Lactobacillus fermentum ME-3:
A New Era In Glutathione Therapy

In 1995 group of scientists were testing a wide range of *Lactobacillus* bacteria for antioxidant activity. While most failed, a strain named *Lactobacillus fermentum* ME-3 exhibited extremely strong antibiotic activity. Further testing revealed that *Lactobacillus fermentum* ME-3, which is often just called ME-3, was found to synthesize glutathione.

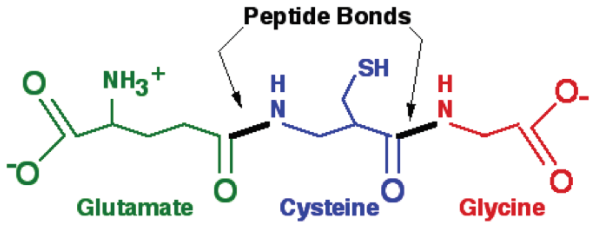
This article will discuss the discovery and scientific research on *Lactobacillus fermentum* ME-3 and review the functions of glutathione including recent studies which suggest that glutathione is an effective and reliable biomarker of aging.

Since glutathione's antioxidant activity is crucial for every cell in the body, the discovery of a strain of probiotic bacteria could synthesize glutathione and boost glutathione levels in humans has significant health and medical implications.

The history of the discovery of *L. fermentum* ME-3 began in 1994, when joint research study was initiated between the University of Linkoping in Sweden and the University of Tartu in Estonia. This purpose of this collaboration was to examine associations between allergies and intestinal microbiota in two comparative populations: Estonians with a low prevalence and Swedes with a high prevalence of allergy. As part of this study, on March 2, 1995, Professor Marika Mikelsaar isolated five strains of *Lactobacillus fermentum* from the intestinal tract of a healthy one-year old Estonian child. Overall, more than 200 human strains *Lactobacillus* bacteria were collected for this study.[1]

In 1996 the Dutch company MONA engaged the University of Tartu to test both the MONA and the U. of Tartu Department of Microbiology's collection of *Lactobacillus acidophilus* strains for antioxidant properties. There was significant disappointment when none of the *L. acidophilus* strains exhibited good antioxidant activity. However, upon testing the lactobacilli strains from the previous Swedish/Estonian study, it was discovered that the *Lactobacillus fermentum* ME-3 strain isolated from one of the Estonian children exhibited extremely high antioxidant activity.

A Complete Glutathione System: Initial studies showed that *Lactobacillus fermentum* ME-3 bacteria contain glutathione.[2] Subsequent investigation revealed that ME-3 bacteria don't just contain glutathione, the bacteria are actively synthesizing glutathione. Follow-up studies revealed that ME-3 boosts glutathione via three independent mechanisms: synthesis, transport and redox recycling. Thus, in addition to synthesizing glutathione, ME-3 is also able to extract glutathione from the surrounding environment, and it can recycle oxidized or "used up" glutathione back to its active or reduced form. Consequently, scientists are calling *Lactobacillus fermentum* ME-3 **"A Complete Glutathione System"** and emphasize that nothing previously has been found to have the capability of boosting glutathione levels by three different mechanisms at the same time.[3]



Structure of Glutathione

Glutathione is a tripeptide amino acid that is made in every cell throughout the body. Since ME-3 produces glutathione, it makes sense that many of ME-3's benefits parallel the primary benefits of glutathione in humans.

The Benefits of Lactobacillus fermentum ME-3
After discovering that *Lactobacillus fermentum* ME-3 expresses strong antioxidant activity, follow-up studies began to reveal that ME-3 produces a wide range of additional health benefits. ME-3's multiple benefits fall within four categories: antioxidant activity, immune system support, anti-inflammatory activity, and detoxification. Consequently, scientists have been studying ME-3 for the past 20 years, and its unique health-promoting benefits are summarized below.

