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Sarcopenia, aging and prospective interventional strategies

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Abstract

Sarcopenia, or age-related muscle decline, occurs in most organisms and burdens both human health and the healthcare system. As our population ages, additional options for treating sarcopenia are needed. Mitochondrial dysfunction is implicated in the onset of sarcopenia, so therapies directed at improving mitochondrial function in muscle should be considered. Many naturally-occurring compounds, derived from commonly consumed foods, possess anti-sarcopenic effects, such asnicotinamide riboside, tomatidine, and Urolithin A. These naturally-occurring compounds can improve mitochondrial health and efficiency by modulating mitochondrial biogenesis, cellular stress resistance, or mitophagy. Further research should assess whether compounds that improve mitochondrial health can attenuate sarcopenia in humans.

Keywords

Sarcopenia; aging; mitochondria; mitophagy; phytochemical; Nicotinamide adenine dinucleotide

1. INTRODUCTION

Aging is associated with a host of disorders that increase morbidity and mortality. With an increasing population of older individuals worldwide[1, 2], it is important to assess common health issues that impact their quality of life. Sarcopenia is age associated loss of skeletal muscle strength and function[3], though this definition is still under consideration[4]. Many age-associated disorders that diminish quality of life affect highly energetic cell types, such is the case with sarcopenia and skeletal muscle. Mitochondria are critical to these energetic cell types, and a mitochondrial perspective of sarcopenia may prove fruitful towards understanding the complex disease. High-energy skeletal muscle tissue relies upon

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mitochondria for proper energy production and contractile function, and mitochondria quantity has been known to decrease in older individuals[5].The association between sarcopenia and mitochondria may also berelevant for finding new, effective treatments. This review will assess the mitochondrial perspective of sarcopenia, and introduce some naturally-occurring compounds with the potential to attenuate the onset of sarcopenia.

From a clinical perspective, sarcopenia is highly problematic for patients, and no current treatment acts as a silver-bullet for it. Patients with sarcopenia have an increased risk of falling and have a general increase in mortality[6]. Sarcopenia is associated witha series of socio-economic problems, including increased hospital stay and high economic burden for both patients and their families[7, 8]. These negative outcomes show the need for additional research on treatments for patients with sarcopenia. Currently, exercise is considered the most effective intervention for sarcopenia[9, 10], yet elderly populations have issues meeting necessary physical activity guidelines[11], showing that additional interventions could assist in treatment. Therefore, supplements for treating sarcopeniaare currently being investigated. Research on these supplements involves various laboratory model organisms, as most organisms experience age-related decline of muscle function that is similar to humans.

Laboratory animal models compliment limited human population studies for research on sarcopenia, and allows for analysis of the underlying mechanisms of sarcopenia. A common, high-throughput model organism to study aging and sarcopenia is the nematode *C. elegans*. *C. elegans* is used extensively due to its relatively short lifespan, low cost of maintenance, availability of genetic manipulation, and conservation of major known age-related signaling pathways seen in humans[12, 13]. The pharynx of the *C. elegans* is of great relevance since behavioral, morphological, and molecular assays can be used on this tissue to assess sarcopenia[14, 15]. *C. elegans* sarcomeres can be assessed through the muscle specific p-*myo-3* driven mitochondrial GFP fluorescence. In wild-type *C. elegans*, body wall muscle cells mitochondria becomes increasingly fragmented as the organism age[16] (Figure 1), which attests to decreased mitochondrial function as *C. elegans* age. Many of the studies on potentially anti-sarcopenic naturally-occurring compounds use*C. elegans* as a model organism. Importantly, a list of genes involved in sarcopenia in *C. elegans* has been discovered, and many of these genes are developmentally conserved, including *sac1*, *as160*, *tbc1d1* and *daf-16*[17]. Studies in this organism is an important first step for transitioning potential treatments to human clinical trials.

2. A MITOCHONDRIA PERSPECTIVE OF SARCOPENIA

The etiologies of sarcopenia are not fully understood, but mitochondrial dysfunction has been strongly implicated in muscular health through metabolism, reactive oxygen species (ROS), or mitochondrial dysfunction and maintenance. Impaired metabolism in muscle cells is implicated in sarcopenia, and decreased catabolism or increasing anabolism may alleviate this by increasing bulk muscle mass[18,19, 20].These include ingesting an assortment of vitamins, amino acids, or creatine. The clinical supplements mentioned have broad effects on the human body[20], but mechanistic insight has been gained recently. For example, supplementation of the amino acid leucine is a necessity for amino acid-dependent attenuation of sarcopenia in elderly adults, but not necessary for attenuating muscle decline

in younger adults[19]. This suggests that sarcopenia is related to, but dissimilar from, normalmuscle decline.

