Astaxanthin

- Astaxanthin is an orange-red pigment xanthophyll carotenoid found in green algae, which is then eaten by shrimp, lobster, crab and salmon, accounting for their pink colour. The algae make high amounts of astaxanthin as an antioxidant to protect from unfavourable conditions such as high ultra violet exposure to reduce the free radical damage.
- In skeletal muscle, astaxanthin stimulated mitochondrial biogenesis through activation of the AMPK pathway. In heat-induced oxidative injury it inhibited ROS production and increased protein expression of PGC-1α and TFAM, preventing mitochondrial fragmentation, depolarisation and apoptosis.
- In rat hearts it could inhibit the opening of the mtPTP and reduce mitochondrial swelling.
- In neurons, astaxanthin inhibited mitochondria-induced apoptosis, preventing the opening of the mtPTP, increased membrane potential and reduced oxidative damage.
- After exposure to mitochondrial toxins, astaxanthin lowered oxidative stress and caspase expression and inhibited apoptosis. It also enhanced mitochondrial function and copy number and increased ETC Complex activity.
- Astaxanthin is a highly fat-soluble substance, which means that it is better absorbed when consumed with fat. Beneficial results have been observed at 2 mg/day with greater results at 8 mg/day.

(Sarada R, Proc Biochem, 2002; Nishida Y, J Cachexia Sarcopenia Muscle, 2020; Baburina Y, Antioxidants, 2019; Jiang W, Biomed Pharmacother, 2020; Yu T, J Cell Physiol, 2019; Wang Y, Acta Histochem, 2019; Wang XJ, Cell Death Discov, 2018; Kim SH, Nutrients, 2018; Wolf AM, J Nutr Biochem, 2010)

B vitamins

- Of all the true vitamins, B vitamins have the greatest impact on cellular metabolism and energy production.
- Vitamin B1 (thiamine) functions in carbohydrate metabolism to convert pyruvate to acetyl-CoA for entry into the TCA cycle; it also facilitates some steps in the ETC. Deficiency disrupts mitochondrial membrane potential.
- Vitamin B2 (riboflavin) plays an important role in fatty acid metabolism and is a major component of Complex I and Complex II of the ETC, is also required for many other metabolic enzymes and is the basis of the electron carrier FAD.
- Vitamin B3 (niacin) is the precursor of NADH and NAD^+ and therefore possibly the most important micronutrient for NAD metabolism. It is the rate-limiting substrate for the sirtuins and can also reduce mitochondrial oxidative stress.
- Vitamin B5 (pantothenic acid) is a precursor of Coenzyme A, essential for the metabolism of carbohydrates and fats and the transport of pyruvate into the TCA cycle. B5 also protects against mitochondrial oxidative stress and increases glutathione content.
- Vitamin B6 (active form: pyridoxal-5-phosphate) is required for functioning of >70 enzymes that participate in energy metabolism and is critical for the delivery of oxygen to the ETC.
- Vitamin B12 (active form methylcobalamin) is involved in several mitochondrial processes including fatty acid metabolism, the formation of creatine and components of protein subunits in the ETC complexes. It also protects against oxidative damage, apoptosis and excess intracellular calcium.
- Folate (active form methyltetrahydrofolate) is a methyl donor, essential for mitochondrial protein and nucleic acid synthesis. It is also needed for de novo purine synthesis.

(Jhala SS, Biochem Biophys Res Commun, 2014; Henriques BJ, Curr Drug Targets, 2016; Henriques BJ, Curr Med Chem, 2010; Pereira LC, Drug Chem Toxicol, 2020; Slyshenkov VS, Free Radic Biol Med, 1996; Wang M, J Cell Biochem, 2019; Froese DS, J Inherit Metab Dis, 2019; Depeint F, Chem Biol Interact, 2006)

β-lapachone

- Derived from the lining of the bark of the South American Pau d'arco, or lapacho, tree, which contains lapachol and β-lapachone, a quinone.
- In obese mice, β-lapachone stimulated the browning of WAT through increased expression of BAT genes for UCP1 and increased energy expenditure relative to controls.
- In mice, β-lapachone increased the ratio of NAD+ to NADH, which resulted in a higher number of intact mitochondria with normal structure, less damage to mitochondrial proteins, increased energy expenditure as measured by oxygen consumption and heat generation. It also improved fatty acid oxidation through upregulation of AMPK and the carnitine shuttle and increased gene expression of PGC-1α, Nrf1 and SIRT1.
- Other studies have confirmed the increase in NAD+ levels, upregulation of UCP1 and increase in mitochondrial number.
- β-lapachone can also stimulate fatty acid oxidation in mouse muscle by upregulation of AMPK and induce mitochondrial biogenesis through activation of SIRT1. In vitro, it can restore mitochondrial membrane potential and normalise elevated ROS levels to a greater extent than CoQ10.

(Choi WH, Diabetes, 2016; Lee JS, PLoS One, 2012; Oh GS, Kidney Int, 2014; Shin S, Cell Signal, 2014; Jeong MH, PLoS One, 2014; Kwak HJ, Am J Chin Med, 2019; Jeong MH, Biochem Biophys Res Commun, 2014; Hwang JH, Diabetes, 2009)

Berberine

- Berberine is a natural isoquinoline alkaloid found in several herbs, including berberis, goldenseal, Orgeon grape and tree turmeric.
- Berberine promotes β-oxidation, upregulates AMPK and SIRT1 and it normalises lipid, glucose and energy imbalances. Specifically, it reduces acetyl CoA accumulation and limited mitochondrial pyruvate supply for gluconeogenesis.
- It protects against the loss of mitochondrial membrane potential and excess mitochondrial fission.
- Berberine can also boost mitochondrial biogenesis by upregulating PGC-1α.
- It also acts as a fasting mimetic to promote autophagy.
- Berberine has shown many of the same effects as metformin.
- Berberine has a short half-life in the body, so to keep blood levels stable it should be taken 3 times per day, dosage totalling up to 1500mg/day before meals.

(Zhu N, Cell Stress Chaperones, 2020; Qin X, Br J Pharmacol, 2019; Qin X, Theranostics, 2019; Li A, EBioMedicine, 2018; Schor J, Nat Med J, 2012)

Butyrate (as sodium butyrate)

- Butyrate is a short chain fatty acid which is a product of microbial fermentation of dietary fibre in the gastrointestinal tract but can also be supplemented. It is the preferred energy source for colonocytes. It functions by inhibiting histone deacetylase (HDAC), the enzyme that facilitates the protection of nuclear DNA by histones, thereby increasing nuclear gene expression.
- In pancreatic β-cells, butyrate prevented toxin-induced apoptosis, mitochondrial dysfunction, over-production of ROS and normalising the activity of mitochondrial fission and fusion genes.
- In skeletal muscle, butyrate increased AMP and ADP content, mtDNA copy number, OXPHOS, β-oxidation, AMPK, UCP3 and PGC-1α, both directly and by feeding butyrate to pregnant rats, when offspring also showed higher TFAM, ATP content and cytochrome c oxidase.
- In damaged hepatocytes, butyrate increased mitochondrial antioxidant activity by upregulating Nrf2, increased expression of AMPK, PGC-1α and mtDNA copy number and reduced apoptosis. It also decreased glycolysis, increased β-oxidation and enhanced activity of the TCA cycle and OXPHOS.
- In adipocytes, butyrate increased the expression of several mitochondrial genes and upregulated PGC-1α and cytochrome c oxidase.
- However, one study found that a combination of butyrate and DHA induced increased mitochondrial-mediated apoptosis through intracellular calcium overload in colonocytes.
- Butyrate may also be attached to calcium and magnesium, but almost no studies have been carried out on this combination.

(Hu S, Int J Mol Sci, 2020; Zhang Y, J Anim Sci, 2019; Xing X, J Physiol Biochem, 2016; Mollica MP, Diabetes, 2017; Huang Y, Br J Nutr, 2017; Jia Y, Exp Physiol, 2017; Hong J, Oncotarget, 2016; Kolar S, Cancer, 2011)

Cannabinoids

- The endocannabinoid system is considered the master regulator of homeostasis in the mammalian body. We all produce our own endocannabinoids, which are similar to phytocannabinoids.
- Cannabinoid receptors are found on the mitochondrial membranes. In neuronal mitochondria, activation of cannabinoid receptors can directly alter mitochondrial energetic activity. An *in vitro* study showed that different cannabinoids can act as either receptor agonists or antagonists, although all inhibited the activity of ETC Complexes II/III and IV through a non-receptor-mediated mechanism. Cannabinoid receptor agonists could also increase mitochondrial biogenesis.
- In cardiac and skeletal muscle mitochondria, cannabinoid receptors are commonly found and can regulate mitochondrial respiration; in some cases, activation was found to decrease coupled respiration or increase pyruvate metabolism. In cardiac myocytes, a cannabinoid receptor agonist reversed mitochondrial membrane depolarisation and restored mitochondrial bioenergetics and expression of genes related to fatty acid oxidation and mitochondrial biogenesis, probably through AMPK upregulation.
- However, in some cells, direct stimulation of the cannabinoid receptor resulted in increased mitochondrial fission and fragmentation, which led to reduced ATP production and increased ROS.
- Cannabinoids can also regulate fluctuations in intracellular calcium, suggesting a role in reducing ischaemic damage. A 2017 study found that imbalances in calcium ions in the mitochondria could drive AD.

(Hebert-Chatelain E, Nature, 2016; Singh N, J Mol Neurosci, 2015; Ma L, Cell Mol Neurobiol, 2018; Mendizabal-Zubiaga J, Front Physiol, 2016; Lu Y, J Cardiovasc Pharmacol, 2020; Drori A, Diabetes Obes Metab, 2019)

Capsaicin

- Capsaicin is a capsaicinoid, an active component of chili peppers.
- It is an agonist of transient receptor potential vanilloid receptor 1 (TRPVR1), induces axonal degeneration of peripheral sensory nerves and is commonly used to treat painful sensory neuropathies.
- In rat neonatal cardiomyocytes capsaicin protected against the anoxia/reoxygenation injury by restoring the NAD+/NADH ratio, mitochondrial Complex I and III activities and cellular energy metabolism.
- Rat hearts undergoing ischaemia/reperfusion injury, capsaicin increased mtSOD activity and reduced ROS production, upregulated SIRT1, downregulated cytochrome c and caspase3, inhibited mtPTP opening and hence reduced apoptosis.
- In hepatocytes from obese mice, capsaicin improved mitochondrial oxidative stress and upregulated TCA cycle and OXPHOS enzymes, improving ATP production.

