AGING, BIOMORPHOSIS, LIFE SPAN AND PHYTONUTRIENTS

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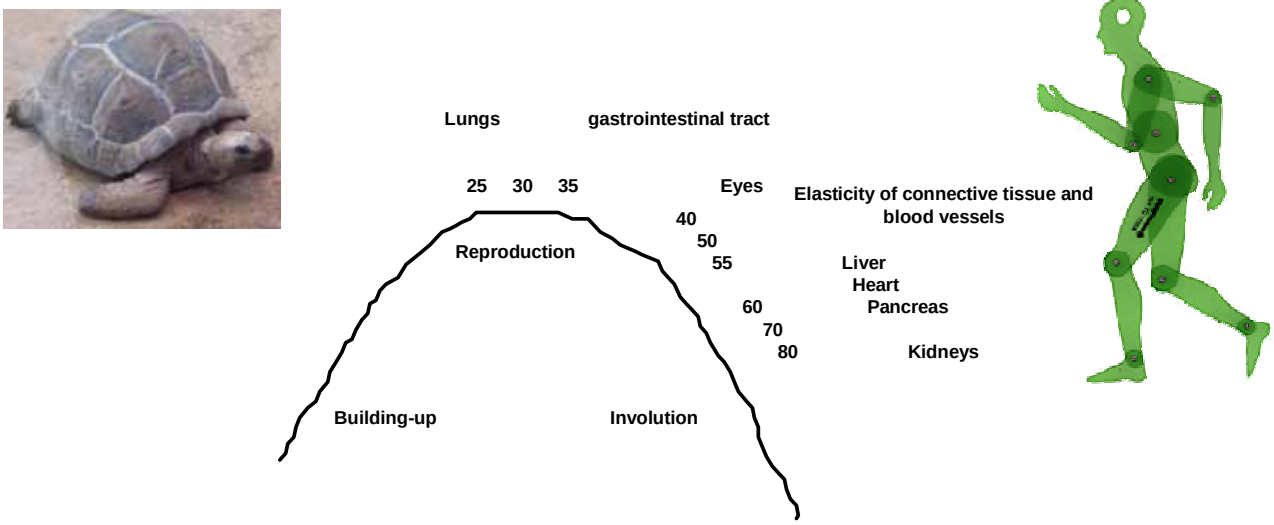
THE PROCESS OF AGING: A MACRO VIEW

Aging in mammals is characterized by senescence, a decline in physiological functions resulting from cumulative damage to tissues that overwhelms the body's natural ability to repair them. Eventually, essential organs and systems begin to degenerate, resulting in chronic diseases and break down of normal body functions.

Is Aging a Disease-like State to be Treated or Is It Biomorphosis?

Biomorphosis - The process of aging is the change of form and performance during the course of life



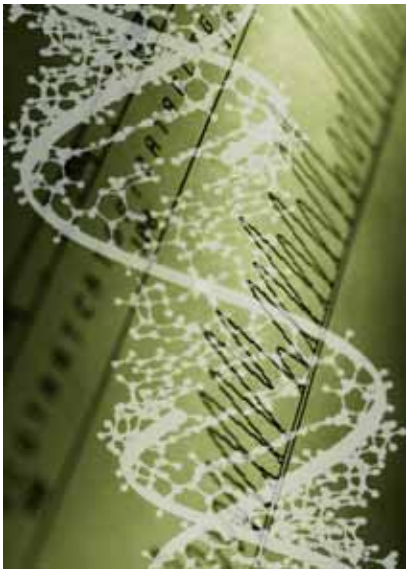
Age - related decline in various organ performance in the course of the life cycle i.e. building-up, reproduction, involution

A large disparity in life span exists in living organisms, ranging from 3 hours in the mayfly to an average of 188 years in the Galápagos tortoise. The human life span is somewhere in between, and the longest living human lived for 122 years.

