Nutrition 31 (2015) 430–436

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Therapeutic value of oral supplementation with melon superoxide dismutase and wheat gliadin combination

Susana Romao Ph.D. *

Viral Immunobiology Lab, Institute of Experimental Immunology, University of Zurich, Switzerland

ARTICLE INFO

Article history:
Received 14 May 2014
Accepted 18 October 2014

Keywords:
Antioxidant
Gliadin
Nutrition
Reactive oxygen species
Superoxide anion
Superoxide dismutase

ABSTRACT

Dietary antioxidant supplementation has been popular in Western countries. Various supplements have been developed in recent years, and research has been gathered from both animal and clinical research trials. In this review, the therapeutic value of oral administration of a combination of melon superoxide dismutase (SOD) and a vegetable polymer (gliadin) is evaluated. Critical examination of the effects of SOD–gliadin supplementation is carried out, with an emphasis on its impact on oxidative stress levels and on endogenous antioxidant pathways. Overall analysis of peer-reviewed published data suggests that intake of SOD–gliadin might have advantageous health effects. These conclusions are dependent on the condition or pathology under consideration. In general, the authors, who analyzed SOD-gliadin supplementation, support the use of SOD–gliadin supplementation as a complementary treatment rather than a therapeutic treatment. To further clarify the importance of dietary SOD–gliadin administration, additional large-scale clinical trials are recommended.

Introduction

The availability of oxygen determines the evolution of complex multicellular organisms. However, oxygen metabolism also generates toxic byproducts called reactive oxygen species (ROS). ROS can cause cellular damage through the oxidation of several essential molecules such as proteins, lipids, or DNA. This is a paradox of aerobic life; although oxygen is an absolute necessity, oxidation is the necessary consequence.

ROS comprise all chemically reactive molecules derived from oxygen. Superoxide anion ($O_2^{\bullet -}$) is the product of a one-electron reduction of molecular oxygen (O_2) and the precursor of all other ROS. Because it is both an anion and a free radical, $O_2^{\bullet -}$ is a very short-lived molecule that can only cross cell membranes through anionic channels. In biological systems, $O_2^{\bullet -}$ diffusion is limited by its rapid dismutation into hydrogen peroxide (H_2O_2) by SOD enzymes [1] or by its combination with nitric oxide to form peroxynitrite [2]. Therefore, $O_2^{\bullet -}$ probably does not cause direct cellular oxidative damage but is certainly crucial to propagate oxidative chain reactions involving highly cytotoxic molecules. In humans, 1% to 3% of all O_2 consumed by the body is transformed into $O_2^{\bullet -}$ [3]. There are three main in vivo sources for $O_2^{\bullet -}$ formation: 1) mitochondrial respiratory chain complexes [4], 2) nicotinamide adenine dinucleotide phosphate-oxidase (NOX) enzymes [5], and 3) xanthine oxidases [6] (Fig. 1). Although all eukaryotic cells depend on mitochondrial activity, only phagocytes and endothelial cells express NOX enzymes. In this case, ROS are primarily used as defense mechanisms against invading pathogens, through release into specialized degradative compartments.

In recent years, increasing evidence demonstrated that in addition to their cytotoxic activity, ROS perform a regulatory function in cellular homeostasis [7]. Redox signaling, distinct from oxidative damage, is associated with low concentrations of oxidants that reversibly modify specific cell targets to transduce a message [8]. To determine which ROS function will act in a certain cellular context, cells manage a delicate oxidation balance. To achieve the appropriate redox stoichiometry, complex protective mechanisms have evolved for controlling the levels of ROS rather than completely eliminating them. Antioxidant activity can occur by direct scavenging of ROS, by limiting the production of oxidants, or by increasing antioxidant defenses in the cell [9]. Antioxidants such as SOD, catalase (CAT) or glutathione peroxidase (GPx) can be synthesized in vivo, and some nonenzymatic antioxidants can be ingested through the diet (e.g., β-carotene or α-tocopherol) [9].

Consultation and manuscript preparation was funded by Isocell Nutra, which produces and commercializes SOD–gliadin supplements (GliSODin®).
* Corresponding author: Tel: +41 44 635 3712; fax: +41 44 635 6883.
E-mail address: susana.romao@uzh.ch

