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**Glutathione** (**GSH**) is an important [antioxidant](/wiki/Antioxidant) in plants, animals, fungi, and some bacteria and archaea. GSH is capable of preventing damage to important [cellular](/wiki/Cell_(biology)) components caused by [reactive oxygen species](/wiki/Reactive_oxygen_species) such as [free radicals](/wiki/Free_radical), [peroxides](/wiki/Peroxide), [lipid peroxides](/wiki/Lipid_peroxidation) and [heavy metals](/wiki/Heavy_metal_(chemistry)).[[1]](#cite_note-1) It is a [tripeptide](/wiki/Tripeptide) with a [gamma peptide linkage](/wiki/Glutamate—cysteine_ligase) between the [carboxyl](/wiki/Carboxyl) group of the [glutamate](/wiki/Glutamate) [side chain](/wiki/Side_chain) and the [amine group](/wiki/Amino_acid) of [cysteine](/wiki/Cysteine), and the carboxyl group of cysteine is attached by normal peptide linkage to a [glycine](/wiki/Glycine).

[Thiol](/wiki/Thiol) groups are [reducing agents](/wiki/Redox), existing at a concentration around 5 [mM](/wiki/Molar_concentration) in [animal](/wiki/Animal) cells. Glutathione reduces [disulfide bonds](/wiki/Disulfide_bond) formed within [cytoplasmic](/wiki/Cytoplasm) [proteins](/wiki/Protein) to [cysteines](/wiki/Cysteine) by serving as an [electron](/wiki/Electron) donor. In the process, glutathione is converted to its oxidized form, [glutathione disulfide](/wiki/Glutathione_disulfide) (GSSG), also called L-(–)-glutathione.

Once oxidized, glutathione can be reduced back by glutathione reductase, using [NADPH](/wiki/NADPH) as an electron donor.[[2]](#cite_note-2) The ratio of reduced glutathione to oxidized glutathione within cells is often used as a measure of cellular [oxidative stress](/wiki/Oxidative_stress).[[3]](#cite_note-3)[[4]](#cite_note-4)

## Contents

* 1 Biosynthesis[[edit](/index.php?title=(none)&action=edit&section=1)]
* 2 Function[[edit](/index.php?title=(none)&action=edit&section=2)]
  + 2.1 Function in animals[[edit](/index.php?title=(none)&action=edit&section=3)]
  + 2.2 Function in plants[[edit](/index.php?title=(none)&action=edit&section=4)]
* 3 Supplementation[[edit](/index.php?title=(none)&action=edit&section=5)]
* 4 Bioavailability[[edit](/index.php?title=(none)&action=edit&section=6)]
* 5 Methods to determine glutathione[[edit](/index.php?title=(none)&action=edit&section=7)]
  + 5.1 Small molecule based glutathione probes[[edit](/index.php?title=(none)&action=edit&section=8)]
    - 5.1.1 Ellman's reagent and Monobromobimane[[edit](/index.php?title=(none)&action=edit&section=9)]
    - 5.1.2 Monochlorobimane[[edit](/index.php?title=(none)&action=edit&section=10)]
    - 5.1.3 5-Chloromethylfluorescein diacetate (CMFDA)[[edit](/index.php?title=(none)&action=edit&section=11)]
    - 5.1.4 ThiolQuant Green[[edit](/index.php?title=(none)&action=edit&section=12)]
  + 5.2 Protein based glutathione probes[[edit](/index.php?title=(none)&action=edit&section=13)]
* 6 Other Biological Implications[[edit](/index.php?title=(none)&action=edit&section=14)]
  + 6.1 Cancer[[edit](/index.php?title=(none)&action=edit&section=15)]
  + 6.2 Cystic fibrosis[[edit](/index.php?title=(none)&action=edit&section=16)]
  + 6.3 Alzheimer's disease[[edit](/index.php?title=(none)&action=edit&section=17)]
* 7 Uses[[edit](/index.php?title=(none)&action=edit&section=18)]
  + 7.1 Winemaking[[edit](/index.php?title=(none)&action=edit&section=19)]
  + 7.2 Cosmetics[[edit](/index.php?title=(none)&action=edit&section=20)]
* 8 Importance of gamma-glutamylcysteine as a precursor for glutathione synthesis in healthy and disease[[edit](/index.php?title=(none)&action=edit&section=21)]
* 9 See also[[edit](/index.php?title=(none)&action=edit&section=22)]
* 10 References[[edit](/index.php?title=(none)&action=edit&section=23)]
* 11 Related research[[edit](/index.php?title=(none)&action=edit&section=24)]
* 12 External links[[edit](/index.php?title=(none)&action=edit&section=25)]

