EMOTHION®

S-Acetyl Glutathione

The effective
-IN BODY- form
of glutathione

White Paper

Gnosis by Lesaffre

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1 INTRODUCTION

Reduced glutathione (GSH) is the most powerful antioxidant agent in all living organisms.

Chronic oxidative stress, some pathologies and aging process can reduce GSH level in the organism.

Restoring GSH level is a good tool to deal with the above states but direct oral supplementation with GSH is not very efficient because of its poor absorption and because of its hydrolytic degradation in the digestive system.

EMOTHION® - manufactured by Gnosis by Lesaffre - **is a clinically studied and patented new orally stable and crystalline form of S-Acetyl-Glutathione**, with enhanced bioavailability and fast action.

EMOTHION® has opened up new possibilities to boost glutathione levels in humans for **improved wellness and health** throughout all stages of life.

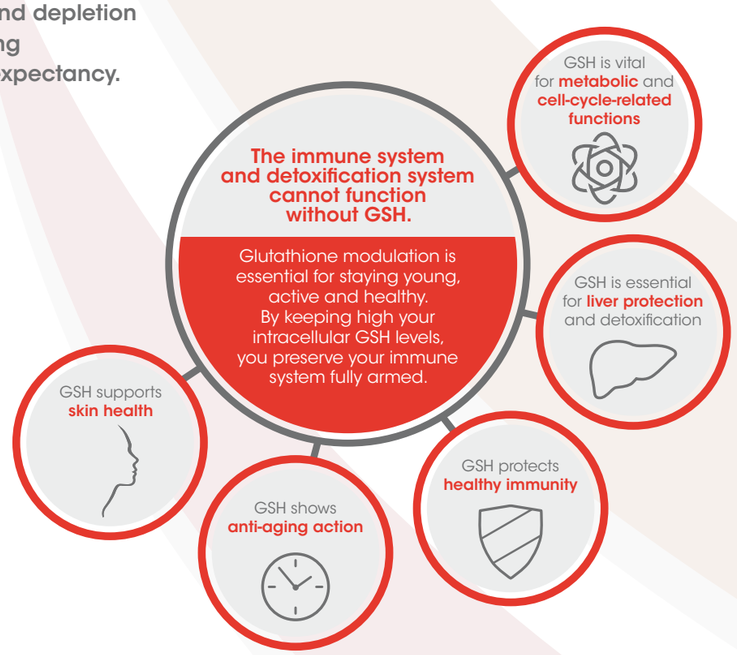
2 GSH THE MASTER ANTIOXIDANT

Oxidative reactions yield high-energy compounds that fuel various biochemical, biophysical, and mechanical functions of aerobic organisms.

These reactions are a continuous persistent source of potentially cytotoxic Reactive Oxygen Species (ROS). Under physiological conditions, ROS produced in the course of normal metabolism are fully inactivated by an elaborate cellular and extracellular antioxidant defence system.

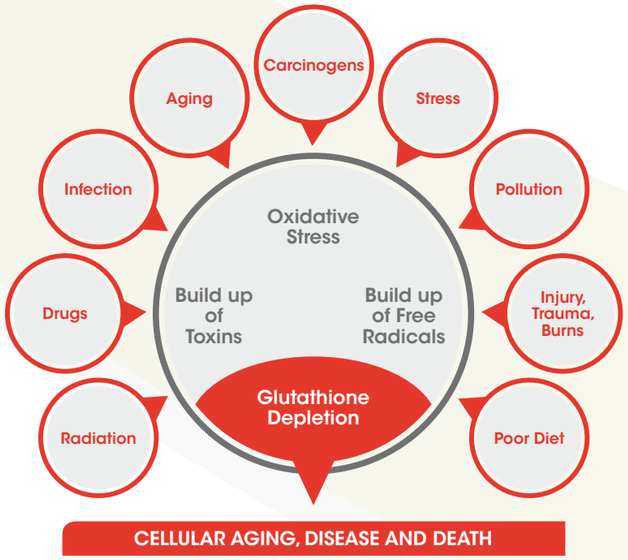
Reduced glutathione (GSH of L-Glutathione) is the most abundant endogenous antioxidant produced by the human body on a cellular level. **GSH minimizes oxidative stress and the downstream of negative effects associated with oxidative stress**.

