OXFORD
HEALTHSPAN

White Paper: Primeadine & Spermidine

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PRIMEADINE
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PRIMEADINE

THE NEW PRIME OF LIFE

Contents

1. Introduction

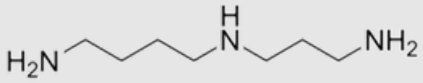
What is Primeadine™?

Primeadine™ is a concentrated wheat germ supplement, rich in naturally occurring polyamines. It contains a standardized dosage of spermidine (1mg), a compound which has been shown to induce the physiological process of "autophagy" or cellular renewal.

What is Spermidine?

Spermidine is a polyamine, an organic compound consisting of two or more amino groups, which is positively charged at physiological pH. Spermidine is present in all human tissues. There are three sources of spermidine:

Figure 1 Chemical structure of spermidine



1) endogenous spermidine made from the precursor amino acid ornithine;
2) microbial spermidine, produced from gut microbes, including *Bacteriodes spp., Fusobacteria spp., Bifidobacterium animalis, Lactis LKM512*; and 3) dietary spermidine, naturally occurring in food.

Endogenous production of spermidine accounts for roughly 1/3 of the body's spermidine, however the ability to produce spermidine endogenously decreases with age. While microbial and dietary intakes make up 2/3 of the body's needs, dietary intakes vary greatly between countries. The average daily intake of spermidine in the United States is estimated to be significantly lower than European average intakes (Zoumas-Morse et al., 2007), and substantially lower than the Japanese or Mediterranean diets (Ali et al., 2011).

What are the Best Dietary Sources of Spermidine?

With respect to food sources, spermidine is found in the greatest amounts in wheat germ and fermented soy (e.g., natto and tempe) (Okamoto et al., 1997). The wheat germ in Primeadine™ is rich in overall polyamine content, with a beneficial ratio of spermidine to spermine and putrescine. By contrast, existing research suggests that foods containing the amino acid precursors, arginine and ornithine, will *not* increase endogenous polyamine production. As a result, increasing dietary intakes of functional foods, like the concentrated wheat germ found in Primeadine™, is one way to ensure adequate polyamine levels with age.

Primeadine™ has High Bioavailability and Stability

The naturally occurring polyamines in Primeadine™ survive enzyme degradation, and are readily absorbed in the GI tract, making them highly bioavailable. As a result, Primeadine™ is a good alternative to other autophagy inducing compounds, such as resveratrol, which have low bioavailability.

While regular wheat germ contains spermidine, it is also a significant source of Omega-6 polyunsaturated fatty acids that can become readily oxidized. The concentrated wheat germ used in Primeadine™ is defatted to remove these potentially rancid fats, and provides a stable, standardized dose of spermidine. (See *Primeadine™ Dosage and Administration* below for more information.)

Supporting Research

In a double blind, placebo controlled trial, concentrated, spermidine rich wheat germ extract supplementation in humans was safe and well tolerated (Schwarz et al., 2018). More than 30 preclinical, peer- reviewed studies have investigated the science behind spermidine. These studies provide extensive evidence regarding the cellular mechanisms of spermidine metabolism and the physiological effects of spermidine supplementation *in vitro* or in animal models.

Registered spermidine clinical trials are now translating this research into human health, the first of which found that wheat germ derived spermidine supplementation positively impacted memory performance in adults with subjective cognitive decline (Wirth et al., 2018).

Benefits

Spermidine levels decline with age (Madeo, et al., 2018), and populations with the highest levels of spermidine dietary intakes are associated with lower all-cause mortality (Kiechl et al., 2018), improved cardiovascular health (Soda, et al., 2012), and increased cortical thickness and hippocampal volume (Schwarz et al., 2020). In animal models, spermidine supplementation has also been shown to be cardioprotective, neuroprotective, and able to enhance the aging immune system. This may be due to the fact that spermidine induces the cellular process of autophagy, and has pleiotropic effects, including anti-inflammatory properties, antioxidant functions, enhancement of mitochondrial function, and improved proteostasis and chaperone activity (Madeo et al., 2018).

