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Review

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

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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].

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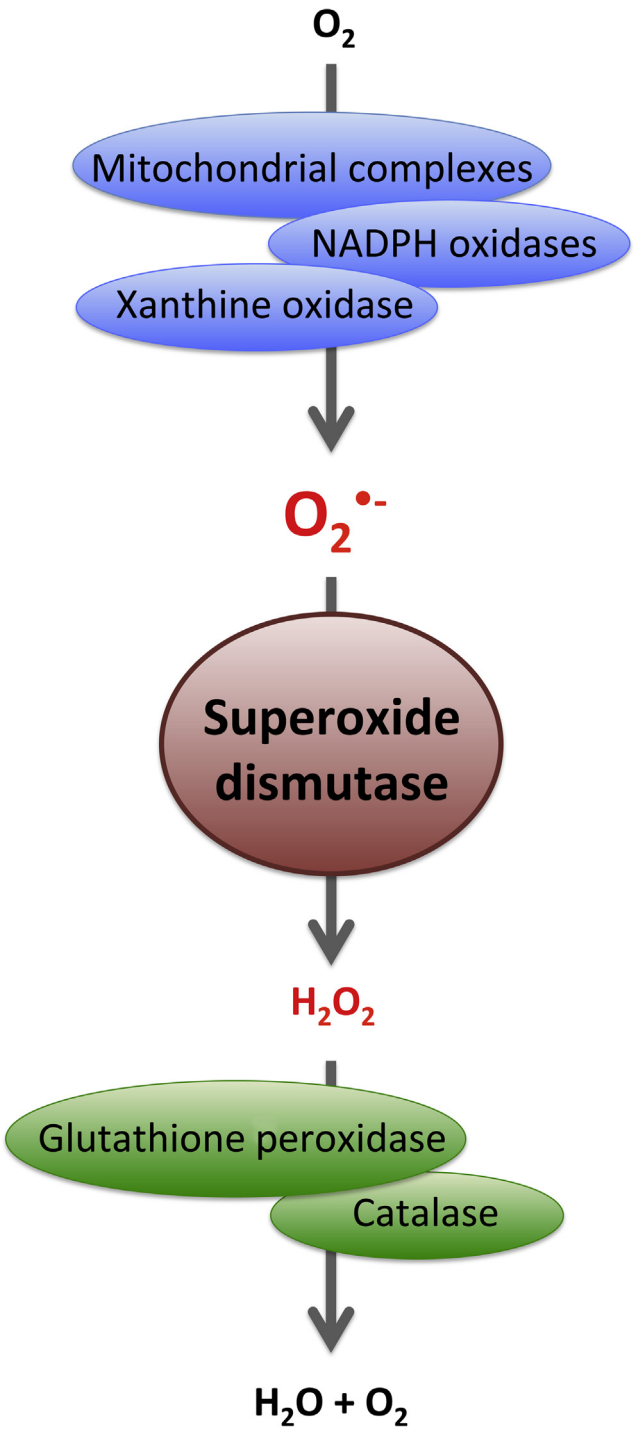

Fig. 1. Schematic representation showing a possible enzymatic cascade for transformation of molecular oxygen (O_2) in eukaryotic cells. Enzymatic conversion of O_2 into superoxide anion ($O_2^{\bullet -}$) can be carried out by the mitochondrial respiratory complexes, by NADPH oxidase or by xanthine 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