Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

TA-65®

Evidence Summary

No direct evidence for neuroprotection. Possibly protects against some aspects of cardiovascular and metabolic disease, which might in turn protect the brain. Likely safe, although long-term intake has not been tested.

Neuroprotective Benefit: No direct effect research available, but could theoretically promote neural stem cell proliferation.

Aging and related health concerns: Limited clinical evidence suggests possible benefits to glucose tolerance and cardiovascular health, though effects are not conclusively attributed to TA-65. May protect against cellular senescence by protecting telomere length during aging.

Safety: One short-term open-label non-randomized clinical trial has tested TA-65 and reported no adverse effects. It has been granted GRAS status as a medical food, but there is a possibility for increased cancer risk and long-term safety studies are needed.

What is it? TA-65 is a plant-based compound made from isolated extracts of *Astragalus membranaceus*, and is a patented product of T.A. Sciences®. It is marketed as a nutraceutical, whose function is to activate telomerase. Telomerase protects against telomere shortening, a common and potentially causative feature of aging.

Neuroprotective Benefit: No direct effect research is available, but could theoretically promote neural stem cell proliferation.

Types of evidence:

- No clinical trials.
- Observational autopsy studies on the theoretical relationship between telomere length and neurodegenerative disease

Theoretically, by protecting against telomere shortening due to cell replication, oxidative damage, or chronic inflammation, TA-65 may protect against neurodegenerative diseases. However, the importance of telomere shortening to neurodegenerative disease is highly speculative and unproven. Shorter leukocyte telomere length does not reliably associate with Alzheimer's disease or Parkinson's disease, although it has more frequently been associated with all-cause dementia. Also, autopsy studies suggest that telomere length of peripheral cell populations (e.g. leukocytes) do not reliably correlate with telomere length in brain regions (Eitan et al., 2014).

Telomerase and telomerase reverse transcriptase (TERT) activity are at high levels during embryonic development. Subsequently they are significantly down regulated and no longer detectable in the adult brain except for within the adult subventricular zone, the olfactory bulb, the hippocampus, and parts of the cerebellum and cortex, with many of these retaining stem cells through adulthood (Eitan et al., 2012). These findings of the limited presence of telomerase in the brain suggest that telomerase activators may not protect the brain unless, perhaps, through stem cell populations.

Aging and related health concerns: Limited clinical evidence suggests possible benefits to glucose tolerance and cardiovascular health, though effects are not conclusively attributed to TA-65. May protect against cellular senescence by protecting telomere length during aging.

Types of evidence:

- 1 clinical trial involving a combination health maintenance program which included TA-65 as well as a dietary supplement pack and physician counseling (Harley et al., 2011, 2013)
- 2 preclinical studies examining TA-65 on health indicators in mice and cellular regeneration in zebra finches (de Jesus et al., 2011, Reicher et al., 2014)
- 1 preclinical trial implementing a telomerase gene therapy, AAV9, another telomerase activator, with mice

Telomerase is composed of a protein called TERT and several telomere-associated proteins. Telomerase protects against telomere shortening, a common and potentially causative feature of aging. Telomere length in leukocytes is a putative, if unreliable, biomarker of biological age, with accelerated shortening observed with chronic disease states like diabetes, cardiovascular disease, and arthritis, and slowed shortening by regular exercise. It is suggested that telomerase serves an anti-apoptotic role, where TERT acts by interrupting apoptotic signaling which results in mitochondrial dysfunction and caspase activation (Fu et al., 1999, Karlseder et al., 1999, Li et al., 1999, Mattson et al., 2000).

There is no direct evidence that TA-65 extends lifespan in any animal model. However, some research suggests potential positive effects on indicators of cellular aging in the immune system. One non-randomized, non-controlled clinical trial with 114 participants (72% male) involving a health maintenance and dietary supplement program called "PattonProtocol-1", reported that TA-65, starting at 5-10 mg daily intake and after several months progressing to 25-50 mg daily intake, increased telomerase activity by two- to three-fold in human neonatal keratinocytes *in vitro*, in a dose-responsive manner. *In vivo* results demonstrated a decline in the percentage of senescent cytotoxic ($CD8^+/CD28^-$) T cells, although this decline was not significant. Most of these decreases were seen in cytomegalovirus (CMV) seropositive subjects. While average telomere length was unaffected, the percentage of short leukocyte telomeres was decreased, suggesting that TA-65 upregulated telomerase (Harley et al, 2011) because telomerase has been shown to preferentially act on the shortest telomeres (Hemann et al., 2001).

