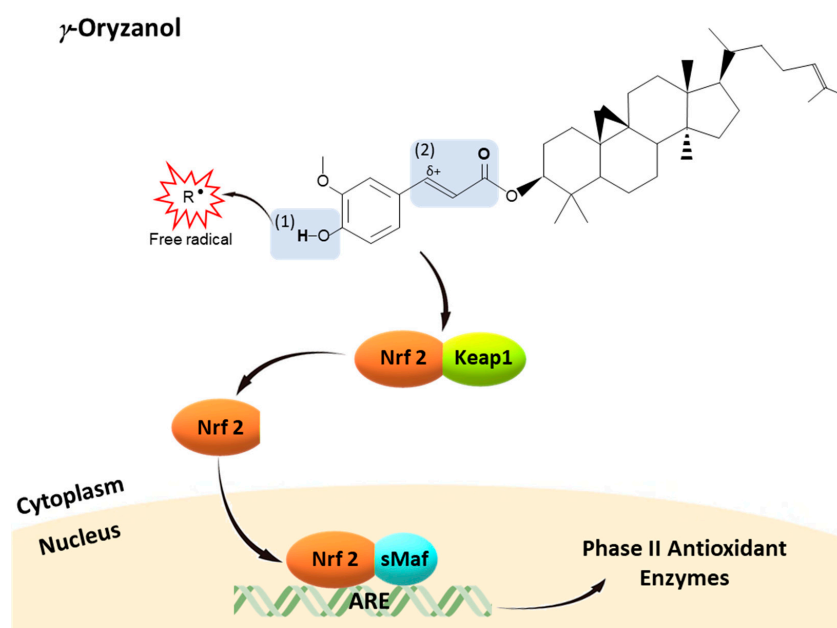


Figure 3. Antioxidants (γ -oryzanol) in rice and structure-activity relationship. (1) The 4-hydroxyl group on the phenolic ring is responsible for hydrogen atom transfer reaction, the hydroxyl group forms a phenoxy radical by transferring its hydrogen atom to a free radical, which contributes to the free radical scavenging properties. This phenoxy radical is highly resonance stabilized because the unpaired electron is able to delocalize across the oxygen to the phenolic ring and α , β -unsaturated carbonyl moiety. (2) The presence of α , β -unsaturated carbonyl moiety of γ -oryzanol is responsible for its electrophilicity. This carbonyl group can delocalize an electron across the oxygen to the olefin, inducing a partial cation (positive charge) at the (olefin) carbon atom, thereby providing this carbon atom an electrophilicity to attract electrons and nucleophiles particularly cysteine residues of Keap1, leading to Nrf2 nuclear translocation and in turn Nrf2-ARE activation.

6. Concluding Remarks

The concept of food and its bioactive nutrients to maintain nucleophilic tone restoring redox homeostasis is of great interest in preventing pathology and even in curing chronic diseases. The fact that these natural compounds, including γ -oryzanol, have been demonstrated as Nrf2 inducers provides new insights into their mechanisms of actions supporting and encouraging their use. Indeed, γ -oryzanol is already used as a prescription drug in Japan to treat various conditions such as hyperlipidemia, irritable bowel syndrome, autonomic ataxia, and menopausal syndrome [224–226]. Γ -Oryzanol is certainly a promising natural dietary compound, being present in high amounts in the principal grain of human diet.

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