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FFHD
Functional Foods in Health and Disease

# Spermidine content of selected dietary supplements: potential for improvement?

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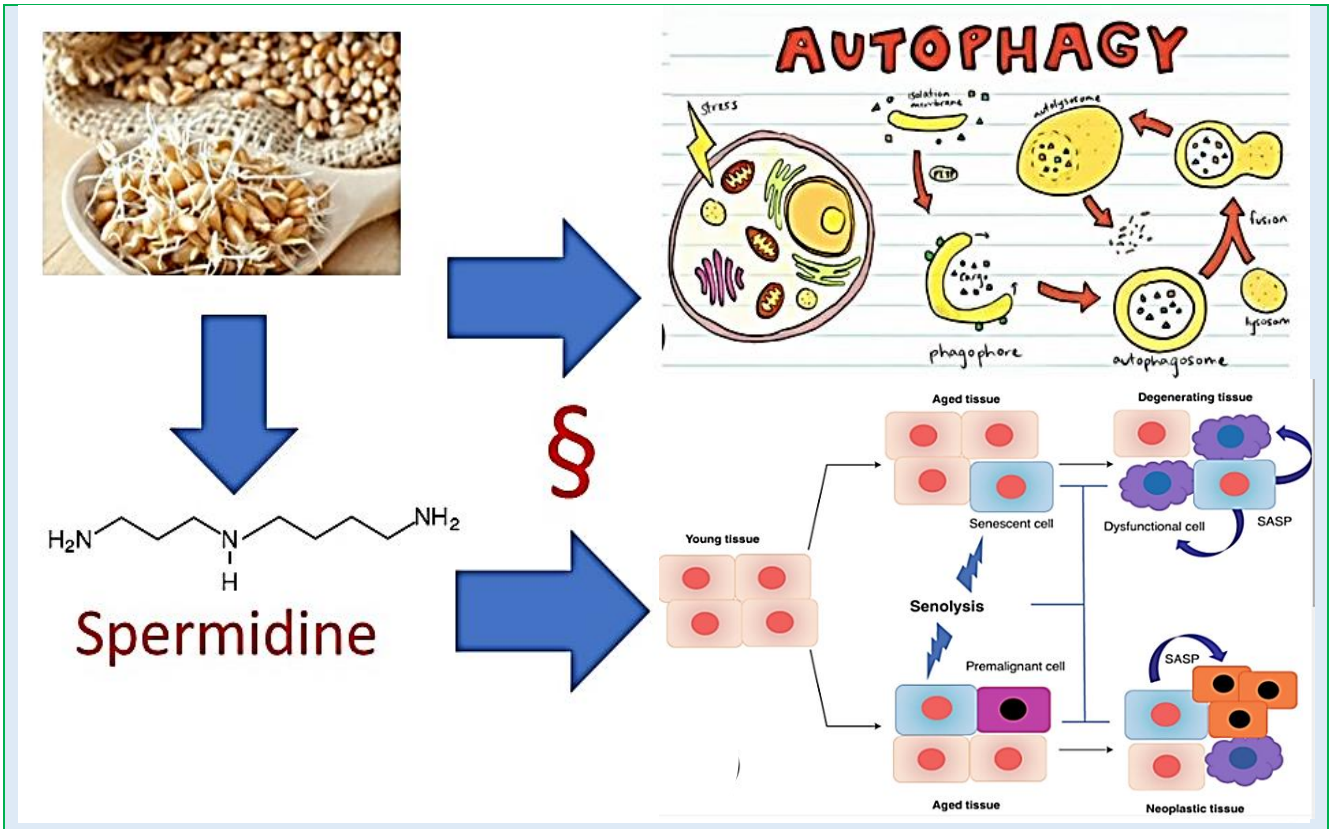
**Submission Date:** April 18th, 2023; **Acceptance Date:** May 2nd, 2023; **Publication Date:** May 15th, 2023