GSH is a critical regulator of oxidative stress and immune function. It protects the brain and acts as a free radical scavenger and inhibitor of lipid peroxidation. Its deficiency and depletion are one of the primary factors causing cellular aging and reduction of life expectancy.



3 WHY GSH DECREASES IN ALL BODY CELLS

Cellular GSH concentrations are reduced markedly in response to protein malnutrition, oxidative stress, and many pathological conditions. What depletes GSH levels in our bodies can be pointed out into two causes: internal and external factors.



CELLULAR AGING, DISEASE AND DEATH

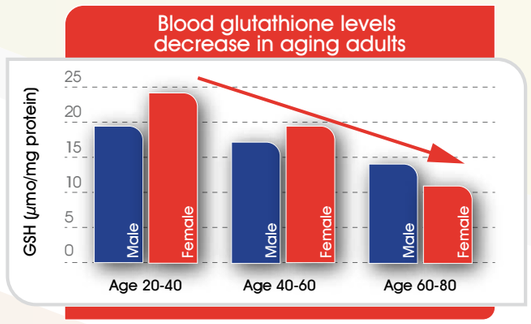
Internal factors include the increasing need for glutathione as an important part of various processes in our bodies, such as food for our immune system, recycling of vitamin C, vitamin E and alpha lipoic acid, repairing our DNA, and protecting our cells from oxidative stress, etc.

External factors are those which deplete glutathione at most.

Many toxic and harmful substances we are exposed to on a daily basis require considerable amounts of glutathione in order to be eliminated through detoxification process.

Low GSH levels have been reported in liver, kidney, heart and blood of aging mice and are suggested to be responsible for worsening the aging process. Several studies showed that plasma GSH levels decrease with age.

This deterioration of GSH homeostasis is in conjunction with other physiological events, in the ageing process and the appearance of age-related diseases.

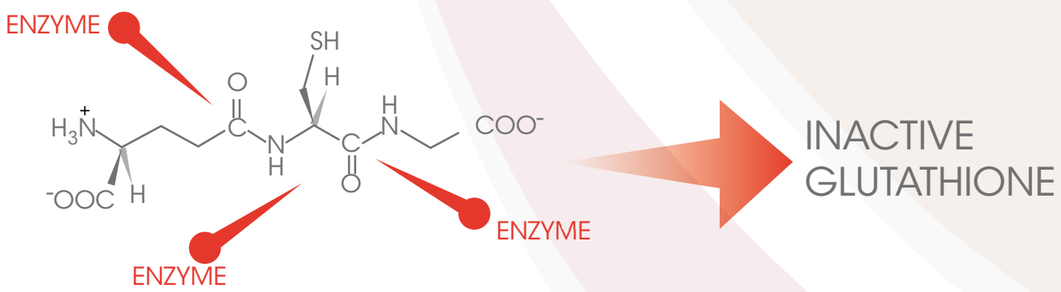


4 GLUTATHIONE AND THE ABSORPTION LIMITS CHALLENGING

It has been demonstrated that GSH is poorly absorbed by oral route. Systemic bioavailability of orally consumed glutathione is low because the molecule, a tripeptide, is the substrate of proteolytic enzymes (peptidases - glutamyl transpeptidase - GGT) of the alimentary canal, and because of the absence of a specific carrier of glutathione at the cell membrane site.

The use of glutathione as a nutritional supplement is limited by its unfavorable biochemical and pharmacokinetic properties:

- It is not directly taken up by cells
- It needs to be broken down into amino acids and re-synthesized into GSH
- The re-synthesis process is often impaired during diseases status



GSH is a linear tripeptide of L-glutamine, L-cysteine, and glycine, technically N-L-γ-glutamyl-cysteinyl glycine or L-Glutathione. The molecule has a sulfhydryl (SH) group on the cysteinyl portion.

