Metabolomics of Vitamins and Antioxidants

Metabolomics of Vitamins and Antioxidants - Human Metabolome Technologies

Antioxidants and selected Vitamins protect cells and organs against free radical and oxidative cellular damage caused by excessive oxidative reactions.

Alternatively, they act as ligands for anti-oxidative, anti-inflammatory or immune pathways, hence can be both protective and restorative .

During a metabolomics profile of cells, tissues and biofluids, the observation of changes in antioxidants and vitamins is common across many therapeutic areas, diseases and biological dysfunctions. Understanding their functions, how they interact, and their role in disease is critical to understanding metabolomic change.

Antioxidant Activities: 3 Categories

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Preventative by removing free radicals before damaging macromolecules and tissues.	*Scavenging free radicals by interrupting or slowing radical damage.*	*Removing peroxides and preventing more reactive oxygen species (ROS).*

Examples of damage caused by excessive concentration of various forms of oxygen and of free-radical activity include:

- Cell membrane damage leading to cell death.
- Oxidation and inactivation of sulfhydryl-containing enzymes resulting in adjustments in biological pathways
- Fatty acid oxidation that may shift fatty acid metabolism
- DNA damage that could lead to mutations and inhibition of genes that are responsible for protein, nucleotide, and fatty acid synthesis.

While a certain level of oxidative products are required for healthy biological mechanisms, excessive levels can detrimentally affect cellular and systemic pathways leading to cellular and health dysfunction.

Understanding the Antioxidative Response

The term 'antioxidant' is derived from the Greek anti, meaning 'against', and the English oxidant, meaning 'a substance that can cause oxidation or is oxidizing in action.

While many antioxidants and vitamins have been known for a long time and some studied in detail, much is yet to be understood how they interact in a living system.

Perhaps the best understood mechanism of free radical-induced cell injury relates to peroxidation of polyunsaturated fatty acids in organelles and plasma membranes leading to lipid damage. The effects of several nutrient antioxidants at various steps in lipid peroxidation have been well-studied.

Nevertheless, the overall role of antioxidants in cellular regulation and the balance between antioxidative and oxidative processes in cells under various states need further study.

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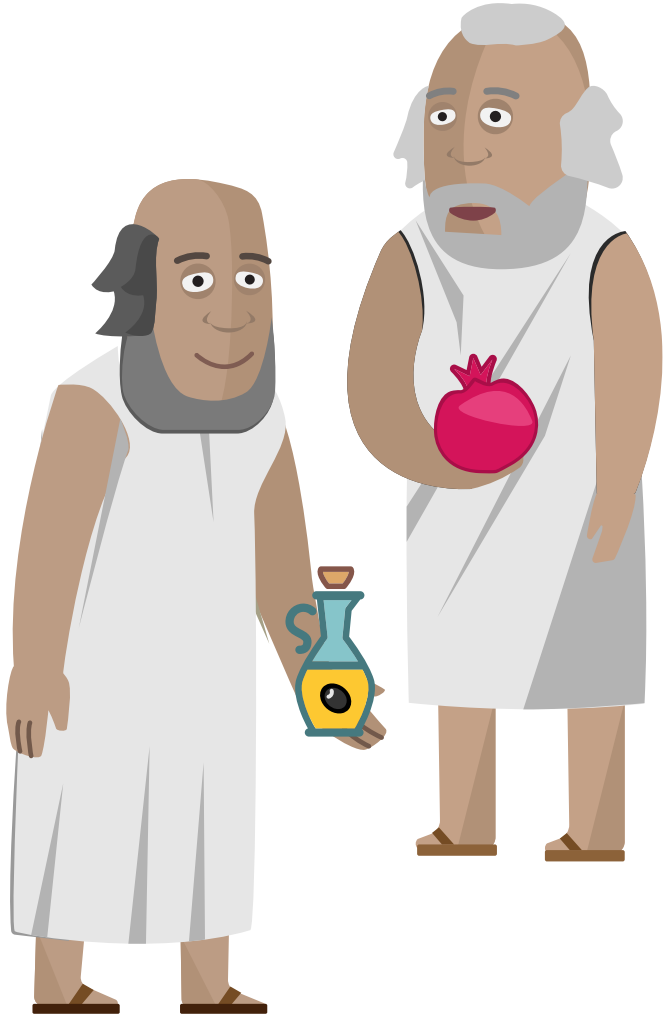

Antioxidants and Disease

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Epidemiological and clinical studies have suggested that nutrient antioxidants may reduce the risk of these diseases.

Oxidized and peroxidized compounds may be causally related to a variety of chronic diseases. Free radicals play a role in the promotion and initiation of some cancers (such as breast, cervical, lung, and gastrointestinal cancers), cardiovascular diseases, cataracts, and degenerative diseases of the central nervous system. There is evidence that suggests a role of free radical-induced cell injury in the aging process .

Vitamin C, vitamin E and beta-carotene and other carotenoids appear to be most effective.

Minerals (zinc, copper, manganese, and selenium) associated with antioxidant enzymes may also be involved in protection against degenerative and chronic diseases since dietary deficiencies of minerals needed for synthesis of antioxidant enzymes can have a deleterious effect on enzyme formation. Relevant mechanisms focusing on the metabolism of nutrient antioxidants as well as their effect on cellular functions and metabolic processes need further study.

In addition, it now appears that the status of nutrient antioxidants maybe influenced by other nutrient factors. For example, increased levels of omega-3 fatty acids in the diet appear to result in a decrease in vitamin E (alpha-tocopherol) levels. Such interactions and their metabolic consequences need to be delineated at the cellular and subcellular levels. The mechanisms, location, and interactive metabolic effects of supplemental nutrient antioxidants on gastrointestinal absorption and transport, and other cellular processes need further study, for individual nutrients as well as for their complementary and synergistic roles

Source of Radicals

Reactive oxygen species (ROS) can play several physiological roles and they are normally generated as by-products of oxygen metabolism. ROS are mainly produced by mitochondria, during both physiological and pathological conditions, that is, $O_2^{\bullet-}$ can be formed by cellular respiration, by lipoxygenases (LOX) and cyclooxygenases (COX) during the arachidonic acid metabolism, and by endothelial and inflammatory cells. ROS production basically relies on enzymatic and nonenzymatic reactions.

Enzymatic reactions able to generate ROS are those involved in respiratory chain, prostaglandin synthesis, phagocytosis, and cytochrome P450 system. Superoxide radical ($O_2^{\bullet-}$) is generated by NADPH oxidase (NOX), xanthine oxidase (XO), and peroxidases. H_2O_2 (a nonradical) is produced by multiple oxidase enzymes such as amino acid oxidase and xanthine oxidase. Hydroxyl radical (OH•), the most reactive among all the free radical species in vivo, is generated by reaction of $O_2^{\bullet-}$ with H_2O_2.

The Antioxidant Response

When maintained at low or moderate concentrations, free radicals play several beneficial roles for the organism. Radicals are needed to synthesize some cellular structures and to be used by the host defense system to fight pathogens. Phagocytes synthesize and store free radicals, in order to be able to release them when invading pathogenic microbes have to be destroyed. your immune cells use free radicals to fight infections.

As a result, your body needs to maintain a certain balance of free radicals and antioxidants.

Probably, the most well-known free radical acting as a signaling molecule is nitric oxide (NO). It is an important cell-to-cell messenger required for a proper blood flow modulation, involved in thrombosis, and is crucial for normal neural activity. NO is also involved in nonspecific host defense, required to eliminate intracellular pathogens and tumor cells.

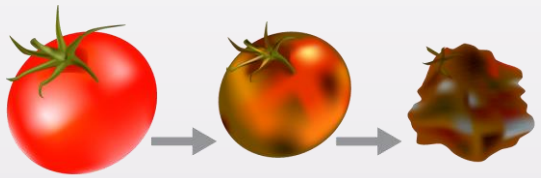
Another physiological activity of free radicals is the induction of a mitogenic response. Endogenous mitogens function to control cell division is a normal and necessary part of the life cycle of multicellular organisms.

