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Cellular Effects of Common Antioxidants

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The following information consists of proposed cellular effects regarding the use of various antioxidants. The information was gathered from scientific sources and experimental research from Medline. Some references for the proposed cellular mechanisms can be found elsewhere in this issue, whereas others can be supplied by special request from the author. It is suggested that practitioners use their best available judgment and sound reasoning when applying these supplements in clinical situations.

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Table

Represented		Proposed mechanism of action	Proposed cellular effects	Traditional and potential uses	Adverse effects	Dose
Common name	Chemicals					
Allopurinol	Allopurinol	Reduces vascular oxidative stress Decreases oxidative stress during ischemia-reperfusion	Xanthine oxidase inhibitor, which reduces formation of free radicals	Antigout Antifibrosis Heart disease	Vomiting, diarrhea, rash, bone marrow suppression, hepatoxicity	10–20 mg/kg/d
α-Lipoic acid	Dihydrolipoic acid (DL-α-lipoic acid)	Antioxidant, anti-inflammatory effects Metal chelator potentiates levels of vitamin C and vitamin E; reduces oxidative stress	Modulates apoptosis; modulates NF-kB activation; increases cellular glutathione levels and improves cellular redox state	Antioxidant, diabetic neuropathy, ischemia-reprofusion injury	Adverse effects may be seen in cats at 30 mg	1–5 mg/kg/d in dogs; unpublished data suggest that supplementing >30 mg/d in cats may not be safe
Bioflavonoids polyphenols	Quercetin, pycnogenol, rutin	Antioxidants Scavenges free radicals Chelates iron	Up-regulates antioxidant enzymes catalase and glutathione perioxidase	Antiaging Promotes cardiovascular health	None	Proportional to human dose
Bioflavonoids polyphenols (green tea extract)	Quercetin, pycnogenol, rutin, pycnogenol, reservatrol	Antioxidants Scavenges free radicals Chelates iron	Up-regulates antioxidant enzymes catalase and glutathione perioxidase	Antiaging Promotes cardiovascular health	None	Proportional to human dose

(grape seed extract)	Anthocyanidins proanthocyanidins	Anti-inflammatory, antimicrobial, hepatoprotective, antithrombotic, antiviral, and anticancer effects	Protect SOD levels Reduce mitochondrial lipid perioxidation Reduce DNA damage May reduce apoptosis May inhibit stress-induced transcription factor NF-kB May inhibit leukotriene synthesis May reduce adhesion molecules	Immune stimulation retinopathy, lymph edema; antiallergies, cancer, improves wound healing		
B-vitamins	Thiamine, riboflavin, niacin, pantothenic acid pyridoxine, choline, B_{12}	Essential for proper mitochondrial function and energy metabolism, reduces mitochondrial toxicity, reduce formation of mitochondrial free radicals	Supplies protons for mitochondrial electron chain, catalyst for energy production, reduce homocysteine cellular dysfunction	Aid metabolism of food, essential for many physiologic functions, support healthy cells, improves immune functions, assists formation of fatty acids and essential neurotransmitters	Unknown	Proportional to human dose 1–5 g/day
Vitamin B_3	Niacinamide	Precursor for NAD+ and improves NAD and NADH content of cells Essential B vitamin	Reduce reactive oxygen species and oxidative damage to cell, decreases calcium influx into cell, may decrease telomere shortening, may suppress leukocyte chemotaxis, inhibits release of proteases	Antiaging Effects immune diseases	Unknown	250–500 mg/day

