

## The Fruits of Ripe Old Age: Potential Role for Polyphenols in the Modulation of Disorders of Energy Regulation in Aging

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The process of aging is accompanied by many disorders of energy regulation. Frailty, an important pathologic syndrome in the elderly, has multiple causes, but it is characterized by sarcopenia (loss of muscle mass), or alternatively dynapenia (loss of muscle strength). [1] There is a related and concomitant increase in fat mass, sometimes referred to as sarcopenic-obesity. [2] Dementia, another significant problem also has many etiologies but the most common cause, Alzheimer's while also pathophysiologically complex is characterized at a cellular level by mitochondrial dysfunction [3]. Atherosclerosis, an important process and the cause of many diseases prevalent in older age can be the result of an excess of energy intake leading to the storage of excess energy in adipocytes that ultimately cause inflammatory changes resulting in vascular occlusion [4].

A class of molecules known as polyphenols that are found in diet in numerous plant sources modulates the adipocyte lifecycle. Polyphenols, through multiple mechanisms, inhibit adipocyte maturation, lipid storage, differentiation, proliferation and promote apoptosis.

Human trials of polyphenols are now occurring. The best studied polyphenol, resveratrol is being tested as a treatment for metabolic syndrome, cancer, and cognitive dysfunction.

Resveratrol is probably the best-studied polyphenol. The polyphenol retards lipid accretion in adipocytes, *in vitro*[5]. It reduces levels of genes promoting the maturation of adipocytes, FAS, SREBP-1c, C/EBP- $\alpha$ , LPL, HSL, and PPAR- $\gamma$ . [6] Resveratrol also acts on the mitochondrial gene SIRT3, which promotes the expression of two mitochondrial proteins: uncoupling protein 1 and Mitofusin 2. [6]

Human studies have suggested resveratrol improves systemic glucose and insulin regulation. Ten elderly overweight persons with an abnormal glucose tolerance took 1-2g/d resveratrol for 4 week. Their insulin sensitivity increased, and they had lower postprandial blood glucose levels [7]. Resveratrol ingestion also lowers serum levels of proinflammatory cytokines in man. Ten individuals took a mixture of 100mg resveratrol and 75mg of other grape polyphenols with a meal rich in fat and carbohydrates. [8] Peripheral blood monocytes and polymorphonuclear cells from these subjects had lower levels of 1L-1 $\beta$ , thioredoxin, Nrf-2, SOD-2, toll-like receptor 4, CD40, and NDq-1. Another ten participants ingested a 40mg resveratrol supplement a day for a month and a half. [9] Monocytes from the subjects also had reduced inflammatory cytokine levels. In a third investigation, another eleven subjects, all overweight had reduced adipocyte levels and lower blood pressure when they consumed 150 mg daily for 4 weeks [10]. Another dietary polyphenol which might have an important impact on energy regulation in aging is quercetin, which is found in numerous vegetables and fruits. In one study, one hundred seventy-two persons ingested 150mg a day quercetin, for four weeks, had a lower blood pressure and cholesterol. [11] A trial is currently ongoing at the National Institute of Health to determine if quercetin can improve oral glucose tolerance in obese diabetics [12]. Epigallocatechin-3-gallate (EGCG), a polyphenol found in green tea, has been tested on overweight men. Forty-eight men ages 40-65 took 400mg of EGCG or a placebo for two

months. [13] Participants who took EGCG had a small but statistically significant reduction in blood pressure.

Research on the applications of polyphenols to treat energy regulatory disorders of aging is only in its early stages. There are many barriers that need to be overcome before polyphenols are practically applied. Polyphenols are rapidly metabolized in the small intestine, and their bioavailability is quite limited, although their metabolites might also be active. [14] In addition, it may be necessary to provide supplementation for long periods of time, perhaps years before clinical manifestations of the disorder become apparent, to successfully treat disease. Polyphenols are found in nature not as isolated substances, but in complex mixtures that are fruits and vegetables. It is not clear if they would be best supplemented as isolated substances, plant extracts, or whole plant forms.

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