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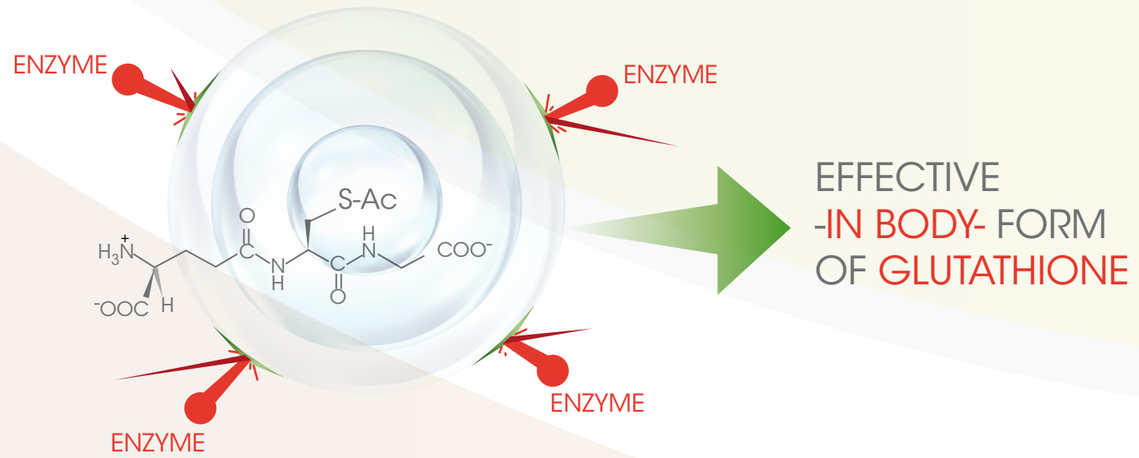
S-Acetyl Glutathione

5 THE EFFECTIVE -IN BODY- FORM OF GLUTATHIONE

EMOTHION® is the crystalline form of S-Acetyl Glutathione, the cutting-edge alternative developed to overcome the poor effectiveness of GSH supplementation, due to its poor absorption and its hydrolytic degradation in the body.

EMOTHION® has more rapid dissolution rate and, therefore, is orally well absorbed. **Once internalised into the cells, EMOTHION® increases GSH level more efficiently than normal GSH**. EMOTHION® is a precursor of glutathione and works as GSH-replenishment agent.