(Qiao Y, Oxid Med Cell Longev, 2020; Şekeroğlu V, Biomed Pharmacother, 2018; Dedov VN, Neuroscience, 2001; Zhu JX, Sichuan Da Xue Xue Bao Yi Xue Ban, 2017; Huang J, Eur J Pharmacol, 2018; He H, Oxid Med Cell Longev, 2017)

L-carnitine

- L-carnitine is a naturally occurring compound found in all mammals and is derived from the amino acids lysine and methionine; biosynthesis involves these amino acids, plus niacin, vitamin B6, vitamin C and iron. Its most important biological function is the transport of long chain fatty acids, the mitochondria's preferred source of fuel, across the inner mitochondrial membrane to initiate β-oxidation (the carnitine shuttle). To do this, L-carnitine attaches to the long chain fats to form acylcarnitine molecules, which can cross the inner mitochondrial membrane. A cellular carnitine deficiency affects its ability to burn fats since none would be transported into the mitochondria. The clinical manifestation of this is elevated triglycerides; therapeutic doses of L-carnitine can significantly lower triglycerides.
- L-carnitine can reduce lactic acid build-up and speed recovery after exercise by restoring the ratio of lactate to pyruvate. It also acts as an antioxidant, protecting from apoptosis and can trigger removal of dysfunctional mitochondria by induction of autophagy. In mitochondrial deficiency it stimulates biogenesis and fusion proteins, enhances mtDNA and upregulated mtSOD and enzymes in the TCA cycle.
- There are various disorders of carnitine insufficiency and mitochondrial fatty acid oxidation, which result in impaired entry of fatty acids into the mitochondria and hence increased lipid and DNA oxidation; patients on valproic acid are also likely to have a carnitine deficiency. L-carnitine aided fatty acid entry into the mitochondria and decreased the DNA damage.
- L-carnitine is found in animal products, particularly meat and dairy produce; there are negligible quantities in plant foods. Our bodies produce some L-carnitine but production declines with age, so that it also becomes more vitamin-like. L-carnitine is synthesised from the precursors lysine and methionine, with the cofactors ion, vitamin C, oxygen, pyridoxal-5-phosphate and vitamin B3 (as NAD^+). Acetyl L-carnitine is better absorbed and crosses the blood-brain barrier but patients may be sensitive to it.
- L-carnitine recommended dose is 2,000mg; do not take more than 4,000mg. L-carnitine should be used with caution with people who have an underactive thyroid a history of seizures.

(De Moraes MS, Arch Biochem Biophys, 2020; Modanloo M, Iran J Kidney Dis, 2019; Choi JW, Metabolism, 2018; Nicassio L, Exp Gerontol, 2017; Liu J, Proc Natl Acad Sci USA, 2002; Hagen TM, Proc Natl Acad Sci USA, 2002; Pekala J, Curr Drug Metab, 2011)

Carnosine

- Carnosine is an endogenous dipeptide consisting of β-alanine and l-histidine. It is abundantly found in the human brain, kidney and skeletal muscle. Sources are exclusively animal.
- In aged or damaged neurons, decreased mitochondrial swelling, membrane permeabilization, ROS production and pro-apoptotic proteins, restored mitochondrial membrane potential and increased mtSOD, mitochondrial fusion proteins and ATP production. In neurons with ischaemic damage, carnosine improved mitochondrial function and mitophagy signalling. In astrocytes subjected to ischaemia-reperfusion injury, carnosine reversed the decline in ATP production.
- Carnosine (intranasal) increased expression of mitochondrial genes and increased mitochondrial function.
- In injured nephrons, carnosine reduced oxidative stress and increased the mitochondrial membrane potential and ATP production.
- In other cells, carnosine maintained the mitochondrial networks, improved mitochondrial function and lowered oxidative stress.

(Dai Z, Food Funct, 2020; Ommati MM, Drug Res, 2020; Bermúdez ML, Mol Genet Metab, 2018; Ouyang L, Brain Res Bull, 2016; Baek SH, Stroke, 2014; Corona C, PLoS One, 2011; Zakharchenko MV, Biochemistry, 2003; Ghanbarinejad V, Adv Pharm Bull, 2019; Ommati MM, Nutr Neurosci, 2019; Ommati MM, Biol Trace Elem Res, 2019)

Coenzyme Q10 (ubiqinone/ubiquinol)

- Coenzyme Q10 (CoQ10) is synthesised in the liver from tyrosine using vitamin B6 but production can be disrupted by ageing and statins. It is also found in some in organ meats, oily fish and whole grains.
- CoQ10 is a mitochondrial membrane antioxidant and stabiliser and can restore membrane potential. Its principal function is within the ETC, where it accepts an electron from Complex I or II, transforms into a reduced form and then carries the electron to Complex III. It also regulates redox, gene expression and apoptosis, aids fatty acid β-oxidation, is an essential cofactor of uncoupling proteins and the mtPTP and decreases mitochondrial fission.
- CoQ10 is produced in cells with the help of L-tyrosine. We produce less CoQ10 with age, with the body slowing production in our late-20s. As the body is less and less able to produce it, it becomes, in effect, a vitamin. Statins, beta-blockers, glucose lowering agents and tricyclic antidepressants lower CoQ10 production even further.
- The ideal dose should raise blood levels above 2.5 mcg/ml but ideally above 3.5 mcg/ml. Take 100mg/day as a maintenance dose, but between 600-3000mg/day in neurological conditions because blood levels need to be saturated with CoQ10 to force it through the blood brain barrier. CVD conditions typically need a dose between 200-600 mg/day, particularly if on statins. Don’t supplement if on chemotherapy as it will increase the tumour cell mitochondrial energy production and make it resistant to chemotherapy. Ubiquinol is the reduced version of CoQ10 and is much better absorbed than ubiquinone.

(Orsucci D, Curr Med Chem, 2011; Chokchaiwong S, Free Radic Res, 2018; Li HN, Neurochem Resm 2017; Duberley KE, Int J Biochem Cell Biol, 2014)

Copper

- Copper is required for normal functioning of cytochrome c oxidase, drawn from a copper pool within the mitochondrial matrix, and for the copper chaperone required for the maturation and retention of CuZnSOD in the intermembrane space.
- In neurons exposed to a mitochondrial toxin, copper reversed the impaired activity of mitochondrial Complexes I, II, IV and V, restored ATP production and reduced apoptosis.
- However, brain mitochondria are highly susceptible to high copper levels, manifesting as early membrane potential loss, profound structural changes and reduced ATP production. Low dose oral copper also decreased hippocampal mitochondrial copy number, mitochondrial biogenesis and cytochrome oxidase activity, disrupted mitochondrial dynamics and increased ROS production,
- Furthermore, in hepatocytes, Cu2+ reduced mitochondrial oxygen consumption and ATP production, inhibition of ETC Complexes I, II and IV, increased lipid peroxidation and mitochondrial ROS production, dissipation of the membrane potential, mitochondrial swelling and release of cytochrome c.
- In other cells, copper decreased mitochondrial membrane potential, ATP production and mitochondria fission and upregulated caspases and apoptosis. Excess copper can also inhibit the carnitine shuttle.

(Borchard S, Toxicol in Vitro, 2018; Saporito-Magriñá C, J Inorg Biochem, 2017; Hosseini MJ, Cell Biochem Biophys, 2014; Leary SC, Biochim Biophys Acta, 2009; Giangregorio N, Molecules, 2020; Kang Z, Toxicol In Vitro, 2019; Winge DR, J Biol Chem, 2018; Rubio-Osornio M, Chem Biol Interact, 2017; Kawamata H, Antioxid Redox Signal, 2010; Chen C, 2019)

Creatine

- The human body builds creatine, an organic acid, from methionine, glycine and arginine and it is stored in the form of creatine phosphate (aka phosphocreatine). A few foods (beef and fish) have a high creatine content. It plays an important role in maintaining mitochondrial production and regeneration of ATP, serving as a reservoir of phosphate bonds for ATP production, particularly in anaerobic respiration, while phosphocreatine is used to re-phosphorylate ADP into ATP.
- Creatine is stored primarily in muscle cells and its chronic depletion is seen principally in disorders involving the muscles, including heart disease, heart failure, muscular dystrophy and Parkinson's. Elevated plasma creatine has been suggested as a marker for mitochondrial diseases.
- It is a popular supplement among athletes (to aid endurance and strength) and body builders (to help with muscle recovery and growth) as it can aid ATP production. Creatine can also enhance mitochondrial biogenesis in skeletal muscle and can protect against mitochondrial depolarisation and oxidative stress, as well as cytosolic calcium dysregulation, enhancing cell survival after injury. Creatine supplementation can also normalise mutations of mitochondrial DNA.
- Over-supplementation may strain kidneys and liver, can cause arrhythmia and can cause the muscles to use extra water, so users should stay hydrated. Be particularly careful in patients with chronic kidney disease or kidney failure. Avoid creatine monohydrate.

(Schlattner U, Biochim Biophys Acta, 2006; Gowaved MA, Exp Ther Med, 2020; Fortalezas S, Neurotox Res, 2018; Chamberlain KA, J Neurosci, 2017; Rambo LM, Amino Acids, 2013)

Ginkgo biloba

- Ginkgo biloba leaf, from the maidenhair tree, contains a large number of beneficial flavonoid compounds, including quercetin.
- In hepatocytes exposed to a mitochondrial toxin, ginkgo upregulated mitochondrial antioxidant enzymes and biogenesis through PGC-1α, TFAM and Nrf2.
- Ginkgo reduced apoptosis by inhibiting export of cytochrome c, partially uncoupled OXPHOS and reduced H2O2 accumulation.
- In ageing, ginkgo extract protected against platelet and hippocampal mitochondrial dysfunction. It also restored ATP levels, particularly Complexes I, IV and V, and mitochondrial membrane potential protected against nitrosative stress.
- After exposure to a mitochondrial toxin, ginkgo restored the mitochondrial membrane potential and ATP production and protected against oxidative damage.
- A daily dose between 120-160 mg is often used effectively in healthy individuals but a dose of 240 mg/day might be necessary in those with chronic disease.

(Abd El-Maksoud EM, Environ Sci Pollut Res Int, 2019; Baliutyte G, J Bioenerg Biomembr, 2014; Bernatoniene J, Phytother Res, 2011; Shi C, Platelets, 2010; Abdel-Kader R, Pharmacol Res, 2007; Eckert A, Ann N Y Acad Sci, 2005)

Ginseng

- Ginseng is the root of plants of the Panax genus, the active ingredients of which are ginsenosides. There are many different types of ginseng: American, Korean red, Indian ginseng (Withania somnifera) and Siberian (Eleutherococcus senticosa). Most studies focus on Korean red.
- In skeletal muscle, Korean red ginseng enhanced ATP production, increased mitochondrial biogenesis through upregulation of Nrf1, TFAM and PGC-1$^{\alpha}$ and raised mtDNA levels.
- In the presence of a cardiac muscle toxin, Korean red ginseng increased oxygen consumption rate and improved tolerance to oxidative damage, with an alcohol solution proving more effective than water. In ischaemia/reperfusion injury, ginseng also restored cardiomyocyte mitochondrial function by maintaining mitochondrial membrane potential, blocking the release of cytochrome c and increasing ATP generation and oxygen consumption rate.
- In metabolic disease, ginseng increased mtDNA copy number and expression of carnitine palmitoyltransferase 1A (the carnitine shuttle), PGC-1α, Nrf1 and TFAM.
- After exposure to a mitochondrial toxin, ginseng inhibited mitochondrial injury and swelling, improved the decreased activity of ETC Complexes and TCA cycle enzymes, normalised the ATP:ADP:AMP ratios, reduced apoptosis and normalised membrane potential through upregulation of AMPK. Similarly, after radiation damage, ginseng decreased cytochrome c release and hence mitochondria-induced apoptosis.