Glutathione Overview: Glutathione is one of the most important antioxidants in the body and it is frequently referred to as "The Master Antioxidant."[4] An increasing number of studies link glutathione depletion with an increase in oxidative stress and a greater incidence of disease and accelerated aging. For example, reduced plasma glutathione levels have been shown to represent an increased risk for cardiovascular disease.[5] Glutathione depletion has also been shown to be a primary cause of the neurodegeneration that leads to Parkinson's disease.[6] Similarly, increased oxidative stress in Alzheimer's disease has been attributed to decreased levels of glutathione in the brain.[7] In one review paper, the authors state the following:

> *"Glutathione (GSH) plays an important role in a multitude of cellular processes, including cell differentiation, proliferation, and apoptosis, and as a result, disturbances in GSH homeostasis are implicated in the etiology and/or progression of a number of human diseases, including cancer, diseases of aging, cystic fibrosis, and cardiovascular, inflammatory, immune, metabolic, and neurodegenerative diseases."*[8]

ME-3's Antioxidant Activity: In 1956 Denham Harmon, MD introduced the Free Radical Theory of Aging in an article titled: *Aging: a theory based on free radical and radiation chemistry.*[9] Although the idea was initially met with skepticism, free radicals and free radical damage are now recognized as one of the primary causes of the aging process.[10] In fact, free radical damage is now associated with all of the common diseases of aging.[11]

In addition to synthesizing glutathione, ME-3 also produces the antioxidant enzymes glutathione peroxidase and glutathione reductase, which contribute to glutathione function and regeneration.[12]

Researching *Lactobacillus fermentum* ME-3's antioxidant activity also revealed that is produces the mitochondrial antioxidant enzyme manganese superoxide dismutase (MnSOD).[13] Because mitochondria utilize about 90% of inhaled oxygen, they are highly vulnerable to free radical oxidative damage.[14] MnSOD is the primary antioxidant that neutralizes highly reactive superoxide radicals (O_2^-), which are primarily generated within mitochondrial membranes.[15] Consequently, MnSOD also plays a critical role protecting cells against free radical oxidative stress.

Lactobacillus fermentum ME-3 provides additional antioxidant support because it helps regenerate other oxidized antioxidants such as vitamin C, vitamin E, lipoic acid and coenzyme Q10 back to their active forms. *Lactobacillus fermentum* ME-3 has the highest Total Antioxidant Activity (TAA) and the highest Total Antioxidant Status (TAS) of any probiotic tested to date.[16]

Table I. Antioxidant-related properties/effects of ME-3.

Property/effect	**Experimental (ES), animal (AS), human (HS) study (references are given in the parentheses)**
Expression of MnSOD, prolonged survival time at presence of high H_20_2, scavenging of superoxide and hydroxyl radicals	ES[17]
Characterized by high TAA and TAS values	ES[17,18]
Containing of GSH and related antioxidative enzymes	ES [18,19]
Working as natural antioxidant in soft cheese spreads with different fats	ES [20]
Maintaining its high TAA during production of probiotic cheese	ES [21]
Removal effect of metals (prooxidants) from environment	ES [22]
Elevation of blood TAS or TAA and TAA in the gut mucosa	HS, AS [18,23,24,25,26]
Elevation of oxiresistance of LDL	HS [18,23,26]
Lowering level of oxLDL	HS [23,24,26]
Lowering level of isoprostanes	HS [23,26,27]
Lowering the glutathione redox ratio in blood, in the gut mucosa, in skin	HS, AS [18,23,24,25,28]
Lowering lipid peroxidation in the gut mucosa	AS [25,28]
Lowering level of BCD-LDL	HS [23,26,29]
Positive effects on postprandial status of OxS, blood lipoprotein's status and urine isoprostanes	HS [26,27]

Legend: BCD-LDL , baseline diene conjugates in low density lipoprotein; GSH ,reduced glutathione; H2=2, hydrogen peroxide; LDL, low density lipoprotein, ; Mn-SOD, manganese superoxide dismutase; oxLLD, oxidised low density lipoprotein; OxS, oxidative stress; TAA, total antioxidative activity; TAS, total antioxidative status.

