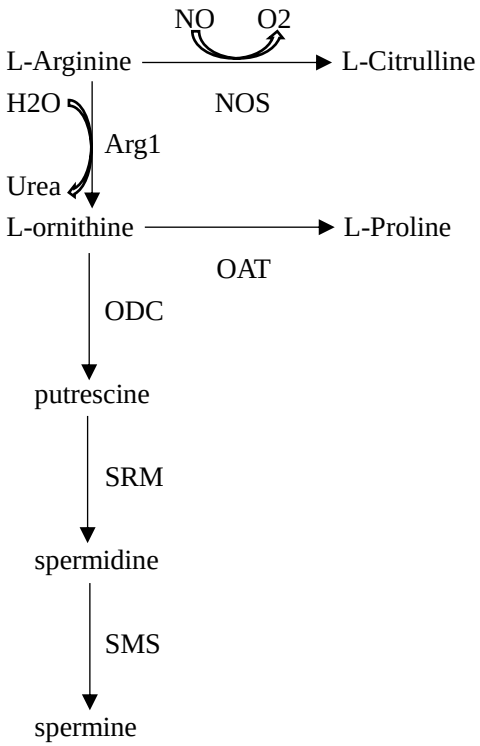
An Efficient Anti-Aging Nutrient: Spermidine

What is Spermidine?

Spermidine belongs to the family of polyamines, which are polycations that will readily interact with negatively-charged molecules, including DNA, RNA, and lipids. This ability to bind to such different molecules means polyamines are involved in many important biological processes, such as DNA stability, cell growth, proliferation, and death. Research has focused on the three main polyamines -- putrescine, spermine, and spermidine[1] -- of which spermidine is the most abundant polyamine in a majority of different human tissues. Unfortunately, intracellular concentrations of spermidine decline during the normal course of human aging. In other words, spermidine levels drop with age, and this is critical because a strong and growing body of emerging research demonstrates that increased spermidine intake may slow down aging and promote longevity and resilience.

In addition to being produced endogenously, polyamines can also be found in food, and spermidine is the polyamine most readily absorbed from the human gut.[2] Naturally occurring in a broad and diverse palette of foods, spermidine can be found in foods such as wheat germ, soybeans, green peppers, cauliflower, broccoli, mushrooms, and a variety of cheeses.[3] In addition to dietary sources and endogenous biosynthesis (from arginine and methionine), the intestinal microbiota can synthesize polyamines such as spermidine as well.[4] Spermidine is the most abundant polyamine in a majority of different human tissues, with intracellular spermidine concentrations declining during the natural course of human aging.[5] Conversely, the administration of spermidine is linked to increased lifespan and decreased occurrence of age-related pathology in pre-clinical models while high dietary intake of spermidine has been associated with reduced overall, cardiovascular and cancer-related mortality[6]. Research has also shown that spermidine intake correlates with cognitive performance and a reduced risk for cognitive impairment in humans.[7, 8] Due to its potential health-protective and lifespan-extending/anti-aging effects, some researchers have classified spermidine as a “caloric restriction mimetic” [9] while others have referred to it as a “longevity elixir”[10], suggesting that spermidine deserves serious consideration as a dietary supplement for the promotion of optimal longevity and health-span.



What Spermidine Can Do?

Recent research has revealed that spermidine supports a range of overall health-protective and longevity benefits including:

-Anti-Aging:

- ***Promoting cell autophagy***
- ***Helping regulate cell apoptosis***
- ***Helping regulate the inflammatory response***
- ***Providing antioxidative properties***
- ***Helping regulate the inflammatory response***

-Sports Nutrition:

- ***Helping maintain skeletal muscle***

-Healthy weight management:

- ***Promoting healthy gut microbiota function and gut barrier integrity***
- ***Helping maintain a healthy weight and plasma lipid profile***

Experimental Research

Polyamine (spermidine, putrescine, spermine) concentrations in mammals are determined by their nutritional uptake, endogenous/cellular biosynthesis, intestinal sources (microbiota), catabolism, urinary excretion, and active transporter systems between compartments. Tissue spermidine concentrations decline with age in model organisms as well as in humans. This decrease results from alterations in one or several factors that determine the bioavailability of spermidine in the body, such as reduced uptake, diminished transport, reduced intracellular biosynthesis (e.g., a decline in the biosynthetic activities of polyamine-producing enzymes), altered microbiome, and/or increase degradation.

