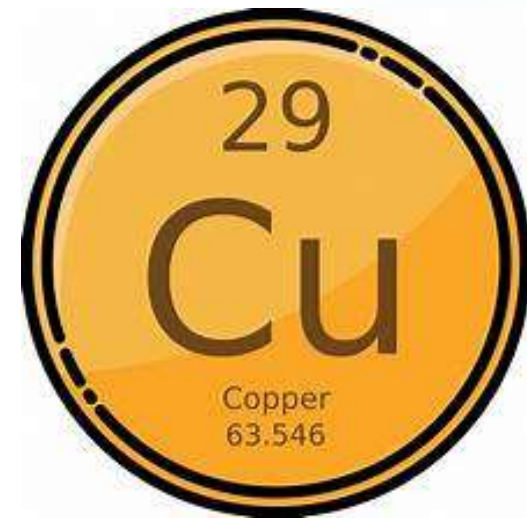


Copper: Friend or Foe?

Presented by Dr. Ron Grabowski, DC, RDN





Ron Grabowski, DC, RDN

Clinical Nutrition Authority/Educator/Researcher

Credentials

Doctor of Chiropractic
Registered Dietitian/Nutritionist
40+ Years Clinical Experience

Professional Experience

Nearly 2,000 Seminars & Lectures (U.S. & Europe)
Author of Articles & Textbooks in Clinical Nutrition
Mentor to Thousands of Practitioners in Functional Testing

Clinical Appointments

New York Hospital
Memorial Sloan Kettering Cancer Center
University of Texas MD Anderson Cancer Center

Areas of Expertise

Thyroid & Nutrient-Related Fatigue
Oxidative Stress & Chronic Inflammation
Fertility & Hormonal Health
Evidence-Based Supplementation
Nutrition for Athletes
Chronic Disease Support

Dann and Darby Defined Five (5) Zones of Nutriture

- | | |
|----|--|
| 1. | Saturation |
| 2. | Unsaturated but functionally unimpaired |
| 3. | Potential deficiency disease |
| 4. | Latent deficiency disease |
| 5. | Clinically manifested deficiency disease |

Physiol Rev 25, 326–346.

Copper Deficiency

- ▶ **Systems Altered:**

- ▶ Cardiovascular
- ▶ Gastrointestinal
- ▶ Hematopoietic
- ▶ Integumentary
- ▶ Musculoskeletal
- ▶ Nervous
- ▶ Reproductive systems

	% of control value
Cardiovascular diseases	
Serum in CAD (81)	93·0
Serum in CAD (30)	83·6
Musculoskeletal diseases	
Serum in femoral neck fractures (46)	78·0
Serum in age-related bone loss (225)	72·5
Subnormal serum in elderly men (23·7 %) and women (32·9 %) (170)	
Serum in postmenopausal O (576)	84·4
Central incisor in low bone mineral density (50)	53·1
Serum in female O (51)	38·2
Nervous system diseases	
Frontal cortex in AD (8)	56·5
Frontal cortex in dementia with Lewy bodies (6)	52·2
Hippocampus in AD (15)	51·1
Amygdala in AD (18)	52·3
Seven brain regions in AD (9)	52·8–70·2

Numbers in parentheses are the number of deficient people (total = 1285).

Low Copper
(organs, plasma, etc.,
in chronic diseases)

* **60 Medical Publications**

	% of control value
Cardiovascular diseases	
Extracellular SOD in gestational diabetes (20)	87.3
Plasma SOD in coronary artery ectasia (40)	46.1
RBC SOD in coronary slow flow (20)	65.3
RBC SOD in CAD (20)	83
Extracellular SOD in Type 2 diabetes mellitus (31)	68.0
Serum SOD in obesity ^a (290)	47.5
Plasma SOD in coronary angiography patients (766)	75.3
Serum SOD in metabolic syndrome ^a (3091)	86.1
Musculoskeletal diseases	
Plasma SOD, RBC SOD in women with O (75)	77.3, 66.6
Serum SOD in O (35)	52.3
Nervous system diseases	
SOD in AD frontal cortex, cerebellum, and hippocampus (12)	65 to 73
RBC SOD in AD (22)	54.9 to 66.4
Caeruloplasmin specific activity in AD (84)	94.7

SOD, superoxide dismutase; RBC, red blood cell; total patients = 4506.

Low Activities of Copper-dependent Enzymes in Chronic Diseases

Copper Absorption

- ▶ Copper is mainly obtained from dietary sources such as organ meat and shellfish.
J Trace Elem Med Biol. 2016;35:107–15.
- ▶ Copper is primarily absorbed by enterocytes in the small intestine, and its uptake is mediated by copper transporter 1 (CTR1), also known as solute carrier family 31 member 1 (SLC31A1). **Mol Cancer. 2023;22:46.**
- ▶ CTR1 appears to play a primary role in this uptake, as indicated by research showing greatly reduced copper accumulation in the peripheral tissues of neonatal mice lacking CTR1. **Cell Metab. 2006;4:235–44.**
- ▶ The six-transmembrane epithelial antigen of the prostate (STEAP) facilitates this process by reducing divalent Cu^{2+} to Cu^{+} .

