PILOT STUDY

Effects of Spermidine-Rich Rice Germ Extract Supplement on Biomarkers of Healthy Aging and Autophagy—Proof-of-Concept Pilot Study

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ABSTRACT

Background • Although epidemiological and preclinical research suggests that the polyamine spermidine improves the efficiency of autophagy, human clinical research demonstrating a specific dose of any source of spermidine capable of increasing biomarkers of autophagy is lacking.

Primary Study Objective • The study aimed to examine the effects of spermidine from Miricell™ rice germ extract (Nutraland USA) on biomarkers/indices of autophagy, neuroprotection, and cardiometabolic health, as well as safety and adverse events.

Methods/Design • This 56-day study was conducted as a single-blinded, interventional, parallel-group, pilot trial. Vitals, diet records, and protocol compliance were recorded at weeks 0 and 8. Blood draws for cardiometabolic markers and adverse event monitoring took place at screening and weeks 0 and 8.

Setting • Conducted at a clinical research laboratory in Ohio.

Participants • Twelve (N=12) healthy men and women (age: 54.5 ± 7.9 years).

Intervention • Random assignment to 1.5 mg or 3.3 mg of spermidine daily from Miricell™ rice germ extract (Nutraland USA).

Primary Outcome Measures • Biomarkers of autophagy [Beclin-1 and Unc-51-like kinase 1(ULK1)], and biomarkers/indices of neuroprotection, including brain-derived neurotrophic factor (BDNF), homocysteine, and cardiometabolic health (high sensitivity C-reactive protein (hs-CRP), lipid panel).

Results • Compared to baseline, only the 3.3 mg dose of spermidine from Miricell™ increased Beclin-1 by 7.3%, ULK-1 by 13.4%, and BDNF by 12.1%. Compared to baseline, the same dose resulted in a 20.8% decrease in hs-CRP, a 20.1% decrease in VLDL, and a 26.9% decrease in triglycerides. Secondary outcomes, including clinical chemistry panel, CBC, vital signs, and adverse events, reflect a good safety profile for the use of 3.3 mg/day of spermidine from Miricell™.

Conclusion • This pilot study found that 3.3 mg/day of spermidine from Miricell™ rice germ extract tends to improve biomarkers of autophagy, neuroprotection, and cardiometabolic health. Appropriate follow-up studies are warranted to confirm these findings. (*Altern Ther Health Med.* [E-pub ahead of print.])

Keywords • spermidine, autophagy, beclin-1, ULK1, rice germ extract, neuroprotection, BDNF, homocysteine, cardiometabolic, CRP, C-reactive protein, VLDL, triglycerides, aging

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INTRODUCTION

Autophagy is a fundamental, evolutionarily conserved cellular process that regulates the breakdown and recycling of intracellular components, ensuring cellular homeostasis and adaptability in eukaryotic cells.[1] This process selectively targets damaged organelles, misfolded proteins, and intracellular pathogens for degradation within lysosomes.[1]

The role of autophagy extends far beyond simple waste disposal, influencing organellar quality control, immune function, cancer biology, metabolism, and cellular stress resistance. These diverse roles make autophagy a key regulator of aging, neurodegeneration, cardiovascular health, and metabolic balance, with broad implications for disease prevention and longevity.[2]

The molecular mechanisms underlying autophagy were largely deciphered through genetic studies in yeast, leading to the discovery of autophagy-related (ATG) genes, which encode

conserved proteins such as Atg8 (LC3 in mammals) and Atg1 (ULK1), both essential for autophagosome formation and cargo recognition.[3] Studies in various model organisms, including yeast, nematodes, and mice, have demonstrated that single-gene mutations affecting nutrient-sensing and stress-response pathways can extend lifespan. Many of these lifespan-extending mutations, such as those affecting the insulin/IGF-1 signaling pathway, mechanistic target of rapamycin, and AMP-activated protein kinase, have been shown to enhance autophagic activity.[4] This suggests that autophagy is not merely a consequence of lifespan extension but may be a fundamental mechanism underlying longevity itself.

Pharmacological and dietary interventions that promote autophagy, including caloric restriction, fasting, rapamycin, and metformin, have similarly been associated with lifespan extension and improved health.[5] These findings support the hypothesis that maintaining autophagic efficiency throughout aging may mitigate cellular damage, preserve metabolic function, and delay the onset of age-related diseases, making autophagy a promising target for interventions aimed at promoting healthy aging.