The intracellular spermidine content is the final result of polyamine uptake from the extracellular space, endogenous biosynthesis, catabolism, and excretion. Biosynthesis of polyamines begins with the formation of putrescine from the amino acid ornithine, which is converted to spermidine-by-spermidine synthase through the addition of a propylamine group derived from the decarboxylation of S-adenosyl-methionine. Subsequently, spermidine is transformed into spermine-by-spermine synthase, which adds a second propylamine group. Catabolism of polyamines involves, on the one hand, the oxidative degradation of spermine to spermidine. On the other hand, the degradation and secretion of both spermidine and spermine require their acetyl-CoA–dependent acetylation by spermine-/spermidine-N1-acetyltransferase 1 (SSAT1) and subsequent oxidation. In a recent study, histone deacetylase 10 (HDAC10), a key regulator of autophagy and cell survival, has been proposed as yet another mediator of polyamine metabolism owing to its ability to deacetylate spermidine.

According to the literature, the main mechanism of spermidine at the molecular level is autophagy. Autophagy is a process of phagocytosis of cytoplasmic proteins or organelles into vesicles, fusion with lysosomes to form autophagy lysosomes, degradation of the contents of the wrapped. It helps to realize the metabolic needs of the cell itself and the renewal of some organelles.

Said differently, autophagy is the main recycling mechanism of the cell, allowing the destruction and re-use of unneeded or damaged molecules or whole organelles. Deficient autophagy has been linked to many age-related health concerns.

Therefore, the majority of research has focused on spermidine based on its ability of autophagy and more recently, animal research has shown that spermidine induces mitophagy, a selective autophagy subroutine that targets damaged and potentially harmful mitochondria, improving mitochondrial abundance and respiration. All considered, spermidine could be a valuable addition to various types of supplements due to its broad range of “metabolic” actions.

Anti-aging

1. Promoting cell autophagy and recycling

Aging represents a significant risk factor for many health concerns, including metabolic, cardiovascular, and cognitive issues. Aging is a degenerative change gradually occurring in the body, which all living organisms need to experience. When the body ages, cells are less able to self-renew, and this inability to recycle in an appropriately healthy way is linked to an increased risk for various health issues. Although aging is an inevitable, multi-faceted process, recent research suggests that spermidine supplementation may have health-protective and longevity effects. Recent research shows that spermidine plays an important role in anti-aging in mice.[11]

According to Eisenberg et al., the mechanism by which spermidine acts at the molecular level to promote longevity is by inducing autophagy. In their study, they divided mice into four groups: 4-month-old mice (life-long) and 18-month-old mice (late-in-life) drank water with or without spermidine.

The administration of spermidine significantly prolonged median lifespan by ~10%. Spermidine-fed animals displayed increased circulating spermidine levels, confirming its systemic bioavailability. Food and water consumption, body weight, and lean/fat mass composition were similar in spermidine-fed and control groups, excluding the possibility that polyamine supplementation extends lifespan by inducing a calorie restriction-like state. Spermidine-supplemented mice had higher levels of the autophagosomal marker LC3-II in cardiac tissue, whereas age-matched controls without spermidine showed a reduced (and non-significant) elevation of this marker, indicating that spermidine increases cardiac autophagic flux *in vivo*. Cellular spermidine content was significantly increased in spermidine-supplemented animals as compared to controls, meaning that spermidine had high bioavailability *in vivo*. Together, these results suggest that autophagy may contribute to spermidine's anti-aging properties.

Spermidine extends lifespan and enhances autophagic flux	
At a glance	
Publication	Eisenberg, T., et al. Nat Med, 2016. 22(12): p. 1428-1438.
Study design	Comparison
Subjects	4- month-old (life-long) and 18-month-old (late-in-life) mice were fed water with or without spermidine
Duration	Entire lifespan of mice
Intervention	Spermidine supplementation (3 mM)
Key findings	▪Spermidine feeding significantly prolonged median lifespan by ~10% ▪Spermidine substantially increased the number of autophagosomes and autolysosomes, via assessment of autophagic flux.