Reactive oxygen species (ROS) play a complex role in etiology of sarcopenia[21, 22]. In aged organisms, increased ROS is associated with higher decline of muscle function due to inactivity[23]. Also, as organisms age, oxidative stress is increased, in parallel with decreased anti-oxidative activity. Yet it is unknown whether ROS is the causative agent or a byproduct of sarcopenia[24]. Counter evidence for ROS exacerbating sarcopenia have been offered. A highly potent anti-sarcopenia intervention is exercise, its known to increase ROS production[25].While supplementation with antioxidants in antioxidant-deficient aged mice improved muscle function and quality[26], the effectiveness of antioxidant supplementation in humans with normal physiological levels of antioxidants is inconclusive[27, 28].Accumulating mechanistic and intervention studies using multiple model organisms suggest a different perspective for ROS.ROS can be advantageous for cells, as it acts as a signaling molecule for regulating hypoxia, innate immunity, and mitophagy responses[29, 30]. ROS may act through a hormetic mechanism, in which physiological levels or moderate increases in ROS (like through exercise and fasting) are beneficial for health by activating essential cellular signaling pathways that protect against oxidative, metabolic and proteotoxic stress[29, 31, 32]. However, persistently disproportionate or supraphysiological levels of ROS induces lethal damage to DNA, proteins, and cells, prompting chronic diseases and aging[33–36]. Future studies should distinguish ROS quantity when assessing its effect on sarcopenia, as this may be the difference between benefit and detriment. The connection of ROS levels, anti-oxidative ability, and sarcopenia in human populations needs further elucidation.

Progression of sarcopenia has been linked with mitochondrial dysfunction, as well as changes in mitochondrial mass and morphology. There is an age-dependent reduction of mitochondrial mass, possibly due to dysfunction of major regulators of mitochondrial biogenesis including AMPK and PGC-1α[37, 38]. In addition to decreased mass, there is age-dependent change of mitochondrial morphology, indicating imbalance between mitochondrial fusion and fission[39]. Since mitochondria constantly undergo damage, partly through normal aging, maintenance of a healthy mitochondrial pool is extremely important and is regulated by a cellular self-clearance system, mitochondrial autophagy (termed mitophagy)[40, 41]. Mitophagy is tightly regulated by an inter-collected complex network with major known executors including PINK1, Parkin, NDP52,optineurin, and NIX/BNIP3L (DCT-1 in C. elegans)[40, 42, 43]. The importance of mitophagy in longevity and healthy aging, which includes maintenance of muscle performance, has been investigated in both mice and *C. elegans*[40, 43, 44]. For instance, specifically older mice with dysfunctional mitophagy have increased fatigue and decreased grip strength, which is an indicator of sarcopenia[45]. In *C. elegans*, there is age-dependent decline of mitophagy, which leads to mitochondrial dysfunction and increased susceptibility to external stressors[43].However, the relationship between mitophagy and muscle function in humans has not been assessed. Taken together, these findings suggest mitochondrial dysfunction plays a significant role in the etiology of sarcopenia in laboratory animal models.

3. PROSPECTIVE INTERVENTIONAL STRATEGIES FOR SARCOPENIA

Based on evidence that mitochondrial dysfunction contributes to sarcopenia, novel strategies for disease intervention have been proposed. These include using bioactive phytochemicals, their derivatives, metabolites, or other synthetic small compounds to target a series of mitochondrial pathways. Since sarcopenia is an age-related disorder, naturally-occurring compounds with strong anti-aging effects have been assessed for anti-sarcopenic properties. These compounds modulate mitochondrial health in various ways, including the NAD^+/SIRT1 pathway, mitochondrial stress pathways, or upregulating mitophagy.

