Botanical Medicine and Phytochemicals in Healthy Aging and Longevity—Part 1

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Introduction

Medical advances are helping more people worldwide to live longer lives. According to the U.S. Population Reference Bureau, the number of Americans age 65 and older is projected to double by the year 2060, to 95 million people. Currently, about 16% of the U.S. population is aged 65 or older. By 2060, that figure will reach 23%. This societal shift is not unique to the United States, of course. The World Health Organization (WHO) estimates that the number of people older than age 60 worldwide will double by the year 2050. Importantly, living longer does not necessarily mean living healthier. WHO defines healthy aging as “the process of developing and maintaining the functional ability that enables well-being in older age.” Whether or not we are living lives that are not only longer but are also characterized by continued well-being is a source of substantial debate among researchers and public health organizations.

With an increase in aging populations, most physicians and health care practitioners will be directly involved in caring for older patients. As practitioners, our goals are always to help bolster the health, quality of life, and function of our elderly patients. Our patients desire not just to live long lives but to live long lives that are healthy as well. An emphasis not just on longevity, but on healthy longevity, transforms the way we approach and think about the gifts and challenges of aging.

To consider how to best foster healthy aging, a complete understanding of the normal physiology of aging itself is essential. The aging process is progressive and gradual, and is influenced by factors such as genetics, lifestyle, and environment. Physiologic changes occur in all organs of the body, but not in a homogenous manner (one organ system in the same individual may age faster or slower than others, for example). In a 2016 review article, van Beek et al. suggest that aging be thought of as a “balance of damage and repair.”¹ Aging is caused by damage to the macromolecules that make up the body. Damages, if not repaired, can then become cumulative over time. Thus, the balance between damage and repair becomes critical. Can these damages be minimized or can the body’s natural repair processes be supported to shift this balance in the direction of healthy longevity?

In this article, we explore these important questions, the mechanisms involved in these processes, and where botanical

medicine and phytochemicals may serve as modifiers of these mechanisms. In Part 1, we consider the roles of telomeres and telomerase, as well as the mechanistic target of rapamycin (mTOR) pathway in healthy aging. In Part 2, we turn our attention to sirtuin proteins, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), activation of AMP-activated protein kinase (AMPK) as a mediator of metabolism, and nuclear factor erythroid 2-related factor 2 (Nrf2) as a regulator of oxidative defense. As we will discuss, each of these factors is involved in either minimizing the damage associated with normal aging processes, or in supporting the mechanisms that repair that damage. It is important to remember that these mechanisms do not act in isolation, and, as we will discuss, that there may also be overlap and interaction of these factors with each other.

Telomeres and Telomerase

Within the nucleus of all cells, DNA chains are tightly coiled into chromosomes. Telomeres are repetitive DNA segments that form caps at the end of the chromosomes. These structures protect the genetic material of the cell and keep the DNA chains from unraveling, sticking to one another, or fraying. Each time a cell divides, the chromosomes are replicated, and with each replication, the telomeres are shortened slightly. The average cell loses from 30 to 200 base pairs from the end of the telomere with each division. As cell division continues, the telomeres then become progressively shorter. Eventually, this can lead to cellular senescence or death.

Some cells express telomerase, the enzyme that helps rebuild and extend the telomeres of chromosomes by adding base pairs. Most human somatic cells have either no telomerase or low levels of telomerase. However, telomerase is active in germ cells (sperm and egg cells) and in certain types of stem cells. Stem cells, of course, can help old or damaged tissues to regenerate.

Telomeres and telomerase, as protectors of cellular DNA, play important roles in health and disease. Consider the example of cancer. Since cancer cells are rapidly dividing, their telomeres may become shorter much faster, putting the cancer cell at greater risk of death. Cancer cells may gain the ability to express telomerase, preserving the rapidly dividing cells longer.