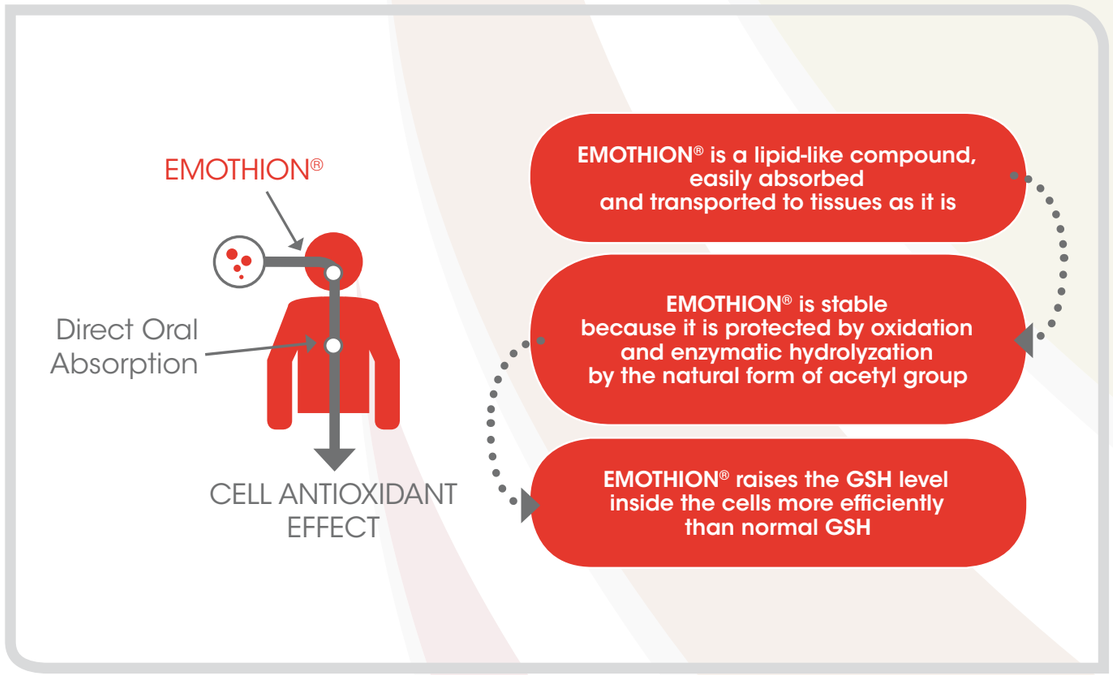


The acetyl group ($COCH_3$) is attached to the sulfur atom of cysteine of the GSH molecule and protects it from the rapid breakdown of GSH into amino acids which occurs in the gastrointestinal tract.

The S-Acetyl Glutathione behaves as a lipid-like compound, and so, it is taken up intact by chylomicrons in the gut with facilitated absorption through the intestinal wall, thus enabling the molecule to pass extensively into the cells.

Once absorbed, **EMOTHION®, as S-Acetyl Glutathione, is more stable than GSH in plasma and is taken up intact by the cells**. Only at this time it is de-acetylated by the abundant cytoplasmatic thioestherases to produce reduced glutathione.

This passage does not require energy expenditure and allows GSH to be immediately available for all the biological functions wherein it is required.[1,2]



EMOTHION®, the greatest innovation

- EMOTHION® is the active form of GSH S-Acetyl Glutathione. Its crystalline form optimizes the absorption of S-Acetyl Glutathione, a molecule that exists in several polymorphic forms which can have different physicochemical characteristics that influence its dissolution rate, solubility and therefore bioavailability.

EMOTHION® offers value-added organoleptic properties. The acetyl group on the sulfur atom of cysteine reduces the unpleasant smell and taste of the sulfur atom that confers the typical aftertaste to glutathione. Orally administered, it is odor-free and tasteless and lift up the GSH supplementation in a compliant practice.

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S-Acetyl Glutathione

6 CLINICAL SUPPORT

The scientific rational for effective GSH supplementation is still a debate and controversial studies have been published. Current data on long-term treatments seem to support the efficacy of oral administration, with an increased availability of GSH in cellular districts, but only after some months from the onset of treatment. However, the increased GSH levels is dose and time dependent.

The intestinal enzymatic degradation which the GSH is subjected to, leads to its poor absorption and a low bioavailability and requires a very long oral GSH supplementation in order to appreciate a possible increase of its levels.

EMOTHION®, on the contrary, directly increases the levels of GSH in the body. This product has been consistently tested versus qualified commercial GSH, both in pre-clinical and clinical trials, in order to provide evidence of its fast and effective benefits.

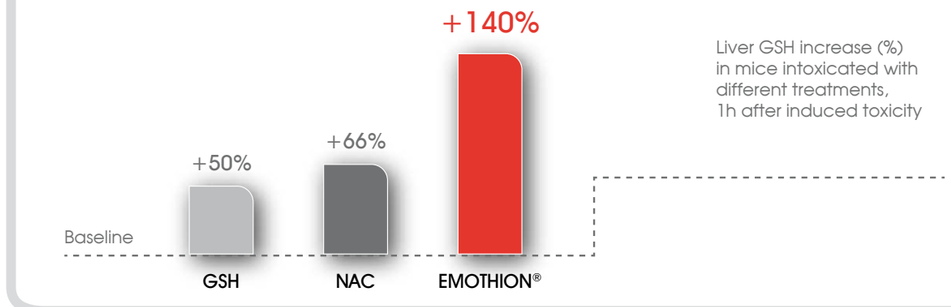
Pre-clinical trial shows boosted protective effect from EMOTHION®

Acute Paracetamol (PA) intoxication in mice is a good model to investigate compounds functional to restore haematic and hepatic GSH levels, protecting from the related acute toxicity.

EMOTHION® has been tested in comparison to GSH and N-acetyl cysteine (NAC). NAC is a popular cysteine precursor commonly used in dietary supplements to reestablish cell GSH levels.

Oral treatment with EMOTHION® resulted in the improved recovery and a higher efficacy and a source of exogenous reduced glutathione in the treatment of acute hepatotoxicity.