http://dx.doi.org/10.1016/j.nut.2014.10.006

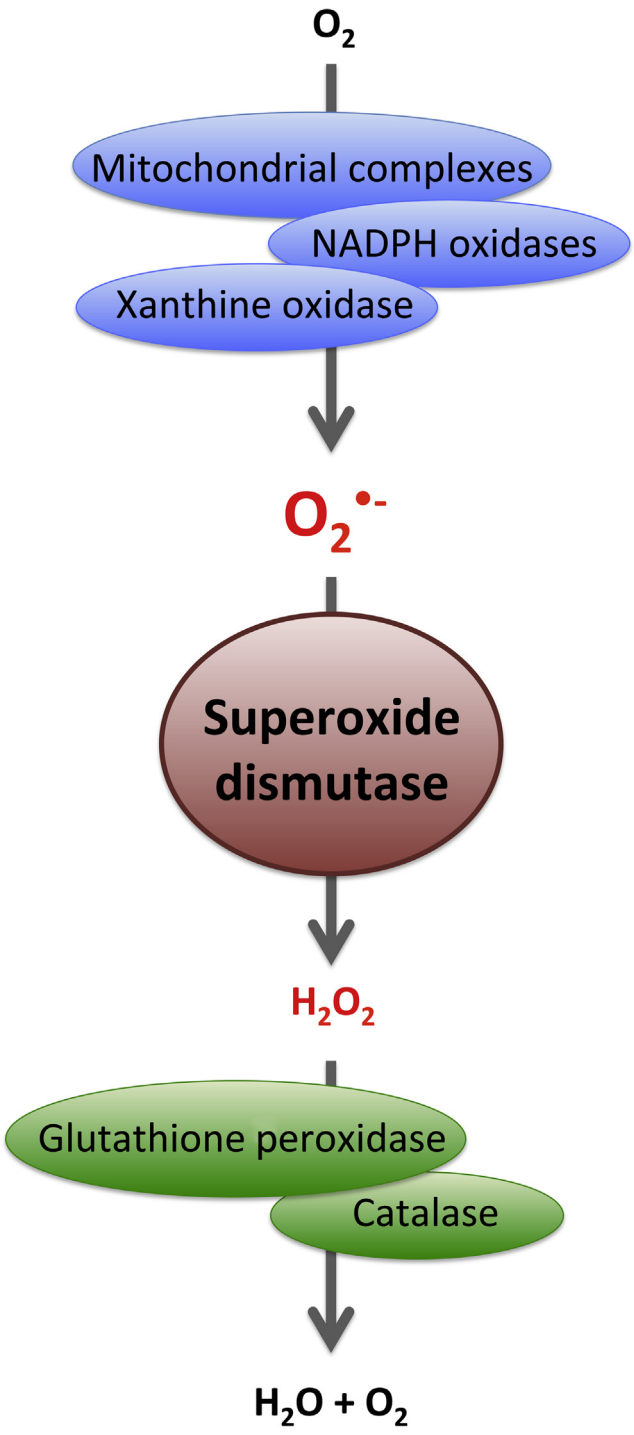

Fig. 1. Schematic representation showing a possible enzymatic cascade for transformation of molecular oxygen (O_2) in eukaryotic cells. Enzymatic conversion of O_2 into superoxide anion ($O_2^{\bullet -}$) can be carried out by the mitochondrial respiratory complexes, by NADPH oxidase or by xanthine oxidases. Superoxide dismutases are responsible for further transformation of $O_2^{\bullet -}$ to H_2O_2. Finally, enzymes such as catalase or glutathione peroxidases are capable of converting H_2O_2 into H_2O and O_2. H_2O_2, hydrogen peroxide; NADPH, nicotinamide adenine dinucleotide phosphate.

It is well established that consumption of antioxidant-rich foods such as fruits and vegetables correlates to an overall positive health status [10]. Broad acceptance of this relationship has been responsible for the steady growth of the dietary supplement industry. However, one must be cautious when analyzing the effectiveness of such compounds, especially in a therapeutic context. Many clinical trials have failed to demonstrate that supplementation with direct-acting antioxidants, especially with the antioxidant vitamin family, could protect against disease. One possible explanation for these disappointing results is connected to a reduced bioavailability or absence of sustained long-term activity of orally administered antioxidants [9]. Alternatively, supplementation with antioxidants might simply perturb the important physiological redox balance and affect normal cellular function [11].

The purpose of this review was to summarize research data published in the last decade on the effects of oral supplementation with plant-derived SOD. Specifically, I focused on a formulation that uses cantaloupe melon–derived SOD combined with gliadin from wheat extract. The potential benefits of SOD–gliadin on steady-state and pathologic settings are described here.

Superoxide dismutase

The SOD enzyme catalyzes the conversion of $O_2^{\bullet -}$ to H_2O_2 and O_2, and is ubiquitous in every aerobic organism, from bacteria to humans. Biochemists Joe McCord and Irwin Fridovich were the first to discover its enzymatic activity and to suggest its essential role in protecting organisms against damage by ROS [12]. SOD is a metalloenzyme, and depending on the particular form of the enzyme, requires cofactors copper and zinc, manganese, iron, or nickel. There are three isoforms of SOD in humans: a cytosolic copper-zinc-SOD (SOD1), a mitochondrial manganese-SOD (SOD2), and an extracellular copper-zinc-SOD (SOD3) [1]. Because H_2O_2 is a coproduct of SOD catalysis and is itself a ROS, the isolated activity of SOD cannot be viewed as antioxidant, but rather as pro-oxidant. However, the accumulation of H_2O_2 was linked to up-regulation of key antioxidant enzymes such as CAT and GPx (Fig. 1) [13,14]. Therefore, it was proposed that increased SOD activity could stimulate other antioxidant enzymes by enhancing oxidative stress signals [15,16]. In this context, because SOD is not consumed upon detoxification of ROS, supplementation with SOD seems to be advantageous over nonenzymatic antioxidants such as vitamins, carotenoids, and thiols. It might also trigger the endogenous antioxidant machinery.

