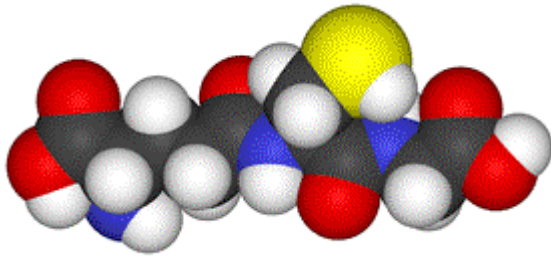


Antioxidant

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Space-filling model of the antioxidant [metabolite glutathione](#). The yellow sphere is the [redox-active](#) sulfur atom that provides antioxidant activity, while the red, blue, white, and dark grey spheres represent oxygen, nitrogen, hydrogen, and carbon atoms, respectively.

An **antioxidant** is a [molecule](#) capable of inhibiting the [oxidation](#) of other molecules. Oxidation is a [chemical reaction](#) that transfers [electrons](#) from a substance to an [oxidizing agent](#). Oxidation reactions can produce [free radicals](#). In turn, these radicals can start [chain reactions](#) that damage [cells](#). Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions. They do this by being oxidized themselves, so antioxidants are often [reducing agents](#) such as [thiols](#), [ascorbic acid](#) or [polyphenols](#).^[1]

Although oxidation reactions are crucial for life, they can also be damaging; hence, [plants](#) and [animals](#) maintain complex systems of multiple types of antioxidants, such as [glutathione](#), [vitamin C](#), and [vitamin E](#) as well as [enzymes](#) such as [catalase](#), [superoxide dismutase](#) and various [peroxidases](#). Low levels of antioxidants, or [inhibition](#) of the antioxidant enzymes, cause [oxidative stress](#) and may damage or kill cells.

As oxidative stress might be an important part of many human diseases, the use of antioxidants in [pharmacology](#) is intensively studied, particularly as treatments for [stroke](#) and [neurodegenerative diseases](#). However, it is unknown whether oxidative stress is the cause or the consequence of disease.

Antioxidants are widely used as ingredients in [dietary supplements](#) in the hope of maintaining health and preventing diseases such as [cancer](#) and [coronary heart disease](#). Although initial studies suggested that antioxidant supplements might promote health, later large [clinical trials](#) did not detect any benefit and suggested instead that excess supplementation may be harmful.^[2] In addition to these uses of natural antioxidants in medicine, these compounds have many industrial uses, such as [preservatives](#) in food and cosmetics and preventing the degradation of [rubber](#) and [gasoline](#).

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History

As part of their adaptation from marine life, terrestrial plants began producing non-marine antioxidants such as [ascorbic acid](#) ([Vitamin C](#)), [polyphenols](#), [flavonoids](#) and [tocopherols](#). Further development of [angiosperm](#) plants between 50 and 200 million years ago, particularly during the [Jurassic](#) period, produced many antioxidant pigments evolved during the late [Jurassic](#) period as chemical defences against [reactive oxygen species](#) produced during [photosynthesis](#).^[3]

The term antioxidant originally was used to refer specifically to a chemical that prevented the consumption of oxygen. In the late 19th and early 20th century, extensive study was devoted to the uses of antioxidants in important industrial

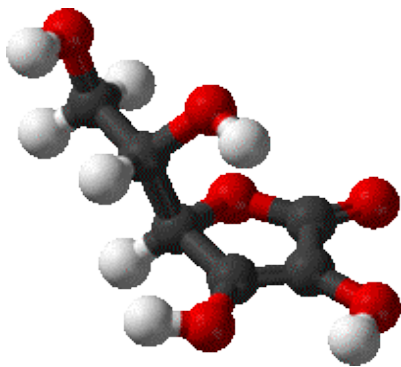
processes, such as the prevention of metal [corrosion](#), the [vulcanization](#) of rubber, and the [polymerization](#) of fuels in the [fouling](#) of [internal combustion engines](#).^[4]

Early research on the role of antioxidants in biology focused on their use in preventing the oxidation of [unsaturated fats](#), which is the cause of [rancidity](#).^[5] Antioxidant activity could be measured simply by placing the fat in a closed container with oxygen and measuring the rate of oxygen consumption. However, it was the identification of [vitamins A, C, and E](#) as antioxidants that revolutionized the field and led to the realization of the importance of antioxidants in the biochemistry of [living organisms](#).^{[6][7]}

The possible [mechanisms of action](#) of antioxidants were first explored when it was recognized that a substance with anti-oxidative activity is likely to be one that is itself readily oxidized.^[8] Research into how [vitamin E](#) prevents the process of [lipid peroxidation](#) led to the identification of antioxidants as reducing agents that prevent oxidative reactions, often by [scavenging reactive oxygen species](#) before they can damage cells.^[9]

The oxidative challenge in biology

Further information: [Oxidative stress](#)



The structure of the antioxidant [vitamin ascorbic acid](#) (vitamin C).