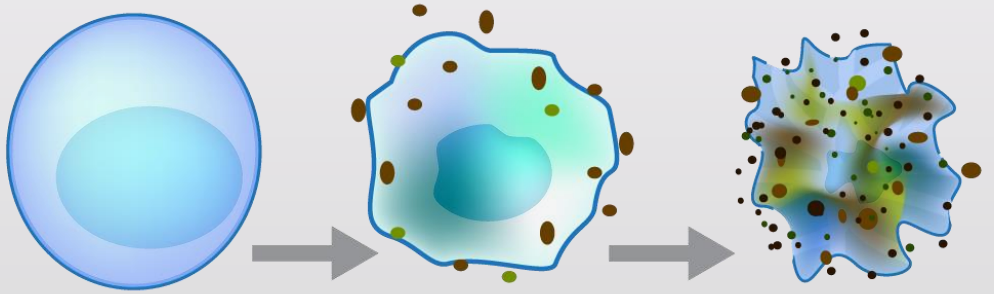
Summarizing, free radicals, when maintained at low or moderate levels, are of crucial importance to human health.

The Antioxidant Response

When free radicals outnumber antioxidants, this imbalance leads to a state called oxidative stress.

Antioxidants neutralize free radicals either by directly providing the extra electron needed to make the pair, or by breaking down the free radical molecule to render it harmless, indirectly they can act as ligands to engage anti oxidative and or anti-inflammatory processes. But it is important to recognize that the term "antioxidant" reflects a chemical property rather than a specific nutritional property.





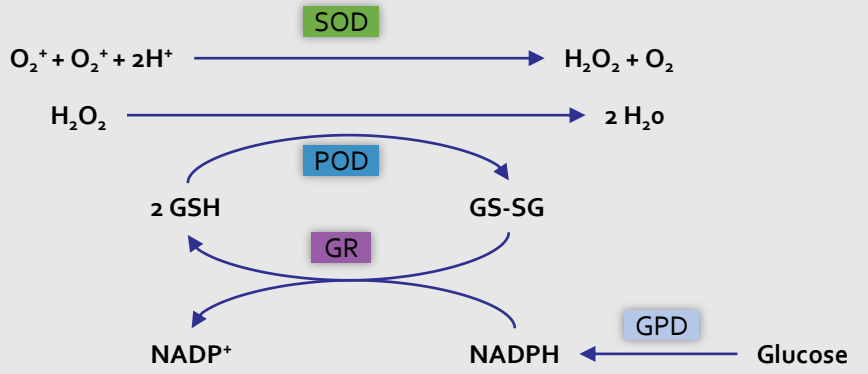
Oxidative Stress

Antioxidative Systems: Enzymes

Superoxide Dismutase

Superoxide dismutase (SOD, EC 1.15.1.1) is a copper containing enzyme that alternately catalyzes the dismutation (or partitioning) of the superoxide (O−2) radical into ordinary molecular oxygen (O2) and hydrogen peroxide (H2O2). SOD is a metalloprotein, requiring a metal cofactor, typically Cu, Zn or Mn:

- Copper and zinc – most used by eukaryotes, including humans. The cytosols of virtually all eukaryotic cells contain an SOD enzyme with copper and zinc (Cu-Zn-SOD).
- Manganese – Nearly all mitochondria, and many bacteria, contain a form with manganese (Mn-SOD): For example, the Mn-SOD found in human mitochondria.



Glutathione Peroxidase

Glutathione peroxidase (GPx) (EC 1.11.1.9) is the general name of an enzyme family with peroxidase activity. The biochemical function of glutathione peroxidase is to reduce lipid hydroperoxides to their corresponding alcohols and to reduce free hydrogen peroxide to water.

Glutathione peroxidase 1 (GPx1) is the most abundant version, found in the cytoplasm of nearly all mammalian tissues, whose preferred substrate is hydrogen peroxide. Glutathione peroxidase 4 (GPx4) has a high preference for lipid hydroperoxides; it is expressed in nearly every mammalian cell, though at much lower levels. Glutathione peroxidase 2 is an intestinal and extracellular enzyme, while glutathione peroxidase 3 is extracellular, especially abundant in plasma

The mechanism involves oxidation of the selenol of a selenocysteine residue by hydrogen peroxide. Hence selenium is essential for function.

Catalase

Catalase (CAT) catalyzes the decomposition of hydrogen peroxide to water and oxygen. It contains four iron-containing heme groups that allow the enzyme to react with hydrogen peroxide. Catalase has one of the highest turnover numbers of all enzymes; one catalase molecule can convert millions of hydrogen peroxide molecules to water and oxygen each second. Catalase is usually located in a cellular organelle called the peroxisome.

Peroxiredoxins

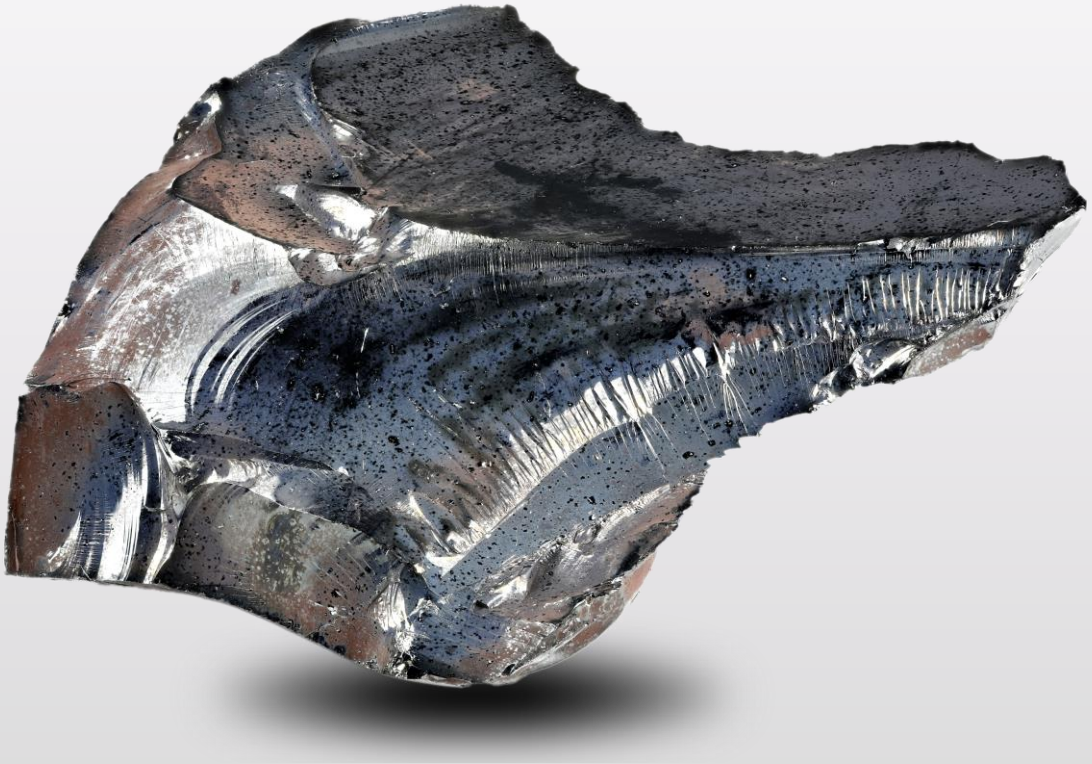
Peroxiredoxins (EC 1.11.1.15; HGNC PRDX) are a ubiquitous family of antioxidant enzymes that also control cytokine-induced peroxide levels and thereby mediate signal transduction in mammalian cells.

This family of enzymes all share the same basic catalytic mechanism, in which a redox-active cysteine (the peroxidatic cysteine) in the active site is oxidized to a sulfenic acid by the peroxide substrate. The recycling of the sulfenic acid back to a thiol is what distinguishes the three enzyme classes.