Also consider the example of aging. The aging process is linked to telomere shortening. While it is not currently completely clear whether or not telomere shortening actually contributes to aging, we do know that shorter telomeres are linked to all-cause mortality.² In Cawthon et al.'s 2003 study, people older than age 60 who had the longest telomeres lived longer than those who had the shortest telomeres (interestingly, the main cause of death among those with the shortest telomeres was infectious disease, and these individuals did not have increased rates of cancer).³ In a 2009 study by Njajou et al., telomere length was not associated with overall survival in the elderly, but it was correlated with years of healthy life.⁴

As is the case with many of these mechanisms, prospective clinical trials evaluating botanical medicines and telomere length or telomerase activity are few and far between. The vast majority of studies looking at integrative medicine interventions and telomeres in humans have been in reference to nutrition, micronutrient intake, or lifestyle factors rather than botanical medicines.^{5–10} This area of research is still in its infancy, which presents both opportunities and challenges. The preclinical data point to several areas of interest, but clinical research would need to be performed to tell us more about how this may play out in people. This article examines some of these preclinical data in greater detail.

Astragalus membranaceus

A. membranaceus, considered a Qi tonifier and adaptogen, has a lengthy history of medicinal use. More than 200 compounds have been extracted from *A. membranaceus*, with saponins, flavonoids, and polysaccharides being the major constituents. Fourteen separate polysaccharides from *A. membranaceus* have been identified.¹¹

In an animal model, *A. membranaceus* has been found to increase glutathione and reduce reactive oxygen species (ROS) via upregulation of Nrf2 (an effect we revisit in Part 2 of this review). *A. membranaceus* has many potential additional targets in promotion of longevity. *A. membranaceus* polysaccharides have been found to extend healthy life span of the nematode *Caenorhabditis elegans* via modulation of microRNA¹² (this nematode has a short life span of 15–25 days, a convenient trait for experiments designed to study life span). *A. membranaceus* polysaccharides also increase superoxide dismutase, catalase, and glutathione peroxidase in a mouse model of aging.¹³

A. membranaceus extracts may also exert their effects via modulation of telomeres. Two human cell line studies have demonstrated that cycloastragenol (CAG), a saponin compound synthesized from astragaloside IV, reduces telomere shortening and promotes telomerase activity.^{14,15}

Two clinical trials examining this effect have also been performed. The first was a 2011 study utilizing a patented CAG supplement in healthy subjects for 12 months. Participants started 5 to 10 mg CAG per day. Some subjects increased the dosage up to 50 mg per day during the course of the trial. The authors do not specify how the starting dose of 5 or 10 mg was selected, or how or why subjects increased their dosages during the trial. Thirty-seven subjects were evaluated

at the 12-month time point. The percent of short telomeres did increase after supplementation with CAG ($P = 0.037$), but mean telomere length did not increase. The authors presented no data regarding a dose/response effect.¹⁶

The second study was a randomized, double-blind, placebo-controlled trial utilizing the same patented CAG extract for one year. Healthy cytomegalovirus (CMV)-positive subjects ($n = 117$) were enrolled. CMV infection, which is generally asymptomatic and present in the majority of people worldwide, may lead to immunosenescence and decreased T cell immunity. The authors sought to determine if the CAG supplement could alleviate telomere attrition in the peripheral blood mononuclear cells of these CMV-positive subjects. Subjects were randomized to receive one of the following interventions: the first group received one proprietary CAG supplement capsule plus 3 placebo capsules daily (low-dose group), the second received four proprietary CAG supplement capsules daily (high-dose group), and the third received four placebo capsules daily. The study consisted of 104-day cycles, with the intervention dosed for 90 days, followed by a 14-day break from taking the capsules. Ninety-seven subjects completed the trial, 23 in the low-dose group, 22 in the high-dose group, and 52 in the placebo group. Baseline telomere length was not significantly different for these three groups. At the conclusion of the trial, subjects in the placebo group had a loss of telomere length ($P = 0.01$), while subjects who took the low-dose CAG supplement experienced a net increase in telomere length ($P = 0.005$). There was no statistically significant change in telomere length in the high-dose group. The authors provide a few suggestions for why the low-dose CAG group appeared to fare better than the high-dose group with regard to telomere length. They speculate that perhaps a lack of compliance with the intervention contributed (although they also specifically note that the primary investigator checked pill supplies at study visits to ensure compliance), or that there may be a bell-shaped dose-response curve with respect to CAG and telomeres.¹⁷