A [paradox](#) in [metabolism](#) is that while the vast majority of complex [life on Earth](#) requires [oxygen](#) for its existence, oxygen is a highly reactive molecule that damages living organisms by producing [reactive oxygen species](#).^[10] Consequently, organisms contain a complex network of antioxidant [metabolites](#) and [enzymes](#) that work together to prevent oxidative damage to cellular components such as [DNA](#), [proteins](#) and [lipids](#).^{[1][11]} In general, antioxidant systems either prevent these reactive species from being formed, or remove them before they can damage vital components of the cell.^{[1][10]} However, since reactive oxygen species do have useful functions in cells, such as [redox signaling](#), the function of antioxidant systems is not to remove oxidants entirely, but instead to keep them at an optimum level.^[12]

The reactive oxygen species produced in cells include [hydrogen peroxide](#) (H_2O_2), [hypochlorous acid](#) (HOCl), and [free radicals](#) such as the [hydroxyl radical](#) ($\cdot\text{OH}$) and the [superoxide anion](#) (O_2^-).^[13] The hydroxyl radical is particularly unstable and will react rapidly and non-specifically with most

biological molecules. This species is produced from hydrogen peroxide in [metal-catalyzed](#) redox reactions such as the [Fenton reaction](#).^[14] These oxidants can damage cells by starting chemical chain reactions such as lipid peroxidation, or by oxidizing DNA or proteins.^[1] Damage to DNA can cause [mutations](#) and possibly [cancer](#), if not reversed by [DNA repair](#) mechanisms,^[15]^[16] while damage to [proteins](#) causes enzyme inhibition, [denaturation](#) and [protein degradation](#).^[17]

The use of oxygen as part of the process for generating metabolic energy produces reactive oxygen species.^[18] In this process, the superoxide anion is produced as a [by-product](#) of several steps in the [electron transport chain](#).^[19] Particularly important is the reduction of [coenzyme Q](#) in [complex III](#), since a highly reactive free radical is formed as an intermediate ($Q\cdot^-$). This unstable intermediate can lead to electron "leakage", when electrons jump directly to oxygen and form the superoxide anion, instead of moving through the normal series of well-controlled reactions of the electron transport chain.^[20] Peroxide is also produced from the oxidation of reduced [flavoproteins](#), such as [complex I](#).^[21] However, although these enzymes can produce oxidants, the relative importance of the electron transfer chain to other processes that generate peroxide is unclear.^{[22][23]} In [plants](#), [algae](#), and [cyanobacteria](#), reactive oxygen species are also produced during [photosynthesis](#),^[24] particularly under conditions of high [light intensity](#).^[25] This effect is partly offset by the involvement of [carotenoids](#) in [photoinhibition](#), which involves these antioxidants reacting with over-reduced forms of the [photosynthetic reaction centres](#) to prevent the production of reactive oxygen species.^{[26][27]}

Metabolites

Overview

Antioxidants are classified into two broad divisions, depending on whether they are soluble in [water](#) ([hydrophilic](#)) or in lipids ([hydrophobic](#)). In general, water-soluble antioxidants react with oxidants in the cell [cytosol](#) and the [blood plasma](#), while lipid-soluble antioxidants protect [cell membranes](#) from lipid peroxidation.^[1] These compounds may be synthesized in the body or obtained from the diet.^[11] The different antioxidants are present at a wide range of concentrations in [body fluids](#) and tissues, with some such as glutathione or [ubiquinone](#) mostly present within cells, while others such as [uric acid](#) are more evenly distributed (see table below). Some antioxidants are only found in a few organisms and these compounds can be important in [pathogens](#) and can be [virulence factors](#).^[28]

The relative importance and interactions between these different antioxidants is a very complex question, with the various metabolites and enzyme systems having [synergistic](#) and interdependent effects on one another.^{[29][30]} The action of one antioxidant may therefore depend on the proper function of other members of the antioxidant system.^[11] The amount of protection provided by any one antioxidant will also depend on its concentration, its reactivity towards the particular reactive oxygen species being considered, and the status of the

antioxidants with which it interacts.^[11]

Some compounds contribute to antioxidant defense by [chelating transition metals](#) and preventing them from catalyzing the production of free radicals in the cell. Particularly important is the ability to [sequester iron](#), which is the function of [iron-binding proteins](#) such as [transferrin](#) and [ferritin](#).^[31] [Selenium](#) and [zinc](#) are commonly referred to as *antioxidant nutrients*, but these [chemical elements](#) have no antioxidant action themselves and are instead required for the activity of some antioxidant enzymes, as is discussed below.

Antioxidant metabolite	Solubility	Concentration in human serum (μM)^[32]	Concentration in liver tissue ($\mu\text{mol/kg}$)
Ascorbic acid (vitamin C)	Water	50 – 60 ^[33]	260 (human) ^[34]
Glutathione	Water	4 ^[35]	6,400 (human) ^[34]
Lipoic acid	Water	0.1 – 0.7 ^[36]	4 – 5 (rat) ^[37]
Uric acid	Water	200 – 400 ^[38]	1,600 (human) ^[34]
Carotenes	Lipid	β-carotene : 0.5 – 1 ^[39] retinol (vitamin A): 1 – 3 ^[40]	5 (human, total carotenoids) ^[41]
α-Tocopherol (vitamin E)	Lipid	10 – 40 ^[40]	50 (human) ^[34]
Ubiquinol (coenzyme Q)	Lipid	5 ^[42]	200 (human) ^[43]

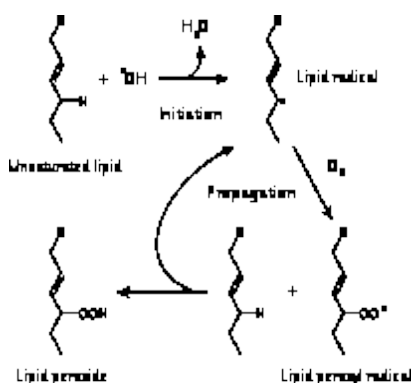
Uric acid

The antioxidant in highest concentration in human blood is [uric acid](#),^[38] which provides about half of the total antioxidant capacity of human serum.^[44] Uric acid is an oxypurine produced from [xanthine](#) by the enzyme [xanthine oxidase](#), and is a waste product of [purine](#) metabolism in primates, birds, and reptiles. An overabundance of this chemical in the body causes [gout](#). The effects of uric acid in conditions such as [stroke](#) and [heart attacks](#) are still not well understood, with some studies linking higher levels of uric acid with increased mortality.^{[45][46]} This apparent effect might either be due to uric acid being activated as a defense mechanism against oxidative stress, or uric acid acting as a pro-oxidant and contributing to the damage caused in these diseases.^{[45][46]}