A follow-up report on the same study found that both fasting glucose and insulin levels declined significantly each year compared to baseline values. Together these reductions signal a probable

improvement in insulin sensitivity, which has been associated with leukocyte telomere length. Additionally, total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels were significantly reduced after 12 months. There was also an observed decline in systolic and diastolic blood pressure after one year. However, when results were stratified by degree of biomarker measure (i.e. high, middle, and low glucose, LDL, and blood pressure), significant reductions were only observed in the high and middle groups, with little or no change in the low to normal measures. In conclusion, some potential benefits were seen from the PattonProtocol-1 treatment, but the study was neither controlled nor randomized. In addition, the treatment included not just TA-65 but also other supplements and health maintenance activities, making it impossible to conclude if the observed responses had anything to do with TA-65 (Harley et al., 2013).

An additional preclinical study demonstrated that female mice treated with TA-65 exhibited increased telomerase activity, elongation of short telomeres, and reduction of DNA damage. TA-65 treatment increased telomerase activity by approximately two-fold and resulted in telomerase-dependent elongation of short telomeres and reduction of DNA damage in mouse fibroblasts haplo-insufficient for the telomerase RNA subunit *in vitro* at three months post-treatment. Treatment of telomerase-proficient and telomerase-deficient cells showed a 1.6-2.9% decrease in the percentage of "signal-free ends" and 1.9-3.3% decrease in short telomeres, compared to the control group. After three months of dietary supplementation *in vivo,* TA-65 treated mice showed a significant 10-fold increase in mouse TERT (mTERT) mRNA and protein levels in the liver. Moderate but insignificant increases were also exhibited in kidney, lung, and brain tissues. These increased levels of mTERT in the liver in TA-65-treated mice correlated with an increase in mRNA levels of two transcription factors regulated by the Mitogen-activated protein kinase (MAPK) pathway, JunB and c-Myc (de Jesus et al., 2011). These results correlate with existing evidence showing that the MAPK pathway mediates TAT2 action, another telomerase activator derived from Astragalus (Fauce et al., 2008).

Results from this study also demonstrated improvements in health-span indicators in female mice. Improvements in glucose uptake capacity were seen at four months post-treatment, as well as lower levels of blood insulin at six months post-treatment, resulting in a better homoeostasis model assessment of insulin resistance. However, while at 12 months post-treatment an improved glucose uptake was observed, lower insulin levels were not seen, suggesting that the potential health benefits of TA-65 may not be retained after discontinuing use. Additionally, TA-65-treated mice showed a lesser accumulation of fat in the liver at older ages when compared to control mice, which might suggest a liver protective property of TA-65. There was also a significant increase in fat content in the subcutaneous and epidermal layer in TA-65-treated 1-year old mice compared to untreated controls;

this significant change was not seen in 2-year old mice, however. Overall, the TA-65-treatment resulted in a significant increase in cell proliferation in the epidermis. TA-65 treatment also increased wound-healing capacity of keratinocytes *in vitro* in addition to increasing accelerated hair regrowth *in vivo*. Finally, 2-year old TA-65-treated mice also showed improved bone density compared to the control group. However, these results did not show an increase in longevity for TA-65-treated female mice. Additionally, this study also evaluated cancer incidence and did not observe a statistically significant cancer incidence for mice treated with TA-65. In summary, the animal study suggests that TA-65 can improve health span but not necessarily lifespan in mice (de Jesus et al, 2011).

An additional study examining the effects of TA-65 on adult male zebra finches demonstrated longer red blood cell telomere lengths as well as increased rates of feather regrowth compared to control birds (Reichert et al., 2014). Flight feather growth is essential for bird individual performances, self-maintenance, and survival, and was therefore used as a proxy for individual tissue renewal capacity (Lindhe Norberg, 2002). This study's results also exhibited a significant correlation between telomere length and feather regrowth rate, extending the potential of the relationship between increased telomerase activity and cell renewal rate (Reichert et al., 2014).

