PILOT STUDY

The Effects of Fisetin on Reducing Biological Aging: A Pilot Study

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ABSTRACT

Fisetin, a natural flavonoid compound, is a senolytic agent that has shown promise in extending the lifespan of aging mice. Our goal was to determine whether Fisetin can reduce human biological aging, as verified by the TruAge test. This would be the first study in healthy human adults over the age of 50 years old to determine if Fisetin can reduce their biological age. Fisetin 500 mg daily was administered for one week per month for six months. The results showed that four out of ten healthy adults experienced a reduction in biological aging, five out of ten saw an increase, and one out of ten had no change. No adverse effects were noted among the ten subjects. Telomere lengths did not statistically change with the use of Fisetin. Because five of ten had an increase in biological age, taking Fisetin as an anti- aging agent is not recommended until more extensive studies are done. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

In this study, we aimed to explore the potential of Fisetin in reducing biological aging in healthy adult humans. This study is the first to investigate whether Fisetin, without other senolytics, can effectively reduce biological age in healthy humans. A concern is that Fisetin is being touted online as a senolytic agent or an anti-aging supplement; no human studies have confirmed its efficacy. The null hypothesis is that Fisetin does not affect biological aging. A secondary outcome, we tested if Fisetin changes telomere lengths.

Hayflick first described cellular senescence in 1961. He demonstrated that human fibroblasts have a finite capacity for cell division before entering an irreversible growth arrest known as replicative senescence.[1] This finding challenged the long-held concept proposed by Alexis Carrel in 1912 that normal cells were intrinsically immortal.[2] Hayflick hypothesized that tissues age because cells lose their self-renewal ability.[1] It took many decades to prove Hayflick's theory that the accumulation of senescent cells leads to aging and organ dysfunction.

When normal somatic cells age, they become damaged and eliminated via apoptosis. However, some somatic cells can develop into senescent ones by becoming apoptosis-resistant. These senescent cells can stave off their annihilation by withstanding their inflammatory bioactive secretome called senescence-associated secretory phenotype (SASP).[3] This anti-apoptotic benefit allows them to survive despite killing neighboring cells.[3, 4, 5] SASP can create secondary senescence caused by eroding telomeres and DNA lesions that hinder tissue repair and regeneration.[3, 5, 6] The results of one study showed that senescent cells transplanted into the knee joints of mice produce osteoarthritis.[7]

A senolytic agent is often used to mitigate the accumulation and improve the elimination of senescent cells. We chose the senolytic Fisetin for our study due to its extensive beneficial range, including anti-inflammatory, anti-carcinogenic, anti-hyperglycemic, and anti-lipidemic properties.[7] It also has neurotrophic, antioxidative, antimicrobial, and anti-cancer effects. Fisetin can prevent nerve cell death by blocking oxidative stress.[8,9] Overall function improved in animal models with acute kidney injury, diabetic-induced kidney disease, and other chronic diseases.[7] Preclinical models showed that senolytics may prevent or delay frailty and multiple disorders, including musculoskeletal, cardiovascular, hematologic and neuropsychiatric conditions, cancer, and other major organ pathologies.[10] Our literature review found no human clinical trials that test Fisetin alone for reducing biological age.

Since senescent cells cannot replicate, we used an intermittent dose of Fisetin of 500 mg daily for one week per

month.[11] A published study used Quercetin, Dasatinib, and Fisetin in 19 healthy patients with an average age of 60 to see if their biological age would be reduced. The dosage of Dasatinib 50 mg, Quercetin 500 mg, and Fisetin 500 mg was taken for three days in a row once a month for six months. In that study, 11 patients received a non-strawberry-based Fisetin, and eight received a strawberry-based Fisetin. The results did not show any statistically significant reduction of biological aging using the TruAge testing.[12]

For this study, we used strawberry-based Fisetin. It is a flavanol, a subtype of a flavonoid. Fisetin is found in the highest concentration in strawberries and lower concentrations in many other fruits and vegetables. It is consumed often in countries such as Japan with no adverse effects.[13] Fisetin can be administered by oral and intravenous routes. The bioavailability shows that serum levels of free Fisetin quickly decline and sulfated/glucuronidated Fisetin increases.[8] The half-life in mice was an average of three hours.[7]

Fisetin has multiple anti-aging attributes. It is a reducing agent that can neutralize reactive oxygen species, lower peroxidation levels, and upregulate glutathione. Fisetin can increase longevity by suppressing the PI3K/AKT/mTOR pathway, thus inhibiting topoisomerase.[13] The inhibition can halt cancer DNA replication and induce cell cycle arrest, preventing cancer cells from replicating.[14] Fisetin can also block the activity of inflammatory cytokines such as interleukin 6 (IL-6), nuclear factor κB (NF-κB), and tumor necrosis factor-alpha (TNFα).[13] In a study of older mice, Fisetin reduced the effects of aging and increased their longevity.[15]

METHODS

Study Design

The pilot study was conducted at the Institute for Hormonal Balance in Orlando, Florida, and involved ten healthy adults over 50. The Fisetin used in the study was obtained from Diatom Rx Nutrients, www.diatomnutrients.com (Newtonville, NJ). The dose of Fisetin was 500 mg a day consecutively for one week per month for six months. It was to be taken on an empty stomach at least one hour before eating. The 6-month study measured biological age by TruAge prior and at the end of the study.

