Dietary phytochemicals that can extend longevity by regulation of metabolism

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Abstract

Diet provides energy and nutrition for human survival, and also provides various joy of taste. Extensive studies have shown that the major components of diet, such as protein, carbohydrate and fat, play important roles in regulating aging and longevity. Whether other dietary ingredients can help prevent aging and extend longevity is a very interesting question. Here based on recent findings, we discussed dietary plant ingredients that can extend longevity by regulation of metabolism, targeting TRP channels, mitophagy, senescence pathways and circadian rhythms. Better understanding of the detailed effects and mechanisms of dietary ingredients on longevity regulation, would be helpful for developing new intervention tools for preventing aging and aging related diseases.

1. Introduction

The composition of food is important for human health and aging [Fontana 2017]. Extensive studies have shown that both the quantity and quality of the nutrients in the food that we take every day are critical in changing health and disease conditions. Nutritional manipulations, such as calorie restriction, time-restricted feeding, intermittent fasting, protein or specific amino acid restriction, play notable roles in regulating aging and longevity [Balasubramanian, Mattison et al. 2017, Brown-Borg and Buffenstein 2017, Ingram and de Cabo 2017, Manoogian and Panda 2017, Mattson, Longo et al. 2017, Most, Tosti et al. 2017, Simpson, Le Couteur et al. 2017].

The major components of food, such as protein, carbohydrate and fat, are indeed important in aging regulation. Besides these components, there are dietary ingredients that we do not take every day, or in big amount. Rather, we take some dietary ingredients in a small amount, or take them at certain frequencies. There are a lot of sayings about which food is good for human beings, and the concepts are normally given by the eating traditions passed generation to generation. Is it true that a certain dietary ingredient can help prevent aging and extend longevity?

In this review, based on recent findings, we focus on several interesting dietary plant ingredients that may help extend lifespan by regulation of metabolism. With more understanding of the mechanisms, dietary ingredients could possibly be developed to powerful intervention tools for preventing aging and aging related diseases, and promoting health span and lifespan in the near future.

2. Plant ingredients targeting TRP channels

Transient receptor potential (TRP) channels are cation channels that sense a wide spectrum of ambient temperatures [Chen, Sooch et al. 2020]. TRPV1, which detects high temperatures and painful stimuli, and TRPA-1, which detects low temperatures, are found to regulate longevity [Xiao, Zhang et al. 2013, Riera, Huising et al. 2014].

Capsaicin （structure shown in Figure 1）[Yasueda, Ito et al. 2013], found in chili pepper, is the agonist of TRPV1 and may have beneficial effect on longevity. This is supported by several human surveys on diets rich in capsaicin (Table 1).

In a recently study conducted in Italy [Bonaccio, Di Castelnuovo et al. 2019], the researchers studied 22,811 residents who participated in the Moli-sani Study (2005 to 2010). The researchers conducted a follow-up survey of participants' health conditions for median follow-up of 8.2 years and compared their eating habits. The results found that people who regularly eat chili pepper (at least four times a week) demonstrated 23% reduction in the risk of all-cause mortality, and their cerebrovascular mortality was reduced by more than half. An interesting fact is that, even for people who do not follow a healthy Mediterranean diet, the intake of chili pepper is still protective against death risk [Bonaccio, Di Castelnuovo et al. 2019]. This suggests the beneficial effect of chili pepper itself on human health.

Prior to the study on chili pepper intake and mortality in Italians, scientists have looked at the health effects of spicy food consumption in Chinese residents, for median follow-up of 7.2 years among 512,891 participants between the ages of 30 and 79 [Lv, Qi et al. 2015]. The results show that relative risk of total mortality was reduced by 14% for people who consumed spicy food 6 or 7 days per week, compared to those who took less than once a week. There are also significant inverse associations between spicy food consumption and cancer, ischemic heart diseases, or respiratory disease caused mortalities [Lv, Qi et al. 2015].

Besides the surveys conducted in Europe and Asia, research on North American population also supported the positive effect of spicy food consumption on aging. In the study conducted in the United States that followed a median of 18.9 years in 16,179 participants, total mortality was reduced by 12% in participants who consumed hot red chili peppers [Chopan and Littenberg 2017].

The above research in three regions all support the correlation between mortality reduction and spicy food consumption. However, whether these associations are a direct result of the intake of spicy foods, or the consequence of other dietary or lifestyle factors, is not clear. The human population study showed that increase of serum vitamin D may slightly account for the association of the reduced mortality and the intake of chili pepper, while other cardiovascular disease (CVD) related biomarkers did not mediate the association of chili pepper with mortality [Bonaccio, Di Castelnuovo et al. 2019].