Ascorbic acid

[Ascorbic acid](#) or "[vitamin C](#)" is a [monosaccharide](#) oxidation-reduction ([redox](#)) [catalyst](#) found in both animals and plants. As one of the enzymes needed to make ascorbic acid has been lost by [mutation](#) during [primate evolution](#), humans must obtain it from the diet; it is therefore a vitamin.^[47] Most other animals are able to produce this compound in their bodies and do not require it in their diets.^[48] Ascorbic acid is required for the conversion of the [procollagen](#) to [collagen](#) by oxidizing [proline](#) residues to [hydroxyproline](#). In other cells, it is maintained in its [reduced form](#) by reaction with glutathione, which can be catalysed by [protein disulfide isomerase](#) and [glutaredoxins](#).^{[49][50]} Ascorbic acid is redox catalyst which can reduce, and thereby neutralize, reactive oxygen species such as hydrogen peroxide.^[51] In addition to its direct antioxidant effects, ascorbic acid is also a [substrate](#) for the redox enzyme [ascorbate peroxidase](#), a function that is particularly important in stress resistance in plants.^[52] Ascorbic acid is present at high levels in all parts of plants and can reach concentrations of 20 [millimolar](#) in [chloroplasts](#).^[53]

Glutathione



The [free radical](#) mechanism of lipid peroxidation.

[Glutathione](#) is a [cysteine](#)-containing [peptide](#) found in most forms of aerobic life.^[54] It is not required in the diet and is instead synthesized in cells from its constituent [amino acids](#).^[55] Glutathione has antioxidant properties since the [thiol](#) group in its [cysteine moiety](#) is a reducing agent and can be reversibly oxidized and reduced. In cells, glutathione is maintained in the reduced form by the enzyme [glutathione reductase](#) and in turn reduces other metabolites and enzyme systems, such as ascorbate in the [glutathione-ascorbate cycle](#), [glutathione peroxidases](#) and [glutaredoxins](#), as well as reacting directly with oxidants.^[49] Due to its high concentration and its central role in maintaining the cell's redox state, glutathione is one of the most important cellular antioxidants.^[54] In some organisms glutathione is replaced by other thiols, such as by [mycothiol](#) in the [Actinomycetes](#), or by [trypanothione](#) in the [Kinetoplastids](#).^{[56][57]}

Melatonin

[Melatonin](#) is a powerful antioxidant that can easily cross cell membranes and

the [blood-brain barrier](#).^[58] Unlike other antioxidants, melatonin does not undergo [redox cycling](#), which is the ability of a molecule to undergo repeated [reduction](#) and [oxidation](#). Redox cycling may allow other antioxidants (such as vitamin C) to act as [pro-oxidants](#) and promote free radical formation. Melatonin, once oxidized, cannot be reduced to its former state because it forms several stable end-products upon reacting with free radicals. Therefore, it has been referred to as a terminal (or suicidal) antioxidant.^[59]

Tocopherols and tocotrienols (vitamin E)

[Vitamin E](#) is the collective name for a set of eight related [tocopherols](#) and [tocotrienols](#), which are [fat-soluble](#) vitamins with antioxidant properties.^{[60][61]} Of these, α -tocopherol has been most studied as it has the highest [bioavailability](#), with the body preferentially absorbing and metabolising this form.^[62]

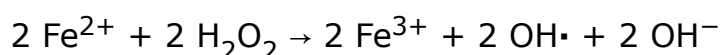
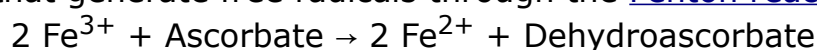
It has been claimed that the α -tocopherol form is the most important lipid-soluble antioxidant, and that it protects membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction.^{[60][63]} This removes the free radical intermediates and prevents the propagation reaction from continuing. This reaction produces oxidised α -tocopheroxyl radicals that can be recycled back to the active reduced form through reduction by other antioxidants, such as ascorbate, retinol or ubiquinol.^[64] This is in line with findings showing that α -tocopherol, but not water-soluble antioxidants, efficiently protects glutathione peroxidase 4 ([GPX4](#))-deficient cells from cell death^[65]. GPx4 is the only known enzyme that efficiently reduces lipid-hydroperoxides within biological membranes.