EMOTHION® restores liver GSH level better than GSH and its precursor N-acetylcysteine (NAC), after GSH depletion by paracetamol (PA) intoxication.



Liver GSH increase (%) in mice intoxicated with different treatments, 1h after induced toxicity

Moreover, the experiment was set up also to evaluate the effect of both precursors and GSH on the biochemical hepatotoxicity markers, in the same model of PA induced toxicity.

Alanine Aminotransferase (ALT) is an enzyme recognized as one of the major index of liver sufferance and is strongly affected by PA intoxication. It is considered as a valid endogenous diagnostic biomarker for liver disease and hepatic toxicity.

EMOTHION® protects liver by reducing ALT level % in mice serum after PA intoxication.

Serum ALT after PA intoxication

GSH	5,400 (IU/L)
NAC	5,200 (IU/L)
EMOTHION®	2,200 (IU/L)

ALT: Alanine Aminotrasferase enzyme levels, a recognized biomarker in liver disease

EMOTHION® treatment was twofold more effective than the other treatments (GSH and NAC).

EMOTHION®, enhanced bioavailability and greater antioxidant defence in humans

A comparative single center, single dose, randomized, open-label, two-sequence, two-period, cross-over study has been carried out in eighteen healthy volunteers, with the purpose to evaluate the newly stable form of crystalline S-Acetyl Glutathione - EMOTHION® - versus qualified commercial GSH reference.

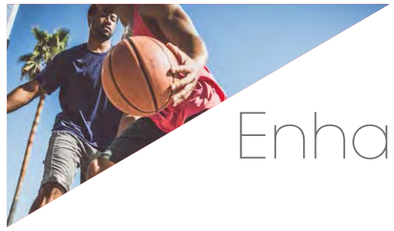
The study measured the levels of both GSH in plasma and in the erythrocyte cell fraction (RBC) after single administration of 3.5 g, in a window of 24 hours.

The aim of this clinical study was to compare the bioavailability of GSH and Emothion® in a single dose oral absorption study in healthy volunteers and the main pharmacokinetic parameters were calculated (C_{max}, t_{max}, $AUC_{0\text{-}24h}$).

Additionally, the ratio of reduced/total glutathione (GSH/Gtot) was calculated. This ratio is considered as a pharmacodynamic endpoint indicating the long term GSH status and the anti-oxidizing power of individuals.

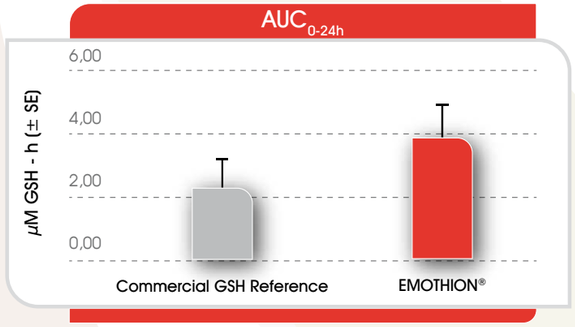
In fact, the ratio of GSH/Gtot is an indicator of cellular health, with reduced GSH constituting up to 98% of cellular glutathione under normal conditions. However, the GSH/Gtot ratio is lower in neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease.

Measuring the GSH/Gtot ratio in pathological tissues and experimental models in comparison to controls' results is an excellent recognized model to assess potential therapeutics efficacy of an active ingredient, such as EMOTHION®, in maintaining cellular redox potential.



Enhanced bioavailability

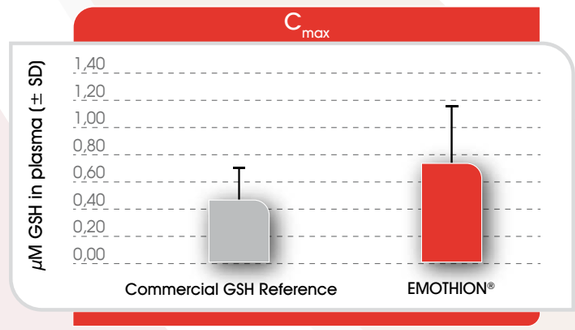
EMOTHION® raises glutathione levels better than the Commercial GSH Reference, after one administration only. EMOTHION® was not detected in the form of S-Acetyl GSH, either in plasma or in the cell fraction, confirming that it is soon quickly de-acetylated and converted in its active metabolite, glutathione.