To find out whether the main bioactive component of chili pepper, capsaicin, play a role in aging, we tested the effect of capsaicin on lifespan in *Drosophila melanogaster*. We found that low concentration of capsaicin could extend lifespan only in females, but not in males [Shen, Shan et al. 2020]. Capsaicin did not change food intake, reproductive fitness, or stress resistance. Decrease in spontaneous activity and the reduction in energy expenditure probably explained the positive effect of capsaicin [Shen, Shan et al. 2020].

TRPV1 knockout mice are long-lived and show decreased production of neuropeptide calcitonin-gene-related peptide (CGRP), which subsequently promotes metabolic health (Figure 2A) [Riera, Huising et

al. 2014]. Activation of TRPV1 can also cause production of anandamide (an endogenous cannabinoid), which regulates the immune homeostasis of the gut in mice (Figure 2B) [Acharya, Penukonda et al. 2017]. More in-depth research to understand how dietary chili pepper and capsaicin exert beneficial effects on human health and prevent aging, would provide more evidence on dietary recommendations.

The cold-sensitive TRPA1 channel can detect low temperatures, and extend lifespan in *C. elegans*, by initiating calcium influx that eventually signals to the transcription factor DAF-16/FOXO (Figure 2C) [Xiao, Zhang et al. 2013, Zhang, Xiao et al. 2015]. Loss of TRPA1 shortens lifespan at cold temperatures but not at warm temperatures, and over-expressing wild-type TRPA1 can extend lifespan at cold temperatures in *C. elegans*. Similarly, transgenic expression of human TRPA1 in worms promotes longevity at cold temperatures but not at warm temperatures. Interestingly, human TRPA1 can be activated by pungent chemical agonists, such as AITC (allyl isothiocyanate), to extend lifespan at warm temperatures, and acts via the same pathway as worm TRPA1. Allyl isothiocyanate (AITC) is a dietary ingredient from the plants, such as *Armoracia rusticana* or the seeds of *Brassica hirta Moench*, and gives the spicy flavor of wasabi and mustard oil. This finding suggests that allyl isothiocyanate may have anti-aging effect in humans by activation of TRPA1 channel. It would be interesting to find out more dietary ingredients from plants that can activate other TRP channels and extend lifespan.

3. Plant ingredients targeting mitophagy

Mitochondria is essential for the production of cellular energy and the metabolism. mtDNA mutations lead to the decline of mitochondrial function during aging [Bratic and Larsson 2013]. Mitophagy, a form of autophagy that eliminates the damaged mitochondria within the cells [Youle and Narendra 2011], provides a therapeutic target for health complications associated with aging.

Pomegranate is a popular fruit because of its health benefits [Johanningsmeier and Harris 2011]. Ellagitannins, an ingredient in pomegranate, can be converted by intestinal microbes into urolithins, such as urolithin A [Espin, Larrosa et al. 2013]. Recent findings show that urolithin A has promising lifespan prolonging effect.

Urolithin A (Structure in Figure 3) was found to be mitophagy activator, and therefore prevent dysfunctional mitochondria accumulation [Ryu, Mouchiroud et al. 2016]. Research showed that the in *C. elegans*, urolithin A feeding from eggs till death yielded a lifespan increase of 45.4%. In addition, urolithin A has the function of preventing the malicious accumulation of dysfunctional mitochondria in cells.

The tests in rodents showed that, for mice on high-fat diet, urolithin A treatment for another 8 months from age of 16 months, improved muscle function robustly compared with the control. For animals on normal chow diet, 6-week urolithin A treatment to 22.5 month old mice also achieved the same positive results, showing the running endurance enhanced by 42% at average. Beneficial effect of urolithin A was observed in young rats as well, with improvement in their exercise capacity [Ryu, Mouchiroud et al. 2016].

Recently, the first human clinical trial (NCT02655393) of urolithin A was conducted to healthy, sedentary elderly human individuals. The results showed a safety profile, and a molecular signature response, which indicated improved mitochondrial health [Andreux, Blanco-Bose et al. 2019]. This supports a promising approach of dietary urolithin A consumption as an intervention to help improve mitochondrial and muscle function, and promote health in late age in humans (Figure 4).

Urolithin A has shown to regulate multiple processes in metabolism. Besides stimulation of mitophagy, Urolithin A also displays anti-inflammatory and anti-obese activity in animal studies. Urolithin A and its synthetic analog UAS03, can enhance gut barrier integrity and reduce inflammation in mice and human cell culture, by activating aryl hydrocarbon receptor (AhR)- nuclear factor erythroid 2–related factor 2 (Nrf2)-dependent pathways [Singh, Chandrashekharappa et al. 2019]. Urolithin A can also increase energy expenditure and prevent diet-induced obesity in mice, by elevating thermogenesis in brown adipose tissue and inducing browning of white adipose tissue [Xia, Shi et al. 2020].