## Biosynthesis[[edit](/index.php?title=(none)&action=edit&section=1)]

The biosynthesis pathway for glutathione is found in some bacteria, such as [cyanobacteria](/wiki/Cyanobacteria) and [proteobacteria](/wiki/Proteobacteria), but is missing in many other bacteria. Most eukaryotes synthesize glutathione, including humans, but some do not, such as [Leguminosae](/wiki/Leguminosae), [*Entamoeba*](/wiki/Entamoeba), and [*Giardia*](/wiki/Giardia). The only archaea that make glutathione are [halobacteria](/wiki/Halobacteria).[[5]](#cite_note-5)[[6]](#cite_note-6) Glutathione is an [essential nutrient](/wiki/Essential_nutrient) for humans. However, since it can be synthesized in the body from the [amino acids](/wiki/Amino_acids) [L-cysteine](/wiki/Cysteine), [L-glutamic acid](/wiki/Glutamic_acid), and [glycine](/wiki/Glycine), it does not have to be present as a supplement in the diet. The [sulfhydryl group](/wiki/Sulfhydryl_group) (SH) of cysteine serves as a [proton donor](/wiki/Proton_donor) and is responsible for its biological activity. Cysteine is the rate-limiting factor in cellular glutathione biosynthesis, since this amino acid is relatively rare in foods.

Cells make glutathione in two [adenosine triphosphate](/wiki/Adenosine_triphosphate)-dependent steps:

* First, *gamma*-glutamylcysteine is synthesized from L-glutamate and cysteine via the enzyme [gamma-glutamylcysteine synthetase](/wiki/Gamma-glutamylcysteine_synthetase) (glutamate cysteine ligase, GCL). This reaction is the rate-limiting step in glutathione synthesis.[[7]](#cite_note-7)\*Second, glycine is added to the C-terminal of *gamma*-glutamylcysteine via the enzyme [glutathione synthetase](/wiki/Glutathione_synthetase).