Antioxidative Systems: Minerals

Selenium

Selenium is the only mineral that functions as an independent antioxidant. It works by targeting natural hydrogen peroxide in the body and converting it to water. Selenium regulates thyroid function and helps the immune system stay strong and healthy. According to the Academy of Nutrition and Dietetics, selenium may reduce cancer risk and promote heart health. The richest sources of selenium include Brazil nuts, meats, mushrooms, seafood and other protein-rich foods.



Mn, Se, Fe, Cu, Zn

Mn, Se, Fe, Cu, Zn are all necessary for antioxidative enzymes as co-catalysts, but require heme or protein binding to elicit function. Mn, Cu and Zn are required by SOD activity. Se is required for glutathione peroxidase.

Antioxidative Systems: Vitamins

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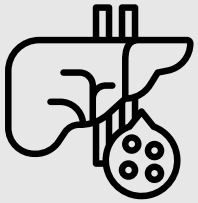
Not all Vitamins have antioxidant properties as their main function. The three main vitamins with detoxification properties are Tocopherol (Vitamin E), Vitamin A and Ascorbic acid (Vitamin C.)

Vitamins are grouped into two categories:

Water-soluble

Water-soluble vitamins are not stored in the body. The nine water-soluble vitamins are vitamin C and all the B vitamins. Any leftover or excess amounts of these leave the body through the urine. They must be consumed on a regular basis to prevent shortages or deficiencies in the body. The exception to this is vitamin B12, which can be stored in the liver for many years.

Fat-soluble



Fat-soluble vitamins are stored in the body's liver, fatty tissue, and muscles. The four fat-soluble vitamins are vitamins A, D, E, and K. These vitamins are absorbed more easily by the body in the presence of dietary fat.

Antioxidative Systems: Water-Soluable Vitamins

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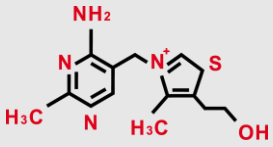
Water-soluble vitamins are those that are dissolved in water and readily absorbed into tissues for immediate use. Because they are not stored in the body, they need to be replenished regularly in our diet. This may cause variable amounts in circulation and tissues due to diet, lifestyle, and health.

Any excess of water-soluble vitamins is quickly excreted in urine and will rarely accumulate to toxic levels.

The water-soluble vitamins include the B-complex group and vitamin C, each of which offer health benefits.

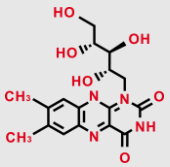
Vitamin B1

Vitamin B1 (thiamine) helps to release energy from foods and is important in maintaining nervous system function.



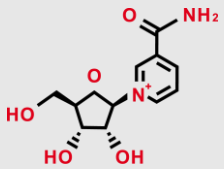
Vitamin B2

Vitamin B2 (riboflavin) helps promotes good vision and healthy skin and is also important in converting the amino acid tryptophan into niacin.



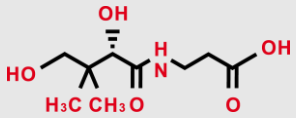
Vitamin B3

Vitamin B3 (niacin) aids in digestion, metabolism, and normal enzyme function as well as promoting healthy skin and nerves.



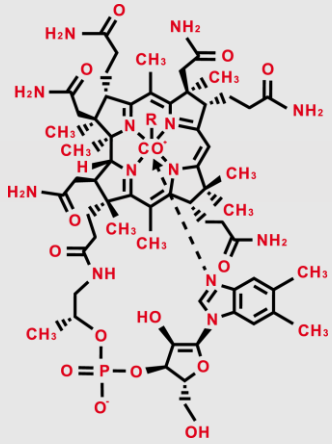
Vitamin B5

Vitamin B5 (pantothenic acid) aids in metabolism and the formation of hormones.



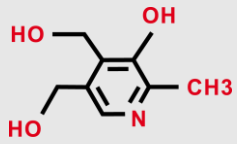
Vitamin B12

Vitamin B12 (cobalamin) aids in the production of normal red blood cells as well as the maintenance of the nervous system.



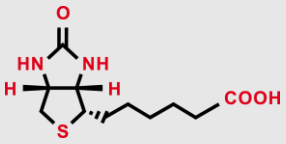
Vitamin B6

Vitamin B6 (pyridoxine) aids in protein metabolism and the production of red blood cell, insulin, and hemoglobin



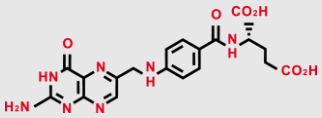
Vitamin B7

Vitamin B7 (biotin) helps release energy from carbohydrates and aids in the metabolism of fats, proteins, and carbohydrates from food



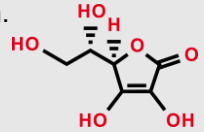
Vitamin B9

Vitamin B9 (folate or folic acid) also aids in protein metabolism and red blood cell formation and may reduce the risk of neural tube birth defects



Vitamin C

Vitamin C (ascorbic acid) is central to iron absorption and collagen synthesis. It aids in wound healing and bone formation while improving overall immune function.



Antioxidative Systems: Fat-Soluble Vitamins

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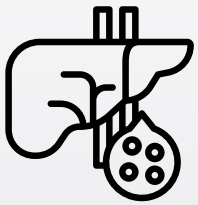


Fat-soluble vitamins are dissolved in fats. They are absorbed by fat globules that travel through the small intestines and distributed through the body in the bloodstream.

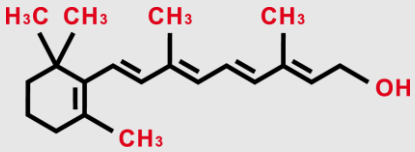
Unlike water-soluble vitamins, excess fat-soluble vitamins are stored in the liver and fatty (adipose) tissues for future use They are found most abundantly in high-fat foods and are better absorbed if eaten with fat.

Because fat-soluble vitamins are not readily excreted, they can accumulate in fats.

There are four types of fat-soluble vitamin, each of which offer different benefits.

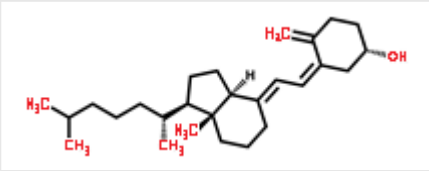
Vitamin A

Vitamin A is integral to bone formation, tooth formation, and vision. It contributes to immune and cellular function while keeping the intestines working properly. Though carotenes are not vitamins, they can be converted to Vitamin A.



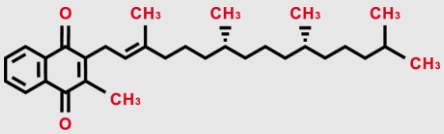
Vitamin D

Vitamin D aids in the development of teeth and bone by encouraging the absorption and metabolism of phosphorous and calcium



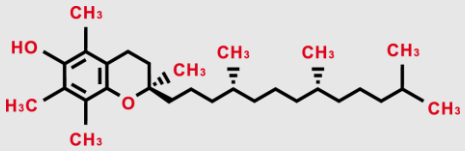
Vitamin K

Vitamin K is central to blood clotting and also keeps bones healthy.



Vitamin E

Vitamin E is an antioxidant that helps fight infection and keeps red blood cells healthy. Vitamin E is the most powerful chain breaking antioxidative vitamin. VitE breaks the radical proliferation chain by reaction with lipid peroxide radicals (LOO*) and becoming a radical itself (E*). Vit E can be restored by Vit C and carotenoids.