**Please cite this article as:** Steichen P., Gruber K., Hippe B., Haslberger A. Spermidine content of selected dietary supplements: potential for improvement? *Functional Foods in Health and Disease* 2023; 13(5): 258-267. DOI: https://www.doi.org/10.31989/ffhd.v13i5.1102

**ABSTRACT**

Dietary spermidine is emerging as a substance with promising health-promoting and healthy ageing-promoting properties. Its autophagy-inducing potential has been especially well-documented. This process is suspected to be at the root of the life-prolonging effects of fasting and in-vivo spermidine supplementation. In humans, high dietary spermidine intake is associated with a lifespan increase of 5.7 years. Numerous studies provide indications of its effects on the cardiovascular, nervous, and immune systems as well as on the formation and development of tumors. Nevertheless, no health claims are currently authorized in the EU for spermidine or spermidine-rich functional foods. When ingested through food or dietary supplements, dosage appears to play an important role in replicating the favorable effects. Currently, there are ongoing proceedings regarding the novelty of a certain manufacturing process of spermidine supplements, but many other plant extracts with high spermidine content from different sources are marketed without the need for novel food authorization. This article discusses the varying test results obtained for the spermidine concentration of popular spermidine supplements. Soybean extract seems to be slightly superior in terms of spermidine concentration, but one wheat germ-based product stood out in this analysis due to a 10 times higher spermidine concentration than comparable products.

**Keywords:** spermidine, food supplements, novel food, botanicals, functional foods, autophagy, spermidine-rich wheat germ extract






## INTRODUCTION

Spermidine is a highly conserved ubiquitous polyamine derived from endogenous synthesis, dietary intake, and production by (gut) microbiota. The origin of its name goes back to the particularly high occurrence in human sperm cells. Spermidine is involved in maintaining cell homeostasis and it plays a role in a variety of cellular processes such as proliferation, growth, regeneration of tissues, and regulation of translation [1]. Spermidine exhibits anti-inflammatory effects and counteracts ageing processes. A central mechanism in the effects mediated by spermidine is the induction and activation of autophagy, the reduction of which is seen as one of the most important drivers of the ageing process [2].

As several animal studies have shown, the life span of model organisms, from yeast to fruit flies then to mice and rats, can be extended by activating autophagy. This process can be triggered in two ways – either by strict calorie restriction or more specifically, calorie restriction mimetics or fasting mimetics, which include spermidine. Using model organisms such as yeast, nematodes (Caenorhabditis elegans), fruit flies (Drosophila melanogaster) and mice, it could be shown that supplementation with spermidine leads to a significant increase in their lifespans. This is attributed to cardio- and neuroprotective effects and a delay in immunosenescence [3].

Human data indicates at least one correlation between serum spermidine levels and lifespan in humans. The spermidine level, which usually tends to decrease with age, is significantly higher in the oldest age group including centenarians [4]. The evaluation of a large-scale prospective cohort study (the Bruneck Study) has shown after 20 years that higher dietary intake of spermidine is associated with a significantly reduced mortality rate. Compared to the risk quotient of 1.0 in the

group with the lowest intake of spermidine, it was 0.56 in the group with the highest intake, which corresponds to a reduction of around 40%. Applied to life expectancy, this corresponds to an increase of 5.7 years in the high-spermidine group [5].

**Spermidine and Health:** According to the Functional Food Center (FFC), functional foods can be defined as "Natural or processed foods that contain biologically active compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms'' [6]. In this chapter, the authors aim to present the best currently available scientific evidence of these properties relating to spermidine-rich botanical extracts.

**Spermidine and the Cardiovascular System:** Age-related cardiac hypertrophy was significantly reduced in a mouse model by spermidine supplementation; the diastolic heart function of old mice was improved to such an extent that it corresponded to that of young mice. This effect was independent of whether the supplementation started early or later in life. Autophagy, mitophagy and mitochondrial respiration in cardiomyocytes were increased as well and it is assumed that the mechano-elastic properties of cardiomyocytes were improved [3]. The cardiac measurements and inflammation parameters in liver cirrhosis-induced myocardial diseases progressed significantly less in rats with spermidine supplementation compared to the control group [7].