(Shin EJ, Molecules, 2020; Huang Y, J Ginseng Res, 2019; Zuo YH, Front Physiol, 2018; Park JK, J Med Food, 2018; Jung DH, Complement Ther Med, 2016; Lee SB, J Pharm Pharmacol, 2016; Mahaboob Basha P, Cell Mol Neurobiol, 2013; Bing SJ, Acta Histochem, 2014; Dong GZ, BMC Complement Altern Med, 2013; Li XT, Am J Chin Med, 2009)

Molecular hydrogen (H_2)

- Molecular hydrogen (H_2) is a biologically active gas that is used medically to ameliorate various systemic pathological conditions. It is the smallest molecule in the universe, has no charge and can easily penetrate any membrane, including the blood brain barrier, without a protein channel or transporter protein.
- Molecular hydrogen is a selective antioxidant, meaning that it only neutralises excess ROS. It can suppress Complex I-generated superoxide and can scavenge the hydroxyl radical and peroxynitrite and suppress cellular fatty acid peroxidation. It also selectively (i.e. as needed) induces autophagy, mTOR and IgF1.
- H_2 can also increase ATP production and increase plasma levels of CoQ10. It can induce the mitochondrial unfolded protein response, which can be beneficial in metabolic disease. It can also reduce cell membrane permeability, reduce the decline in membrane potential and act as an anti-apoptotic molecule.
- H_2 can reduce the excessive effects of exercise-induced ROS and inflammation without abolishing the beneficial effects of exercise. This is because H_2 is a stable molecule which does not react with the free radical signalling induced by exercise, yet can scavenge the more cytotoxic hydroxyl radicals and peroxynitrite. H2 administration promotes mitochondrial biogenesis, ATP production, increased NAD+/NADH ratio, heat-shock proteins and sirtuins.
- H_2 can also act as a mitohormetic effector by upregulating Nrf2, which activated the antioxidant response element (ARE) and inducing other protective proteins.
- Hydrogen can be inhaled as a gas at low concentrations or infused into water (known as hydrogen water). Because it is a signal modulator, molecular hydrogen is best taken cyclically or pulsed, not continuously.

(Ishihara G, Biochem Biophys Res Commun, 2020; Gvozdjáková A, Can J Physiol Pharmacol, 2020; Iuchi K, Can J Physiol Pharmacol, 2019; Sobue S, Biochem Biophys Res Commun, 2017; Nogueira JE, Free Radic Biol Med, 2018; Ohta S, Curr Pharm Des, 2011; Murakami Y, PLoS One, 2017; Kura B, Can J Physiol Pharmacol, 2019; Le Baron TW, Can J Physiol Pharmacol, 2019; Ohsawa I, Nat Med, 2007)

Iron

- Iron homeostasis is essential for mitochondrial function, and particularly for the mitochondrial synthesis of haem and formation of iron-sulphur clusters, which are essential for the assembly, stability and function expression of Complexes I, II and III in the ETC. Iron deficiency is associated with loss of mitochondrial proteins and reduced activity of the iron-sulphur clusters, resulting in decreased ATP production and increased lactate production.
- However, cardiomyocytes exposed to increased iron concentration demonstrated a decreased expression of mitochondrial Complexes.
- Neurons with iron overload displayed decreased ATP production through decreased Complex I proteins, with mitochondrial fragmentation, elevated intra cellular calcium and the release of cytochrome c and caspase activation leading to apoptosis.
- In other cells, iron overload caused upregulated pro-apoptotic proteins, permeabilisation of the membrane, with release of cytochrome c and caspase activation leading to apoptosis, impaired OXPHOS, depolarisation of the mitochondrial membrane potential, increased ROS production and inhibition of mitochondrial fusion and fission proteins.

(Leermakers PA, FASEB J, 2020; Ward DM, Annu Rev Physiol, 2019; Dziegala M, Cells, 2018; Yao X, Front Pharmacol, 2019; Huang XT, J Neurochem, 2018; Hoes MF, Eur J Heart Fail, 2018; Volani C, Metallomics, 2017; Stiban J, Biochemistry, 2016; Tian Q, PeerJ, 2016; Lee DG, Toxicology, 2016)

Ketone supplements and medium chain triglycerides

- Ketones are a break-down product of fat and are manufactured in the livermitochondrial when there is insufficient stored glucose to turn into energy. They can be induced by medium chain triglycerides (MCTs), such as those found in coconut oil. Whereas long chain saturated fatty acids require chylomicron carriers through the lymphatic system and the carnitine shuttle to enter the mitochondria, MCTs do not require chylomicrons or the carnitine shuttle and can create ketones more efficiently.
- MCTs up-regulate the expression and protein levels of genes involved in mitochondrial biogenesis and metabolism, mediated in part through the activation of AMPK signalling pathways. They also improve oxidation of fatty acids.
- A combination of β-hydroxybutyrate and acetoacetate decreased neuronal apoptosis and decreased glutamate-induced mitochondrial ROS production, and the associated excitotoxicity, by increasing the NAD+/NADH ratio, and hence NADH oxidation, in the mitochondrial respiratory chain. Individually, acetoacetate and β-hydroxybutyrate can also scavenge ROS. Ketones can easily cross the blood brain barrier.
- β-hydroxybutyrate doubled the number of ETC proteins and increased mitochondrial number, UCP1, and mitochondrial biogenesis-regulating proteins in BAT.
- Ketones suppressed ROS generation and reversed the decreases in ATP levels caused by mitochondrial toxins. β-hydroxybutyrate was able to enhance mitophagy.
- Supplements include ketone salts, ketone oils (such as MCT oil) and ketone esters.

(Wang Y, PLoS One, 2018; Maalouf M, Neuroscience, 2007; Kim DY, J Neurochem, 2010; Clegg ME, Int J Food Sci Nutr, 2010; Thai PN, Front Physiol, 2019; Srivastava S, FASEB J, 2012; Haces ML, Exp Neurol, 2008; Branco AF, Eur J Clin Invest, 2016)

Lipoic acid

- Lipoic acid is an organosulphur fatty acid derived from caprylic acid and can be manufactured in the body, although production declines with age. It is found mainly in the mitochondria, where it is able to cross the mitochondrial membranes. Here it is a critical cofactor in mitochondrial α-keto acid dehydrogenases and an essential nutrient for the PDC, and hence energy production, but also augments the β-oxidation capacity of the mitochondria.
- It can restore the balance of NADH to NAD^+, which may be imbalanced (excess NADH) from high levels of glucose. It also stabilises and regulates mitochondrial multienzyme complexes, increasing ATP production. It also increases the mitochondrial membrane potential.
- Lipoic acid acts as an enzymatic cofactor able to regulate metabolism, energy production and mitochondrial biogenesis. Its mitochondrial antioxidant capacity prevents excess free radical formation by upregulating mtSOD through Nrf-2-mediated gene expression.
- It may also act through upregulating SIRTs 1 and 3 and AMPK in skeletal muscles and can lower hypoxia-induced apoptosis.
- The body can only use the R- form of α-lipoic acid but many products contain the synthetic S- form as well, so you are only getting 50% of the useable form. Much of the research has been done on the synthetic form but it is only the R- form that benefits the mitochondria. Dosage of 600 – 1,800 mg/day has been recommended.

(Dos Santos SM, Oxid Med Cell Longev, 2019; Deveci HA, Biomed Pharmacother, 2019; Solmonson A, J Biol Chem, 2018; Lei L, Cell Signal, 2016; Valdecantos MP, Obesity, 2012; Wang L, Int J Clin Exp Med, 2013; Liu J, Proc Natl Acad Sci USA, 2002; Hagen TM, Proc Natl Acad Sci USA, 2002; Golbidi S, Front Pharmacol, 2011; Lee Y, Biochem Biophys Res Commun, 2006; Lee WJ, Arterioscler Thromb Vasc Biol, 2005; Doggrell SA, Expert Opin Invest Drugs, 2004; Nicholson G, Integr Med, 2014)

Magnesium

- Magnesium is the 4th most abundant mineral in the human body, playing a role in over 300 enzyme reactions. Dysregulation of magnesium homeostasis is involved in many chronic diseases.
- Mitochondria act as an intracellular magnesium store, accounting for 1/3 of total cellular magnesium. Much of this intracellular magnesium is bound to ATP, which helps stabilise ATP and assists utilisation in the cell; without sufficient magnesium, a phosphate ion cannot bind correctly to ADT to make ATP. A magnesium deficiency restricts blood flow and oxygen delivery and slows OXPHOS in all cells.
- Magnesium is also a natural calcium antagonist and can prevent excess calcium ions flowing into the cell and damaging the mitochondria and will also prevent opening of the mtPTP.
- Magnesium can improve mitochondrial function with increased ATP, decreased mitochondrial ROS and calcium overload and restored mitochondrial membrane potential.
- Organic forms of magnesium (aspartate, citrate, lactate, fumarate, acetate, ascorbate, gluconate) have greater solubility and bioavailability in comparison to inorganic forms (oxide, sulphate, chloride carbonate). A magnesium chelate is considered safe at doses up to 600 mg/day; higher doses appear safe but may cause loose stools.

(Blum DJ, Biochemistry, 2012; Grober U, Nutrients, 2015; Golshani-Hebroni S, Gene, 2016; Liu M, JCI Insight, 2019; Kubota T, Biochim Biophys Acta, 2005; Yamanaka R, Sci Rep, 2016)

Manganese

- Manganese is an essential component of mitochondrial MnSOD, located in the mitochondrial matrix, which can help reduce excessive mitochondrial ROS production, prevent mtDNA damage and stabilise the mitochondrial membrane.
- In toxin-exposed hepatocytes, manganese lessened the mtDNA damage.
- In patients with T2D, blood Mn was elevate and MnSOD was upregulated and found to correlate to mtDNA oxidative damage in peripheral blood mononuclear cells.
- However, excessive manganese exposure is highly toxic in in the brain, inducing a condition called manganism, which resembles Parkinson's disease. Elevated manganese is associated with mitochondrial membrane depolarisation, increased membrane permeabilization, mitochondrial swelling and reduced ATP production leading to apoptosis in neurons. In astrocytes manganese also reduced mitochondrial oxygen consumption, ATP production, mitochondrial mass and fusion proteins but increased mitochondrial fission without upregulating mitophagy, indicating a high level of damaged mitochondria.
- In other cells, manganese exposure increases total ROS generation but particularly H_2O_2 production from Complex II by inducing the opening of the mtPTP. Manganese also decreased antioxidant production and mitochondrial membrane potential and induced mtDNA strand breaks.

(Rivas-García L, Food Chem Toxicol, 2020; Bakthavatchalu V, Oncogene, 2012; García-Ramírez M, Diabetes Metab, 2008; Anetor JI, Biol Trace Elem Res, 2007; Epperly MW, Radiat Res, 2002; Heidari R, Clin Exp Hepatol, 2019; Ahmadi N, 2018; Sarkar S, Neurotoxicology, 2018; Bonke E, Free Radic Biol Med, 2016; Yoon H, Environ Health Toxicol, 2011; Yang H, Toxicol Mech Methods, 2009; Jiao J, Environ Toxicol Pharmacol, 2008)

Melatonin

- Melatonin is a hormone that has several functions in the body but most importantly regulates the sleep-wake cycle; it is primarily released by the pineal gland. In its other functions it could more properly be called an antioxidant vitamin and anti- or pro-inflammatory as needed.
- The antioxidant effect of melatonin can protect the mitochondria. It is one of the few antioxidants to enter the mitochondria and enhances vitamin D signalling to optimize mitochondrial function. It can also reduce oxidative stress and apoptosis through inhibition of the formation of the mtPTP and recharge glutathione.
- Melatonin can also protect the mitochondria by scavenging ROS, maintaining membrane potential and improving function, including the fission/fusion balance. SIRT1 is also increased with melatonin treatment.
- It can also increase mitochondrial biogenesis through upregulation of PGC-1α.
- With respect to energy production, melatonin can increase Acetyl CoA and ATP production, normalizing ETC Complex function, and inhibit lactate production.