3.1 Small compounds targeting the NAD^+/SIRT1 pathway

SIRT1 is a NAD^+-dependent deacetylase which participates in multiple cellular processes such as cell survival, circadian rhythm, DNA repair, metabolism, and mitochondrial homeostasis[46, 47]. SIRT1 plays an important role in longevity in yeast (homolog Sir2), *C. elegans* (Sir2.1), and mice (SIRT1), and has been implicated in the prevention of age-related diseases, including type 2 diabetes, cancer, Alzheimer's disease, and age-related muscle dysfunction[38, 40, 46–48]. Data from *C. elegans* and rodents suggest an age-dependent decrease of SIRT1 activity is due to NAD^+ depletion[49, 50], and thus reestablishing NAD^+/SIRT1 activity through NAD^+ precursor or SIRT1 allosteric activator supplementation is likely to have health benefits.

NAD^+ is a critical co-factor involved in multiple cellular processes including metabolism, DNA repair, mitochondrial turnover and antioxidantresponses. Increasing NAD+ levels extends lifespan in laboratory animals through mitochondrial maintenance[51–53]. In mice, impaired intramuscular NAD^+ synthesis decreases skeletal muscle mass and strength with age[54]. Exogenous NAD^+ sources, including nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), can be derived from milk and other related food products[55] (Figure 2).These exogenous NAD+ sources exhibit promising muscle protection activities. For example, 7-day NMN treatment (intraperitoneal injection, 500 mg NMN/kg body weight/day) on 22-month old wild type mice exhibited increased oxidative phosphorylation and ATP production in gastrocnemius muscle[56]. Improvement of muscle strength was not seen, probably due to the short-term treatment. Another NAD+ precursor, NR, also increased muscle function and lifespan extension in wild-type mice. Old C57BL/6J mice (22–24 months)fed regular chow diet supplemented with NR(400 mg/kg/day) had slight but statistically significant extension of lifespan, and improved muscle function[57]. Compared with controls, NR supplementation increased muscle ATP production, oxidative phosphorylation, and physical muscle performance (running distance and grip strength)[57]. Mechanistically, NR prevented muscle stem cell senescence in both wild-type mice and in the *Mdx* mouse model of muscular dystrophy through inducing the mitochondrial unfolded protein response (UPR^{mt}) and upregulation of prohibitin proteins involved in stress response[57].UPR^{mt} compensates for imbalances in mitochondrial proteostasis by facilitating expression of both mitochondrial DNA and nuclear DNA derived proteins[52].We recently showed that a 2-week NR supplementation (intraperitoneal injection, 500 mg NMN/kg body weight/day) significantly ameliorated mitochondrial dysfunction in two DNA-repair

deficiency disease mouse models (XPA and what)[49]. Collectively, these data demonstrate the potential anti-aging and anti-sarcopenia benefits of exogenous NAD^+.

In addition to NAD^+ supplementation, an alternative strategy to increase SIRT1 activity is using sirtuin-activating compounds (STACs). Currently, there are three generations of STACs, all of which act on a common allosteric mechanism to stimulate sirtuin activity[46]. Some first generation STACs are naturally-occurring compounds, with resveratrol being the best described. Resveratrol is a natural phenol found in grapes and berries[58, 59]. Studies from mice suggest that resveratrol can improve mitochondrial health through activation of the NAD^+/SIRT1-PGC-1α axis[38, 60]. Middle aged mice (approximatelyone year) treated with resveratrol (0.04% in chow, approximately 22 mg/kg/day) for 6 months had increased survival and muscle performance through rotarod analysis[38]. While a high fat diet induced higher levels of glycolytic muscle fibers (type IIb), resveratrol normalized fat-diet induced glycolytic muscle fibers to wild type levels, and increased oxidative fast twitch fibers (type IIa and IIx)[60]. Interestingly, administration of resveratrol (0.05% resveratrol in chow for 18 months) to middle-aged C57BL/6 mice for 10 months did not appear to eliminate sarcopenia, but increased anti-oxidative activity through enhanced mitochondrial SOD2 activity and preserved fast-twitch fiber contractile function[61]. Based on these studies, resveratrol can have a significant benefit on mice if administered at an early age, though this benefit may be compromised if administration begins later. Consistent with this hypothesis, the mechanical stretch of muscle can induce expression of SIRT1 and its downstream proteins (like SOD2) in an early growth factor 1 (EGR1)-dependent manner[62]. This activation is lost in aged animals due to loss of EGR1. Second generation synthetic STACs may bestow various health benefits as well, ranging from neuroprotection to improved muscle function and extension of lifespan[63, 64]. The second generation STAC SRT1720 (100 mg/kg body weight/day) was given to young male C57BL/6J mice for the entirety of their life. In addition to extension of mean lifespan (8.8%) by SRT1720 compared with control, SRT1720 also increased mitochondrial biogenesis and improved muscle performance (rotarod analysis)[63]. Another synthetic STAC, SRT2104, fed to male mice (200 mg/kg body weight/day) for four weeks prior to hind limb suspension had increased trabecular bone quality and attenuated muscle loss due to disuse[65].In summary, STACs are likely able to improve mitochondrial function, and may improve sarcopenia, though further investigation is needed.