Spermidine may also influence atherosclerotic processes. In a mouse model, reduced necrotic cores of atherosclerotic plaques and fewer lipid accumulations were found after spermidine supplementation [8]. It was also shown in the mouse model that inflammatory changes in the aorta and aortic valves in old mice could be significantly reduced with spermidine supplementation. Along with this, a significantly less pronounced shortening of the telomeres was registered, which could be an additional "anti-ageing" effect of spermidine [9]. In a rat model of hypertension, reduced systemic blood pressure and reduced cardiac hypertrophy were seen as a result of spermidine supplementation [10].

There is epidemiological evidence on spermidine intake and cardiovascular disease. One study analyzed data from 48 countries and generated a statistical correlation between polyamines in the diet and cardiovascular disease mortality. Spermidine was significantly inversely correlated with cardiovascular disease mortality [11]. Human data from the Bruneck study also shows an association between diets rich in spermidine and lower blood pressure. The difference in systolic blood pressure between the tertile, with the highest and lowest uptake of spermidine, was 2.84 mmHG (-5.17, -0.50, p=0.017) [3].

Oxidative stress and reduced autophagy activity are common observations in inflammatory processes and cardiovascular disease. The treatment of isolated thrombocytes from individuals in risk groups (e.g. smokers, patients with metabolic syndrome or atrial fibrillation with autophagy activators) including spermidine, significantly reduced their aggregation tendency and overall oxidative stress [12].

A prospective cohort study has shown that a higher serum spermidine level may be associated with a better prognosis after myocardial infarction. The study included 377 acute myocardial infarction patients with a mean follow-up of 12.3 months. Compared to the hazard ratio of 1.0 in the group with the lowest spermidine levels (≤ 7.59 ng/mL), the hazard ratio for recurrence in the group with the highest spermidine level (≥ 15.38 ng/mL) was 0.450. [13]

**Spermidine and the Nervous System and Brain:** The decrease in spermidine levels with age may also affect the brain and the nervous system. This is for instance the case in fruit flies, in which the neuroprotective effects of spermidine could be demonstrated for the first time in a model organism. The spermidine level in the brains of old animals could be raised to the level of young animals, and the decline in olfactory short- and medium-term memory could be decelerated [14]. The additional supply of spermidine increased the performance of the brain of rapidly ageing mice in another study. The animals performed significantly better in memory tests and showed better spatial learning [15]. Spermidine is suspected to support mitochondrial function and reduce inflammatory mediators and neuronal apoptosis [16].

The formation of misfolded proteins in the brains of aged mice was prevented by spermidine, which was attributed to increased autophagy-mediated degradation of beta fibrils [17]. In a mouse model of Alzheimer's disease, spermidine decreased soluble beta-amyloid and pro-inflammatory cytokines [18]. In another rat model, increased autophagy activity and reduced inflammatory markers were also registered as a result of spermidine administration [19]. The animals were less anxious, and their exploratory behavior increased.

In humans, the analysis of data from the Bruneck study showed a positive correlation between dietary intake of spermidine and cognitive performance based on the standardized mini-mental-state test. In addition, a high intake of spermidine was associated with a lower risk of cognitive impairment with increasing age [15]. The correlation of serum spermidine levels with mild cognitive impairment was examined in a longitudinal study with 3,774 participants with a mean age of 57.4 years. There was an albeit non-linear, positive correlation between spermidine levels and the risk of mild cognitive impairment [20]. Higher dietary intake of spermidine was associated with greater hippocampal volume, greater mean cortical thickness, and greater cortical thickness in parietal and temporal lobes, which are common AD-affected regions, independently of cognitive performance [21].