(Carrillo-Vico A, Int J Mol Sci. 2013; Acuna-Castroviejo D, Front Biosci, 2007; Maron FJM, J Steroid Biochem Mol Biol, 2020; Mehrzadi S, Expert Opin Ther Targets, 2020; Fang Y, Front Endocrinol, 2020; Aral C, Cell Biol Int, 2020; Jiang LL, Eur Rev Med Pharmacol Sci, 2019; Chang JY, J Diabetes Res, 2019; Tan DX, J Pineal Res, 2002)

N-Acetyl Cysteine (NAC)

- NAC is a precursor of L-cysteine that binds with glutamine and glycine to form glutathione, but it is also known for scavenging free radicals in its own right.
- In pancreatic β-cells, NAC improved the mtDNA fragmentation, increased mitochondrial caspace-induced apoptosis, decreased mitochondrial membrane permeability and decreased ATP production caused by glucolipotoxicity, which were mediated in part by enhanced oxidative DNA damage and mTOR/AMPK-dependent cell signalling.
- In hyperglycaemia-induced cardiomyocyte injury, both metformin and NAC could ameliorate the decreased ATP production and cell viability, however NAC showed a significantly greater effect in decreasing cytosolic and mitochondrial ROS. The mechanism of action of NAC was via enhancing endogenous CoQ10 levels.
- In hepatocytes with induced toxicity, NAC reduced mitochondrial dysfunction and ROS damage. In other cells, NAC can reduce mitochondria-induced apoptosis but high doses may inhibit OXPHOS and induce uncoupling.
- In CNS trauma and kidney injury, NAC dose-dependently preserved mitochondrial structure and function and reduced oxidative stress.
- Doses up to 1200mg/day have been found safe. Single amino acids are best taken on an empty stomach.

(Alnahdi A, Biomolecules, 2020; Dludla PV, Toxicol Rep, 2019; Raza H, PLoS One, 2016; Jiao Y, PLoS One, 2016; Zhu Y, Toxicol in Vitro, 2015; Hart AM, Neuroscience, 2004; Aparicio-Trejo OE, Free Radic Biol Med, 2019; Sharaf MS, Free Radic Biol Med, 2015)

NAD+ and precursors: NADH, Nicotinamide riboside and nicotinamide mononucleotide

- NAD+ is an important signalling molecules (via sirtuins and PARPs) but declines with age. To maintain NAD+ levels, most NAD+ is recycled via salvage pathways rather than generated de novo. The majority of NAD+ is salvaged from nicotinamide or from the various forms of niacin taken up in the diet. Substances that inhibit NAD+ degradation include luteolin, quercetin and apigenin.
- NADH is required for entry into the ETC. It is a potent antioxidant and regenerates the antioxidant capacity of other antioxidants.
- Nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) are more efficient precursors of NAD^+ than niacin because they enter the biochemical pathway after the rate-limiting step in NAD synthesis. They both enhance ATP production where availability of NAD^+ is limited.
- NR has been approved as a Novel Food in the EU, allowing it to be used as a non-flushing source of niacin in food supplements. NR is a nucleoside made from niacinamide and ribose.
- NR can upregulate SIRTs 1 and 3, PGC-1α and other transcription factors for mitochondrial biogenesis, the carnitine shuttle, UCP2 and increased mtDNA. It can generally improve mitochondrial function in neurons by maintaining the NAD^+ pool and is an effective treatment for mitochondrial myopathy in mice.
- NR doses up to 1000mg/day have been found to be safe; supplements have a half-life of 2.7 hours and are best taken on an empty stomach. Dosages >1000mg/day may cause insomnia, anxiety, fatigue and overstimulation. Do not take at night as it suppresses melatonin production and activates SIRT1.
- Nicotinamide mononucleotide (NMN) upregulates SIRTs 1 and 3, restores mitochondrial function, reduces oxidative stress by upregulating mitochondrial SOD and inhibits apoptosis. It also increases production of Acetyl CoA, the substrate for the TCA cycle.
- NAD+ is available as Basis (NAD+ and pterostilbene) from Elysium. Microdose NADH from Birkmayer.

(Birkmayer JG, Ann Clin Lab Sci, 1996; Rajman L. Cell Metabolism. 2018; Reibnegger GJ, J Tumor Marker Oncol, 2003; Lee HJ, Nutr Res Pract, 2019; Schondorf DC, Cell Rep, 2018; Wang S, Redox Biol, 2018; Khan NA, EMBO Mol Med, 2014; Kiss T, Geroscience, 2020; Xie X, J Affect Disord, 2020; Klimova N, J Neurosci Res, 2019; Conze D, Scientific Reports volume 9, 2019; Canto C, Cell Metab, 2012; Martens CR, Nat Commun. 2018; 9: 1286; Trammell SAJ, Nat Commun. 2016; 7, 12948)

Omega-3 fatty acids (long chain)

- Long chain omega-3 fatty acids, principally found in oily fish, have a beneficial role in mitochondrial dynamics and biogenesis through increased expression of PGC1-α. They can restore the age-related decrease in respiration, improve ATP production and upregulate mitochondrial fusion, increasing levels of anti-apoptotic proteins. They can also increase mitochondrial oxygen consumption, mitochondrial content, glycolytic capacity and metabolic rate and reduce mitochondrial ROS.
- Docosahexaenoic acid (DHA) can inhibit the effects of toxic very long chain fatty acids on mitochondria. Omega-3 PUFA increase membrane cardiolipin, a phospholipid that is essential for optimal mitochondrial function. In particular, cardiolipin needs to be saturated in DHA in order to signal caspase-3 to trigger apoptosis. If DHA is deficient, this promotes continuation of dysfunctional cells which would be better removed. DHA is particularly effective in neuronal mitochondria where it upregulated Nrf2 and antioxidant enzymes to resist calcium-induced membrane permeabilisation and decrease the increased ROS production and loss of calcium homeostasis following hypoxia. DHA can also help regenerate mitochondrial membranes and increase fluidity and upregulates SIRT1 expression in the brain and endothelial cells.
- Eicosapentaenoic acid (EPA) protected the mitochondria through decreasing oxidative stress of the mitochondrial matrix and upregulating SIRT3. It also protected against toxin-induced apoptosis and decrease in ATP production and enhanced mitochondrial biogenesis through upregulation of PGC-1α. EPA could also attenuate the age-related decline in mitochondrial respiratory capacity in skeletal muscle.

(De Oliveira MR, Trends Food Sci Tech, 2017; Afshordel S, Prostaglandins Leukot Essent Fatty Acids, 2015; Vaughan RA, Lipids Health Dis, 2012; Nury T, Int J Mol Sci, 2020; Migliaccio V, Int J Mol Sci, 2019; Mayurasakorn K, PLoS One, 2016; Leger T, Oxid Med Cell Longev, 2019; Johnson ML, Aging Cell, 2015; Jung SB, Biochem Biophys Res Commun, 2013; Thomas J, JNIM, 2015; Stanley WC, Curr Opin Clin Nutr Metab Care, 2012)

Pyrroloquinoline quinone (PQQ)

- PQQ has been found in interstellar dust and is bacterial in nature. PQQ and its principal metabolite IPQ, are widely distributed in animal and plant tissue. Mammals do not have the ability to produce PQQ, suggesting that one day it may be classified as an essential nutrient; Japanese scientists published in Nature their molecular evidence that PQQ was a previously unidentified B vitamin.
- Although little researched as yet, its most commonly observed mitochondrial property in animals appears to be triggering biogenesis through upregulation of SIRT1 and PGC-1α, as well as Nrf and TFAM activation independently of PGC-1α. A human study found similar results, together with increased peak oxygen consumption during exercise. It can also inhibit neuronal apoptosis.
- PQQ can also protect against toxin-induced slowing of the respiratory chain, restoring fission/fusion balance. PQQ also seems to be an essential co-factor in one of the protein subunits of Complex I of the ETC and it can reverse the adverse effects of Complex I inhibitors.
- PQQ is considered a ‘super antioxidant’ because it is far more stable than other antioxidants and can carry out more redox cycling reactions as a result.
- Dosage: limited trials but appears safe up to and including 60mg/day and probably beyond. A dose of 20mg/day was sufficient to improve memory. Others suggest 10-20mg/day.

(Kasahara T, Nature, 2003; Chowanadisai W, J Biol Chem, 2010; Stites TE, J Nutr, 2000; Hwang PS, J Am Coll Nutr, 2019; Lu J, Neurosci Lett, 2018; Saihara K, Biochemistry, 2017; He B, Zhonghua Zheng Xing Wai Ke Za Zhi, 2017; Zhang J, Nutr Res, 2015)

D-Ribose

- D-ribose is a naturally occurring 5-carbon monosaccharide, present in all living cells but principally stored in the mitochondria of muscle cells. It is a key component in many biological processes. Together with adenine, ribose forms the adenosine molecule of ATP, as well as the electron carriers NADH and $FADH_2$. It also produces RNA and DNA and manufactures other critical molecules; of all the naturally occurring sugars, D-ribose is the only one that can function in all these essential metabolic processes. The availability of ribose in the muscle is a limiting factor for the rate of re-synthesis of ATP.
- Ribose is not directly available in the diet; it can only be created in the body when it is broken down from glucose through the pentose phosphate pathway, from where it creates nucleotides for DNA molecules and promotes cellular metabolism. But this breakdown process itself takes energy and the pentose phosphate pathway occurs slowly, so the best way to replenish D-ribose quickly is to supplement. Supplemental ribose bypasses the pentose phosphate pathway.
- When glucose-containing food is ingested, the body processes it through multiple pathways. One pathway generates ribose, which signals the body to synthesise ATP. Another pathway activates the breakdown of glucose through glycolysis, harnessing the released energy to form ATP through other processes. It prevents the activation of pro-apoptotic genes in neurons.
- Although there is technically no such thing as a D-ribose deficiency, in those with chronic stress the cells cannot keep up with the demand. This is when ribose supplementation can help. D-ribose is a unique sugar, in that it does not raise blood glucose as the body does not recognise it as a fuel and is has no caloric value. Ribose is not used by cells as a primary energy fuel; instead, it is preserved for the important metabolic task of stimulating purine nucleotide synthesis and salvage.
- Clinical studies have used between 5 -15 g daily. When supplementing with 15 g it is advised to separate into three 5g doses and take with meals. It should not be taken long term. Those with diabetes or hypoglycaemia should be careful taking ribose because it triggers insulin production which removes additional glucose from the bloodstream, worsening hypoglycaemia. Patients taking warfarin should not take ribose. Gut disturbance is the only noted side effect.

(Mahoney DE, Adv Biosci Clin Med, 2018; Teitelbaum J, Integr Med, 2008; Hellsten Y, Am J Physiol Regul Integr Comp Physiol, 2004)

Selenium

- In polycystic ovaries, selenium improved mitochondrial function and dynamics, inhibited apoptosis and alleviated oxidative stress.
- In neurons, nephrons, osteoblasts and other cells exposed to oxidative or heavy metal toxicity, selenium decreased ROS production, intracellular calcium accumulation, mitochondrial membrane depolarisation, cytochrome c release, caspase activation and apoptosis while increasing levels of antioxidants.
- Selenium can alleviate mitochondrial structural damage, suppression of ETC Complex activity, membrane hyperpolarisation and oxidative stress and reduce fission proteins, mitochondrial fragmentation, caspases and apoptosis induced by glutamate toxicity or hypoxia in neurons, as well as increasing Nrf1 and PGC-1α.
- In trophoblast mitochondria, selenium enhanced mitochondrial respiration, increased mitochondrial content and upregulated mitochondrial biogenesis.
- However, in hepatocyte mitochondria, both selenium excess and deficiency caused oxidative stress and lower levels of mtSOD.