Current trends in the health and wellness marketplace are focused towards the needs of a rapidly increasing population of aging baby boomers who seek lifestyle, nutritional and cosmetic interventions to slow down or mask the aging process, and to potentially extend life span. Recent scientific evidence validates the supportive role of dietary interventions in healthy aging and longevity. Phytonutrients

with adaptogenic benefits, probiotics, and micronutrients that supplement dietary sources; improve resistance to oxidative stress, enhance the quality of life during aging, and potentially contribute to increased lifespan.

AGING AT THE MOLECULAR LEVEL



The molecular biology of aging has been much in focus in recent years, and the process of senescence has been identified and described at the cellular level. Genetic, lifestyle, environmental and other factors influence the molecular biology of aging.

Oxidative stress resulting from free radical pathology is implicated in the aging process. Vital components of the cell such as the mitochondria (the energy centers), functional proteins, lipids and DNA are damaged by free radicals. Cross linking and glycation of connective tissue proteins, such as collagen, results in the formation of advanced glycation end products (AGE) which accumulate with age, and induce stiffening of cartilage and extracellular matrix, resulting in cataracts in the eyes and arthritis in the joints.

In the cardiovascular system aging is associated with a decrease in elasticity and an increase in stiffness of the arteries. Glucose tolerance progressively declines with age, and there is a high prevalence of type 2 diabetes in the aging population. Kidney functions, liver functions and sensory perception also deteriorate with age. Malabsorption of vital nutrients in the elderly, results in a compromised immune system and lowered resistance to infection. Hormonal imbalances associated with menopause and aging, affect bone turnover, muscle mass, strength and mental capabilities. In males, aging is often associated with impaired prostate functions.

Recent research findings lend credence to the fact that metabolism, gene expression, and aging intersect at the molecular level. The indices of aging have been linked to the morphology of cellular DNA. A telomere is a region of highly repetitive DNA at the end of a linear chromosome that functions as a disposable buffer which is gradually depleted during the continued cell replication. Many aging-related diseases are linked to shortened telomeres.

A major breakthrough in the anti-aging research commenced with the identification of a few genetic pathways that are regulatory master keys in the aging process, a major one being the Silent information regulator 2 (Sir2) pathway. Sir2 family of proteins (sirtuins) are NAD-dependent protein deacetylase or ADP-ribosyltransferase that have been shown to regulate aging and longevity in a number of model organisms including yeast and round worms, in response to nutritional and hormonal cues. An analogous gene, SIRT1 was located in humans. Sirtuins play in the modification of nuclear receptors and the corresponding age-associated metabolic diseases. Nuclear receptors sense a variety of environmental triggers, including dietary components and steroid hormones, and influence metabolic functions and the aging process.

BIOMARKERS OF AGING AND NUTRITIONAL INTERVENTIONS TO SUPPORT HEALTHY AGING

Biomarkers or physiological indices of aging include lean body mass, bone density, strength, BMR (basal metabolic rate), body fat percentage, aerobic capacity, blood pressure, insulin sensitivity, cholesterol/HDL ratio, memory / cognitive functions, immune functions and body temperature regulation.

There is an increasing amount of scientific evidence to support the beneficial "anti-aging" effects of several phytonutrients at the molecular level. For example, plant flavanoids inhibit the age-related atherosclerotic deposits in animals by influencing vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemotactic protin-1 (MCP-1) gene expression (Lee, CH et al; 2001). The micronutrient mineral selenium, long known to offer protection against several forms of cancer, was shown to exert its anti-senescence influence in animal models, at the genetic level. *In vitro* experiments revealed that selenium supplementation significantly increased cellular telomerase activity and hTERT (human telomerase reverse transcriptase) gene expression and augmented telomere length. (Liu, Q et al.; 2003). SeleniumSelect®[1] (L-selenomethionine), SelenoForce™ (selenium enriched garlic), and MethySelene®) are bioavailable sources of organic selenium.