People who reported subjectively perceived cognitive impairments (n=28) were included in the analysis of a randomized controlled phase II study. After 12 weeks, memory performance was moderately increased in the group (mean age 70.4 years) which supplemented 1.2 mg of spermidine per day [22]. The following phase IIb study with 100 subjects (mean age 69 years) and a duration of 12 months however revealed no differences between the spermidine group (0.9 mg per day) and the placebo group concerning memory performance. According to exploratory analysis, positive effects on inflammatory processes and verbal memory appear possible. The memory-boosting effect of spermidine may not be as pronounced as its prevention of age-related memory impairment and the chosen dosage of 0,9 mg per day may have been too low to demonstrate more significant results [23].

As part of a multi-center study, the influence of spermidine supplementation on the cognitive performance of 85 residents of supervised facilities between the ages of 60 and 96 was recorded. Over a 12-week period, study participants received spermidine-enriched breakfast pastries equivalent to 3.3 mg per day in one group or 1.9 mg per day in the other. An increase of daily spermidine intake by 35% or 20% respectively compared to the average intake before the intervention was assumed. Both groups improved their total score results, but it was more pronounced in the group with higher spermidine intake. The most pronounced effects were seen in people with no dementia and mild dementia. The results of this study are an indication that dosages of spermidine under 3 mg per day may not be sufficient in order to lead to improvements in cognition in humans [24].

**Spermidine and the Immune System and Cancer:** A supportive effect on the immune system has been repeatedly demonstrated for spermidine. In a mouse model, the immune response to bacterial infections was enhanced and the immune response to vaccinations in older mice could be improved with spermidine [1]. In a psoriasis mouse model, spermidine was able to suppress the activation of inflammatory dendritic cells and improve symptoms of the disease [25].

Bypassing autophagy is one of the strategies used by some viruses. Cell culture experiments provide evidence that autophagy activators can drastically reduce viral replication. This applies to incubation with spermidine both before and after infection [26]. The autophagy activity and functionality of isolated B lymphocytes from elderly subjects were enhanced by spermidine [27]. Comparable results were obtained with T lymphocytes [28].

A study population of 87,602 postmenopausal women was used to calculate the correlation between polyamide intake and colorectal cancer incidence after 12.4 years. No significant positive link between dietary polyamides and the risk of colorectal cancer could be identified. The risk of colorectal cancer insignificantly decreased with average-to-high polyamine intake and a very-low polyamine intake moderately increased the risk [29]. This coincides with the findings of the Bruneck study, which importantly reported not only a decrease in overall mortality by high spermidine intake but also of all cancers [5].

Still, it has to be pointed out that during the malignant transformation of cells the concentration of polyamines, and therefore also of spermidine, typically increases within the serum of cancer patients and the affected tissues. This is due to the essential role polyamines play during cell proliferation and the growth processes [30]. This effect has been observed for instance in a recent pilot study on patients suffering from B-cell lymphomas. A significant difference in serum spermidine concentrations could be identified between the healthy cohort and lymphoma patients [31]. Due to such findings, there is a scientific discussion that high dosages of spermidine supplements may provide a growth advantage for malignant cells over associated stroma. Different effects may apply to cancer patients than to healthy individuals, especially during chemotherapy, but more research is needed [5][32]. Attempts to slow down tumor growth by inhibiting spermidine production have had little success and they have so far been limited to a few types of tumors, such as subtypes of breast cancer [33].

**Dosage and Safety:** Based on toxicity studies, the NOAEL (No Observed Adverse Effect Level) in the mouse model is set at 5 g/kg body weight [34]. When investigating cardioprotective effects in a rat model, the dose range was between 5 and 50 mg/kg body weight. The effect was dose-dependent, with significant positive effects being observed at 10 mg/kg body weight [7].

The dietary intake of spermidine in humans varies greatly depending on dietary habits and is estimated to range between 5 and 25 mg per day but it can be even higher in some cases. Intakes in the EU average 12.6 mg per day with higher levels in Spain and Italy, attributed to the Mediterranean Diet [35]. For the intake of spermidine-rich wheat germ extract as a dietary supplement, an upper limit of 6 mg per day is mandated in the EU. The daily upper limit of 6 mg of spermidine from spermidine-rich wheat germ extract does not necessarily apply to all other spermidine-rich plant extracts [36].