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Represented		Proposed mechanism of action	Proposed cellular effects	Traditional and potential uses	Adverse effects	Dose
Common name	Chemicals					
Carnitine	L-Carnitine	Reduces oxidative stress Cytoprotective May modulate cellular stress Essential for mitochondrial energy production and vitamin C–dependant synthesis; essential factor in fatty acid metabolism	Improve mitochondrial oxidation Transports fatty acids from cytoplasm to mitochondria Reduces damage to mitochondrial electron chain Improves cellular redox state	Neurodegeneration, heart disease, hepatic disease, lipidosis, weight loss	Unknown	20–150 mg/kg tid
Carnosine	L-Carnosine	Antioxidant, detoxifies free radicals and acts as metal ion scavenger	Scavenger of free radical aldehyde Suppresses heme oxygenase activity May reduce glycation of proteins	Antiaging	None reported	Proportional to human dose
Chondroitin	Chondroitin sulfate	Improves synthesis of GAGs, antioxidant effects, antifibrotic effects Reduces proteoglycan degradation	Restores SOD and catalase, and glutathione perioxidase activity in cartilage cells May reduce lipid perioxidation May reduce DNA fragmentation	Osteoarthritis	Unknown; may alter glycemic control	Label dose on veterinary products; proportional to human dose on human products

Coenzyme Q_{10}	Ubiquinone	Has antioxidant; pro-oxidant effects Scavenges free radicals Essential for mitochondrial energy production and catalyst for ATP production	Modulates intracellular oxidation reduction reactions, transfer of reducing equivalents in the mitochondrial electron transport chain Protects against lipid perioxidation Improves extracellular superoxide dismutase activity Improves mitochondrial function and reduces oxidative stress	Heart disease Hepatic disease Energy production Neuroprotective cardiomyopathy, hypertension	Rare	1–2 mg/kg/d
Creatine	Creatine monohydrate	S phosphocreatine; is the ready energy source for muscle function; may promote protein muscle synthesis	Modulates creatine mitochondrial transport Improves ATP synthesis Reduces cell death, alters mitochondria permeability transition pores	May enhance athletic performance; may ameliorate progress of neuromuscular diseases; may improve geriatric muscle wasting	Unknown	Label dose on veterinary products
Carotinoids	β-Carotene, lutein, lycopene, zeaxanathin, crytpxanthin, astaxanthin α-carotene	Antioxidant, pro-oxidant, immune stimulant, scavenges free radicals, reduces lipid perioxidation	Reduce oxidative stress, may reduce DNA damage, may inhibit oxidant-induced cytokine production Can form free radicals and inhibit oxidative phosphorylation up-regulate connexin genes and may improve GJIC	Cancer prevention, retinal disorders	None	Proportional to human dose

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Represented		Proposed	Proposed	Traditional		
Common name	Chemicals	mechanism of action	cellular effects	and potential uses	Adverse effects	Dose
Choline	Choline chloride, phosphatidylcholine (lecithin)	Promotes lipid transport; is a structural component of biologic membranes, neurotransmitters, and transmethylation reactions	Precursor to acetylcholine Reduces perioxidative damage to cell membranes	Heart disease, fatigue, senility, performance enhancer	None	Proportional to human dose
DHA (from fish oil)	Docosahexaenoic acid	Reduces oxidative stress Immune modulator, omega-3 fatty acid with anti-inflammatory properties	Modulates cell membrane synthesis and mitochondrial membrane phospholipids; may facilitate apoptosis	Cancer, immune-mediated disease Kidney disease	Unknown	60 mg/kg/d (d/d) or proportional to human dose
DHEA	Dehydroepiandrosterone	CNS antioxidant effects, immune modulator, precursor to sex hormones; modulates plasma membrane proteins; cytoprotective of cells	Improves thioredoxin antioxidant system and cell redox May stimulate Th2 response; may modulate NF-jB activation	Lupus, antiaging, neurodegeneration Anabolic effects hypercholes terolemia, mood elevator, obesity	May increase cancer growth abnormalities	5–50 mg/d
DMSO, MSM	DMSO, MSM	Reduce oxidative stress, anti-inflammatory, natural solvent	Hydroxy radical scavenger May reduce cell membrane injury; promote GJIC	Arthritis, inflammation, interstitial cystitis, spinal cord injury	Garlic odor (DMSO)	250–1000 mg (MSM)

