Botanicals and Nutrients to Support Cellular Homeostasis and Mitochondrial Function

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Discussion

Healthy cellular metabolism and homeostasis are essential for well-being throughout all stages of life. The cellular energy system produces energy through energy transfer via catabolic and anabolic functions. Dysfunctional cellular metabolism, diminished mitochondrial capacity, and conditions of oxidative stress influence the development and progression of many conditions including cardiovascular, metabolic, and neurodegenerative. These factors are also hallmarks of biological aging.[1-4]

Numerous studies demonstrate the primary role of inflammatory and oxidative processes at the cellular level in age-related, metabolic, cardiovascular, and neurodegenerative disease.[2,5-7] Excess generation of ROS (reactive oxygen species) and other free radicals at the cellular level causes lipid oxidation and reduces cell membrane fluidity. This causes loss of enzyme and receptor activity, damages proteins in the cellular membrane, and can cause cell inactivation.[1,2] As the natural antioxidant capacity of the aging cell decreases, cellular repair mechanisms become impaired and cellular damage becomes more predominant.[5]

Cross linking and glycation of connective tissue proteins, such as collagen, results in the formation of AGE (advanced glycation end products), which accumulate with aging and cause physiological damage. AGEs are more prevalent in the elderly and in those with diabetes, arteriosclerotic disease, Alzheimer's, and other diseases. They are correlated with neurodegenerative disease, inflammatory conditions, and progression of chronic disease.[8]

POLYPHENOLS: STILBENES

Diets high in plant polyphenols are correlated with increased health and decreased incidence of chronic degenerative disease.[2,3] Studies find an inverse relationship between fruit and vegetable consumption and incidence of cardiovascular disease, stroke, and mortality.[5,9] This is attributed to the flavonoids, stilbenes, isoflavonoids, and lignans in plants. These structurally similar compounds are all derived from the phenylpropanoid pathway.[9]

Polyphenolic compounds act as antioxidants working through multiple pathways. They exert a powerful influence on normalizing cell-signaling and supporting healthy cellular function. They exert anti-inflammatory and immunomodulatory activity.[1,2] Polyphenols are found to be cardio-protective, neuroprotective, and cyto-protective.[10,11]

Stilbenes, a sub-group of polyphenols, exert a wide array of influence on human biological and cellular processes.[9] Plants high in stilbenes include wine grapes, berries (including bilberries and blueberries), cocoa, and many herbs.[5] Research indicates that plant stilbene compounds offer protective benefits as they are found to activate cellular defense mechanisms, alleviate oxidative stress, and calm inflammation.[5] Flavonoids and stilbenes are found to inhibit progression of AGE through multiple pathways and are noted for their ability to reduce inflammation and oxidative stress at the cellular level.[8]

Stilbenes are found to be cardio-protective in human and animal studies.[8] They are noted to exert anti-obesity influence through several mechanisms, thus offering potential benefit in many metabolic disorders. They inhibit lipid synthesis in adipocytes, modulate lipolysis, and activate AMPK (adenosine monophosphate-activated protein kinase).[8] AMPK plays a major role in maintaining energy homeostasis, especially in response to metabolic stress. It plays a key role in regulating glucose and lipid homeostasis.[5,12] Because of its role in cellular homeostasis, researchers are interested in utilizing AMPK pathways therapeutically to address metabolic disorders and chronic diseases including cancer.[12]

Stilbenes work through multiple pathways to influence cellular physiology and pathophysiology. They are found to influence cellular cAMP (cyclic AMP) signaling, which plays a role in cellular response to hormones and neurotransmitters.