Fast effective EMOTHION® induced a $AUC_{0\text{-}24h}$ 68.8% higher than reduced GSH, after comparison of GSH plasma levels.

Greater antioxidant defence

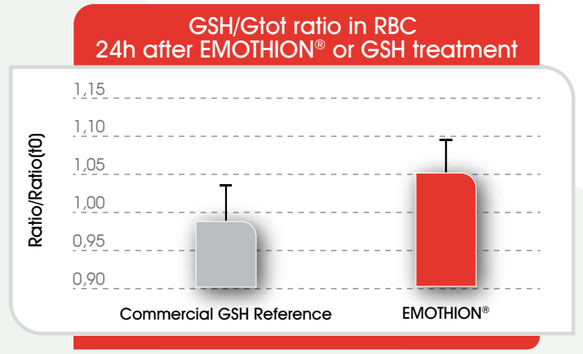
Oral supplementation of EMOTHION® generates a higher GSH rate (C_{max}) that may be helpful to counteract GSH consumption and enhance antioxidant defences during particular stressful conditions, such as infections, inflammation, physical exercise or postprandial phase.



EMOTHION® induced a C_{max} 57.4%, higher than reduced GSH.

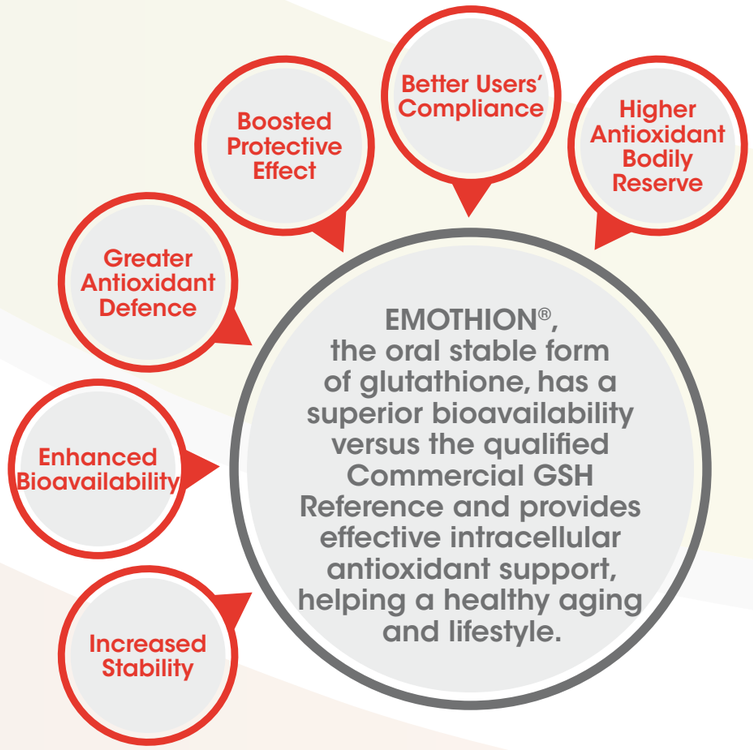
Higher antioxidant bodily reserve

EMOTHION® induced a ratio in the RBC that is significantly higher than the Commercial GSH Reference at long term determination, 24 hours after dosing.



In subjects supplemented with EMOTHION®, GSH/Gtot ratio increased significantly from basal level ($p < 0.01$) while it remained unchanged in the group supplemented with the Commercial GSH Reference, up to 24 hours after supplementation.

EMOTHION® treatment boosts the benefits of glutathione supplementation for fast antioxidant defence.