Interestingly, SOD supplementation efficacy seems to depend on the source of the enzyme. For example, in a mouse model, murine SOD is less likely to have an effect compared with SOD from another species. In a study comparing human, bovine, and rat SOD in a rat experimental model, the human and bovine enzymes, despite presenting similar biochemical properties, conferred much higher pharmacologic activity [17]. Therefore, treatment of human disorders with human enzyme will probably also not yield any beneficial effects. Classically, bovine SOD was used for experimental research [12] as well as in early clinical trials to test SOD administration effects on several human disorders [18,19]. With the outbreak of Creutzfeldt-Jacob disease, bovine-derived products for human consumption were limited, and suitable alternatives were developed from plant-extracted forms of SOD. In this context, a variety of nongenetically modified cantaloupe melon (*Cucumis melo* L.C.) presents particularly high levels of SOD (100 U/mg) and a lesser extent of other antioxidant elements (e.g., 10 U/mg CAT and 1 U/mg GPx) [20,21], which makes it an appropriate source for this enzyme.

Since 2000, melon extract with naturally enriched SOD has been developed for use as a dietary supplement. However, due to the low pH and high proteolytic activity in the digestive tract, oral administration of the SOD enzyme alone renders it

chemically inactive and thus ineffective. To demonstrate this, a study was conducted that assessed the enzymatic activity of free melon-derived SOD in a medium mimicking the digestive milieu [15]. To circumvent this bioavailability problem, several research groups designed different coatings to encapsulate SOD, mainly using lipids and proteins. Liposomal encapsulation was one of the first strategies successfully applied to protect bovine SOD from inactivation. As tested previously [22], the maximum bioavailability after ingestion of liposomal-encapsulated SOD increased up to fourfold. Specific formulations with melon extract also can be found in the literature. The most extensively studied SOD coating is wheat-derived gliadin (Tables 1 and 2). Importantly, wheat gliadin was shown to protect SOD from gastric degradation [15] while simultaneously displaying bio-adhesion properties [23]. This change in bio-adhesion could potentially enhance the adherence of the enzyme to the epithelium of the small intestine, thus prolonging SOD intestinal association. Because SOD is a high-molecular-weight protein, absorption at the small intestine is unlikely. Although gliadin activated a tight-junction regulating protein that could increase intestinal permeability [24], there is no evidence to support the ability of SOD to cross the intestinal barrier.

Hereafter, the terms *protected SOD, encapsulated SOD, coated SOD*, and *bioactive SOD* are used interchangeably and refer to the SOD–gliadin formulation that resists gastrointestinal inactivation.

Beneficial health aspects of SOD–gliadin oral administration

ROS have been implicated in a range of pathologies such as cancer, cardiovascular diseases (CVDs), degenerative diseases, and infectious diseases [7]. For many scientists studying ROS-related disorders, the manipulation of antioxidant levels offers the possibility to ameliorate particular conditions. Two of the most cited publications on supplementation with melon SOD extract are from the research groups of Xavier Leverve [25] and Bernard Dugas [21]. In the first study, 20 healthy volunteers were tested to determine whether SOD combined with gliadin could prevent cellular damage after induction of oxidative stress. The experimental design included a daily dose of SOD–gliadin (1000 U SOD activity) or placebo for 14 d before exposure to 100% O_2 in a hyperbaric chamber for 60 min. Hyperbaric oxygen (HBO) therapy is used to treat a variety of diseases, however, it also may cause adverse effects. DNA damage is a well-documented side effect of HBO and can be monitored using a single-cell gel electrophoresis or "comet assay" [26]. Therefore, participants in this study were tested for DNA damage, and the results showed a significant decrease in DNA strand breaks in the SOD–gliadin-treated group compared with the placebo group. Additionally, treated participants also demonstrated a diminished concentration of plasma markers for oxidative stress. Other parameters, such as SOD, CAT, and GPx activity levels in the blood remained mainly unchanged. In the second study of melon SOD–gliadin supplementation, Vouldoukis et al. [21] also tested the efficacy of the product as a redox modulator. For this, murine macrophages were activated with interferon (IFN)-γ and subsequently challenged with immunoglobulin (Ig) G1 immune complexes (IC) to induce $O_2^{\bullet -}$ production. First, the authors confirmed that the crude melon extract could demonstrate antioxidant capacity in vitro by eliminating $O_2^{\bullet -}$ production in activated macrophages in a dose-dependent manner. Moreover, cells isolated from animals treated daily with SOD–gliadin for 28 d produced threefold less $O_2^{\bullet -}$ in response to IFN-γ/IgG1-IC activation as assessed by ferricytochrome C reduction. Importantly, neither unprotected SOD nor gliadin alone could reduce oxidant production in the same assay. Subsequently, a number of other publications presented data examining the effects of orally active SOD–gliadin supplementation both in experimental and clinical research. For simplicity, these studies are grouped here by the similarity of the model or the condition examined.