3.2 Compounds that enhance cellular stress resistance

Regulation of cellular stress-related pathways may prevent age-related physiological decline. A major cellular stress response pathway is the nuclear erythroid 2-related factor 2/ antioxidant response element (Nrf2/ARE) pathway which participates in anti-oxidative response[66]. Activation of Nrf2 causes many downstream effects, including upregulating anti-oxidative stress[67, 68], anti-apoptotic pathways[69], anti-inflammatory proteins[70], and mitochondrial biogenesis[43, 71, 72]. Phytochemical plumbagin, derived from the *Plumbago* genus of flowering plants (Figure 2), directly activates Nrf2/ARE and increases neuronal resistance to damage by oxidative stress[73] and excitotoxicity[74]. Plumbagin and its synthetic derivatives, such as naphthazarin, were shown to increase maximal lifespan in *C. elegans* through an Nrf2-dependent mechanism (*C. elegans* homolog SKN-1)[75].Sulforaphane, found

in broccoli and other similar foods, is another naturally-occurring Nrf2 activator with some mitochondrial effect[76] and may be effective in ameliorating muscular dystrophy, a disease with muscle wasting phenotypes[77]. Repression of the Nrf2 pathway contributes to Hutchinson-Gilford progeria syndrome (HGPS). HGPS is etiologically related to mutations of nuclear architectural proteins lamin A and C. HGPS patients show profound growth delays and premature aging phenotypes, including cardiac and skeletal muscle pathologies[66, 78]. It has been suggested that inhibition of Nrf2/ARE activity contributes to premature aging in experimental models of HGPS by increasing chronic oxidative stress. Reestablishment of the Nrf2/ARE pathway using small compound Nrf2 activators ameliorates disease phenotypes[66]. Amyotrophic lateral sclerosis (ALS) is a progressively debilitating disease with motor neuron degeneration and irreversible muscle atrophy. Studies examining ALS mice muscles suggest a retrograde Nrf2/ARE activity in disease progression[79]. In line with these findings, aged *Nrf2*$^{-/-}$ mice exhibited impaired antioxidant activity and accelerated muscle cell death compared with wild-type mice[80]. The direct role for the Nrf2/ARE pathway in preserving muscle function warrants further investigation.

The naturally-occurring compound tomatidine exhibits anti-sarcopenia activity in mice possibly through the regulation of cellular stress[81, 82]. Tomatidine is a metabolite of α-tomatine, which is abundant in unripe green tomatoes, and elicits broad effects on cells, possessing antibiotic, anti-inflammatory, and anti-carcinogenic properties[83, 84]. Interestingly, recent studies in mice showed that tomatidine can improve muscular strength and decrease adiposity through inhibition of activating transcription factor 4 (ATF-4)[81,82].Two-month supplementation with tomatidine (0.05%)in 22 months old male C57BL/6 mice significantly reduced age-dependent decline of skeletal muscle mass, strength, and quality. At a molecular level, tomatidine inhibited the activity of ATF-4, a bZIP transcription factor subunit regulating oxidative and other stress responses[85]. Consistent with this finding, mice with muscle-specific knock out of ATF4 showed reduced age-related muscle atrophy[82]. Ursolic acid, a pentacyclic triterpenoid found in apples, may also exhibit anti-sarcopenic activity in aged mice through modulation of stress responses[86, 87]. The specific mechanism by which these compounds improve muscle function requires further elucidation. Many phytochemicals were shown to exhibit beneficial effects on cells and organisms through a hormetic mechanism[88, 89].A compelling avenue of research would be to address if the anti-sarcopenic properties of tomatidine and ursolic acid are due to a similar hormetic mechanism.

