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# Immunomodulatory and anti-inflammatory properties of an orally bioavailable sod-gliadin complex

Eric Postaire[1*], Laurent Intes[2] and François Vix[2]

[1] Académie nationale de Pharmacie, 4 avenue de l'Observatoire, F75006 Paris, France

[2] Isocell, 53 rue du Général Marcial Vallin, F75015 Paris, France

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***Corresponding Author**

Eric Postaire

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**Abstract**

Superoxide Dismutase (SOD) constitutes part of the body's front line in antioxidant defenses, helping to maintain the physiological oxidant-antioxidant balance. However, this balance can be disrupted by a number of factors that include aging, smoking, pollution, exposure to sunlight, high intensity exercise, infection and the subsequent immune response. The body experiences oxidative stress under these types of conditions, which has been linked to the increased risk of chronic disease. Oral supplementation of the enzyme, in order to boost the body's antioxidant defense system, has been ineffective due to the biochemical conditions experienced as the enzyme passes through the gastrointestinal tract. This passage degrades the enzyme, rendering it useless. This publication reviews the science related to GliSODin®, a trade name for SOD extracted from cantaloupe melon and combined with wheat gliadin. Clinical research and scientific evidence is presented to demonstrate that gliadin protects SOD during passage through the stomach, thus allowing absorption of the SOD enzyme once inside the intestine.



## Introduction

Production of reactive oxygen species (ROS) is a normal process in oxygen-breathing organisms. Under normal physiological conditions, a balance between these species and the body's anti-oxidant defenses exists; however, certain conditions, such as smoking, pollution, exposure to sunlight (UV radiation), metabolism of sugars related to high intensity exercise, the natural progression of aging infection and the subsequent immune response, can increase the production of ROS like the superoxide ion ($O_2^{\cdot-}$) and the hydroxyl radical ($OH^{\cdot}$). This will disrupt the natural balance and ultimately lead to oxidative stress [1].

The detrimental health effects that can result from prolonged exposure to oxidative stress include: DNA damage that can cause cancer, atherosclerosis (hardening of the arteries) leading to cardiovascular disease, inflammation, fibrosis, rheumatoid arthritis, metabolic syndrome, diabetes and neurodegenerative diseases like Alzheimer's [2].

Superoxide dismutase, catalase, and glutathione peroxidase work in conjunction with each other. This is essential in creating the front line in the body's natural antioxidant enzyme defense system [3]. Superoxide anion is the starting point of cascade reactions in free radical production.

SOD was dubbed the "enzyme of life" upon its discovery in 1968. Superoxide Dismutase is the first antioxidant mobilized by the cell and used as a defense mechanism against oxidative stress. The enzyme reacts with the superoxide ion and turns it into hydrogen peroxide ($H_2O_2$). This is then catabolized by catalase and glutathione peroxidase to produce molecular oxygen ($O_2$) and water ($H_2O$).

These antioxidant enzymes have a distinct advantage over other antioxidants consumed from diet or nutritional supplements, like vitamins A, C, E, carotenoids, and thiols. These enzymes are biological catalysts, reducing many times and more rapidly reactive oxygen species, without being consumed themselves. By reacting at the beginning of the process, enzymes avoid the later occurrence of oxidized biological molecules. On the other hand, a non-catalytic or stoichiometric relationship exists for most vitamins, carotenoids and thiols. In other words, a defined relationship exists. For example: once Vitamin C removes an ROS, more Vitamin C must be supplemented and consumed in order to replenish any depleted Vitamin C stores that had been used during the ROS removal process.

**2- Oral administration of SOD**

Oral administration of SOD and other antioxidant enzymes contained in a variety of plant extracts is ineffective under normal conditions. During passage through the gastrointestinal pathway the enzyme is deactivated, rendering it ineffective as an antioxidant; however, studies have shown that when combining SOD with a wheat gliadin biopolymer, this system temporarily protects the SOD during passage through the gastrointestinal tractand thanks to the bioadhesive properties of gliadin, promotes its diffusion in the intestinal mucosa. One explanation of this efficiency, presented by Clemente et al., showed that gliadin increases the permeability of the intestine by promoting the release of a zonulin, thereby allowing the macromolecule SOD to be transported through the intestinal barrier [4].