Antioxidative Systems: Vitamins

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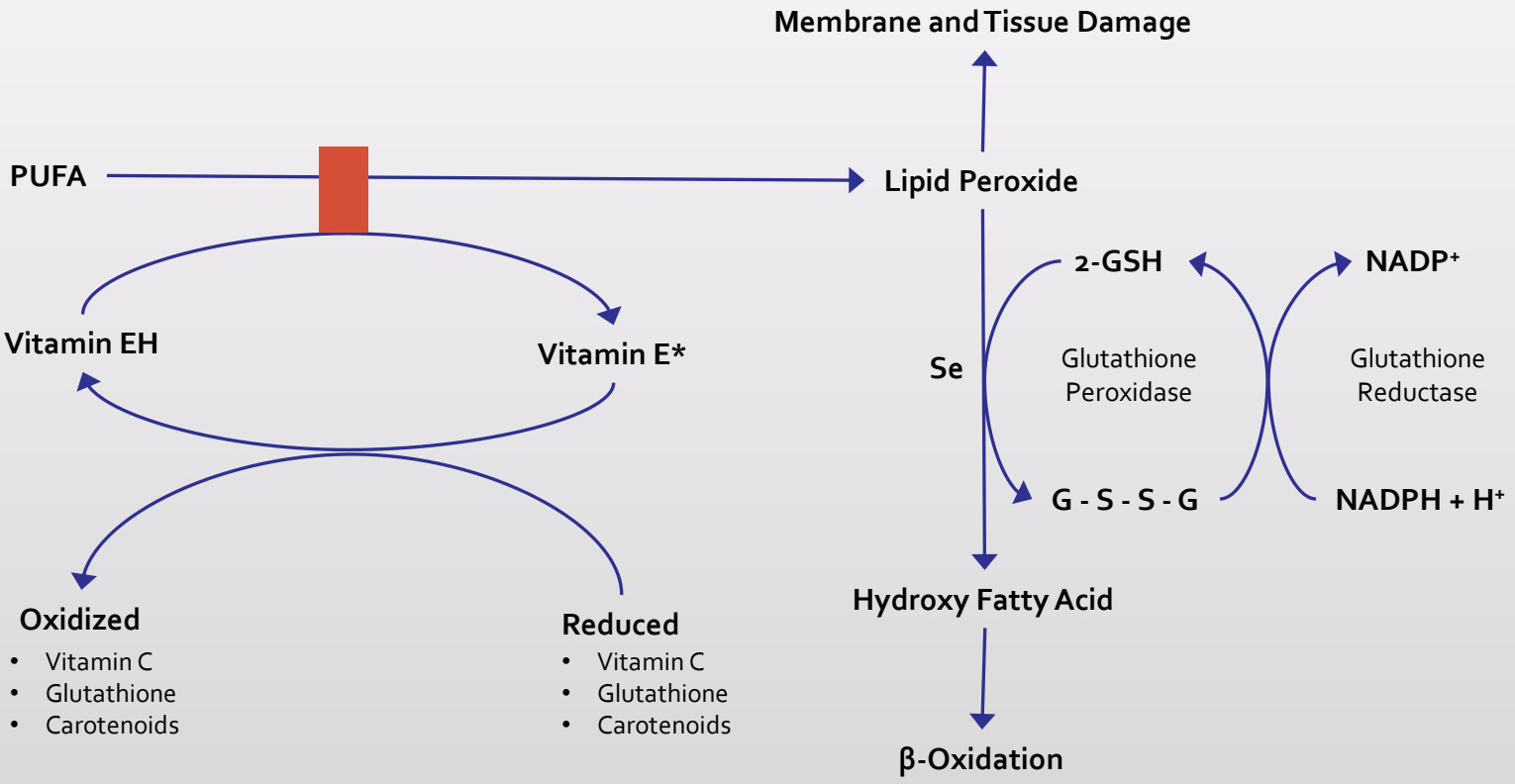
How vitamins interact with each other is still an unraveling story. One well known system involves Vit C and Vit E in the **Glutathione pathway**.



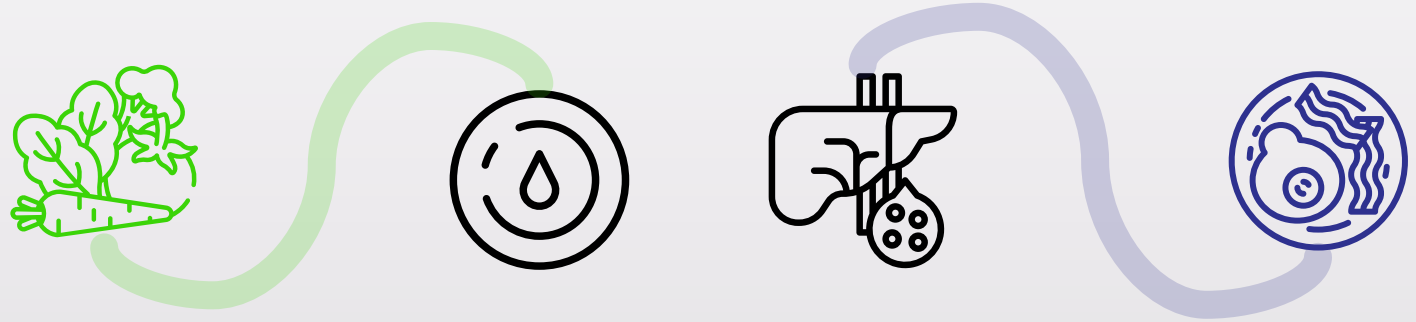
Antioxidative Systems: Vitamins

These enzymes and vitamins act as a first defense against oxidative stress and cover many types of reactive species.

Reactive Species	Antioxidant
Superoxide free radical (O_2)	SOD, Vit E, Vit A (beta-carotene)
Hydroxy free radical (HO)	SOD, Vit E, Vit A (beta-carotene)
Hydrogen Peroxide (H_2O_2)	CAT, Glutathione
Lipid Peroxide (LOO)	Glutathione
Alkyl peroxy free radical (ROO)	Vitamin E and Vitamin C

Antioxidative Systems: Vitamins

With the exception of vitamin B12, which is supplied by only foods of animal origin, the water-soluble vitamins are synthesized by plants and found in both plant and animal foods. Fat-soluble vitamins are found in association with fats and oils in foods and in the body.



Because free radicals are so pervasive in health and disease, there is a need of an adequate supply of antioxidants. Your body's cells naturally produce some antioxidants, such as alpha lipoic acid and glutathione. The foods we eat supply other antioxidants, such as vitamins C and E. Plants are full of compounds known as phytochemicals many of which seem to have antioxidant properties as well. For example, after vitamin C has "quenched" a free radical by donating electrons to it, a phytochemical called hesperidin (found in oranges and other citrus fruits) restores the vitamin C to its active antioxidant form. Carotenoids (such as lycopene in tomatoes and lutein in kale) and flavonoids (such as flavanols in cocoa, anthocyanins in blueberries, quercetin in apples and onions, and catechins in green tea) are also antioxidants.

There are hundreds, probably thousands, of different natural substances that can act as antioxidants. The most familiar ones are vitamin C, vitamin E, beta-carotene, and other related carotenoids. They're joined by glutathione, coenzyme Q10, lipoic acid, flavonoids, phenols, polyphenols, phytoestrogens, and many more.

Some substances that act as antioxidants in one situation may be pro-oxidants—electron grabbers—in a different situation. They almost certainly evolved as parts of elaborate networks, with each different substance (or family of substances) playing slightly different roles. This means that no single substance can do the work of the whole crowd.

13 Essential vitamins are required for the body to work properly.

1. Vitamin A
2. Vitamin C
3. Vitamin D
4. Vitamin E
5. Vitamin K
6. Vitamin B1 (thiamine)
7. Vitamin B2 (riboflavin)
8. Vitamin B3 (niacin)
9. Vitamin B6 (pyridoxine)
10. Vitamin B12 (cyanocobalamin)
11. Pantothenic acid (B5)
12. Biotin (B7)
13. Folate (folic acid or B9)

Some are endogenous (we make what we need), others we either don't make enough, or what we need comes from our diet.

Vitamin nomenclature is somewhat complex, with common chemical names gradually replacing the original letter designations created in the early era of vitamin discovery. Nomenclature is further complicated by the recognition that vitamins are parts of families with, in some cases, multiple active forms. Some vitamins are found in foods in precursor forms that must be activated in the body before they can properly fulfill their function. For example, beta(β)-carotene, found in plants, is converted to vitamin A in the body and the different active forms of Vitamin B6.