Baseline antioxidant capacity

As a proof of principle, scientists have determined whether gliadin-coated SOD had an effect on general antioxidant defenses in the absence of a pathologic condition. An increase in endogenous SOD activity was registered for mice treated with SOD–gliadin for 28 d [15]. As expected, if mice were supplemented with either uncoated SOD or gliadin alone, treatment had no influence on antioxidant defenses, strengthening the idea that the protective effect of SOD is only possible upon effective

Table 1
Summary of recent human research studies on SOD–gliadin dietary intake effects

Condition	Model	Supplementation	Effects	No effects	Other notes	Study
Hyperbaric oxygen-related cell damage	Human (N = 20)	SOD–gliadin 14 d 1000 U-NBT/d	↓DNA damage ↓Isoprostane blood levels	SOD or CAT levels in blood	Participants were professional divers	[25]
Atherosclerosis	Human (N = 34)	SOD–gliadin 2 y 500 U-NBT/d	↑SOD and CAT activity in blood ↓Carotid artery IMT ↓Oxidative stress in blood	Blood pressure or cholesterol levels	Participants had risk factors for atherosclerosis. Participants also under rigorous diet	[16]
Fatigue	Human (N = 38)	SOD–gliadin 12 wk 500 mg/d		Perceived fatigue, SOD activity in blood or oxidative stress	SOD–gliadin activity not tested before randomization. Study on women (aged 50–65 y) with longstanding unexplained fatigue	[37]
Actinic erythema	Human (N = 49)	SOD–gliadin 4 wk	↓Skin redness ↑Capillary network ↑MED score for phototype II	Erythema clinical score	Healthy participants exposed to solar simulator	[38]
Intensive physical exercise	Human (N = 19)	SOD–gliadin 6 wk 500 mg/d	↑SOD activity in blood ↓Serum levels of C-reactive protein ↓Oxidative damage in muscle	GPx blood levels	Participants were athletes subject to 2000 m rowing test	[39]

CAT, catalase; GPx, glutathione peroxidase; IMT, intima media thickness; MED, minimal erythema dose; NBT, nitroblue tetrazolium; SOD, superoxide dismutase; ↑, increased ↓, decreased.
None of the studies reported adverse side effects of oral supplementation with SOD.

Table 2
Summary of recent animal research studies on SOD–gliadin dietary intake effects

Condition	Model	Supplementation	Effects	No effects	Other notes	Study
IFN-γ/IgG1 IC activated Mφ	C57 BL/6 mice (ex vivo and in vivo)	SOD–gliadin 28 d 5 U-NBT/d	↓ $O_2^{\bullet -}$ production in cell cultures ↓TNF-α in cell cultures ↑IL-10 in cell cultures	n.s.		[21]
Baseline healthy status	Balb/c mice (in vivo)	SOD–gliadin 28 d 0.1–5 mg/d	↑SOD activity in blood and liver ↑CAT, GPx activity in blood ↑RBCs resistance to hemolysis ↓Hepatocytes apoptosis	n.s.	Shows protection of SOD–gliadin in digestive track mimicking conditions	[15]
Type 2 diabetes	*db/db* mice (in vivo)	SOD–gliadin 12 wk	↓Albumin levels in urine ↓Oxidative stress in kidney	Body weight or glucose levels		[28]
Type 2 diabetes	Wistar rats (ex vivo and in vivo)	SOD–gliadin 4 wk	↑SOD and CAT activity in heart ↑GSH levels in cardiac muscle ↓Cardimyocytes apoptosis ↓LPO in plasma	n.s.	Effects reported for SOD–gliadin-treated diabetic rats were compared with diabetic control animals	[29]
Ischemia/reperfusion injury	Aortic cross-clamping in pigs	SOD–gliadin 14 d 1250 U/d	↓DNA damage ↓Apoptotic cells in spinal cord	SOD, CAT, GPx levels in blood	No ameliorated organ function	[32]
Fibrosarcoma	C57 BL/6 mice (ex vivo and in vivo)	SOD–gliadin 30 d 10 mg/kg•d^{-1}	↑SOD activity in tumors ↓Metastasis development ↓Oxidative stress in tumors	SOD activity in blood Infiltrating cells in tumors Tumor incidence	Effects are lost after intraperitoneal administration of SOD–gliadin. Tendency for reduction on tumor growth with supplementation	[34]
Viral infection	FIV-infected cats	SOD–gliadin 30 d 100 mg/d	↑SOD activity in blood ↑CD4/CD8 ratio	GPx levels or oxidative stress in blood		[35]
Cognitive memory	C57 BL/6 mice	SOD–gliadin 5 wk 100 mg/kg•d^{-1}	↓LPO in hippocampal neurons ↓Escape latency time ↑Neurogenesis	Body weight. Only slight increase on hippocampal SOD activity levels	Animal model of stress-induced impairment of spatial memory	[36]