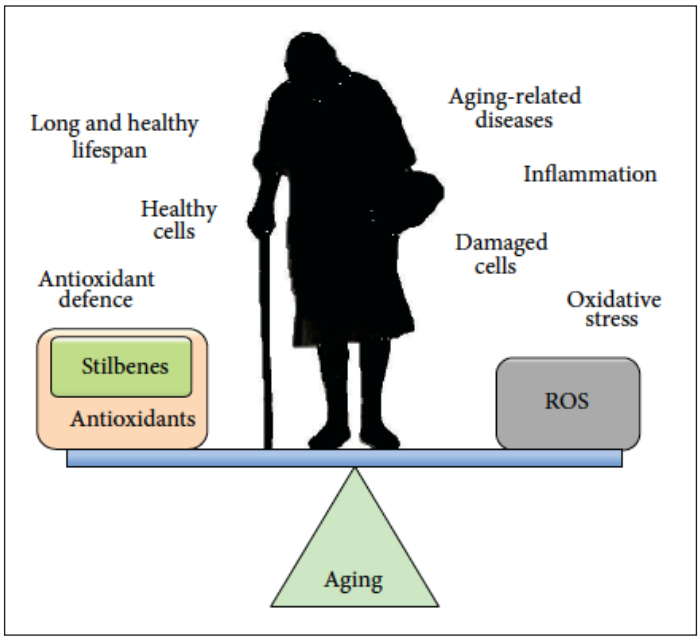

Image Source: *See reference #5*

Stilbenes influence pathways involved with NO (nitrogen oxide) synthesis through their influence on NOS (nitric oxide synthase) enzymes. They are noted for their ability to promote production of endogenous antioxidants.[5,13]

Two stilbenes of note are resveratrol and pterostilbene.[9] The stilbene resveratrol is shown to possess powerful anti-cancer, anti-inflammatory, and antioxidant activity.[9] Resveratrol in high doses can activate AMPK through inhibition of ATP production.[5] Pterostilbene is found in some berries, in grapes, and in the heartwood of Pterocarpus. It demonstrates significant antioxidant activity comparable to that of resveratrol. It is found to prevent lipid peroxidation and to be anti-diabetic.[9]

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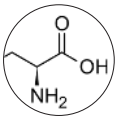


Selenium (as Selenomethionine)

Selenium, an essential trace mineral, is found in Brazil nuts, whole grains, fish, and sunflower seeds as selenomethionine. Selenomethionine is a selenium analog of methionine that exerts antioxidant and anti-inflammatory influence. Selenium comprises a key component of selenoproteins such as glutathione peroxidase. As such, it exerts antioxidant properties and helps prevent formation of free radicals. Glutathione peroxidase helps maintain cell membrane integrity through its ability to reduce reactive oxygen metabolites thereby decreasing oxidative damage to lipids, lipoproteins, and DNA.[14-18] Selenium inhibits lipid peroxidation and is found to decrease the binding of various chemical compounds to DNA. Over 25 selenoproteins are known to exist in human biochemistry throughout the body. As a cofactor in various metabolic pathways, selenium can act to modulate cell signal transduction.[14-18]

Polygonum (*Polygonum cuspidatum*)

Polygonum has been used widely for centuries in Chinese medicine to prevent and treat disease. In modern research it is found to exert antimicrobial, anti-inflammatory, neuroprotective, and cardio-protective functions.[19,20]

Resveratrol is extensively researched for its multiple profound health benefits.[21-23] Numerous studies report its role in preventing age-related conditions including diabetes, cardiovascular, cancer, and neurodegenerative, which share a common foundation of inflammatory processes with cellular dysregulation.[21,22] Research finds that resveratrol binds to numerous cell-signaling molecules, activates transcription factors, induces antioxidant enzymes, modulates cell-cycle regulation, and inhibits expression of inflammatory processes.[24]

A potent antioxidant, resveratrol works through multiple cellular pathways to support normal function.[25] Due to its inherent properties as a polyphenolic compound, resveratrol is neuroprotective and can help inhibit progression of age-related neurological decline and disease.[25] Resveratrol is found to block tumor initiation, promotion, and progression. One mechanism is through its ability to downregulate the inflammatory response. It inhibits the synthesis and release of pro-inflammatory mediators, and modifies eicosanoid synthesis. It inhibits iNOS (inducible nitric oxide synthase) and COX-2 (cylooxygnase-2) through its ability to inhibit NF-kB or other pathways.[23] Well-recognized for its cardiovascular benefits, resveratrol is found to support endothelial health, inhibit low-density lipoprotein oxidation, and suppress platelet aggregation.[26-28]

Hawthorn (*Crataegus monogyna*)

The fruit, leaves, flowers, and bark of the hardy Hawthorn shrub have been used as food and medicine for millennia.[29] Hawthorn is revered as a medicinal herb for cardiovascular health in many cultures.[29,30] The Europeans used Hawthorn to strengthen heart health and function and the American Eclectic physicians esteemed it above other herbal remedies for cardiac conditions.[31]

