REVIEW ARTICLE

The Glutathione Theory of Aging

Ross Pelton, RPh, PhD, CCN

ABSTRACT

The Glutathione Theory of Aging reviews the multiple biological functions of glutathione, including its status as the *Master Antioxidant,* and its role as a key regulator of detoxification, immune function and anti-viral activity. Sub-optimal glutathione levels are common because many diet, lifestyle, and environmental factors contribute to glutathione depletion, and the body's ability to synthesize glutathione declines as people age. Studies reveal that most age-related chronic degenerative diseases are associated with low glutathione levels. This article also introduces people to *Lactobacillus fermentum* ME-3, which is a unique strain of probiotic bacteria thar synthesizes glutathione. Boosting glutathione levels is an important proactive step people can take to promote good health and achieve healthy longevity. (*Altern Ther Health Med.* 2024;30(10):54-58).

Ross Pelton, RPh, PhD, CCN, is a pharmacist, and certified clinical nutritionist (CCN). Ross "brands" himself as The Natural Pharmacist and he is the author of *The Drug-Induced Nutrient Depletion Handbook*. *ATHM* readers can use the following link to get a FREE copy of Ross' Quick Reference Guide to Drug-Induced Nutrient Depletions: naturalpharmacist.net/dind Join Ross in the Life Extension Revolution. Ross' website, bio and blog are at: naturalpharmacist.net

Corresponding author: Ross Pelton, RPh, PhD, CCN
E-mail: rosspelton70@gmail.com

INTRODUCTION

Over 100 000 scientific studies have been published regarding the biological effects of glutathione. It is a multi-tasking compound that is made in every cell. Its primary functions include regulation of antioxidant activity, detoxification, and regulation of the body's immune function. Consequently, glutathione is an important regulator of the health of every cell in the body.

Many people have depleted levels of glutathione and most chronic degenerative diseases are associated with low glutathione levels.[1,2] Low glutathione results in increased production of free radicals, increased levels of inflammation, and an increased accumulation of toxins in the body, which all contribute to accelerated biological aging.

The primary goals of this article are to discuss glutathione's wide-ranging functions in the body, the history, and discovery of *Lactobacillus fermentum* ME-3, which is a unique strain of probiotic bacteria that synthesizes glutathione, and to explain why boosting glutathione levels is one of the most important proactive step people can take to slow down biological aging, thereby increasing their health span and their life span.

GLUTATHIONE: THE MASTER ANTIOXIDANT

Glutathione is referred to as the *Master Antioxidan*t because it is made in every cell, and consequently, it is one of the most prevalent antioxidants in the human body.[3] One of glutathione's primary "jobs" is to protect all the components inside every cell in your body against oxidative stress and free radical damage. Glutathione is also a required cofactor for glutathione peroxidases, which are enzymes that provide additional antioxidant protection throughout the body.[4]

In addition to neutralizing free radicals, glutathione also increases the effectiveness of other antioxidants because it can recycle, or regenerate oxidized or "used up" antioxidants like vitamin C and vitamin E back to their active/reduced form.[5]

GLUTATHIONE: THE BODY'S MASTER DETOXIFIER

Glutathione plays a critical role in many detoxification processes, and it helps detoxify every cell in the body. Tissue levels of glutathione are highest in the liver, which is the body's primary organ for detoxification. Glutathione protects the body from a wide range of environmental toxins as well as those that are produced within the body, such as hydroxyl radical, superoxide, hydrogen peroxide, and hydroperoxides.[6,7,8]

Glutathione is a cofactor for a superfamily of detoxification enzymes named glutathione S-transferases, which are responsible for detoxifying a wide range of carcinogens and environmental toxins.[9] Glutathione also independently binds with heavy metal toxins such as mercury, lead, cadmium, and arsenic to eliminate them from the body.[10]

GLUTATHIONE REGULATES IMMUNE FUNCTION

Glutathione is essential for the function and activity of white blood cells (WBCs), and it has been reported that even a partial depletion of glutathione results in a profound inhibition of immune function.[11]

WBCs are a critical part of your immune system. Using a military metaphor, WBCs function like scouts or an early warning surveillance team. They circulate throughout your body, constantly on the lookout for bacteria, viruses, and other foreign invaders. Hence, WBCs are our first line of defense against infections. A sub-category of WBC called natural killer or NK cells, is involved in the identification of cancer cells and the control of tumor growth and metastasis.[12]

WBCs, which account for about 1% of your blood, are formed in the bone marrow and released into the bloodstream. When a foreign invader is identified, the bone marrow releases a massive number of WBCs into circulation, which travel to the site of the infection to fight the invader. Most people have experienced getting a cut that becomes red, swollen, inflamed, and painful. These effects are due to the 'army' of WBCs that have traveled to the site of the injury to fight and kill the invading pathogen.