Spermidine, along with spermine and putrescine, are polyamines synthesized in every living cell and are contained in foods. They possess many physiological activities similar to polyphenols, including antioxidant and anti-inflammatory properties, cell and gene protection, and autophagy activation. Research has reported that increased polyamine intake (primarily spermidine) over a long period increases blood spermine levels and inhibits aging-associated pathologies and pro-inflammatory status in humans and mice, while also extending the life span of mice.[6]

Spermidine has been shown to improve the efficiency of autophagy.[7,8,9,10] In a follow-up study of a cohort of 829 participants over 20 years, spermidine showed the strongest inverse relation with mortality, among 146 nutrients investigated. This effect was dose-dependent, and the researchers explained that spermidine effectively induced autophagy and could reduce the acetylation of histones, which are crucial for cell homeostasis in aging. Therefore, a diet rich in spermidine, mainly comprising foods of vegetable origin, was associated with a decrease in the risk of all-cause mortality in the general community.[9]

To the best of our knowledge, all previous human research on spermidine promoting autophagy has been limited to epidemiological studies; thus, the appropriate dosage level in dietary supplements for promoting autophagy remains unknown. Consequently, we performed a proof-of-concept, interventional pilot study to measure and document the effects of a branded form of spermidine (Miricell™ rice germ extract, Nutraland USA) on biomarkers of healthy aging and autophagy.

METHODS

Study Design and Participants

This was a 56-day, single-blind, interventional, parallel-group, pilot study. Six men and six women [age: 54.5 ± 7.9 years, mass: 93.1 ± 18.0 kg, and body mass index (BMI): 31.1 ± 2.2 kg/m^2] completed the study. Participant inclusion and exclusion criteria are detailed in Table 1.

Table 1. Inclusion/Exclusion Criteria

Main inclusion criteria:
• Body mass index 18.5-34.9 (inclusive) • Subject agreed to maintain their existing dietary patterns throughout the study period. • Subject agreed to refrain from alcohol, caffeine, and strenuous exercise for 24 hours before each test day. • Subject was willing and able to comply with the study protocol. • Subject gave voluntary, written, informed consent to participate in the study.
Main exclusion criteria:
• Individuals who were determined to have liver, renal, cardiovascular, or other metabolic disease. • Use of any dietary supplements or medications that may confound the study or its endpoints. • Alcohol consumption (>2 standard alcoholic drinks/day or >10 drinks/week) or drug abuse/dependence. • Smokers. • Clinically significant abnormal laboratory results at screening. • Allergy or sensitivity to study product ingredients. • Individuals who were cognitively impaired and/or who are unable to give informed consent. • Individuals with diabetes, asthma, rheumatoid arthritis, colitis, irritable bowel syndrome/irritable bowel disease, gout, or fibromyalgia. • Any other condition which, in the primary investigator's opinion, might adversely affect the subject's ability to complete the study, its measurements, or pose a significant risk to the subject.

Table 2. Study Schematic

	Screening (Visit 1)	Visit 2 (Week 0)	Visit 3 (Week 8)
Screening Procedures:			
Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Medical History	X		
Height, Weight, BMI	X		
Diet Collection		X	X
Biomarkers of autophagy (Beclin-1, ULK1)		X	X
Indices of neuroprotection (BDNF, homocysteine)		X	X
Indices of cardio-metabolic health: C-reactive protein, CMP, lipid panel, CBC	X		X
Vitals (HR and BP)		X	X
3-day Diet Records/Analysis/Repeat		X	X
Protocol Compliance (diet and physical activity log check)		X	X
Dispense Test Product		X	
Adverse Events Monitoring	X	X	X

Abbreviations: BMI, body mass index; ULK1, Unc-51-like kinase; BDNF, brain-derived neurotrophic factor; CMP, comprehensive metabolic panel; CBC, complete blood count; HR, heart rate; BP, blood pressure.

The primary outcomes were biomarkers of autophagy, including Beclin-1 and ULK1. The secondary outcomes include biomarkers and indices of neuroprotection, such as BDNF, homocysteine, cardiometabolic health (e.g., hs-CRP, lipid panel), CMP (comprehensive metabolic panel), and CBC (complete blood count). Tertiary outcomes were also collected (i.e., heart rate and blood pressure, BMI, adverse event data), and informed consent was obtained along with medical history, 3-day Diet Records, diet, and physical activity patterns. The study schematic, including biomarkers, is in Table 2.

Study Setting and Intervention

The study site was a clinical research laboratory in Ohio [e.g., The Center for Applied Health Sciences (CAHS)]. The intervention was one capsule containing 1.5 mg or 3.3 mg of spermidine daily from the Miricell™ rice germ extract (Nutraland USA), daily for 8 weeks. Subjects attended CAHS for all visits.