The dosage of 1.2 or 0.9 mg of spermidine per day used in human studies corresponds to about 10% of the dietary intake in industrialized countries. With a body weight of 70 kg, 1.2 or 0.9 mg per day correspond to about 0.017 or 0.013 mg/kg body weight. Dosages as low

as 0.9 mg per day may not be sufficient to achieve effects on the cognitive level [23]. On the website www.clinicaltrials.gov, several studies in the preparatory phase are currently registered, where higher doses of spermidine up to 6 mg per day are administered.

The available amount of spermidine in the organism is determined by endogenous synthesis, production by gut microbiota and exogenous supply. Furthermore, the human body has the ability to modulate spermidine availability by catabolic metabolism and renal excretion [37]. Exogenous polyamines are comparably stable substances, rapidly absorbed in the small intestine and, to a large extent, absorbed into tissues [38].

**The Legal Situation of Spermidine Supplements:** The successful novel food application for spermidine-rich wheat germ extract was filed in 2017 in Austria under the old Novel Food Regulation when the competent authorities of member states were still responsible for the safety assessment of novel food applications. Before 2018, there was the option of a simplified procedure for food business operators to bring foods to the EU market if they were "substantially equivalent" to an existing food, based on the opinion of a member state. Now after authorization, which was granted due to substantial equivalence with the wheat germ of common wheat, every food business operator can place this botanical extract on the market if it complies with the required specifications [39][40][41].

However, whether the novel food application for this plant extract was, in fact, necessary is debatable. Not every new plant extract is automatically a novel food. If a novel production process that changes the composition and structure of the food is applied affecting its nutritional value, metabolism, or levels of undesirable substances, then the Novel Food Regulation should apply. Normally, if the botanical extract is produced from a traditional food using traditional processes that have a history of safe food use, and if the botanical extract is used in a way that is consistent with its history of safe use, then it should not be a novel food. If the botanical extract is used in a way that is significantly different from its traditional use, or if a product with novel characteristics is created that can no longer be expected to be safe only by its history of safe use, then it likely adheres to the novel food authorization. The question arises of whether the assessment of the novelty of the food is sometimes skipped before the process of safety assessment [42].

Since spermidine-rich wheat germ extract has received a novel food authorization and spermidine-rich botanical extracts of other plants like microalgae or soy lack this authorization, there is uncertainty about whether these other extracts without novel food authorization can legally be sold within the EU. As mentioned before, unless a novel production process is used or a product with novel characteristics is created, these products are not novel foods [36]. However, the vast majority of studies have been conducted with spermidine-rich wheat germ extract.

The Court of Justice of the European Union will soon answer one question regarding another spermidine-rich food supplement once and for all. This case is centered around the flour of buckwheat seedlings that are germinated in an aqueous solution rich in synthetic spermidine. Here, a novel production process is used, and the product is most probably a novel food [43]. Regarding synthetic spermidine itself, this substance would need a novel food authorization, unless an EU member state confirms its usage in food before the 15$^{th}$ of May 1997 [42].

Spermidine and spermidine-rich wheat germ extract have no registered health claim in the EU. The only legal possibility to place health claims on spermidine supplements is the addition of other vitamins and minerals that have several authorized health claims on a

wide array of physiological functions. After this, positive effects on cell function, the heart, the immune system, or cognitive function could be advertised, with reference that the effects are attributed to the added nutrients.

**Dietary supplements and spermidine content:** The promising study results on spermidine have aroused great interest in the relevant supplements. There are several products available from different manufacturers, the quality of which is difficult for consumers to assess. The quality of spermidine preparations is determined by the starting material (with germinated wheat being the most common), production conditions, concentration and galenic that do justice to air-sensitive substances. As a comparative study of the content of different products has shown, their spermidine content per gram differs by up to two orders of magnitude. (Table 1).