Cistanche Genus Plants

Plants of the *Cistanche* genus, the desert broomrape, are considered tonifying in Traditional Chinese Medicine (TCM), and are known in TCM as the “ginsengs of the desert.”¹⁸ *Cistanche* species are rich in glycosides as well as polysaccharides. In a mouse model of aging, *Cistanche deserticola* polysaccharides dosed at 25 mg/kg for six weeks were found to enhance telomerase activity in heart and brain tissue.¹⁹ Acteosides from *Cistanche tubulosa*, also applied in a mouse model of aging, were also found to increase telomerase activity in heart and brain tissue, when given at a dose of 40 mg/kg for two weeks.²⁰ The underlying mechanisms for these effects are not completely understood, but *C. deserticola*, for example, has been shown to have anti-inflammatory and antioxidant effects.²¹ Clinical trials specifically investigating the effects of *Cistanche* extracts on telomere function in humans have not been performed. A small 2013 trial ($n = 18$) of *C. deserticola* glycosides administered to people with Alzheimer's disease demonstrated

no significant differences in measures of cognitive function, clinical global impression, or activities of daily living following 48 weeks of supplementation. *Cistanche* supplementation was also found to be well tolerated, with all adverse reactions being mild.²²

Panax ginseng

P. ginseng is a popular herb that has been used in TCM for thousands of years, and is traditionally believed to support physical and mental vitality. Ginsenosides (a group of triterpene saponins extracted from the plant's root) are considered some of the major medicinal constituents of ginseng. Ginsenosides have been found to extend life span in a nematode model.²³

In a model of cellular senescence, the ginsenoside Rg1 has been found to increase telomerase expression and prevent terminal restriction fragment shortening (terminal restriction fragment analysis is considered the gold standard assay for measuring telomere length).²⁴ In a mouse model of hematopoietic stem cell aging, Rg1 was also determined to reduce the number of cells entering the G1 phase, decrease telomere shortening, and increase telomerase activity.²⁵ While numerous clinical trials of Rg1 and other ginseng extracts have been performed for various conditions, no clinical trials evaluating the effects of *P. ginseng* extracts specifically for telomere function in people have been performed to date.

Angelica sinensis

The root of *A. sinensis*, Dong quai, is traditionally used to support circulation and immune function, and for female health and menstrual concerns. Polysaccharides extracted from the root of Dong quai have antioxidant, neuroprotective, and immune modulating properties.²⁶ In a mouse model of hematopoietic stem cell aging, Dong quai polysaccharide increased telomerase and telomere length. It also reduced expression of P53 protein.²⁷ Recall that P53 protein acts as a transcription factor for DNA repair and apoptosis, and that P53 activation also modulates aging and cellular senescence. The appropriate level of P53 expression is likely to be dependent on the cellular or tissue context.²⁸ While increasing levels of P53 may offer benefits in some contexts, cellular stressors (such as radiation, used in the study above as part of the aging model) may also lead to apoptosis via increased P53 expression. Hematopoietic cells appear to be especially vulnerable to this type of damage,²⁸ and in the study above, radiation led to overexpression of P53, while Dong quai was protective and reduced P53. No clinical trials examining the effects of Dong quai extracts on telomeres are currently available.

Why Polysaccharides?

Note that with three of the four botanical medicines discussed above, the active constituent often chosen for study has been a polysaccharide compound. Polysaccharides are macromolecules with complex chemical structures. One fascinating aspect of these compounds is that while some plant polysaccharides promote telomerase to reduce senescence in healthy cells, others have been shown to reduce telomerase in tumor cells,

contributing to an anticancer effect.^{19,29,30} For example, polysaccharides from reishi (*Ganoderma lucidum*) and shiitake (*Lentinula edodes*) mushrooms have been found to inhibit telomerase activity in cancer cells.^{30–32} Polysaccharides appear to be modulators or regulators of telomerase activity, but this activity may depend on the specific disease or tissue context.³³ Of course, the effects of polysaccharides go far beyond telomeres (including antioxidative and anti-inflammatory actions). The botanical medicines listed above are only a few examples of polysaccharide-containing plants, and there are many opportunities for future study in this area.

