SYNONYMS
GSH glutathione

EFFECT
The tripeptide glutathione is one of the main substances that can be used by the body to protect cells. Three very important functions of glutathione when providing that protection are the detoxifying properties, the immune-strengthening properties and the antioxidative function.

In principle, the body is able to create glutathione from the components from which it is constructed, i.e. the amino acids cysteine, glutamine and glycine, but there are many circumstances in which there are insufficient stores of not only cysteine, but also glutamine. Every day, the body is exposed to many factors that make a demand on the body's glutathione stores: stress, pollution, radiation, infection, medication, poor nutrition, ageing, sport and injury. Insufficient protection by glutathione can contribute to cell damage, ageing and, over time, illness. Glutathione depletion plays a determinative role in a large number of disorders. Keeping the glutathione stores at a high level is therefore also the holy grail of complementary medicine.

Until recently, many scientists were convinced that glutathione could not be absorbed intact, and that therefore the best method of boosting glutathione levels was through precursors such as NAC (N-Acetyl Cysteine) and with substances such as alpha lipoic acid. It was recently revealed that glutathione can actually be absorbed in significant quantities, meaning supplementation with glutathione is a justified and properly directed choice in order to stimulate the glutathione levels in cells.

Glutathione (γ-L-glutamyl-L-cysteinylglycine; GSH), is a tripeptide (combination of three amino acids), that can be created by the body from 3 amino acids: cysteine, glutamine and glycine. The thiol group (SH group) of cysteine is the active part of the molecule. The abbreviation GSH, which is used for reduced glutathione, alludes to this thiol group (SH) bound to the glutathione molecule (G).

Glutathione can be found in all living organisms and in all cells of the body in relatively high concentrations. It is the main sulphur compound in the body which does not form part of proteins. The glutathione antioxidant system is one of the main cellular defence mechanisms.

Glutathione exists in two forms: either the reduced form (GSH), or the oxidised form, commonly written as GSSG (also called glutathione disulphide). If the term “glutathione” is used, this usually means reduced glutathione. Glutathione only has a protective action in the body when in reduced form.

Glutathione occurs in fresh vegetables and fruit, fish and meat products, but especially asparagus, avocado, and walnuts are rich in glutathione. The glutathione concentrations can differ significantly between different foods. The intake of glutathione can also vary significantly between individuals. In normal circumstances, glutathione is produced by the body as required. As the age increases, and when there is greater oxidative stress, the body's own production can, however, be somewhat inadequate.

In the body there is often a high demand for glutathione and it is consumed rapidly in times of illness, stress, fatigue and physical exertion. In addition, there are a number of known causes of glutathione depletion, such as (ionising) radiation, stress, bacterial or viral infections, environmental toxins, smoking, the use of medication, (professional)sport, chemical pollution and heavy metals, a surplus of iron, surgery, burns and deficiencies of glutathione precursors or co-factors. By means of the antioxidant cascade, the body tries to recycle (reduce) used (oxidised) glutathione. In the latter process, other antioxidants such as vitamin C, vitamin E and alpha lipoic acid are used.

The cell's glutathione status is an important indicator of the cell function and the viability of the cell. When continuous oxidative stress by a number of the aforementioned factors depletes the body's glutathione stores to a point where the antioxidative protective mechanisms are inadequate, we speak of “distress”. The tissues with the highest percentage of polyunsaturated fatty acids (such as, for example, nerve tissue) are then the most vulnerable. Local free radical reactions can result in an increasingly expanding area of tissue damage. Cells that are too heavily damaged kill themselves (apoptosis) and this mechanism (apoptosis on account of glutathione depletion) plays a role in many degenerative disorders.