CAT, catalase; FIV, feline immunodeficiency virus; GPx, glutathione peroxidase; IFN-γ/IgG1 IC, interferon-γ/immunoglobulin G1 immune complexes; IL, interleukin; LPO, lipid peroxidation; Mφ, macrophage; n.s., not stated; $O_2^{\bullet -}$, superoxide anion; RBC, red blood cell; SOD, superoxide dismutase; TNF, tumor necrosis factor; ↑, increased ↓, decreased.
None of the studies reported adverse side effects of oral supplementation with SOD.

gastrointestinal bioavailability of the compound. Moreover, other antioxidant defenses such as CAT and GPx were also increased in the plasma and livers of mice. Other assays designed to monitor alterations in cellular resistance to oxidative stress suggest that SOD–gliadin intake might also influence cell survival. This was shown by a decrease in hepatocyte apoptosis (20% versus 72% in the control group) and an increased resistance to hemolysis of erythrocytes and to mitochondrial membrane depolarization upon challenge with 3-morpholinosydnonimine [15].

Metabolic disorders

Several authors have addressed bioactive SOD supplementation in the context of metabolic diseases. In the case of diabetes, a condition that is usually associated with increased oxidative stress, dietary antioxidants (vitamins C and E) could diminish vascular complications without affecting blood glucose or insulin levels [27]. One study [28] analyzed SOD–gliadin administration in a diabetic dyslipidemia (*db/db*) mouse model for type 2 diabetes. This study focused on diabetic nephropathy, a common complication of the disease, and revealed an overall improvement in kidney function. Two lines of evidence support this conclusion. First, there is a significant decrease in oxidative stress biomarkers in the kidney and urine of SOD–gliadin supplemented animals compared with control animals. Measurement of 8-hydroxydeoxyguanosine, a common marker for oxidative stress–derived DNA damage, was used to assess this. Second, urinary albumin excretion, a risk factor for kidney failure, was also inhibited by treatment with SOD–gliadin. Similar to other studies, blood glucose and body weight values did not change during treatment. A recent report using a diabetic rat model demonstrated that SOD–gliadin treatment decreases oxidative stress levels in heart tissue and may also reduce cardiac apoptosis caused by diabetes [29].

Cardiovascular diseases

Several lines of evidence indicate that cardiovascular pathologies are associated with ROS overproduction [30]. Results from animal studies encouraged researchers to pursue antioxidant treatment to reduce the risk for CVD. For instances, *Sod1*$^{-/-}$ mutant mice, which do not exhibit cytoplasmic SOD activity, were shown to be more susceptible to ischemia/reperfusion (I/R) injury [31]. Interestingly, a study conducted in a porcine model of aortic cross-clamping suggested that I/R-related DNA damage

was reduced after pretreatment with SOD–gliadin for 2 wk [32]. Additionally, the study demonstrated a trend toward a reduction in the number of apoptotic cells in the spinal cords of SOD–gliadin-treated animals, in agreement with its protective effect against I/R injury. Despite these encouraging results, an analysis of the kidneys, a vulnerable organ during I/R, did not display the same cell survival phenotype. This, together with a lack of evidence for improved organ function, impeded the authors from clearly confirming a potential clinical use for SOD–gliadin in I/R injury. Nonetheless, the examined parameters point toward the use of encapsulated-SOD as a preventive auxiliary treatment, preferably administered before surgeries involving aortic cross clamping.

Some authors have also addressed specific vascular disorders such as atherosclerosis. A research study on individuals at risk for developing atherosclerosis demonstrated a striking difference between the control and the protected SOD–supplemented group when examining carotid thickness [16]. Individuals receiving SOD–gliadin daily (500 U SOD activity) or placebo for a period of 2 y were subjected to B-scan ultrasonography to measure the intima media thickness (IMT), a standard detection method for atherosclerotic lesions. Decreased carotid IMT measurements were seen in patients after 365 d of treatment with SOD–gliadin. Moreover, the supplemented group registered an increase in SOD and CAT levels in the blood compared with the placebo group. Additionally, lipid peroxidation, used as a measurement of oxidative stress, was reduced after SOD–gliadin intake. Together, these data suggest a potential role for SOD–gliadin supplementation in the prevention of atherosclerotic lesions, possibly through its general antioxidant action.

Inflammation and cancer

Chronic induction of ROS is linked to inflammation, which can mediate other pathologies such as cancer [33]. Tumor cells display reduced SOD activity and overexpression of this enzyme can decrease malignancy [34]. A report on a mouse model for fibrosarcoma proposes that the SOD–gliadin complex decreases metastasis development, which is correlated with a reduction of oxidative stress in the tumor tissue [34]. In this cancer model, QR-32 tumor cells and a gelatin sponge were co-implanted to promote both inflammation and tumor development in C57 BL/6 mice. In tumors from the SOD–gliadin-treated group, SOD activity was considerably increased (approximately twofold). However, no differences were registered for inflammatory cell infiltration at the tumor site. Additionally, although primary tumor growth was not significantly altered, metastatic potential could be inhibited in tumor cells derived from SOD–gliadin-treated animals. In 2004, results from a study claimed that the SOD–gliadin formulation has anti-inflammatory properties [21]. The assumptions were based on the observation that in murine models, encapsulated SOD supplementation induced interleukin-10 production. Up-regulation of this antiinflammatory cytokine also resulted in decreased production of tumor necrosis factor-α, therefore reducing proinflammatory responses.