The mTOR Pathway

mTOR is a protein kinase and part of the phosphoinositide 3-kinase (PI3K) family of kinases. The mTOR pathway is a central regulator of cell growth, and controls anabolism and catabolism in response to environmental elements. Factors such as fasting and feeding, oxygen levels, amino acid availability, inflammation, DNA damage, and the presence or absence of various growth factors or cytokines all influence mTOR activity.³⁴ This pathway is involved in numerous cellular processes, including the following:

- Protein synthesis (essential for cell growth)
- Lipid synthesis (also essential for cell growth)
- Autophagy
- Apoptosis
- Mitochondrial metabolism
- Mitochondrial biogenesis (the process by which cells increase mitochondrial mass or change mitochondrial composition in response to external factors such as physical activity)

The effects of these activities are wide ranging in the body, and are crucial for growth, cellular proliferation (and therefore cancer), metabolism, and immune function. Overactivation of mTOR has been linked to cellular aging and type 2 diabetes.³⁵

Rapamycin (named for Rapa Nui, or Easter Island, where it was originally discovered when isolated from a soil bacterium) is an mTOR inhibitor and the only pharmacologic agent known to increase life span across all models studied, from yeast to nematodes to mammals.³⁶ A number of mTOR inhibitors or rapalogs are also U.S. Food and Drug Administration approved as oncology drugs. Might botanical medicine also have some potential to affect the mTOR system? Again, the research in this area is preclinical in nature, but may offer some clues.

Rhodiola rosea

The root of *R. rosea*, also known as Arctic root or roseroot, grows in high-altitude areas (ranging from roughly 11,500 feet to 16,000 feet in elevation) in central Asia, Europe, and North America, including, as the name implies, across arctic regions.³⁷ Salidroside, a glucoside compound, is one of the plant's active constituents and may be extracted from the

root. Salidroside has been found to extend life span in fish, as well as in a *Drosophila* model of Huntington's disease.^{38,39} In preclinical models, salidroside has been found to have a number of interesting effects that are mediated by activation of the mTOR pathway. It may protect the endothelium against oxidative injury, promote the differentiation of bone marrow stem cells into neural cells, and protect neurons from ischemic injury.^{40–42} In cancer cell line studies, salidroside may inhibit the mTOR pathway, resulting in an antiproliferative and proapoptotic effect. As with the plant polysaccharides as discussed above, the effects of salidroside on the mTOR pathway may be tissue dependent, with differing effects in normal tissue and tumor cells.⁴³

An additional cell study supports the use of *Rhodiola* to regulate mTOR expression. A botanical agent made from extracts of *Rhodiola wallichiana* (which grows in alpine regions in Pakistan and northern India and is also known as Wallich's *Rhodiola*) was examined for its protective effects on cardiomyocytes in a hypoxia-induced model of cellular oxidation. Not only did application of this *Rhodiola* extract reduce oxidative stress, but it also increased cellular viability, increased mitochondrial oxygen consumption, decreased apoptosis, increased autophagy, and reduced mTOR levels.⁴⁴

Curcumin

Curcumin, the polyphenolic extract of the root of *Curcuma longa*, may also have an impact on the processes that regulate aging. Curcumin has been shown to improve life span in a nematode model, a *Drosophila* model, and in mice.⁴⁵ These affects have largely been attributed to a reduction of ROS and a downregulation of several genes related to aging.