Very little glutathione circulates in the blood. Transport mainly takes place in the form of cystine, the oxidised and more stable form of cysteine. The body's cells import cystine from the bloodstream, reconvert cystine into cysteine, and use that to form GSH (with the help of, amongst others, ascorbate). Conversely, via the antioxidant cascade, glutathione can reduce oxidised forms of vitamin C and vitamin E and thus reaktivate them.
Antioxidative protection: Glutathione plays a central role in the body’s defence against oxidative stress. The SH group (thiol group) of the cysteine group is a stronger electron donor than many other compounds in the cell, and combined with the relatively high intracellular concentrations (several millimoles) that results in extremely powerful antioxidative properties. For these reasons, GSH is often able to scavenge reactive components before they damage cell structures such as DNA, RNA, proteins and membranes. Reduced glutathione can act as a scavenger (free radical scavenger) for almost all notorious free radicals and reactive oxygen species, such as the hydroxyl radical, superoxide and fatty acid radicals. When reduced glutathione relinquishes an electron it is oxidised. Two of these oxidised molecules then form a disulphide bridge and ultimately form glutathione-disulphide or oxidised glutathione (GSSG). On account of the strong antioxidative properties of GSH, the maintenance of adequate GSH levels in the body is of paramount importance. For this reason, under normal circumstances, in the cells GSH is then quickly regenerated from GSSG with the help of the glutathione reductase enzyme. The structures of GSH and GSSG and their reactions are shown in figure 1. The ratio between the reduced and the oxidised form of glutathione (GSH/GSSG ratio) is a sensitive indicator of the degree of oxidative stress.

Approximately a third of the glutathione present in the body is present in "mixed" disulphides with other compounds that contain thiol groups, such as cysteine, co-enzyme A and free cysteine groups on proteins. The enzyme glutathione reductase can also reduce "mixed" disulphides back to (amongst others) reduced free glutathione. Glutathione has, amongst others, the following actions:

- **Glutathione makes other antioxidants suitable for reuse:** On account of the powerful reducing effect, GSH also significantly contributes to the reuse of other antioxidants that have become oxidised and, therefore, become ineffective. Glutathione is able to make the other antioxidants in the antioxidant cascade (vitamin C, vitamin E, alpha lipoic acid and co-enzyme Q10) again suitable for reuse, on account of which the capacity of the antioxidant system is significantly stimulated.
- **Detoxification of xenobiotics:** Because GSH binds to fat-soluble toxins, such as heavy metals, solvents and some pesticides in the liver, these are made water-soluble, so that they can be excreted with the urine. Should this not happen, the toxicity will accumulate and serious hypoxia will occur (oxygen deficiency) in the liver cells. If this condition of hypoxia continues for a longer period of time, that can seriously weaken the condition of the liver, through which the phase II reactions (making toxic compounds water-soluble) will be disrupted. That can result in, instead of rapid excretion of a less toxic compound, slower excretion of a much more toxic compound (metabolically activated in the liver). The liver is the largest GSH reservoir. Research has revealed that a low glutathione level will result in decreased liver function. A portion of the effect of the well-known liver phytotherapeutic Silybum marianum is on account of the fact that Silybum is able to increase the glutathione level in the liver.
- **Red blood cells:** The liver also excretes some glutathione directly into the bloodstream, where it determines the strength of red blood cells and, at the same time, also protects the white blood cells.
- **Immune system:** Glutathione is of major importance to the immune system. Healthy growth and activity of the immune system depends on glutathione. Dr Gustavo Bounous, an expert in the field of glutathione, says that the availability of glutathione is the limiting factor in the activity of our lymphocytes. After contact with the antigen, lymphocytes have to be able to quickly multiply and, furthermore, produce antibodies and interleukins. This process requires a lot of oxygen and when lymphocytes have not built up sufficient stores of glutathione, that can result in oxidative damage.
- **Virus protection:** The protection against viruses is poorer the lower the concentrations of glutathione and other antioxidants in the cells. Viruses travel around the body in a protective capsule of proteins. Once at their destination, the capsule is destroyed and the viruses are released. Glutathione suppresses the breakdown of the protein capsules, meaning the viruses cannot be released.
- **The lungs:** The lungs have the greatest need for glutathione. The levels in the lung epithelium are more than 100 times higher than the plasma levels. Therefore, for all respiratory diseases, the possibility of glutathione deficiency should be considered. The mucosa of the airways increases as a result of exposure to oxidants. Glutathione usually prevents the occurrence of excessive formation of mucus. For that reason, the build-up of mucus in the airways is often an early sign of glutathione deficiency.
- **Nervous system:** The nervous system is extremely susceptible to damage by free radicals on account of the high concentration of powerful unsaturated (often omega-3) fatty acids in the cell membrane of the myelin sheath around the nerve cells. Furthermore, the oxygen demand in the brain is extremely high: although the brain counts for approximately 2% of the weight of the body, it uses approximately 20% of all oxygen used by the body. Protection against the reactive oxygen species that constantly occur in the mitochondria, is therefore also an important task in the brain and glutathione plays an essential role in this process. Glutathione detoxifies the fatty acid peroxides and other waste products of free radical damage and also neutralises reactive oxygen species.