Ethical Approval

The study received approval from the Advarra IRB on March 19, 2024 (Pro00077995). Written informed consent was obtained from all the study participants.

Data Analysis

This exploratory, pilot study was not powered to assess statistical significance. Thus, we report raw data and use percentage changes to evaluate potential changes from week 0 to week 8. However, the safety screening bloodwork (CBC, CMP, and lipid panel) was analyzed with mixed factorial ANOVAs and when sphericity was violated Greenhouse-Geisser adjustment was used to correct the *P* values. Sidak post hoc comparisons were made when a statistically significant ($P \leq .05$) or trend ($P > .05$ to $\leq .10$) for a main effect or interaction occurred.

RESULTS

The study was completed with 12 subjects (n=6 for both the 1.5 mg and the 3.3 mg spermidine groups). Also, as presented below, the 1.5 mg group generally did not experience positive changes in various outcomes compared to the 3.3 mg group.

Primary Outcomes

For the primary outcomes, Table 3 provides changes between week 0 and week 8. Figure 1 shows the percentage change associated with the 3.3 mg dose of spermidine from Miricell™ in Beclin-1 and ULK1 compared to baseline (+7.25% and +13.36%, respectively).

Secondary Outcomes

For the secondary outcomes, Table 4 provides changes between week 0 and week 8. Figure 2 shows the percentage change associated with the 3.3 mg dose of spermidine from Miricell™ in BDNF (+12.05%). Regarding cardiometabolic markers, Figure 3 shows the percentage change associated with this same dose, which resulted in a decrease in hs-CRP, VLDL, and triglycerides compared to baseline (- 20.83%, -20.05% and 26.9%, respectively).

Tertiary Outcomes

In addition to primary outcomes, other secondary and tertiary outcomes were assessed via CBC, CMP, and lipid panels (shown in Table 5). All outcomes in the panels were within normal clinical ranges, with no evident adverse health risks. There was an observed increase in DBP in the 1.5 mg group from pre- to post-supplementation.

Safety and Adverse Effects

The secondary and tertiary outcomes reflect a good safety profile for the use of 3.3 mg/day of spermidine from Miricell™. Oddly, the 1.5 mg group observed an increase in DBP from pre- to post-supplementation. The plausible reason for this is hypothesized in the discussion below.

One participant in the 3.3 mg group complained about intermittent constipation throughout the study, but resolved the issue by increasing fiber intake; thus, it was unlikely related to the study product or procedures.

Table 3. Beclin-1, ULK1

Variable	Group	Week 0	Week 8
Beclin-1 (au)	1.5 mg	0.995 ± 0.231	0.998 ± 0.224
	3.3 mg	0.969 ± 0.194	1.039 ± 0.163
ULK1 (au)	1.5 mg	1.491 ± 1.365	1.391 ± 1.254
	3.3 mg	0.524 ± 0.054	0.594 ± 0.111