Hallmarks of Aging

Spermidine's pleiotropic effects have also identified it as an antiaging drug target (Partridge et al., 2020). According to Partridge et al. (2020, Figure 2), spermidine influences five of the nine hallmarks of aging: 1) epigenetic changes; 2) impaired proteostasis; 3) mitochondrial dysfunction; 4) stem cell dysfunction; and 5) impaired intercellular communication. More recently, spermidinemediated age protection *in vivo* was also associated with decreased telomere attrition, suggesting that spermidine may inhibit this additional hallmark (Wirth et al., 2021).

While rapamycin ximpacts six of the nine hallmarks of aging, it has well known immune suppression properties. By contrast, spermidine does not have these adverse effects, and preclinical research suggests it may revive the aging immune system (Alsaleh et al., 2020).

Figure 2 Agents and their influence on different hallmarks of ageing[1]

	DNA damage	Eroded telomeres	Epigenetic changes	Impaired proteostasis*	Mitochondrial dysfunction	Altered nutrient sensing	Stem cell dysfunction	Cellular senescence	Impaired intercellular communication
Spermidine		☑	☑	☑ ☑	☑ ☑		☑		☑ ☑
Rapamycin				☑ ☑	☑	☑	☑ ☑	☑	☑
Senolytics								☑	☑
Metformin						☑		☑	☑
Acarbose			☑			☑			
NAD+ enhancers									☑
NSAIDs						☑			☑
Lithium		☑		☑	☑				
Reverse transcriptase inhibitors	☑								
Systemic circulating factors			☑ ☑				☑ ☑		☑ ☑
Glucosamine				☑	☑	☑			
Glycine						☑			☑
17α -oestradiol						☑			☑

☑ Compound inhibits the hallmark ☑ Role in ageing phenotype or lifespan shown experimentally

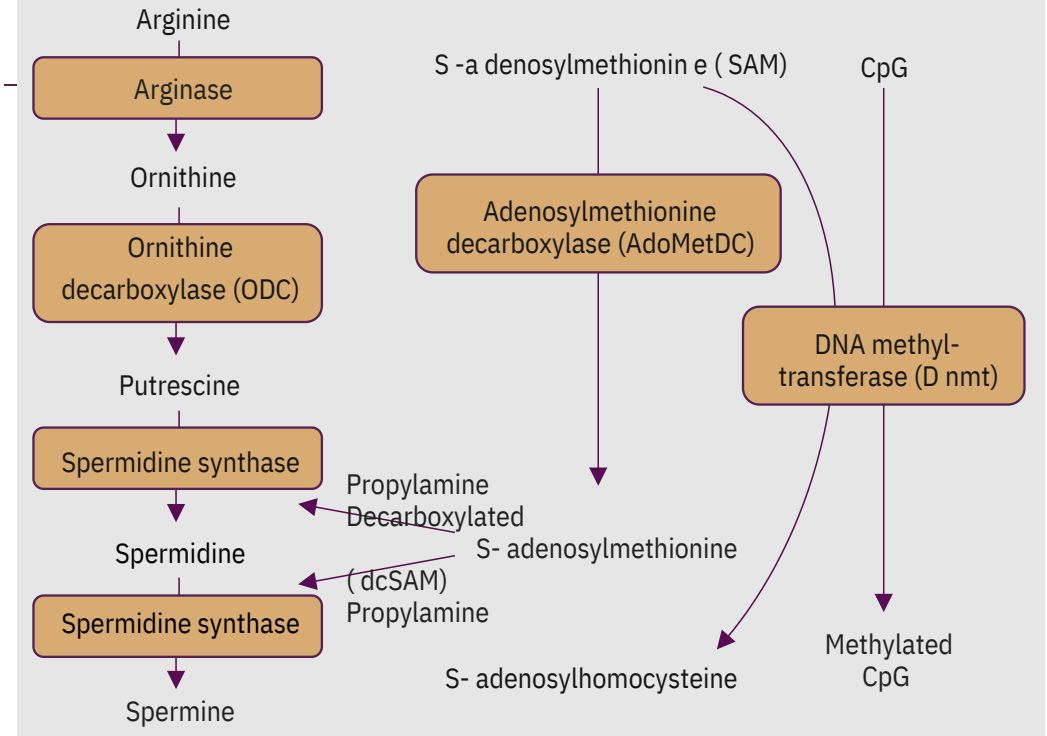
*Impaired proteostasis also includes autophagy