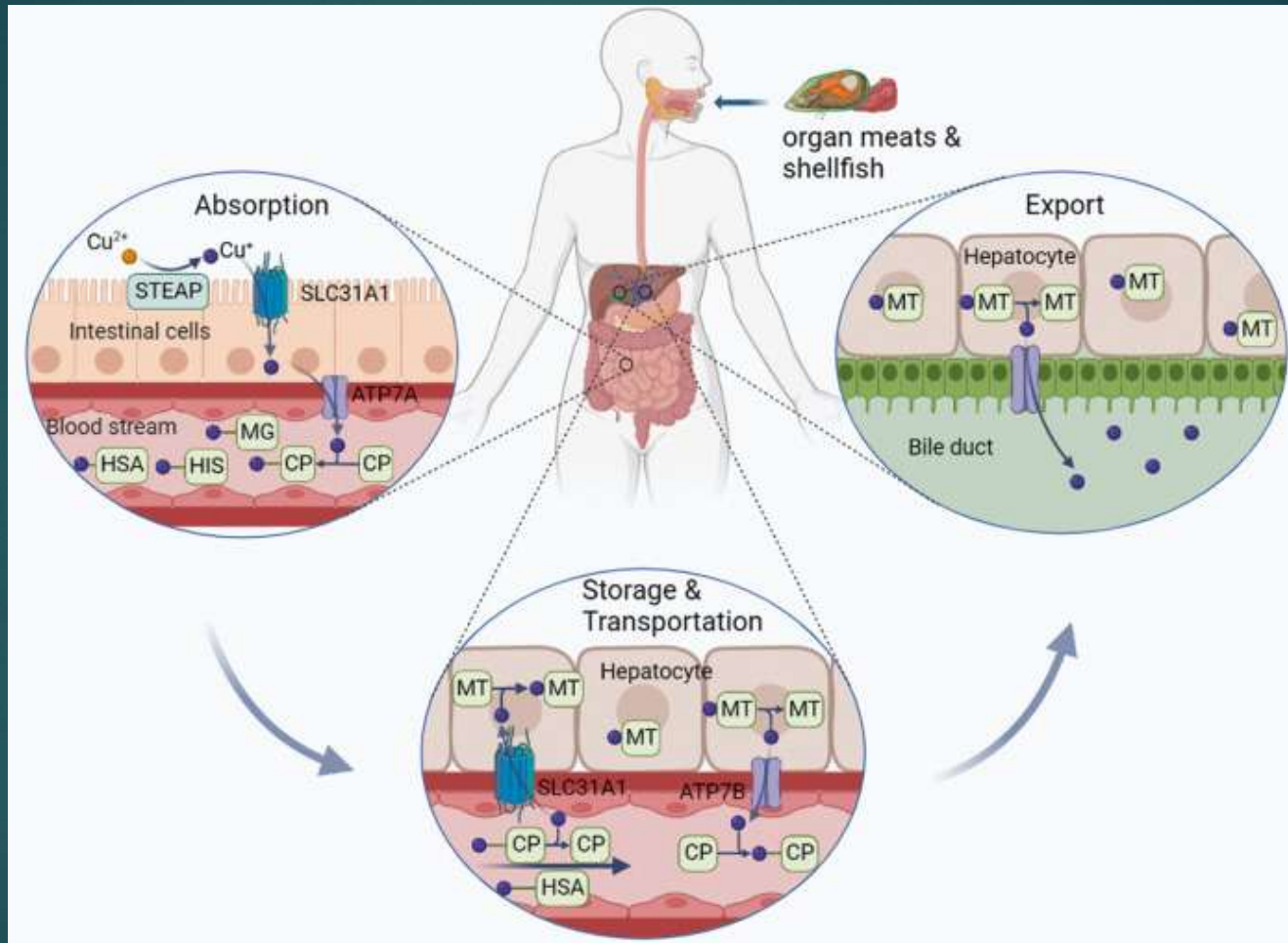
Copper Storage and Transportation

- ▶ After uptake by the intestinal epithelial cells, copper is transported and exported into the bloodstream by the ATPase copper transporter 7 A (ATP7A). **Am J Clin Nutr. 2008;88:846s–50s.**
- ▶ Copper is transported through the portal system to the liver by binding to soluble chaperones such as human serum albumin (HSA), ceruloplasmin, histidine, and macroglobulin. **J Cell Sci. 2021;134:96–114.**
- ▶ Copper uptake by the hepatocytes in the liver is also mediated by CTR1.
- ▶ The liver is **crucial** in regulating copper metabolism by storing and excreting copper.
- ▶ Copper storage is mediated by the copper-binding protein metallothionein (MT), a reducing molecule rich in thiol groups with a high affinity for copper ions. **Angew Chem Int Ed Engl. 2020;59:7830–5.**
- ▶ MT plays a crucial role in copper homeostasis by storing and releasing excess copper when required.
- ▶ Copper transport is performed by ATPase copper transporter 7B (ATP7B) in hepatocytes, which pumps copper ions from the liver back into the bloodstream.
- ▶ Copper ions then bind to their soluble partners and are transported to specific tissues and organs.

Int J Biochem Cell Biol. 2010;42:206–9.

Copper Elimination

- ▶ Copper is primarily eliminated via biliary excretion [7].
- ▶ Excess copper is secreted by the liver into the bile and then excreted through feces. *Proc Nutr Soc.* 2004;63:31–9.
- ▶ The ATP7B transporter regulates the elimination of copper from the liver to bile canaliculi. *Gastroenterology.* 2008;134:1215–23.
- ▶ In cases of ATP7B dysfunction, such as Wilson's disease, copper accumulates in the liver, leading to liver damage and subsequent health issues. *Gastroenterology.* 2012;142:947–56.e5.
- ▶ Copper metabolism is a complex process that involves multiple mechanisms to regulate copper absorption, transport, storage, and elimination.



Cellular Copper Homeostasis

- ▶ The maintenance of intracellular copper homeostasis is a complex and tightly regulated process involving the coordinated action of copper transporters, chaperones, and cuproenzymes.
- ▶ Copper concentration is maintained within a narrow range through the collaborative action of these copper-dependent proteins.

Copper Uptake

- ▶ In mammalian cells, copper uptake is primarily mediated by CTR1, a transmembrane protein that forms a trimeric channel to facilitate the passage of Cu ions across the plasma membrane. **Biol Chem. 2013;288:18035–46.**
- ▶ CTR1 expression is regulated by copper levels.
- ▶ Low copper levels upregulate CTR1 expression to increase copper uptake, whereas high levels downregulate CTR1 expression to prevent copper cytotoxicity.

Mol Pharm. 2012;81:455–64.

J Nutr. 2006;136:21–6.

Intracellular Copper Distribution

- ▶ After entering the cell, copper is first delivered to cytoplasmic copper chaperones, which then transport it to intracellular compartments such as the mitochondria, trans-Golgi network (TGN), and nucleus.
- ▶ In mammalian cells, three (3) major copper chaperones have been identified:
 - ▶ Antioxidant 1 copper chaperone (ATOX1)
 - ▶ Copper chaperone for superoxide dismutase (CCS)
 - ▶ Cytochrome c oxidase copper chaperone 17 (COX17).

Int J Biochem Cell Biol. 2009;41:1233–6.

J Nutr. 2004;134:1003–6.

ATOX1

- ATOX1 delivers copper to ATP7A and ATP7B in the TGN.

J Mol Med Berl. 2023;101:527–42.

- ▶ ATOX1 has been shown to function as a new type of copper-dependent transcription factor that mediates copper-induced cell proliferation.

J Biol Chem. 2008;283:9157–67.