3.3 Mitophagy-inducing compounds

Mitophagy plays a significant role in mitochondrial maintenance in muscles, and mitophagy-inducing agents may hold anti-sarcopenic functions[90]. Urolithin A is an end-product of a group of naturally-occurring compounds, ellagitannins (ETs), which are found in pomegranates[44] (Figure 2). A recent study in *C. elegans* and mice suggests that urolithin A is a mitophagy-inducing compound which increases muscle function[44]. In aged *C. elegans*, urolithin A was able to maintain a healthy mitochondrial pool through both mitochondrial biogenesis and cleavage of damaged mitochondria via mitophagy, which contributed improvement of healthspan and lifespan. Interestingly, in younger *C. elegans*, mitophagy was induced without mitochondrial biogenesis, and yielded lower mitochondrial content and

lower respiration[44]. Mechanistic insight into how urolithin A induces mitophagy is still limited.

4. Conclusions and future perspectives

Improving the quality of life in older individuals will alleviate pressure on various socio-economic systems, especially health care[91]. Skeletal muscle atrophy and dysfunction disrupts older individuals from living a healthy lifestyle, and administration of bioactive compounds to preserve muscle function may address this problem. Studies from laboratory animal models suggest the aforementioned naturally-occurringcompounds target mitochondrial biogenesis, cellular stress response, and mitophagy, andhave promising anti-sarcopenic function. Supplementation of these naturally-occurring compounds may ameliorate sarcopenia in older individuals, especially when clinically assessed with other medical treatment options. However, further clinical trials are warranted. Importantly, some of these compounds are currently in clinical trials, including NR and urolithin A (https://clinicaltrials.gov/). Major tasks in the field include a) further elucidation of the molecular mechanisms of sarcopenia, which will facilitate drug design; and b) studies on the optimal pharmacokinetic conditions of these compounds in humans. In conclusion, pharmacological intervention of muscle atrophy and other aging-related phenotypes holds promise to improving human healthspan.

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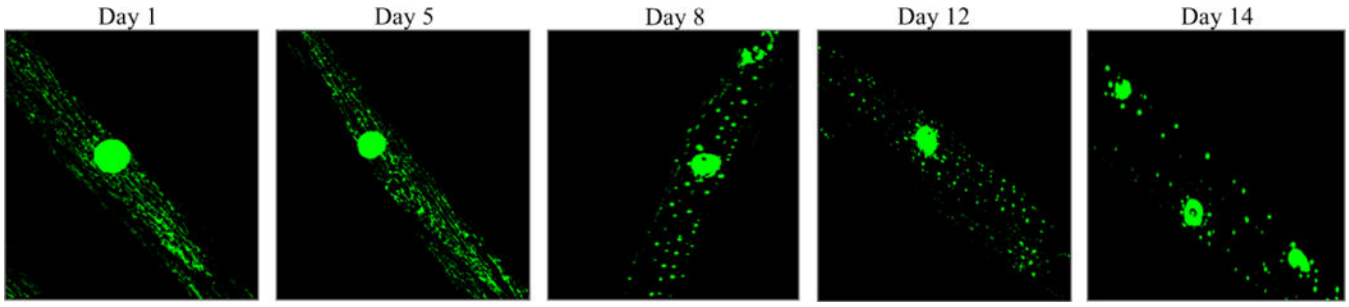

Figure 1. *C. elegans* muscle specific mitochondrial fragmentation with age

Both the nucleus and the mitochondria within a muscle cell of C. elegans are seen here. The quality of mitochondria can be assessed by the relative morphology and connectivity.In healthy organisms, mitochondria are maintained as a network in muscle cells and other cells, which increases efficiency. This network can be compromised as the organism naturally ages and in premature aging diseases (progeria). This fragmentation of mitochondrial network is associated with decreased healthspan, and is likely tied to mitophagy and other mitochondrial quality control processes. Compounds that alleviate this excessive fragmentation may improve muscle health. (I realy like this images, so clear. I think, it will be nice to include also some with e.g. tomatodin or NR treatment for confirming this reviews contents, if it's possible)

