Trehalose Complex™

(Neuroprotective, Neurotrophic, and Memory-Enhancing Formula)

Supplement Facts

Serving Size: 1 Level Teaspoon (approximately 4.0 grams)
Servings per Container: Approximately 60

Amount Per Serving		%DV†
Trehalose	3,100 mg	*
D-Ribose (Bioenergy Ribose™)	550 mg	*
Modified Citrus Pectin	235 mg	*

† - % Daily Value * - Daily Value Not Established

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Introduction

Most of our neurons are in place by the time we are two years old. After that, only a very few stem cells remain to help replace damaged nerves. Thus, in most cases, the neurons you have at age two must last the rest of your life. The neurons that control your hand movements, for example, at age two are the very same cells that control your hands at age 102. Along the way, perhaps some of the neurons along the pathway have perished, which is part of the reason why memory declines and people often grow less coordinated over time. The active, living neurons, however, may be over 100 years old. Although the neurons live, their component parts are replaced as needed to prevent the accumulation of damage: for example, the lipids of the cell membrane or cellular proteins are continuously renewed.

Trehalose Complex , the Trehalose, D-Ribose, and Modified Citrus Pectin (MCP) formula from D'Adamo Personalized Nutrition acts on multiple levels to:

- Protect nerves from the destructive forces of aging and environmental toxicity.
- Stimulate the activity of your own stem cells to replace damaged or non-functioning nerves.
- Energize your existing nerves to maximize their functional capacity.
- Improve the connections and conductivity between nerves to improve the activity of the brain and nervous system.

These combined actions have the net effect of boosting memory and cognitive function in those whose nervous systems are suffering from the ravages of modern environmental toxins

as well as mitigating the effects of aging on cognition and recall. Regular consumption of Trehalose Complex , especially in mature and seasoned adults, can be a powerful preventive measure to ensure healthy brain function throughout the advanced years of life.

Description/Background

Trehalose

Trehalose, also known as mycose or tremalose, is a natural alpha-linked disaccharide formed by an α,α-1,1-glucosidic bond between two α-glucose units. Trehalose is found naturally in many animals, plants, and microorganisms. In animals, Trehalose is found in high amounts in shrimp and also in insects, including locusts, butterflies, grasshoppers, and bees, in which blood sugar is Trehalose. (1)

Trehalose is the molecule that gives many of these organisms the ability to withstand dry spells and prolonged droughts, also known as anhydrobiosis. It has high water retention capabilities and is used in food and cosmetics for that property. The carbohydrate is thought to form a gel phase as cells dehydrate that prevents disruption of internal cell organelles by effectively splinting them in position. Rehydration then allows normal cellular activity to resume without the major, lethal damage that would normally follow a dehydration/rehydration cycle. (2)

Taking full advantage of Trehalose's properties to preserve tissue and protein, it is already being used medically in organ protection solutions for organ transplants. Trehalose has the added advantage of being an antioxidant, and it is being used as a protein-stabilizing agent in emerging research. (3) It is that protein-stabilizing effect that has been shown to have such benefit in preserving the healthy function of nerves.

Amyloidogenic proteins undergo an alternative-folding pathway under stressful conditions leading to formation of fibrils having cross beta-sheet structure, which is the hallmark of many neurodegenerative diseases. In initial studies, Trehalose was shown to prevent this abnormal protein folding and to contribute to protein stability, which hinted at its efficacy against the amyloid formation associated with neurodegenerative disorders. (4)

A key event in Alzheimer's disease pathogenesis is the conversion of the peptide beta-amyloid (Abeta) from its soluble monomeric form into various aggregated morphologies ("plaques") in the brain. Preventing aggregation of Abeta is being pursued actively as a primary therapeutic strategy for treating Alzheimer's. In a 2005 study, researchers showed that Trehalose is effective in inhibiting aggregation of Abeta and reducing its cytotoxicity. They concluded that the use of Trehalose could be recommended as part of a therapeutic cocktail to control Abeta peptide aggregation and toxicity. (5) Additional studies have confirmed this inhibitory effect and elucidated the precise molecular mechanism by which Trehalose inhibits Abeta oligomeric aggregation. (6-9)

In a 2008 follow-up study, researchers used two amyloid-forming proteins, W7FW14F apomyoglobin and insulin, as model systems to determine the molecular mechanism by which Trehalose affects the amyloid aggregation process. They found that it acted at different stages

of the fibrillization process depending on the protein model used. Trehalose dose-dependently inhibited fibril formation in the W7FW14F apomyoglobin model and increased the lag phase in the insulin model. The results suggested that Trehalose might inhibit the formation of "on-pathway" or "off-pathway" oligomeric intermediates depending on the nature of the aggregating protein. (10)

One recent study showed that in addition to delaying Abeta aggregation, Trehalose is able to reduce the increased cell membrane permeability that is induced by accelerated conversion of high order oligomers to fibrils such as Abeta. The researchers postulated that the observed effects on Abeta membrane interaction may be due to a more general phenomena associated with Trehalose's capacity to enhance Abeta oligomer stability and/or direct interaction of Trehalose with the membrane surface. (11)