Elevated oxidative stress and an inadequate glutathione system therefore also plays a role in various neurological disorders, such as seizures, ischemia reperfusion damage and neurodegenerative disorders such as ALS (Amyotrophic Lateral Sclerosis) and Alzheimer’s, Parkinson’s and Lou Gehrig’s disease.

**INDICATIONS**

Depletion of the glutathione stores in the cells probably plays an important role in a number of major and common diseases, which are directly or indirectly connected to oxidative stress.

**The best substantiated indications for the use of glutathione are the following:**

- **Ageing and age-related illnesses:** The ageing process is associated with increased oxidative stress. At the same time, there is a fall in the plasma GSH levels, whilst the amount of GSSG increases. Many of the chronic age-related illnesses are associated with decreased antioxidative capacity; decreased levels of glutathione are found in those illnesses. Age-related illnesses are more common in people with low glutathione levels than in people with normal glutathione levels. Ageing is also associated with decreased immune function. Many lymphocytic functions change through ageing, such as reduced proliferation, reduced production of interleukin 2 and decreased expression of IL-2 receptors. The same changes also occur in the event of increased oxidative stress and decreased glutathione concentrations, a phenomenon that is also associated with ageing. It is therefore plausible that many of the chronic and acute disorders in elderly persons are linked to a decreased glutathione status.
- **Cirrhosis of the liver, hepatitis:** In patients with hepatitis, cirrhosis of the liver or liver damage on account of alcohol use, the
concentration of glutathione in plasma and erythrocytes is abnormally low and the glutathione that is present is present almost exclusively in oxidised form. Certain medicines (for example paracetamol) can dramatically lower the amount of glutathione in the liver.

- **Airways disorders:** Glutathione deficiency is associated with various disorders of the airways, lung damage in newborns and asthma. The lungs are particularly vulnerable to oxidative damage.
- **Cardiac infarction:** Patients with acute cardiac infarction and men with coronary heart conditions have low GSH levels. Glutathione that was administered to a group of these patients (by injection, intravenously) prior to the bypass surgery, also improved, post-surgery, the renal function and the arterial blood flow.
- **Hypoglycaemia:** Patients with an impaired glucose tolerance, including patients with hypoglycaemia, have decreased glutathione levels in the blood and in the red blood cells. Light to moderate exercise helps to normalise the GSH status in diabetics. However, strenuous exercise again results in depletion of GSH.
- **Neurodegenerative diseases:** Oxidative stress plays a significant role in the occurrence of seizures, as well as the neurological damage that can occur as a result of this. The glutathione concentrations in the brain can therefore possibly reduce the progress of seizures and the neurological damage resulting from that. During periods of fasting, the brain protects itself against a deficiency of glutathione by recycling the existing glutathione stores already present with the aid of vitamins C and E, co-enzyme Q10, alpha lipoic acid and other nutrients of the antioxidant cascade system.
- **Toxicity of mercury (amalgam) and cadmium (smoking):** Mercury and cadmium generate extremely toxic hydroxyl radicals, that make a substantial demand on cellular glutathione stores. Glutathione is able to bind to mercury compounds, therefore limiting its toxicity.

