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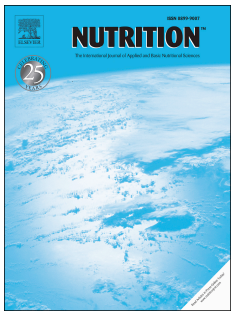

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The therapeutic value of oral supplementation with a combination of melon superoxide dismutase and wheat gliadin

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Abstract

Dietary antioxidant supplementation has been used frequently by Western society. Different supplements have been developed over the past 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 consequences 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, authors 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.

Key words: reactive oxygen species (ROS), superoxide anion ($O_2^{\bullet -}$), superoxide dismutase (SOD), gliadin, antioxidant, nutrition

Introduction

The availability of oxygen determined the evolution of complex multicellular organisms. However, oxygen metabolism also generates toxic byproducts called reactive oxygen species (ROS). These can cause cellular damage through the oxidation of several essential molecules such as proteins, lipids or DNA. This is a paradox of aerobic life; while 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 superoxide dismutase enzymes (SODs) [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 3 main in vivo sources for $O_2^{\bullet-}$ formation: i) mitochondrial respiratory chain complexes [4]; ii) NADPH oxidase (NOX) enzymes [5] and iii) xanthine oxidases [6] (Figure 1). While 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 demonstrates 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 in order 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 non-enzyme antioxidants can be ingested through the diet (e.g. β-carotene or α-tocopherol) [9].

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 impact normal cellular function [11].

The purpose of this review is to summarize research data published in the last decade on the effects of oral supplementation with plant-derived SOD. Specifically I will focus 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 pathological settings are described here.

Main text

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]. Superoxide dismutase is a metalloenzyme, and depending on the particular form of the enzyme, requires cofactors copper and zinc, manganese, iron or nickel. In humans there are 3 isoforms of SOD: a cytosolic copper-zinc-SOD (SOD1), a mitochondrial manganese-SOD (SOD2) and an extracellular copper-zinc-SOD (SOD3) [1]. Since 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 upregulation of key antioxidant enzymes such as Cat and GPx (Figure 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 non-enzymatic 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 to 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 pharmacological 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 non-genetically 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., Cat (10 U/mg), GPx (1 U/mg) [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. Vouldoukis and colleagues [15] demonstrated this by assessing enzymatic activity of free melon-derived SOD in a medium mimicking the digestive milieu. 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 by Regnault et al. [22], the maximum bioavailability after ingestion of liposomal-encapsulated SOD increased up to 4-fold. Specific formulations with melon extract can also be found in the literature. The most extensively studied SOD coating is wheat-derived gliadin (Table I and II). Importantly, wheat gliadin was shown to protect SOD from gastric degradation [15] while simultaneously displaying bioadhesion properties [23]. This change in bioadhesion could potentially enhance the adherence of the enzyme to the epithelium of the small intestine, thus prolonging SOD intestinal association. Since SOD is a high molecular weight protein, absorption at the small intestine is unlikely. Although gliadin was described to activate a tight-junction regulating protein which 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

Reactive oxygen species have been implicated in a range of pathologies such as cancer, cardiovascular diseases, degenerative diseases or 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, a trial with 20 healthy volunteers tested if SOD combined with gliadin could prevent cellular damage after oxidative stress induction. Experimental design included a daily dose of SOD-Gliadin (1000 U SOD activity) or placebo for 14 days prior to 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 may also 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, subjects 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 when compared to the placebo group. In addition, treated subjects 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 and colleagues [21] also tested the efficacy of the product as a redox modulator. For this, murine macrophages were activated with interferon-γ (IFN-γ) and subsequently challenged with IgG1 immune complexes (IC) in order 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 days produced 3-fold 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 below 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 pathological condition. An increase in endogenous SOD activity was registered for mice treated with SOD-Gliadin for 28 days [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 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 Sin-1 challenge [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 (vitamin C and E) could diminish vascular complications without affecting blood glucose or insulin levels [27]. Naito et al. [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 to control animals. This was assessed by measurement of 8-hydroxydeoxyguanosine (8-OHdG), a common marker for oxidative stress-derived DNA damage. 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 of cardiovascular disease. 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 weeks [32]. In addition, the study demonstrated a trend towards 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 towards the use of encapsulated-SOD as a preventive auxiliary treatment, preferably administered prior to surgeries involving aortic cross-clamping.