However, the roles and importance of the various forms of vitamin E are presently unclear,^{[66][67]} and it has even been suggested that the most important function of α -tocopherol is as a [signaling molecule](#), with this molecule having no significant role in antioxidant metabolism.^{[68][69]} The functions of the other forms of vitamin E are even less well-understood, although γ -tocopherol is a [nucleophile](#) that may react with [electrophilic](#) mutagens,^[62] and tocotrienols may be important in protecting [neurons](#) from damage.^[70]

Pro-oxidant activities

Further information: [Pro-oxidant](#)

Antioxidants that are reducing agents can also act as pro-oxidants. For example, vitamin C has antioxidant activity when it reduces oxidizing substances such as hydrogen peroxide,^[71] however, it will also reduce metal ions that generate free radicals through the [Fenton reaction](#).^{[72][73]}



The relative importance of the antioxidant and pro-oxidant activities of antioxidants are an area of current research, but vitamin C, for example, appears to have a mostly antioxidant action in the body.^{[72][74]} However, less

data is available for other dietary antioxidants, such as vitamin E,^[75] or the [polyphenols](#).^[76]

Enzyme systems

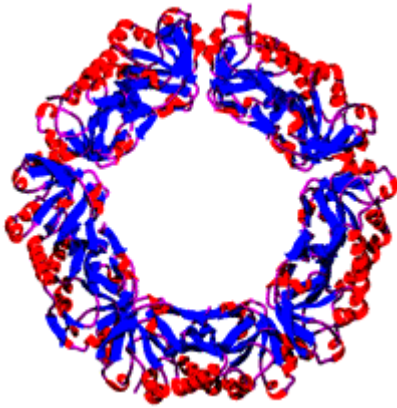
Overview

As with the chemical antioxidants, cells are protected against oxidative stress by an interacting network of antioxidant enzymes.^{[1][10]} Here, the superoxide released by processes such as [oxidative phosphorylation](#) is first converted to hydrogen peroxide and then further reduced to give water. This detoxification pathway is the result of multiple enzymes, with superoxide dismutases catalysing the first step and then catalases and various peroxidases removing hydrogen peroxide. As with antioxidant metabolites, the contributions of these enzymes to antioxidant defenses can be hard to separate from one another, but the generation of [transgenic mice](#) lacking just one antioxidant enzyme can be informative.^[77]

Superoxide dismutase, catalase and peroxiredoxins

[Superoxide dismutases](#) (SODs) are a class of closely related enzymes that catalyze the breakdown of the superoxide anion into oxygen and hydrogen peroxide.^{[78][79]} SOD enzymes are present in almost all aerobic cells and in extracellular fluids.^[80] Superoxide dismutase enzymes contain metal ion cofactors that, depending on the isozyme, can be [copper](#), zinc, [manganese](#) or [iron](#). In humans, the copper/zinc SOD is present in the [cytosol](#), while manganese SOD is present in the [mitochondrion](#).^[79] There also exists a third form of SOD in [extracellular fluids](#), which contains copper and zinc in its active sites.^[81] The mitochondrial isozyme seems to be the most biologically important of these three, since mice lacking this enzyme die soon after birth.^[82] In contrast, the mice lacking copper/zinc SOD (Sod1) are viable but have numerous pathologies and a reduced lifespan (see article on [superoxide](#)), while mice without the extracellular SOD have minimal defects (sensitive to [hyperoxia](#)).^{[77][83]} In plants, SOD isozymes are present in the cytosol and mitochondria, with an iron SOD found in [chloroplasts](#) that is absent from [vertebrates](#) and [yeast](#).^[84]

[Catalases](#) are enzymes that catalyse the conversion of hydrogen peroxide to water and oxygen, using either an iron or manganese cofactor.^{[85][86]} This protein is localized to [peroxisomes](#) in most [eukaryotic](#) cells.^[87] Catalase is an unusual enzyme since, although hydrogen peroxide is its only substrate, it follows a [ping-pong mechanism](#). Here, its cofactor is oxidised by one molecule of hydrogen peroxide and then regenerated by transferring the bound oxygen to a second molecule of substrate.^[88] Despite its apparent importance in hydrogen peroxide removal, humans with genetic deficiency of catalase — "[acatalasemia](#)" — or mice [genetically engineered](#) to lack catalase completely, suffer few ill effects.^{[89][90]}



Decameric structure of AhpC, a bacterial 2-cysteine peroxiredoxin from Salmonella typhimurium.^[91]

Peroxiredoxins are peroxidases that catalyze the reduction of hydrogen peroxide, organic hydroperoxides, as well as peroxynitrite.^[92] They are divided into three classes: typical 2-cysteine peroxiredoxins; atypical 2-cysteine peroxiredoxins; and 1-cysteine peroxiredoxins.^[93] These enzymes 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.^[94] Over-oxidation of this cysteine residue in peroxiredoxins inactivates these enzymes, but this can be reversed by the action of sulfiredoxin.^[95] Peroxiredoxins seem to be important in antioxidant metabolism, as mice lacking peroxiredoxin 1 or 2 have shortened lifespan and suffer from hemolytic anaemia, while plants use peroxiredoxins to remove hydrogen peroxide generated in chloroplasts.^{[96][97][98]}

Thioredoxin and glutathione systems

The thioredoxin system contains the 12-kDa protein thioredoxin and its companion thioredoxin reductase.^[99] Proteins related to thioredoxin are present in all sequenced organisms with plants, such as Arabidopsis thaliana, having a particularly great diversity of isoforms.^[100] The active site of thioredoxin consists of two neighboring cysteines, as part of a highly conserved CXXC motif, that can cycle between an active dithiol form (reduced) and an oxidized disulfide form. In its active state, thioredoxin acts as an efficient reducing agent, scavenging reactive oxygen species and maintaining other proteins in their reduced state.^[101] After being oxidized, the active thioredoxin is regenerated by the action of thioredoxin reductase, using NADPH as an electron donor.^[102]