2. Helping regulate cell apoptosis

Cell death is a natural and vital component of normal cell turnover. Along those lines, the study of the process of cell death has an emerging area of biomedical research. It is known that there are at least two ways of cell death, namely cell necrosis, and apoptosis. Cell necrosis has long been recognized as one of the modes of cell death, while apoptosis has more recently been recognized and studied. Recently, spermidine has been found to play a role in cell apoptosis.

To illuminate the effect of spermidine on apoptosis, Ting-Ting Xu et al. set out to detect the expression of apoptotic proteins in spermidine-treated mice. In their study, a novel object recognition test (ORT), which is a commonly used behavioral assay to investigate various aspects of learning and memory, and an open field test (OFT), a common measure of exploratory behavior and general activity, were used to investigate the neuroprotective effect of spermidine on SAMP8 mice, a senescence-accelerated aging model. After treatment with spermidine, learning and memory were greatly improved in SAMP8 mice. For example, spermidine significantly improved the time duration of exploring the novel object in ORT. Mice in the spermidine group were more likely to demonstrate better quality and quantity of activity in OFT compared to controls. The results of this study provide evidence that spermidine has anti-aging properties that may beneficially impact cognitive health and function.

In addition to this, SAMP8 mice were divided into spermidine and control groups, and apoptosis-related markers, including caspase-3, Bax, Bcl-2, were assessed. Spermidine sharply decreased the expression of Bax and cleaved Caspase-3 while it increased the level of Bcl-2 and significantly decreased TUNEL-positive cells in the brain slice of spermidine groups in both the hippocampus and frontal cortex. These results provide evidence that spermidine may promote healthy brain aging by helping regulate apoptosis.[12]

Spermidine depresses apoptosis and inflammation.	
At a Glance	
Publication	Xu, T.T., et al., Aging (Albany NY), 2020. 12(7): p. 6401-6414.
Study design	Comparison
Participants	Three-month-old male senescence-accelerated mouse prone 8 (SAMP8) mice drink water with or without spermidine.
Duration	8 weeks
Intervention	Spermidine supplementation (2 mM)
Key findings	▪Spermidine increased discrimination index, modified number, inner squares distance, and times. ▪Western blot results (Bcl-2, Bax and Caspase-3, NLRP3, IL-18, IL-1β) showed that spermidine prevented apoptosis and inflammation.

3. Providing antioxidative properties

One of the important contributors to the inflammatory response is oxidative stress. While a healthy inflammatory response is a normal and necessary bodily process, excess inflammation can be problematic. Inflammation can be driven by excessive oxidative stress, which is a reflection of an imbalance between the production of reactive oxygen species (ROS) and the biological system's ability to remove them. The overproduced ROS by the activated macrophages and neutrophils, components of the immune system that are recruited under inflammatory conditions, act as an important contributor to the manifestation of inflammation. ROS are also involved in the production of inflammatory cytokines in the lipopolysaccharide (LPS)-stimulated macrophages and neutrophils. Consequently, the suppression of the production of pro-inflammatory factors by blocking macrophage

and neutrophil activation is emerging as a potentially useful approach to help support the body's natural antioxidant defenses and to help promote a healthy inflammatory response, which has significant implications for whole-body health and longevity.

Jin-Woo Jeong et al. demonstrated the *in vitro* and *in vivo* antioxidant potential of spermidine. In their study, the potential of spermidine for reducing pro-inflammatory and oxidative effects in LPS-stimulated RAW 264.7 macrophages and zebrafish was explored. Their data indicate that spermidine attenuated the nuclear translocation of nuclear factor-kappa B (NF-κB) p65 subunit, the body's primary pro-inflammatory signaling pathway, and reduced LPS-induced intracellular accumulation of ROS in RAW 264.7 macrophages. Moreover, spermidine prevented the LPS-induced nitric oxide (NO) production, an inflammatory mediator, and ROS accumulation in zebrafish larvae and was found to be associated with diminished recruitment of neutrophils and macrophages.[13] The results of this study suggest that spermidine offers antioxidative potential that may help promote a healthy inflammatory response.