Some authors have also addressed specific vascular disorders such as atherosclerosis. A research study on human subjects at risk of developing atherosclerosis demonstrated a striking difference between the control and the protected-SOD supplemented group when examining carotid thickness [16]. Subjects receiving SOD-Gliadin daily (500 U SOD activity) or placebo for a period of 2 years were subjected to B-scan ultrasonography in order to measure the intima media thickness (IMT), a standard detection method for atherosclerotic lesions. After 365 days of treatment with SOD-Gliadin, patients had decreased carotid IMT measurements. Moreover, the supplemented group registered an increase in SOD and Cat levels in the blood when compared to the placebo group. In addition, lipid peroxidation, used as a measurement of oxidative stress, was reduced upon 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 C57BL/6 mice. In tumors from the SOD-Gliadin treated group, SOD activity was considerably increased (approximately 2-fold). However, no differences were registered for inflammatory cell infiltration at the tumor site. In addition, even though primary tumor growth was not significantly altered, metastatic potential could be inhibited in tumor cells derived from SOD-Gliadin treated animals. In 2004, Vouldoukis and coworkers [21] claimed that the SOD-Gliadin formulation has anti-inflammatory properties. Their assumptions were based on the observation that in murine models, encapsulated-SOD supplementation induced IL-10 production. Upregulation of this anti-inflammatory cytokine also resulted in decreased production of TNF-α, therefore reducing pro-inflammatory 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]. Though 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, in order 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 C57BL/6 model [36]. In these experiments, stress was induced by physical restraint daily for 12 h over the course of 5 weeks. During this period, animals either received a normal diet or a diet supplemented with SOD-Gliadin. After 5 weeks, lipid peroxidation in the brain was markedly reduced upon 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 done by Houghton and colleagues [37]. In this study, women from 50 to 65 years of age with longstanding unexplained fatigue were subjected to SOD-Gliadin supplementation or placebo for 12 weeks (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 levels scores. The lack of phenotype might be explained by the absence of antioxidant activity of SOD supplementation in this particular protocol. Indeed, the authors state 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 have also been considered. For instance, oxidative skin damage as a result of UV exposure can be ameliorated by SOD-Gliadin treatment. This was reported in a human study where subjects from different phototypes were tested for UV-induced skin redness [38]. Compared to 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 where volunteer professional athletes were subjected to daily treatment with SOD-Gliadin (500 mg) or placebo for 6 weeks [39]. In this study, blood samples were drawn from the subjects after a 2000 meter 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 towards 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. Since 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 mentioned above might also 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 by Yuan and colleagues [43] hypothesizes that specific genotypes might also determine the type of effect induced by antioxidant rich diets. Even though this particular report was only performed during a 2-week 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 cardiovascular diseases, or special physiological situations like the practice of intensive sports. Bioactive melon SOD oral intake might represent a meaningful quality of life improvement. In addition, 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 in order to reinforce the recommendation for dietary intake of gliadin-coated melon-derived SOD.

Disclosure statement / Conflict of interest

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Figures

Figure 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 oxidases or by xanthine oxidases. Superoxide dismutases are responsible for further transformation of $O_2^{\bullet -}$ to hydrogen peroxide (H_2O_2). Finally, enzymes such as catalase or glutathione peroxidases are capable of converting H_2O_2 into water (H_2O) and O_2.

Tables

Table I – Summary of recent human research studies on SOD-Gliadin dietary intake effects.

Table II – Summary of recent animal research studies on SOD-Gliadin dietary intake effects.

Table I. Summary of recent human research studies on SOD-Gliadin dietary intake effects.