The glutathione system includes glutathione, glutathione reductase, glutathione peroxidases and glutathione S-transferases.^[54] This system is found in animals, plants and microorganisms.^{[54][103]} Glutathione peroxidase is an enzyme containing four selenium-cofactors that catalyzes the breakdown of hydrogen peroxide and organic hydroperoxides. There are at least four different glutathione peroxidase isozymes in animals.^[104] Glutathione peroxidase 1 is the most abundant and is a very efficient scavenger of

hydrogen peroxide, while glutathione peroxidase 4 is most active with lipid hydroperoxides. Surprisingly, glutathione peroxidase 1 is dispensable, as mice lacking this enzyme have normal lifespans,^[105] but they are hypersensitive to induced oxidative stress.^[106] In addition, the glutathione S-transferases show high activity with lipid peroxides.^[107] These enzymes are at particularly high levels in the liver and also serve in [detoxification](#) metabolism.^[108]

Oxidative stress in disease

Further information: [Pathology](#), [Free-radical theory of aging](#)

Oxidative stress is thought to contribute to the development of a wide range of diseases including [Alzheimer's disease](#),^{[109][110]} [Parkinson's disease](#),^[111] the pathologies caused by [diabetes](#),^{[112][113]} [rheumatoid arthritis](#),^[114] and [neurodegeneration](#) in [motor neuron diseases](#).^[115] In many of these cases, it is unclear if oxidants trigger the disease, or if they are produced as a secondary consequence of the disease and from general tissue damage;^[13] One case in which this link is particularly well-understood is the role of oxidative stress in [cardiovascular disease](#). Here, [low density lipoprotein](#) (LDL) oxidation appears to trigger the process of [atherogenesis](#), which results in [atherosclerosis](#), and finally cardiovascular disease.^{[116][117]}

A [low calorie diet](#) extends median and [maximum lifespan](#) in many animals.

This effect may involve a reduction in oxidative stress.^[118] While there is some evidence to support the role of oxidative stress in aging in model organisms such as [Drosophila melanogaster](#) and [Caenorhabditis elegans](#),^{[119][120]} the evidence in mammals is less clear.^{[121][122][123]} Indeed, a 2009 review of experiments in mice concluded that almost all manipulations of antioxidant systems had no effect on aging.^[124] Diets high in fruit and vegetables, which are high in antioxidants, promote health and reduce the effects of aging, however antioxidant vitamin supplementation has no detectable effect on the aging process, so the effects of fruit and vegetables may be unrelated to their antioxidant contents.^{[125][126]} One reason for this might be the fact that consuming antioxidant molecules such as polyphenols and vitamin E will produce changes in other parts of metabolism, so it may be these other effects that are the real reason these compounds are important in human nutrition.^{[68][127]}

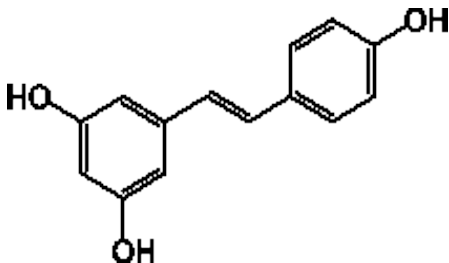
Health effects

Disease treatment

The [brain](#) is uniquely vulnerable to oxidative injury, due to its high metabolic rate and elevated levels of polyunsaturated lipids, the target of lipid peroxidation.^[128] Consequently, antioxidants are commonly used as [medications](#) to treat various forms of brain injury. Here, superoxide dismutase mimetics,^[129] [sodium thiopental](#) and [propofol](#) are used to treat [reperfusion injury](#) and [traumatic brain injury](#),^[130] while the experimental drug [NXY-059](#)^{[131][132]} and [ebselen](#)^[133] are being applied in the treatment of stroke.

These compounds appear to prevent oxidative stress in neurons and prevent [apoptosis](#) and neurological damage. Antioxidants are also being investigated as possible treatments for neurodegenerative diseases such as [Alzheimer's disease](#), [Parkinson's disease](#), and [amyotrophic lateral sclerosis](#),^{[134][135]} and as a way to prevent [noise-induced hearing loss](#).^[136]

Disease prevention



Structure of the [polyphenol antioxidant resveratrol](#).

People who eat fruits and vegetables have a lower risk of [heart disease](#) and some neurological diseases,^[137] and there is evidence that some types of vegetables, and fruits in general, protect against some cancers.^[138] Since fruits and vegetables happen to be good sources of antioxidants, this suggested that antioxidants might prevent some types of diseases. This idea has been tested in [clinical trials](#) and does not seem to be true, as antioxidant supplements have no clear effect on the risk of chronic diseases such as cancer and heart disease.^{[137][139]} This suggests that these health benefits come from other substances in fruits and vegetables (possibly [flavonoids](#)), or come from a complex mix of substances.^{[140][141]}

It is thought that oxidation of low density lipoprotein in the blood contributes to heart disease, and initial [observational studies](#) found that people taking Vitamin E supplements had a lower risk of developing heart disease.^[142] Consequently, at least seven large clinical trials were conducted to test the effects of antioxidant supplement with Vitamin E, in doses ranging from 50 to 600 mg per day. None of these trials found a [statistically significant](#) effect of Vitamin E on overall number of deaths or on deaths due to heart disease.^[143] Further studies have also been negative.^{[144][145]} It is not clear if the doses used in these trials or in most dietary supplements are capable of producing any significant decrease in oxidative stress.^[146] Overall, despite the clear role of oxidative stress in cardiovascular disease, controlled studies using antioxidant vitamins have observed no reduction in either the risk of developing heart disease, or the rate of progression of existing disease.^[147]
^[148]

While several trials have investigated supplements with high doses of antioxidants, the "*Supplémentation en Vitamines et Minéraux Antioxydants*" (SU.VI.MAX) study tested the effect of supplementation with doses comparable to those in a [healthy diet](#).^[149] Over 12,500 French men and women took either low-dose antioxidants (120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta carotene, 100 µg of selenium, and 20 mg of zinc) or [placebo](#) pills for an average of 7.5 years. The investigators found there was no statistically

significant effect of the antioxidants on overall survival, cancer, or heart disease. In a [post-hoc analysis](#) they found a 31% reduction in the risk of cancer in men, but not women.