DMG	*N,N*-dimethylglycine (pangamic acid)	Antioxidant; may improve oxygen use and promote liver detoxification; may enhance immune function	May modulate homocysteine metabolism (by methionine pump); may enhance both humoral and cell-mediated immune response	Athletic endurance, circulatory stimulant, hyperlipidemias, metabolic enhancer	Unknown	1–3 mg/kg; doses of 50–400 mg/d have been recommended
DMAE	Dimethylaminothanol	Intermediate phospholipid metabolite; may enhance insulin activity	May stimulate DNA synthesis in fibroblasts	Antiaging, stimulates fibrous tissue	Unknown	Proportional to human dose; rarely used clinically
EPA	Eicoapentaenoic acid	Antioxidant , stabilizes cell membranes, modulates immune functions; modulates eicosanoid production; may reduce cancer cachexia	Reduces cellular reactive oxygen species, reduces inflammatory cytokines Depresses nitric oxide production May alter cell membrane phospholipids; down-regulates NF-kB; may induce apoptosis in cancer cells; may inhibit lipoxygenase; may reduce TNF- synthesis and IL-2 production	Arthritis, cancer, immune modulator, cardiovascular disease, kidney disease	May reduce blood clotting	60 mg/kg

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Represented		Proposed mechanism of action	Proposed cellular effects	Traditional and potential uses	Adverse effects	Dose
Common name	Chemicals					
Glutamine	L-Glutamine	Antioxidant effects Preferred fuel for enterocytes; may enhance cellular immunity, modulate tumor cell metabolism, and improve clinical outcome in stress situations	Regulates cell redox, provides fuel for mitochondrial, may stimulate DNA synthesis; may block apoptosis essential donor for nucleotide precursor synthesis; may modulate inflammatory activities of IL-8 and TNF-α; precursor to GABA and L-glutamic acid	Gastrointestinal supplement for bowel disease; conditionally essential in chronic debilitating illness	None	500 mg/kg divided daily
GAGs and precursors	Glucosamine Hcl, glucosamine sulfate, chondroitin sulfate	Reduce oxidative stress to chondrocytes, Building block of cartilage (GAGs); modify joint damage; may stimulate synthesis of proteoglycans in vascular endothelium and bladder mucosa	May inhibit degradative enzymes; may inhibit nitric oxide activity; may modulate cytokine activity	Osteoarthritis, rheumatoid arthritis, wound healing, feline lower tract disease	May increase bleeding and partial thromboplastin time; studies done on one brand (Cosequin) show no hematologic adverse effects	Veterinary forms labeled for arthritis; proportional to human dose

Ginkgo biloba	Ginkgo flavone glycosides	Antioxidant, scavengers free radicals, improves mitochondrial functions	Improves mitochondrial membrane Stimulates complex I & III of the mitochondrial electron chain Protects against mitochondrial oxidative uncoupling Forms cell redox Ratio of reduced glutathione to oxidized glutathione	Improves memory, and promotes better circulation	Proportional to human dose	
Glutathione (reduced form)	L-glutathione	Primary intracellular antioxidant; primary agent for detoxification of drugs; reduces oxidative stress	GSH/GSSH measures oxidative stress Modulates apoptosis; primes DNA synthesis	Beneficial in all pathologic states Antiaging, immune enhancer, liver disease	Unknown	Proportional to human dose Absorption is questionable when dosed orally
Lactoferrin	Siderophillin	Anti-inflammatory, antioxidant effects, binds metal ions, antiviral effects; may enhance immune function	Stimulates glycolysis and mitochondrial ATP Enhances phagocytic activity; regulates iron activity	Feline stomatitis, immune disorders	Unknown	40 mg/kg topically
Mannitol	D-mannitol	Exogenous antioxidant	Hydroxyl radical (OH) scavenger	Renal failure Osmotic agent Ischemia injuries, cerebral edema, glaucoma	Fluid and electrolyte abnormalities	0.25–1g/kg dose IV slowly repeat as needed
Melatonin	Melatonin	Antioxidant; may enhance T (helper) cell response to antigen; regulates circadian cycles; may up-regulate cell lineage–specific stem cell activity	May protect DNA and cellular membranes from oxidative stress; may stimulate IL-2 release by T helper cells and lymphocytes	Insomnia, anticancer effects alopecia in certain breeds; regulates circadian rhythm; may be used for episodes of thunder-phobia	Mild hypothermia may suppress male infertility; may increase adverse lung effects in asthmatics	0.3–5 mg total, depending on animal size; 6 mg tid for alopecia in boxers