Chart originally appeared in: *Lactobacillus fermentum* ME-3 – an antimicrobial and antioxidative probiotic. Microb Ecol Health Dis. 2009 Apr;21(1):1-27.

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Promotes Cardiovascular Health: *Lactobacillus fermentum* ME-3 has a beneficial effect on several cardiovascular risk factors. In a 2-week double-blind, placebo-controlled trial, individuals taking ME-3 achieved reductions oxidized LDL-cholesterol (71 U/l to 63 U/l), BDC-LDL (23.8 umol/l to 22.0 umol/l), and triglycerides 2.1 mmol/l to 1.9 mmol/l) and beneficial increases in PON (110.0 U/l to 133.4 U/l) and HDL-cholesterol (1.4 mmol/l to 1.5 mmol/l).[30] At the end of this trial, these same markers had gotten slightly worse for the placebo subjects.

Enhances Detoxification: Glutathione is critical regulator of detoxification in every cell of the body, but especially in the liver and kidneys. Glutathione detoxifies toxins in food, heavy metals, air pollutants, pharmaceuticals and a wide range of other toxins. Because ME-3 synthesizes glutathione, scientists conclude it will increase the body's detoxification capabilities. It is important to realize glutathione gets depleted during the process of detoxifying things that are quite common many people's lives such as alcohol[31], artificial sweeteners such as aspartame[32], and tobacco smoke.[33] Acetaminophen, which is a common ingredient in many OTC and prescription analgesics depletes glutathione very rapidly which is why acetaminophen overdose is the leading cause of acute liver failure in the United States.[34]

Promotes liver health: The liver is the primary organ for detoxification. There are two main phases of detoxification in the liver, which are called Phase 1 and Phase 2 detoxification pathways. A significant number of free radicals are generated during Phase 1, which can result in liver damage if adequate antioxidants (especially glutathione) are not available to quench them.[35]

Reduces Inflammation: *Lactobacillus fermentum* ME-3 has been shown to significantly inhibit levels of several key inflammatory markers including glycated hemoglobin (HbA1c), high sensitivity C-reactive protein (hs-CRP) and interleukin 6 (IL-6), and it is also capable of stimulating production of the anti-inflammatory and anti-diabetic peptide adiponectin.[36]

Promotes Healthy Bacterial Balance: ME-3 produces significant amounts of short-chain fatty acids (SCFAs), hydrogen peroxide, and nitric oxide.[37] These postbiotic™ metabolites function in several ways to promote the growth of beneficial bacteria and suppress the growth of pathogens, which helps maintain a healthy microbiome.

Detoxifies Organophosphate Pesticides: Organophosphates were developed in the 1940s as highly toxic biological warfare agents. Today they are one of the most widely used pesticides worldwide. In addition to being sprayed on agricultural food crops, they occur in many pesticide and insecticide products commonly used on residential lawns and gardens. They are also used in plasticizers, as antifoaming agents in lubricants and hydraulic fluids and flame retardants.

Lactobacillus fermentum ME-3 s increases the activity of paraoxonase enzymes (called PON1), which helps detoxify organophosphates.[38]