**Table 1.** Spermidine content of selected dietary supplements.

| Spermidine content of selected dietary supplements | |
|---|---|
| **Product** | **Spermidine (mg/g)** |
| **Tec sperm** | 9,836 |
| **Spermidine ERWO** | 3,504 |
| **Zein Pharma Spermidine Mono** | 2,030 |
| **Spermidine Köhler, Köhler Pharma GmbH** | 1,995 |
| **BIOGENA Spermidine Superior** | 1,753 |
| **B1 Life Spermidine** | 1,583 |
| **Longevity Labs spermidine LIFE Original 365+** | 1,112 |
| **Sinoplasan Spermidine** | 0,637 |
| **Spermidine Supplementa** | 0,081 |

**Source:** Chemcon, Technisches Büro für technische Chemie GmbH, July 2022

Different starting materials were used for the production of the food supplements analyzed in this comparative study. Tec sperm, spermidineLIFE Original 365+ and Sinoplasan Spermidine are made from wheat germ, Spermidine ERWO and B1 Life Spermidine are made from buckwheat seedlings and Zein Pharma Spermidine Mono, Spermidine Köhler and BIOGENA Spermidine Superior are made from soybeans. The product Spermidine Supplementa could not be identified by online research [44-51].

It becomes apparent from this analysis that soy-based supplements consistently show a high concentration of spermidine, ranging from 1,753 mg/g to 2,030 mg/g. Buckwheat seedlings also seem to be a good starting material for spermidine supplements with concentrations ranging from 1,583 mg/g to 3,504 mg/g. The production process of these supplements is not specified on the respective websites but there is reason to suppose that these products are made from the flour of buckwheat seedlings that are germinated in an aqueous solution rich in synthetic spermidine. If that is the case, depending on the ruling of the Court of Justice of the European Union, these products may need a novel

food authorization in the future and will have to leave the market in the meanwhile [43].

Wheat germ extract is the starting substance of choice for the rest of the products on this list and the concentration of spermidine in those products mostly ranges from 0,637 mg/g to 1,112 mg/g. However, Tec sperm is also based on wheat germ, but it contains 9,83 mg of spermidine per gram, which is almost 10 times more than competing supplements. This increased concentration could be related to a superior extraction method. According to food package labelling, one Tec sperm capsule contains 169 mg of wheat germ extract with a spermidine content of 5 mg [4]. Spermidine Life Original 365+, the second-highest wheat germ-based food supplement in this list contains 1300mg of spermidine with a spermidine content of 2 mg [50].

## CONCLUSION

With rapid advances in the research on spermidine in recent years, the demand for food supplements containing this substance is rising steadily. Nonetheless, no health claims for spermidine or botanicals containing this substance have been approved as of now. Food supplement manufacturing companies seem to have diverse approaches to the formulation of spermidine-containing food supplements, which results in vast differences in the concentration of the polyamine. Wheat germ, soybean, and buckwheat seedlings seem to be the starting materials of choice, although the specific manufacturing process of buckwheat seedlings may soon categorize these supplements as novel foods. The typical range of spermidine concentration in food supplements is between one and two mg/g. Most differences in spermidine concentration can be explained away by minor differences in extraction methods and by the use of different starting substances. Generally, soybean extract seems to be slightly superior to wheat germ extract in terms of spermidine concentration. One obvious outlier product could be identified in this analysis. Spermidine is almost ten times more concentrated in this one wheat germ-based supplement than in the competition. This could be a sign that there is still potential for the food supplement industry to extract spermidine more efficiently. The optimization of the extraction process and the appropriate packaging of spermidine supplements should be further investigated to potentially lower production costs and save resources.

**Abbreviations:** mmHG: millimeter of mercury, Functional Food Center: FFC, AD: Alzheimer's Disease, NOAEL: No Observed Adverse Effect Level, EU: European Union

**Competing Interests:** Authors declare no conflict of interest.

**Acknowledgement/Funding**: This work received no special funding.

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