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Represented		Proposed	Proposed	Traditional		
Common name	Chemicals	mechanism of action	cellular effects	and potential uses	Adverse effects	Dose
Methionine	DL-methionine	Antioxidant, source of sulfur; essential for energy production and muscle building Methionine also has pro-oxidant effects	Component of glutathione redox system; precursor to *S*-adenosylmethionine	Controversial use in liver support	High doses may increase iron levels, cause pancreatic damage, or induce neurologic change	Human dose is 800–1000 mg/d
NAC	*N*-acetyl-L-cysteine	Increases glutathione levels; radical oxygen scavenger; improves mitochondrial function	Improves cell redox state, modulates apoptosis; may inhibit TNF-α and stress-mediated NF-jB activation	Neurodegenerative conditions, bronchitis, liver toxicity, acetaminophen toxicity	Unknown	25 mg/kg tid
Phospholipids	Phosphatidylserine, phosphatidylcholine (lecithin)	Essential components of cell membranes, regulates CNS neurotransmitters Antioxidant, anti-inflammatory, antifibrobitic	Membrane phospholipid that facilitates signal transduction; may reduce proinflammatory effects of lipid perioxidation Decreases leukocyte infiltration	Cognitive dysfunction, mood enhancer, depression kidney damage	None reported	25–100 mg/kg bid

SAM-e	*S*-adenosylmethionine	Involved in three major biochemical pathways (transmethylation, transsulfuration, and ainopropylation); up-regulates genes for proteoglycan synthesis; may facilitate DNA production and brain neurotransmitters	Component of glutathione perioxidase; inhibits oxidation of lipids; scavenges free radicals and protects cellular DNA; hepatic microsomal oxidation and detoxification	Liver damage, osteoarthritis, and depression in humans Antiaging? Acetaminophen toxicity	20 mg/kg/d	
Selenium	Selenium sodium selenite, sodium selenate	Antioxidant; modulates thyroid hormone; synergy with vitamin E; binds to some toxins Improves hepatic function; increases bile flow; aids liver detoxification enzyme activity	Increases cellular glutathione levels, cofactor in many antioxidant enzymes, major component of GSH-perioxidase	Muscular diseases; may help prevent cancer in humans; useful in managing pancreatitis in dogs Very high levels are hepatoxic	High levels are toxic; lethal dose in dogs is 2 mg/ kg	5–50 μg/d IV 0.3 mg/kg for acute pancreatitis
Silymarin	Silibinin	Antioxidant, anticancer Hypocholesterolemic effects Antihepatotoxic agent	Regulator of intracellular glutathione, reduces mitochondrial oxidation, protects against lipid perioxidation, cell membrane stabilizers may increase DNA synthesis	Hepatitis, hepatic fibrosis, hyperlipidemias	Rare allergic reaction	50–150 mg/kg orally, bid for hepatotoxicosis, lower doses for chronic use 7–15 mg/kg/d
	(Milk thistle)	Anti-inflammatory	Free radical scavenger	Liver detoxicant		
SOD	Superoxide dismutase	Endogenous antioxidant enzyme; neutralizes superoxide radicals	Protects mitochondrial membranes from oxidation	Osteoarthritis, inflammatory bowel disease, heart disease, chronic diseases	Unknown	5–20 IU/kg; not well explored yet