Animal [glutamate cysteine ligase](/wiki/Glutamate_cysteine_ligase) (GCL) is a [heterodimeric enzyme](/wiki/Heterodimer) composed of a catalytic and a modulatory subunit. The catalytic subunit is necessary and sufficient for all GCL enzymatic activity, whereas the modulatory subunit increases the catalytic efficiency of the enzyme. Mice lacking the catalytic subunit (i.e., lacking all *de novo* GSH synthesis) die before birth.[[8]](#cite_note-8) Mice lacking the modulatory subunit demonstrate no obvious phenotype, but exhibit marked decrease in GSH and increased sensitivity to toxic insults.[[9]](#cite_note-9)[[10]](#cite_note-10)[[11]](#cite_note-11) While all animal cells are capable of synthesizing glutathione, glutathione synthesis in the liver has been shown to be essential. Mice with genetically induced loss of GCLC (i.e., GSH synthesis) only in the liver die within a month of birth.[[12]](#cite_note-12)[[13]](#cite_note-13) Major transport into the blood stream is driven by an [electrochemical gradient](/wiki/Electrochemical_gradient), specifically through the [transport proteins](/wiki/Transport_protein) RcGshT and RsGshT.[[14]](#cite_note-14) Similarly, [bile](/wiki/Bile) is a medium in which GSH and GSSG is exported to.[[13]](#cite_note-13)[[15]](#cite_note-15) The plant [glutamate cysteine ligase](/wiki/Glutamate_cysteine_ligase) (GCL) is a redox-sensitive [homodimeric enzyme](/wiki/Homodimer), conserved in the plant kingdom.[[16]](#cite_note-16) In an oxidizing environment, intermolecular disulfide bridges are formed and the enzyme switches to the dimeric active state. The midpoint potential of the critical cysteine pair is -318 mV. In addition to the redox-dependent control, the plant GCL enzyme is feedback inhibited by [GSH](/wiki/GSH).[[17]](#cite_note-17) GCL is exclusively located in [plastids](/wiki/Plastid), and [glutathione synthetase](/wiki/Glutathione_synthetase)i(GS)s dual-targeted to plastids and cytosol, thus GSH and [gamma-glutamylcysteine](/wiki/Gamma-glutamylcysteine) are exported from the plastids.[[18]](#cite_note-18) Both glutathione biosynthesis enzymes are essential in plants; knock-outs of GCL and GS are lethal to embryo and seedling.[[19]](#cite_note-19)

## Function[[edit](/index.php?title=(none)&action=edit&section=2)]

Glutathione exists in both reduced (GSH) and oxidized ([GSSG](/wiki/Glutathione_disulfide)) states. In the reduced state, the thiol group of cysteine is able to donate a [reducing equivalent](/wiki/Reducing_equivalent) (H++ e−) to other molecules, such as reactive oxygen species to neutralize them, or to protein cysteines to maintain their reduced forms. With donating an electron, glutathione itself becomes reactive and readily reacts with another reactive glutathione to form [glutathione disulfide](/wiki/Glutathione_disulfide) (GSSG). Such a reaction is probable due to the relatively high concentration of glutathione in cells (up to 7 mM in the liver).[[20]](#cite_note-20) Generally, interactions between GSH and other molecules with higher relative [electrophilicity](/wiki/Electrophilicity) deplete GSH levels within the cell. An exception to this case involves the sensitivity of GSH to the electrophilic compound's relative concentration. In high concentrations, the organic molecule [Diethyl maleate](/wiki/Diethyl_maleate) fully depleted GSH levels in cells. However, in low concentrations, a minor decrease in cellular GSH levels was followed by a two-fold increase.[[21]](#cite_note-21)[[22]](#cite_note-22) GSH can be regenerated from GSSG by the enzyme [glutathione reductase](/wiki/Glutathione_reductase) (GSR):[[2]](#cite_note-2) NADPH reduces FAD present in GSR to produce a transient FADH-anion. This anion then quickly breaks a disulfide bond (Cys58 - Cys63) and leads to Cys63's nucleophilically attacking the nearest sulfide unit in the GSSG molecule (promoted by His467), which creates a mixed disulfide bond (GS-Cys58) and a GS-anion. His467 of GSR then protonates the GS-anion to form the first GSH. Next, Cys63 nucleophilically attacks the sulfide of Cys58, releasing a GS-anion, which, in turn, picks up a solvent proton and is released from the enzyme, thereby creating the second GSH. So, for every GSSG and NADPH, two reduced GSH molecules are gained, which can again act as antioxidants scavenging reactive oxygen species in the cell.