Urolithin A is a first-in-class natural food metabolite confirmed to be effective in human clinical trial that can stimulates mitophagy and improve mitochondrial functions. Mitophagy may be the key in

treating age related conditions and diseases. Targeting deubiquitylating enzymes to stimulate mitophagy might be a promising approach [Harrigan, Jacq et al. 2018].

Resveratrol, a polyphenol abundant in mulberries and red grapes, attenuates oxidative damage by activation of mitophagy in Alzheimer's disease cellular model [Wang, Jiang et al. 2018]. In diabetic mouse model, resveratrol inhibits mitophagy and increases mitochondrial biogenesis in skeletal muscle, and therefore prevents skeletal muscle atrophy [Wang, Sun et al. 2018]. Thus, activation and inhibition of mitophagy may both be beneficial, depending on the situation. Further identification of dietary ingredients that prevent aging by regulation of mitophagy, would provide us more understanding of the mechanisms, and provide dietary supplementation approach for promoting mitochondrial health during aging.

4. Plant ingredients targeting senescence pathways

With aging, senescent cell burden increases [Zhu, Armstrong et al. 2014]. Senescent cells can release factors, such as proinflammatory cytokines and chemokines, to healthy cells nearby, and therefore cause the local and systemic dysfunction [Xu, Tchkonia et al. 2015]. Transplanting senescent cells can lead to physical dysfunction and reduced survival even in young mice. An important finding is that senolytics, which induce apoptosis in senescent cells, can increase health and survival of old mice (Figure 5) [Xu, Pirtskhalava et al. 2018].

Fisetin (Structure in Figure 6) [Kim, Kim et al. 2015], a natural flavonoid ingredient from many fruits and vegetables, such as strawberry, demonstrated potent senolytic activity and low side effect, and has been found to have a significant positive effect on the health and longevity of older mice. Both acute and intermittent treatment of fisetin decreased the level of senescence markers in progeroid syndrome mouse model and in aged wild-type mice. In old wild-type mice, fisetin administration can reduce age-related pathology and extend lifespan. Test in human tissues also showed senotherapeutic activity [Yousefzadeh, Zhu et al. 2018].

Fisetin has shown beneficial effects in Alzheimer’s’ disease model as well. Fisetin feeding to *APPswe/ PS1dE9* double transgenic AD mice at early life stage, which is from 3 to 12 month old, can prevent

progressive memory loss and learning disabilities. This correlates with elevated p25 level and anti-inflammatory pathways [Currais, Prior et al. 2014]. In SAMP8 mice, a model of sporadic AD and dementia, fisetin again reduces cognitive dysfunction, and helps the markers associated with stress, synaptic function and inflammation recover to normal [Currais, Farrokhi et al. 2018].

In addition, fisetin has positive role on metabolism regulation. Fisetin can attenuate metabolic dysfunction in mice on high fructose diet, possibly by suppressing NF-κB and activating the Nrf2 pathway [Shi, Li et al. 2018]. Fisetin can also alleviate insulin resistance and glucose intolerance in mice on high fat diet [Ge, Xu et al. 2019]. In streptozotocin induced diabetic rat model, fisetin ameliorates the development of diabetic cardiomyopathy injury [Althunibat, Al Hroob et al. 2019].

There are several flavonoid ingredients from plants that have shown senolytic activity, such as quercetin, curcumin, and luteolin [Yousefzadeh, Zhu et al. 2018]. Quercetin, which is initially identified to have senolytic properties when combined with dasatinib, targets BCL-2 and related anti-apoptotic pathways [Zhu, Doornebal et al. 2017]. The combination of dasatinib plus quercitin can improve physical function and extend lifespan in old rodents [Xu, Pirtskhalava et al. 2018], and prevent cognitive deficits in mouse model of Alzheimer's disease [Zhang, Kishimoto et al. 2019]. The combination of dasatinib plus quercitin also showed in clinical trial to help improve physical function in patients with idiopathic pulmonary fibrosis (IPF), a senescence-associated disease [Justice, Nambiar et al. 2019]. Recent screening on flavonoids showed that fisetin, curcumin, and luteolin exibited more potent senotherapeutic activity than quercetin [Yousefzadeh, Zhu et al. 2018]. Among these, fisetin is the most potent senolytic. Piperlongumine, which is a natural ingredient from a variety of species in the genus Piper, has been found to be a promising senolytic agent as well [Wang, Chang et al. 2016].

Given that these chemicals are natural plant ingredients found in common foods, dietary supplementation may help reduce the number of senescent cells and benefit the health of elderly. Further research and evaluation by clinical trials would be helpful to establish therapeutic intervention to yield health benefit in aging and aging-relate disease.

5. Plant ingredients targeting circadian rhythms

The circadian clock orchestrates daily oscillations of essential physiological processes. Rhythm

amplitude shows the difference between peak and trough of the circadian cycle, indicating the robustness of oscillation. Reduced amplitude has been associated with pathological conditions [Vitaterna, Ko et al. 2006, Marcheva, Ramsey et al. 2010].