[1]Adapted from Partridge, et al. 2020; telomere protection, Wirth, et al. 2021

2. Mechanisms of Action

Spermidine has numerous mechanisms of action, many of which are *autophagy dependent*. Spermidine may also activate various subtypes of autophagy, such as mitophagy (the removal of damaged mitochondria), lipohapgy (the release of lipids by adipocytes), and virophagy (the direct elimination of unwanted viruses). By contrast, other mechanisms of action may be *autophagy independent*, including the conservation of arginine for nitric oxide production and the conservation of SAMe for DNA methylation.

Figure 3 Endogenous production of spermidine and spermine



[7]

Autophagy. Induction of autophagy via deacetylation of cytosolic and nuclear proteins (Madeo et al., 2018).

Caloric Restriction Mimetic. Spermidine mimics the beneficial effects of caloric restriction and fasting, acting as a CRM via protein and histone deacetylation and decreasing acetyl-CoA availability (Madeo et al., 2018).

Antioxidant. Spermidine may act as a ROS scavenger and protect DNA from oxidative damage in vitro and in vivo (Ramos-Molina, Queipo-Ortuño, Lambertos, Tinahones, & Peñafiel, 2019). Potent inhibition of oxidative stress in mice (Eisenberg, et al., 2009).

Anti-inflammatory. Anti-inflammatory effects of spermidine in lipopolysaccharide-stimulated BV2 microglial cells (Choi & Park, 2012).

Rejuvenation of CD8+ T cell Response. Spermidine supplementation rejuvenates T cell response in elderly mice in an autophagy dependent manner (Puleston et al., 2014).

Increases Nitric Oxide Production. Spermidine improves endothelial function by increasing nitric oxide production (Ramos-Molina et al., 2019), which may be due to metabolic effects on arginine bioavailability for nitric oxide production (Madeo et al., 2018).

Stabilization of DNA/RNA. Due to its positive charge, spermidine can readily bind to negatively charged DNA, RNA, proteins and phospholipids (Ramos-Molina et al., 2019), and may protect DNA from radiation induced damage (Douki, Bretonniere, & Cadet, 2000).

Enhances Mitochondrial Function & Mitophagy. (Madeo et al., 2018)

Inhibition of Platelet Aggregation. (de la Peña, Sosa-Melgarejo, Ramos, & Méndez, 2000).

Inhibition of Cellular Senescence. (Ramos-Molina et al., 2019).

Conservation of SAMe for DNA Methylation. Endogenous production of spermidine requires AdoMet as a cofactor, and increased dietary spermidine may increase available SAMe pools for DNA methylation (Ramos-Molina et al., 2019).

Intestinal Barrier Function. Polyamines are necessary for the development and maintenance of the gastrointestinal tract and promote intestinal barrier function (Ramos-Molina et al., 2019).

Spermatogenesis. Polyamine expression correlates with stages of spermatogenesis. (Lefevre, Palin, & Murphy, 2011).

Glucose Homeostasis and Insulin Sensitivity. Serum polyamine levels are associated with T2DM (Ramos-Molina et al., 2019).

3. Preclinical & Clinical Trials

Longevity

Autophagy and spermidine levels both decrease with age in humans. Spermidine supplementation increases median lifespan in mice, worms, and flies. Higher spermidine dietary intakes in humans are associated with reduced mortality and longevity.

- Polyamine enhanced diet high in spermidine prolongs lifespan (Minois, Carmona-Gutierrez, & Madeo, 2011) and decreases age-associated pathology and mortality *in vivo* (Soda et al., 2009).
- Higher spermidine intake is linked to lower mortality in humans (Kiechl et al., 2018), and is related to gross domestic product and longevity in Asian countries (Binh et al., 2010).

Brain Health & Cognition

Spermidine induced autophagy may remove neurotoxic protein aggregates that are responsible for neurological disorders, ameliorates age-induced memory impairment *in vivo* by restoring synaptic dynamics, and improves cognition in those with subjective cognitive decline.