In healthy cells and tissue, more than 90% of the total glutathione pool is in the reduced form (GSH) and less than 10% exists in the disulfide form (GSSG). An increased GSSG-to-GSH ratio is considered indicative of [oxidative stress](/wiki/Oxidative_stress).[[23]](#cite_note-23) Glutathione has multiple functions:

* It maintains levels of reduced [glutaredoxin](/wiki/Glutaredoxin) and [glutathione peroxidase](/wiki/Glutathione_peroxidase)[[24]](#cite_note-24)\*It is one of the major endogenous antioxidant produced by the cells, participating directly in the neutralization of free radicals and reactive oxygen compounds, as well as maintaining exogenous antioxidants such as vitamins C and E in their reduced (active) forms.[[25]](#cite_note-25)[[26]](#cite_note-26)[[27]](#cite_note-27)\*Regulation of the [nitric oxide](/wiki/Nitric_oxide) cycle is critical for life, but can be problematic if unregulated.[[28]](#cite_note-28)\*It is used in metabolic and biochemical reactions such as DNA synthesis and repair, protein synthesis, prostaglandin synthesis, amino acid transport, and enzyme activation. Thus, every system in the body can be affected by the state of the glutathione system, especially the immune system, the nervous system, the gastrointestinal system, and the lungs.[Template:Citation needed](/wiki/Template:Citation_needed)
* It has a vital function in iron metabolism. Yeast cells depleted of GSH or containing toxic levels of GSH show an intense iron starvation-like response and impairment of the activity of extramitochondrial ISC enzymes thus inhibiting oxidative [endoplasmic reticulum](/wiki/Endoplasmic_reticulum) folding, followed by death.[[29]](#cite_note-29)\* It has roles in progression of the [cell cycle](/wiki/Cell_cycle), including [cell death](/wiki/Cell_death).[[4]](#cite_note-4) GSH levels regulate redox changes to nuclear proteins necessary for the initiation of [cell differentiation](/wiki/Cellular_differentiation). Differences in GSH levels also determine the expressed mode of cell death, being either [apoptosis](/wiki/Apoptosis) or cell [necrosis](/wiki/Necrosis). Manageably low levels result in the systematic breakage of the cell whereas excessively low levels result in rapid cell death.[[30]](#cite_note-30)

### Function in animals[[edit](/index.php?title=(none)&action=edit&section=3)]

GSH is known as a [substrate](/wiki/Substrate_(biochemistry)) in [conjugation](/wiki/Xenobiotic_metabolism#Phase_II_–_conjugation) reactions, which is catalyzed by [glutathione S-transferase](/wiki/Glutathione_S-transferase) enzymes in [cytosol](/wiki/Cytosol), [microsomes](/wiki/Microsome), and [mitochondria](/wiki/Mitochondria). However, GSH is also capable of participating in nonenzymatic conjugation with some chemicals.

In the case of [*N*-acetyl-*p*-benzoquinone imine](/wiki/NAPQI) (NAPQI), the reactive [cytochrome P450](/wiki/Cytochrome_P450_oxidase)-reactive [metabolite](/wiki/Metabolite) formed by [paracetamol](/wiki/Paracetamol) (acetaminophen), which becomes toxic when GSH is depleted by an overdose of acetaminophen, glutathione is an essential antidote to overdose. Glutathione conjugates to NAPQI and helps to detoxify it. In this capacity, it protects cellular protein thiol groups, which would otherwise become covalently modified; when all GSH has been spent, NAPQI begins to react with the cellular [proteins](/wiki/Protein), killing the cells in the process. The preferred treatment for an overdose of this painkiller is the administration (usually in atomized form) of [*N*-acetyl-L-cysteine](/wiki/Acetylcysteine) (often as a preparation called Mucomyst[[31]](#cite_note-31)), which is processed by cells to L-cysteine and used in the *de novo* synthesis of GSH.

Glutathione (GSH) participates in [leukotriene](/wiki/Leukotriene) synthesis and is a [cofactor](/wiki/Cofactor_(biochemistry)) for the enzyme [glutathione peroxidase](/wiki/Glutathione_peroxidase). It is also important as a [hydrophilic](/wiki/Hydrophilic) molecule that is added to [lipophilic](/wiki/Lipophilic) toxins and waste in the liver during [biotransformation](/wiki/Biotransformation) before they can become part of the [bile](/wiki/Bile). Glutathione is also needed for the detoxification of [methylglyoxal](/wiki/Methylglyoxal), a toxin produced as a byproduct of metabolism.

