



DaVinci®

*Laboratories
of Vermont*

Innovative by nature

PHYTO BENEFITS™

BALANCE IS KEY

Oxidative Stress and Patient Health



IDENTIFYING THE PROBLEM: MITOCHONDRIAL DAMAGE

The Reactive Oxygen Species aspects of the Free Radical Theory of Aging (FRTA), first put forth in 1972, propose that ROS cause aging through effecting cellular damage throughout the body.

ROS are created through the production of energy in the mitochondria, as they take in nutrients and convert them. The mitochondria and their DNA, therefore, are highly susceptible to free radical damage. These organelles do have a protective response, but are limited in their ability to stave off onslaughts of oxidative damage that contribute to cellular aging and changes in cellular states.

Though researchers cite other, cumulative causes of aging, one thing is certainly clear: "Increasing age in mammals correlates with increased levels of mitochondrial DNA (mtDNA) mutations."¹

HOW PRODUCTION OF FREE RADICALS AFFECTS HEALTH

The Free Radical Theory of Aging is supported by evidence of increased ROS production by mitochondria in aged tissues and by evidence of increased oxidative damage in aged cells. The theory is not just about "age," though; it includes the idea that "enhanced and unopposed metabolism-driven oxidative stress has a major role in diverse chronic age-related diseases."²

How? Free radicals may stimulate certain pathways related to the cellular state of senescence and to cell death. They may also be involved in genetic expression, creating a cascade that "is more active during aging and has been linked with age-associated pathologies," like chronic diseases.³

In optimal conditions, cells keep oxidative stress at bay by producing free radical scavenging enzymes. This is part of our organismal antioxidant defense system, which includes enzymes like glutathione peroxidase and reductase, superoxide dismutase (SOD), catalase (CAT) "and low-molecular antioxidants such as glutathione and plasma proteins."⁴

In aging, increased free radical production and decreased cellular antioxidant production can create the buildup of damaged proteins and other molecules that may affect cellular states--the imbalance known as oxidative stress.⁵

Specific to the metabolic health, detoxification and immune health, oxidative stress during aging can have far-reaching effects. Key aspects to focus on in order to support a healthy aging process, then, will include mitochondrial and exogenous production of free radicals.

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PRODUCTION OF ROS IN THE MITOCHONDRIA

The interplay between Reactive Oxygen Species and mitochondria is complex. Developing an understanding of it begins with understanding the process of ATP reformation.

In aerobic organisms, mitochondria act as a home for energy production or reformation of ATP, which occurs through the metabolic pathway of oxidative phosphorylation. In eukaryotes, this pathway occurs in the inner mitochondrial membrane and involves an electron transport chain of five protein complexes. Oxidation-reduction reactions, or redox reactions, occur through the protein acceptors in the chain, which are progressively more likely to cause reduction the further along the chain they are. The last acceptor in the chain is molecular oxygen.

Generally, the oxygen is reduced to produce water. But in some electrons that move through the chain the reduction is incomplete, causing the creation of one of several free radicals, such as the superoxide radical (O_2^-) and hydrogen peroxide (H_2O_2), which is produced as O_2^- leaks from the mitochondria.

The respiratory chain is not the only model for generating free radicals, as various other catabolic and anabolic processes can do the same. In fact, several enzymes inside the cells can also produce ROS. The family of NADPH oxidases (NOX) is known to be a valuable source of production.⁶

It's important to understand that damage to the mitochondrial inner membrane touches off a cycle, a loop for the increased production of free radicals. Because ROS generate mtDNA mutations, causing a defective respiratory chain (RC), and a defective RC will generate more ROS, damage continues to develop in a vicious cycle.

EXOGENOUS PRODUCTION

Aside from their emergence as a product of cellular metabolism, ROS may result as a response to varied environmental stimuli, such as UV rays, chemical oxidants, toxins, transition metals and inflammatory cytokines.⁷

It is crucial to remember that ROS, when produced in normal amounts, can and do act as mediators for other necessary functions and processes in the body. It is when excess amounts are produced--and not dealt with by the body's antioxidant defense system—that the negative health effects come to light.

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METABOLIC HEALTH AND OXIDATIVE STRESS

In studies where treatment to reduce ROS production was used, scientists have observed a reversal of metabolic changes.⁸ Further, researchers have established that ROS have a causal role in several forms of metabolic dysfunction, including those that involve insulin.^{9,10}

There appear to be, then, “mechanistic links between oxidative stress generated by adipose tissue in the context of obesity and its impact on metabolic complications development.”¹¹

When adipocytes are exposed to given stressors, including inflammatory cytokines and oxidative damage (both a cause and result of inflammation), cellular responses mediated by cellular kinases are induced. Some of these kinases impair insulin action through stimulating Insulin Receptor Substrate (IRS) serine phosphorylation.¹² Excessive serine phosphorylation of IRS proteins could impair insulin signaling, causing resistance.¹³ It is important to note that balancing these same kinases can support healthy physiologic levels of gene expression.¹⁴

DETOXIFICATION AND OXIDATIVE STRESS

Not only is the quality of the detoxification process affected by enhanced oxidative stress, but a buildup of ROS, and therefore, oxidative stress, can occur as a result of the process. Thus, detoxification and oxidative stress are inextricably linked.