Many [nutraceutical](#) and [health food](#) companies sell formulations of antioxidants as dietary supplements and these are widely used in [industrialized countries](#).

^[150] These supplements may include specific antioxidant chemicals, like the [polyphenol](#), [resveratrol](#) (from grape seeds or [knotweed](#) roots),^[151] combinations of antioxidants, like the "ACES" products that contain beta carotene (provitamin **A**), vitamin **C**, vitamin **E** and **Selenium**, or herbs that contain antioxidants - such as [green tea](#) and [jiaogulan](#). Although some levels of antioxidant vitamins and minerals in the diet are required for good health, there is considerable doubt as to whether these antioxidant supplements are beneficial or harmful, and if they are actually beneficial, which antioxidant(s) are needed and in what amounts.^{[137][139][152]} Indeed, some authors argue that the hypothesis that antioxidants could prevent chronic diseases has now been disproved and that the idea was misguided from the beginning.^[153]

Rather, dietary polyphenols may have non-antioxidant roles in minute concentrations that affect cell-to-cell signaling, [receptor](#) sensitivity, inflammatory [enzyme](#) activity or [gene regulation](#).^{[154][155]}

For overall [life expectancy](#), it has even been suggested that moderate levels of oxidative stress may increase lifespan in the worm *Caenorhabditis elegans*, by inducing a protective response to increased levels of reactive oxygen species.

^[156] The suggestion that increased life expectancy comes from increased oxidative stress conflicts with results seen in the yeast [Saccharomyces cerevisiae](#),^[157] and the situation in mammals is even less clear.^{[121][122][123]} Nevertheless, antioxidant supplements do not appear to increase life expectancy in humans.^[158]

Physical exercise

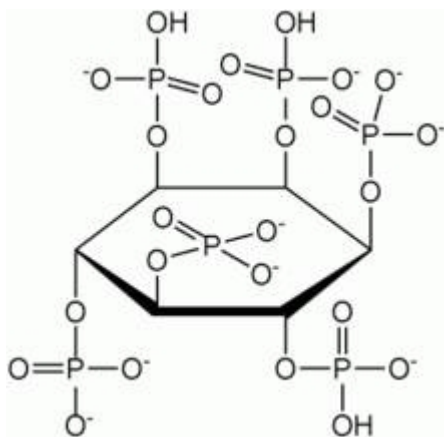
During exercise, oxygen consumption can increase by a factor of more than 10.^[159] This leads to a large increase in the production of oxidants and results in damage that contributes to muscular fatigue during and after exercise. The [inflammatory response](#) that occurs after strenuous exercise is also associated with oxidative stress, especially in the 24 hours after an exercise session. The immune system response to the damage done by exercise peaks 2 to 7 days after exercise, which is the period during which most of the adaptation that leads to greater fitness occurs. During this process, free radicals are produced by [neutrophils](#) to remove damaged tissue. As a result, excessive antioxidant levels may inhibit recovery and adaptation mechanisms.^[160] Antioxidant supplements may also prevent any of the health gains that normally come from exercise, such as increased [insulin sensitivity](#).^[161]

The evidence for benefits from antioxidant supplementation in vigorous exercise is mixed. There is strong evidence that one of the adaptations resulting from exercise is a strengthening of the body's antioxidant defenses, particularly the glutathione system, to regulate the increased oxidative stress.^[162] This effect may be to some extent protective against diseases which are associated with oxidative stress, which would provide a partial explanation for

the lower incidence of major diseases and better health of those who undertake regular exercise.^[163]

However, no benefits for physical performance to athletes are seen with vitamin E supplementation.^[164] Indeed, despite its key role in preventing [lipid membrane](#) peroxidation, 6 weeks of vitamin E supplementation had no effect on muscle damage in ultramarathon runners.^[165] Although there appears to be no increased requirement for vitamin C in athletes, there is some evidence that vitamin C supplementation increased the amount of intense exercise that can be done and vitamin C supplementation before strenuous exercise may reduce the amount of muscle damage.^{[166][167]} However, other studies found no such effects, and some research suggests that supplementation with amounts as high as 1000 mg inhibits recovery.^[168]

Adverse effects



☐

Structure of the metal chelator [phytic acid](#).

Relatively strong reducing acids can have [antinutrient](#) effects by binding to [dietary minerals](#) such as iron and zinc in the [gastrointestinal tract](#) and preventing them from being absorbed.^[169] Notable examples are [oxalic acid](#), [tannins](#) and [phytic acid](#), which are high in plant-based diets.^[170] [Calcium](#) and iron deficiencies are not uncommon in diets in [developing countries](#) where less meat is eaten and there is high consumption of phytic acid from beans and unleavened [whole grain](#) bread.^[171]

Foods	Reducing acid present
Cocoa bean and chocolate , spinach , turnip and rhubarb . ^[172]	Oxalic acid
Whole grains , maize , legumes . ^[173]	Phytic acid
Tea , beans , cabbage . ^{[172][174]}	Tannins