This detoxification reaction is carried out by the [glyoxalase system](/wiki/Glyoxalase_system). [Glyoxalase I](/wiki/Glyoxalase_I) (EC 4.4.1.5) catalyzes the conversion of methylglyoxal and reduced glutathione to *S*-D-lactoyl-glutathione. [Glyoxalase II](/wiki/Glyoxalase_II) (EC 3.1.2.6) catalyzes the hydrolysis of *S*-D-lactoyl-glutathione to glutathione and [D-lactic acid](/wiki/Lactic_acid).

Glutathione, along with [oxidized glutathione](/wiki/Oxidized_glutathione) (GSSG) and [S-nitrosoglutathione](/wiki/S-nitrosoglutathione) (GSNO), have been found to bind to the [glutamate](/wiki/Glutamate) recognition site of the [NMDA](/wiki/NMDA_receptor) and [AMPA receptors](/wiki/AMPA_receptor) (via their γ-glutamyl moieties), and may be [endogenous](/wiki/Endogenous) [neuromodulators](/wiki/Neuromodulator).[[32]](#cite_note-32)[[33]](#cite_note-33)[[34]](#cite_note-34) At [millimolar](/wiki/Millimolar) concentrations, they may also modulate the redox state of the NMDA receptor complex.[[33]](#cite_note-33) In addition, glutathione has been found to bind to and activate [ionotropic receptors](/wiki/Ionotropic_receptor) that are different from any other [excitatory amino acid receptor](/wiki/Excitatory_amino_acid_receptor), and which may constitute *glutathione receptors*, potentially making it a [neurotransmitter](/wiki/Neurotransmitter).[[35]](#cite_note-35)

### Function in plants[[edit](/index.php?title=(none)&action=edit&section=4)]

In plants, glutathione is crucial for biotic and abiotic stress management. It is a pivotal component of the [glutathione-ascorbate cycle](/wiki/Glutathione-ascorbate_cycle), a system that reduces poisonous [hydrogen peroxide](/wiki/Hydrogen_peroxide).[[36]](#cite_note-36) It is the precursor of [phytochelatins](/wiki/Phytochelatins), glutathione oligomers that [chelate](/wiki/Chelate) heavy metals such as [cadmium](/wiki/Cadmium).[[37]](#cite_note-37) Glutathione is required for efficient defence against plant pathogens such as [*Pseudomonas syringae*](/wiki/Pseudomonas_syringae) and [*Phytophthora*](/wiki/Phytophthora) *brassicae*.[[38]](#cite_note-38) [Adenylyl-sulfate reductase](/wiki/Adenylyl-sulfate_reductase), an enzyme of the [sulfur assimilation](/wiki/Sulfur_assimilation) pathway, uses glutathione as an electron donor. Other enzymes using glutathione as a substrate are [glutaredoxin](/wiki/Glutaredoxin). These small [oxidoreductases](/wiki/Oxidoreductases) are involved in flower development, [salicylic acid](/wiki/Salicylic_acid), and plant defence signalling.[[39]](#cite_note-39)

## Supplementation[[edit](/index.php?title=(none)&action=edit&section=5)]

[Calcitriol](/wiki/Calcitriol) (1,25-dihydroxyvitamin D3), the active metabolite of [vitamin D3](/wiki/Cholecalciferol), after being synthesized from [calcifediol](/wiki/Calcifediol) in the kidney, increases glutathione levels in the brain and appears to be a catalyst for glutathione production.[[40]](#cite_note-40) It takes about ten days for the body to process vitamin D3 into calcitriol.[[41]](#cite_note-41) [*S*-adenosylmethionine](/wiki/S-Adenosyl_methionine) (SAMe), a cosubstrate involved in methyl group transfer, has also been shown to increase cellular glutathione content in persons suffering from a disease-related glutathione deficiency.[[42]](#cite_note-42)[[43]](#cite_note-43)[[44]](#cite_note-44) Low glutathione is commonly observed in wasting and negative nitrogen balance, as seen in cancer, HIV/AIDS, [sepsis](/wiki/Sepsis), trauma, burns, and athletic overtraining. Low levels are also observed in periods of starvation. These effects are hypothesized to be influenced by the higher glycolytic activity associated with [cachexia](/wiki/Cachexia), which result from reduced levels of oxidative phosphorylation.[[45]](#cite_note-45)[[46]](#cite_note-46)