In a human cell line study, application of curcumin has been shown to reduce oxidative stress and have a protective effect by inhibiting phosphorylation of mTOR.⁴⁶ In a mouse model, curcumin has also been shown to inhibit mTOR signaling, leading to enhanced autophagy and decreased cellular apoptosis.⁴⁷ Not only may curcumin work by inhibiting mTOR phosphorylation, it may also work by causing dissociation of regulatory-associated protein of mTOR (raptor protein from mTOR).⁴⁸ This same mechanism (a dissociation of the raptor protein from mTOR) is also responsible for rapamycin's inhibitory effects.⁴⁹

While numerous clinical trials have been conducted on curcumin supplementation, demonstrating anti-inflammatory or anticancer effects,^{50–56} no human trials investigating a direct effect of curcumin on mTOR have been performed.

Resveratrol

While resveratrol is perhaps best known for its effects as an activator of sirtuin⁵⁷ (which we will discuss in Part 2 of this review), resveratrol's actions may also be mediated through an impact on mTOR. Interest in this plant polyphenol found in grapes, red wine, and berries, initially came about with the detection of its antioxidant and free radical-scavenging properties. Multiple preclinical studies examining the role of mTOR in these antioxidative activities of resveratrol have been performed.

Cell studies provide the first evidence of resveratrol effects on mTOR. A 2017 cell study examined the effects of resveratrol on fibroblasts from both pathologic scar tissue and normal skin tissue from human donors. Application of resveratrol resulted in a statistically significant ($P < 0.05$) reduction in expression of both mTOR and ribosomal protein S6 kinase, otherwise known as 70S6K (a key downstream target of mTOR that modulates autophagy), in pathologic scar fibroblast cells. This inhibition appeared to occur in a dose-dependent manner.⁵⁸

As mentioned above, the mechanisms involved in aging are interrelated and interact with each other. Crosstalk may occur, for example, between sirtuins and mTOR, and sirtuin deficiency may lead to increased mTOR signaling.^{59,60} One question that arises from this is whether or not effects of resveratrol on mTOR may simply be related to its activity on sirtuin. The answer appears to be no. A 2010 cell line study found that resveratrol exerted effects on mTOR by both sirtuin-dependent, and sirtuin-independent mechanisms of action.⁶⁰ An additional 2010 cell study found that resveratrol effects on mTOR were sirtuin independent, and were also independent of Akt (a downstream effector of PI3K) signaling. In this study, resveratrol seemed to work by increasing the association of mTOR with its inhibitor, DEP domain-containing mTOR-interacting (DEPTOR) protein.⁶¹ DEPTOR protein normally inhibits mTOR by directly binding to it and reducing its kinase activity. Therefore, increasing DEPTOR binding results in a downregulation of mTOR activity. An important side note is that DEPTOR levels are often low in many tumors, leading to upregulation of mTOR.⁶² Substances that either increase DEPTOR or enhance and regulate DEPTOR binding could theoretically be important in inhibiting cancers.

Animal studies provide additional evidence on mTOR and resveratrol. A 2018 study examined the effects of resveratrol in an experimentally induced cell model of oxidative endothelial damage. Palmitic acid (the long-chain saturated fat commonly found in palm oil) was used to induce ROS in human aortic endothelial cells as well as in mice. In these experimental models, application of resveratrol was found to reduce superoxide formation and improve endothelial dysfunction induced by palmitic acid. Resveratrol was also found to reduce mTOR phosphorylation in a dose-dependent manner, leading to improved autophagy.⁶³ Recall that autophagy is an important normal mechanism by which intracellular proteins or damaged organelles such as mitochondria are cleared and eliminated. Autophagy prevents cellular necrosis, promotes normal senescence, and protects cells against genome damage. By helping cells adapt to and respond to stress, autophagy can delay cellular apoptosis and extend the life span of the cell.⁶⁴ It therefore plays a very important function in aging and neurodegeneration, and many interventions that have been found to extend life span in model organisms have been found to work via stimulation of autophagy.⁶⁵

Additional animal studies also support mTOR as a mechanism by which resveratrol may exert its effects. In a mouse model of scleroderma, resveratrol was used to activate sirtuin-1, which led to a reduction in inflammation and fibrosis.