Spermidine provides antioxidative properties	
At a Glance	
Publication	Jin-Woo Jeong, et al., Biomol Ther (Seoul), 2018. 26(2): p. 146-156.
Study design	Comparison
Participants	The zebrafish larvae were treated with spermidine, LPS, spermidine+ LPS.
Duration	24 hours
Intervention	Incubation in water with Spermidine (500 μM) or 10 μg/mL LPS was injected into the yolk using a microinjector.
Key findings	▪Spermidine suppresses LPS-induced accumulation of ROS in RAW 264.7 macrophages. ▪Spermidine downregulates LPS-induced NO and ROS production in zebrafish.

4. Helping regulate the inflammatory response

Spermidine treatment at the time of hyperlipidemia in aged mice reduced IL-6 levels, improved mitochondrial function with reduced Parkin levels within the aorta. These effects were accompanied by reduced atherogenesis. While spermidine has been shown to induce autophagy and mitophagy, it is possible that spermidine may be mediating its effects via multiple pathways such as helping regulate inflammatory pathways or providing antioxidative support. Furthermore, the treatment of more than several months of spermidine in normolipidemic conditions might have beneficial effects on vascular aging. [14]

In several transgenic mouse models, the dysregulation of polyamine metabolism has been shown to have an impact on metabolic health and function (e.g., the regulation of glucose, lipid, and energy homeostasis). In fact, emerging evidence suggests that increased levels of polyamines in adipose, liver, or skeletal muscle tissues could stimulate energy expenditure and confer weight management and hepatoprotective support. In particular, the polyamines spermidine and spermine are essential factors at early stages of adipocyte differentiation as they modulate the expression levels of transcriptional factors implicated in the adipogenesis regulation. [15]

Likewise, in animal models, supplementation with spermidine could have a beneficial effect on several age-related issues including cognitive- and cardiovascular-related concerns. Several in vitro studies have shown that the administration of spermidine in cell lines of neuronal origin inhibits the process of cellular senescence. It has been proposed that the mechanism by which polyamines produce these beneficial anti-aging effects could be through the activation of autophagy, either through the inhibition of the activity of the acetyltransferase EP300, which is involved in the modulation of autophagic flux, or the stabilization of pro-autophagic factors such as MAP1S. [16]

Natural polyamines (spermidine and spermine) are small, positively-charged molecules that are ubiquitously found within organisms and cells. They exert numerous (intra)cellular functions, and emerging research suggests that they may promote longevity, health-span, and whole-body health.

Spermidine regulates the inflammatory response	
At a Glance	
Publication	Tyrrell, D.J., et al., Circ Res, 2020. 126(3): p. 298-314.
Study design	Comparison
Participants	18 months old aged mice treated with or without spermidine
Duration	10 weeks
Intervention	Supplement with spermidine (500 μM) in the drinking water
Key findings	▪Spermidine supplementation can reduce the production of IL-6, Parkin and TLR9 in thoracic aortas and promote the production of MyD88. ▪Spermidine can activate TLR9-MyD88-IL-6 signaling in the aorta.

Sports Nutrition

1. Helping maintain skeletal muscle

Skeletal muscle mass represents roughly 40-50% of human body weight as the largest tissue and the major amino acid reservoir. One of the major hallmarks of aging is a reduction in the amount of skeletal muscle, which has major potential ramifications on both the longevity and health-span (i.e., length and quality of life). As mentioned, spermidine has been identified as having potential anti-aging properties, which have been linked to its ability to promote autophagy, which can provide anti-aging support for various tissues in the body, including heart, brain, and skeletal muscle.

Jing-jing Fan et al. examined the effects of a combination of spermidine and exercise on skeletal muscle maintenance in aging rats. In their experiment, they used D-gal-induced aging model rats, which were subjected to the intervention with spermidine (5 mg/kg/day), swimming (60 min/day, 5 days/week), or a combination of the two for 42 days.

