

The Anti-Aging Efficacy of Natural Compounds

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Based on increased life expectancy, it is estimated that there will be over 1.2 billion older adults (over 60 years old) worldwide in 2025 [1]. Older adults are more susceptible to different clinical conditions, such as tumors, neurodegenerative diseases and cardiovascular diseases. This is at least partially attributed to an age related increase in frailty and immunosenescence, and perhaps mitochondrial dysfunction [1-4]. Maintenance of physical function in older adults is therefore a major public and clinical priority. In this regard the application of small natural compounds is a promising avenue of therapeutical intervention.

It has been estimated that more than 50% of all the drugs in the world are natural products and their derivatives, and plant-based health remedies are promising [5-7]. In these years, a number of small natural compounds have been discovered exhibiting possible anti-aging potential as exemplified by the elongation of lifespan in both invertebrate and vertebrate-based experimental models, and the amelioration of a wide spectrum of aging-related metabolic phenotypes. For example, the traditional Asian vegetable bitter melon (*Momordica charantia*) has been thoroughly examined and a large number of medicinal components have been isolated and characterized. Bitter melon contains different potential medicinal proteins (lectins, ribosome inactivating proteins; ribonucleases, protease inhibitors) and small organic compounds (triterpenes, flavonoids, eleostearic acids). Many of them have shown antitumor, anti-diabetic activities as well as the ability to attenuate oxidative stress and neuroinflammation [5,8]. Aging has been linked to all these pathologies and bitter melon is therefore a promising candidate to ameliorate these symptoms.

Another famous and challenging example is resveratrol which is a polyphenol found in red wine. Resveratrol has been reported to extend the lifespan of many evolutionarily distant species, such as yeast (*Saccharomyces cerevisiae*), worm (*Caenorhabditis elegans*), fruit flies (*Drosophila melanogaster*), and a vertebrate fish (*Nothobranchius furzeri*) [9]. Resveratrol seems to mimic the effects of caloric restriction to confer anti-aging and anti-diabetogenic activities with the molecular mechanisms being unveiled these years. Using mice, Baur et al. found that resveratrol increased lifespan of mice on a high fat diet, presumably through increased insulin sensitivity, increased mitochondrial number, and increased AMPK and PGC-1 α activity [9]. The mechanism has recently been made clearer showing that resveratrol activates the CamKK β -AMPK pathway by elevating cAMP due to inhibition of cAMP phosphodiesterases [10]. The beneficial effect of resveratrol has, however, encountered some controversy since this compound has no effect on lifespan in normal ad-lib fed mice [11]. Indeed, GlaxoSmithKline recently terminated a study investigating the antineoplastic effect of this drug due to observed kidney failure in the treated cohort (www.clinicaltrials.gov). It therefore seems we are still a long way from reaching a conclusion regarding resveratrol. With multiple clinical trials under way and new articles published daily we will certainly soon get a more complete picture.

Other interesting examples, include rapamycin (also named sirolimus), which is a product of the bacterium *Streptomyces hygroscopicus* in a soil sample from Easter Island (Rapa Nui) [12]. Rapamycin is thought to extend lifespan in yeast, nematodes, fruit flies, and mice by exhibiting anti-neoplastic and anti-cellular stress

activities. In 2009, Harrison et al. uncovered that rapamycin could pharmacologically extend lifespan in both genders of mice by the regulation of mTOR (the mammalian Target of Rapamycin), a conserved Ser/Thr kinase that regulates cell growth and metabolism in response to environmental cues [13,14]. Although the exact mechanism leading to lifespan extension is unknown increased autophagy may be responsible [15]. Supporting this, a recent study showed that rapamycin may be a potentially viable therapeutic choice for the disease Cockayne syndrome (CS) by upregulation of mitophagy [16]. The premature aging disorder CS is a devastating autosomal recessive disease characterized by neurodegeneration, cachexia, and accelerated aging. CS cells are defective in transcription coupled repair of UV-induced damage and repair of oxidative damage [17]. It was recently observed that CS cells exhibit increased free radical production and an accumulation of damaged mitochondria caused by decreased mitophagy [16]. Treatment with the autophagic stimulator rapamycin ameliorated the bioenergetic phenotype of CS cells through up-regulation of mitophagy.

Because the anti-aging potential of bitter melon, resveratrol and rapamycin could be through the improvement of mitochondrial function this organelle may be a key player for the treatment and prevention of age-related disease. The development of high throughput assays to evaluate mitochondrial pharmacological augmentation will undoubtedly prove key in uncovering new natural anti-aging compounds.

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