Nonpolar antioxidants such as eugenol—a major component of oil of cloves—have toxicity limits that can be exceeded with the misuse of undiluted essential oils.^[175] Toxicity associated with high doses of water-soluble antioxidants such as ascorbic acid are less of a concern, as these compounds can be excreted rapidly in urine.^[176] More seriously, very high doses of some antioxidants may have harmful long-term effects. The beta-Carotene and Retinol Efficacy Trial (CARET) study of lung cancer patients found that smokers given supplements containing beta-carotene and vitamin A had increased rates of lung cancer.^[177] Subsequent studies confirmed these adverse effects.^[178] These harmful effects may also be seen in non-smokers, as a recent meta-analysis including data from approximately 230,000 patients showed that β -carotene, vitamin A or vitamin E supplementation is associated with increased mortality but saw no significant effect from vitamin C.^[179] No health risk was seen when all the randomized controlled studies were examined together, but an increase in mortality was detected only when the high-quality and low-bias risk trials were examined separately. However, as the majority of these low-bias trials dealt with either elderly people, or people already suffering disease, these results may not apply to the general population.^[180] This meta-analysis was later repeated and extended by the same authors, with the new analysis published by the Cochrane Collaboration; confirming the previous results.^[181] These two publications are consistent with some previous meta-analyses that also suggested that Vitamin E supplementation increased mortality,^[182] and that antioxidant supplements increased the risk of colon cancer.^[183] However, the results of this meta-analysis are inconsistent with other studies such as the SU.VI.MAX trial, which suggested that antioxidants have no effect on cause-all mortality.^{[149][184][185][186]} Overall, the large number of clinical trials carried out on antioxidant supplements suggest that either these products have no effect on health, or that they cause a small increase in mortality in elderly or vulnerable populations.^{[137][139][179]}

While antioxidant supplementation is widely used in attempts to prevent the development of cancer, it has been proposed that antioxidants may, paradoxically, interfere with cancer treatments.^[187] This was thought to occur since the environment of cancer cells causes high levels of oxidative stress, making these cells more susceptible to the further oxidative stress induced by treatments. As a result, by reducing the redox stress in cancer cells, antioxidant supplements could decrease the effectiveness of radiotherapy and chemotherapy.^{[188][189]} On the other hand, other reviews have suggested that antioxidants could reduce side effects or increase survival times.^{[190][191]}

Measurement and levels in food

Further information: [List of antioxidants in food](#), [Polyphenol antioxidants](#)



[Fruits](#) and [vegetables](#) are good sources of antioxidants.

Measurement of antioxidants is not a straightforward process, as this is a diverse group of compounds with different reactivities to different reactive oxygen species. In [food science](#), the [oxygen radical absorbance capacity](#) (ORAC) has become the current industry standard for assessing antioxidant strength of whole foods, juices and food additives.^{[192][193]} Other measurement tests include the [Folin-Ciocalteu reagent](#), and the [Trolox equivalent antioxidant capacity](#) assay.^[194]

Antioxidants are found in varying amounts in foods such as vegetables, fruits, grain cereals, eggs, meat, legumes and nuts. Some antioxidants such as [lycopene](#) and ascorbic acid can be destroyed by long-term storage or prolonged cooking.^{[195][196]} Other antioxidant compounds are more stable, such as the polyphenolic antioxidants in foods such as whole-wheat cereals and tea.^{[197][198]} The effects of cooking and food processing are complex, as these processes can also increase the [bioavailability](#) of antioxidants, such as some carotenoids in vegetables.^[199] In general, processed foods contain fewer antioxidants than fresh and uncooked foods, since the preparation processes may expose the food to oxygen.^[200]

Antioxidant compounds	Foods containing high levels of these antioxidants ^{[174][201][202]}
Vitamin C (ascorbic acid)	Fresh Fruits and vegetables
Vitamin E (tocopherols, tocotrienols)	Vegetable oils

Polyphenolic antioxidants ([resveratrol](#), [flavonoids](#)) [Tea](#), [coffee](#), [soy](#), [fruit](#), [olive oil](#), [chocolate](#), [cinnamon](#), [oregano](#) and [red wine](#)

[Carotenoids](#) (lycopene, carotenes, [lutein](#)) Fruit, vegetables and eggs.[203]

Other antioxidants are not vitamins and are instead made in the body. For example, [ubiquinol](#) (coenzyme Q) is poorly absorbed from the gut and is made in humans through the [mevalonate pathway](#).[43] Another example is [glutathione](#), which is made from amino acids. As any glutathione in the gut is broken down to free cysteine, [glycine](#) and [glutamic acid](#) before being absorbed, even large oral doses have little effect on the concentration of glutathione in the body.[204][205] Although large amounts of sulfur-containing amino acids such as [acetylcysteine](#) can increase glutathione,[206] no evidence exists that eating high levels of these glutathione precursors is beneficial for healthy adults.[207] Supplying more of these precursors may be useful as part of the treatment of some diseases, such as [acute respiratory distress syndrome](#), [protein-energy malnutrition](#), or preventing the liver damage produced by [paracetamol](#) overdose.[206][208]

Other compounds in the diet can alter the levels of antioxidants by acting as [pro-oxidants](#). Here, consuming the compound causes oxidative stress, which the body responds to by inducing higher levels of antioxidant defenses such as antioxidant enzymes.[153] Some of these compounds, such as [isothiocyanates](#) and [curcumin](#), may be [chemopreventive](#) agents that either block the transformation of abnormal cells into cancerous cells, or even kill existing cancer cells.[153][209]