Cytoplasmic Copper-chaperone (CCS)

- ▶ CCS is a soluble cytoplasmic copper-chaperone protein that transfers copper ions to the copper-binding site of superoxide dismutase 1 (SOD1). **Acc Chem Res.** 2001;34:119–28.
- ▶ **SOD1** is a major antioxidant enzyme that catalyzes the conversion of superoxide radicals into oxygen and hydrogen peroxide, thereby maintaining reactive oxygen species (ROS) homeostasis and protecting the cells from oxidative stress damage.
Chem Sci. 2016;7:6251–62.
- ▶ This function has been shown where the absence of SOD1 increased oxidative stress and led first to liver cell damage and eventually liver cancer. **Oncogene.** 2005;24:367–80.

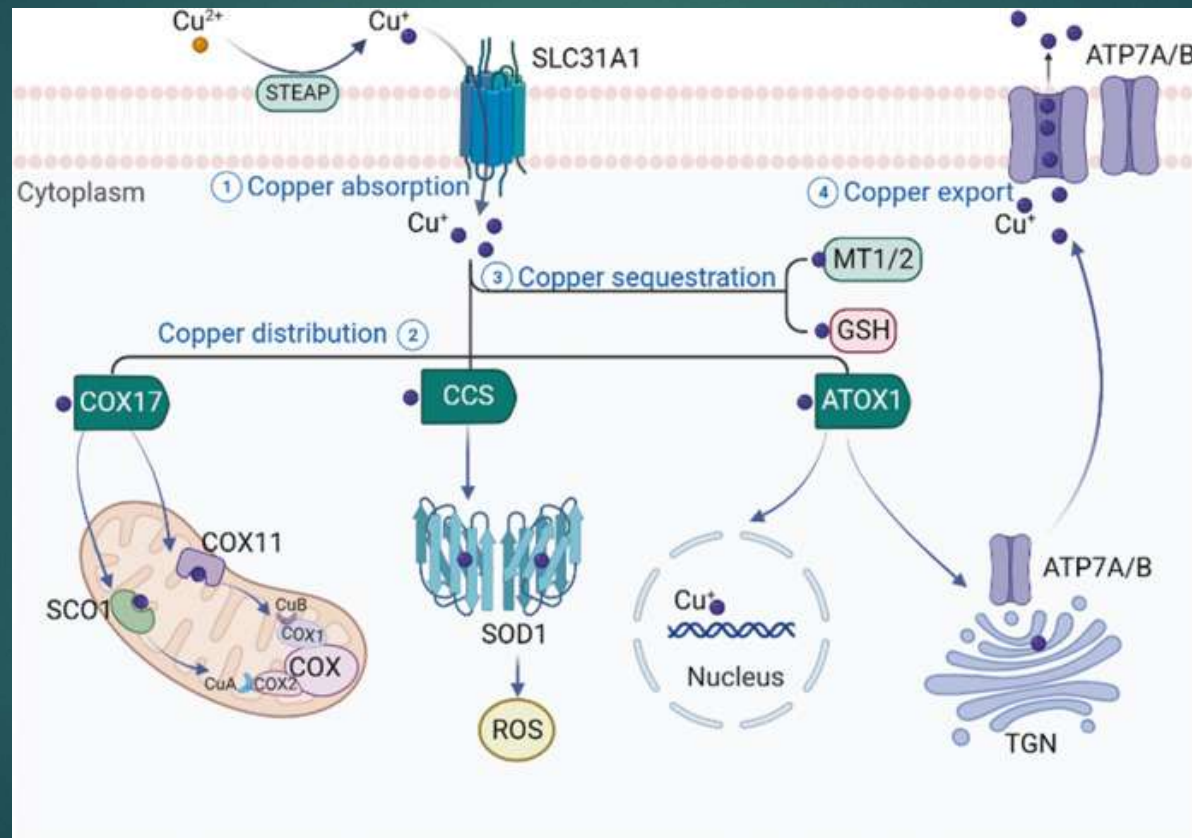
COX17

- ▶ COX17 is responsible for delivering copper ions to the assembly of cytochrome c oxidase (COX), a key component of the electron transport chain involved in cellular respiration. **Plant Sci. 2022;322:111345.**
- ▶ COX11 and SCO1, which are also important components of the COX assembly, donate copper to Cu(B) and Cu(A) sites in COX2 and COX1 core subunits of COX in the mitochondrial inner membrane, respectively.
- ▶ COX17 also acts as a copper donor within the mitochondrial intermembrane space (IMS). **J Biol Chem. 2004;279:35334–40.**
- ▶ COX17 is thus essential for proper COX assembly, with mutations in COX17 shown to further reduce COX activity, resulting in mitochondrial dysfunction and oxidative stress. **Mol Cell Biol. 2002;22:7614–21.**

Intracellular Copper Storage and Export

- ▶ Intracellular copper export is mainly mediated by ATP7A and ATP7B, which are copper transporters located in the TGN that regulate copper delivery to secretory pathways and the plasma membrane.
Physiol Rev. 2007;87:1011–46.
- ▶ Under normal conditions, ATP7A and ATP7B transport copper ions from the TGN to other cellular compartments for various cellular functions.
- ▶ At **excessive intracellular copper levels**, ATP7A and ATP7B are activated to export excess copper ions from the TGN and sequester them in copper-binding proteins such as metallothionein [40].
- ▶ These proteins regulate copper homeostasis by reducing uptake and increasing efflux.
- ▶ Mutations in ATP7A and ATP7B can lead to copper metabolism disorders such as **Menkes disease** and **Wilson's disease**. **Biomedicines. 2021;9:123–142.**

Schematic Diagram of Cellular Copper Metabolism



Cell Death Discov. 2024 Jan 13;10(1):25.

Anemia and Copper

- ▶ Anaemia in copper deficiency has been studied for more than 90 years.
- ▶ Neuropathy can occur without it.

Mayo Clin Proc 81, 1371–1384.

- ▶ Anaemia is a comparatively insensitive index of deficiency.

Johns Hopkins Med J 124, 139–150.

- ▶ Copper deficiency can masquerade as myelodysplastic syndrome.

N Engl J Med 381, e28. (2019)

Case Rep Oncol 13, 62–68. (2020)

Osteoporosis

- ▶ There should be no medical doubt that copper deficiency can cause osteoporosis.
Klevay LM (2010) Copper. In Encyclopedia of Dietary Supplements, 2nd ed., pp. 175–184
 - ▶ Most of the twenty-nine relevant, medical publications describe deficient children. **Trace Elem Med Biol 16, 149–154. (2002)**
- ▶ Strain hypothesized that diets low in copper may contribute to postmenopausal osteoporosis and noted that milk and milk products are among the poorest dietary sources of copper in confirmation of an earlier observation.
Med Hypotheses 27, 333–338.
Johns Hopkins Med J 124, 139–150.
- ▶ Graham and Cordano noticed that bone demineralization precedes anaemia in copper deficiency.
- ▶ Copper supplementation has been beneficial.