## Bioavailability[[edit](/index.php?title=(none)&action=edit&section=6)]

Glutathione is only in a small extent bioavailable to humans; the human body is capable of maintaining a consistent level of GSH. Introduction of GSH into the body using orally is, in fact, scarcely effective to increase its plasma and / or intracellular concentration. At the base of its poor [bioavailability](/wiki/Bioavailability) is the nature of the glutathione which, being a peptide, is the substrate of peptidase and protease of the alimentary canal, and the absence of a specific *carrier* of glutathione at the level of cell membrane.[[47]](#cite_note-47)[[48]](#cite_note-48)

## Methods to determine glutathione[[edit](/index.php?title=(none)&action=edit&section=7)]

### Small molecule based glutathione probes[[edit](/index.php?title=(none)&action=edit&section=8)]

#### Ellman's reagent and Monobromobimane[[edit](/index.php?title=(none)&action=edit&section=9)]

Reduced glutathione may be visualized using [Ellman's reagent](/wiki/Ellman's_reagent) or [bimane](/wiki/Bimane) derivatives such as [monobromobimane](/wiki/Bromobimane). The monobromobimane method is more sensitive. In this procedure, cells are lysed and thiols extracted using a [HCl](/wiki/Hydrogen_chloride) [buffer](/wiki/Buffer_solution). The thiols are then reduced with [dithiothreitol](/wiki/Dithiothreitol) and labelled by monobromobimane. Monobromobimane becomes fluorescent after binding to GSH. The thiols are then separated by [HPLC](/wiki/High-performance_liquid_chromatography) and the fluorescence quantified with a fluorescence detector.

#### Monochlorobimane[[edit](/index.php?title=(none)&action=edit&section=10)]

Monochlorobimane can be used to quantify glutathione [in vivo](/wiki/In_vivo). The quantification is done by [confocal laser scanning microscopy](/wiki/Confocal_laser_scanning_microscopy) after application of the dye to living cells.<ref name=Meyer\_2001>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> This quantification process relies on measuring the rates of fluorescence changes and is limited to plant cells.

#### 5-Chloromethylfluorescein diacetate (CMFDA)[[edit](/index.php?title=(none)&action=edit&section=11)]

CMFDA was initially used as a cell tracker. Unfortunately, it has also been mistakenly used as a glutathione probe. Unlike monochlorobimane, whose fluorescence increases upon reacting with glutathione, the fluorescence increase of CMFDA is due to the hydrolysis of the acetate groups inside cells. Although CMFDA may react with glutathione in cells, the fluorescence increase does not reflect the reaction. Therefore, studies using CMFDA as a glutathione probe should be revisited and re-interpreted.[[49]](#cite_note-49)[[50]](#cite_note-50)

#### ThiolQuant Green[[edit](/index.php?title=(none)&action=edit&section=12)]

The major limitation of these bimane based probes and many other reported probes is that these probes are based on irreversible chemical reactions with glutathione, which renders these probes incapable of monitoring the real-time glutathione dynamics. Recently, the first reversible reaction based fluorescent probe-ThiolQuant Green (TQG)-for glutathione was reported.[[51]](#cite_note-51) ThiolQuant Green can not only perform high resolution measurements of glutathione levels in single cells using a confocal microscope, but also be applied in flow cytometry to perform bulk measurements.