(Atef MM, Arch Biochem Biophys, 2019; Ataizi ZS, Metab Brain Dis, 2019; Bas E, Anticancer Drugs, 2019; Yazıcı T, Biol Trace Elem Res, 2018; White SH, J Anim Sci, 2017; Radenkovic F, Biochem Pharmacol, 2017; Ma YM, BMC Neurosci, 2017; Hu L, Int J Mol Sci, 2016; Chen Z, Chem Biol Interact, 2016; Khera A, Placenta, 2015; Mehta SL, BMC Neurosci, 2012; Kumari S, PLoS One, 2012)

Sulphoraphane

- Sulphoraphane is a bioactive sulphur-containing isothiocyanate found in cruciferous vegetables and sprouts, principally broccoli. It is produced from glucorphanin, a glucosinolate, which is converted into sulphoraphane through the enzyme myrosinase. Isothiocyanates are produced by plants as natural pest repellents and when consumed by humans, they trigger upregulation of protective enzymes in the cells, as with resveratrol, as an example of hormesis.
- Sulphoraphane upregulates Nrf2, which is involved in mitochondrial biogenesis, and also endogenous antioxidant production. So sulphoraphane is an 'indirect' antioxidant because instead of acting directly, as does vitamin C, it triggers the cell to produce its own antioxidants as needed. This is a far more comprehensive and targeted response, compared to the random effect of consuming antioxidant supplements, which indiscriminately suppress free radicals, including the beneficial free radicals.
- After exposure to a mitochondrial toxin, sulphoraphane could improve mitochondrial structure and function, restore the membrane potential and enhance the antioxidative stress ability. It also upregulated several key enzymes of the TCA cycle and ETC.
- Sulphoraphane also alleviates mitochondrial swelling, stimulates biogenesis through upregulation of PGC-1α, Nrf1 and TFAM and improves mitochondrial membrane potential, ATP production and lipolysis and decreases mitochondrial fission and mitochondria-induced apoptosis.
- In adipocytes, sulphoraphane increased mitochondrial content and ETC activity, with upregulation of SIRT1, PGC-1α and UCP1, increased AMPK phosphorylation and enhanced efficiency of glucose and fatty acid oxidation.
- The optimal dose of sulphoraphane is unknown, but based on rat studies effective doses in humans might be 7-34 mg for a 150lb person, 9-45 mg for a 200lb person and 11-57 mg for a 250lb person.

(Bi M, Basic Clin Pharmacol Toxicol, 2017; Lin CF, J Formos Med Assoc, 2019; Lei P, Mol Nure Food Res, 2019; De Oliveria MR, Mol Neurobiol, 2018; Carrasco-Pozo C, Oxid Med Cell Longev, 2017; O'Mealey GB, Redox Biol, 2017; Zhang HQ, Mol Nutr Food Res, 2016; Choi KM, J Nutr Biochem, 2014)

Taurine

- Taurine is sulphur-containing conditionally essential amino acids, made from methionine and cysteine, i.e. from protein-rich foods. It is one of the most abundant amino acids in the human body.
- Taurine protected against toxin-induced collapse of the mitochondrial membrane potential in neurons, elevation in cytoplasmic calcium ions and apoptosis.
- It also decreased mitochondrial ROS productions and upregulated mtDOS by suppressing calcium overload and improving mitochondrial respiratory functions.
- Taurine preserved ATP production, prevented mitochondrial depolarisation and swelling and increased mitochondrial dehydrogenases activity. After culture in a mitochondrial toxin it reinforced the MAM and mitochondrial cristae.
- Several human mitochondrial diseases, such as MELAS, showed a lack of taurine modification of mitochondrial tRNAs

(El Idrissi A, Adv Exp Med Biol, 2003; Zhang R, Nephron, 2020; Ahmadi N, J Biochem Mol Toxicol, 2018; Stacchiotti A, Nutrients, 2018; Suzuki T, Wiley Interdiscip Rev RNA, 2011)

Tauroursodeoxycholic acid (TUDCA)

- Tauroursodeoxycholic acid (TUDCA) is an ambiphilic bile acid. It is the taurine conjugate form of ursodeoxycholic acid (UDCA). It is a secondary bile acid produced by gut bacteria. Humans are found to have trace amounts of TUDCA. In the US it is a licenced treatment for primary biliary cirrhosis and cholestasis.
- In ageing or injured neurons, TUDCA restores the mitochondrial membrane potential, inhibits release of cytochrome c, mitochondrial apoptosis, damage and ROS generation and upregulates mitophagy through Parkin recruitment. TUDCA is able to cross the blood brain barrier and in neural stem cells, it can similarly inhibit apoptosis, preserve mitochondrial integrity and function, promote mitochondrial biogenesis and increase mitochondrial antioxidant status.
- In cardiac cells exposed to oxidative stress, TUDCA inhibited opening of the mtPTP and prevented mitochondrial damage.
- In damaged cells, TUDCA increased mitochondrial antioxidants and inhibited apoptosis by inhibiting translocation of pro-apoptotic proteins, cytochrome c release and activation of caspases.

(Soares R, Mol Neurobiol, 2018; Xie Y, Am J Transl Res, 2016; Fonseca I, Mol Neurobiol, 2017; Colell A, Hepatology, 2001; Rodrigues CM, J Neurochem, 2000; Xavier JM, Cell Cycle, 2014; Rodrigues CM, Biochemistry, 2003; Ishigami F, Transplantation, 2001)

Vitamin A

- Vitamin A is the name of a group of fat-soluble retinoids, including retinol and retinyl esters, both if which are available in the human diet, as is provitamin A carotenoids. Preformed vitamin A is found in foods from animal sources, including dairy products, fish and meat (especially liver), while β-carotene (which contributes 30-35% of dietary vitamin A in Western countries but a higher percentage elsewhere) is found in plants but must be metabolised to retinal and retinoic acid, the active forms of vitamin A.
- While vitamin A deficiencies are found in a number of chronic diseases (and supplementation to normalise levels is recommended), additional supplementation of any form of vitamin A can be detrimental, except in cancer when it can be beneficial. Similarly, supplementation of β-carotene can have negative effects on health, especially in people who smoke or consume alcohol.
- Supplementation of retinoic acid in mice with normal levels did not help prevent neuronal apoptosis after hypoxia. However in a model for neural stem cells, retinoic acid can beneficially regulate mitochondrial morphology and function via PGC-1α.
- In WAT, retinoic acid can induce mtDNA replication and transcription, mitochondrial biogenesis and OXPHOS and in colonocytes a high vitamin A diet upregulated the mitochondrial transcription factors Nrf1 and TFAM. However, in other cells, various forms of retinoic acid can inhibit Complex I and ATP synthase and induce opening the mtPTP and apoptosis.
- In neurons, hepatocytes and cardiomyocytes, vitamin A or retinyl palmitate supplementation increased mitochondrial oxidative and nitrosative stress, with decreased mtSOD and impaired respiratory chain activity; neuronal mitochondria were rendered more susceptible to toxins such β-amyloid.
- Supplementation of β-carotene has mixed results; some studies show improved ATP production but others show decreased mitochondrial membrane potential, inhibited mitochondrial respiration and decreased cellular ATP.

(Jiang W, Mol Brain, 2018; Mu Q, Artif Cells Nanomed Biotechnol, 2018; Reifen R, Nutrition, 2015; De Oliveira MR, Brain Res Bull, 2012; De Oliveira, Brain Res Bull, 2011; Da Rocha RS, Free Radic Res, 2010; De Oliveira MR, Acta Neuropsychiatr, 2012; De Oliveira MR, Cell Biol Toxicol, 2009; Papa F, Biochem Biophys Res Commun, 2017; Tucci P, J Bioenerg Biomembr, 2008; Notario B, Mol Pharmacol, 2003; Tourniaire F, J Lipid Res, 2015; Weinrich T, Mar Drugs, 2019; Sliwa A, Acta Biochim Pol, 2012)

Vitamin D

- Vitamin D is a fat-soluble steroid obtained mainly from the action of sunshine on cholesterol in the skin but is also found in oily fish. Vitamin D blood levels are measured as 25(OH)D but the biological actions of vitamin D are carried out via the binding of vitamin D3 (calcitriol, 1α,25(OH)2D3) to the vitamin D receptor (VDR). Activation of 25(OH)D to the active vitamin D3 occurs via a mitochondrial redox reaction.
- Many of the cells' VDR are located in the mitochondria, where they interact with proteins of the mtPTP, such that impairment of the mtPTP leads to reduction in mitochondrial levels of the VDR. The VDR plays a central role in protecting cells from excessive mitochondrial respiration and production of ROS that leads to cell damage. In BAT calcitriol/VDR suppress mitochondrial respiration, as measured by oxygen consumption rates.
- Vitamin D administration with a mitochondrial toxin restores mtDNA number, mitochondrial biogenesis, cytochrome c oxidase, cellular oxygen consumption and mitochondrial function.
- In rat cardiac dysfunction, vitamin D increased tissue reserves of reduced glutathione (GSH), superoxide dismutase (SOD), ATP production and mitochondrial membrane cardiolipin. Similarly, in skeletal muscle vitamin D increased oxygen consumption and improved mitochondrial function and mtDNA depletion, while in osteoblasts, vitamin D in part lowers mitochondria-induced apoptosis.

(Lee CT, J Steroid Biochem Mol Bio, 2019; Ashcroft SP, Am J Physiol Cell Physiol, 2020; Blajszczak CC, J Steroid Biochem Mol Biol, 2019; Hussien NI, Gen Physiol Biophys, 2019; Schnell DM, J Nutr Biochem, 2019; Ricca C, Int J Mol Sci, 2018; Ricciardi CJ, Eur J Nutr, 2015; Sinha A, J Clin Endocrinol Metab, 2013; Silvagno F, PLoS One, 2013; Duque G, Bone, 2004; Campbell GR, AIDS, 2013)

Zinc

- In ischaemic cardiomyocytes, zinc improved OXPHOS and abundance of Complex 1 proteins, increased mitophagy, stabilised PINK1 and prevented mitochondrial ROS generation, apoptosis, opening of the mtPTP and dissipation of the mitochondrial membrane potential at reperfusion. However, in vascular smooth muscle cells, accumulation of zinc in the mitochondria increases mitochondrial ROS production.
- In neurons with oxidative stress, zinc reduced ROS production and mitochondrial swelling and increased mnSOD levels and activity of ETC enzymes.
- However, zinc accumulation is known in ischaemia or where toxins inhibit Complexes I and II; it is believed to enter mitochondrial through the Ca2+ uniporter. High neuronal mitochondrial zinc levels from any cause can induce increased ROS production, reduced mitochondrial antioxidants, dissipation of the membrane potential, decreased oxygen consumption rate and ATP turnover, opening of the mtPTP and cytochrome c release, increasing neuronal apoptosis. In brain micro-vessels, ischaemia/reperfusion also induced mitochondrial zinc accumulation in endothelial cells, increasing ROS production and fission proteins and collapsing mitochondrial networks.
- In other cells, zinc can reduce oxidative stress, mitochondrial dysfunction and apoptosis. It is required for the synthesis of CuZnSOD in the intermembrane space.
- Hypoxia can induce zinc accumulation in other cells, which triggers increased ROS production.