Alzheimer's Disease

- ▶ It is hypothesized that copper deficiency is a plausible cause of Alzheimer's disease. **Med Hypotheses 70, 802–807. (2008)**
- ▶ Patients are thinner than normal; weight loss precedes dementia and is associated with greater dementia and neurobehavioural symptoms.
- ▶ Cytochrome oxidase depends on copper for activity; at least fourteen publications reveal decreased activity in brain of Alzheimer's patients.
- ▶ Brain copper and caeruloplasmin have been shown to be decreased.

Copper and Locus Coeruleus

- ▶ Hundreds of articles associate the locus coeruleus with Alzheimer's disease.
- ▶ This locus has the highest concentration of copper in brain, and probably the body; it may have a place in memory. **Owen CA Jr (1982) Physiological Aspects of Copper**
- ▶ Chemical analysis reveals lower copper in the locus of Alzheimer's disease patients than in similar people without dementia, a new approach to the disease will have been identified.
- ▶ Locus coeruleus volume decreases as Alzheimer dementia increases.

Alzheimers Dement 13, 236–246. (2017)

- ▶ Tyrosine hydroxylase histochemistry in the locus can be used to assess early neuronal degeneration. **Acta Neuropathol Commun 5, 8. (2017)**
 - ▶ This enzyme falls by two-thirds in copper-deficient rat brain.

Owen CA Jr (1981) Copper Deficiency and Toxicity, 1st ed.

Down's Syndrome

- ▶ Superoxide dismutase (SOD1) depends on copper for activity; its gene is on chromosome 21.
- ▶ This enzyme is elevated in Down's syndrome (trisomy 21) and is decreased in people with monosomy.
- ▶ Individuals with Down's syndrome have a higher-than-average requirement for dietary copper because copper is incorporated into superoxide dismutase and is unavailable for other uses.

Copper and Neuropathy

- ▶ A new and severe neuropathy is being found increasingly in the last decade.
- ▶ It resembles that of pernicious anaemia, but it responds to copper rather than vitamin B₁₂.
- ▶ Poor balance is the most common presenting complaint and probably is from cerebellar injury.
- ▶ The neuropathy seems rare enough to be published, but common enough that 10–15 cases can be reported from single clinics.

J Clin Neuromuscul Dis 10, 1–3.

J Clin Neuromuscul Dis 12, 122–128.

- ▶ It may be as common as the neuropathy from vitamin B₁₂ deficiency and may be the most important alternative in differential diagnosis of the latter.

Ropper AH & Samuels MA (2009) Adams and Victor's Principles of Neurology, 9th ed.

Nutritional Optic Neuropathy

- ▶ These deficiencies predominantly present with deficits in central and color vision, as the papillo-macular bundle is particularly vulnerable to metabolic insults.

Prog Retin Eye Res. 2004;23(1):53–89.

- ▶ Among these micronutrients essential to visual function is copper, a trace element primarily absorbed in the proximal small bowel.
- ▶ Copper deficiency due to insufficient intake is remarkably rare and is most commonly due to malabsorption.
- ▶ Among those most at risk are gastric bypass (Roux-en-Y) surgery patients.
 - ▶ Studies show 10–20 % of patients are deficient in copper post-surgery. **Int J Obes. 2012;36(3):328–335.**
- ▶ It is essential to consider nutritional deficiencies when evaluating the visual complaints of patients with a history of gastric surgery, especially those with vision loss affecting both eyes.

Ischaemic Heart Disease

- ▶ The discovery that copper deficiency can increase plasma cholesterol in rats substantially was unprecedented. **Am J Clin Nutr 26, 1060–1068.**
- ▶ This observation has been confirmed in more than thirty independent laboratories, worldwide. **Klevay LM (2010) Copper. In Encyclopedia of Dietary Supplements, 2nd ed., pp. 175–184**
- ▶ The copper deficiency theory may be the simplest and most general explanation of the etiology and pathophysiology of ischaemic heart disease.
- ▶ A considerable number of adults consume less copper than recommended amounts, probably because copper in the Western diet has decreased since the 1930s.

Copper and Aneurysms

- ▶ The pathogenesis of thoracic aortic aneurysms (TAAs) is multifactorial, with genetic and environmental factors implicated in causing the microstructural changes in content or architecture of the connective fibers elastin and collagen, which are responsible for the integrity of the aorta. **Circ Res. 2016;118:535–46.**
- ▶ It is thought that deficiency in trace minerals may play a role, and copper (Cu) is of particular interest.
- ▶ Cu deficiency in animals is associated with an increased risk of aneurysm, and experimental models in animals have established a cause-and-effect relationship between Cu deficiency and aneurysm and dissections in pigs, mice and turkeys.
Cell. 2022;185:1630–45.
- ▶ Some data indicate that Cu is significantly reduced (**~25% less**) in aorta tissue from aneurysmal versus non-aneurysmal patients.

Related Pathologies and TAA's

- ▶ Marfan syndrome, which can arise from different mutations of the fibrillin gene, is a well-known cause of TAA and dissection.
- ▶ Marfan patients comprise 5–10% of TAAA cases and, without surgical intervention, have a 50% lifetime chance of developing aortic dissection. **Signal Transduct Target Ther. 2022;7:378.**
- ▶ Turner's syndrome and Ehlers–Danlos syndrome are also associated with an increased incidence of the aortic aneurysm.
- ▶ Genetic causes for non-syndromic familial TAA have also been identified.
- ▶ Relevant mutations have been reported in the genes: TAA and Dissection (thought to be responsible for 20–30% of TAA), Familial Aortic Aneurysm, Transforming Growth Factor Beta Receptor, Myosin Heavy Chain, and Smooth Muscle Alpha-Actin.
Cell Death Dis. 2023;14:105.
- ▶ The association of the bicuspid aortic valve with TAAA has also been noted, with the aortic valve sharing the exact embryological origin as the ascending aorta.
Mol Asp Med. 2005;26:268–98.

Lysyl Oxidase and Copper

- ▶ In humans, the Cu-dependent enzyme lysyl oxidase (LOX) functions in cross-linking elastin and collagen fibers, which are key contributors to aortic stretch and strength. *Am J Physiol Cell Physiol.* 2018;315:C186–c201.
- ▶ Cu deficiency can thus result in a disruption in aortic wall architecture and therefore cause aortic disease.
- ▶ Inactivation of the LOX gene using gene engineering has resulted in large ruptured aortic aneurysms in the perinatal period in mice.

Cell Res. 2022;32:417–8.