### Protein based glutathione probes[[edit](/index.php?title=(none)&action=edit&section=13)]

Another approach, which allows to measure the glutathione redox potential at a high spatial and temporal resolution in living cells is based on redox imaging using the [redox-sensitive green fluorescent protein](/wiki/Redox-sensitive_green_fluorescent_protein) (roGFP)<ref name=Meyer\_2007>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> or redox sensitive yellow fluorescent protein (rxYFP)<ref name=Maulucci\_2010>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> GSSG because its very low physiological concentration is difficult to measure accurately unless the procedure is carefully executed and monitored and the occurrence of interfering compounds is properly addressed. GSSG concentration ranges from 10 to 50 μM in all solid tissues, and from 2 to 5 μM in blood (13–33 nmol per gram Hb). GSH-to-GSSG ratio ranges from 100 to 700.[[52]](#cite_note-52)

## Other Biological Implications[[edit](/index.php?title=(none)&action=edit&section=14)]

### Cancer[[edit](/index.php?title=(none)&action=edit&section=15)]

Once a tumor has been established, elevated levels of glutathione may act to protect cancerous cells by conferring resistance to chemotherapeutic drugs.[[53]](#cite_note-53)

### Cystic fibrosis[[edit](/index.php?title=(none)&action=edit&section=16)]

Several studies have been completed on the effectiveness of introducing inhaled glutathione to people with cystic fibrosis with mixed results.[[54]](#cite_note-54)[[55]](#cite_note-55)

### Alzheimer's disease[[edit](/index.php?title=(none)&action=edit&section=17)]

Whilst extracellular Aβ plaques, NFT, inflammation in the form or reactive astrocytes and microglia, and neuronal loss are all consistent pathological features of AD, a mechanistic link between these factors is yet to be clarified. Although the majority of past research has focused on fibrillar Aβ, soluble oligomeric Aβ species are now considered to be of major pathological importance in AD. Up-regulation of GSH may be protective against the oxidative and neurotoxic effects of oligomeric Aβ.

## Uses[[edit](/index.php?title=(none)&action=edit&section=18)]

### Winemaking[[edit](/index.php?title=(none)&action=edit&section=19)]

The content of glutathione in [must](/wiki/Must), the first raw form of wine, determines the [browning](/wiki/Browning_(biochemistry)), or caramelizing effect, during the production of [white wine](/wiki/White_wine) by trapping the [caffeoyltartaric acid](/wiki/Caffeoyltartaric_acid) quinones generated by enzymic oxidation as [grape reaction product](/wiki/Grape_reaction_product).[[56]](#cite_note-56) Its concentration in wine can be determined by mass spectrometry.[[57]](#cite_note-57)