Figure 1. Percentage Change - Autophagy

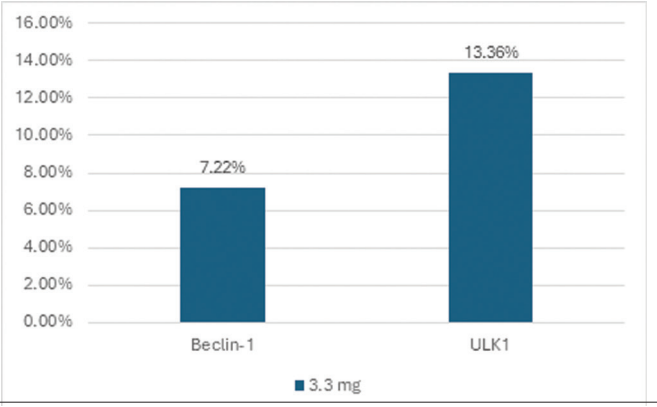

Figure 2. Percentage Change - BDNF

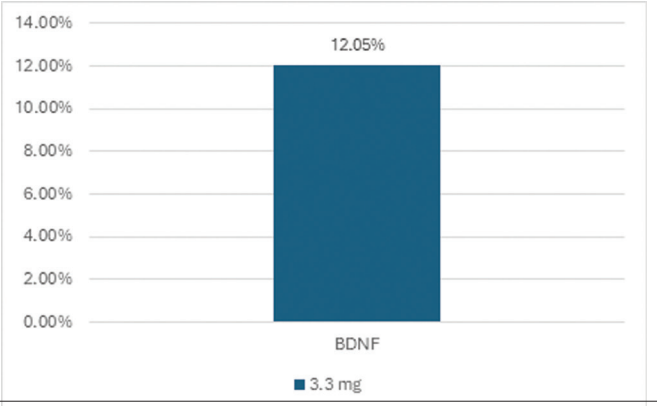

Table 4. BDNF, hs-CRP, VLDL, and Triglycerides

Variable	Group	Week 0	Week 8
BDNF (pg/uL)	1.5 mg	1770.8 ± 298.0	1678.2 ± 395.4
	3.3 mg	1228.0 ± 340.3	1376.0 ± 455.3
hs-CRP (mg/L)	1.5 mg	1.4 ± 1.3	2.6 ± 4.6
	3.3 mg	2.4 ± 2.1	1.9 ± 1.5
VLDL (mg/dL)	1.5 mg	20.5 ± 9.0	21.0 ± 8.2
	3.3 mg	24.7 ± 11.5	19.5 ± 5.4
Triglycerides (mg/dL)	1.5 mg	113.8 ± 52.0	116.7 ± 43.7
	3.3 mg	150.2 ± 78.6	109.8 ± 30.9

Figure 3. Percentage Change - Cardiometabolic

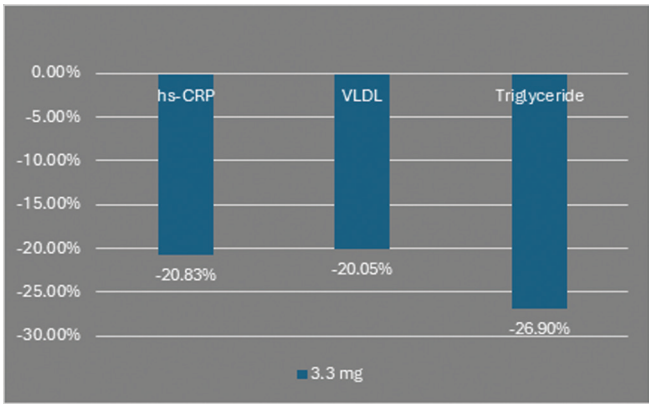

Table 5. Other Secondary and Tertiary Outcomes

Variable	Time	Treatment	Time × Treatment
Homocysteine (umol/L)	0.260	0.228	0.886
HS-CRP (mg/L)	0.698	0.910	0.324
WBC (x10E3/uL)	0.199	0.891	0.080
RBC (x10E6/uL)	0.453	0.373	0.735
Hemoglobin (g/dL)	0.889	0.712	0.816
Hematocrit (%)	0.948	0.618	0.895
Glucose (mg/dL)	0.922	0.121	0.626
BUN (mg/dL)	0.677	0.294	0.040[a]
Creatinine (mg/dL)	0.230	0.372	0.740
BUN/Creatinine ratio (au)	0.599	0.443	0.062[b]
eGFR (mL/min/1.73)	0.570	0.241	0.658
Sodium (mmol/L)	0.755	0.787	0.028
Potassium (mmol/L)	0.586	0.395	0.586
Chloride (mmol/L)	0.802	0.585	0.618
CO_2 (mmol/L)	0.329	0.823	0.886
Calcium (mg/dL)	0.516	0.949	0.407
Total Protein (g/dL)	0.424	0.391	0.220
Albumin (g/dL)	0.049	0.422	0.473
Globulin (g/dL)	0.794	0.486	0.309
A/G ratio (au)	0.378	0.539	0.378
Bilirubin (mg/dL)	0.186	0.276	0.782
Alkaline Phosphatase (IU/L)	0.821	0.206	0.225
AST (IU/L)	0.522	0.295	0.830
ALT (IU/L)	0.957	0.508	0.323
Total Cholesterol (mg/dL)	0.717	0.716	0.897
Triglycerides (mg/dL)	0.203	0.611	0.148
HDL (mg/dL)	0.907	0.481	0.907
VLDL (mg/dL)	0.253	0.783	0.172
LDL (mg/dL)	0.449	0.470	0.573
LDL/HDL (au)	0.331	0.121	0.671
Total/HDL (au)	0.771	0.125	0.694
SBP (mmHg)	0.521	0.803	0.074
DBP (mmHg)	0.036	0.684	0.055
HR (bpm)	0.338	0.241	0.162
BM (kg)	0.935	0.527	0.913

[a]Indicates a statistically significant main effect and/or interaction ($P \leq .05$).
[b]Indicates a trend for a main effect and/or interaction ($P \leq .10$).