Infection

Feline immunodeficiency virus (FIV) is a suitable animal model for its human homolog, HIV/AIDS. A study aiming at investigating the effects of melon protected SOD intake on FIV-infected cats concluded that SOD–gliadin treatment could play a role in preventing disease progression [35]. Although viral loads were not changed between supplemented and unsupplemented groups, CD4/CD8 ratios increased significantly, indicating disease progression. Classically, FIV infection drives CD4 T-cell depletion; thus, the effects observed after melon coated SOD administration might possibly represent an effect of this supplementation on the survival of CD4 T cells. Nevertheless, to clearly elucidate the role of melon-derived SOD intake in infection, it is essential to await investigations in other infectious disease models.

Brain function

The effects of coated SOD ingestion on cognition are also documented. For example, stress-induced impairment of cognitive memory was alleviated by SOD–gliadin treatment in a C57 BL/6 model [36]. In these experiments, stress was induced by physical restraint daily for 12 h over the course of 5 wk. During this period, animals either received a normal diet or a diet supplemented with SOD–gliadin. After 5 wk, lipid peroxidation in the brain was markedly reduced with supplementation. More importantly, spatial learning, which was affected in the control group, improved in the SOD-treated group. Another attempt to clarify the role of SOD administration in brain function was undertaken in a study of women aged 50 to 65 y with longstanding unexplained fatigue [37]. The women were were subjected to SOD–gliadin supplementation or placebo for 12 wk (500 mg). Perceived fatigue scores were registered throughout the assay by periodic interviews. In this tested group, SOD–gliadin treatment had no influence in fatigue-level scores. The lack of phenotype might be explained by the absence of antioxidant activity of SOD supplementation in this particular protocol. Indeed, the authors stated that enzymatic activity was not measured previously to randomization, which might have compromised the assay. For this reason, future studies are needed to clearly elucidate the influence of protected SOD ingestion in human fatigue and stress.

Others

The beneficial effects of dietary melon SOD combined with gliadin in other health-related areas also have been considered. For instance, oxidative skin damage as a result of ultraviolet (UV) exposure can be ameliorated by SOD–gliadin treatment. This was reported in a human study where participants from different phototypes were tested for UV-induced skin redness [38]. Compared with the control group, SOD-treated phenotype II participants showed an increase in the minimum amount of UV radiation needed to induce sunburn, together with a faster recovery from induced redness.

Sports nutrition is another area in which antioxidants have traditionally been studied. Reports exist evaluating the effect of SOD–gliadin supplementation on intensive physical exercise. A clinical trial was performed during which volunteer professional athletes were subjected to daily treatment with SOD–gliadin (500 mg) or placebo for 6 wk [39]. In this study, blood samples were drawn from the athletes after a 2000-m rowing exercise test. Results showed increased SOD activity in the blood and also demonstrated differences in certain oxidation markers in the muscle. In addition, C-reactive protein levels were diminished in the SOD-treated group, suggesting the activation of anti-inflammatory pathways. Thus, these data show a trend toward a beneficial effect of SOD–gliadin supplementation during intense physical activity.

Mechanism of action for SOD–gliadin

Apart from its direct capacity to detoxify $O_2^{\bullet -}$, oral supplementation with melon SOD combined with wheat gliadin was shown to increase endogenous antioxidant defenses. However, experimental data defining a detailed mechanism of action for oral administration of coated SOD are yet to be presented. One could speculate that the systemic effects reported after SOD intake arise from a cascade of events that is initiated at the small intestine, where SOD is released. Such events might depend on the transactivation of transcription factors through the antioxidant response element (ARE)/nuclear factor E2-related factor (Nrf2) axis [40]. Others have hypothesized a role for nitric oxide (NO) [36]. In this case, NO might be generated at the intestines and later released in the blood as a response to non–self-SOD–gliadin. Because NO is a known key biological messenger and can freely diffuse through tissues, it is reasonable to assume that it may also transduce the SOD–gliadin-mediated signal from the intestine into target cells. This hypothesis has not yet been experimentally addressed.

The ARE/Nrf2 and the NO mechanisms just mentioned also might be related. This is supported by some evidence in the literature that suggests that NO may modulate the expression of antioxidant genes through the ARE/Nrf2 axis [41,42]. A recent study hypothesized that specific genotypes might also determine the type of effect induced by antioxidant-rich diets [43]. Although this particular report was only performed during a 2-wk period using a limited number of volunteers, it would be interesting to follow up on this concept.