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

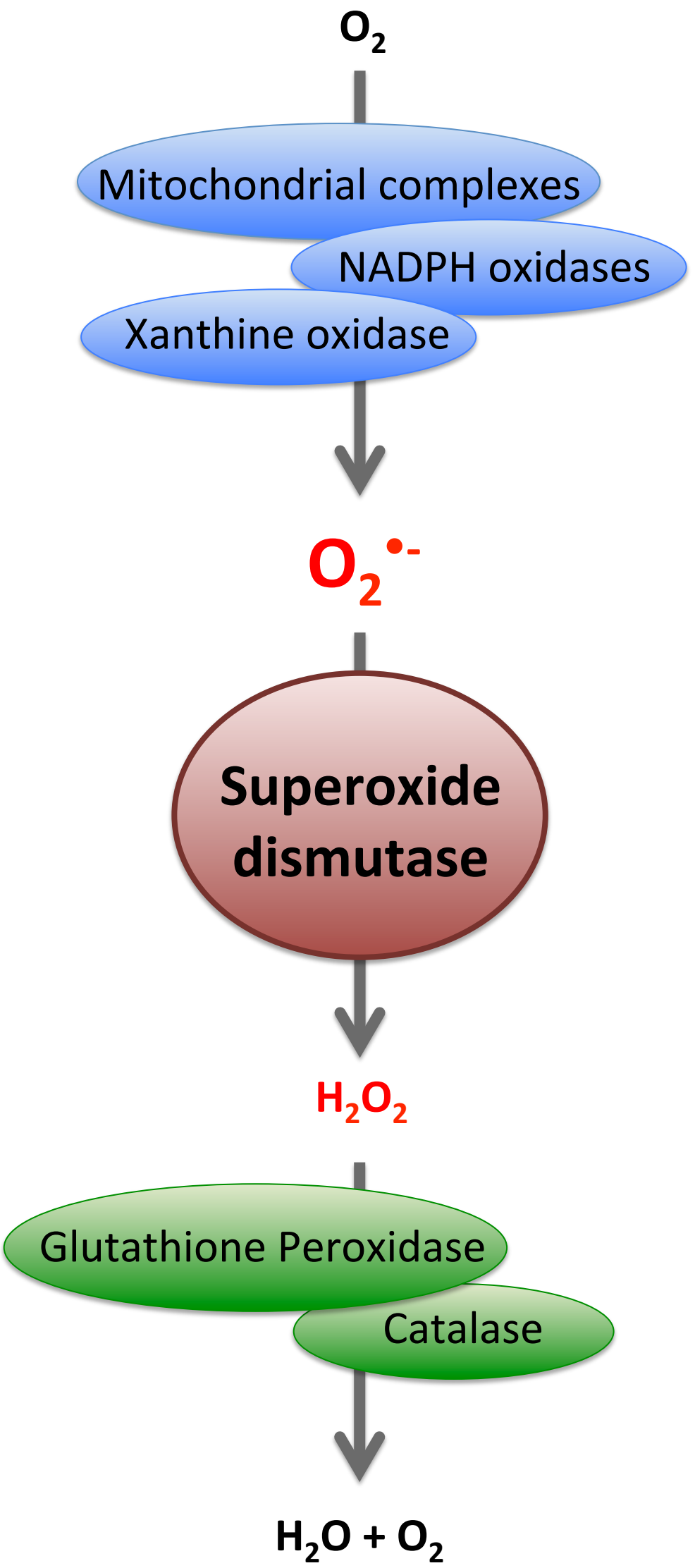
Note: None of the above mentioned studies report adverse side effects of oral supplementation with SOD. ↑=increased ↓=decreased.

Table II. Summary of recent animal research studies on SOD-Gliadin dietary intake effects.

Condition	Model	Supplementation	Effects	No effects	Other notes	Ref
IFN-γ / IgG1 IC activated mϕ	C57BL/6 mice (ex vivo and in vivo)	SOD-Gliadin 28 days 5U-NBT/day	↓ $O_2^{\bullet-}$ 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 days 0.1-5mg/day	↑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 weeks	↓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 weeks	↑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 to diabetic control animals	[29]
Ischemia/Reperfusion injury	Aortic cross-clamping in pigs	SOD-Gliadin 14 days 1250U/day	↓DNA damage ↓Apoptotic cells in spinal cord	SOD, Cat, GPx levels in blood	No ameliorated organ function	[32]
Fibrosarcoma	C57BL/6 mice (ex vivo and in vivo)	SOD-Gliadin 30 days 10mg/kg/day	↑SOD activity in tumors ↓Metastasis development ↓Oxidative stress in tumors	SOD activity in blood Infiltrating cells in tumors Tumor incidence	Effects are lost upon i.p. administration of SOD-gliadin. Tendency for reduction on tumor growth upon supplementation	[34]
Viral infection	FIV-infected cats	SOD-Gliadin 30 days 100 mg/day	↑SOD activity in blood ↑CD4/CD8 ratio	GPx levels or oxidative stress in blood.		[35]
Cognitive memory	C57BL/6 mice	SOD-Gliadin 5 weeks 100 mg/kg/day	↓Lipid peroxidation 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]

Note: None of the above mentioned studies report adverse side effects of oral supplementation with SOD. ↑=increased ↓=decreased. n.s. = not stated.

Figure 1


O_2
Mitochondrial complexes
NADPH oxidases
Xanthine oxidase
$O_2^{\bullet-}$
Superoxide dismutase
H_2O_2
Glutathione Peroxidase
Catalase
$H_2O + O_2$

Highlights:

- The intake of Melon SOD combined with gliadin increases endogenous antioxidant levels
- SOD-Gliadin supplementation acts as an auxiliary treatment to improve life quality
- Large-scale trials are required to reinforce the recommendation to supplement with SOD-gliadin