### Cosmetics[[edit](/index.php?title=(none)&action=edit&section=20)]

Glutathione plays an important role in preventing [oxidative damage](/wiki/Oxidative_damage) to the skin.[[58]](#cite_note-58) In addition to its many recognized biological functions, glutathione has also been associated with skin lightening ability.[[59]](#cite_note-59) The role of glutathione as a skin whitener was discovered as a side effect of large doses of glutathione.[[60]](#cite_note-60) Glutathione utilizes different mechanisms to exert its action as a skin whitening agent at various levels of [melanogenesis](/wiki/Melanogenesis). It inhibits [melanin synthesis](/wiki/Melanin_synthesis) by means of stopping the neurotransmitter precursor [L-DOPA](/wiki/L-DOPA)’s ability to interact with [tyrosinase](/wiki/Tyrosinase) in the process of melanin production.[[61]](#cite_note-61) Glutathione inhibits the actual production as well as [agglutination](/wiki/Agglutination) of melanin by interrupting the function of L-DOPA. Another study found that glutathione inhibits melanin formation by direct inactivation of the enzyme tyrosinase by binding and [chelating](/wiki/Chelating) [copper](/wiki/Copper) within the enzyme’s active site.[[62]](#cite_note-62) Glutathione’s antioxidant property allows it to inhibit melanin synthesis by quenching of [free radicals](/wiki/Free_radicals) and [peroxides](/wiki/Peroxides) that contribute to tyrosinase activation and melanin formation.[[63]](#cite_note-63) Its antioxidant property also protects the skin from UV radiation and other environmental as well as internal stressors that generate free radicals that cause skin damage and [hyperpigmentation](/wiki/Hyperpigmentation).[[64]](#cite_note-64) In most mammals, melanin formation consists of [eumelanin](/wiki/Eumelanin) (brown-black pigment) and [pheomelanin](/wiki/Pheomelanin) ( yellow-red pigment) as either mixtures or co-polymers.[[65]](#cite_note-65) Increase in glutathione level may induce the pigment cell to produce pheomelanin instead of eumelanin pigments.[[66]](#cite_note-66) A research by Te-Sheng Chang found lowest levels of reduced glutathione to be associated with eumelanin type pigmentation, whereas the highest ones were associated with the pheomelanin.[[67]](#cite_note-67) As a result, it is reasonable to assume that depletion of glutathione would result in eumelanin formation. Prota [[68]](#cite_note-68) observed that decreased glutathione concentration lead to in the conversation of [L-Dopaquinone](/wiki/L-Dopaquinone) to [Dopachrome](/wiki/Dopachrome) increasing the formation of brown-black pigment (eumelanin).

## Importance of gamma-glutamylcysteine as a precursor for glutathione synthesis in healthy and disease[[edit](/index.php?title=(none)&action=edit&section=21)]

Gamma-Glutamylcysteine (GGC) is the immediate precursor to GSH. GGC supplementation would circumvent feedback inhibitory control of GCL by the end product GSH. Accordingly, a method of elevating GSH levels with the notable advantage of bypassing negative feedback inhibition has been described. Because of this, GGC has been the focus of therapeutic efforts since Puri and Meister 1983. The first documented use of GGC in brains appears to be Pileblad and Magnusson, 1992. Astroglia cells are capable of utilising GGC.[[69]](#cite_note-69) Direct delivery of the GSH precursor GCC to brain has been reported to effectively replenish levels of GSH in the brain.[[70]](#cite_note-70) Most of the work done on GGC has been preclinical, based on in vivo animal models, or in vitro brain cultures. In order for the therapeutic value of GGC elevation against AD to be vindicated, three empirical hurdles have to be cleared. The first is to demonstrate that delivery of GCC into the brain can indeed increase GSH.[[70]](#cite_note-70) The second is to demonstrate that the increase in GGC can indeed reduce oxidative stress in the brain,[[71]](#cite_note-71) a condition frequently linked with cognitive decline.

## See also[[edit](/index.php?title=(none)&action=edit&section=22)]

* [Glutathione synthetase deficiency](/wiki/Glutathione_synthetase_deficiency)
* [Ophthalmic acid](/wiki/Ophthalmic_acid)
* [roGFP](/wiki/RoGFP), a tool to measure the cellular glutathione redox potential
* [Glutathione-ascorbate cycle](/wiki/Glutathione-ascorbate_cycle)
* [Bacterial glutathione transferase](/wiki/Bacterial_glutathione_transferase)
* [Thioredoxin](/wiki/Thioredoxin), a cysteine-containing small proteins with very similar functions as reducing agents
* [Glutaredoxin](/wiki/Glutaredoxin), an antioxidant protein that uses reduced glutathione as a cofactor and is reduced nonenzymatically by it
* [Bacillithiol](/wiki/Bacillithiol)
* [Mycothiol](/wiki/Mycothiol)
* [gamma-L-Glutamyl-L-cysteine](/wiki/Gamma-L-Glutamyl-L-cysteine)

## References[[edit](/index.php?title=(none)&action=edit&section=23)]

[Template:Reflist](/wiki/Template:Reflist)

## Related research[[edit](/index.php?title=(none)&action=edit&section=24)]

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