The combination of SOD extracted from cantaloupe melon (*Cucumis melo* L.C.) combined with wheat gliadin biopolymer (GliSODin®) significantly improves the delayed release of SOD as evidenced *in vitro* by the increase of its activity in a medium mimicking digestive conditions [5].

Numerous studies have been conducted in many countries, including Japan, France, Indonesia, Algeria, etc. This shows the international interest that GliSODin is arousing in the world and in a wide variety of medical fields such as cancer, NASH, allergology and many others.

**3- GliSODin® Evidence from animal studies: major studies**

***3.1- Comparison enteral GliSODin 1 IU and 5 IU as an antioxidant and anti-inflammatory in LPS-Induced sepsis model rats [6]***

The studies aimed to determine the effect of enteral administration of GliSODin 28 days before inducing sepsis in rats. This experimental study aimed to compare four groups of male Wistar rats, including negative and positive control rats and those supplemented withGliSODin 1 IU/day and GliSODin 5 IU/day. All rats were given the same standard, except the supplementation for 28 days. Sepsis was induced by intraperitoneal injection of LPS 10 mg/kg. Enteral administration of GliSODin for 28 days was used as antioxidant prophylaxis against oxidative stress due to sepsis. The results showed that enteral administration of GliSODin of 1 IU/day and 5 IU/day significantly increased SOD levels based on examination after 14 and 28 days. Also, it significantly decreased MDA ($p < 0.001$), TNF-$\alpha$ ($p < 0.001$), and lactate levels in rats induced by sepsis. However, the increase in lactate levels was above >1.64 mmol/l, indicating a high mortality rate. There was no significant difference in SOD, MDA, TNF-$\alpha$, and Lactate levels between SOD 1 IU and SOD 5 IU. This descriptive data show that SOD 5 IU has a better result in MDA, TNF-$\alpha$, and Lactate levels than SOD 1 IU.

***3.2- Positive effects of an oral supplementation by GliSODin, in an animal model of dietary-induced oxidative stress* [7].**

The authors investigated the potential protective effects of two antioxidant molecules: GliSODin and an antioxidant agent N-acetylcysteine (NAC). GliSODin, given orally to rats fed a chow diet, as 180 U/d during 2 weeks in a preconditioning treatment, and then for 8 weeks, combined toa highfructose/high iron diet (Fr/Fe), had more positive effects than NAC (100 mg/d), not only on oxidative stress parameters, but also on features of the metabolic-syndrome. DNA oxidative damages, lipid peroxidation, and fasting glycaemia were lower in rats receiving Glisodin than in those supplemented by NAC. In addition, insulin sensitivity was improved and mesenteric fat was significantly lower in rats fed the Fr/Fe diet plus GliSODin than in animals fed NAC supplementation.

These data suggest potential beneficial effects of oral

GliSODin supplementation in preventing metabolic alterations related to the metabolic syndrome.

***3.3- GliSODin Prevents Diet-Induced NASH Onset by Reducing Fat Synthesis and Improving Liver Function* [8]**

The aim of this study was to evaluate the antioxidant activity of GliSODin and its efficacy in the prevention of NASH induced by a high fat and cholesterol diet in a mouse model.

First, the metabolic changes induced by GLISODIN were evaluated.

Overweight was suppressed in the GLISODIN group.

Liver hypertrophy was clearly suppressed in the GLISODIN group and epididymal and mesenteric adipose tissue weights were reduced.

On the other hand, plasma total cholesterol in the GLISODIN group and triglycerides in the liver were significantly reduced.

Secondly, histological analysis of the livers revealed a decrease in lipid droplet hypertrophy in the GliSODin group. Furthermore, where the control group showed clear hepatic fibrosis, the GliSODin group did not show recognizable hepatic fibrosis.

To confirm whether GliSODin suppression of liver fibrosis is regulated at the level of gene expression, the expression of collagen type 1 alpha (col1a1), collagen type 3 alpha 1 (col3a1) (fibrosis markers), and transforming growth factor beta (TGF-β) (an upstream regulator of col1a1 and col3a1) were determined.