(Zhang G, J Mol Cell Cardiol, 2018; Bian X, Free Radic Res, 2018; Salazar G, Free Radic Biol Med, 2017; Adebayo OL, Life Sci, 2016; Pivovarova NB, J Neurochem, 2014; Sadli N, Cell Physiol Biochem, 2013; Sheline CT, Neurodegener Dis, 2013; He K, J Neurochem, 2010; Chanoit G, Am J Physiol Heart Circ Physiol, 2008; Qi Z, Toxicol Appl Pharmacol, 2019; Slepchenko KG, Int J Physiol Pathophysiol Pharmacol, 2016; Dineley KE, Mitochondrion, 2005; Dineley KE, J Neurochem, 2003; Bossy-Wetzel E, Neuron, 2004; Gazaryan IG, J Biol Chem, 2007; Varghese J, Eur J Pharmacol, 2009; Rajapakse D, Oxid Med Cell Longev, 2017; Kawamata H, Antioxid Redox Signal, 2010)

Flavonoids

- Flavonoids are polyphenols found in plants and fungi and are in part responsible for giving fruits and vegetables their colour. There are over 6,000 flavonoids, usually grouped into anthocyanins, anthocyanidins, procyanidins, flavones and flavanols, flavonones, flavonols, flavans and isoflavones.
- The major flavonoids have been considered individually, as follows:

Apigenin
Baicalin/Baicalein
Curcumin
Epicatechin
Epigallocatechin-3-gallate (EGCG)
Grape seed extract
Icariin
Kaempferol
Luteolin
Milk thistle
Myricetin
Naringin/Naringenin
Nobiletin
Quercetin
Resveratrol
Rutin

Apigenin

- Apigenin is a bioflavonoid found in many fruits and vegetables.
- After exposure to mitochondrial toxins, apigenin lowered ROS production, DNA damage and apoptosis, increased mitochondrial antioxidants and biogenesis and normalized membrane potential. It also upregulated OXPHOS, particularly with respect to Complex I, thereby lowering electron leak, and ATP synthase.
- In skeletal muscle, apigenin can improve depressed mitochondrial function and biogenesis and upregulate AMPK. In cardiomyocyte ischaemia/reperfusion injury, apigenin reduced ROS production and increased mtSOD, restored mitochondrial membrane potential and prevented the opening of the mtPTP, decreasing cytochrome c release and caspase activation and apoptosis.
- Apigenin can increase NAD+ levels and improve glucose and lipid metabolism through upregulation of AMPK and SIRT1.
- Apigenin has oestrogenic activity, so care should be taken for women with a history of oestrogen-responsive cancers or on hormone replacement therapy. Having said that, apigenin is principally known for its ability to induce apoptosis in cancers (see Cancer section).
- Dosage is normally 3-10 mg per kilogram of bodyweight.

(Nisha VM, Appl Biochem Biotechnol, 2014; Ahmad A, Pestic Biochem Physiol, 2019; Choi WH, Mol Nutr Food Res, 2017; Zhong Y, Toxicon, 2017; Duarte S, Int J Mol Sci, 2013; Escande C, Diabetes, 2013; Lu J, Exp Ther Med, 2019; Wei X, Clin Sci, 2017; Mohammad FE, J Biochem Mol Toxicol, 2017; Huang H, Oxid Med Cell Longev, 2019)

Baicalin/Baicalein

- Baicalin and its aglycone baicalein are principally found in *Scutellaria baicalensis* (Chinese skullcap), *Scutellaria radax* and *Scutellaria lateriflora* (American skullcap); baicalein is its aglycone. May have poor bioavailability, so quality is important.
- Baicalein can protect mitochondria from loss of membrane potential, inhibit caspase activation to block apoptosis, suppress extracellular ROS production and upregulate SOD production in a range of cells.
- In diabetic pancreatic β-cells, baicalin preserved the integrity of the inner mitochondrial membrane and increased mitochondrial number. It had an additive effect with metformin.
- In neurons, baicalein and baicalin inhibited toxin-induced hypoxia, apoptosis, and ROS production, normalising mtSOD levels, mitochondrial membrane potential, ATP production and mitochondrial biogenesis and protected against increase in intracellular calcium. Similar results were seen in other cells exposed to mitochondrial toxins. It also reduced oxygen consumption and ROS production without altering ATP production.
- In rat liver and kidney, baicalin protected from ischaemia/reperfusion injury, preventing mitochondrial swelling and caspase activation. In vitro, administration of baicalin prior to toxin exposure improved mitochondrial biogenesis via PGC-1α, mproved membrane potential and ATP production and decreased oxygen consumption.
- In cardiomyocytes exposed to H_2O_2, baicalein dose-dependently inhibited ROS production, mtDNA fragmentation and cytochrome c release, thereby preventing apoptosis.
- Recommended dosage is 200-800 mg/day.

(Waisundara VY, Diabetes Metab Res Rev, 2009; Zhang S, J Mol Neurosci, 2010; Huang HH, Am J Chin Med, 2014; Li XX, Eur J Pharmacol, 2012; Im AR, Evid Based Complement Alternat Med, 2012; de Oliveira MR, Pharmacol Res, 2015; Liu B, Free Radic Biol Med, 2012; Lee IK, Environ Toxicol Pharmacol, 2011; Zhang X, Sci Rep, 2017; Li XX, Eur J Pharmacol, 2012; Li N, J Biol Chem, 2003)

Curcumin

- Curcumin is a polyphenolic compound which is an abundant component of turmeric. It has shown beneficial effects in a number of diseases.
- Curcumin enhanced the mitochondrial fusion/fission ratio in neurons, increased biogenesis and upregulated mitochondrial function and cell viability. It also attenuated mitochondrial dysfunction-induced oxidative stress.
- In hepatocytes, it also inhibited ROS production and ATP depletion induced by a high fat diet, increased mtDNA copy number and biogenesis transcription factors PGC1α, Nrf1 and TFAM and restored mitochondrial membrane potential.
- Curcumin activates SIRT1 to reduce mitochondrial oxidative damage, upregulated Nrf2 and increases mitophagy.
- Several preparations include piperine (bioperine) to make curcumin more bioavailable. However this can damage the CYP450 enzymes, so preferable to take an oil-based capsule.

(Yang Y, Free Radic Biol Med, 2013; Reddy PH, J Investig Med, 2016; de Oliveria MR, Biotechnol Adv, 2016; Trujillo J, Arch Pharm, 2014; Kim DS, Recent Pat CNS Drug Discov, 2012; Kuo JJ, Int J Mol Med, 2012)

Epicatechin

- The flavanol (–)-epicatechin is found mainly in dark chocolate and other cocoa products. It is able to cross the blood brain barrier. Catechins are the most readily absorbable flavonoid.
- Mitochondrial H_2O_2 production can be inhibited by epicatechin, as well as reducing the ROS-mediated mitochondrial damage after ionising radiation injury.
- In skeletal muscle, epicatechin can stimulate mitochondrial biogenesis by upregulating Nrf2 and TFAM. It can also enhance cristae density and improve mitochondrial structure. In cardiomyocytes, epicatechin increased mitochondrial respiration and decreased release of cytochrome c but also raised ROS production and rigidity of mitochondrial membranes.
- Epicatechin reversed the inhibition of Complex I and reduced ATP production after exposure to a mitochondrial toxin, decreased ROS production and apoptosis and restored levels of mtSOD. In coronary artery endothelial cells it can also stimulate mitochondrial function by upregulating protein levels of Complex I and II through activation of nitric oxide.
- In induced diabetes, epicatechin increased mitochondrial proteins (particularly Complexes III, IV and V), transcription factors and SIRT1, restoring mitochondrial activity, ATP production and biogenesis. It also improved redox state by upregulating antioxidants, as well as Nrf1 and Nrf2.
- In injured nephrons, epicatechin reduced ROS production, mitochondrial fragmentation and cytochrome c release and restored Complex II and IV enzymes.

(Lagoa R, Biochim Biophys Acta, 2011; Shimura T, FASEB J, 2019; Moreno-Ulloa A, Eur J Pharmacol, 2018; Silva Santos LF, J Arrhythm, 2017; Ramirez-Sanchez I, FEBS J, 2014; Ramírez-Sánchez I, Diab Vasc Dis Res, 2016; Nichols M, Neuroscience, 2015; Watanabe N, Lipids Health Dis, 2014; Taub PR, Clin Transl Sci, 2012; Tanabe K, Am J Physiol Renal Physiol, 2012; Panneerselvam M, Mol Nutr Food Res, 2013; Moreno-Ulloa A, Bioorg Med Chem Lett, 2013; Rowley TJ, J Nutr Biochem, 2017; Kopustinskiene DM, Biomed Res Int, 2015)

Green tea extract: Epigallocatechin-3-gallate (EGCG)

- Green tea contains polyphenols and catechins, of which EGCG is the most abundant. EGCG belongs to the class flavan-3-ols (catechins) esterified with gallic acid.
- In toxin-induced mitochondrial dysfunction, EGCG upregulated ATP synthase, NADH dehydrogenase, PGC-1α, TFAM mRNA and cytochrome c oxidase and increased mtDNA copy number. It also provided significant neuroprotection from oxidative stress-induced apoptosis.
- EGCG restored damaged mtDNA, abolished toxin-induced mtDNA mutations and restored mitochondrial antioxidant production.
- EGCG increased Complexes II, III and IV and malate dehydrogenase activity. It can modulate mitochondrial functions impacting mitochondrial biogenesis, ATP production and anabolism, and mitochondria-related apoptosis.
- In healthy mice, EGCG induced a general tissue reduction in oxidative damage and in skeletal muscle ETC Complexes were upregulated, together with an increase in AMPK levels, suggesting reduced energy availability which coincided with reduced carbohydrate uptake.
- EGCG was the top bioflavonoid for restoring reduced mitochondrial membrane potential and ATP levels and decreasing ROS production.

(Reddyvari H, J Adv Res, 2017; Santamarina AB, J Nutr Biochem, 2015; Rehman H, PLoS One, 2013; Ye Q, BMC Complement Altern Med, 2012; Serrano JC, Mol Nutr Food Res, 2013; Dragicevic N, J Alzheimers Dis, 2011; Schroeder EK, Antioxid Redox Signal, 2009; De Oliveria MR, Pharmacol Res, 2016)

Grape seed extract

- Grape seed extract is rich in proanthocyanidins.
- In damaged renal cells, grape seed extract inhibited apoptosis and decreased mitochondrial swelling and oxidative stress while increasing mitochondrial antioxidants, and upregulated SIRT1, PGC-1α, Nrf1, TFAM and AMPK and increased mtDNA copy number to prevent ATP depletion.
- Grape seed extract prevented oxidative stress, inhibited the opening of the mtPTP and prevented apoptosis in damaged neurons. It also restored mitochondrial membrane potential and ATP generation.
- In radiation-damaged lung fibroblasts and other injured cells, grape seed extract reduced mitochondrial ROS production and restored mitochondrial respiration, membrane potential and ATP production through increase particularly in Complex I activity. It also upregulated the TCA cycle enzymes, increased oxygen consumption, reduced mitochondrial swelling and calcium content and inhibited cytochrome c oxidase release and apoptosis.
- In obese brown adipose tissue, grape seed extract upregulated SIRT1 and Nrf1 and increased mitochondrial respiration. Similarly, in obese skeletal muscle, grape seed extract lowered ROS production and enhanced the ability to oxidise pyruvate and increased ETC Complex activity.
- Clinical trials show that dosage from 200-2000mg/day is effective and safe. However, grape seed extract may inhibit some liver enzymes, impacting the metabolism of anti-seizure drugs, SSRI antidepressants, antibiotics and antifungals (azoles). It could also prevent blood clotting and may interfere with blood thinners such as warfarin.