Phase I of liver detoxification is otherwise called oxidation, activation or modification. All are true. The liver excretes the group of substances known as cytochrome P-450, low-specificity enzymes that convert toxic molecules to more water-soluble forms through incorporation of an oxygen atom (with an NADH cofactor) into the non-active hydrocarbons. Biotransformation, as this process is called, allows toxin excretion, either through the kidneys or the colon. Nutrients required for healthy Phase I reactions include B vitamins, folic acid, glutathione, carotenoids and vitamins C and E.

Perhaps contrary to the overall mission of the body’s normal detoxification process, the oxidation that occurs in Phase I produces a high quantity of free radicals. Sometimes, this process is even the cause of the toxin in question’s harmful nature.¹⁵ Phase II is a necessary follow-up designed to deal with this onslaught of oxidative stress.

Phase II of liver detoxification involves the conjugation pathways. Conjugation refers to addition, wherein the liver adds one of its powerful, charged antioxidants to the now activated xenobiotic metabolites to effectively neutralize the free radical. Phase III has often been called the elimination phase, wherein xenobiotics are actually excreted.¹⁶

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IMMUNE HEALTH AND OXIDATIVE STRESS

When we discuss ROS and the immune system, it is important to recognize both the functional role of ROS and the potential deleterious effects of their accumulation and subsequent cell damage.

As a functional component: The immune system's natural protective actions are themselves a source of ROS, as activated neutrophils produce free radicals. During the same physiologic process, phagocyte activation results in NADPH oxidase assembly. As previously mentioned, enzymes in the NOX family of NADPH oxidases have an ability to generate ROS. Specifically, NADPH oxidase catalyzes O₂-production.¹⁷

The immune system uses the superoxide produced in this process to kill bacterial invaders.¹⁸

As a stressor: A very recently published study revealed that the immune response that effectively uses ROS to kill pathogens becomes impaired through oxidative stress, as the cellular damage affects T cells, which can die off as they divide, thereby never amassing the numbers necessary to attack the pathogen.¹⁹

Remember, ROS themselves are not the representatives of increased oxidative stress. But their accumulation can be. Therefore, balance is the crucial idea behind addressing excessive free radical production and keeping oxidative stress in check.

FINDING THE RIGHT SUPPORT

We have seen that oxidative stress can affect immune system function and metabolic health, and that the detoxification process and ROS are inextricably linked. We've learned that our natural antioxidant defense/balance system includes certain, valuable enzymatic reactions. We've recognized that, ultimately, systemic oxidative stress is a result of a generation/elimination imbalance. If free radicals are in an imbalance with antioxidants, the results are the negative health effects previously discussed within this paper. That means balance is a primary goal when considering system health, and that the introduction of free radical scavengers may support a healthy oxidative balance.*

The plant compounds known interchangeably as phytonutrients or phytochemicals serve various functions for plant vitality. Legumes, herbs, spices and nuts are sources of phytonutrients; fruits and vegetables are concentrated sources. When we consume these phytonutrient-rich plants, we offer our bodies natural free radical scavenging support.

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The value of a supplement regimen that incorporates nutrients from phytochemicals in order to support normal oxidative balance cannot be overstated.*

Phyto Benefits™ provides evidence-based extracts from the most powerful botanicals in natural medicine.* This compilation formulation covers the concerns associated with supporting healthy levels of oxidative stress, detoxification capabilities, metabolic processes and immune health.*

HOW PLANT COMPOUNDS IN PHYTO BENEFITS™ SUPPORT HEALTHY OXIDATIVE BALANCE*

Broccoli is one nutrient-rich plant food; a branded, researched version of its sprout extract, **sulforaphane**, makes Phyto Benefits™ a unique supplement choice. Found also in other cruciferous vegetables, sulforaphane acts by supporting normal induction of Nrf2-dependent enzymes like CYP2A6, a member of the cytochrome P450 oxidase system and the enzyme responsible for nicotine metabolism.*^{20,21} The action of sulforaphane as a supplement involves its ability to support healthy modulation of the CYP enzymes.*

Green tea has long been hailed as a free radical scavenger and energy supporter.* Its major catechin, EGCG, has gained increasing notoriety in natural medicine for its particular free radical scavenging activities.* We also know that it supports normal tyrosine phosphorylation, which can in turn support healthy expression of iNOS and thereby normal rates of production of NO, a free radical.*²²

Curcuminoids are principal components of turmeric, a popular spice and home remedy to support liver health and serious free radical neutralization.* In antioxidant supportive actions, curcumin has been compared to vitamins C and E, with indications that it even more effectively supports the body's ability to neutralize free radicals than do these popular choices.*²³ Curcuminoids merge with free radicals to prevent further oxidation, and support normal inhibition of enzymes that participate in the synthesis of substances like prostaglandins and leukotrienes.* Further, curcumin supports bile production, thereby supporting the elimination process.*

In Phyto Benefits™, the unique, branded Meriva® Phytosome gives new value to curcumin, as the phytosome delivery is proven to enhance bioavailability.²⁴