All three factors were suppressed in the GliSODin group compared with the control group: these changes in gene expression may help prevent the development of NASH.

Finally, genes for inflammatory markers, including tumor necrosis factor alpha (TNF-$\alpha$) and interleukin 1-beta (IL-1β), were downregulated by GliSODin administration. This had already been demonstrated in previous studies.

Genes involved in lipid synthesis were also evaluated in this study. The expression of the transcription factor sterol regulatory element-binding protein 1c (SREBP1c), which regulates fatty acid synthesis genes, including stearoyl-CoA desaturase 1 (SCD1), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS).

These genes tend to be downregulated after GLISODIN administration. The authors consider that this reduction of fatty acid synthesis in the liver could mitigate inflammation and oxidative stress.

In conclusion, these results indicate that GliSODin prevents NASH by reducing oxidative stress and liver inflammation, an intrinsic pathological feature of NASH.

***3.4- Protective role of GliSODin on the status of lipid peroxidation and antioxidant defense against azoxymethane (AOM)-induced experimental colon carcinogenesis [9]***

This study investigated the protective effect of a natural antioxidant (GliSODin) against azoxymethane-induced oxidative stress and carcinogenesis in rat colon.

Azoxymethane (AOM) is a potent carcinogen commonly used to induce colon cancer in rats and mice, with the cytotoxicity of AOM being mediated by oxidative stress.Twenty male Wistar rats were randomly divided into four groups (five rats/group). The control group was fed a basal diet. AOM-treated group (AOM) was fed a basal diet and received intraperitoneal injections of AOM for 2 weeks at a dose of 15 mg/kg. The GliSODin treatment group (SOD) received oral supplementation of GliSODin (300 mg/kg) for 3 months, and the fourth combined group received AOM and GliSODin (AOM + SOD). All animals were continuously fed *ad libitum* until the age of 16 weeks when all rats were sacrificed. The colon tissues were examined microscopically for pathological changes and aberrant crypt foci (ACF) development, oxidant status (lipid peroxidation-LPO), and enzyme antioxidant system (glutathione [GSH], GSH-S-transferase, catalase, and SOD).

The results showed that AOM induced ACF development and oxidative stress (GSH depletion and lipid peroxidation) in rat colonic cells. The concomitant treatment of AOM with GliSODin significantly ameliorated the cytotoxic effects of AOM.

In conclusion the results of this study provide *in vivo* evidence that GliSODin reduced the AOM-induced colon cancer in rats, through their potent antioxidant activities.

***3.5- Prevention of inflammation-mediated acquisition of metastatic properties of benign mouse fibrosarcoma cells by administration of GliSODin* [10]**

Weakly tumorigenic and nonmetastatic QR-32 cells derived from a fibrosarcoma in C57BL6 mouse are converted to malignant cells once they have grown after being coimplanted with a gelatin sponge which induces inflammation. The authors administered GliSODin, and as control vehicle, gliadin and saline, starting 2 days before the coimplantation and continued daily throughout the experiment. In the GliSODin group, the incidence of tumors was lower (41%) than in the gliadin or saline group (83 and 79%, respectively). It should be noted that the inhibitory effect of GliSODin was lost

when an individual component of GliSODin was administered, i.e., SOD alone and gliadin alone. The effect of GliSODin was also abolished when administered intraperitoneally.

When perfused *in situ* with nitroblue tetrazolium, an indicator of superoxide formation, the tumour masses from gliadin and saline groups displayed intense formazan deposition, whereas, those from GliSODin group had less deposition. Enzymatic activity of SOD was also increased in GliSODin group. Arising tumor cells in gliadin and saline groups acquired metastatic phenotype, but those in GliSODingroup showed reduced metastatic ability. These results suggested that the orally active SOD derivative prevented tumor progression promoted by inflammation, which is thought to be through scavenging inflammatory cell-derived superoxide anion.

**4- GliSODin Evidence from human studies: major studies**

***4.1- GliSODin as preventive agent vs atherosclerosis* (11)**

Thirty-four subjects without clinical signs/symptoms of cardiovascular disease but considered to be at significant risk for clinically relevant atherothrombosis were included in this randomized study. The duration of the study was of two years.