- Spermidine reverses subjective cognitive decline in humans (RCT) (Wirth et al., 2018).
- Spermidine supplementation ameliorates age-induced memory impairment in flies (Gupta et al., 2016).
- Spermidine is neuroprotective via inhibition of caspase 3mediated Beclin 1 cleavage. (Yang et al., 2017).
- Spermidine may improve motor dysfunction in frontotemporal lobar dementia (FTLD-U) and amyotrophic lateral sclerosis (ALS) (Wang et al., 2012).

Cardiovascular Support

Spermidine is preferentially taken up by cardiomyocytes, and may provide cardioprotection against age-related cardiovascular diseases. Spermidine improves cardiomyocyte function via the induction of autophagy, mitophagy, and improvements in mitochondrial function. Spermidine supplementation improves blood pressure and reduces heart failure in hypertensive rats, and improves arterial stiffness and diastolic function in elderly mice.
Exogenous spermidine intake may increase arginine bioavailability
with a related increase in nitric oxide production. Increased dietary spermidine intakes are associated with improvements in blood pressure in humans, and inversely correlated with cardiovascular
disease incidence and death.

- Improves diastolic function, left ventricular elasticity, and mitochondrial function in an elderly mice model (Eisenberg et al., 2016; de Cabo & Navas, 2016).
- Intake of dietary spermidine in humans inversely correlates with the incidence of cardiovascular disease (Eisenberg et al., 2016) and CVD mortality (Soda et al., 2012).
- Cardiovascular benefits of spermidine appear to be due to importation of polyamines by cardiomyocytes (Nilsson & Persson, 2019).
- Spermidine supplementation reduced the formation of atheroslerotic plaques in ApoE deficient mice fed a high fat diet (Michiels, Kurdi, Timmermans, De Meyer, & Martinet, 2016).
- Spermidine enhances arteries and reverses arterial aging. (LaRocca, Gioscia-Ryan, Hearon Jr, & Seals, 2013).

Immune Support

Spermidine supplementation may increase memory T cells and reduce inflammatory cytokines. Spermidine dependent autophagy may support the disposal of pathogenic microorganisms by the immune system, and may potentiate the effect of vaccines in an aging immune system.

- Spermidine potentiates response to the influenza vaccine in elderly mice (Puleston & Simon, 2015).
- Spermidine delays infection by SARS-CoV-2 and inhibits progression of infection in human cells in vitro. Note: BioRxiv pre-print. (Gassen et al., 2020)

Autoimmunity

- Spermidine suppresses inflammatory DC function by activating the FOXO3 pathway and counteracts autoimmunity (Li et al., 2020).
- Spermidine supplementation alleviated psoriasis like symptoms in a mice model (Li et al., 2020).
- Spermidine supplementation protects from autoimmune demyelination in a mouse model of multiple sclerosis (Yang et al., 2016).

Cancer

Spermidine reduces growth of transplantable tumors, stimulates anti-cancer immune surveillance in combination with chemotherapy, and suppresses tumorigenesis induced by chemical insults in mice (Madeo et al., 2018). High polyamine intake is associated with a lower risk of colorectal cancer in a large cohort (n=87,602) of post-menopausal women (Vargas et al., 2015).

Endocrine Function & Obesity

Spermidine activates lipophagy, and exogenous spermidine may be a therapeutic treatment for Type 2 diabetes and obesity. (Fernandez-Garcia et al., 2019). Spermidine and spermine supplementation reduces salivary cortisol levels in men and women by 58% in 30 days, and normalizes hormones, including DHEA, testosterone, progesterone and estradiol (Bendera & Wilson, 2019).

Osteoporosis Prevention

Oral spermidine supplementation prevents osteoporosis in a mice model of post-menopause via inhibition of osteoclast formation (Yamamoto et al., 2012).

Circadian Rhythm

Oral spermidine supplementation in mice reverses age associated disruption of circadian rhythm (Zwighaft et al., 2015).

Hair Health

Spermidine boosts keratin production and prolongs the anagen phase of hair follicles, enhancing hair growth and reducing hair loss (Rinaldi, Marzani, Pinto, & Ramot, 2017). Spermidine promotes human hair growth and modulates human epithelial stem cell function (Ramot et al., 2011).