Since senescent cells do not self-replicate, senolytics are not for daily but for short-term use. They should be cycled to be effective. A prior study by Dr. Lee et al. used the senolytic agents Dasatinib, Quercetin, and Fisetin for three consecutive days per month for six months.[12] The dosing of Fisetin in the current study was based on the results of the previous paper. To determine the efficacy of Fisetin as a solo senolytic agent, we chose to investigate the potential of administering one week of Fisetin (3500 mg) per month versus three days (1500 mg) per month to reduce biological age.

All the patients volunteered for the study; none took any senolytic agents such as Dasatinib with Quercetin. All patients paid for their supplements and testing. The patients did not receive an honorarium. The study's inclusion criteria were any patient from the Institute for Hormonal Balance over 50 years old. The test group consisted of 10 Caucasians, four women (40%) and six men (60%), aged 53 to 72 with an average age of 62. The study excluded patients under 50, those with a history of congestive heart failure (CHF), kidney failure, diabetes, or chronic obstructive pulmonary disease (COPD), those with prior use of Fisetin or an allergic reaction to it, and those being treated for cancer. Patients younger than 50 were excluded from the study because testing an older population to see a reduction in biological age is more attainable. The study focused only on healthy patients, so those with chronic diseases were excluded to avoid the risk of accelerating their conditions.

Below is a list of all the patient's medications and supplements:

Medications	# of patients taking	Supplements	# of patients taking
Progesterone	3	NMN	2
Estradiol	3	*N*-Acetyl Cysteine	2
Testosterone	1	Zinc	10
Desiccated Thyroid	1	Vitamin D	10
Semaglutide	4	Omega 3	1
Low Dose Naltrexone	1	Vitamin C	1
Cialis	1	Endothelial Support	4
Propecia	1	B Complex	7
Clomiphene	1	Glutathione	2
HCG	1	Magnesium	5
		Selenium	1
		CoQ10	1
		Broccoli seed extract	2
		Melatonin	1
		CBD	1
		Diindolylmethane	1
		Nitric Oxide precursor	5
		Vitamin E	1
		Enzymes	1
		Quercetin	1

Abbreviations: NMN, Nicotinamide Mononucleotide; HCG, human chorionic gonadotropin; CBD, Cannabidiol; CoQ10, coenzyme Q10

The four patients on Semaglutide used it for weight loss, not for the treatment of diabetes. Only one person had hypothyroidism and used desiccated thyroid; another patient used Clomiphene and HCG to optimize his testosterone levels. In addition, during the six-month study, no new medications or supplements were added except for taking the prescribed dose of Fisetin.

Epigenetics plays a significant role in aging by methylating DNA, which regulates gene expression.[16] DNA methylation (DNAm) patterns have been employed to measure biological age, known as the epigenetic clock. Epigenetic clocks have emerged as a widely-used biomarker for predicting health span and age-related diseases.[18,19] The first-generation clocks, such as the Hannum clock and Horvath clock, utilize CpG (regions on the DNA where a phosphate follows a cytosine nucleotide and then a guanine nucleotide) sites that are highly associated with chronological age to estimate an individual's biological age.[19, 20] Horvath's model has been widely used as it is the state-of-the-art pan-tissue epigenetic clock for humans.[3,4,5,21] The second-generation epigenetic clocks PhenoAge and GrimAge measure mortality and healthspan.[22,23] The third-generation epigenetic clock DunedinPACE measures the rate of aging.[24] In our study, the biological age is based on Horvath's first-generation clock because of its extensive validation history.[25,26,27]

Each patient's biological age was collected by blood sample at baseline and six months. We used TruAge to

measure biological age and predicted telomere lengths. TruAge was developed by TruDiagnostic Inc. (Lexington, Kentucky). Peripheral whole blood samples were obtained using the lancet and capillary method, then mixed with lysis buffer to preserve the cells. DNA extraction was performed, and 500 ng of DNA was subjected to bisulfite conversion using the EZ DNA Methylation Kit from Zymo Research, following the manufacturer's protocol. The bisulfite-converted DNA samples were randomly allocated to designated Illumina Infinium EPIC850k Beadchip wells. The samples were amplified, hybridized onto the array, and subsequently stained. After washing steps, the variety was imaged using the Illumina iScan SQ instrument to capture raw image intensities, enabling further analysis. The algorithms analyzed by TruAge include first- (Horvath and Hannum), second- (phenoAge, systemsAge, OMICAge, and GrimAge), and third-generation clocks (DunedinPACE). This study predicted telomere length via DNA methylation data using DNAmTL.