GLUTATHIONE'S ANTI-VIRAL ACTIVITY

Since COVID-19, an increasing number of studies have been published reporting on glutathione's anti-viral activity. Studies have reported that glutathione helps to protect against viral infections and that boosting/replenishing glutathione levels can be therapeutically useful in the treatment of various viral infections.[13]

Glutathione levels are low in people with viral infections such as HIV, hepatitis C, Epstein-Barr, West Nile, herpes, and COVID-19. The title of a paper published in the early stages of the COVID-19 pandemic stated that glutathione deficiency is the most likely cause of serious manifestations and death in COVID-19 patients.[14]

GLUTATHIONE DEPLETION

Every time a molecule of glutathione neutralizes a free radical, the body's supply of glutathione is depleted. Similarly, when a molecule of glutathione binds to a toxin, the resulting glutathione-toxin compound gets eliminated from the body, which also depletes glutathione. Consequently, glutathione levels are constantly being depleted and the health of most people will improve if steps are taken to boost glutathione levels.

Some of the major factors that cause glutathione depletion are environmental toxins, poor diets, alcohol, smoking, nutritional deficiencies, and protein malnutrition, especially in the elderly. Also, the following classes of drugs deplete glutathione: acid blockers, antacids, antibiotics, anti-viral medications, tricyclic antidepressants, oral contraceptives, and acetaminophen, which is an ingredient in many OTC and prescription pain medications.

Acetaminophen deserves special attention because it is the most widely used pain medication in the United States and is also the leading cause of acute liver failure. Acetaminophen is safe when taken as directed in small doses. However, it depletes glutathione rapidly when taken in high doses or when taken continuously over extended periods. Many people who take acetaminophen-containing pain medications also consume alcohol. This greatly increases the risk of liver damage because both substances are metabolized in the liver. In the U.S., acetaminophen toxicity is responsible for over 50% of cases of acute liver failure and about 20% of liver transplant cases.[15]

Depleted glutathione levels result in a greater body burden of toxins, increased free radical damage, and accelerated aging. Thus, keeping glutathione at optimal levels is critical for healthy aging. Also, studies have shown that the body's ability to synthesize glutathione declines with age and this could be a major contributing factor to health problems that accelerate as people age.[16]

STRUCTURE OF GLUTATHIONE

Glutathione is a compound consisting of three amino acids- glycine, cysteine, and glutamic acid. Glutathione exists in two forms. Reduced glutathione (GSH) is the active form. Oxidized glutathione (GSSG), the inactive form, occurs when two molecules of glutathione are joined together.

The ratio of GSH to GSSG (reduced to oxidized, or active to inactive) is an important determinant of cellular health. Healthy cells have a GSH/GSSG ratio of over 100, which indicates a high level of antioxidant protective ability. When cells are exposed to high levels of free radicals or other forms of oxidant stress, the GSH/GSSG ratio often drops to below 10. Thus, the glutathione GSH/GSSG ratio is an important indicator of cellular health, and the overall health of an organism, or a human.

Three important classes of glutathione-dependent enzymes also regulate important aspects of health. Glutathione peroxidases are antioxidants, the glutathione S-transferases are detoxification enzymes that neutralize and eliminate a wide range of toxins, and glutathione reductase converts inactive GSSG back to the active GSH form.

DISEASES ASSOCIATED WITH LOW GLUTATHIONE

Most common chronic degenerative diseases also referred to as age-related diseases, are associated with low glutathione levels. This includes cancer, cardiovascular, inflammatory, immune, metabolic, and neurodegenerative diseases.[17,18]

Loss of cognitive function is one of the greatest fears people have about aging. Glutathione levels are known to be low in the brains of people with Parkinson's disease, Alzheimer's disease, schizophrenia, bipolar disorder, depression, ADHD, and other brain disorders.[19,20,21]

GLUTATHIONE: A BIOMARKER OF AGING

Telomeres are repeating segments of DNA (often described as protective "caps") on the ends of chromosomes that protect our genes from damage. Telomeres become shorter each time a cell divides. Telomere length and the rate of telomere shortening are recognized as one of the best biomarkers of aging.[22] Glutathione has been found to play a role in the preservation of telomere function.[23] In 2009, three scientists were awarded the Nobel Prize for their discoveries on how

telomeres and the enzyme telomerase protect our chromosomes and our genes from damage. This explains one of the ways glutathione slows down the process of biological aging.