The authors observed minor improvements in clinical (BMI, systolic and diastolic BP) and biological criteria (total and LDL-cholesterol) at D.0 in all subjects; this was due to modifications of their diet (12) and lifestyle when compared to D-360. However they did not find changes in their anti-oxidant status –that remained poor, or their IMT with numbers too high when considering the age of these subjects. Conversely, during the treatment period, all clinical and biological numbers remained stable, and modifications of the antioxidant status became significant at D270 but only the GliSODin group. Changes in the carotid IMT started to be visible at D545, but became statistically significant at or after D730.

They compared subjects with diet changes only and slight increase in IMT with subjects of the GliSODin-treated group; in GliSODin-treated subjects, IMT decreased and reached significance at D365; and at D545 and D730 it reached $p<0.001$.

In conclusion, they demonstrated that supplementation with GliSODinwas effective in controlling the thickness of the carotid artery intima and media layers as measured by ultrasonography-B. They could demonstrate the preventive efficacy of GliSODin at a preclinical stage in subjects with risk factors of cardiovascular disease.

This study also has the advantage of demonstrating the safety of GliSODin after two years of treatment in humans at 500 mg per day

***4.2- GliSODin in addition to phototherapy for treating non-segmental vitiligo (13)***

A 24-week monocentric interventional prospective randomized placebo-controlled trial was conducted in the tertiary center for vitiligo care in the department of Dermatology of Nice University hospital, Nice, France. Subjects with non-segmental vitiligo affecting more than 5% of the total body surface were included. The subjects received gliadin-protected SOD, GliSODin(GP-SOD; 1 g/day for 12 weeks followed by 0.5 g/day for 12 weeks) or placebo in combination with twice-weekly sessions of NB-UVB. The primary endpoint was the total repigmentation rate at 24 weeks, compared with baseline, as assessed by investigator-assessed Vitiligo Extent Score (VES) on standardized pictures.

A total of 50 patients were included. After 24 weeks, a greater improvement in VES was observed in the GP-SOD group (19.85%; SE 4.63, $P < 0.0001$) compared with the placebo group (8.83%; SE 4.72, $P = 0.0676$). Tolerance was good in both groups. No related side effect was reported.

In conclusionthe use of GliSODin appears to be a useful add-on to phototherapy in the treatment of vitiligo patients.

***4.4- Randomized, open label, comparative, five-arm, controlled study evaluating the benefit and tolerability of oral GliSODin as add-on neutraceutical therapy with standard therapy in Indian patients with melasma (14)***

A randomized, open label, single centre, comparative, five arm study was conducted in 47patients with facial mixed melasma, for 12 weeks to evaluate the efficacy, safety and tolerability of two regimens (BD & OD) of GliSODin as add-on treatment with triple combination cream in melasma patients compared with two regimens (BD & OD) of beta-carotene (BC) and placebo. Primary outcome measure was improvement in Melasma Area and Severity Index (MASI) score, and secondary outcome measures were quality of life score, patient satisfaction score, global assessment by investigator and patients.

There was significant reduction in MASI score with add-on treatment with GliSODin BD (67.97%) as compared to BC BD (43.04%), BC OD (33.68%) and placebo (22.60%). There was significant reduction in MASI score with GliSODin (51.93%) as compared to placebo

(22.60%). The subjective assessments reported by patient and evaluator also ranked SOD BD as a superior regimen.

In conclusion, by inhibiting oxidative stress, GliSODin Combination offers significantly better efficacy and higher treatment satisfaction as add-on treatment compared to beta-carotene in Indian patients.

***4.3- Clinical efficacy of GliSODin for the treatment of aging-related dysfunction in motor organs (15)***

Locomotive syndrome is a concept proposed in Japan involving decreased mobility due to osteoarthritis, osteoporosis, and sarcopenia. This double-blind, randomized study aimed to investigate the effects of GliSODin on locomotive syndrome.