Resveratrol was also found to improve mTOR in both fibroblast cells taken from people with scleroderma and in tissue from the mice with experimentally induced scleroderma.⁶⁶

In one last animal study from 2019 (a mouse skin transplant model), treatment with resveratrol resulted in a reduction of mTOR expression. Combined administration of an immunosuppressant with resveratrol also resulted in a decrease in inflammatory cell infiltration of skin graft tissue as well as in cytokine production. Application of resveratrol resulted in reduced phosphorylation of mTOR in a dose-dependent manner.⁶⁷ This study provides an important reminder that the mTOR pathway plays a key role in T cell differentiation, and therefore in the immune response.

Resveratrol has also been found to extend life span in a number of model organisms, including yeast, flies, bees, fish, and mice, with mechanisms for these effects likely being multiple.⁶⁸ At this time, no human studies specific to mTOR and resveratrol supplementation have been performed.

Green Tea

Green tea, one of the most frequently consumed beverages the world over, contains a number of medicinal constituents. These include the catechin epigallocatechin-3-gallate (EGCG) as well as theanine, an amino acid. Both of these compounds may offer benefits related to modulation of mTOR expression.

Takarada et al. studied the effects of theanine on mTOR signaling in murine neural progenitor cells (NPCs), the central nervous system cells that differentiate into glial and neuronal cells. Theanine was found to substantially alter phosphorylation of mTOR in NPCs, and to increase the size of murine hippocampal neurospheres.⁶⁹ Since cellular senescence of NPCs may be involved in some neurodegenerative conditions, therapies that influence these crucial stem cells may have important implications for pathologies or aging of the brain.

Holczer et al. examined EGCG's effects on mTOR, specifically looking at endoplasmic reticulum (ER) stress in a human cell line. There are numerous reasons for focusing on ER stress in this type of study. The ER is intimately involved in cellular homeostasis, and prolonged stress to the ER can trigger cellular apoptosis. Aging is associated with numerous changes to the way the ER responds to stress, including alterations to chaperoning and enzyme activity within the organelle.⁷⁰ Damages induced by ER stress are also apparent in many pathologic processes, including diabetes, atherosclerosis, cancer, obesity, neurodegenerative disease, and many inflammatory conditions.^{70,71} In Holczer's study, human embryonic kidney cells were pretreated with EGCG, and then with a substance that induces ER stress. In this study, the substance used was either thapsigargin or tunicamycin. Thapsigargin is a sesquiterpene lactone extracted from the toxic plant *Thapsia garganica*, and works by disrupting calcium storage in the ER. Tunicamycin is a substance produced by *Streptomyces* bacteria species that disrupts protein folding in the ER. EGCG was found to have a protective effect on the cells under these experimental conditions, and it significantly improved cell viability and delayed apoptosis by increasing

autophagy. EGCG also helped downregulate the mTOR pathway.⁷¹ In addition to EGCG, other plants or plant substances found to impact ER stress include curcumin, pterostilbene, *Oplopanax horridus*, the icariin flavonoid from *Epimedium brevicornum*, quercetin, berberine, and baicalein, although in many cases no data are available specific to the role of mTOR in these plants' activities.⁷²

Conclusions

Successful aging requires achieving a balance between normal aging-related cellular changes and the body's inherent repair mechanisms. We all want to maintain our cognitive and physical health as we age, and be free of disease. In Part 1 of this review, we have examined some of the early evidence on botanical medicine and phytochemicals that may help achieve those goals by either supporting telomere function, or by regulating the mTOR pathway. In Part 2 of this review, we move on to discuss PGC-1 α , sirtuin proteins, AMPK, and Nrf2. While this review is largely a discussion of mechanistic theories of aging, the end goal is always to look at translating this to therapeutic outcomes and thinking about how these theories may impact our patients' health. The study of botanical medicine and telomeres or mTOR is largely preclinical at this time, and there are many opportunities to conduct clinical research in these areas. Such research would help us better understand how these mechanisms may translate into real outcomes in promoting healthy aging and longevity for the patients we care for. ■

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