Antioxidative Systems: Plant Phytochemicals

Phytochemicals in plants, are believed to have greater antioxidant effects than vitamins or minerals. These are called the non-nutrient antioxidants and include phytochemicals, (such as lycopene and carotenoids in tomatoes and anthocyanins found in cranberries).

Beta-Carotene and Vitamin

Beta-carotene is a carotenoid, not actually a vitamin, and is the precursor for the formation of vitamin A. Vitamin A plays a role in vision, reproduction, bone growth and a healthy immune system. Carotenoid-rich foods may help prevent prostate cancer, according to the Academy of Nutrition and Dietetics. Vitamin A is found in foods such as carrots and sweet potatoes and other orange, yellow and red produce.

Other Carotenoids

Although beta-carotene is the only pro-vitamin A carotenoid, it's not the only carotenoid typically observed in plasma and tissues. That's because the richly colored carotenoids lutein, zeaxanthin, and lycopene exhibit antioxidant properties. Lutein and zeaxanthin help protect the macula of your eye by absorbing up to 90 percent of harmful ultraviolet light. Observational studies show that eating a diet rich in these carotenoids may even help slow the development of age-related macular degeneration. Spinach, kale, collards and other dark leafy greens are among the best sources of lutein and zeaxanthin. Lycopene, a red carotenoid found in fresh tomatoes, tomato products, watermelon and pink grapefruit, is a powerful antioxidant that may help protect against prostate cancer.

While most phytochemicals are non-essential, they provide additional and necessary antioxidant support for health. However, high-dose supplements of antioxidants may be linked to health risks in some cases. Supplementing with high doses of beta-carotene may increase the risk of lung cancer in smokers. Supplementing with high doses of vitamin E may increase risks of prostate cancer and one type of stroke.

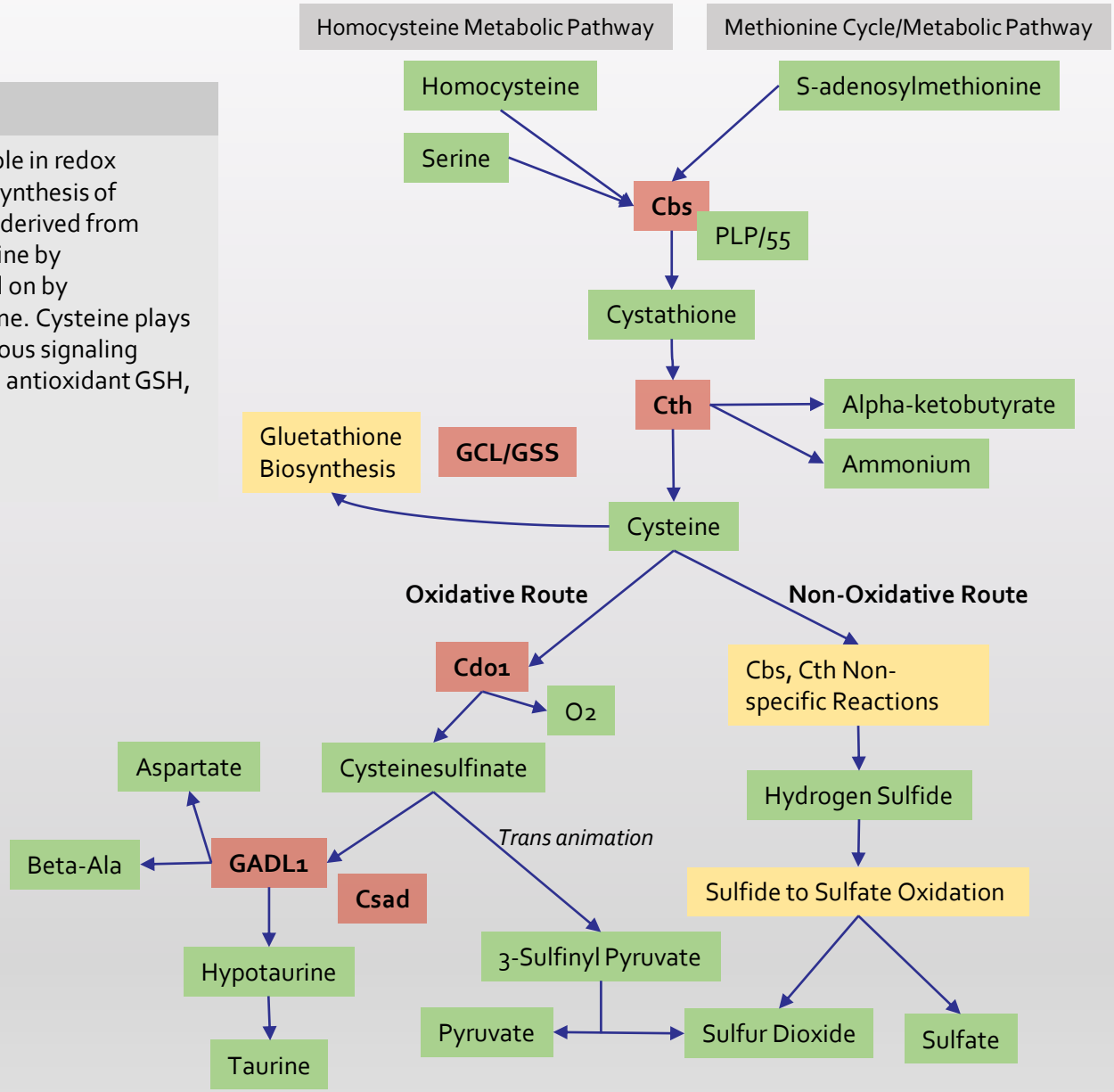
Mechanisms of Action

Like vitamins, phytochemical antioxidants behave in a similar manner with similar mechanisms of action:

- Phytochemicals act as radical scavengers . Examples of antioxidants which scavenge free radicals are phenolic compounds, flavonoids and phenolic acids.
- Antioxidants which prevent the enzymatic activity required for auto oxidation. Examples are flavonoids, phenolic acids and gallates which deactivates the lipoxygenases.

Transsulfuration Pathway

The transsulfuration pathway plays a central role in redox regulation in cells and is the only route for biosynthesis of cysteine in mammals. Homocysteine, which is derived from dietary methionine, is converted to cystathionine by cystathionine β-synthase (CBS), which is acted on by cystathionine γ-lyase (CGL) to generate cysteine. Cysteine plays a central role in synthesis of proteins, the gaseous signaling molecule hydrogen sulfide (H_2S), the powerful antioxidant GSH, and taurine.

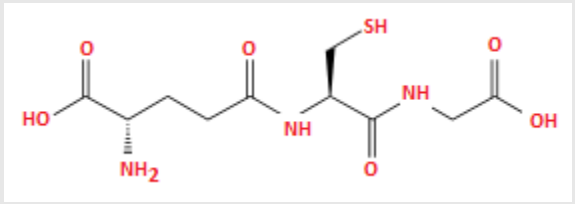


Glutathione

Glutathione This well-known tripeptide is perhaps the most famous natural antioxidant. Glutathione plays a crucial role in cell signaling via two pathways:

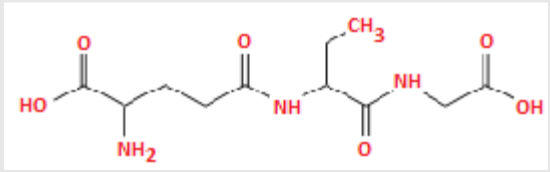
1. the modification of the redox potential toward oxidative values linked to the GSH concentration decrease and/or GSSG increase can activate transcription factors, which provokes gene activation and the synthesis of proteins with antioxidant properties

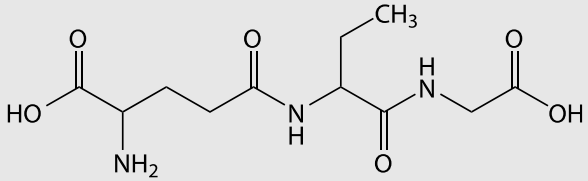
2. the formation of the disulfide bond between protein thiol groups and GSH generates mixed disulfides, that is, S-glutathiolated proteins (PSSGs). Glutathione can also be obtained from the diet but is primarily synthesized de novo from the amino acids cysteine, glutamate, and glycine via the sequential actions of γ-glutamylsynthetase and GSH synthetase

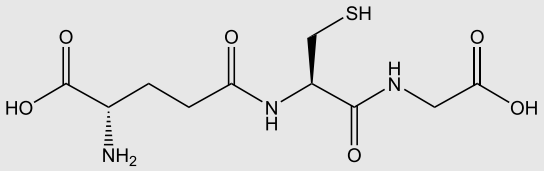


Ophthamic Acid

Ophthamic acid 2-aminobutyric acid (2-AB) has been reported as a basic component of ophthalmic acid, which is produced when glutathione is synthesized. activation of glutathione synthetic pathway under oxidative damage led to 2-AB accumulation. -AB promotes glutathione synthesis.