Phyto Benefits™ also includes P40p™, a pomegranate fruit extract standardized to 40% punicosides. Punicosides are hydrolizable ellagitanins and the key active compounds in pomegranate. Punicosides is actually a generic group name for punicalins, punicalagins (a+b), ellagic acid glycoside and ellagic acid.²⁵

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Ellagitannins in pomegranate interact with gut microflora, supporting normal production of short chain fatty acids.* Short chain fatty acids support the activation of peroxisome proliferator-activated receptors (PPARs), the receptors for prostaglandins.²⁶ Moreover, ellagic acid, the hydrolysis product of ellagitannins, supports normal activation of multiple pathways, including the notable NF-kB pathway.²⁷ Punicosides, then, are an important addition to a formula designed to support healthy oxidative balance, as NF-kB plays a role in affecting expression of the antioxidant defense system enzymes, including SOD1 and SOD2, as well as glutathione peroxidase-1 and Glutathione S-transferase pi (GST-pi).²⁸

Aside from the flavonoids contained in pomegranate extracts, Phyto Benefits™ also features the flavonoid called quercetin, most popularly known for its support of healthy histamine function.* Quercetin is a member of the flavone class of flavonoids and is found in onions, apples, broccoli and berries.

As a flavonoid, quercetin supports free radical scavenging through the high reactivity of its hydroxyl group.* Further, quercetin supports normal levels of xanthine oxidase activity.²⁹ The xanthine oxidase pathway appears to play a part in oxidative tissue injury. The enzyme itself is a source of free radical production, as it reacts with oxygen to create and release superoxide.³⁰ By supporting healthy levels of its activity, quercetin supports overall oxidative balance.*

One branded ingredient in Phyto Benefits™, Lyc-O-Mato® Tomato Extract, has been standardized to 5% Lycopene, but also contains other carotenoids, including beta-carotene, phytoene and phytofluene, mixed tocopherols and phytosterols. Importantly, the extraction process for this patented ingredient is designed to preserve the benefits of the fruit and allow for enhanced bioavailability. The nutrients are partially dissolved and suspended in a natural tomato oil base, supporting lycopene absorption.*

Lycopene supports the normal induction of phase II metabolizing enzymes.* It also supports normal expression of the connexin 43 gene, which allows intercellular gap junctional communication.*³¹ Healthy GJC or GJC restoration is associated with decreased proliferation in many human tumor cells.

Finally, Phyto Benefits™ includes Polyognum cuspidatum Root Extract, standardized to 50% trans-resveratrol. Trans-resveratrol works at the genetic level. Its principal mode of action is the support for normal inhibition of certain phosphodiesterases (PDEs), enzymes that help regulate cell energy.* Specifically, researchers identified that one PDE, PDE4, is the “predominant PDE activity in skeletal muscle, the tissue where the metabolic effects of resveratrol are best elucidated.”³²

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Through support for normal inhibition of PDE4, resveratrol offers support for indirect activation of the enzyme Sirtuin 1, which deacylates the PGC-1 alpha (a peroxisome proliferator), thereby reducing the gene expression of specific molecular mediators.* The effect of Sirtuin 1 activation is healthy mitochondrial aerobic capacity and oxidative dephosphorylation, both of which are crucial to maintaining oxidative balance.³³

THE RIGHT SUPPORT FOR OXIDATIVE BALANCE: IN YOUR PRACTICE

Ultimately, systemic oxidative stress is a result of a generation/elimination imbalance. If free radicals are in an imbalance with antioxidants, the results are the negative health effects previously discussed within this paper. That means balance is a primary goal when considering system health, and that the introduction of free radical scavengers may support a healthy oxidative balance.*

Phyto Benefits™ provides a complement of branded and extensively researched botanical extracts to support multiple facets of health, through addressing free radical production and elimination processes.* Through its support of oxidative balance, this unique member of DaVinci's new Benefits Line also supports patients' detoxification capabilities, metabolic processes and immune health.*

Nature knows how to keep our bodies balanced – but we often aren't sure ourselves. Teach your patients about the power of botanical support for their health with Phyto Benefits™.*

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SUPPLEMENT FACTS

Serving Size 1 Capsule
Servings Per Container 60

Amount Per Serving	% Daily Value	
BroccoPhane™ Broccoli Sprout Extract (standardized to 400 ppm Sulfurophane)	100 mg	*
Green Tea (Camellia sinensis L.) Leaf Extract (Standardized to 70% EGCG)	100 mg	*
Meriva® Curcumin Phytosome® (Curcuma longa root extract/ Phosphatidylcholine complex)	100 mg	*
P40p™ Pomegranate (Punica granatum) Fruit Extract (Standardized to 40% Punicosides)	100 mg	*
Quercetin Dihydrate	100 mg	*
Lyc-O-Mato® Tomato Extract (Standardized to 5% Lycopene)	50 mg	*
Polygonum cuspidatum Root Extract (Standardized to 50% trans-resveratrol)	50 mg	*
*Daily Value not established.		

Other ingredients: hypromellose (capsule), microcrystalline cellulose, vegetarian leucine.



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