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Superoxide Dismutase/Gliadin:
A Health Promoting and Anti-Aging Nutraceutical Product

PRODUCT MONOGRAPH

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THE SUPEROXIDE DISMUTASE/GLIADIN ("GliSODin™") PRODUCT

- **Oxygen metabolism is essential for life.**

Oxygen metabolism is not only essential for respiration; it is also an effective mechanism that controls the natural defence system at the cellular and tissue level (1). The oxygen derivatives produced by cells are essential for the anti-microbial and immune (innate and adaptive) defences. Under "normal" conditions, these free radicals must be considered cell-transducing signals that control the basic expression of different genes and proteins that control "normal cell physiology". Gene and cellular functions responsible for maintaining human health are principally controlled by intracellular mechanisms of oxygen-reduction (redox). However, the uncontrolled production of these oxygen free radical species leads to the development of inflammatory and/or degenerative diseases. The delicate balance between intracellular oxidants and anti-oxidants is regulated at the cellular level by cell-to-cell interactions, hormones, cytokines and other mediators, thus influencing health, aging and longevity.

Free radicals and/or chemical related compounds, when produced in excess, are responsible for cellular toxicity and contribute to the longterm development of most inflammatory-related diseases. In fact, the molecular and cellular activities of free radicals are highly dependent upon the threshold of production of these chemical entities. Under "normal" conditions the potential excess production of free radicals is buffered by anti-oxidant enzymes and/or quenching molecules.

The disturbance of the delicate equilibrium between oxidant and anti-oxidant molecules is mainly initiated by pathogens (virus, bacteria etc.) and/or antigens (nutritional products, allergens, vaccine etc.) and is regulated positively or negatively by various immune reactions (2,3). The majority of free radical actions can be divided in seven Immuno-Redox overlapping categories:

1. cytokine, growth factor, hormone and mediator action and secretion,
2. ion transport,
2. alteration of cell signalling,
3. transcription,
4. gene activation and/or repression,
5. alteration of mitochondrial functions, and
6. cell death by apoptosis

These observations led to the development of a large number of anti-oxidant products (nutrients and drugs). However, until now the development of these products has not been optimal for two main reasons. Previous products often had poor bioavailability, and the complexity of the dynamic equilibrium between free radicals and the related anti-oxidants has always been underestimated.

- **Superoxide Dismutase (SOD):**

Among anti-oxidants, the Superoxide Dismutase (SOD) enzyme family (4,5) appears to be the most potent system to revitalize and reduce the rate of cell destruction. It promotes the removal of the super-oxide anion free radical by dismutation and therefore constitutes an important system for protecting cells and tissues against degeneration and death.

Zinc and copper also aid the body's utilization of SOD. SOD levels tend to decline with age, while free radical production increases. Supplemental SOD's potential as an anti-aging treatment is currently being explored.

There are three chemical variants of this enzyme in mammals. The two copper/zinc forms are the cytoplasmic and the extracellular Cu/Zn-SOD. These two kinds of Cu/Zn-SOD neutralize the production of free radicals resulting from normal and/or adaptive metabolic activities that take place in the cytoplasm of the cells and in other biological fluids. The manganese form (Mn-SOD) is active in the mitochondria, organelles within the cells where energy is produced.

SOD occurs naturally in barley grass, broccoli, brussel sprouts, cabbage, wheat grass, melon and most green plants. Bovine-derived SOD has also been used as a therapeutic agent, and it is also available in nutritional supplement forms. However, to produce health effects, SOD nutritional supplements must be protected against the digestive process in the stomach. In addition, it must be absorbed in its native form at the small intestine to elicit its pharmacological properties.

- **Glisodin™: the first SOD deliverable by the oral route**

SOD's are proteins with very specific shapes that determine the enzyme's function. When exposed to the acidic environment of the stomach and to digestive enzymes, SOD's lose their specific shape, destroying its functionality. This is why it has been difficult to produce an oral SOD active nutritional supplement (6).

These anti-oxidant enzymes have now been coated in a protective vegetal prolamine (wheat gliadin) layer that not only prevents the stomach's digestion but also promotes the delivery of the bioactive molecule in the small-intestine mucosa (patent FR 2 729 296, WO 96 21 462; EP 804 225, US 6 045 809 and JP 520 616).

Orally deliverable SOD is manufactured by combining a vegetarian source of SOD with a wheat-based biopolymer (gliadin).

Orally deliverable SOD is the first functional health food SOD delivered by the oral route that vitalizes the body's anti-oxidant activity.