In late 2009, researchers at the University of Wisconsin undertook molecular simulations to examine the specific effects of Trehalose on the conformational stability of Abeta and its effect on the interaction between Abeta and the phospholipid bilayer membrane. In aqueous solution, Abeta exhibited a random coil conformation, but in the presence of Trehalose, it adopted an alpha helical conformation. The researchers then showed that the insertion of Abeta into a cell membrane is more favourable when the peptide is folded into an alpha helix than in a random coil conformation. These findings suggest that at least some of the observed actions of Trehalose may be a result of its ability to promote the insertion of these favourable alpha-helical Abeta into nerve cell membranes. (12)

In the murine model of Alzheimer's disease with Parkinsonism, 1% Trehalose in the drinking water was shown to revert the disease phenotype while being increasingly neuroprotective the earlier it was begun. The researchers found a new mechanism for the action of Trehalose as well, showing that it increases the removal of abnormal proteins through enhancement of autophagy the process by which the body rids itself of damaged or disordered cellular components. The study authors noted the excellent safety profile of Trehalose even at high concentrations and recommended further clinical studies of the effects of Trehalose in human neurodegenerative diseases. (13)

D-Ribose

D-Ribose (or simply Ribose) is a simple, 5-carbon monosaccharide, or pentose sugar. It is used by all the cells of the body and is an essential compound in energy metabolism. Ribose also provides the structural backbone of our genetic material, DNA and RNA, certain vitamins and other important cellular compounds. (14)

Ribose is an essential component in stimulating natural energy production. (15) Research has shown that Ribose reduces the effects of stress on the body associated with arduous activity and helps improve athletic performance. Ribose also helps heart and skeletal muscles maintain healthy energy levels, and it accelerates energy recovery when tissues are stressed by exhausting exercise or overwork. (16)

Ribose is made in the body from glucose through a metabolic pathway called the Pentose Phosphate Pathway. Unfortunately, in heart and muscle cells, important enzymes that regulate the activity of this Pathway are lacking. (17) As such, forming Ribose in heart and

muscle cells is a slow process. This delay in Ribose synthesis in heart and muscle tissues also delays energy recovery when energy pools have been depleted by disease or exercise.

The physiologically functional form of Ribose, called 5-phosphoribosyl-1-pyrophosphate (PRPP), regulates the metabolic pathway that synthesizes energy transfer compounds (Krebs cycle intermediates) in all living tissue. This pathway is called the Purine Nucleotide Pathway. If PRPP is not available in sufficient quantity, synthesis of these energy transfer molecules slows, and tissue recovery is delayed. (18)

If the cellular pool of energy transfer molecules is depleted by disease, overwork, or exercise it must be replenished. PRPP is required to stimulate the metabolic pathway used by the body to restore this cellular energy pool. Supplemental Ribose bypasses the slow rate-limiting step of the Pentose Phosphate Pathway, forms PRPP very quickly, and accelerates the process of energy transfer molecule synthesis. (19)

Multiple studies have shown that energy levels in the heart can be dramatically lowered by exercise or changes in normal cellular energy metabolism. (20,21) Depleted cardiac energy reserves may be associated with increased cardiac stress, reduced blood flow to the periphery of the body, fatigue, and decreased exercise tolerance. Ribose is the key nutrient for quickly restoring cardiac energy. (22)

Three or four workouts per week may not allow enough rest time between sessions for the pools of heart and muscle energy transfer molecules to return to normal levels. Taking Ribose supplementally shortens the time needed by heart and muscle tissue to replace these transfer molecules that are lost through vigorous exercise. (23) Maintaining optimal levels of these energy transfer molecules in the cells helps to keep heart and skeletal muscles in good physiological condition, increase power and endurance, and reduce fatigue. Recent research has also shown that Ribose supplementation during exercise reduces free radical formation. (24)

One of the most important energy transfer molecules for which Ribose forms the substrate is adenosine diphosphate ribose (ADP-Ribose). ADP-Ribose is an ester formed between Ribose and the terminal phosphate of ADP. It is produced by the hydrolysis of nicotinamide-adenine dinucleotide (NAD), which is itself a coenzyme composed of ribosylnicotinamide 5'-diphosphate coupled to adenosine 5'-phosphate by a pyrophosphate linkage. Ribosylnicotinamide is an enzymatic product of nicotinamide riboside kinase, which utilizes nicotinamide (the amide of niacin or vitamin B3) and phosphorylated D-Ribose as its substrates. (25)

ADP-ribose is formed into chains by the important regulator of gene expression, Poly (ADP-Ribose) polymerase (PARP), which is used by the body in a number of cellular processes involving DNA repair, post-translational modification of other proteins of epigenetic significance, and apoptosis (programmed cell death). (26) Mild activation of the PARP1 enzyme has been shown to facilitate DNA repair in nerve cells, while excessive activation can lead to a significant decrease in NAD, ATP depletion, and apoptosis. (27)