A decline in insulin sensitivity is often observed during aging. Obesity is also known to lower insulin sensitivity (Escriva, F et al.; 2007). Dietary and lifestyle measures that contribute to maintaining a healthy body weight have anti-aging benefits as well. Nutritional interventions designed to provide

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ammunition against oxidative stress and positively influence the physiological indices of aging, are key components of a healthy aging regimen.

CALORIE RESTRICTION AND LIFE SPAN

Calorie restriction (CR) by 30-40% of the daily intake extends lifespan in a wide spectrum of organisms and is the only regimen known to lengthen the lifespan of mammals (Lin, SJ et al.; 2002) Studies in rhesus monkeys revealed that CR decreases body weight and fat mass, improves glucoregulatory function, decreases blood pressure and blood lipids, and decreases body temperature. These effects may be responsible for the effects of CR in delaying the onset of age-related disease and maintaining function later into life (Mattison, J.A. et al.; 2003). Calorie restriction was found to enhance the expression of key metabolic enzymes associated with protein renewal during aging (Spindler, SR 2001). In Emory mice, dietary calorie restriction had beneficial effects on lifespan, eye lens cataract prevalence and progression, plasma glucose levels and liver glutathione levels (Taylor, A. et al.; 1995). Other studies suggest that CR may alter gene expression for gluconeogenic, glycolytic, and nitrogen-metabolizing enzymes. CR may decrease enzymatic capacity for glycolysis and increase the enzymatic capacity for hepatic gluconeogenesis and the disposal of byproducts of muscle protein catabolism. (Dhahbi JM et al.; 1999).

Calorie restriction is reported to reduce the accumulation of advanced glycation end products (AGE) in animal models (Lingelbach, LB et al.; 2000) Age-related increase in oxidative DNA damage to aortic cells in mice is reported to be reduced by food restriction (Guo, Z.M. et al.; 2001). Prevention of excessive glycoxidation is suggested to control tissue alterations occurring in aging (Meli, M. et al.; 2003) . Carbohydrate energy restriction is reported to prevent oxidative damage to brain cells sparked by exhaustive exercise (de Oliveira SL et al.; 2003). The neuroprotective effect of dietary restriction and the administration of 2-deoxyglucose, a non-metabolizable analog of glucose in a cerebral ischemia model suggests that outcome following stroke may be improved in individuals who follow a regimen of reduced food intake (Yu ZF, et al.; 1999)

The 'carnivore connection' is postulated to play a critical role in the role of the glycemic index of dietary carbohydrate in the evolution of insulin resistance and hyperinsulinaemia. Historically, humans consumed diets rich in protein and complex carbohydrates with low glycemic index, wherein insulin resistance offered advantages to survival and reproduction. The industrial revolution changed the

quality of dietary carbohydrate through milling of cereals. This made starch more digestible and postprandial glycemic and insulin responses increased 2-3 fold compared with coarsely ground flour or whole grains. Hyperinsulinemia is a physiological response to maintaining glucose homeostasis in the face of such high glycemic diets, and combined with insulin resistance is a common feature in most modern age diseases.(Colagiuri S, et al.; 2002).

ANTIOXIDANT PHYTONUTRIENTS AND LONGEVITY

Reduced food intake may not be practical while tackling contemporary work and lifestyle demands. Therefore alternative approaches that mimic the effects of calorie restriction present an attractive option in the quest for longevity. Polyphenolic phytonutrients offer multifunctional benefits in this context.

Curcuminoids : Antioxidant Phytonutrients from Turmeric Roots

The chemopreventive roles of dietary antioxidant phytonutrients against various forms of cancer are well researched. These include curcumin, resveratrol, ellagic acid, green tea catechins, quercetin and others. Many of these compounds are reported to provide health benefits through their molecular roles in the hepatic cytochrome P450 monooxygenase system of enzymes responsible for a major portion of drug metabolism in humans.