- **GliSODin™ formula:**

GliSODin™ (in 100 g)	
Mineral content	0.05 g
Carbohydrates	91.6 g
Protein	2.6 g

- **Class:**

Anti-oxidant
Anti-inflammatory
Immuno-regulatory

- **Dosage**

GliSODin™: 250 mg two times daily, taken with meals

- **Contra-indications**

Allergy to gluten or to any other constituent of the dietary product

Not for pregnant women and young children (from 0 to 4 years of age)

- **Indications of supportive function in the prevention and alleviations of symptoms of inflammatory, hepatic, allergic, metabolic, cardiovascular, and neurological disorders**

- **Safety**

The orally deliverable SOD appears to be well tolerated. The product has no acute or chronic toxicity.

NUTRACEUTICAL APPLICATIONS

Based on the antigenic nature of vegetal SOD, the GliSODin™ complex induces adaptive systems of redox regulation and immunomodulation (7).

Quality of Life: GliSODin™ complex is being actively investigated to clarify the strong indications that it can help alleviate a wide range of symptoms linked to cellular inflammation. GliSODin™ is also being studied to follow up on indications that its consumption may help slow the cellular aging process.

Priority Management: While conventional medicine generally acts to alleviate specific symptoms, the GliSODin™ product maintains its general ability to promote tissue health and reduce the damage to certain injured vital organs, notably the liver.

Individuality of Dose: The dosing of GliSODin™ depends on the clinical status of the subject. The base dose is the equivalent of 100 IU SOD per day and may be increased if necessary to 500 IU SOD per day. GliSODin™ has a very low toxicity.

GliSODin™ versus usual anti-oxidant drugs: As a dietary supplement, GliSODin™ is unique in that it is a natural extract that can regulate production of anti-oxidant enzymes and molecules in the body. GliSODin™ is a natural detoxifying enzyme that promotes natural defenses of the organism.

Benefits from using the GliSODin™ product: Chronic, infectious, inflammatory, degenerative and cancer tax the body energy stores and immune capacities. GliSODin™ replenishes the energy needed to enhance the natural defense system and alleviate symptoms of cellular stress.

The daily pressures of life, noise and environmental pollution, and other stresses pose a cumulative harmful health threat that may contribute to the onset of disease. GliSODin™ has been reported to reduce the effects of stress-induced free radical production.

IMMUNITY, OXIDATIVE STRESS AND PHARMACOLOGY

IMMUNITY:

- **The GliSODin™ product and the immune-system**

The immuno-redox concept of GliSODin™ is based on the fact that the body organizes innate and specific immune defenses against foreign elements (nutriments, pathogens, drugs etc.) and that these two waves of defence are tightly linked rather than dissociated.

The innate immunity is immediately mobilized upon initial contact with the gliadin coating of **GLISODin™**. The body recognizes the gliadin as a “heterologous” (or antigenic) material which triggers an immune response. The specific immunity stimulated involves cells, cytokines and antibodies that can attack and destroy the invading agents. The specific immune response is relatively slow but the conferred immunity is long lasting.

Evidence of immuno-modulation by the GLISODin™ product: After reaching the intestinal mucosa without being degraded in the intestinal tract, **GLISODin™** comes into contact with the different components of the immune system and regulates the local and systemic immune functions:

Activation of macrophages and epithelial cells:

GLISODin™ was found to stimulate the production of nitric oxide (NO) and to control the production of superoxide anion by gastrointestinal epithelial cells and macrophages. This production of NO in superoxide, anion-free conditions controls the gene and protein expression of various cytokines (TNF, IL-8, etc.) and of anti-oxidant enzymes (extracellular SOD, etc.) thus propagating (via the innate immune system) the pharmacological properties of heterologous SOD (7).

The antigenic nature of the vegetarian SOD also promotes the differentiation of phagocytic cells into specialized dendritic cells that will trigger the specific immune system to promote a “tolerogenic” immune response and thus propagate the pharmacological messages of nutritional SOD's (tolerance and stimulation of body anti-oxidants)

Effect to skin, Red Blood Cells (RBC) and White Blood Cells (WBC) in normal situations.

GLISODin™ administration suppressed the destructive process caused by skin fibrosis. **GLISODin™** intake also stimulated the body's own SOD production and other anti-oxidant activities in RBC's and WBC's.

OXIDATIVE STRESS:

- **GLISODin™ and oxidative damage**

Variants of the oxygen molecule are involved influence numerous cellular and tissular metabolism. (1,2). However, reactive oxygen species stimulate inflammation and/or degenerative processes. Free radicals may injure cells and tissue directly via oxidative degradation of essential cellular components or injure cells indirectly by altering cell and tissue enzyme equilibrium. These free

radicals induce the up regulation of several genes involved in the immune and inflammatory response. Nutrients rich in anti-oxidants such as vitamin C, vitamin E and/or **GliSODin™** may protect against oxidant-mediated inflammation and/or degeneration by scavenging free radicals, inhibiting various intracellular signalling pathways and promoting the body's natural anti-oxidant defenses.