Conclusions

Few subjects divide the scientific nutrition community as much as antioxidant supplementation. Due to mixed results and to the complexity of the redox pathways, it is not prudent to generalize about beneficial effects of antioxidant compounds for all situations. The purpose of this review was to perform a methodical analysis of recent findings on antioxidant supplementation, with a specific focus on the administration of melon SOD combined with wheat gliadin. According to peer-reviewed published data, this particular protected melon SOD formulation appears to have advantageous effects on conditions that call for an increased expression of antioxidant enzymes. Such conditions are often oxidative stress-driven pathologies like CVDs, or special physiological situations like the practice of intensive sports. Bioactive melon SOD oral intake might represent a meaningful quality-of-life improvement. Additionally, it is important to emphasize that most studies on the SOD–gliadin formulation indicate that supplementation presents auxiliary effects rather than curative properties. Notably, there are no reports on adverse side effects of oral SOD–gliadin supplementation. Nevertheless, large-scale experimental trials should be carried out to reinforce the recommendation for dietary intake of gliadin-coated melon-derived SOD.

References

[1] Fridovich I. Superoxide radical and superoxide dismutases. Annu Rev Biochem; 1995:97–112.
[2] Radi R, Peluffo G, Alvarez MN, Naviliat M, Cayota A. Unraveling peroxynitrite formation in biological systems. Free Radic Biol Med 2001;30:463–88.
[3] Fang YZ, Yang S, Wu G. Free radicals, antioxidants, and nutrition. Nutrition 2002;18:872–9.
[4] Turrens JF. Mitochondrial formation of reactive oxygen species. J Physiol 2003;552:335–44.
[5] Segal BH, Grimm MJ, Khan ANH, Han W, Blackwell TS. Regulation of innate immunity by NADPH oxidase. Free Radic Biol Med 2012;53:72–80.
[6] Kuppusamy P, Zweier JL. Characterization of free radical generation by xanthine oxidase. Evidence for hydroxyl radical generation. J Biol Chem 1989;264:9880–4.
[7] Brieger K, Schiavone S, Miller FJ Jr, Krause KH. Reactive oxygen species: from health to disease. Swiss Med Wkly 2012;142:w13659.
[8] Bindoli A, Rigobello MP. Principles in redox signaling: From chemistry to functional significance. Antioxid Redox Signal 2013;18:1557–93.
[9] Halliwell B. Biochemistry of oxidative stress. Biochem Soc Trans 2007;35:1147.
[10] Vetrani C, Costabile G, Di Marino L, Rivellese AA. Nutrition and oxidative stress: A systematic review of human studies. Int J Food Sci Nutr 2013;64:312–26.
[11] Bjelakovic G, Gluud C. Surviving antioxidant supplements. J Natl Cancer Inst 2007;99:742–3.
[12] McCord JM, Fridovich I. Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein). J Biol Chem 1969;244:6049–55.
[13] Nelson SK, Bose SK, Grunwald GK, Myhill P, McCord JM. The induction of human superoxide dismutase and catalase in vivo: a fundamentally new approach to antioxidant therapy. Free Radic Biol Med 2006;40:341–7.
[14] Goyal MM, Basak A. Human catalase: looking for complete identity. Protein Cell 2010;1:888–97.
[15] Vouldoukis I, Conti M, Krauss P, Kamaté C, Blazquez S, Tefit M, et al. Supplementation with gliadin-combined plant superoxide dismutase extract promotes antioxidant defences and protects against oxidative stress. Phytother Res 2004;18:957–62.
[16] Cloarec M, Caillard P, Provost JC, Dever JM, Elbeze Y, Zamaria N. GliSODin, a vegetal sod with gliadin, as preventative agent versus atherosclerosis, as confirmed with carotid ultrasound-B imaging. Eur Ann Allergy Clin Immunol 2007;39:45–50.
[17] Baret A, Jadot G, Michelson AM. Pharmacokinetic and antiinflammatory properties in the rat of superoxide dismutases (Cu SODs and Mn SOD) from various species. Biochem Pharmacol 1984;33:2755–60.
[18] Stern LZ, Ringel SP, Ziter FA, Menander-Huber KB, Ionasescu V, Pellegrino RJ, et al. Drug trial of superoxide dismutase in Duchenne's muscular dystrophy. Arch Neurol 1982;39:342–6.
[19] Rosenfeld W, Evans H, Concepcion L, Jhaveri R, Schaeffer H, Friedman A. Prevention of bronchopulmonary dysplasia by administration of bovine superoxide dismutase in preterm infants with respiratory distress syndrome. J Pediatr 1984;105:781–5.
[20] Carillon J, Del Rio D, Teissèdre PL, Cristol JP, Lacan D, Rouanet JM. Antioxidant capacity and angiotensin I converting enzyme inhibitory activity of a melon concentrate rich in superoxide dismutase. Food Chemistry 2012;135:1298–302.
[21] Vouldoukis I, Lacan D, Kamaté C, Coste P, Calenda A, Mazier D, et al. Antioxidant and antiinflammatory properties of a Cucumis melo LC. extract rich in superoxide dismutase activity. J Ethnopharmacol 2004;94:67–75.
[22] Regnault C, Soursac M, Roch-Arveiller M, Postaire E, Hazebroucq G. Pharmacokinetics of superoxide dismutase in rats after oral administration. Biopharm Drug Dispos 1996;17:165–74.
[23] Arangoa MA, Ponchel G, Orecchioni AM, Renedo MJ, Duchêne D, Irache JM. Bioadhesive potential of gliadin nanoparticulate systems. Eur J Pharm Sci 2000;11:333–41.
[24] Lammers KM, Lu R, Brownley J, Lu B, Gerard C. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. Gastroenterology 2008;135:194–204.
[25] Muth CM, Glenz Y, Klaus M, Radermacher P, Speit G, Leverve X. Influence of an orally effective SOD on hyperbaric oxygen-related cell damage. Free Radic Res 2004;38:927–32.
[26] Gröger M, Radermacher P, Speit G, Muth CM. Genotoxicity of hyperbaric oxygen and its prevention: what hyperbaric physicians should know. Diving Hyperb Med 2008;38:200–5.
[27] Chang YC, Chuang LM. The role of oxidative stress in the pathogenesis of type 2 diabetes: From molecular mechanism to clinical implication. Am J Transl Res 2010;2:316–31.
[28] Naito Y, Akagiri S, Uchiyama K, Kokura S, Yoshida N, Hasegawa G, et al. Reduction of diabetes-induced renal oxidative stress by a cantaloupe melon extract/gliadin biopolymers, oxykine, in mice. Biofactors 2004;23:85–95.
[29] Trea F, Ouali K, Baba-Ahmed F, Kadi Y. Glisodin®, a melon extract that attenuates cardiac cell death via suppression of oxidative stress in the heart of Wistar rat with streptozotocin-induced diabetes. Phytothérapie 2013;11:339–47.
[30] Förstermann U. Oxidative stress in vascular disease: causes, defense mechanisms and potential therapies. Nat Clin Pract Cardiovasc Med 2008;5:338–49.
[31] Kawase M, Murakami K, Fujimura M, Morita-Fujimura Y, Gasche Y, Kondo T, et al. Exacerbation of delayed cell injury after transient global ischemia in mutant mice with CuZn superoxide dismutase deficiency. Stroke 1999;30:1962–8.
[32] Kick J, Hauser B, Bracht H, Albicini M, Öter S, Simon F, et al. Effects of a cantaloupe melon extract/wheat gliadin biopolymer during aortic cross-clamping. Intensive Care Med 2007;33:694–702.