(Bao L, Br J Nutr, 2015; Cai X, Food Funct, 2016; Rigotti M, J Food Biochem, 2020; Sun Q, Aging, 2019; Fu K, CNS Neurol Disord Drug Targets, 2019; Yang X, Sci Rep, 2017; Miltonprabu S, Toxicol Rep, 2015; Lu Z, Ren Fail, 2016; Zhang Z, J Toxicol Sci, 2014; Pajuelo D, Br J Nutr, 2012; Pajuelo D, J Agric Food Chem, 2011; Karthikeyan K, Life Sci, 2007)

Icariin

- Icariin is a prenylated flavonol glycoside derived from kaempferol and is the main active compound of the Epimedium plant species.
- In damaged neurons and podocytes and ischaemic or hypertophic cardiomyocytes, icariin increased mtSOD expression and mitochondrial membrane potential, upregulated ATP production and decreased mitochondrial apoptotic proteins. In damaged neurons it could also upregulate both Nrf1 and Nrf2 to promote mitochondrial biogenesis.
- In diseased neurons, icariin can also increase mitochondrial number, length and size and enhance motility (important in neurons). It also altered the fission/fusion ratio in favour of fusion and restored cytochrome c oxidase (Complex IV) activity.
- Icariin can upregulate SIRT1 and PGC-1α expression in neurons following ischaemia, while inhibiting H_2O_2 production.
- In bone marrow mesenchymal stem cells, icariin reduced the effects of iron overload by downregulating mitochondrial fission proteins and caspases and export of cytochrome c, and hence decreasing apoptosis, and normalised mitochondrial membrane potential and ROS production.
- Usually sold for sexual dysfunction (because it can increase blood flow), it is available in the UK but sometimes on sites that principally advertise its aphrodisiac properties.

(Zhu HR, Neuropharmacol, 2010; Zhang L, Basic Clin Pharmacol Toxicol, 2010; Li H, Front Physiol, 2018; Wu B, Br J Pharmacol, 2018; Qiao C, Mol Cell Endocrinol, 2018; Chen Y, Int J Mol Sci, 2016; Chen Y, CNS Neurosci Ther, 2016; Zhang RY, Zhongguo Zhong Yao Za Zhi, 2013; Hua W, Biochim Biophys Acta Mol Basis Dis, 2010; Song YH, Biomed Pharmacother, 2016; Yao X, Front Pharmacol, 2019)

Kaempferol

- Kaempferol is a flavonol and a phytoestrogen, found in many fruits, vegetables and herbs.
- Exposure of the vascular endothelium to chemotherapy drugs induced excessive ROS production and apoptosis but kaempferol reduced mitochondrial pro-apoptotic proteins, inhibited the opening of the mtPTP and restored the NAD+/NADH ratio.
- In cells exposed to other toxins, kaempferol prevented dissipation of the mitochondrial membrane potential, inhibition of Complex IV, mtDNA damage, elevated intracellular calcium and excessive ROS production.
- In neurons, ischaemia induced injury due to succinate accumulation leading to mitochondrial fission; fission could be inhibited by kaempferol. In damaged neurons, kaempferol upregulated the mitochondrial Ca^{2+} uniporter to allow more intracellular calcium into the mitochondria, improved TCA cycle flux and maintained mitochondrial functional integrity. Upregulation of the mitochondrial Ca^{2+} uniporter was also seen in other cells, as a way of maintaining calcium homeostasis in the cell.
- In ischaemic cardiomyocytes, kaempferol reduced excessive ROS production, inhibited release of cytochrome c and opening of the mtPTP, restored mitochondrial membrane potential and upregulated SIRT1.
- Kaempferol reduces mitochondrial H_2O_2 production and inhibits Complex I; the extent of this inhibition was dependent on the concentration of CoQ10, suggesting competition between the flavonoids and ubiquinone for binding sites in the Complex.

(Wu B, Biochim Biophys Acta Mol Basis Dis, 2017; Wu W, Biomed Pharmacother, 2020; Choi EM, Food Chem Toxicol, 2011; Guo Z, Eur J Pharmacol, 2015; Chitturi J, J Neurotrauma, 2019; Lagoa R, Biochim Biophys Acta, 2011; Montero M, Biochem J, 2004; Murugan M, Front Syst Neurosci, 2016; Yao X, Theriogenology, 2019)

Luteolin

- Luteolin is a flavone produced by many fruits and vegetables and is known as a citrus bioflavonoid.
- After exposure to a mitochondrial toxin, luteolin restored Complex I and IV activity and balance of ROS and mtSOD and prevented dissipation of the mitochondrial membrane potential, elevation in intracellular calcium and cytochrome c release leading to apoptosis.
- In cardiomyocytes subject to oxidative damage, luteolin decreased ROS production, restored mtSOD balance and mitochondrial membrane potential, inhibited opening of the mtPTP and promoted mitophagy.
- Activation of mast cells by extracellular DNA was suppressed by luteolin.
- Most luteolin supplements also contain rutin, with dosage 100-300 mg per serving.

(Choi EM, Toxicol in Vitro, 2011; Xu H, Front Physiol, 2020; Wang Y, Int J Mol Med, 2018; Yang JT, J Cardiovasc Pharmacol, 2015; Liu Z, Phytother Res, 2018; Asadi S, J Neuroinflammation, 2012)

Milk thistle (Silybum marianum)

- Milk thistle is a herb which belongs to the ragweed and daisy family. Silymarin, which contains silybin and silybinin, is one of its important components.
- In ageing mice, silybum raised mtSOD, improved mitochondrial function and decreased pro-apoptotic proteins, while silymarin increased mitochondrial biogenesis and membrane potential.
- In toxin-induced mitochondrial dysfunction, silybin improved mitochondrial function through the upregulation of SIRT3, upregulated mitochondrial biogenesis and prevented mitochondrial ROS production and cardiolipin oxidation.
- In damaged pancreatic β-cells, osteoblasts, hepatocytes and cardiomyocytes, silybinin restored mitochondrial function, increased mtSOD, membrane potential and anti-apoptotic proteins and decreased intracellular calcium and release of cytochrome c, with upregulation of SIRT1.
- Low doses of silybinin increased mitochondrial membrane potential and ATP production but high doses reversed this.
- Standardised milk thistle extracts should contain 70–80% silymarin. Ideally, the silybin content should also be mentioned and account for c40% (the higher the better). The typical silymarin dosage used in most studies was c420 mg/day divided into 2 or 3 doses but dosage may be higher in liver disease and cancer.

(Zhu SY, Pharmacogn Mag, 2014; Li Y, Front Pharmacol, 2017; Serviddio G, Free Radic Biol Med, 2013; Pietrangelo A, J Bioenerg Biomembr, 2002; Esselun C, Oxid Med Cell Longev, 2019; Sun Y, Mol Cell Biochem, 2019; Zhou B, J Pharmacol Sci, 2006; Mao YX, Cell Death Dis, 2018; Bin Feng, Free Radic Biol Med, 2017; Rolo AP, Hepatol Res, 2003)

Myricetin

- Myricetin is a flavonol found in many vegetables and fruits and is formed from dihydromyricetin (amelopsin); myricitrin is a metabolite of myricetin.
- In hypoxic or aged skeletal muscle, myricetin restored mitochondrial structure, function and membrane potential, increased biogenesis and mtDNA content through upregulation of AMPK and SIRT1 and improved ETC activity through increased gene expression of Complexes.
- In toxin-exposed cardiomyocytes, myricitrin maintained mitochondrial membrane potential and increased mitochondrial anti-apoptotic proteins, leading to lower caspase activation and apoptosis. Similar results were seen on toxin-exposed neurons, with an improved balance of ROS and mtSOD and increased ATP production; myricetin had a stronger effect in neurons than myricitrin.
- In chondrocytes, dihydromyricetin alleviated mitochondrial dysfunction through upregulation of SIRT3 and in damaged skeletal muscle it stimulated mitochondrial fusion and biogenesis, increased mtDNA, preserved the mitochondrial membrane potential and enhanced OXPHOS. Similarly in injured hepatocytes and endothelial cells, dihydromyricetin reversed depleted ATP production, improved the balance in ROS and mtSOD through activation of SIRT3 and decreased apoptosis.

(Zou D, PLoS One, 2015; Sun J, Evid Based Complement Alternat Med, 2016; Cai Z, Biochem Biophys Res Commun, 2015; Wang YH, J Mol Neurosci, 2014; Franco JL, Environ Toxicol Pharmacol, 2010; Wang J, Int J Biol Sci, 2018; Huang Y, Cell Physiol Biochem, 2018; Zeng X, Antioxid Redox Signal, 2019; Hou X, Life Sci, 2015; Jung HY, Sci Rep, 2017)

Naringenin/Naringin

- Naringenin is a flavanone, commonly found in grapefruit as well as other fruits and herbs. Naringin is its glycoside.
- In ROS- or toxin-damaged neurons, high dose naringenin or naringin lowered ROS production, restored antioxidant defences, mitochondrial membrane potential. ETC Complexes and ATP production and decreased apoptosis through Nrf2 upregulation. Naringenin is also an iron-chelator in cases of mitochondrial overload.
- In cells with ROS- or toxin-induced mitochondrial dysfunction, naringenin reversed impairment of TCA cycle enzymes, restored the activity of Complexes I and V and ATP production, upregulated antioxidants and reduced apoptosis, through Nrf2 upregulation. Naringin had a similar effect on mitochondrial function, mitochondrial ROS and SOD and apoptosis and upregulated Complex IV.
- In damaged hepatocytes, naringenin normalised ROS generation and antioxidant levels and reduced cytochrome c release, preventing apoptosis.
- In toxin-damaged cardiomyocytes, naringin increased mitochondrial membrane potential, increased the balance of anti-apoptotic protein, inhibited cytochrome c release and inhibited caspases, thereby lowering apoptosis, and lowered mitochondrial lipid peroxides. In hypoxic cardiomyocytes, naringenin decreased mitochondrial oxidative stress and cytochrome c release, enhanced mitochondrial biogenesis by upregulating PGC-1α, SIRT3, AMPK, TFAM and Nrf1 and increased activity of Complexes II, III and IV.

(Wang K, Int J Mol Med, 2017; de Oliveira MR, Neurochem Res, 2017; Kapoor R, Apoptosis, 2013; Kulasekaran G, Mol Cell Biochem, 2015; Sahu BD, Toxicol Appl Pharmacol, 2014; Huang H, Int J Mol Med, 2013; Kumar A, Food Chem Toxicol, 2010; Rajadurai M, Phytother Res, 2009; Chtourou Y, Neurochem Res, 2015; Oluwafeyisetan A, Curr HIV Res, 2016; Kampa RP, Exp Dermatol, 2019; Yu LM, Food Funct, 2019; Kapoor R, Toxicol Rep, 2014)

Nobiletin

- Nobiletin is a flavone found principally in citrus fruit.
- In aged skeletal muscle, nobiletin activates genes for mitochondrial ETC Complexes and enhances OXPHOS activity, particularly Complex II activation and supercomplex formation, increasing ATP production and reducing ROS levels.
- In hypothyroid neurons, nobiletin increased ATP production and normalised activity of TCA cycle enzymes.
- In glutamate toxicity and calcium overload, nobiletin induced a partial decrease in mitochondrial membrane potential in neurons to allow potassium influx to reduce calcium overload and excess ROS production.
- Nobiletin can also decrease neuronal mitochondrial oxygen consumption in the presence of glutamate and malate but increases it in the presence of succinate. It can also increase ADP production and decrease excess ROS production.
- In hepatic ischaemia and reperfusion, nobiletin decreased the expression of autophagic proteins and increased mitochondrial dynamics and biogenesis, upregulating SIRT1 and PGC-1α.