Evidence of free radical regulation by the GliSODin™ product:

The damaging effects of free radicals particularly superoxide anion and peroxynitrite can be prevented or minimized by SOD. The ability of **GliSODin™** to lessen free radical damage and to regulate the production of superoxide radicals by balancing the good and bad effects of free radicals is being explored in various ongoing studies.

a) Free radical regulation

It is important to remember that free radicals are not detrimental in all instances. Generation of oxygen species is an indispensable action to sustain life. For example,

- 1) superoxide anion is an active oxygen species that plays an important role in the anti-microbial defence system and,
- 2) nitric oxide plays an important role in the regulation of normal vascular, neurological and immune functions.

b) anti-oxidant regulation

In various studies the **GliSODin™** product was found to concomitantly stimulate the production of nitric oxide and to diminish the superoxide anion production by phagocytic and epithelial cells. In that case, nitric oxide promoted the natural anti-oxidant defenses and thus protected cells against the deleterious effects of inflammation. This suggests that the orally deliverable SOD is not simply an enzyme that reduces the toxicity of superoxide anion but actually a free radical regulator.

- **GliSODin™ is a natural product that sits at the functional crossroads of oxidative stress and immunity.**

The weakening of the immune system as we age is implicated in the increase in neurodegenerative diseases, cancer, and opportunistic infections. The aging process is increasingly considered to be the sum of the ongoing deleterious free radical reactions in the cells, tissues, and organs. Life span may therefore be significantly influenced by the rate of free radical-mediated cell degradation. **GliSODin™** influences the production (e.g. cytokines) and the expression (e.g. cluster determinants) of products and mediators involved in the control of immunity and cell division. It may therefore contribute to the prevention or management of conditions associated with the aging process.

- **Other applications of GliSODin™**

GliSODin™ is a dietary supplement can reduce the immune system weakening effect of certain conventional drugs.

PHARMACOLOGY

- The steady concentrations of SOD in the three blood fractions (plasma, red and white blood cells) varies with the individual and is generally associated with the individual's overall health.
- Animal pharmacokinetics studies indicate that the circulating SOD level in RBC progressively increases from the first hour after GliSODin™ administration, with a dose independent maximum at 12 hours. The return to the baseline level is obtained after 24 h.
- In a small human study, 400 mg of GliSODin™ administration appeared to demonstrate the bioavailability profile of the product. The antigenic nature of GliSODin™ is an important factor. SOD levels are tabulated here.

<u>Healthy volunteers</u>	<u>Placebo</u>	<u>GliSODin™ (2 x 200 mg)</u>
<u>MS</u>	<u>47.7</u>	<u>224.2</u>
<u>TI</u>	<u>140.8</u>	<u>84.9</u>
<u>YM</u>	<u>64.2</u>	<u>223.1</u>
<u>SH</u>	<u>115.2</u>	<u>182.4</u>
<u>KH</u>	<u>127.3</u>	<u>172.9</u>
<u>JF</u>	<u>140.0</u>	<u>80.0</u>
<u>TM</u>	<u>102.6</u>	<u>128.9</u>

These data suggested that the GliSODin™ product reached the intestinal tract intact and acted as a SOD-normalizer or more probably as an anti-oxidant-normalizer in healthy people. **More extensive human trials are currently underway which will more definitively measure the effect on blood SOD levels of GliSODin™ oral administration.**

- The proposed detailed mechanism of action: Oral GliSODin™ is absorbed at the level of the small intestine via enterocytes and/or M cells and then is presented to the innate mucosal immune system mainly by macrophages and dendritic cells, finally polarizing the adaptive and specific immune system to produce cytokines and antibodies that will propagate the SOD-protective effect to the overall organism likely via the lymphatic network.

- Limited human studies (skin fibrosis, loss of cognitive functions etc.) indicate that this **GliSODin™** should be further evaluated considered as add-on therapy to usual conventional drug treatment. **GliSODin™** seems to promote the therapeutical effects of various drugs –including certain chemotherapeutic drugs- while at the same time significantly reducing the drugs' toxicity.

. **SOD Gliadin: The Ultimate Defense Against Disease and Aging**, by Carl Germano, Twins Streams, Kensington Publishing Corp., 2001, provides substantial additional documentation for the beneficial effect of SOD – and especially SOD/Gliadin (**GliSODin™**) described in this paper.

A FREE COPY OF CARL GERMANO'S BOOK IS AVAILABLE FROM P.L.THOMAS & CO., info@plthomas.com, 973-984-0900 x214

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