Their data demonstrated that spermidine coupled with exercise could attenuate D-gal-induced aging-related losses in skeletal muscle by inducing autophagy and helping regulate apoptosis with characteristics of more autophagosomes, activated mitophagy, enhanced mitochondrial quality, alleviated cell shrinkage, and less swollen mitochondria under transmission scanning microscopic observation. Meanwhile, spermidine coupled with exercise could induce autophagy through activation of the AMPK-FOXO3a signaling pathway with characterization of increased Beclin1 and LC3-

II/LC3-I ratio, up-regulated anti-apoptotic Bcl-2, down-regulated pro-apoptotic Bax and caspase-3, as well as activated AMPK and FOXO3a. Therefore, this study provides evidence that spermidine supplementation combined with long-term, regular exercise may help maintain skeletal muscle mass with aging through activation of autophagy and mitophagy processes as well as helping promote a "just right" level of apoptosis.[17]

Spermidine combined with exercise helps maintain skeletal muscle in an aging animal model.	
At a Glance	
Publication	Fan, J., et al., Oncotarget, 2017. 8(11): p. 17475-17490.
Study design	Comparison
Participants	Four-month-old male Sprague-Dawley (SD) rats including normal control without treatments, spermidine treatment, exercise, exercise, and spermidine groups.
Duration	6 weeks
Intervention	Spermidine (5mg/kg/day), swimming training at the exercise intensity of 45 min/d.
Key findings	▪Spermidine and exercise reduced damage of skeletal muscle and suppressed or rescued the decline of sectional area of skeletal muscle fibers. ▪Spermidine combined with exercise enhanced AMPK-FOXO3a signal pathway in D-gal-induced aging gastrocnemius muscle

Healthy weight management

1. Promoting healthy gut microbiota function and gut barrier integrity

The prevalence of obesity has increased worldwide in the past ~50 years and has reached epidemic proportions.[1]The pathophysiology of obesity is multifactorial and linked with imbalanced energy metabolism, and it is influenced by complex interactions between genetic, epigenetic, dietary, lifestyle, and environmental factors. Obesity greatly increases the risk for a variety of health concerns and can negatively impact quality of life. Therefore, evidence-based ways to promote healthy weight management are especially attractive to researchers, practitioners, and consumers alike. Interestingly, emerging research suggests that gut barrier function and the gut microbiota may be driving forces in the development of obesity. For example, poor intestinal barrier function may contribute to intestinal permeability, which, in turn, can trigger a pro-inflammatory cascade that can contribute to metabolic dysfunction. On the other hand, healthy gut microbial balance and function are important for metabolic health and the production of short-chain fatty acids, such as butyrate, that can impact metabolic health, appetite-regulating hormones and more.

Ma et al. revealed some intriguing findings pertaining to the relationship between spermidine intake and body weight in humans. Specifically, the authors calculated dietary spermidine intake from the NHANES dietary data and nutrient database for polyamine intake. Their analysis revealed that daily spermidine intake was negatively correlated with body mass index (BMI) and waist circumference, and spermidine intake positively correlated with metabolic health (e.g., glucose metabolism, insulin sensitivity). In other words,

lower spermidine intake appeared to be correlated to overweight/obesity and greater likelihood of poor metabolic health. [2] These findings suggested that spermidine intake might be one potential factor that contributes to the prevalence of obesity, thus the researchers explored the potential mechanism of spermidine on obesity in mice.

To assess the effects of spermidine on mice (high-fat diet, HFD, induced obesity), spermidine was administered to mice in their drinking water. After 16 weeks of administration, spermidine intake reduced diet-induced body weight gain in a dose-dependent manner without affecting food and water intake compared to high-fat controls. Spermidine also improved metabolic health in the mice.

To determine the effect of spermidine on the gut microbiota, high-throughput sequencing of 16S rRNA in the cecal content was performed. The amount of *Firmicutes* increased by 4.4%, while that of *Bacteroidetes* decreased by 4.2% in diet-induced-obesity (DIO) mice, which were rescued by spermidine. In other words, spermidine prevented this microbial shift, and this is relevant and important because the *Bacteroidetes* have been associated with adequate body weight but the *Firmicutes* with obesity.