At the fundamental level, phytonutrients such as quercetin and curcumin have been shown to up regulate antioxidant gene expression in animal models (Shahed, AR et al; 2001). Interestingly, curcumin is reported to inhibit the expression of inflammatory enzymes, as well. Cyclooxygenase (COX-2) gene expression is reported to be characteristic of colon cancer and several high grade tumors. A non-toxic concentration of curcumin was found to significantly inhibit the expression of the COX-2 gene, suggesting its beneficial role against colon cancer (Goel, A et al; 2001).

A number of research institutions including The National Cancer Institute (NCI) in the United States, are currently in the advanced stages of evaluating Curcumin as a potential therapeutic intervention in

several degenerative disease conditions associated with aging. Several of these studies use Curcumin C^3 Complex®[2], a branded natural extract prepared from turmeric roots containing curcumin, demethoxycurcumin and bisdemethoxycurcumin, collectively known as curcuminoids. Patented for its unique composition ratio and use, research shows that C^3 Complex is a 'bioprotectant" that effectively inhibits free radical formation and propagation (Majeed, M et al.; US Patent 5,861,415).

A sample list of such research activities is provided below:

Research activities

- ✓ Colorectal Cancer
- ✓ Immunological Mechanism in Alzheimer's Disease
- ✓ Treatment of Alcoholic Hepatitis
- ✓ Free Radical Trapping Properties of Curcuminoids
- ✓ Anti-inflammatory and Anti-Cancer Potentials
- ✓ Use of Curcuminoids in Cystic Fibrosis
- ✓ Pharmacokinetics in Normal Healthy Volunteers
- ✓ Curcuminoids in Pancreatic Cancer

The research institutions involved include UCLA School of Medicine, University Hospitals of Cleveland, MD Anderson Cancer Center, Rutgers University, Tufts University School of Medicine, Massachusetts General Hospital, Brown University, Penn State University, and others in the United States and worldwide.

The multifunctional health benefits of the curcuminoids are well researched and these antioxidant compounds are potentially useful in preventing inflammation and several types of cancer (Shishodia, S et al.; 2005). A common spice used in South Asian cooking, turmeric and more appropriately the curcuminoids have been preclinically and/or clinically validated for beneficial effects in a number of disease conditions ranging from Alzheimer's disease to cystic fibrosis.

The antioxidant effects of curcuminoids combined with their known inhibitory effects on cyclooxygenase 2 (COX-2) render them useful as ingredients in anti-aging formulations, and in topical formulations designed to maintain general skin health and integrity. Oxidative stress and inflammation are major players in the aging process. The anti-inflammatory role of curcuminoids is well

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established. Curcuminoids have been shown to inhibit nuclear factor kappaB (NFκB) a transcription factor that triggers inflammatory mediators. NFκB has been implicated in a variety of chronic disease conditions ranging from cardiovascular diseases to cancer (Kumar, A et al.; 2004).

A recent study postulates that curcumin can potentially slow down aging process (Salvioli, S et al.; 2007) and is therefore potentially delays senescence and the onset or progression of many age-related diseases.

- ***Tetrahydrocurcuminoids Significantly Increases Life Span***

An innovative patented colorless curcuminoids derivative is C[3] Reduct™[3] (Tetrahydrocurcuminoids), an effective bioprotectant composition, that also protects the skin and lightens skin tone. A predominant molecular mechanism of action is the inhibition of cross-linking of proteins, which in turn supports healthy aging (Majeed, M et al; US Patent No. 6,653,327). Nutritional and topical benefits include photoprotection, skin lightening effects and a boost in skin luminosity. Recent research revealed that the Tetrahydrocurcuminoids are more potent antioxidants than the parent curcuminoids attributed to specific structural characteristics present in Tetrahydrocurcuminoids. (Portes, E et al.; 2007). Tetrahydrocurcuminoids are major metabolites of curcuminoids *in vivo*, as determined in experimental studies (Hoehle, SI et al; 2006). The composition contains Tetrahydrocurcumin, Tetrahydrodemethoxycurcumin and Tetrahydrobisdemethoxycurcumin.