Nobiletin (Structure in Figure 7) , a citrus flavonoid ingredient, has been found to regulate circadian rhythms and delay aging. Nobiletin was found to be able to enhance the clock amplitude in a cell-based circadian reporter assay, In a mouse model of metabolic disorder, nobiletin could effectively enhance the tissue clock protein levels, improve energy metabolism regulation, and prevent metabolic disease [He, Nohara et al. 2016]. Nobiletin targets retinoid acid receptor-related orphan receptors (RORs), nuclear receptors functioning in the stabilization loop of the molecular oscillator, and demonstrates the beneficial effect in a Clock gene-dependent manner (Figure 7).

In aged mice fed with a regular diet, nobiletin extended median lifespan, and has beneficial effects on circadian activity, body temperature, sleep and glucose metabolism. When mice were given metabolic challenges by feeding with high fat diet, nobiletin showed a more significant effect on the physiological function of aged mice. Several skeletal muscle-related functions have been significantly improved, including grip, athletic endurance, and runner running. Further study indicated that improving and optimizing mitochondrial respiratory function in skeletal muscle was the mechanism [Nohara, Mallampalli et al. 2019]. Nobiletin also protected cholesterol and bile acid metabolism in high fat diet fed aged mice [Nohara, Nemkov et al. 2019]. However, the beneficial metabolic effects of nobiletin in high fat diet fed mice is independent of AMPK activation [Morrow, Burke et al. 2020]. Research in *C. elegans* supported the anti-aging and lifespan extension effect of nobiletin [Yang, Wang et al. 2020].

In aged mouse models, nobiletin showed markedly beneficial effects as well. In senescence-accelerated SAMP8 mice, nobiletin improves cognitive impairment, and reduces oxidative burden and tau phosphorylation [Nakajima, Aoyama et al. 2013]. Nobiletin alleviated cognitive deficits and pathological features in animal models of Alzheimer's disease and Parkinson's disease [Nakajima and Ohizumi 2019].

There have been studies searching for small molecules that modulate circadian rhythms. High-throughput screen using reporter cells has identified several synthetic small molecules that enhance clock amplitude [Chen, Yoo et al. 2012, Doruk, Yarparvar et al. 2020]. The screening used the heterozygous *Clock*$^{\Delta 19/+}$ *PER2::Luc* reporter cells, which exhibit about one-third rhythm amplitude of wild-type *Clock*$^{+/+}$ cells, and the compounds that can restore the reporter rhythm amplitude were selected. High-throughput screen also identified natural compounds that enhance reporter rhythm as well [He, Nohara et al. 2016]. The most potent one is nobiletin, the natural flavone ingredient in citrus. Tangeretin, a close analog of nobiletin and also a natural plant ingredient, also showed the ability to enhance rhythm amplitude. The finding that nobiletin, an agonist of retinoid acid receptor-related orphan receptors (RORs), can promote circadian metabolism and healthy aging, suggests that more research on dietary compounds with clock-enhancing effect, would provide promising intervention that enhances health during aging.

6. Conclusions and future directions

Diet provides human beings with the energy and nutrition they need to survive, and it also provides humans' life with joy. Among the many foods, which ones can help human beings enjoy food and also help achieve healthy aging? This is a very interesting question.

Substantial evidence has accumulated that interventions on main components of daily food, including caloric restriction, protein restriction, low protein high carbohydrate diets, and essential amino acid restriction, can increase lifespan in animal models [Simpson, Le Couteur et al. 2017]. What other dietary ingredients can help prolong lifespan?

Recently, urolithin A, an end-product from ellagitannins in the pomegranate fruit, has shown promising benefit in promoting healthy muscle function during aging, in a human clinical trial [Andreux, Blanco-Bose et al. 2019]. Quercetin, another ingredient from plant, together with dasatinib to act as senolytics, also helped improving physical function in patients with idiopathic pulmonary fibrosis (IPF), a senescence-associated disease, in a clinical trial [Justice, Nambiar et al. 2019]. These findings demonstrate the potential powerful role of dietary natural plant ingredients in health promotion during aging.