In the 1980s, Drs. John Richie and Calvin Lang began researching how glutathione affects health and aging. In a landmark study, they added a glutathione precursor to the drinking water of adult mosquitoes and measured their glutathione levels and their life span. The outcome was quite surprising. An increase in glutathione levels from 50-100% resulted in increased lifespans of 30-38%. Consequently, Drs. Richie and Lang proposed the glutathione deficiency hypothesis, which suggests that a low level of glutathione is a primary biochemical cause of biological aging.[24]

Studies have shown that centenarians have higher glutathione levels compared to people between 60-79 years of age selected as controls. The researchers proposed that higher glutathione level in the centenarians was a key factor in their longevity.[25]

HIGHER GLUTATHIONE = INCREASED LIFESPAN AND INCREASED HEALTHSPAN

Since many factors previously discussed contribute to glutathione depletion, it can be assumed that most people have low levels of glutathione. It is also well established that low glutathione levels are associated with increased risks of a wide range of health problems. On the other hand, scientific evidence in animals and humans consistently shows that increasing glutathione levels slows the process of biological aging. Consequently, boosting glutathione levels is one of the most important proactive steps people can take to create and maintain good health and achieve healthy longevity.

INTRODUCING *LACTOBACILLUS FERMENTUM* ME-3

The Most Effective Method to Boost Glutathione

In 1995, Professor Marika Mikelsaar at the University of Tartu in Estonia isolated a strain of bacteria named *Lactobacillus fermentum* ME-3 (often referred to as ME-3) from the intestinal tract of a healthy 1-year-old child. Testing revealed that ME-3 exhibited extremely high antioxidant activity. Follow-up research reported that ME-3's high antioxidant activity is due to its ability to synthesize glutathione.

Since *Lactobacillus fermentum* ME-3 synthesizes glutathione, it has attracted a great deal of scientific attention. Studies in animal models and human clinical trials report that taking ME-3 orally provides a wide range of health benefits that parallel the health benefits of glutathione.

ME-3: A Complete Glutathione System

ME-3 has been shown to increase glutathione by three different mechanisms which are: (a) ME-3 synthesizes glutathione; (b) ME-3 accumulates glutathione from the environment; (c) ME-3 recycles oxidized (inactive) glutathione back to its reduced (active) state.

Lactobacillus fermentum ME-3 is the only organism or substance known to date that can increase glutathione by three independent mechanisms. Consequently, ME-3 is often referred to as a "complete glutathione system."

Additional Benefits of *Lactobacillus fermentum* ME-3

Supports cardiovascular health. *Lactobacillus fermentum* ME-3 has been shown to have a positive effect on several cardiovascular risk factors. Results from a 2-week double-blind, placebo-controlled human clinical revealed that subjects taking ME-3 had reductions in oxidized LDL-cholesterol and triglycerides, and an increase in HDL-cholesterol.[26] During this same study period, the values of these same markers got slightly worse for the placebo control subjects.

ME-3 Synthesizes Manganese Superoxide Dismutase. *Lactobacillus fermentum* ME-3 also produces the mitochondrial antioxidant enzyme manganese superoxide dismutase (MnSOD).[27] Mitochondria consume over 90% of the oxygen used by cells, which makes them especially vulnerable to oxidative free radical damage.[28] Since MnSOD plays a critical role in protecting mitochondria and preserving energy production, it is referred to as the guardian of the powerhouse.[29]

Reduces Inflammation. *Lactobacillus fermentum* ME-3 has been shown to significantly inhibit levels of several key inflammatory markers including glycated hemoglobin (HbA_{1c}), high sensitivity C-reactive protein (hs-CRP), and interleukin 6 (IL-6); and it is also capable of stimulating the production of anti-inflammatory and anti-diabetic peptide adiponectin.[30]