The cardioprotective activity of Hawthorn is attributed primarily to the flavonoid and OPC (oligomeric proanthocyanadin) content, which is especially concentrated in its leaves and flowers.[29,32-34] Hawthorne contains an abundance of flavonoids including catechins, triterpene saponins, and OPCs. OPCs are known as powerful free radical scavengers. With such an abundance of flavonoids, including OPCs, Hawthorn exerts potent antioxidant activity.[29,32,33,35] Hawthorn has the ability to scavenge ROS (reactive oxygen species), up-regulate antioxidant enzymes, including SOD (super oxide dismutase), and to enhance GSH (reducing glutathione) concentration.[29]

Hawthorn is found to support blood vessel integrity and to enhance coronary blood flow and oxygen utilization. In studies, Hawthorn's flavonoids reveal diversified action, exerting multiple influences on the heart that suggest a modulatory influence. In studies with human subjects, Hawthorn is found to significantly improve cardiac function.[32] The cardio-protective ability of Hawthorn is primarily attributed to its free-radical scavenging ability. Another flavonoid extracted from Hawthorn is found to have potent anti-ischemic activity.[32] Studies report that Hawthorn exerts a beneficial influence on blood lipid profiles.[32]

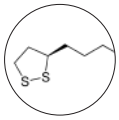
Quercetin, a major polyphenolic flavonoid in Hawthorn, exerts wide influence including antioxidant, anti-inflammatory, and vaso-relaxant. Hawthorn extract is shown to affect both VSMCs (vascular smooth muscle cells) and endothelial cells, and to increase NOS activity and NO release.[29]

Pterocarpus marsupium

Pterocarpus marsupium (PM) is native to areas of the Indian continent and Sri Lanka. Ayurvedic medicine utilizes all parts of the tree for medicinal properties. The heartwood is known as an astringent, traditionally used for treatment of inflammation and diabetes.[36,37] PM demonstrates anti-hyperglycemic activity. It is found to possess potent insulinotropic and insulin-like properties.[38]

The phenolic compound pterostilbene is a naturally-occurring analogue of resveratrol and occurs in many plants including the Vitis, Vaccinium, and Pterocarpus families.[39,40] Ayurvedic medicine utilizes a special preparation of Pterocarpus as a cardio tonic.[40,41] Pterostilbene is found to benefit dyslipidemia and enhance cardiovascular health.[40] It is also found to exert antioxidant, anti-inflammatory, antidiabetic, and anti-proliferative activity.[39,42]

R-Alpha Lipoic Acid



Alpha lipoic acid (ALA), also called thiotic acid, is well-known for its wide-spectrum of antioxidant activity; able to quench free radicals in both aqueous and lipid domains. It demonstrates the ability to recycle other antioxidants including glutathione, coenzyme Q10, vitamins C and E, and even itself. ALA is well-known as a redox-coupling agent that works with glutathione in a cyto-protective role. ALA has the ability to raise levels of intracellular glutathione. It functions as a coenzyme essential for ATP production and contributes to cellular health. For these and other reasons, ALA is often called a universal antioxidant. ALA is the primary water-soluble antioxidant and acts as a major detoxification agent.[43,44]

R-ALA is the biologically active form of ALA. The R-ALA isomer is produced within the body where it is bound to protein. R-ALA is an essential cofactor for mitochondrial enzyme complexes involved with catabolic processes.[45]

Quercetin Dihydrate (from *Sophora japonica*)

Quercetin is a flavonol abundantly found in many foods including onions, curly kale, leeks, apples, and *Camellia sinensis*.[46-48] Quercetin benefits those suffering from allergies primarily due to its anti-histamine activity.[49] It is anti-inflammatory, antioxidant, and exerts free-radical scavenging activities.[50,51] Quercetin benefits cellular health. Widely researched for its ability to inhibit abnormal cell growth, it is reported to be anti-angiogenic and able to induce normal apoptosis.[52-54]

Like many polyphenolic compounds, quercetin is found to be neuroprotective.[49,50] It inhibits free-radical damage and lipid peroxidation.[51] Quercetin modulates inflammatory pathways including the COX and LOX.[55-58] Studies find it down-regulates NFkB and EGF (epidermal growth factor) expression, and improves cell-signaling.[58-61]

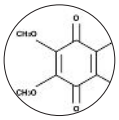
Grape Pomace (*Vitis vinifera*)

Grape skin and seed extracts are widely known and highly studied because of their phenolic compounds, which demonstrate numerous health benefits. Grape pomace is found to contain numerous polyphenolic compounds, particularly catechin, epicatechin, tannins, and OPCs.[62] Grape pomace also contains many stilbenes, including resveratrol.[5] Phenolic compounds from