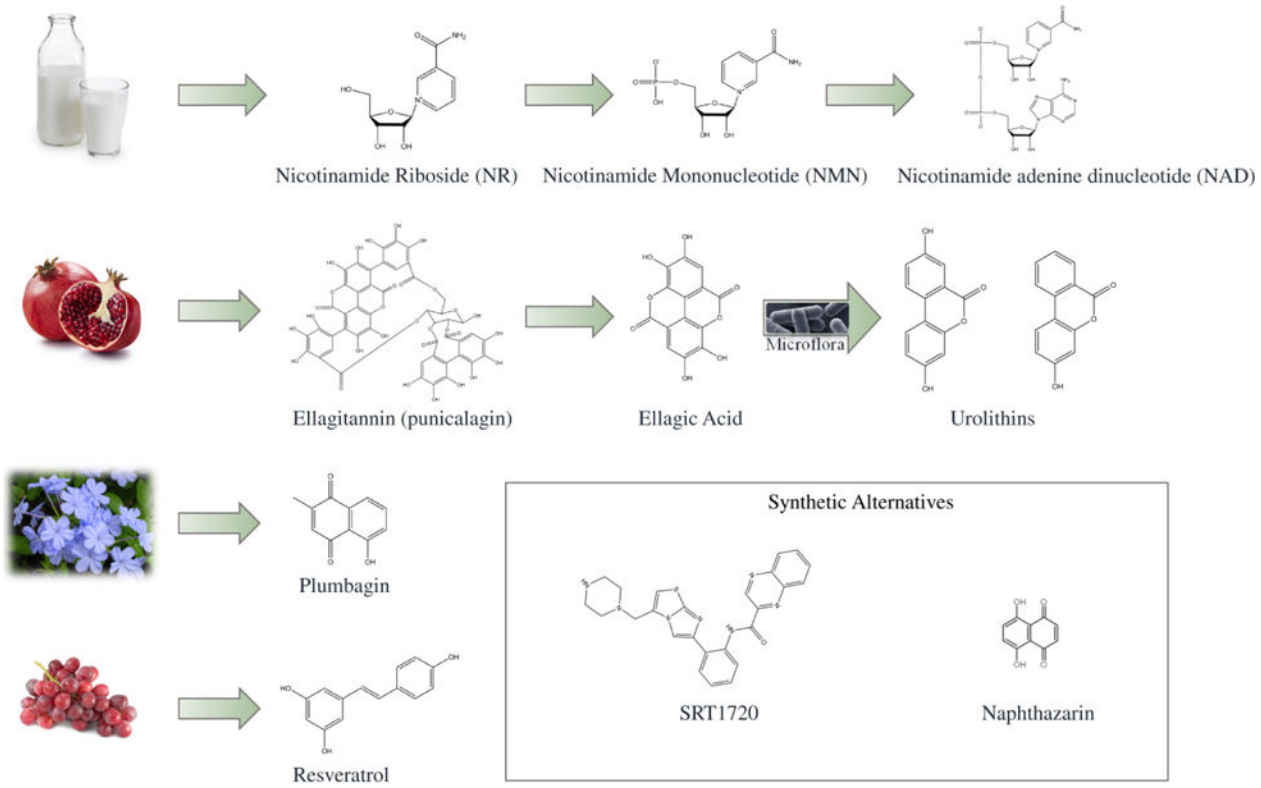

Figure 2. Representativebioactive small compounds exhibit mitochondrial benefits

Many of these naturally-occurring compounds are derived from common foods, such as milk,pomegranate, plumbago and grapes. Phytochemicals can be innately synthesized by the plant, such as the case for plumbagin and resveratrol. They can also be metabolized in the body to produce the potential anti-sarcopenic compound, such as the metabolism of NR to NAD^+, or the conversion of ellagitannins to urolithins with help of intestinal microflora. Synthetic derivatives of naturally-occurring compounds are also effective in modulating mitochondrial function through similar mechanisms, which is seen with the resveratrol-derived SRT1720 or the plumbagin-derived naphthazarin.

For images used here, Milk: Krans, B. (2014). “Almond Milk vs. Cow Milk vs. Soy Milk vs. Rice Milk”; Promagranate: TrimDownClub (2015). “10 Things We Love About Pomegranates (Plus Pomegranate Recipes)”; Plumbago: brewbooks (2005). Plumbagoauriculata. Wikimedia Commons; Grapes: Council, C. N. C. (2012). “Chicken With Grapes and Rosemary Recipe.”