[33] Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? Free Radic Biol Med 2010;49:1603–16.
[34] Okada F, Shionoya H, Kobayashi M, Kobayashi T, Tazawa H, Onuma K, et al. Prevention of inflammation-mediated acquisition of metastatic properties of benign mouse fibrosarcoma cells by administration of an orally available superoxide dismutase. Br J Cancer 2006;94:854–62.
[35] Webb CB, Lehman TL, McCord KW. Effects of an oral superoxide dismutase enzyme supplementation on indices of oxidative stress, proviral load, and CD4:CD8 ratios in asymptomatic FIV-infected cats. J Feline Med Surg 2008;10:423–30.
[36] Nakajima S, Ohsawa I, Nagata K, Ohta S, Ohno M, Ijichi T, et al. Oral supplementation with melon superoxide dismutase extract promotes antioxidant defences in the brain and prevents stress-induced impairment of spatial memory. Behav Brain Res 2009;200:15–21.
[37] Houghton CA, Steels EL, Fassett RG, Coombes JS. Effects of a gliadin-combined plant superoxide dismutase extract on self-perceived fatigue in women ages 50–65 y. Phytomedicine 2011;18:521–6.
[38] Mac-Mary S, Sainthillier JM, Courderotmasuyer C, Creidi P, Humbert P. Could a photobiological test be a suitable method to assess the antioxidant effect of a nutritional supplement Glisodin? Eur J Dermatol 2007;17:254–5.
[39] Skarpanska-Stejnborn A, Pilaczynska-Szczesniak L, Basta P, Deskur-Smielecka E, Woitas-Slubowska D, Adach Z. Effects of oral supplementation with plant superoxide dismutase extract on selected redox parameters and an inflammatory marker in a 2,000-m rowing-ergometer test. Int J Sport Nutr Exerc Metab 2011;21:124–34.
[40] Carillon J, Rouanet JM, Cristol JP, Brion R. Superoxide dismutase administration, a potential therapy against oxidative stress related diseases: several routes of supplementation and proposal of an original mechanism of action. Pharm Res 2013;30:2718–28.
[41] Dhakshinamoorthy S, Porter AG. Nitric oxide-induced transcriptional up-regulation of protective genes by Nrf2 via the antioxidant response element counteracts apoptosis of neuroblastoma cells. J Biol Chem 2004;279:20096–107.
[42] Siow RCM, Li FYL, Rowlands DJ, de Winter P, Mann GE. Cardiovascular targets for estrogens and phytoestrogens: transcriptional regulation of nitric oxide synthase and antioxidant defense genes. Free Radic Biol Med 2007;42:909–25.
[43] Yuan L, Zhang L, Ma W, Zhou X, Ji J, Li N, et al. Glutathione S-transferase M1 and T1 gene polymorphisms with consumption of high fruit-juice and vegetable diet affect antioxidant capacity in healthy adults. Nutrition 2013;29:965–71.