Detoxifies Organophosphate Pesticides. Organophosphates are one of the most widely used pesticides worldwide. These highly toxic compounds are sprayed on agricultural food crops, and they are commonly used on residential lawns and gardens. *Lactobacillus fermentum* ME-3 increases the activity of paraoxonase enzymes (called PON1), which helps to detoxify organophosphates.[31]

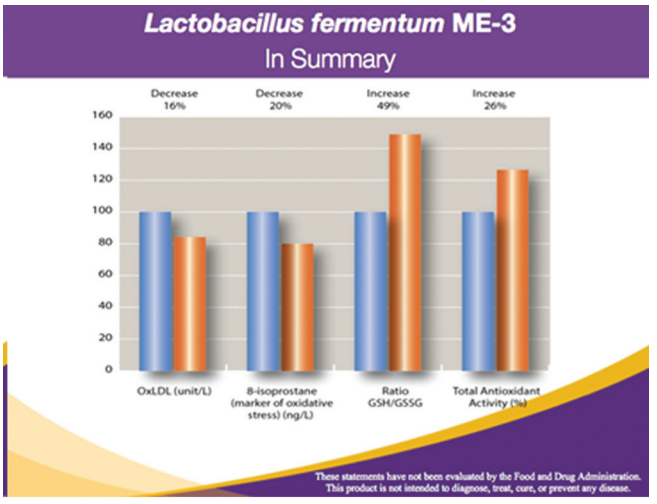
METHODS TO BOOST GLUTATHIONE

Interest in glutathione is growing fast because people are becoming more aware of glutathione's diverse health benefits and the role it plays in the prevention and treatment of age-related chronic degenerative diseases. However, there is confusion and controversy over choosing the best method of boosting glutathione levels to maximize health outcomes cost-effectively. There are several common methods of boosting glutathione and the pros and cons of each method will be discussed. These include (1) ingesting glutathione orally, (2) taking glutathione precursors, (3) intravenous (IV) glutathione, and (4) taking *Lactobacillus fermentum* ME-3 orally.

Oral Glutathione. Oral glutathione supplements are not well absorbed because the intestinal enzyme, gamma-glutamyl transpeptidase (GGT), breaks it down before it can be absorbed.[32] Most studies on oral glutathione report little or no increase in plasma glutathione levels.[33] Although taking glutathione orally is the most convenient way, its poor absorption explains why this form is seldom used in scientific studies.

Glutathione Precursors. The nutritional supplement *N*-acetyl cysteine (NAC) is the most used nutritional agent to boost glutathione levels. However, studies report that NAC is very poorly absorbed with only 10% being available after oral ingestion. After ingestion, intestinal enzymes convert about 90% of the NAC into the amino acid cysteine, which is

Figure 1. Benefits of ME-3 Administration Reported from Clinical Trials



unstable and quickly gets oxidized to cystine. Cystine has very low solubility; it is the least soluble of the naturally occurring amino acids.[34,35] Thus, *N*-acetyl cysteine is not an effective method of boosting glutathione levels.

Intravenous (IV) Glutathione. Many complementary and functional medicine physicians and/or clinics offer IV glutathione therapy. Some of the key benefits include inflammation reduction, boosting immune function, improving mental clarity and cognitive function, increasing energy, and slowing the aging process. However, glutathione gets oxidized very quickly, its half-life is only about 10 minutes.[36] Hence, people getting IV glutathione often get infusions 2 or 3 times a week. Thus, IV glutathione infusions can be time-consuming and expensive (average price $200-$350/treatment).

LACTOBACILLUS FERMENTUM ME-3 HUMAN CLINICAL TRIALS

Human clinical trials reveal that oral ingestion of *Lactobacillus fermentum* ME-3 results in substantial and consistent increases in glutathione levels. In addition to boosting glutathione levels, tests in animals and humans report oral ingestion of ME-3 provides a wide range of health benefits. The scientific evidence indicates that taking *Lactobacillus fermentum* ME-3 orally is the best method to boost glutathione levels. Here is a summary of the scientific studies that document and explain the benefits of taking *Lactobacillus fermentum* ME-3 orally.