Science. 2022;375:1254–61.

Ceruloplasmin and Copper

- ▶ Ceruloplasmin carries copper in the plasma, and low plasma or serum levels **do not** correlate with tissue levels.
- ▶ Cu is assimilated into the ceruloplasmin composition by metallothionein during synthesis in the liver.
- ▶ The absence of metallothionein (Wilson's disease) can result in the decrease of serum ceruloplasmin levels, leading to the accumulation of Cu in the liver, kidneys, skin, brain (with associated neurological symptoms). **Int J Biochem Cell Biol. 2010;42:206–9.**
- ▶ Ceruloplasmin level may be high due to infection, inflammation or oestrogen influence, and diabetes is also associated with raised plasma Cu concentration.
- ▶ Several factors not directly related to the Cu status, but often related to changes in ceruloplasmin levels, make plasma Cu an unreliable marker of Cu status, except in more severe deficiency states.

Copper and Cuproptosis

- ▶ Copper is an essential trace element involved in mitochondrial respiration, antioxidant defense, and neurotransmitter synthesis.

Curr Biol. 2011;21:R877–83.

Nat Chem Biol. 2008;4:176–85.

- ▶ Copper homeostasis is tightly regulated.
- ▶ Copper excess or deficiency can lead to pathological alterations, and thus negatively affect human health. **Signal Transduct Target Ther. 2022;7:378.**

Potential Mechanisms of Atherosclerosis Development due to Copper Dyshomeostasis

- ▶ Oxidative stress
- ▶ Inflammation
- ▶ Endothelial dysfunction
- ▶ Lipid metabolism
- ▶ Cuproptosis

Evidence Linking Copper Excess and Atherosclerosis

- ▶ Extensive research has revealed a correlation between elevated copper levels and cardiovascular disease.
- ▶ Several prospective cohort studies have shown a significant correlation between elevated serum copper levels and higher mortality rates related to cardiovascular diseases, particularly coronary heart disease.
Eur J Clin Nutr. 1996;50:431–7.
- ▶ Elevated copper levels have also been shown to be an independent risk factor for ischemic heart disease.
Am J Epidemiol. 1991;134:268–76.
- ▶ Stadler et al. directly detected and quantified transition metal ions in human atherosclerotic plaques and found increased copper levels in the diseased intima. **Arterioscler Thromb Vasc Biol. 2004;24:949–54.**
- ▶ Studies on populations with acute myocardial infarction (AMI) also support these findings, with patients with AMI exhibiting significantly higher serum copper levels than those without AMI.
Mymens Med J. 2023;32:39–43.

Evidence Linking Copper Deficiency and Atherosclerosis

- ▶ Copper deficiency is also recognized as a major contributing factor to the development of atherosclerosis.
- ▶ This is evidenced by the benefit of high dietary copper and copper supplementation.
- ▶ The Institute of Medicine recommends a daily dietary allowance of 900 ug of copper for adults, with a tolerable upper limit of 10,000 µg/day (10mg) to prevent liver damage. **J Am Diet Assoc. 2001;101:294–301.**
- ▶ Recommendations vary between national authorities; most recommend an intake of 800 to 2400 ug/day. **J Trace Elem Med Biol. 2016;35:107–15.**
- ▶ Substantial research suggests that adequate copper intake reduces the risk of atherosclerosis.

Copper Supplementation and Atherosclerosis

- ▶ Rock et al. found that copper supplementation in middle-aged individuals enhanced the antioxidative capacity of cells, which may help prevent vascular damage and thus reduce the risk of atherosclerosis.
Free Radic Biol Med. 2000;28:324–9.
- ▶ Another cohort study showed an association between adequate dietary intake of copper (equal to or above the estimated average requirement) and a reduced risk of all-cause- and cardiovascular disease-related mortality.
 - ▶ This association was limited to copper intake from food sources. **Ann Intern Med. 2019;170:604–13.**
- ▶ Studies on animal models corroborate these findings with Lamb et al., showing that dietary copper deficiency or excess increases susceptibility to atherosclerosis of the aorta in cholesterol-fed rabbits.
Int J Exp Pathol. 2001;82:287–94.

Copper Excess and Oxidative Stress

- ▶ Elevated levels of free copper ions tend to interact more with hydrogen peroxide through Fenton reactions, leading to the production of highly-reactive hydroxyl radicals. **Curr Med Chem. 2005;12:1161–208.**
- ▶ Free radicals cause lipid peroxidation, protein oxidation, and DNA damage, ultimately contributing to the initiation and progression of atherosclerosis.
J Hypertens. 2000;18:655–73.
- ▶ Increased copper levels have been shown to reduce the activity of antioxidant enzymes, such as Cu/Zn-SOD, catalase, and glutathione peroxidase, in the red blood cells, whole blood, live tissue, and brain tissue of rats.
- ▶ Copper is also capable of causing DNA strand breaks and the oxidation of bases via oxygen-derived free radicals. **Mol Biotechnol. 2007;37:48–51.**

Copper Deficiency and Oxidative Stress

- ▶ Copper deficiency has also been suggested to contribute to the development and progression of atherosclerosis via oxidative stress.
- ▶ Copper is an essential cofactor of various antioxidant enzymes, including Cu/Zn-SOD, ceruloplasmin, and lysyl oxidase. **N. Am J Med Sci. 2015;7:41–6.**
- ▶ Copper deficiency may thus impair the function of these enzymes, leading to an impaired antioxidant defense system and increased susceptibility to oxidative stress. **Am J Clin Nutr. 1996;63:797s–811s.**

SOD1

- ▶ Decreased activity of *SOD1*, which encodes Cu/Zn SOD, has also been observed in the liver and red blood cells of copper-deficient rats. *J Nutr.* 2003;133:28–31.
- ▶ The decrease in *SOD1* caused by copper deficiency leads to a reduction in NO levels;
 - ▶ May promote endothelial dysfunction
 - ▶ Reduce vascular relaxation
 - ▶ Increase oxidative stress
 - ▶ Contributing to atherosclerosis development.

Copper Excess and Inflammation

- ▶ Excess copper has been implicated in atherosclerosis pathogenesis due to its ability to induce inflammation.
- ▶ High copper levels were previously reported to stimulate pro-inflammatory cytokine production and thereby promote inflammation within arterial walls.

Mini Rev Med Chem. 2020;20:2067–78.

- ▶ In primary cardiac cells, Cu^{2+} increases the release of interleukin-6 (IL-6) and activates MAP kinases, which are linked to cardiac inflammation and hypertrophy.

Cardiovasc Toxicol. 2009;9:86–94.