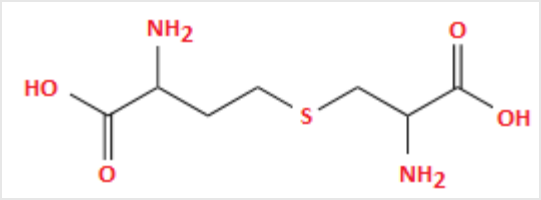


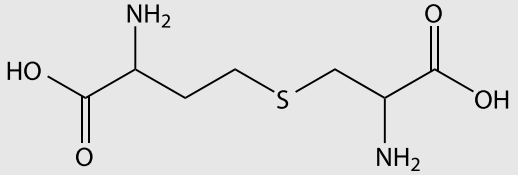




Cystathionine

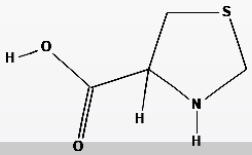
Cystathionine is an intermediate in the synthesis of cysteine. Cystathionine is produced by the transsulfuration pathway which converts homocysteine into cystathionine. Cystathionine is then used by the enzymes cystathionine gamma-lyase (CTH), cysteine dioxygenase (CDO), and sulfinoalanine decarboxylase to produce hypotaurine and then taurine. Alternately, the cysteine from the cystathionine gamma-lyase can be used by the enzymes glutamate–cysteine ligase (GCL) and glutathione synthetase (GSS) to produce glutathione.

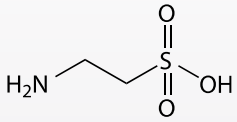


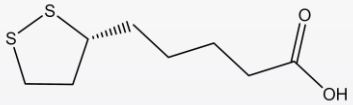


Antioxidative Systems: Endogenous Antioxidants

Metabolomics of Vitamins and Antioxidants - Human Metabolome Technologies

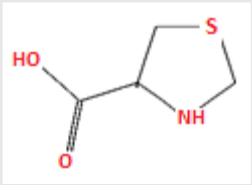






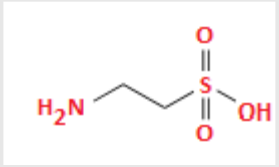
Thioproline

Thioproline (SPro), a proline analogue, is generated in oxidant-exposed cells. SPro served as an efficient nitrile trapping agent. SPro acts as an effective antioxidant by sacrificial oxidation. SPro can be incorporated into cellular proteins and induce changes in protein expression profiles of treated cells.



Taurine

Taurine is a ubiquitous sulfur-containing amino acid found in high concentration in the heart and brain. Although it has antioxidant activity, it is not a classical free radical scavenger, therefore, its mechanism remains unclear. Taurine may prevent the formation of superoxide by post-transcriptional modification of mitochondrial tRNA.



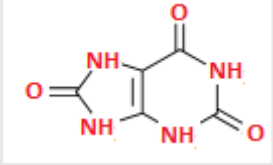
α-Lipoic acid

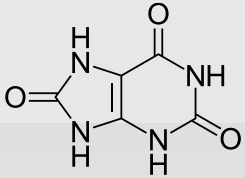
α-Lipoic acid, along with its major metabolite dihydrolipoic acid (DHLA), is a potent antioxidant via scavenging of oxygen free radicals and inhibition of lipid peroxidation. Lipoate also contributes in other antioxidant systems by enhancing the effects of SOD, coenzyme Q10 and glutathione, and by regenerating other antioxidants such as vitamins C and E.

Uric acid

Uric acid is produced by a xanthine oxidoreductase (XOR)-catalyzed reaction from its precursor inosine, and shown to have both antioxidant and pro-oxidant properties in vitro by scavenging and production of reactive oxygen species (ROS). Uric acid has been shown to gain antioxidant properties by scavenging singlet oxygen, peroxyl radical, hydroxyl radical, and peroxynitrite.

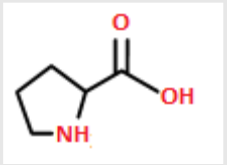
In addition to antioxidant properties, uric acid is known to have pro-oxidant properties by generating ROS such as superoxide anions, an activity that is mediated by activation of nicotinamide adenine dinucleotide phosphate oxidase in adipocytes, as well as vascular smooth muscle and endothelial cells.





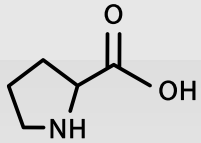
Proline

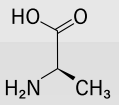
Proline protect cells against H_2O_2, but not as effective against superoxide. Proline is oxidized to glutamate by two mitochondrial enzymes, proline dehydrogenase (PRODH) and Δ1-pyrroline-5-carboxylate dehydrogenase (P5CDH). The PRODH flavoenzyme catalyzes the rate-limiting two-electron oxidation of proline to Δ1-pyrroline-5-carboxylate (P5C) and the subsequent transfer of reducing equivalents from the reduced flavin cofactor to the mitochondrial electron transport chain. P5C is then converted to glutamate in a NAD+-dependent reaction catalyzed by P5CDH.

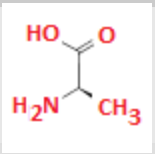


Alpha-Alanine

Alpha-Alanine dipeptides have also shown to have antioxidative and anti-inflammatory properties.