### Glutathione has three different roles in protecting the body against mercury toxicity:
1. Firstly, glutathione binds to methylmercury (organic mercury), thus forming a complex. This prevents methylmercury from binding to cell proteins and damaging enzymes and tissue. Glutathione-mercury complexes also reduce the intracellular damage by preventing mercury penetrating the tissues and becoming an intracellular toxin.
2. Secondly, complex formation with glutathione is the main way in which the body disposes of mercury compounds. Glutathione and cysteine stimulate the excretion of mercury in the bile and urine, thereby reducing the accumulation of mercury toxicity in the renal tissue. The higher the levels of glutathione, the more mercury is excreted. Mercury that has accumulated in the central nervous system is also assisted across the blood-brain barrier in a glutathione-mercury complex.
3. Thirdly, glutathione improves the antioxidative capacity of cells and therefore protects them against hydrogen peroxide, singlet oxygen, hydroxyl radicals, fatty acid peroxides and other harmful components that can occur in cells as a result of the toxic effect of mercury. Research with cell lines that had become resistant to mercury toxicity revealed that the glutathione levels in those cell lines were five times higher than in the parent cells. The researchers concluded that the reason for resistance is because of the protective effect of glutathione against mercury toxicity.

### Sport
Glutathione is also of importance to sportsmen and women. Many free radicals are generated during exercise. Glutathione can help to limit the tissue damage that arises from that.

### Trauma
There is evidence that, on account of the stress of injuries, glutathione deficiencies can occur. Following (abdominal) surgery, the glutathione levels in skeletal muscles and plasma were found to be markedly lower than beforehand. This was found to sometimes be associated with decreased activity of the enzyme that produces glutathione.

### CONTRA-INDICATIONS
When a person is undergoing cancer treatment, caution should be exercised because some cancer cells can use glutathione to defend themselves against chemotherapeutics.

### SIDE EFFECTS
Glutathione is deemed to be safe. No negative effects of supplementation with glutathione or one of its precursors are known.

### INTERACTIONS
No information is known about potential interactions with mainstream or natural medicines.

### DOSAGE
Every day, take a supplement containing 100 mg of glutathione with a meal.

If the amount of glutathione dosed is too low, there is a fair chance that too great a percentage of glutathione is then broken down by the proteases in the intestine. A way of avoiding the proteases is by dissolving the content of one or more capsules in water, stirring this well and then drinking it. Research has shown that the direct contact of glutathione with the mucous membrane of the mouth has a favourable effect on absorption.

However, this trick is not necessarily required. By taking a glutathione supplement in a normal manner at doses of 100 mg to 200 mg per day, more than 60% of the glutathione is already absorbed. At higher doses, the efficiency of the absorption again reduces.
SYNERGISM

In order to increase the glutathione levels in the body, other nutrients can also be used. The availability of the amino acid L-cysteine is the main limiting factor in glutathione synthesis. An important oral source of cysteine is NAC (N-Acetyl Cysteine), which is more stable and is absorbed better than L-cysteine itself (see the NAC background information). Some researchers claim that NAC is absorbed better in the cell than glutathione itself. It is, in any case, an important synergist when a glutathione supplement is given. In the body, NAC is converted into cysteine and is then incorporated in glutathione. It has been found that NAC supplementation effectively increases the glutathione levels. The amino acid L-Methionine is a cysteine precursor and, for that reason, can also be used to increase the body's own glutathione production. However, higher doses of L-methionine can sometimes cause nausea. The activated form of L-methionine, S-Adenosyl Methionine (SAMe), is better tolerated.

Glutathione is a component of the glutathione tripeptide and therefore a direct building block of glutathione. Glutathione can be produced by the body itself and is therefore often considered to be non-essential, but in recent years it has, however, been shown that under certain circumstances, L-glutamine can actually be essential. During stress, fasting, heavy forms of sport, cirrhosis and serious (liver-based) diseases, deficiencies can easily arise.

In addition, all components of the antioxidant cascade are important synergists of glutathione. Vitamin C, vitamin E, alpha lipoic acid and co-enzyme Q10 all help to regulate glutathione and one another.

REFERENCES

19. Schafer FQ, Buettnner GR. Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathione couple.