Uses in technology

Food preservatives

Antioxidants are used as [food additives](#) to help [guard against food deterioration](#). Exposure to oxygen and sunlight are the two main factors in the oxidation of food, so food is preserved by keeping in the dark and sealing it in containers or even coating it in wax, as with cucumbers. However, as oxygen is also important for plant [respiration](#), storing plant materials in [anaerobic](#) conditions produces unpleasant flavors and unappealing colors.[210] Consequently, packaging of fresh fruits and vegetables contains an ~8% oxygen atmosphere. Antioxidants are an especially important class of preservatives as, unlike [bacterial](#) or [fungal](#) spoilage, oxidation reactions still occur relatively rapidly in frozen or refrigerated food.[211] These preservatives include natural antioxidants such as ascorbic acid (AA, E300) and tocopherols (E306), as well as synthetic antioxidants such as [propyl gallate](#) (PG, E310), [tertiary butylhydroquinone](#) (TBHQ), [butylated hydroxyanisole](#) (BHA, E320) and [butylated hydroxytoluene](#) (BHT, E321).[212][213]

The most common molecules attacked by oxidation are unsaturated fats; oxidation causes them to turn [rancid](#).[214] Since oxidized lipids are often discolored and usually have unpleasant tastes such as metallic or [sulfurous](#) flavors, it is important to avoid oxidation in fat-rich foods. Thus, these foods are rarely preserved by drying; instead, they are preserved by [smoking](#),

[salting](#) or [fermenting](#). Even less fatty foods such as fruits are sprayed with sulfurous antioxidants prior to air drying. Oxidation is often catalyzed by metals, which is why fats such as butter should never be wrapped in [aluminium foil](#) or kept in metal containers. Some fatty foods such as olive oil are partially protected from oxidation by their natural content of antioxidants, but remain sensitive to photooxidation.[\[215\]](#) Antioxidant preservatives are also added to fat-based [cosmetics](#) such as [lipstick](#) and [moisturizers](#) to prevent rancidity.

Industrial uses

Antioxidants are frequently added to industrial products. A common use is as [stabilizers](#) in [fuels](#) and [lubricants](#) to prevent oxidation, and in gasolines to prevent the polymerization that leads to the formation of engine-fouling residues.[\[216\]](#) In 2007, the worldwide market for industrial antioxidants had a total volume of around 0.88 million tons. This created a revenue of circa 3.7 billion US-dollars (2.4 billion Euros).[\[217\]](#)

They are widely used to prevent the oxidative degradation of [polymers](#) such as [rubbers](#), [plastics](#) and [adhesives](#) that causes a loss of strength and flexibility in these materials.[\[218\]](#) Polymers containing [double bonds](#) in their main chains, such as such as [natural rubber](#) and [polybutadiene](#), are especially susceptible to [oxidation](#) and [ozonolysis](#). They can be protected by [antiozonants](#). Solid polymer products start to crack on exposed surfaces as the material degrades and the chains break. The mode of cracking varies between oxygen and [ozone](#) attack, the former causing a "crazy paving" effect, while ozone attack produces deeper cracks aligned at right angles to the tensile strain in the product. Oxidation and [UV degradation](#) are also frequently linked, mainly because [UV radiation](#) creates free radicals by bond breakage. The free radicals then react with oxygen to produce [peroxy](#) radicals which cause yet further damage, often in a [chain reaction](#). Other polymers susceptible to oxidation include [polypropylene](#) and [polyethylene](#). The former is more sensitive owing to the presence of [secondary carbon atoms](#) present in every repeat unit. Attack occurs at this point because the free radical formed is more stable than one formed on a [primary carbon atom](#). Oxidation of polyethylene tends to occur at weak links in the chain, such as branch points in [low density polyethylene](#).

Fuel additive	Components[219]	Applications[219]
AO-22	N,N'-di-2-butyl-1,4-phenylenediamine	Turbine oils, transformer oils , hydraulic fluids , waxes , and greases
AO-24	N,N'-di-2-butyl-1,4-phenylenediamine	Low-temperature oils
AO-29	2,6-di-tert-butyl-4-methylphenol	Turbine oils, transformer oils, hydraulic fluids, waxes, greases, and gasolines

AO-30	2,4-dimethyl-6-tert-butylphenol	Jet fuels and gasolines, including aviation gasolines
AO-31	2,4-dimethyl-6-tert-butylphenol	Jet fuels and gasolines, including aviation gasolines
AO-32	2,4-dimethyl-6-tert-butylphenol and 2,6-di-tert-butyl-4-methylphenol	Jet fuels and gasolines, including aviation gasolines
AO-37	2,6-di-tert-butylphenol	Jet fuels and gasolines, widely approved for aviation fuels

See also



[Pharmacy and Pharmacology portal](#)

- [Forensic engineering](#)
- [Free radical theory](#)
- [Nootropics](#)
- [Nutrition](#)
- [Phytochemical](#)
- [Mitohormesis](#)
- [Polymer degradation](#)
- [Antiozonant](#)
- [Evolution of dietary antioxidants](#)
- [Superfood](#)

Further reading

- Nick Lane *Oxygen: The Molecule That Made the World* (Oxford University Press, 2003) [ISBN 0-198-60783-0](#)
- Barry Halliwell and John M.C. Gutteridge *Free Radicals in Biology and Medicine*(Oxford University Press, 2007) [ISBN 0-198-56869-X](#)
- Jan Pokorny, Nelly Yanishlieva and Michael H. Gordon *Antioxidants in Food: Practical Applications* (CRC Press Inc, 2001) [ISBN 0-849-31222-1](#)

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