Metabolism is an important mechanism in aging regulation, and deterioration in metabolism is closely related with aging. In this review, dietary plant ingredients targeting TRP channels, mitophagy, senescence pathways and circadian rhythms were discussed on longevity extending effect (Table 2). An important question is how we can efficiently find out promising dietary components. A screening of 5,300 small molecules based on reporter cells only helped researchers identified two natural ingredients, nobiletin and tangeretin, with circadian rhythm amplitude enhancing effect [He, Nohara et al. 2016]. Testing on compounds with similar structure might be a good strategy, since tangeretin is a close analog of nobiletin [Nichols, Jackson et al. 2011] (Figure 8) in targeting circadian rhythms. It is also supported by the fact that fisetin [Kim, Kim et al. 2015], quercetin [dos Santos, Kuster et al. 2014], curcumin [Zunino, Storms et al. 2013], and luteolin [Pratheeshkumar, Son et al. 2012] are all flavonoids (structures in Figure 9) and have senolytic activity [Yousefzadeh, Zhu et al. 2018]. Additionally, piperlongumine (structure in Figure 9) [Aodah, Pavlik et al. 2016], which is a potential senolytic agent, is structural related to quercetin [Kirkland and Tchkonia 2017]. Besides the challenge in the initial identification, it takes efforts to clarify the molecular mechanism of action and direct targets of dietary ingredients with longevity extending effect.

Further research unravelling the detailed effects and mechanisms of dietary ingredients on longevity regulation, would be helpful for humans to develop more interventions to achieve healthy aging, and meanwhile, to allow individually customed dietary approach that balance between health and personal preferences.

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References

Acharya N, Penukonda S, Shcheglova T, et al. (2017). "Endocannabinoid system acts as a regulator of immune homeostasis in the gut." Proc Natl Acad Sci U S A **114**(19): 5005-5010. DOI: 10.1073/pnas.1612177114.

Althunibat O Y, Al Hroob A M, Abukhalil M H, et al. (2019). "Fisetin ameliorates oxidative stress, inflammation and apoptosis in diabetic cardiomyopathy." Life Sci **221**: 83-92. DOI:

10.1016/j.lfs.2019.02.017.
Andreux P A, Blanco-Bose W, Ryu D, et al. (2019). "The mitophagy activator urolithin A is safe and induces a molecular signature of improved mitochondrial and cellular health in humans." Nature Metabolism **1**(6): 595-603. DOI: 10.1038/s42255-019-0073-4.
Aodah A, Pavlik A, Karlage K, et al. (2016). "Preformulation Studies on Piperlongumine." PLoS One **11**(3): e0151707. DOI: 10.1371/journal.pone.0151707.
Balasubramanian P, Mattison J A and Anderson R M (2017). "Nutrition, metabolism, and targeting aging in nonhuman primates." Ageing Res Rev **39**: 29-35. DOI: 10.1016/j.arr.2017.02.002.
Bonaccio M, Di Castelnuovo A, Costanzo S, et al. (2019). "Chili Pepper Consumption and Mortality in Italian Adults." J Am Coll Cardiol **74**(25): 3139-3149. DOI: 10.1016/j.jacc.2019.09.068.
Bratic A and Larsson N G (2013). "The role of mitochondria in aging." J Clin Invest **123**(3): 951-957. DOI: 10.1172/JCI64125.
Brown-Borg H M and Buffenstein R (2017). "Cutting back on the essentials: Can manipulating intake of specific amino acids modulate health and lifespan?" Ageing Res Rev **39**: 87-95. DOI: 10.1016/j.arr.2016.08.007.
Chen X, Sooch G, Demaree I S, et al. (2020). "Transient Receptor Potential Canonical (TRPC) Channels: Then and Now." Cells **9**(9). DOI: 10.3390/cells9091983.
Chen Z, Yoo S H, Park Y S, et al. (2012). "Identification of diverse modulators of central and peripheral circadian clocks by high-throughput chemical screening." Proc Natl Acad Sci U S A **109**(1): 101-106. DOI: 10.1073/pnas.1118034108.
Chopan M and Littenberg B (2017). "The Association of Hot Red Chili Pepper Consumption and Mortality: A Large Population-Based Cohort Study." PLoS One **12**(1): e0169876. DOI: 10.1371/journal.pone.0169876.
Currais A, Farrokhi C, Dargusch R, et al. (2018). "Fisetin Reduces the Impact of Aging on Behavior and Physiology in the Rapidly Aging SAMP8 Mouse." J Gerontol A Biol Sci Med Sci **73**(3): 299-307. DOI: 10.1093/gerona/glx104.
Currais A, Prior M, Dargusch R, et al. (2014). "Modulation of p25 and inflammatory pathways by fisetin maintains cognitive function in Alzheimer's disease transgenic mice." Aging Cell **13**(2): 379-390. DOI: 10.1111/acel.12185.
Doruk Y U, Yarparvar D, Akyel Y K, et al. (2020). "A CLOCK-binding small molecule disrupts the interaction between CLOCK and BMAL1 and enhances circadian rhythm amplitude." J Biol Chem **295**(11): 3518-3531. DOI: 10.1074/jbc.RA119.011332.
dos Santos A E, Kuster R M, Yamamoto K A, et al. (2014). "Quercetin and quercetin 3-O-glycosides from Bauhinia longifolia (Bong.) Steud. show anti-Mayaro virus activity." Parasit Vectors **7**: 130. DOI: 10.1186/1756-3305-7-130.
Espin J C, Larrosa M, Garcia-Conesa M T, et al. (2013). "Biological significance of urolithins, the gut microbial ellagic Acid-derived metabolites: the evidence so far." Evid Based Complement Alternat Med **2013**: 270418. DOI: 10.1155/2013/270418.
Fontana L (2017). "The science of nutritional modulation of aging." Ageing Res Rev **39**: 1-2. DOI: 10.1016/j.arr.2017.08.002.
Ge C, Xu M, Qin Y, et al. (2019). "Fisetin supplementation prevents high fat diet-induced diabetic nephropathy by repressing insulin resistance and RIP3-regulated inflammation." Food Funct **10**(5): 2970-2985. DOI: 10.1039/c8fo01653d.
Harrigan J A, Jacq X, Martin N M, et al. (2018). "Deubiquitylating enzymes and drug discovery:

emerging opportunities." Nat Rev Drug Discov **17**(1): 57-78. DOI: 10.1038/nrd.2017.152.
He B, Nohara K, Park N, et al. (2016). "The Small Molecule Nobiletin Targets the Molecular Oscillator to Enhance Circadian Rhythms and Protect against Metabolic Syndrome." Cell Metab **23**(4): 610-621. DOI: 10.1016/j.cmet.2016.03.007.
Ingram D K and de Cabo R (2017). "Calorie restriction in rodents: Caveats to consider." Ageing Res Rev **39**: 15-28. DOI: 10.1016/j.arr.2017.05.008.
Johanningsmeier S D and Harris G K (2011). "Pomegranate as a functional food and nutraceutical source." Annu Rev Food Sci Technol **2**: 181-201. DOI: 10.1146/annurev-food-030810-153709.
Justice J N, Nambiar A M, Tchkonia T, et al. (2019). "Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study." EBioMedicine. DOI: 10.1016/j.ebiom.2018.12.052.
Kim J H, Kim M Y, Kim J H, et al. (2015). "Fisetin Suppresses Macrophage-Mediated Inflammatory Responses by Blockade of Src and Syk." Biomol Ther (Seoul) **23**(5): 414-420. DOI: 10.4062/biomolther.2015.036.
Kirkland J L and Tchkonia T (2017). "Cellular Senescence: A Translational Perspective." EBioMedicine **21**: 21-28. DOI: 10.1016/j.ebiom.2017.04.013.
Lv J, Qi L, Yu C, et al. (2015). "Consumption of spicy foods and total and cause specific mortality: population based cohort study." BMJ **351**: h3942. DOI: 10.1136/bmj.h3942.
Manoogian E N C and Panda S (2017). "Circadian rhythms, time-restricted feeding, and healthy aging." Ageing Res Rev **39**: 59-67. DOI: 10.1016/j.arr.2016.12.006.
Marcheva B, Ramsey K M, Buhr E D, et al. (2010). "Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes." Nature **466**(7306): 627-631. DOI: 10.1038/nature09253.
Mattson M P, Longo V D and Harvie M (2017). "Impact of intermittent fasting on health and disease processes." Ageing Res Rev **39**: 46-58. DOI: 10.1016/j.arr.2016.10.005.
Morrow N M, Burke A C, Samsoondar J P, et al. (2020). "The citrus flavonoid nobiletin confers protection from metabolic dysregulation in high-fat fed- mice independent of AMPK." J Lipid Res. DOI: 10.1194/jlr.RA119000542.
Most J, Tosti V, Redman L M, et al. (2017). "Calorie restriction in humans: An update." Ageing Res Rev **39**: 36-45. DOI: 10.1016/j.arr.2016.08.005.
Nakajima A, Aoyama Y, Nguyen T T, et al. (2013). "Nobiletin, a citrus flavonoid, ameliorates cognitive impairment, oxidative burden, and hyperphosphorylation of tau in senescence-accelerated mouse." Behav Brain Res **250**: 351-360. DOI: 10.1016/j.bbr.2013.05.025.
Nakajima A and Ohizumi Y (2019). "Potential Benefits of Nobiletin, A Citrus Flavonoid, against Alzheimer's Disease and Parkinson's Disease." Int J Mol Sci **20**(14). DOI: 10.3390/ijms20143380.
Nichols L A, Jackson D E, Manthey J A, et al. (2011). "Citrus flavonoids repress the mRNA for stearoyl-CoA desaturase, a key enzyme in lipid synthesis and obesity control, in rat primary hepatocytes." Lipids Health Dis **10**: 36. DOI: 10.1186/1476-511X-10-36.
Nohara K, Mallampalli V, Nemkov T, et al. (2019). "Nobiletin fortifies mitochondrial respiration in skeletal muscle to promote healthy aging against metabolic challenge." Nat Commun **10**(1): 3923. DOI: 10.1038/s41467-019-11926-y.
Nohara K, Nemkov T, D'Alessandro A, et al. (2019). "Coordinate Regulation of Cholesterol and Bile Acid Metabolism by the Clock Modifier Nobiletin in Metabolically Challenged Old Mice." Int J Mol Sci **20**(17). DOI: 10.3390/ijms20174281.