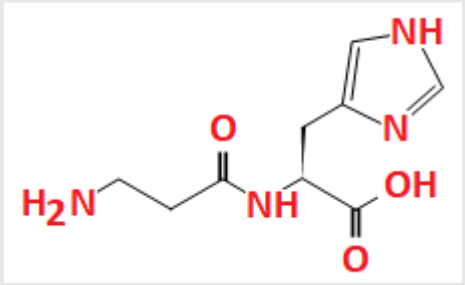


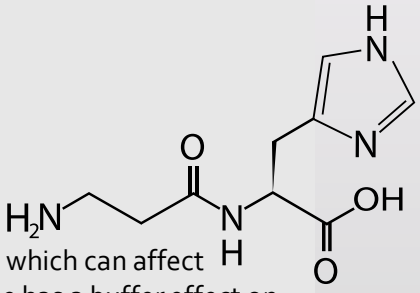




Carnosine

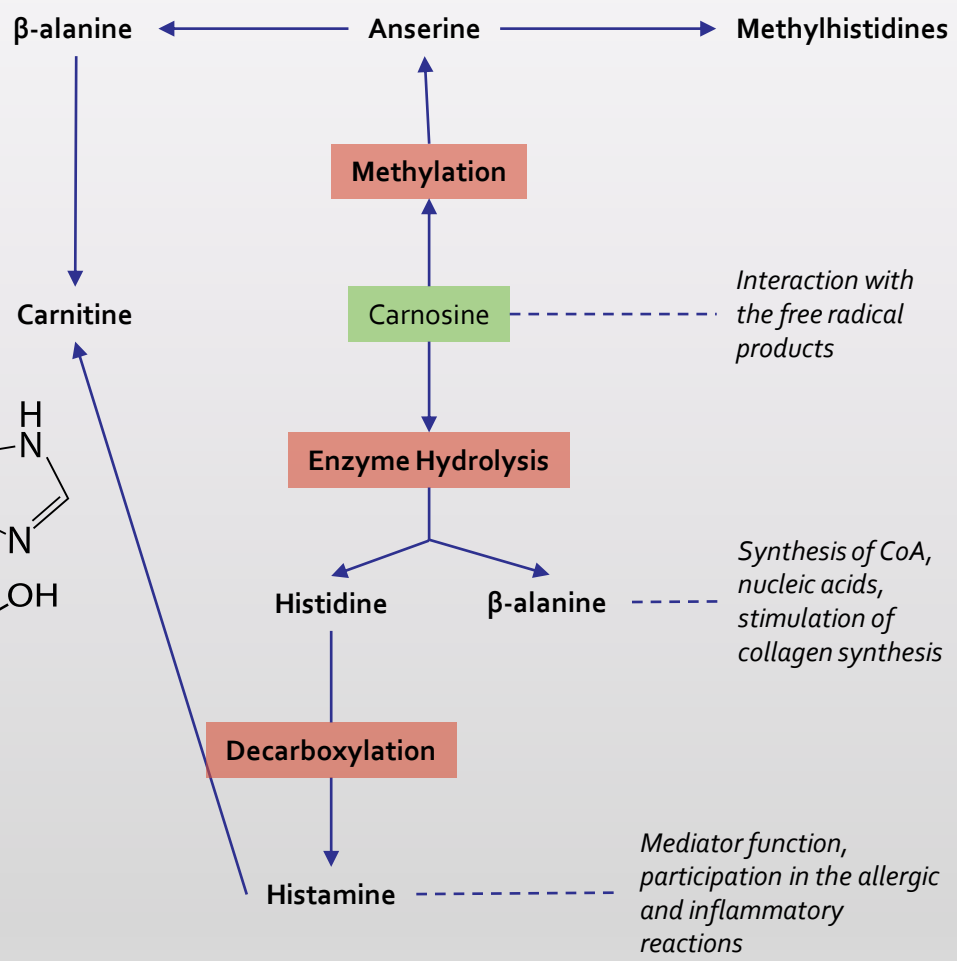
Carnosine consists of beta-alanine and L-histidine endogenously synthesized found in muscle and other tissues acting as scavenger of reactive oxygen species (ROS) and alpha-beta unsaturated aldehydes created by peroxidation of fatty acid cell membranes during oxidative stress. Carnosine can oppose protein glycation. Dietary administration of L-carnosine reduces plasma levels of advanced glycation end products (AGEs) in diabetic rats.





Carnosine is a Zn2+ chelator in glial cells, which can affect mitochondrial ATP production. Carnosine has a buffer effect on lactic acid in the muscle. L-Carnosine has also been found in olfactory bulb, brain, kidney, and spleen tissues. As a metal chelator, it may also complex with copper, cobalt, nickel, or cadmium.

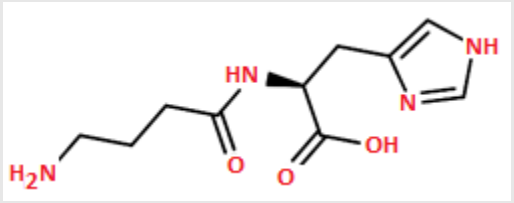
It also reduces lung myeloperoxidase (MPO) activity, production of reactive oxygen species (ROS), and TNF-α and IL-6 levels, as well as alveolar hemorrhage, interstitial edema, and pulmonary leukocyte infiltration in a mouse model of LPS-induced lung injury.

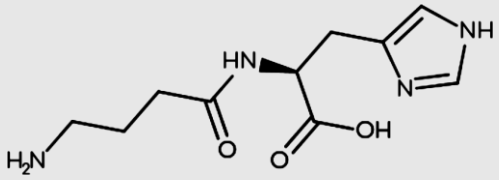


Metabolic Pathway of Carnosine

Homocarnosine

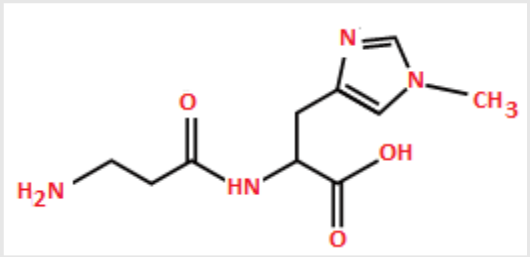
Homocarnosine is composed of γ-aminobutyryl-l-histidine existing as a major constituent of brain and skeletal muscles. Homocarnosine is localized in GABAergic neurons in human brain. Homocarnosine inhibits lipid peroxidation. Homocarnosine decreases lactate dehydrogenase (LDH) and prostaglandin E2.

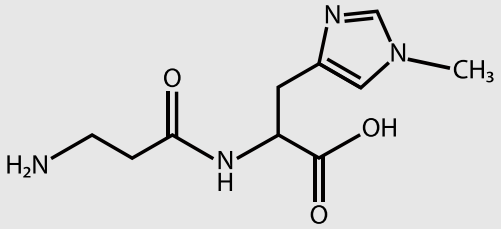




Anserine

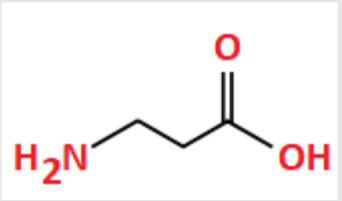
Anserine is a dipeptide containing β-alanine and 3-methylhistidine. Anserine can be found in the skeletal muscle and brain of mammals and birds. Due to its presence in lean muscles, like fish and poultry, there have been studies showing that inclusion of anserine in the diet may be beneficial for blood clearance and food absorption, and has also been found to reduce glial inflammatory activity.

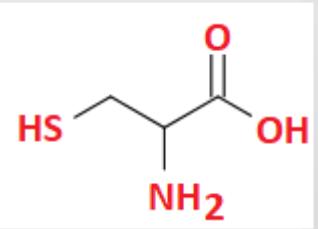


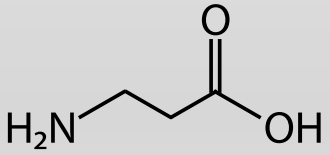


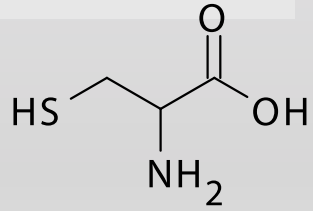
Beta-Ala-Lys

Beta-Ala-Lys is found in mammal muscle. β-alanine–containing peptides are believed to be important antioxidants, pH buffers, and neuromodulators found in olfactory bulb, cerebral cortex, and skeletal muscle. Synthesis of β-alanine appears to be a rate-limiting factor for carnosine similar peptide levels in mammals. In animal tissues, β-alanine may be largely produced by reductive degradation of uracil. GADL1 could be involved in β-alanine and peptide production in mammalian tissues. As cysteine sulfinic acid (CSA) is a substrate of GADL1, it was suggested that GADL1 is also involved in the biosynthesis of hypotaurine and taurine.