DISCUSSION

Senolytics are exciting new therapies that might reduce mortality or improve quality of life. One marker for senescence is senescence-associated β-galactosidase (SA-βgal).[28] A distinctive feature of senescent cells is the increased expression of cell cycle-inhibitory proteins, collectively known as cyclin-dependent kinase inhibitors. The cyclin-dependent kinase inhibitors with the most prominent role in senescent cell accumulation during aging are $p16^{INK4A}$ and $p21^{CIP1}$.[29, 30] Unfortunately, there is no universal senescence marker since all our organs age differently and not all senescent cells behave the same way.[31] Only a tissue biopsy of a particular organ would be necessary to confirm its senescence, an impractical procedure in a clinical setting.

In a prior study by Lee et al., 19 subjects were treated with Dasatinib and Quercetin over six months. The treatment protocol was Dasatinib 50 mg and Quercetin 500 mg for three days per month for six months. Another 19 subjects were treated with six months of Dasatinib, Quercetin, and Fisetin one year later. The treatment protocol was Dasatinib 50 mg, Quercetin 500 mg, and Fisetin 500 mg for three days per month for six months. Significant increases in the acceleration of subjects' epigenetic age were observed in first-generation epigenetic clocks at three and six months, along with a notable decrease in telomere length. However, no significant differences were observed in second and third-generation clocks. Adding Fisetin to the treatment resulted in non-significant increases in epigenetic age acceleration, suggesting a potential mitigating effect of Fisetin on the impact of Dasatinib and Quercetin on epigenetic aging. All the subjects were generally healthy and did not have chronic diseases like poorly controlled diabetes, end-stage renal failure, COPD, or debilitating heart failure.[12]

In the current study, Fisetin reduced the biological age of four of the ten patients (patients 2, 4, 6, 8) and increased the telomere lengths in three (patients 1, 2, 4). See Figure 1. Telomeres are specialized structures of repetitive DNA sequences at the end of the chromosomes. Telomeres shorten with each cell division, eventually leading to cellular senescence. Currently it is unknown if the size of telomere length is related to the change in biological aging. Three of the ten patients had a 0.1-0.2 kilobase (kb) increase in telomere length, while one had a decrease in telomere length and the other six patients had no change in their telomere lengths. Of the three patients (patients 1, 3, 4) who had an increase in

Table 1. Pre and 6-month Post Fisetin Measures of Biological Age and Telomere Length

Patient	Dates: Pre and 6-Month Post Fisetin	Biological Age	Chronological Age	Telomere lengths
1 (F)	07/12/2022	57.49	61.47	7.0 kb
	01/05/2023	58.15	61.96	7.1 kb
2 (M)	08/10/2022	65.72	67.43	6.8 kb
	06/07/2023	63.95	68.26	6.8 kb
3 (M)	08/17/2022	65.68	59.97	6.6 kb
	06/12/2023	65.54	60.79	6.8 kb
4 (F)	09/06/2022	63.92	53.26	6.8 kb
	04/06/2023	57.09	53.77	6.9 kb
5 (M)	09/06/2022	60.1	50.71	6.8 kb
	03/13/2023	63.26	51.43	6.7 kb
6 (F)	08/24/2022	66.46	62.69	6.8 kb
	11/24/2023	64.86	63.49	6.8 kb
7 (M)	08/19/2022	63.28	71.28	6.9 kb
	02/08/2023	64.35	71.72	6.9 kb
8 (M)	10/05/2022	52.3	51.11	7.1 kb
	05/27/2023	51.12	51.75	7.1 kb
9 (F)	05/26/2022	54.88	64.86	7.0 kb
	12/19/2022	59.32	65.43	7.0 kb
10 (M)	05/12/2022	69.44	67.78	6.6 kb
	12/19/2022	70.11	68.38	6.6 kb

Figure 1. Fisetin's Effect on Biological Age

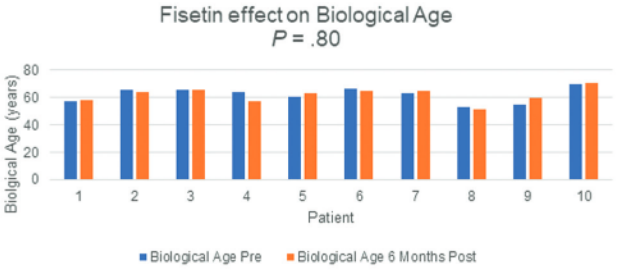

Figure 2. Fisetin's Effect on Telomere Length (kb)