Lactobacillus fermentum ME-3: Results from Human Clinical Trials

Reduced Cardiovascular Risk. The first column (Figure 1) shows that individuals taking ME-3 had a 16% reduction in the levels of oxidized LDL-cholesterol compared to placebo controls.[37]

Reduced 8-Isoprostanes. The second column (Figure 1) indicates that people taking ME-3 had a 20% reduction in levels of 8-isoprostanes, which implies reduced amounts of free radical damage due to ME-3's antioxidant activity.[38]

Elevated Glutathione. The study reported in the third column (Figure 1) shows that people taking ME-3 daily for three weeks (6 billion CFU/day) had a remarkable increase of 49% in the ratio of reduced to oxidized glutathione.[39] No other product to date has displayed a comparable increase in glutathione levels.

Reducing Oxidative Stress and Inflammation.[40] The fourth column (Figure 1) reports the increase in total antioxidant activity (TAA) gained by the individuals taking *Lactobacillus fermentum* ME-3 (the corresponding data is obtained from the following 2 studies).

Study #1: Improved Atopic Dermatitis. Many patients with atopic dermatitis have genetic polymorphisms in glutathione-dependent enzymes, which results in increased oxidative stress, inflammation, and impaired skin membrane barrier function.[41] Individuals taking ME-3 experienced a significant reduction in inflammation with accompanying improvements in skin condition, blood markers, and self-assessment rating scores.[42]

Study #2: Improved Stroke Recovery. Stroke patients consuming ME-3 exhibited significant improvements in both the Scandinavian Stroke Scale (from 33 up to 42) and the Functional Independence Measure inventory (from 21 up to 40). Stroke patients also experienced impressive improvements in the following blood markers: oxidized LDL-cholesterol, glutathione levels, ratio of reduced to oxidized glutathione, total antioxidant capacity, and paraoxonase enzyme activity, as well as reductions in markers of inflammation and free radical damage.[43]

Lactobacillus fermentum ME-3 Survives Stomach Acid and Produces Glutathione

In a human clinical trial, it was shown that ME-3 is capable of surviving transit through the harsh acid environment in the stomach and when it arrives in the small intestines, it adheres to the intestinal lining and begins producing glutathione. After 21 days, the concentration of live ME-3 bacteria doubled in the test subjects.[44]

Prevention of Intestinal Permeability/Leaky Gut

Bacterial imbalance in the intestinal tract causes inflammation. This results in intestinal permeability or leaky gut, which is associated with chronic inflammation and the acceleration of biological aging. A study with *Lactobacillus fermentum* ME-3 revealed that ME-3 helps prevent intestinal permeability.[45]

TREATMENT OF GLYCATION AND DIABETES COMPLICATIONS

Diabetes and obesity are epidemics with enormous health consequences. Also, elevated blood sugar causes glycation, which is a significant risk factor for cardiovascular disease. A study was conducted with a strain of mice, bred to spontaneously develop type 2 diabetes, and become obese. The mice treated with ME-3 had improved glucose tolerance, underwent less glycation, and gained much less weight compared to the control mice. Thus, treatment with ME-3 was shown to have

therapeutic potential to reduce glycation and the incidence of common diabetes-related health complications.[46]

SCIENTIFIC NOMENCLATURE CHANGE

In 2020 there was an official nomenclature change for several species of *Lactobacillus* bacteria. Among the changes, the species formerly referred to as *Lactobacillus fermentum* ME-3 is now named *Limosilactobacillus fermentum* ME-3. Although the new name henceforth appears in scientific publications, the older traditional name continues to be used in general communication.[47]

With its wide range of documented benefits linked to glutathione synthesis, *Lactobacillus fermentum* ME-3 is one of the strongest multi-functional probiotics ever discovered.

HOW TO OBTAIN PRODUCTS CONTAINING *LACTOBACILLUS FERMENTUM* ME-3

The University of Tartu owns the patent on the method to produce *Lactobacillus fermentum* ME-3. Commercial products containing ME-3 are available in many countries, including the U.S. under the brand name Reg'Activ. Products containing *Lactobacillus fermentum* ME-3 are easily available by doing an internet search for Reg'Activ or *Lactobacillus fermentum* ME-3.

Taking a product that contains *Lactobacillus fermentum* ME-3 is the most effective method of increasing glutathione levels; however, consulting a physician is strongly recommended before consumption. In boosting glutathione levels, *Lactobacillus fermentum* ME-3 provides support for antioxidant protection, immune and anti-viral activity, and detoxification, which will likely improve health, and increase lifespan and healthspan.

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