Pratheeshkumar P, Son Y O, Budhraja A, et al. (2012). "Luteolin inhibits human prostate tumor growth by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis." PLoS One **7**(12): e52279. DOI: 10.1371/journal.pone.0052279.

Riera C E, Huising M O, Follett P, et al. (2014). "TRPV1 pain receptors regulate longevity and metabolism by neuropeptide signaling." Cell **157**(5): 1023-1036. DOI: 10.1016/j.cell.2014.03.051.

Ryu D, Mouchiroud L, Andreux P A, et al. (2016). "Urolithin A induces mitophagy and prolongs lifespan in C. elegans and increases muscle function in rodents." Nat Med **22**(8): 879-888. DOI: 10.1038/nm.4132.

Shen J, Shan J, Zhu X, et al. (2020). "Sex specific effects of capsaicin on longevity regulation." Exp Gerontol **130**: 110788. DOI: 10.1016/j.exger.2019.110788.

Shi Y S, Li C B, Li X Y, et al. (2018). "Fisetin Attenuates Metabolic Dysfunction in Mice Challenged with a High-Fructose Diet." J Agric Food Chem **66**(31): 8291-8298. DOI: 10.1021/acs.jafc.8b02140.

Simpson S J, Le Couteur D G, Raubenheimer D, et al. (2017). "Dietary protein, aging and nutritional geometry." Ageing Res Rev **39**: 78-86. DOI: 10.1016/j.arr.2017.03.001.

Singh R, Chandrashekharappa S, Bodduluri S R, et al. (2019). "Enhancement of the gut barrier integrity by a microbial metabolite through the Nrf2 pathway." Nat Commun **10**(1): 89. DOI: 10.1038/s41467-018-07859-7.

Vitaterna M H, Ko C H, Chang A M, et al. (2006). "The mouse Clock mutation reduces circadian pacemaker amplitude and enhances efficacy of resetting stimuli and phase-response curve amplitude." Proc Natl Acad Sci U S A **103**(24): 9327-9332. DOI: 10.1073/pnas.0603601103.

Wang D, Sun H, Song G, et al. (2018). "Resveratrol Improves Muscle Atrophy by Modulating Mitochondrial Quality Control in STZ-Induced Diabetic Mice." Mol Nutr Food Res **62**(9): e1700941. DOI: 10.1002/mnfr.201700941.

Wang H, Jiang T, Li W, et al. (2018). "Resveratrol attenuates oxidative damage through activating mitophagy in an in vitro model of Alzheimer's disease." Toxicol Lett **282**: 100-108. DOI: 10.1016/j.toxlet.2017.10.021.

Wang Y, Chang J, Liu X, et al. (2016). "Discovery of piperlongumine as a potential novel lead for the development of senolytic agents." Aging (Albany NY) **8**(11): 2915-2926. DOI: 10.18632/aging.101100.

Xia B, Shi X C, Xie B C, et al. (2020). "Urolithin A exerts antiobesity effects through enhancing adipose tissue thermogenesis in mice." PLoS Biol **18**(3): e3000688. DOI: 10.1371/journal.pbio.3000688.

Xiao R, Zhang B, Dong Y, et al. (2013). "A genetic program promotes C. elegans longevity at cold temperatures via a thermosensitive TRP channel." Cell **152**(4): 806-817. DOI: 10.1016/j.cell.2013.01.020.

Xu M, Pirtskhalava T, Farr J N, et al. (2018). "Senolytics improve physical function and increase lifespan in old age." Nat Med **24**(8): 1246-1256. DOI: 10.1038/s41591-018-0092-9.

Xu M, Tchkonia T, Ding H, et al. (2015). "JAK inhibition alleviates the cellular senescence-associated secretory phenotype and frailty in old age." Proc Natl Acad Sci U S A **112**(46): E6301-6310. DOI: 10.1073/pnas.1515386112.

Yang X, Wang H, Li T, et al. (2020). "Nobiletin Delays Aging and Enhances Stress Resistance of Caenorhabditis elegans." Int J Mol Sci **21**(1). DOI: 10.3390/ijms21010341.