- ▶ Copper-induced oxidative stress also contributes to inflammation because excessive copper generates ROS, which causes oxidative damage to lipids, proteins, and DNA and promotes inflammation.

Copper Deficiency and Inflammation

- ▶ Copper deficiency has also been linked to atherosclerosis development through its impact on inflammation.
- ▶ Copper deficiency may result in decreased expression of adhesion molecules, such as ICAM-1 and VCAM-1, which facilitate leukocyte adhesion onto activated endothelial cells. *Immunol Lett.* 2001;76:139–44.
- ▶ Copper deficiency impairs the activity of Cu/Zn-SOD as previously mentioned, leading to an increased accumulation of ROS and exacerbation of oxidative stress, which can further promote inflammation and atherosclerosis development. *J Nutr.* 1979;109:1570–6.

Copper Excess and Endothelial Dysfunction

- ▶ Excessive copper can disrupt the balance between the production and degradation of nitric oxide (NO), a key regulator of vascular tone and endothelial function. **Circulation. 2006;113:1708–14.**
- ▶ Increased copper levels can upregulate inducible NO synthase (iNOS) expression, resulting in excessive NO production and peroxynitrite, a potent oxidant that causes further oxidative damage. **Physiol Rev. 2007;87:315–424.**
- ▶ Copper also interacts with atherosclerosis risk factors such as homocysteine and thereby causes increased hydrogen peroxidation and oxidative stress.
 - ▶ A study revealed that incubation with homocysteine and copper for 4 hours can cause significant damage to endothelial cells. **J Clin Invest. 1986;77:1370–6.**

Copper Deficiency and Endothelial Dysfunction

- ▶ Endothelial dysfunction can result in decreased production of NO, a vasodilator and inhibitor of platelet aggregation, and thereby promote a proatherogenic environment. **Diabetes Care. 2009;32:S314–21.**
- ▶ Copper deficiency can also lead to decreased NO levels by reducing the levels of SOD1.
- ▶ Reduced NO levels can then inhibit endothelial function and vasodilation, increase oxidative stress, and thereby promote atherosclerosis.

N. Am J Med Sci. 2015;7:41–6.

Copper Excess and Lipid Metabolism

- ▶ Excess copper strongly contributes to atherosclerosis development via its effects on the ox-LDL, which plays a central role in atherosclerosis [89].
- ▶ Copper participates in the oxidation of LDL particles, and alterations in copper levels may affect the susceptibility of LDL particles to oxidation.
- ▶ Excess copper levels can increase the oxidation of LDL particles and trigger the production of ox-LDL, which then contributes to atherosclerosis development. **Free Radic Biol Med. 1992;13:341–90.**

Copper Deficiency and Lipid Metabolism

- ▶ Copper is involved in the synthesis of fatty acids and cholesterol, insufficient copper levels may lead to impaired lipid metabolism and, thus, the development of fatty liver disease.
- ▶ Copper deficiency has shown to increase total cholesterol levels.
- ▶ Insufficient copper levels can affect the activity of sterol regulatory element-binding proteins 1 and 2 (SREBP-1 and SREBP-2), which are transcription factors involved in fatty acid and cholesterol metabolism.

IUBMB Life. 2017;69:263–70.

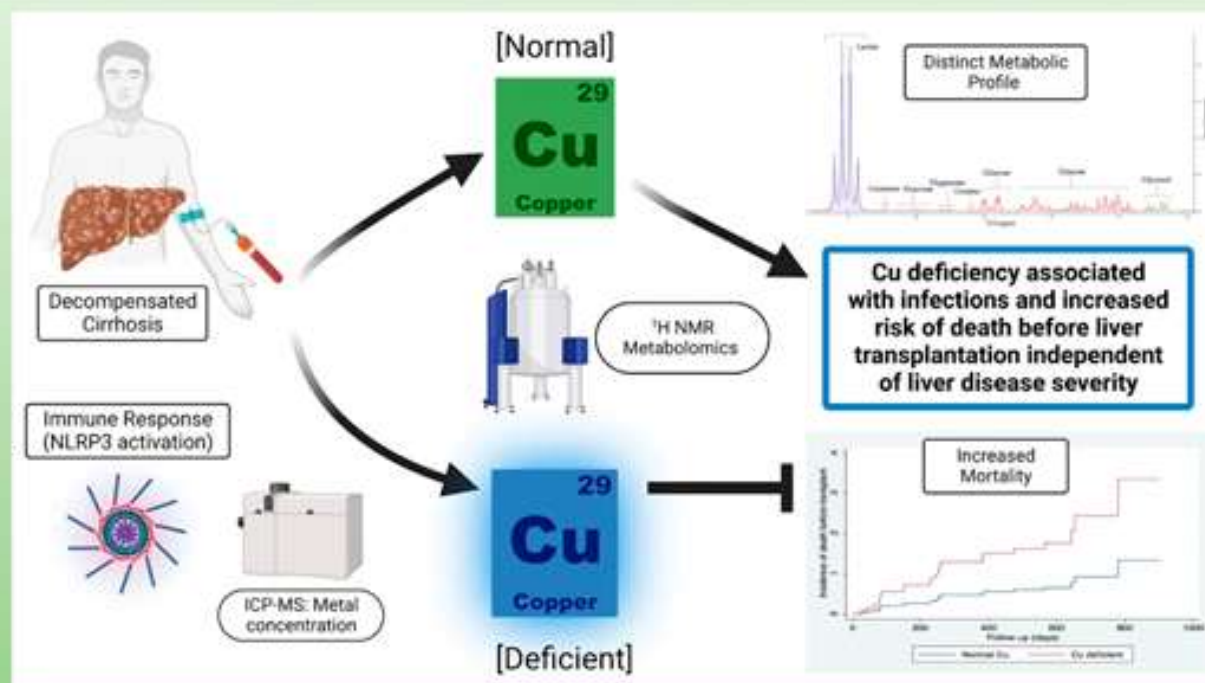
Copper Deficiency and Hypertension

- ▶ Copper inhibits the activity of angiotensin-converting enzymes, such that copper deficiency leads to increasing angiotensin levels.
 - ▶ Water and sodium retention and hypertension.

Biol Trace Elem Res. 1991;29:45–9.