Abbreviations: HS-CRP, high sensitivity C-reactive protein; WBC, white blood cells; RBC, red blood cells; BUN, blood urea nitrogen; eGFR, estimated Glomerular Filtration Rate; A/G ratio, albumin-to-globulin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

DISCUSSION

Modulating autophagy represents a strategy for promoting healthy aging, and dietary spermidine intake has previously been shown in epidemiological research to increase autophagy.[7,8,9,10] To the best of our knowledge, and within the limitations of this pilot study, it appears that this was the first human clinical trial to show that supplemental spermidine, as 3.3 mg/day from Miricell™ rice germ extract (Nutraland USA), increased Beclin-1 and ULK1, biomarkers of autophagy. Likewise, supplementation with this same dose of Miricell™ spermidine increased BDNF and decreased hs-CRP, VLDL, and triglycerides as biomarkers of cardiometabolic health. Alternatively, the 1.5 mg group showed undesirable increases or decreases in ULK1, BDNF, hs-CRP, VLDL, and triglycerides. We hypothesize that the reason for this is as follows: The undesirable changes would likely have been evident in a placebo group had this pilot study included a placebo arm. Instead, the 1.5 mg group simply provided an insufficient dose of spermidine to offset these changes.

Autophagy is a central mechanism in maintaining cellular integrity and systemic homeostasis, particularly in the context of aging and stress adaptation. By facilitating the removal of damaged organelles, misfolded proteins, and toxic aggregates, autophagy reduces the intracellular burden of waste products that accumulate with age. This housekeeping function is essential for preventing cellular dysfunction and preserving tissue health, especially in metabolically active or long-lived cells such as neurons and cardiomyocytes.[11]

As organisms age, the progressive decline in autophagic efficiency contributes to increased vulnerability to oxidative stress, mitochondrial dysfunction, and chronic inflammation—hallmarks of aging. Enhancing autophagy has been shown to improve cellular stress responses, support proteostasis, and maintain metabolic flexibility under nutrient-deprived or hypoxic conditions. These effects collectively promote stress resilience and may slow the progression of age-associated decline in physiological function.[12]

Altogether, these observations underscore the role of autophagy not only as a degradative pathway but as a key regulator of longevity and cellular adaptation. Therapeutic strategies aimed at restoring or enhancing autophagic flux, such as caloric restriction, intermittent fasting, or dietary supplements like spermidine, may hold considerable promise in extending health span and promoting resistance to age-related degeneration.[13]

In this study, Beclin-1 and ULK1 were used as markers of autophagy. Beclin-1 is a well-established regulator of autophagy. It functions in conjunction with other proteins to form Class III Phosphoinositide 3-Kinase (PI3K) complexes to generate phosphorylated phosphatidylinositol (PtdIns), which are lipids essential for not only autophagy but also other membrane trafficking processes.[14] ULK1 is an important protein in autophagy for mammalian cells, and it is homologous to Atg1 in yeast. It is part of the ULK1-complex, which is needed in the early steps of autophagosome biogenesis. ULK1 directly phosphorylates Beclin-1 at Ser 14 and activates the pro-autophagy class III phosphoinositide 3-kinase complex to promote autophagy induction and maturation.[15]

Another biomarker used in this study was BDNF. BDNF plays an important role in neuronal survival and growth, serves as a neurotransmitter modulator, and participates in neuronal plasticity, which is essential for learning and memory.[16] It is widely expressed in the CNS, gut, and other tissues.[17] Decreased levels of BDNF are associated with neurodegenerative diseases with neuronal loss, such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, and Huntington's disease. Thus, BDNF may be useful in the prevention and management of several diseases, including diabetes mellitus.[16]

A key limitation of this study is its small sample size, which limited the statistical power to detect significant differences across the measured biomarkers. While preliminary trends suggest potential benefits related to promoting resistance to age-related degeneration, these findings should be interpreted with caution. Small cohorts increase the risk of type II error (i.e., failing to detect a real effect) and reduce generalizability, particularly when evaluating complex, multifactorial processes such as aging and cellular resilience. To validate these observations and to

robustly assess the efficacy of the intervention, future studies should include larger, adequately powered randomized controlled trials. Expanding the sample size would also allow for subgroup analyses (e.g., age, sex, baseline health status) that could uncover differential responses and enhance clinical relevance.

CONCLUSION

This single-blinded pilot study found that 3.3 mg/day of spermidine from Miricell™ rice germ extract tends to improve biomarkers of autophagy, neuroprotection, and cardiometabolic health. Follow-up studies with a larger cohort, adequate statistical power, and placebo control are warranted to confirm these findings.

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AUTHOR DISCLOSURE STATEMENT

Tim N. Ziegenfuss serves on the Scientific Advisory Board for Nutraland USA but receives no royalties from sales of Miricell™. Gene Bruno is the Chief Scientific Officer for Nutraland USA. Michael La Monica declares no conflict of interest related to this study.

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