The microbiota and correlation analyses prompted them to further investigate whether the gut microbiota was required for spermidine-mediated alleviation of metabolic syndrome in DIO mice. Antibiotics were applied to deplete the existing microbiota in DIO- and spermidine-treated mice, which was confirmed by 16S rRNA sequencing. Antibiotic treatment did not affect body weight in DIO- or spermidine-treated mice. However, the protective effects of spermidine on colon length and endotoxemia were abolished after antibiotic treatment. Additionally, the researchers found that spermidine improved gut barrier integrity and function by autophagy-dependent and autophagy-independent pathways.

All results indicated that spermidine changes gut microbiota function in diet-induced obese mice and promotes weight loss and metabolic health.

Spermidine promotes healthy gut microbiota function and gut barrier integrity	
At a Glance	
Publication	Ma, L., et al., Gut Microbes, 2020. 12(1): p. 1-19.
Study design	Comparison
Participants	Eight-week-old male C57BL/6 J mice: normal chow; high-fat diet then treats with or without 20 mg/kg spermidine in drinking water.
Duration	16 weeks
Intervention	Spermidine (20mg/kg/day) in drinking water
Key findings	▪ The high glucose, insulin, and the homeostatic model assessment of insulin resistance (HOMA-IR) are generally associated with lowered spermidine intake. ▪The amount of *Firmicutes* increased by 4.4%, while that of *Bacteroidetes* decreased by 4.2% in DIO mice, which were rescued by spermidine.

2. Helping maintain a healthy weight and plasma lipid profile

Fat is a constituent part of the human body

where it is stored in the subcutaneous tissue. From an evolutionary standpoint, stored body fat represents a critical, energy-dense storage substance. However, excessive body fat (i.e., obesity) can be highly problematic over time, contributing to an increased likelihood of a number of health complications and diminished quality of life. While overconsumption of any macronutrient can be stored as body fat, dietary fat is the most easily stored in subcutaneous depots. Further, there is evidence that excessive dietary fat intake may be linked to an increased risk of certain health issues. Excessive body fat can also make it more difficult to move physically, and high blood lipids are likely to be a major contributing factor to a variety of concerns related to cardiovascular health. Numerous studies have provided evidence that spermidine may provide support for healthy weight management and lipid levels. [18]

For example, Ma et al., assessed the impact of spermidine on high-fat diet (HFD)-induced obese mice. They divided C57BL/6J mice into two groups: both groups were fed HFD for 16 weeks, then treated with or without spermidine via drinking water for additional 8 weeks.

Their study found that spermidine administration lowered fat mass and plasma lipid profile in HFD-induced obese mice without affecting body weight. In addition, spermidine attenuated hepatic steatosis by regulating lipid metabolism and enhancing antioxidant capacity. Moreover, spermidine reduced adipose tissue inflammation by decreasing inflammatory cytokine and chemokine expression. The researchers also found that spermidine promoted brown adipose tissue (BAT) thermogenesis, which is relevant and important for healthy weight management because, unlike typical (white) adipose tissue, BAT dissipates energy as heat (i.e., increases energy expenditure).

Spermidine promotes healthy weight management and lipid levels	
At a Glance	
Publication	Ma et al., Life Sciences,2021,265:
Study design	Comparison
Participants	C57BL/6J mice were fed a HFD for 16 weeks to induce obesity, and then treated with or without spermidine via drinking water for additional 8 weeks.
Duration	24 weeks.
Intervention	Spermidine (3mM) in drinking water
Key findings	▪Spermidine administration lowered fat mass and plasma lipid profile in HFD-induced obese mice.

Safety Dosage

Currently, there is a limited amount of published human research on spermidine, but its toxicity appears to be low. In a human cohort (participants with subjective cognitive decline, n=30, 60 to 80 years of age), a 3-month randomized, placebo-controlled, double-blind Phase II trial was conducted with supplementation of a spermidine-rich plant extract (dosage: 1.2 mg/day). No differences were observed between spermidine and placebo-treated groups in vital signs, weight, clinical chemistry, and hematological parameters of safety, as well as in self-reported health status at the end of intervention. [7]

In conclusion, spermidine is safe for human consumption and may contribute to improve outcomes in anti-aging, sports nutrition and weight management.

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