- ▶ Copper is a cofactor of SOD, which is a major player in the antioxidant defense system.
- ▶ Copper deficiency may increase the levels of superoxide free radicals, leading to elevated angiotensin levels and consequent hypertension. **Hypertension. 2012;60:476–86.**

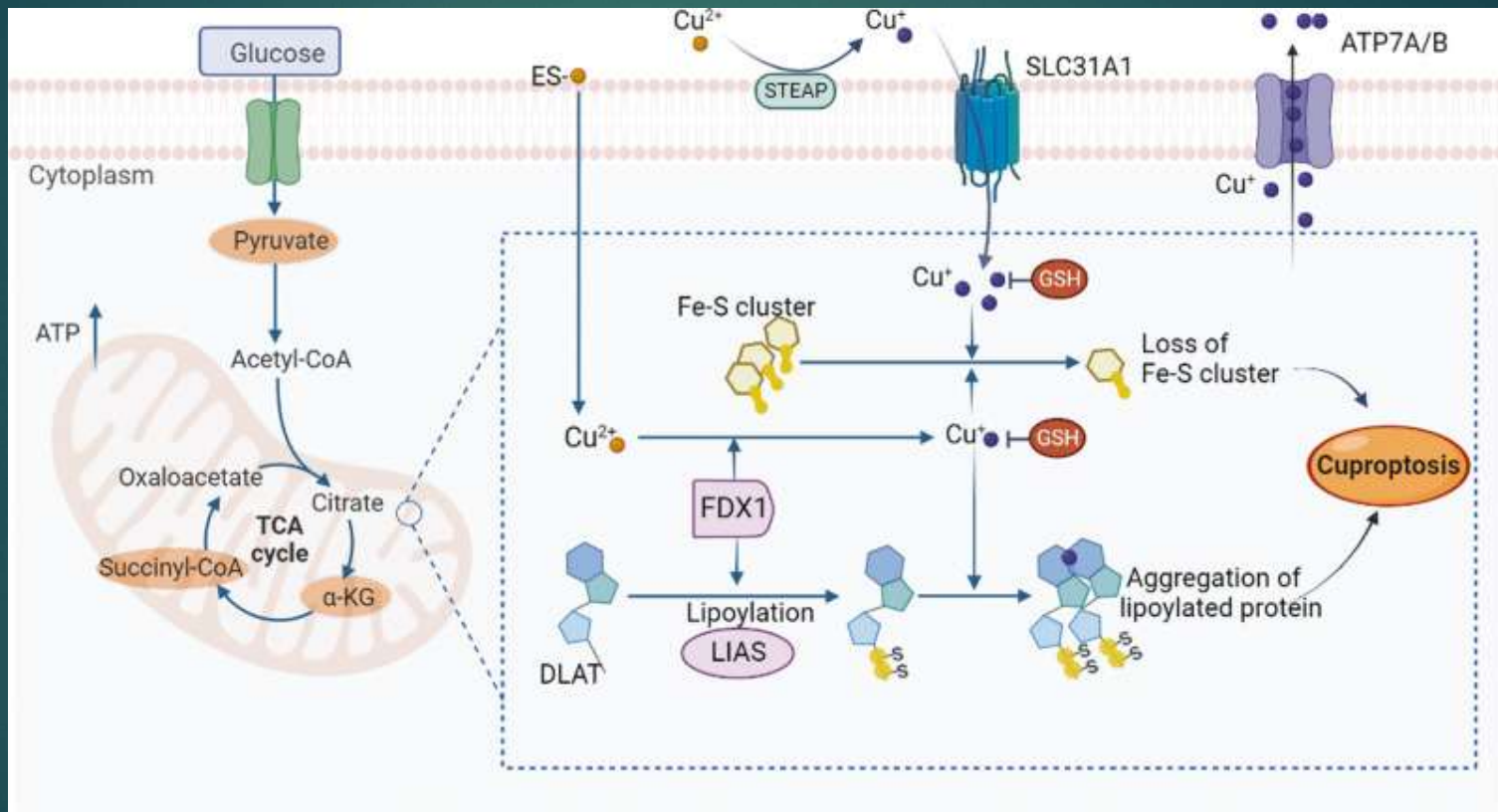
Copper Deficiency is an Independent Risk Factor for Mortality in Patients with Advanced Liver Disease



Copper-induced Cell Death to Cuproptosis

- ▶ The discovery of copper-induced cell death dates to the early 1980s.
Biochem J. 1984;219:1–14.
- ▶ Increased copper levels were found to promote ROS generation and thereby lead to oxidative stress, DNA damage, ultimately cell death.
Toxicology. 2003;189:147–63.
- ▶ **March 2022, Tsvetkov et al.** published a groundbreaking study unveiling the mechanism of copper-induced cell death, which was termed cuproptosis. **Science. 2022;375:1254–61.**
- ▶ Cuproptosis represents a unique form of cell death triggered by an excess of copper ions.

Cuproptosis



Cell Death Discov. 2024 Jan 13;10(1):25.

Copper Functions in Cancer

- ▶ Extensive research has revealed unique metabolic patterns of copper in different cancers.

*Biochim. Biophys. Acta Mol. Cell Res.*1868, 118893 (2021).

- ▶ Compared to normal tissues, tumor tissues exhibit a higher demand for copper.
- ▶ Elevated levels of copper in the tumor tissue and serum have been observed in patients with oral, thyroid, breast, lung, pancreatic, gallbladder, colorectal, prostate, and gynecological cancers, and are significantly associated with poor prognostic outcomes. *Redox Biol.*42, 101900 (2021).
- ▶ This increased copper demand is primarily because copper is required as a cofactor for multiple enzymes involved in cellular energy metabolism (such as CCO) and antioxidant defenses (such as SOD), thereby meeting the substantial energy needs of rapidly dividing tumor cells.
- ▶ Copper can also negatively affect tumors due to its redox activity and improper binding with functional macromolecules. *Cell Chem. Biol.*25, 585–594.e587 (2018).
- ▶ An **imbalance** in copper homeostasis could play a dual role, in promoting or suppressing tumors in various contexts.

Copper and Cuproplasia

- ▶ Researchers coined the term “cuproplasia” in 2022, which is described as copper-dependent cellular growth and proliferation and exemplifies “metalloplasias”.

*Nat. Rev. Cancer*22, 102–113 (2022).

- ▶ The process encompasses the interactions of copper with various cellular mechanisms, including kinase signaling pathways, autophagy, the ubiquitin-proteasome system (UPS), epigenetic regulation, and metabolic pathways.

Copper and Autophagy

- ▶ Copper stimulates autophagy to regulate cuproplasia in response to various stressors such as nutritional starvation, metabolic imbalance, hypoxia, oxidative stress, and oncogene activation.
- ▶ Cancer cells generate nutrients and energy through a cellular process known as autophagy, supporting the survival and proliferation of the tumor cells.