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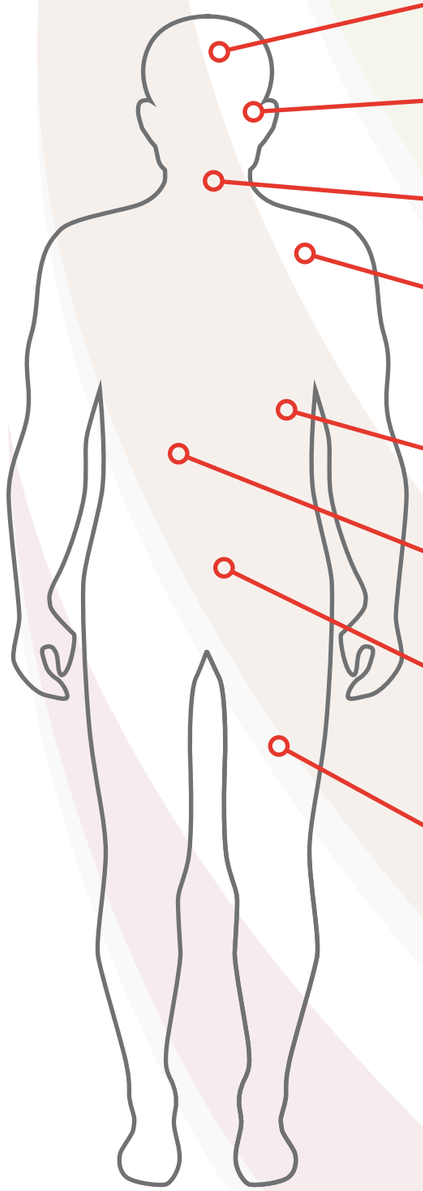
S-Acetyl Glutathione

7 USE TIPS



Cognitive Health

EMOTHION® may support cognitive health through the increase of GSH levels, the most prevalent antioxidant in the brain. The brain is particularly vulnerable to oxidative damage due to the high levels of unsaturated lipids, oxygen, redox metal ions, and relatively poor antioxidant systems. Increasing glutathione levels remains a promising therapeutic strategy to slow or prevent mild cognitive impairment (MCI) and Alzheimer's disease (AD), where the oxidative stress has been associated with their onset and progression [19].

Anti-aging

GSH is central and critical to all of the primary processes of cellular protection. Oral supplementation of EMOTHION® raises the level of GSH that naturally decreases with age, improving cellular health and function, helping to repair the damage caused by free radicals and their accumulation in the body cells [5, 14].

Anti-inflammatory

EMOTHION® provides ready-to-use GSH that helps to fight inflammation at the source, where the inflammatory status occurs, helping to repair the oxidative damage and its progression.
Low-grade and chronic inflammation is a highly significant risk factor for elderly people, as most if not all age-related diseases share an inflammatory pathogenesis [15].

Skin Health

By raising the GSH levels, EMOTHION® may improve quality, health and appearance of skin, the body's first line of defence against exogenous injuries, such as oxidants, UV rays, toxins and infections. By topical and oral application the GSH released by EMOTHION® may minimize age spots and wrinkles of exposed skin. Glutathione is also known as whitening and skin-lightening [24].

Immune Function

EMOTHION® is useful to increase GSH levels proposed to increase the innate and the adaptive immunity as well as conferring protection against infections [16].

Liver Health

EMOTHION® protects liver functions through the natural replenishing of GSH, the primary factor affecting liver activities and health. The liver contains the majority of the body's glutathione, used to detoxify the body and to regulate immune function [17, 18].

Energy Production and Cellular Metabolism

EMOTHION® provides free glutathione which can assist cellular metabolism through the prevention of anomalies and dysfunction of mitochondria, the organelle responsible for cellular energy production.
Loss of function in mitochondria can result in the excess fatigue and other symptoms that are common in almost every chronic disease [20, 21].

Athletic Performance and Recovery

The GSH frees by EMOTHION® may benefit athletic performance, by controlling oxidative stress and free radical formation during exercise. Increased strength and endurance, decreased recovery time from injury, less pain and fatigue and an increase in muscle-promoting activities may be associated with the use of glutathione. GSH improves the health and quality of mitochondria as it directly affects their energy producing capabilities [22, 23].

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Via Lavoratori Autobianchi, 1
20832 Desio (MB) - ITALY
+39 (0)362 16 70 001

137 rue Gabriel Péri
59700 Marcq-en-Baroeul - FRANCE
+33 (0)3 20 81 61 00

www.gnosisbylesaffre.com

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