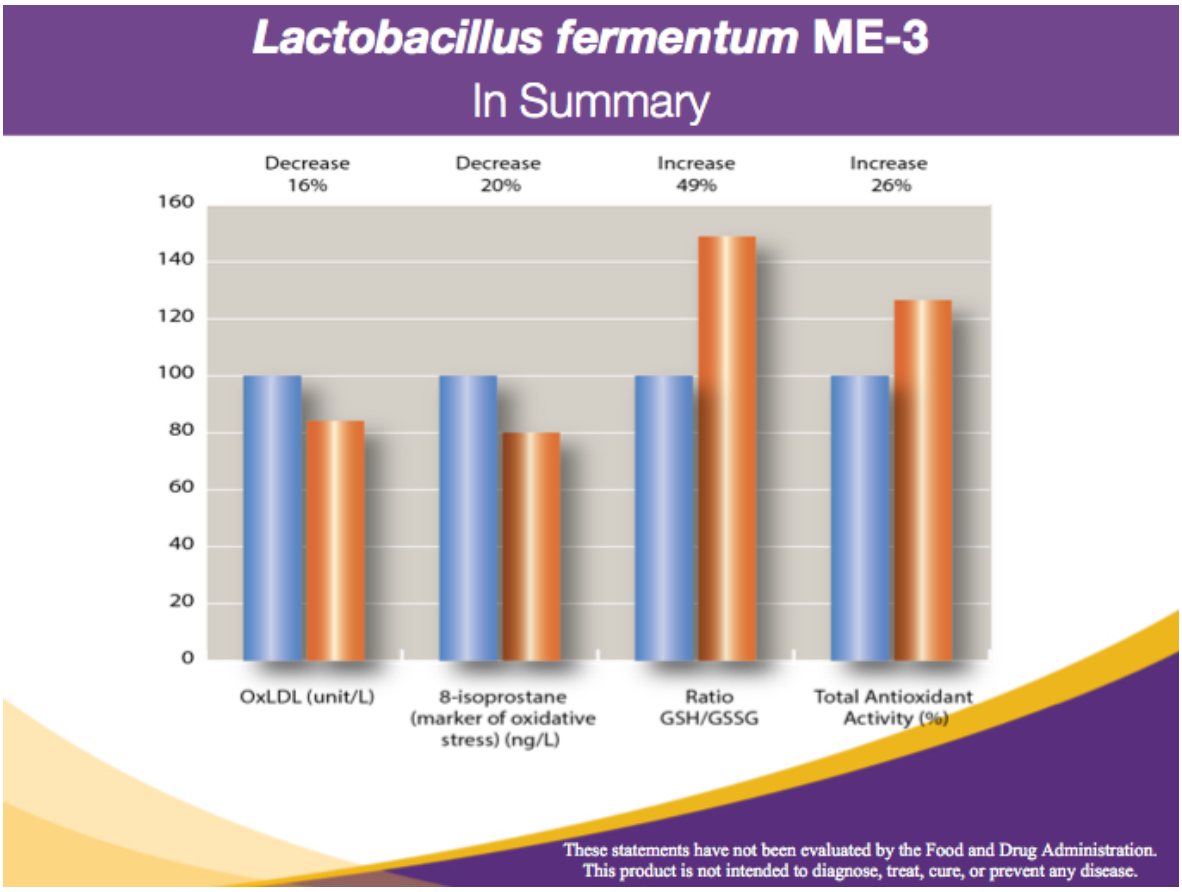
In a U.S. government funded study titled Forth National Report on Human Exposure to Environmental Chemicals, it was reported that 93% of children tested had measurable metabolites of organophosphates.[39] Also, 2004 report stated, "Almost every person is, or has been, exposed to organophosphate insecticides in their home, work or environment."[40] These compounds are highly toxic, especially to the developing nervous system in young children. Studies have linked childhood organophosphate exposure to higher incidence of ADHD[41] and autism[42]. A probiotic such as ME-3 that improves detoxification of organophosphates may help reduce the risks to neurological diseases such as autism and ADHD.

Immune Function: Lymphocytes are a critical component of the immune system. Their primary job is to defend us against bacteria, viruses and other foreign invaders. When faced with a challenge, the body dramatically increases the production of lymphocytes to fight the inflection. Glutathione is required for the production and function of lymphocytes. Thus, glutathione levels are a critical regulator of immune function.[43]

Stability: To be effective, a probiotic must be able to survive exposure to the highly acidic conditions in the stomach and digestive enzymes and bile acids present in the small intestine.

The results of *in vitro* studies report that *Lactobacillus fermentum* ME-3 survives at pH values ranging from 4.0 to 2.5 without a loss in viable cell count. Even at pH 2.0, the ME-3 strain survived for up to 6 hours. When exposed to bile acids, ME-3 survived for 24 hours without significant loss of live bacteria.[44] Although testing in the human body has not been conducted, *in vitro* testing suggests that *Lactobacillus fermentum* ME-3 may be able to tolerate exposure to harsh acidity in the stomach and exposure to bile acids in the small intestine. Hence, *Lactobacillus fermentum* ME-3 thrives and survives in conditions that simulate the harsh environments of the human gastrointestinal tract.