*Mol. Cell*40, 280–293 (2010).

*iScience*8, 74–84 (2018).

- Copper inhibits pyruvate dehydrogenase, which in turn suppresses the conversion of pyruvate to acetyl-CoA, a metabolite required for histone acetylation by histone acetyltransferases (HATs) and global transcription. *Mol. Cell*23, 207–217 (2006).
- ▶ Decreased acetylation can lead to increased proliferation and differentiation of tumor cells.

Copper and Angiogenesis

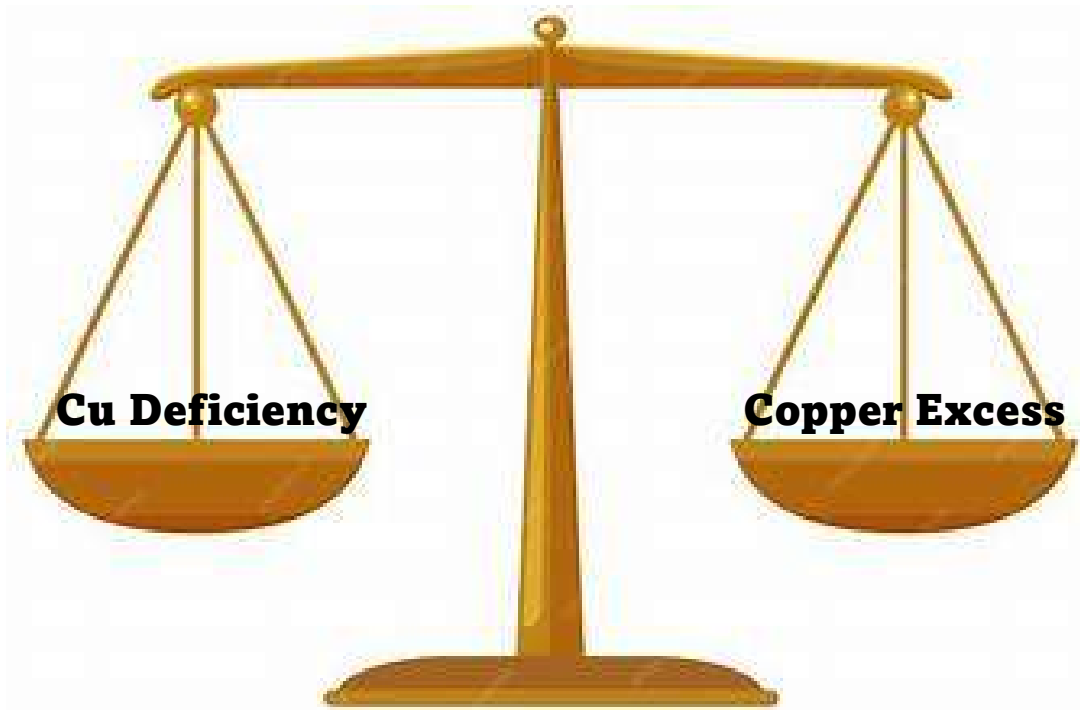
- ▶ Angiogenesis is a crucial process for the transport of oxygen and nutrients to tumors, facilitating tumor progression. *Signal Transduct. Target Ther.*8, 198 (2023).
- ▶ Copper acts as a pivotal “switch” in angiogenic signaling by activating a multitude of pro-angiogenic and inflammatory factors.

*J. Exp. Clin. Cancer Res.*39, 204 (2020).

- ▶ Copper binds directly to angiogenin (ANG), modulating its affinity towards endothelial cells and vascular smooth muscle cells, thereby promoting angiogenesis.

*Biochem. Biophys. Res. Commun.*236, 604–610 (1997).

*Int. J. Biochem. Cell Biol.*60, 185–196 (2015).



Copper Status



**Thank
you**

Practitioner Support

- To open a CSS/Genova Diagnostics account:

<https://www.gdx.net/>

- CSS customer service: csscustomerservice@gdx.net

- To schedule a complimentary 30-minute educational session:
www.cellsciencesystems.com/resultsreview

Patient Information: PATIENT II, PRETEND

DOB: 11/04/1977 Gender: F Lab ID: 68220
Received: 07/02/2022 Collected: 07/01/2022 Reported: 07/12/2022
Clinic ID: 10804 HCP: Sample Physician

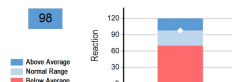


CLIA#1000283906
Lab Director
Harold Alvarez, M.D.

REDOX SCORE

98

The Redox Score is an indication of your resistance to oxidative stress, relative to the general population. An average or below average response can be improved by appropriate use of nutrients and antioxidants as determined by the Antioxidant Protection Assay and guidance from your practitioner.



ANTIOXIDANT PROTECTION ASSAY (APA)

Antioxidants / Anti-inflammatories

Acai Berry	124% Highly Protective	Lycopene	114% Protective
Andrographis	117% Protective	Maitake	123% Highly Protective
Astaxanthin	118% Protective	Mangosteen	110% Protective
Astragalus	120% Highly Protective	Melatonin	123% Highly Protective
Beta-Carotene	120% Highly Protective	Milk Thistle	119% Protective
Bilberry	>140% Highly Protective	Moringa	119% Protective
Boswellia	122% Highly Protective	NADH	
Camu Camu		Noni Berry	
Catalase		Piperine	
Chlorophyll		Pomegranate	
Cinnamon		Pycnogenol	>140% Highly Protective
Coenzyme Q10		Pyroloquinoline	
Delta tocotrienol		Quercetin	
Echinacea		Resveratrol	
Elderberry	120% Highly Protective	Rhodiola	
Garlic	112% Protective	Selenium	
Ginger	111% Protective	Shiitake	
Ginkgo Biloba	120% Highly Protective	SOD	
Glutathione	>140% Highly Protective	Sulforaphane	
Goji Berry	116% Protective	Turmeric	
Grape Seed		Vitamin C	
Green Tea		Wild Cherry Bark	
Lavender	124% Highly Protective	Zeaxanthin	
Lipoic Acid	119% Protective	Zinc	
Lutein			

≥ 120%	provides high protection against oxidative stress
110% - 119%	some protective effect against oxidative stress
100% - 109%	no significant protective effect

*The term **protective** describes the cell protection effect, i.e. the individual benefit of a specific nutrient to increase the antioxidative capacity

These laboratory results are not intended to diagnose a disease state. The performance characteristics of all assays have been verified by Cell Science Systems, Corp. All information provided is only a suggested guideline and should not be substituted for professional medical advice, diagnosis, or treatment.

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Redox Assay & Antioxidant Protection Assay