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Represented		Proposed mechanism of action	Proposed cellular effects	Traditional and potential uses	Adverse effects	Dose
Common name	Chemicals					
Taurine	L-taurine	Antioxidant reduces ischemic damage; improves endogenous and exogenous antioxidant defense; modulates CNS activity (osmoregulation, neuroprotection, and neuromodulation)	Modulates intracellular calcium levels; maintains cell membrane, restores glutathione levels in cells, vital for the proper use of sodium potassium and calcium; bile acid conjugation	Congestive heart failure, diabetes, liver disease; hypertension, anxiety, CNS disturbances, dilated cardiomyopathy of cats and cocker spaniels	None	250–500 mg bid
Vitamin C	Ascorbic acid, sodium ascorbate, magnesium ascorbate, esterified ascorbate	Antioxidant, pro- oxidant under certain circumstances, aids synthesis of collagen, catecholamines, steroids, carnitine, iron absorption, and improves immune function, antihistamine activity	Reduces TNF-α– induced activation of NF-jB; may modulate apoptosis; may protect DNA by reduction of reactive oxygen species; may reduce oxidation of LDLs; may improve endothelial GJIC	Allergies, chronic inflammation, immune function, macular degeneration, cataracts, cancer prevention; may reduce effectiveness of chemotherapeutic agents	Increases oxalate crystalluria; may interfere with activity of glycosides in urine; depleted by tetracyclines salicylates	50 mg/kg, up to 1000 mg/d in large dogs; doses of 3–5 g/d have been used without adverse effect in large dogs

Vitamin E	D-alpha-tocopherol (active form), DL-alpha-tocopherol, mixed tocopherol, tocotrienols	Antioxidant, neuroprotective and antiatherogenic effects; suppresses lipid peroxidation; modulates synthesis of coenzyme A and ATP; modulates immune response; improves oxygen use	Fat-soluble membrane stabilizer; modulates apoptosis; modulates growth factors; may decrease androgen concentrations; may decrease LDL oxidation; may reduce adhesion molecules; may decrease transcription factor NF-kB	Cancer prevention, cholestatic liver disease, cardiovascular disease, diabetes, inflammatory disorders, immune function enhancement, senility	Rare; potential effects of anticoagulants and digoxin	10–20 IU/kg, up to 800 IU/d for large dogs
Zinc	Zinc gluconate zinc sulfate, zinc methionine	Antioxidant enzyme system factor; antifibrotic stabilizes cell membranes; aids protein synthesis; component of SOD	Oxygen scavenger through induction of metallothionein, zinc-dependent transcription factor; modulates apoptosis NF-kB modulates genetic expression of cytokines (IL-2); modulates T-cell function and ratio	Zinc responsive dermatitis, improves immunity, wound repair, skin disorders, viral infections, mental health, Wilson's disease (binds copper), sexual maturation	High doses can cause gastritis, hemolytic anemia, icterus, hypotension	Zinc methionine, 4 mg/kg/d po; zinc sulfate, 10 mg/kg/d po; zinc gluconate, 5 mg/kg/d po

Abbreviations: CNS, central nervous system; DHA, docosahexaenoic acid; DHEA, dehydroepiandrosterone; DMAE, dimethylaminoethanol; DMG, dimethylglycine; DMSO, dimethylsulfoxide; EPA, eicoapentaenoic acid; GABA, γ-aminobutyric acid; GAGs, glycosaminoglycans; GJIC, gap junctional intercellular communication; HTP, hydroytryptophan; IL, interleukin; LDL, low-density lipoprotein; MSM, methylsulfonylmethtane; NAC, *N*-acetylcysteine; NF-kB, nuclear factor kappa B; SAM-e, *S*-adenosylmethionine; SOD, superoxide dismutase; TNF, tumor necrosis factor.