Lactobacillus fermentum ME-3: Summary of Human Clinical Trials



1. **Reduction in Oxidized LDL-Cholesterol:** The first column shows that individuals taking ME-3 had a 16% reduction in the levels of oxidized LDL-cholesterol compared to placebo controls.[45]

2. **Reduced 8-Isoprostanes:** The second column reports that people taking ME-3 had a 20% reduction in levels of 8-isoprostanes, which indicates reduced amounts of free radical damage due to ME-3's antioxidant activity.[46]

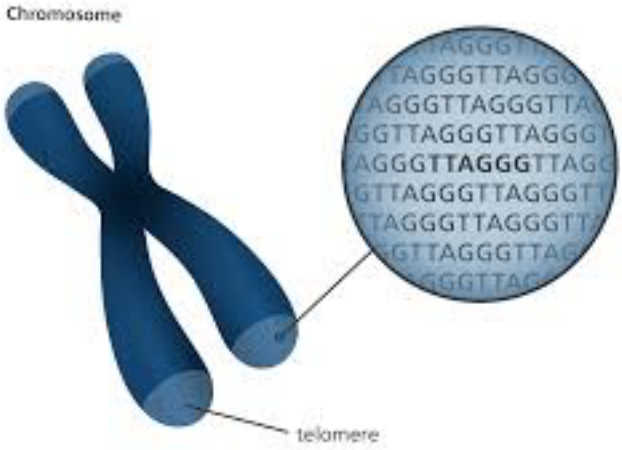
3. **Elevated Glutathione:** The study reported in the third column shows that people taking ME-3 had a remarkable 49% increase in the ratio of reduced to oxidized glutathione.[47]

4. **Probiotics, Oxidative Stress, Inflammation and Diseases:** [48] The fourth column reports the increase in Total Antioxidant Activity (TAA) gained by the individuals taking *Lactobacillus fermentum* ME-3. (data for this comes from the following 2 studies; individual results are not shown on graph)

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.[49] Individuals receiving ME-3 experienced significant reduction in inflammation with accompanying improvements in skin condition, blood markers and in self-assessment rating scores.[50]

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, paraoxonase enzyme activity as well as reductions in markers of inflammation and free radical damage.[51]

Conclusion: A new understanding that has emerged from the Human Microbiome Project is the concept of keystone strains of probiotic bacteria. Keystone strains are defined as sub-dominant strains of probiotic bacteria that are capable of exerting large biological effects. *Lactobacillus fermentum* ME-3, which produces glutathione, is a keystone strain of probiotic bacteria. When ingested by humans in doses ranging from 4 to 6 billion bacteria per daily dose, ME-3 has been shown to provide substantial reduction in inflammatory markers as well as improvements in antioxidant protection and detoxification. These biological changes are known to contribute to improvements in a wide range of health conditions. Consequently, lutathione-induced improvements in health correlate with the concept that glutathione levels are a biomarker of aging.



Glutathione: A Reliable Biomarker of Aging

In the late 1980s & 1990s Drs. Calvin Lang & John Richie started studying glutathione's effect on aging. Their previous studies in mosquitoes, mice and humans had shown that a deficiency of glutathione in many tissues and organisms is a general phenomenon of aging. They hypothesized that if glutathione deficiency could be corrected it would result in an increase in life span. In their initial study, they administered a glutathione precursor to the drinking water of mosquitoes

which resulted in a 50-100%. The outcome was a 30-38% increase in life spans over control values.[52]

In a related study, Canadian researcher Dr. G. Buonous studied the effects of a glutathione-rich diet (whey protein) on glutathione levels and survival of 21-month-old mice (equivalent to 55-60 years old in humans) over six months, which was the equivalent of 80 years old in humans. Both tissue glutathione levels and longevity increased significantly over controls.[53] Also, paralleling the decline in glutathione levels with aging in animals, other studies reported that glutathione levels gradually decline with aging in healthy men and women ranging in age from 20 to 94.[54,55]