A research group in Japan explored the potential role of green tea polyphenols and tetrahydrocurcumin in increasing the life spans of animal models. Their studies revealed that the **increase in life expectancy beyond 24 months under the conditions of the experiment was 125.9% in tetrahydrocurcumin treated mice**, and 72.6% in polyphenols treated animal models, as compared to untreated controls (Kitani, K et al.; 2004).

In a follow-up study, (Kitani, K et al.; 2007) the effect of feeding of the two natural antioxidants, tetrahydrocurcumin (THC) and green tea polyphenols (PPs) on the survival of male C57BL/6 mice was examined. Mice that started to receive diets containing THC (0.2%) at the age of 13 months had significantly longer average life spans than control mice (11.7% increase, $p < 0.01$). The 10% longest

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survival was also significantly greater in THC-treated mice (6.5% increase, $p < 0.01$). In contrast, mice that started to receive THC in their 19th month of life, showed no significant difference from the control mice in either the average life span, or the 10% longest survival.

In mice that received water containing PPs (80 mg/l), the average life span was also significantly longer than in the control mice (plus 6.4%, $P < 0.05$), although the 10% longest survival was not significantly different from that in the control mice ($P > 0.05$). The body weights of the THC (but not PP) fed mice, were slightly (2-4%) but significantly ($p < 0.05$) lower than the values for the corresponding ages in the control mice in the first six months of treatment.

- ***Resveratrol and Life Span***

Other polyphenols such as quercetin found in apples and tea, and resveratrol (found in grapes and red wine) were found to increase SIRT1 activity in a laboratory screening. Interestingly, resveratrol was found to increase SIRT1 activity 13-fold (Hall, SS; 2003). Health benefits of resveratrol include protection against atherosclerosis, antioxidant/ antiglycation activity, modulation of hepatic apolipoprotein and lipid synthesis, as well as inhibition of platelet aggregation, and the production of proatherogenic eicosanoids by human platelets and neutrophils. These findings partly validate the hypothesis that red wine consumption in southern France may have a bearing on the low incidences of coronary heart disease in that population, despite a high intake of saturated fats; a phenomenon which is commonly known as the "French Paradox." (Renaud, S, 2002; Stipp, D; 2007).

An interesting study performed on short-lived seasonal fish (average lifespan of only thirteen weeks) revealed that if the fish received resveratrol in the early stages of life, their average and maximum lifespan increased significantly in a dose dependent manner (Valenzano, DR et al.; 2006).

An animal model study with three groups of mice, one group fed a high calorie diet, a second group with received a normal diet, and the third group was given resveratrol along with a high calorie diet. The results showed that when the high calorie fed mice reached old age (114 weeks), greater than 50% had died compared to less than 33% of the high calorie fed mice receiving resveratrol (Baur, JA et al.;

2006). Results also showed that mice receiving resveratrol had lower plasma levels of insulin, glucose and insulin-like growth factor (IGF) 1, all of which are markers for the onset of diabetes in humans if elevated. After the mice died, researchers examined their hearts and found that inflammation and deterioration were considerably lower in the resveratrol supplemented group and normal diet group, as compared to the high calorie fed mice not receiving resveratrol.

Resvenox™[4] is a resveratrol composition containing >98% trans-resveratrol and blends well with dietary supplement, functional food and cosmetic formulations.

Alpha-lipoic Acid and Healthy Aging

Another biological antioxidant, alpha-lipoic acid (thioctic acid) found in living cells and available as a dietary supplement, is also reported to potentially increase life span. Roundworms receiving the compound showed significant increase in their mean and maximal lifespan (Brown, MK et al.; 2006). These results corroborate observations from preclinical and clinical studies that use of lipoic acid later in life helps in improving the quality of life by preventive free radical damage to proteins (Sethumadhavan, S et al; 2006).

CONCLUSIONS

This article provides a few examples of phytonutrient interventions that are potentially helpful in prolonging life span. This selection represents only a small fraction of the plethora of natural ingredients and dietary interventions that support healthy aging and longevity. For additional information on these materials, please contact Sabinsa Corporation.

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