For 6 months, GliSODin(500.4 mg/day) or a placebo were administered to 24 and 22 women, respectively (aged 50–80 years), with knee or lower back discomfort or pain. Using baseline and 6-month data, changes in the Verbal Rating Scale and in subjective symptoms (determined using the Japanese Knee Osteoarthritis Measure, Locomo 25, the Roland–Morris Disability questionnaire, and the Chalder Fatigue Scale) were assessed, along with various oxidative markers, antioxidants, inflammatory markers, renal and liver function biochemical markers, bone metabolism markers, body composition, and motor function.

GliSODin administration tended to be associated with a larger improvement in subjective symptom scores, a reduction in oxidative markers (malondialdehyde and diacron reactive oxygen metabolites) and tumor necrosis factor-$\alpha$, and a significant increase in non-fat mass between baseline and 6 months. However, no statistically significant differences were observed between the groups for outcomes at 6 months.

In conclusions, GliSODin tended to improve the subjective symptoms of participants who had knee or lower back pain or discomfort. GliSODin administration may help to prevent the progression of locomotive syndrome.

***4.5- Influence of GliSODin on Hyperbaric Oxygen-related Cell Damage [16]***

In this double blind randomized placebo controlled study, 17 experienced and trained scuba divers (placebo-group n=9; GliSODin-group n=8) were exposed to hyperbaric oxygen (HBO) according to a routine treatment protocol consisting of 100% oxygen breathing at a pressure of 2.5 ATA for a total of 2 x 30 min periods, interspersed with a period of 10 min of air breathing.

Oral administration of GliSODin 1000 mg/day or corresponding vehicle was initiated after blinding and randomization 14 days prior to HBO treatment.

DNA strand breaks (tail moments) were determined using the comet assay. Whole blood concentrations of reduced (GSH) and oxidized (GSSG) glutathione and F2-isoprostanes, SOD, glutathione peroxidase (GPx) and catalase (CAT) activities and red cell malondialdehyde (MDA) content were determined.

After HBO exposure the tail moment (p=0.0.3) and isoprostane levels (p=0.0.49) were significantly lower in the group that received GLISODIN. Neither SOD and CAT nor GSH and GSSG were significantly affected by this preparation or HBO exposure. By contrast, blood GPx activity, which tended to be lower in the SOD group already before the HBO exposure (p=0.076); was significantly lower afterwards (p=0.045)

The authors concluded that GliSODin mixture is able to protect against DNA damage, which coincided with reduced blood isoprostane levels, and may therefore be used as an antioxidant.

***4.6- Use of GliSODin in accelerating symptom relief in asthmatic and house dust mite allergic children receiving house dust mite immunotherapy [17]***

The objective of this study was to evaluate the efficacy of GliSODin in lung function (FEV1 reversibility) and respiratory symptoms (drug scores, symptoms scores) in asthmatic and house dust mite allergic children receiving house dust mites immunotherapy.

Forty subjects aged 6–17 years old with asthma, tested positive for house dust mite allergy on skin prick test, and received immunotherapy were enrolled in this study. All subjects completed clinical based assessments and diary-based assessments for drug and symptom scores. Following a four-week baseline assessment, all subjects were randomized to receive GliSODin or placebo. Respiratory symptoms (drug and symptoms score) and FEV1 were evaluated at the end of the 1st, 2nd, 3rd, and 4th weeks after randomization. Drug score, symptoms score, and FEV1 reversibility test results were analyzed using a Paired t test and repeated measure of ANOVA.

The results showed that there was a significant difference in drug scores, symptoms score, and FEV1 reversibility test outcomes between GliSODin and placebo. GliSODin group showed a significant decrease in all outcome measures compared to those in placebo group.

The authors concluded that the use of GliSODin as antioxidants is effective in accelerating symptom relief for children with asthma and house dust mite allergy receiving house dust mite immunotherapy.

## 5- Conclusion

Progress in the demonstration of the efficacy of GliSODin, both in animals and in humans, is very important thanks to its immunomodulatory properties characterized by an antioxidant and anti-inflammatory effect. Confirmation is still needed in three areas: NASH, Vitiligo and allergy.

For this, collaborations with clinicians are useful to make the link between translational studies and clinical research.

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