Yasueda A, Ito T and Maeda K (2013). "Review: Evidence-based Clinical Research of Anti-obesity Supplements in Japan." Immunol Endocr Metab Agents Med Chem **13**(3): 185-195. DOI:

10.2174/1871522213666131118221347.
Youle R J and Narendra D P (2011). "Mechanisms of mitophagy." Nat Rev Mol Cell Biol **12**(1): 9-14. DOI: 10.1038/nrm3028.
Yousefzadeh M J, Zhu Y, McGowan S J, et al. (2018). "Fisetin is a senotherapeutic that extends health and lifespan." EBioMedicine **36**: 18-28. DOI: 10.1016/j.ebiom.2018.09.015.
Zhang B, Xiao R, Ronan E A, et al. (2015). "Environmental Temperature Differentially Modulates C. elegans Longevity through a Thermosensitive TRP Channel." Cell Rep **11**(9): 1414-1424. DOI: 10.1016/j.celrep.2015.04.066.
Zhang P, Kishimoto Y, Grammatikakis I, et al. (2019). "Senolytic therapy alleviates Abeta-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model." Nat Neurosci **22**(5): 719-728. DOI: 10.1038/s41593-019-0372-9.
Zhu Y, Armstrong J L, Tchkonia T, et al. (2014). "Cellular senescence and the senescent secretory phenotype in age-related chronic diseases." Curr Opin Clin Nutr Metab Care **17**(4): 324-328. DOI: 10.1097/MCO.0000000000000065.
Zhu Y, Doornebal E J, Pirtskhalava T, et al. (2017). "New agents that target senescent cells: the flavone, fisetin, and the BCL-XL inhibitors, A1331852 and A1155463." Aging (Albany NY) **9**(3): 955-963. DOI: 10.18632/aging.101202.
Zunino S J, Storms D H, Newman J W, et al. (2013). "Oral or parenteral administration of curcumin does not prevent the growth of high-risk t(4;11) acute lymphoblastic leukemia cells engrafted into a NOD/SCID mouse model." Int J Oncol **42**(2): 741-748. DOI: 10.3892/ijo.2012.1734.

Figure Legend

Figure 1. Structure of capsaicin.

Figure 2. TRPV1, TRPA1 and metabolic health.

A. Stimulation of TRPV1 promotes CGRP secretion via CRTC1/CREB signaling. CGRP inhibits insulin secretion, harms metabolic health, and leads to aging.

B. TRPV1 activation can lead to production of Anandamide (AEA), which is an endogenous intestinal cannabinoid. AEA binds to its receptor, cannabinoid receptor 2 (CB2), and regulate immune homeostasis in the gut/pancreas, such as differentiation $CD4^+$ cells and the Tr1 cells.

C. TRPA1 activation can induce calcium influx. A calcium-sensitive PKC then can signal to promote the nuclear activity of the transcription factor DAF-16/FOXO, and thus regulate the expression level of DAF-16/FOXO target genes.

Figure 3. Structure of Urolithin A.

Figure 4. Urolithin A is a mitophagy activator. Urolithin A improves mitochondrial health and muscle function both in rodents and human beings.

Figure 5. Cellular senescence and Senolytics. Senescent cells accumulate with aging, and can act like ‘zombie’ to release factors such as pro-inflammatory cytokines and chemokines to neighboring cells, and lead to local and systemic dysfunction. Senolytics can selectively clear senescent cells, and slow

the progress of aging and age-related diseases.

Figure 6. Structure of Fisetin.

Figure 7. Nobiletin and circadian rhythms. Nobiletin is an agonist of the ROR nuclear receptors and is a clock amplitude enhancer. Nobiletin binds to and activates RORs, and enhance Bmal1 transcription in the core CLOCK:BMAL1 loop.

Figure 8. Structures of tangeretin and nobiletin.

Figure 9. Structures of fisetin, curcumin, luteolin, quercetin and piperlongumine.

Table 1. Human surveys on consumption of spicy foods and mortality.

Country	Number of Participants	Conclusion	Reference
Italy	22,811	23% reduction in the risk of all-cause mortality by regular consupmtion	Bonaccio, Di Castelnuovo et al. 2019
China	512,891	14% reduction in relative risk of total mortality by regular consupmtion	Lv, Qi et al. 2015
US	16,179	12% reduction in total mortality by spicy food consumption	Chopan and Littenberg 2017

Table 2. Dietary phytochemicals that extend longevity by regulation of metabolism.

Target	Dietary plant ingredient	Mechanism of action
TRP channels	Capsaicin, AITC (allyl isothiocyanate)	TRPV1 agonist and regulation of neuropeptide calcitonin-gene-related peptide (CGRP) production; TRPA1 agonist and signals to DAF-16/FOXO.
mitophagy	Urolithin A, deubiquitylating enzymes inhibitors, resveratrol	activation or inhibition of mitophagy and improvement of muscle function
senescence pathways	Fisetin, quercetin, piperlongumine, curcumin, and luteolin	targeting BCL-2 and related anti-apoptotic pathways
circadian rhythms	Nobiletin, tangeretin	targeting retinoid acid receptor-related orphan receptors (RORs) and enhancing circadian rhythm amplitude