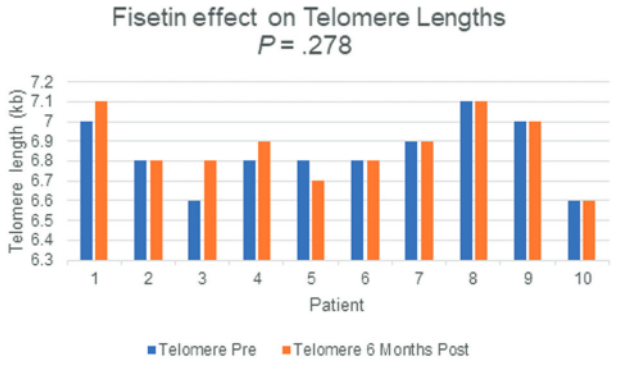

Table 2. Three Patients with Increased Telomere Lengths and Their Biological Age

Patient	Telomere length	Biological Age
1 (Female)	7.0 kb increased to 7.1 kb	Older
3 (Male)	6.6 kb increased to 6.8 kb	No Change
4 (Female)	6.8 kb increased to 6.9 kb	Younger

telomere length, one (patient 4) had a reduction in biological aging. In contrast, another (patient 3) had no change in biological age and the third, (patient 1) had an increase in biological age. Thus, no relationship exists between Fisetin's ability to decrease biological aging and an increase in telomere length. See Figure 2 and Table 2. A two-tailed *t* test showed no statistical difference in Fisetin reducing biological aging ($P = .80$) or increasing telomere lengths ($P = .28$).

In this study, five of the ten patients had an increase in their biological age over six months. Medications and supplements may have affected their results. Other methods have proven effective in reducing biological age. Metformin has been considered an anti-aging medication because it reduces mTOR and AMPK pathways.[32] Glucagon-like peptide 1 (GLP-1) agonists may play a role in slowing the aging process with GLP-1 agonists interacting with the Sirt1, mTOR, and AMPK pathways.[33] Estradiol may have a positive effect on the aging process. A study using the GlycanAge (a biomarker based on glycans attached to immunoglobulin G) test showed that estradiol reduced the glycan age.[34] Astragalus extract supplement can increase telomere lengths with telomerase activation.[35] To elicit a different outcome for a future study on Fisetin, eliminating the confounding variable of medications and supplements would require patients to stop them before the study.

Another possible confounding factor is stress. It is the most common cause of an increase in biological age. In interviews, none of the patients referred to life-altering events like a death in the family, a move, or bankruptcy.

It is a concern that Fisetin 500 mg daily for one week per month increased five out of ten patients' biological age. Although senescence varies in all individuals, using Fisetin in healthy adults does not seem prudent as it might increase their biological age. These results also correlate to the findings in the six-month study of Dasatinib, Quercetin, and Fisetin. Adding Fisetin to the treatment resulted in a non-significant increase in epigenetic age acceleration.[11] Perhaps the ones who responded to Fisetin (4/10) in the Fisetin-only study might have had some early senescence. There is a range of senescence from early to advanced stages similar to the range in diabetes from prediabetes to end-stage diabetes with multiple organ failure. Until there is a universal marker for senescence, we have no idea if someone will benefit from a senolytic agent. In contrast, the other five healthy patients with increased biological age are of concern, so more studies are needed to address this issue.

Limitations

The study lacked ethnic variability, the sample size was small, and all the subjects were healthy. Another confounding variable is the influence of each patient's medications and supplements. In addition, currently, there is no universal serum marker for senescence. If a universal senescence marker were found, another study would be needed to evaluate whether Fisetin would be beneficial.

CONCLUSION

Out of ten healthy adults taking strawberry-based Fisetin 500 mg daily one week per month for six months, four showed a reduction in biological aging. In contrast, one out of ten showed no change, and five out of ten showed increased biological aging. In conclusion, Fisetin did not statistically reduce biological age ($P = .80$) or increase telomere lengths ($P = .28$). These results also correlate to the finding in the six-month study of Dasatinib, Quercetin, and Fisetin, where adding Fisetin to Dasatinib and Quercetin resulted in a non-significant increase in epigenetic age acceleration.[11] Because five out of ten showed an increase in biological age, taking Fisetin as an anti-aging supplement is not recommended until more extensive studies are done. Further studies focusing on specific age, ethnic background, and gender while subjects are not taking other therapeutics in advance could elucidate more precise results.

AUTHOR DISCLOSURE STATEMENT

Edwin Lee, MD, and Morgan Burns, NP, have no financial interests to disclose.

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