One study that investigated a telomerase gene therapy other than TA-65 also showed potential implications for improvements in cellular aging. The TERT-based therapy implemented a recombinant AAV serotype, AAV9, with 1- and 2-year old mice. Increasing TERT-activity in this way improved various biomarkers such as increasing bone mineral density, reducing fasting insulin, and also showed enhanced performance in neuromuscular and memory tests. All of these improvements were coincidentally accompanied by increased levels of mTERT mRNA in relevant cells. Additionally, results demonstrated a significant extension of lifespan in treated mice compared to the control mice. To investigate potential mechanisms behind these observed effects, this study examined telomere lengths and found that most tissues from treated mice exhibited longer telomeres than the untreated controls. This study also assessed cancer incidence and did not observe increased incidence in treated mice compared to control groups (de Jesus et al., 2012).

Safety: One short-term open-label non-randomized clinical trial has tested TA-65 and reported no adverse effects. It has been granted GRAS status as a medical food, but there is a possibility for increased cancer risk and long-term safety studies are needed.

Clinical studies with TA Sciences have reported few adverse events and zero cases have been attributed to TA-65 specifically by subjects' medical providers (Harley et al., 2013). In November 2014, TA-65 was determined by an independent review panel as Generally Recognized as Safe (GRAS) for medical food use according to provisions of the Federal Food, Drug and Cosmetic Act, administered by the US Food and Drug Administration (FDA) (TA Sciences).

Cancer: Although telomerase inhibitors are being tested as cancer treatments, suggesting a theoretical risk of telomerase activators like TA-65, a mouse study reported that TA-65 does not increase tumorigenesis. No clinical evidence is available. Due to telomerase activators' ability to increase cell proliferation, one study evaluated if TA-65 treatment was associated with increased cancer incidence in mice. TA-65-treated mice had a similar cancer incidence compared to control mice, with a decreased number of sarcomas and slightly increased lymphoma incidence. There was a non-significant trend for an increase in liver cancer in TA-65 treated mice (Bernardes de Jesus et al, 2011). On the other hand, telomerase inhibitors are under investigation as a treatment for cancer. One study demonstrated that telomerase inhibition, through inhibition of the catalytic protein subunit of telomerase, human telomerase reverse transcriptase (hTERT), led to telomere shortening and consequent apoptosis in a p53-independent manner. hTERT inhibition also limited the growth of tumors in cells *in vitro* and limited their tumorigenic capacity *in vivo* (Hahn et al., 1999). Recently, Geron and Jannsen Biotech, Inc. announced a collaboration to develop and commercialize, imetelstat, which is Geron's telomerase inhibitor product candidate as a cancer therapy (Geron 2014). The initiation of such studies suggests a theoretical risk posed by long-term use of telomerase activators. However, there is currently only preclinical evidence available on this safety concern, and evidence mostly reveals the potential of telomerase inhibition on tumor apoptosis. However, it will be important to continue further research to determine whether telomerase activation acts specifically on a pathway responsible for tumor initiation and development, or rather if is effective in simply aiding existing tumor proliferation.

Dosing and Sources: TA-65 is licensed as a nutraceutical by TASciences ®. The optimal dose has not been established.

Future research: Long-term randomized and controlled studies are needed, whether observational or RCT, and with larger sample sizes, in order to test further potential of TA-65 as a telomerase activator,

whether it can have substantial effects on neuroprotection or anti-aging, and also whether it is safe for long-term consumption. There are no trials on record that are currently underway for TA-65.

Search terms:

Pubmed:

- TA-65
- TA-65, cognitive
- TA-65, aging
- TA-65, dementia
- TA-65 cancer
- TA-65, telomerase activator
- TA-65, safety
- TA-65, Alzheimer's disease
- TA-65, mortality
- TA-65, longevity
- TA-65, side effects
- TA-65, neuroprotective
- TA-65, memory

Clinicaltrials.gov:

- TA-65
- Telomerase activator
- Telomerase therapy
- TAT2
- Cycloastragenol

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