Glutathione reductase is an enzyme that increases levels of reduced/active glutathione. Researchers in Denmark measured levels of glutathione reductase in 41 centenarians who were 100 to 105 years old and compared them with a similar group of average individuals between the ages of 60-79. The results showed that glutathione reductase levels in centenarians were higher than those in the younger elderly subjects. Also, glutathione reductase activity was highest in the centenarians who had the highest functional capabilities. Consequently, higher glutathione reductase activity, which increases reduced glutathione levels, seems to be associated with better health and increased lifespan.[56]

Paralleling the fact that higher glutathione levels are associated with better health and increased longevity are studies reporting that lower glutathione levels are associated with chronic diseases and that glutathione levels are a biomarker that can be used monitor the severity and progress of diseases.[57] In fact, lower glutathione levels are associated with a wide range of chronic degenerative diseases such as arthritis, HIV/AIDS, various cancers, cataracts, diabetes, heart disease, leukemia, kidney failure, hearing loss, macular degeneration, and urinary, GI and musculoskeletal diseases.[58,59,60,61]

The evidence linking glutathione levels with greater health and increased longevity are causing some researchers to proclaim that glutathione is a reliable biomarker of aging. For example, a 2016 study published in Oxidative Medicine and Cellular Longevity is titled: ***Glutathione as a biomarker in Parkinson's Disease: Associations with Aging and Disease Severity.***[62]

Glutathione & Mitochondrial DNA: Low levels of glutathione have been shown to be associated with progressive loss of mitochondrial function, which results from accumulated damage to mitochondrial DNA (mtDNA).[63] In animal studies, the ability to protect mitochondrial DNA from damage is directly proportional to longevity.[64]

Telomeres & Telomerase: Telomeres are repeat sections of DNA located on the ends of each chromosome. The purpose of telomeres is to protect the ends of chromosomes, which allows cells to divide without damaging our genes. However, telomere shortening is a biomarker of aging. With each cellular division, telomeres shorten slightly and telomere shortening is the main cause of age-related breakdown of cells.[65,66] In 2009, the Nobel Prize in Physiology or Medicine was awarded to three scientists for the discovery of how our chromosomes and DNA are protected by telomeres and the enzyme telomerase.[67]

Telomerase is an enzyme that can place additional DNA repeat sections on the ends of telomeres. Preliminary results from animal studies and human cell culture studies suggest that therapies which increase telomerase activity and lengthen telomeres hold the key to life extension and reducing the rate of aging.[68]

Glutathione & Telomerase: Glutathione levels have been shown to parallel telomerase activity, which is an important indicator of lifespan. The results of this study reveal that glutathione is a key regulator of telomerase activity. Furthermore, the authors of this study state that telomerase activity was found to be maximal when the ratio of reduced/oxidized glutathione was high.[69] A study with elderly humans revealed that higher glutathione levels are associated with a lower incidence of illnesses and higher levels of self-rated health, which is what would be expected if elevated glutathione levels are increasing telomerase activity and lengthening telomeres.[70]

Because glutathione deficiency is associated with increased risks to chronic degenerative diseases and increased glutathione levels are associated with better health and increased longevity, it has been suggested that glutathione blood levels may be an effective and reliable marker of physiological/functional aging.[71]

The body of research that has been reviewed in this article shows clearly that higher glutathione levels are associated with better health and life extension. Thus, one of the most effective proactive steps people can take to improve their health and their longevity is to boost their glutathione levels.

Boosting Glutathione With *Lactobacillus fermentum* ME-3: In human clinical trials, individuals taking ME-3 achieved a 49% increase in the ratio of reduced to oxidized glutathione. Although Lactobacillus fermentum ME-3 is a stain of probiotic bacteria, products containing ME-3 should not be categorized as probiotics. Glutathione is so critically important to health that products containing ME-3 should be categorized as anti-aging and life extension products. Having a safe, effective way to boost glutathione levels daily has the potential to be a revolution is health and medicine.

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