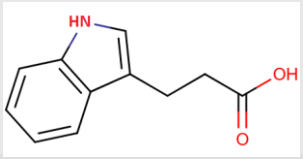


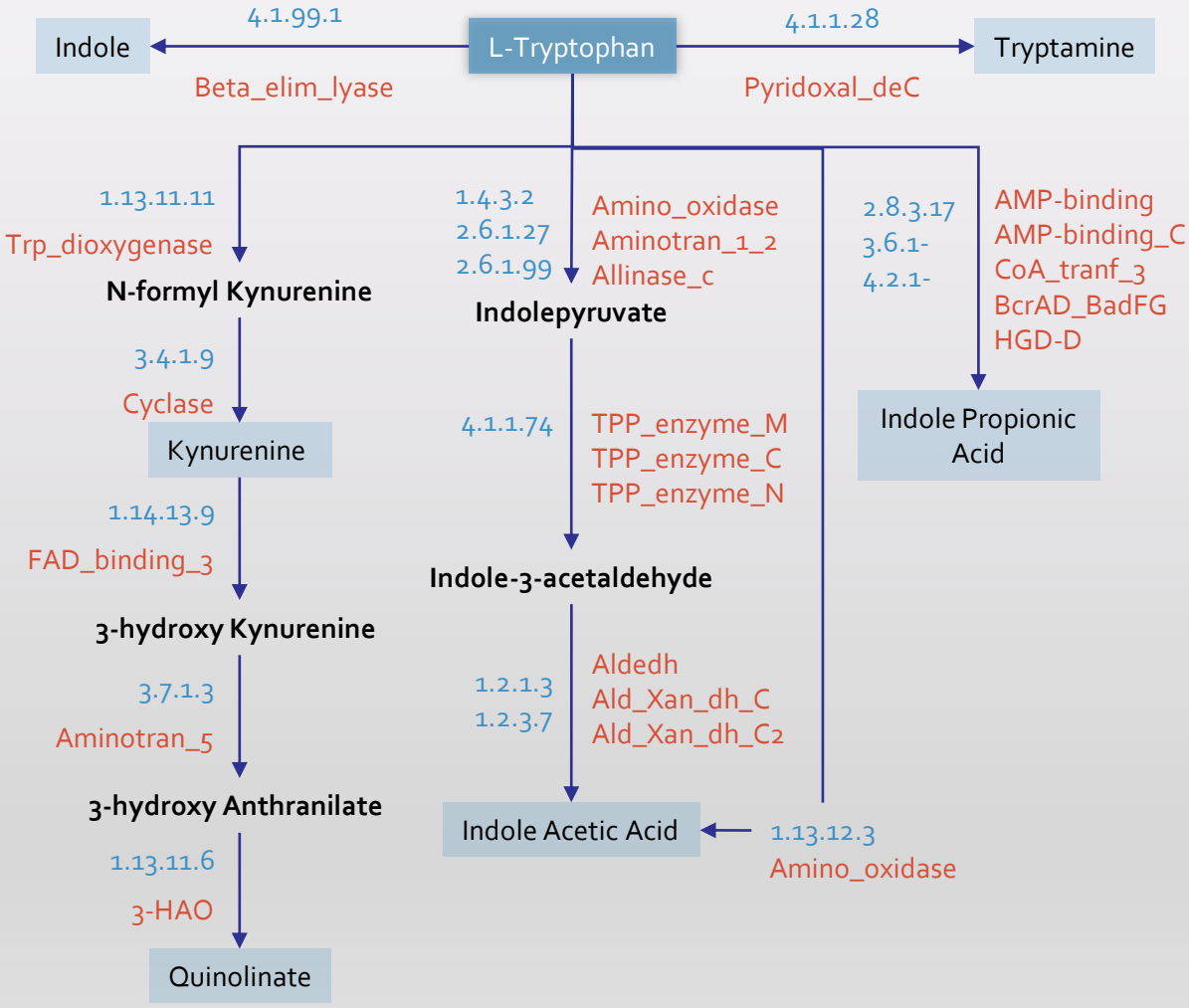


Microorganisms are rich source of bioactive compounds and antioxidants. While free tryptophan cannot be considered as an antioxidant, and tryptophan residues in proteins are not especially good targets of oxidative stress, its observed antioxidant abilities can be attributed to tryptophan metabolites from bacterial transformation.

Indole Propionic Acid

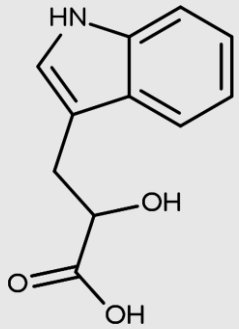
Indole Propionic Acid (IPA) is produced from tryptophan in the human gut exclusively by one species of gut bacteria (Clostridium sporogenes). Research indicates that if dysbiosis is occurring, these are amongst the first bacteria to be negatively impacted, resulting in lower IPA levels. Thus, IPA is a critical marker for a healthy gut microbiome. IPA is also considered to be one of the strongest antioxidants in the body. IPA has been shown to protect cells from oxidative stress damage. Additionally, IPA plays a crucial role in maintaining a healthy gut by strengthening the tight junctions (spaces) between the cells lining the gut. This is important for maintaining intestinal structural integrity and decreasing intestinal permeability. Intestinal permeability can lead to substances exiting the intestine into the bloodstream, leading to conditions such as food allergies.

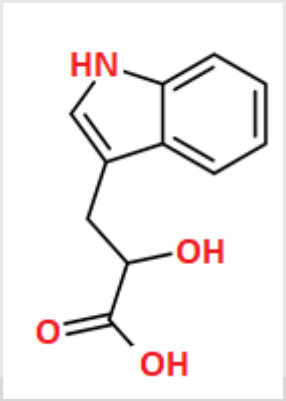




Indole-3-Lactic Acid

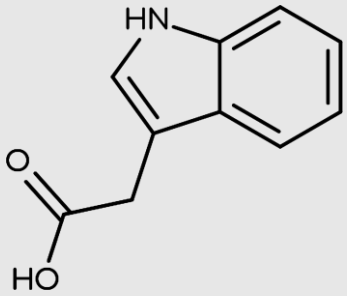
Indole-3-Lactic Acid (ILA) is a tryptophan metabolite and precursor to indole-3-propionic acid (IPA) and is important for health. Low levels of ILA may also indicate low levels of Bifidobacterium in the intestine. Bifidobacterium can assist with conversion of tryptophan to ILA and low levels of Bifidobacterium can lead to further dysbiosis. However, high levels of ILA may also lead to gut dysfunction and discomfort because, at high levels, ILA can be toxic to the beneficial bacteria in the microbiome. Excessive high levels of ILA may also indicate dysbiosis of the gut metabolome, because the bacterium Clostridium sporogenes that uses ILA to make indole-3-propionic acid (IPA) may be too low to effectively convert ILA to IPA. If the quantity of beneficial bacteria decreases significantly, there is a chance that invasive bacterial species can proliferate, leading to further dysbiosis.

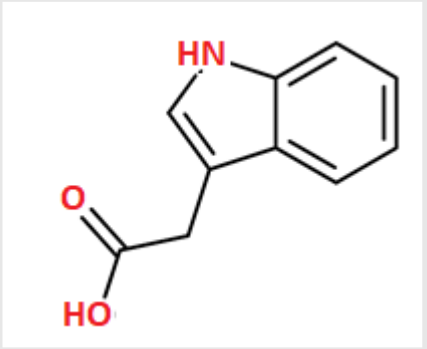




Indole-3-Acetic Acid

Indole-3-Acetic Acid (IAA) is an indirect precursor to IPA and is also an auxin produced in plants. IAA has been shown to possess antioxidant activity. However, low IAA should be considered in the context of other metabolites in the tryptophan branch, specifically indole-3-propionic acid (IPA). If both IAA and IPA are low, this can be a marker of gut dysbiosis. High levels of IAA have been reported to inhibit the growth and survival of the beneficial Lactobacillus species of gut bacteria, which converts sugars such as glucose and fructose to lactic acid, which may inhibit the growth of some harmful bacteria. High levels of IAA also have been associated with poor kidney and heart health.





Summary

Metabolomics of Vitamins and Antioxidants - Human Metabolome Technologies

The generation of free radicals and peroxides in biological systems is part of normal metabolism. However, when levels are high, a condition of oxidative stress can be detrimental to host organism cells and tissue and/or survival. Endogenous and diet supplies of antioxidants and vitamins counter and control oxidative stress.

How these metabolites work individually and synergistically is still under considerable research. However, such metabolites are critical components as biomarkers and restoring agents of disease and disease progression.

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Metabolomics of Vitamins and Antioxidants - Human Metabolome Technologies

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