(Nohara K, Nat Commun, 2019; Jojua N, Nutr Neurosci, 2015; Dusabimana T, Exp Mol Med, 2019; Lee JH, Korean J Physiol Pharmacol, 2018; Sharikadze N, Nat Prod Commun, 2016)

Quercetin

- Quercetin, a polyphenol and member of the flavonoid family, is one of the most prominent dietary antioxidants, found in many plant foods.
- Quercetin reduced the harmful effects of endoplasmic reticulum stress by reducing mitochondrial ROS production and increasing mitochondrial membrane potential and biogenesis.
- In the endothelium, quercetin alleviated mitochondrial fragmentation suppressed mitochondrial fission.
- In hepatocytes exposed to a mitochondrial toxin or glucose-induced stress, quercetin reduced mitochondrial ROS production and lipid peroxidation and upregulated antioxidants, dose-dependently recovering Complex I activity, increasing OXPHOS and reducing proton leak. In NSAID-damaged endothelium, quercetin protected against Complex I inhibition.
- Similar antioxidant results were seen in cardiomyocytes, together with inhibition of mitochondrial caspases, mtPTP opening and apoptosis. In skeletal muscle, quercetin increased mRNA expression of PGC-1α and SIRT1, mtDNA and cytochrome c concentration and suppressed ROS production. In ischaemia/reperfusion, quercetin protected mitochondrial function.
- Quercetin protected against neuronal oxidative toxicity and mitochondrial dysfunction.
- However, other studies have shown that quercetin induces impaired mitochondrial function and opening of the mtPTP.
- Dosage in clinical trials varied from 100mg-1,000mg/day. Quercetin supplements suffer from poor bioavailability and are best taken with fats/oils, in liposomal form or in alcohol-based tinctures.

(Boots AW, Eur J Pharmacol, 2008; Nisha VM, Appl Biochem Biotechnol, 2014; Chen C, Acta Biochim Biophys Sin, 2019; Mahdavinia M, Iran J Basic Med Sci, 2019; Chen X, Toxicol Mech Methods, 2019; Houghton MJ, Free Radic Biol Med, 2018; Davis JM, Am J Physiol Regul Integr Comp Physiol, 2009; Ruiz ML, Oxid Med Cell Longev, 2015; Godoy JA, Mol Neurobiol, 2017; Sandoval-Acuña C, Chem Biol Interact, 2012; Mukai R, J Nutr Biochem, 2016; Ortega R, J Bioenerg Biomembr, 2009; Brookes PS, Free Radic Biol Med, 2002)

Resveratrol and Pterostilbene

- Resveratrol (3,4',5-trihydroxystilbene) is a flavonoid, best known as a component of red wine but also found in grapes, berries and peanuts. It can cross the blood-brain barrier, benefitting neuronal mitochondria. Pterostilbene (methylated resveratrol) has a similar chemical structure and function and works synergistically with resveratrol, but resveratrol itself has poor bioavailability, with 75% being excreted in urine, whereas pterostilbene is much better absorbed and has greater metabolic stability. Both can mimic caloric restriction.
- Resveratrol is a potent stimulator of mitochondrial biogenesis through activation AMPK and upregulation of PGC1α, SIRT1, Nrfs and TFAM and citrate synthase activity. It can improve muscle mitochondrial respiration, increase mitochondrial size, density, mtDNA content and mitochondrial enzyme activity and oxidative capacity. It is also an antioxidant and can trigger or inhibit apoptosis, depending upon dosage; higher dosage trigger apoptosis inn cancer cells. In plants it functions as a biotoxin to deter predators, so it is thought that its effect in the body can act via hormesis. Pterostilbene also restores SIRT1 levels.
- Some studies have shown adverse effects of resveratrol on mitochondrial function.
- Generally, doses range from 100-500mg/day. Resveratrol may interact with and increase the effectiveness of medications such as blood thinners and NSAIDs; in particular, it inhibits aggregation of platelets in high-risk patients who are resistant to aspirin.

(Bayeva M, JACC, 2013; De Paepe B, Nutrients, 2017; De Oliveira MR, Biochim Biophys Acta, 2016; Jardim FR, Mol Neurobiol, 2018; Allard JS, Mol Cell Endocrinol, 2009; Guo Y, Eur J Pharmacol, 2016; Yang J, J Biol Chem, 2009; Timmers S, Cell Metab, 2011; Lagouge M, Cell, 2006; Milne JC, Nature, 2007; Hou X, J Biol Chem, 2008; Dasgupta B, PNAS, 2007; Dai H, Pharmacol Ther, 2018)

Rutin

- Rutin (aka rutoside, quercetin-3-O-rutinoside and sophorin) is the glycoside combining the flavonol quercetin and the disaccharide rutinose. It is a citrus flavonoid found in a wide variety of plants.
- In endothelial cells, rutin protected against ROS-induced apoptosis by attenuating excessive ROS production and preventing mtDNA fragmentation, mitochondrial membrane potential dissipation and antioxidant depletion. In nephrotoxicity, rutin decreased ROS production and upregulated mtSOD, restored mitochondrial membrane potential and reduced caspase activation.
- In injured neurons or neurotoxicity, rutin restored normal levels of mitochondrial membrane potential, mtSOD and other antioxidants, lipid peroxides, coupling, pro-apoptotic proteins and cytochrome c release, which resulted in downregulated caspases and reduced apoptosis. It also reduced the unfolded protein response and the opening of the mtPTP.
- In skeletal muscle with mitochondrial dysfunction, rutin increased mitochondrial size, mtDNA content and mitochondrial biogenesis by upregulating gene expression of PGC-1α, NRF1, TFAM, AMPK and SIRT1.
- In cardiomyocytes, rutin showed mild uncoupling ability, which was thought to be protective. In cardiotoxicity, rutin lowered mitochondrial lipid levels and lipid peroxidation and upregulated mitochondrial antioxidants, expression of ETC Complex proteins and hence ATP production.
- Up to 4 g/day orally was well-tolerated and effective in clinical studies, with no side effects.

(Gong G, Eur J Pharmacol, 2010; Zhai X, Neuroimmunomodulation, 2016; Seo S, Nutrients, 2015; Elmazoglu Z, Interdiscip Toxicol, 2017; Mostafa DG, Neurol Res, 2019; Trumbeckaite S, Biomed Pharmacother, 2006; Punithavathi VR, Cardiovasc Toxicol, 2010; Suganya SN, Metab Brain Dis, 2017; Qu S, Phytother Res, 2019)

Isoflavones

- Isoflavones are phytoestrogens, whose chemical structure is similar to oestrogen. They are found in a number of plants and herbs, with the highest amounts in soy and kudzu.
- Phytoestrogens are able to pass through cell membranes due to their low molecular weight and stable structure and they are able to interact with the enzymes and cell receptors.
- Isoflavones with mitochondrial action include:
  - Genistein
  - Daidzein
  - Puerarin, a glucoside of daidzein.

Genistein

- In obese hepatocytes, genistein increased UCP2 expression, mitochondrial antioxidants and TCA cycle enzymes.
- In damaged or ischaemic neurons, genistein restored the mitochondrial membrane potential and decreased opening of the mtPTP, ROS production and mtDNA deletion. It could also increase mitochondrial antioxidants, improve the balance of anti- versus pro-apoptotic proteins and decrease release of cytochrome c and caspase 3 activation.
- In cardiomyoblasts with oxidative damage, genistein improved the mitochondrial membrane potential, oxygen consumption and antioxidant status, reducing ROS production.
- In damaged endothelial cells, a combination of genistein and daidzein inhibited apoptosis and upregulated mitochondrial proteins expression.
- In injured nephrons, genistein increased mitochondrial biogenesis through upregulation of PGC-1α and SIRT1.

(Lee YM, Nutrition, 2006; Yu HL, Zhonghua Yu Fang Yi Xue Za Zhi, Zhonghua Yu Fang Yi Xue Za Zhi 2010; Huang YH, Br J Nutr, 2010; Xi YD, J Bioenerg Biomembr, 2011; Wang Y, Neural Regen Res, 2016; Farruggio S, Int J Mol Med, 2019; Qian Y, Neurochem Int, 2012; Ma WW, Neurochem Res, 2013; Fuchs D, J Proteome Res, 2007; Rasbach KA, J Pharmacol Exp Ther, 2008)

Daidzein

- In ischaemic neurons, daidzein reduced mitochondrial swelling, elevated the mitochondrial membrane potential, increased mtSOD and glutathione peroxidase activities and decreased mitochondrial lipid peroxides.
- In skeletal muscle cells with dysfunctional mitochondria, daidzein increased synthesis of mitochondrial ETC Complex proteins, SIRT1 activation and TFAM expression, which promoted mitochondrial biogenesis through increased PGC-1α and Nrf1 and increased mitochondrial content.
- In damaged endothelial cells, a combination of genistein and daidzein inhibited apoptosis and upregulated mitochondrial proteins expression.
- In injured nephrons, daidzein increased mitochondrial biogenesis through upregulation of PGC-1α and SIRT1.

(Yuan W, Neural Regen Res, 2017; Yoshino M, J Nutr Biochem, 2015; Fuchs D, J Proteome Res, 2007; Rasbach KA, J Pharmacol Exp Ther, 2008)

Puerarin

- Puerarin has shown difficulty in reaching the mitochondria of cardiomyocytes due to the lack of mitochondrial targeting. When formulated as mitochondria-targeted micelles, it protected against apoptosis in ischaemic cardiomyocytes by lowering ROS production, the ratio of pro- to anti-apoptotic proteins and caspase 3. Puerarin, without the micelle formulation, could inhibit hypoxic cardiomypocyte calcium-induced mitochondrial swelling and opening of the mtPTP.
- In cardiomyocytes, arterial smooth muscle cells or skeletal muscle exposed to H_2O_2 stress or hypoxia, puerarin reduced mitochondrial membrane depolarisation, inhibited mtPTP opening and upregulated the mitochondrial calcium-activated potassium channel. It also increased Complex I activity, increased ATP production, decreased ROS production, upregulated mitochondrial biogenesis and promoted mitophagy and fatty acid oxidation.
- When exposed to mitochondrial toxins, puerarin protected against loss of mitochondrial membrane potential, lipid peroxidation, opening of the mtPTP, cytochrome c release and caspase activation, restored ATP production and increased the ratio of anti- to pro-apoptotic proteins in nephrons and osteoblasts.
- In neurons, puerarin protected against toxin-induced cell injury through reduction of ROS, increase in the ratio of anti- to pro-apoptotic proteins, preservation of the mitochondrial membrane potential and preventing cytochrome c release and upregulation of caspases.

(Li WQ, Int J Nanomedicine, 2019; Gao Q, Conf Proc IEEE Eng Med Biol Soc, 2005; Yang B, Zhongguo Ying Yong Sheng Li Xue Za Zhi, 2008; Yao H, Zhongguo Ying Yong Sheng Li Xue Za Zhi, 2010; Song XB, Chem Biol Interact, 2016; Wang ZK, Biol Trace Elem Res, 2016; Zhu X, J Biochem Mol Toxicol, 2016; Yu D, Int J Mol Med, 2015; Chen X, Life Sci, 2018; Chen XF, Nutr Diabetes, 2018; Chen C, PLoS One, 2012; Bo J, Neurosci Res, 2005)