4. Contraindications

There are several clinical conditions where the use of wheat germ and/or polyamines may be contraindicated.

Celiac Disease, Wheat Allergy & Gluten Sensitivity Primeadine™ contains concentrated wheat germ, and is not suitable for individuals with Celiac disease or wheat allergy. Primeadine™ contains 40mg of wheat germ agglutinin per 3 capsule dose. As such, it may or may not be suitable for individuals with gluten sensitivity. While our clinical advisers have found that some individuals on a gluten free diet are able to tolerate the low dose of gluten found in Primeadine™, health professional supervision is advised in these cases.

SIBO

Wheat germ is a source of fructooligosaccarides, and, like all FODMAPs, may cause gastro-intestinal symptoms in individuals diagnosed with small intestinal bacterial overgrowth ("SIBO"). Professional discretion is advised in these cases.

Cancer

Research suggests that there is a potential requirement of polyamines for cancer cell growth (Madeo et al., 2018). This is analogous to the need for glucose for cancer cell growth. Animal studies have found no increase in cancer in healthy mice fed a diet high in polyamines (Eisenberg et al., 2016; Soda et al., 2009). While some studies suggest that polyamine intake may even be chemopreventive (see, e.g.,Vargas et al., 2015, re colon cancer), future studies are needed to address the associations of dietary polyamines with other types of cancer. As a result, Primeadine™ intake is not advised in cases of cancer.

5. The Primeadine™ Product

Safety

The concentrated wheat germ found in Primeadine™ has been strictly inspected and audited in accordance with the Japanese Institute for Health Food Standards ("JIHFS") GMP Standards for Health Foods and Health Food Raw Materials, and confirmed to meet the requirements of these standards. The JIHFS GMP Standards conform to the Health Food GMP Guideline of the Japanese Ministry of Health, Labour and Welfare.

Primeadine™ is further tested in the United States for purity before encapsulation in an FDA certified cGMP plant.

Primeadine™ Dosage and Administration

The recommended daily dosage of Primeadine™ is 910mg of concentrated wheat germ extract, containing 1mg of spermidine. The dosage was based on safety studies and existing human clinical trials (Schwarz et al., 2018; Schwarz et al., 2020), which use a concentrated wheat germ extract containing approximately 1mg of spermidine. There is one registered human trial currently underway using a dosage of 4mg spermidine from concentrated wheat germ. The European Food Safety Agency has stated that dosages up to 6mg of spermidine from concentrated wheat germ are likely safe in humans. Practitioner discretion is advised in determining dosage based on this information. We will continue to update our recommendations as more human trials are published.

Primeadine™ Clinical Effects

Our customers have reported various short term (within 1 month of use), medium term (1-2 months of use), and longer term effects (3 months or longer). Short term effects include increases in Heart Rate Variability ("HRV") and Deep Sleep (as measured by the Oura Ring).

Short to medium term effects include improvements in hair quality and thickness (including eyelash elongation), nail health, and skin appearance. Longer term effects include reductions in belly fat, cellulite, and overall weight loss. Health care professionals have also reported an optimization in blood pressure and cholesterol levels in their patients with longer term use. Because some of the beneficial results of Primeadine™ are associated with longer term use, we recommend a minimum of a 2-3 month initial trial, and have provided a discount for customers for multiple bottle purchases. It's important to note that we are seeing more clinical results in individuals over the age of 50, and clinical effects may not be as apparent in younger users. Our clinical experience also suggests that results may be more apparent in individuals with pre-existing deficits (e.g., those with low baseline HRV appear more likely to see an increase in HRV). While these results have been reported by a combination of individual customers and health care practitioners who are using Primeadine™ with their patients, it's important to emphasize that individual results may vary.

Product Storage and Recommendations

Primeadine™ is heat sensitive and should always be stored in a cool and dry location away from direct sunlight and any source of heat. It has been lab tested and is stable at temperatures between 41-75 degrees Fahrenheit. However, at temperatures exceeding 104 degrees Fahrenheit, there is a decline in polyamine content of approximately 8%. It is therefore not recommended that the contents of capsules be mixed with hot water, tea, coffee or similar heated liquids.

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