Grape seeds are shown to benefit endothelial health and function.[63] They activate responses in the endothelium that cause endothelium-dependent relaxation (EDR) of blood vessels, which supports healthy blood pressure and healthy blood circulation.[62,64]

Grape seed contains an abundance of flavonoids including catechins, epicatechin, anthocyanadins, proanthocyanidins, and OPCs (oligomer proanthocyanidins).[65] OPCs are widely known for their antioxidant activity and are noted for their anti-inflammatory, antibacterial, anti-allergic, and vasodilatory actions.[66] OPCs are found to inhibit lipid peroxidation and platelet aggregation. They support healthy capillary permeability and strength.[66,67]

Coenzyme Q10



CoQ10 (CQ) is a fat-soluble compound essential for cellular health and energy metabolism. It is widely known for its role in mitochondrial bioenergetics and potent antioxidant capacity.[68,69] The ubiquinone family is so-named because these compounds are ubiquitous in living organisms.[68] CQ is synthesized endogenously and is found in foods.

CQ is essential for ATP synthesis in the mitochondria. As a component of lipoproteins, it is found in almost all cellular membranes where it functions as a powerful antioxidant. CQ exerts potent antioxidative capacity and is found to inhibit lipid peroxidation and to be cardio-protective.[68-72]

Tissue levels of CQ are found to decline with age. Levels of ubiquinone or ubiquinol are altered in many conditions including neurodegenerative, cardiovascular, and metabolic conditions.[69] CQ influences expression of genes involved with cell-signaling, cellular metabolism, and cell transport.[70] The reduced form known as ubiquinol is found to be more bioavailable.[73]

Ginkgo (*Ginkgo biloba*)

With a history of medicinal use dating back to 2800 BC, Ginkgo was traditionally used to relieve cough and asthma. Modern research focuses on Ginkgo's unique ability to increase cerebral blood and oxygen flow and to protect and enhance brain health. Studies report that Ginkgo extract is a powerful antioxidant with anti-inflammatory and neuroprotective qualities.[74-76] Ginkgo is found to protect brain cells during a stroke and to reduce brain damage after stroke.[77] Ginkgo extract suppresses amyloid-B toxicity which contributes to neuronal degeneration.[78] A study with mice found Ginkgo helps reduce copper-induced neurotoxicity in Parkinson's by reducing overall copper content.[79]

Ginkgo is high in flavonols, which exert complex activity including antioxidant influence. It is especially high in the flavonol quercetin.[80] Ginkgo is found beneficial for the cardiovascular system as it calms vascular inflammation and helps reduce atherogenesis.[81,82]

Black Pepper (*Piper nigrum*)

Black Pepper is widely known for its ability to enhance the bioavailability of herbs and nutrients. In Chinese and Ayurvedic medicine it is added to formulas for its ability to help circulate other compounds throughout the body. The pungent piperine gives pepper its pungent quality.[83]

Piperine is a powerful and highly-researched compound. It is found to enhance bioavailability of herbs and nutrients. One way that piperine is thought to enhance bioavailability is through influencing the cellular biomembrane and intestinal enzymes.[84-86]

Piperine is known to be antioxidative, antimutagenic, antibacterial, and hepatoprotective.[85,87] Piperine also exerts anti-inflammatory, immunomodulatory, and antioxidant activity.[83,88-90] Piperine is found to reduce levels of pro-inflammatory mediators including COX-2, IL factors, and TNF-alpha. It supports healthy glutathione and SOD (super oxide dismutase) levels.[91,92] It is found to inhibit VEGF and to modulate cytokine and growth factor responses.[93]

Ginger (*Zingiber officinale*)

This world-renowned and well-loved herb has been used as cooking spice, herbal remedy, and revered medicine for centuries. Ginger acts as a gentle diffusive stimulant on circulation along with a mild relaxing effect. Herbalists also use Ginger to enhance the digestion of other herbs in a formula.[94]

Ginger demonstrates anti-inflammatory activity[95,96] It influences prostaglandin metabolism, is a potent inhibitor of thromboxane synthesis, and is found to significantly inhibit platelet aggregation and inflammation.[97] It is also found to inhibit expression of COX-2 and activation of NF-kB.[95,96]

Gingerols are the compounds that contribute the pungent quality to ginger. These bioactive compounds influence multiple activities. They demonstrate antioxidant, antimicrobial, anti-inflammatory, and antitumor activity.[98]

For more information on any of the ingredients listed here, including extensive research or individual monographs compiled by Donnie Yance, please email info@naturaedu.com.

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