The D-Ribose in Trehalose Complex helps gently upregulate the activity of the PARP enzymes by providing increased levels of an otherwise rate-limited substrate for its activity. Increased DNA damage repair via mild activation of the PARP family of enzymes with relatively moderate dosing of Ribose follows the hormetic biphasic dose response curve by

initiating only the brain's cellular DNA repair mechanisms at this concentration. PARP's mild activation is modulated by the relatively high dose of Trehalose in the formula, which subsequently acts to prevent further Abeta misfolding and aggregation. (28)

Modified Citrus Pectin

Modified Citrus Pectin is produced from citrus pectin via pH and temperature modification that breaks it into shorter, non-branched, galactose-rich, carbohydrate chains. These shorter chains dissolve more readily in water and are better absorbed and utilized by the body than ordinary, long-chain pectins. It is believed the shorter polysaccharide units afford MCP its ability to access and bind tightly to galactose-binding lectins (galectins) on the surface of certain types of cancer cells. (29)

Research indicates that in order for metastasis to occur, cancerous cells must first clump together; galectins on their surface are thought to be responsible for much of this metastatic potential. Galactose-rich, modified citrus pectin has a binding affinity for galectins on the surface of cancer cells, resulting in an inhibition, or blocking, of cancer cell aggregation, adhesion, and metastasis. (30,31) Due to the life-threatening nature of metastatic cancer, most research on anti-metastatic therapies has either been in in vitro cell cultures or in animal studies. Although it is still unclear exactly how these study results translate to humans, MCP studies are promising.

In one study, researchers examined modified citrus pectin's effectiveness against prostate cancer metastasis in the murine model. Subjects were injected with prostate adenocarcinoma cell lines and given drinking water containing various MCP concentrations. Oral MCP did not affect primary tumor growth but significantly reduced metastases when compared to control animals. (32) One human study examined the effect of MCP on prostate specific antigen (PSA) doubling time in seven prostate cancer patients. PSA is an enzymatic tumor marker, and its doubling time reflects the speed at which the cancer is growing. Modified Citrus Pectin was administered orally at a dosage of 15 grams per day in three divided doses. Four of seven patients exhibited more than 30-percent lengthening of PSA doubling time. Lengthening of the doubling time represents a decrease in the cancer growth rate. (33)

As with prostate adenocarcinoma, research demonstrates metastasis of breast cancer cell lines requires aggregation and adhesion of the cancerous cells to tissue endothelium in order for it to invade neighboring tissue. (34) The anti-adhesive properties of Modified Citrus Pectin were studied in an in vitro model utilizing breast carcinoma cell lines MCF-7 and T-47D. MCP blocked the adhesion of malignant cells to blood vessel endothelia, thus inhibiting metastasis. (35) A more recent human study examined galectin expression in 27 patients with invasive breast cancer. The study revealed that increasing histologic grades of breast cancer exhibited a decrease in galectin-3 expression, possibly resulting in increased cancer cell motility and metastasis. (36)

One of the better animal models for studying metastasis is the highly metastatic mouse B16-F1 melanoma. Using this system, researchers determined that MCP significantly decreased tumor metastasis to the lung by more than 90 percent. In comparison, regular citrus pectin

administration resulted in a significant increase (up to three-fold) in tumor metastases. The study authors concluded that MCP's interference in the metastatic process might lead to a reduced ability to form tumor cell aggregates and metastases. (37,38)

Galectin-3 is a β-galactoside binding lectin with roles in diverse processes, including proliferation, apoptosis, inflammation and fibrosis, which are dependent on different domains of the molecule and subcellular distribution. In addition to its role in cancer metastasis, galectin-3 is also known to be upregulated in acute kidney injury. The relative importance of its different domains and functions, however, are poorly understood in the underlying pathogenesis. A recent study found MCP to be protective in nephropathy via modulation of early proliferation and later galectin-3 expression, apoptosis, and fibrosis. MCP-treated subjects demonstrated reduced galectin-3 in association with decreased renal fibrosis, macrophages, pro-inflammatory cytokine expression, and apoptosis. The researchers concluded that MCP may be an effective strategy to reduce renal injury in the long term, perhaps via the carbohydrate binding-related functions of galectin-3. (39)

Synergistic Products

- *Attentia* (Cognitive, Adaptogenic, and Neuroprotective Support in all types)
- *Fucus Plus* (Fucosylation Support for Improved Nerve Connections and Conductivity in all types)
- *Nitricycle* (Cerebral Circulation and Relaxation Support in all types)
- *Methyl 12 Plus* (Healthy Methylation Support for Optimal Neurotransmitter Production and Function in all types)
- *Histona Ulterior* (Nerve Cell Membrane Stabilization, Cerebral Circulation, and Mood Support in all types)

Dosage

Typical dosage is 1 teaspoon, twice daily for maintenance, may increase to 1 Tablespoon, twice daily for extra therapeutic levels.

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