

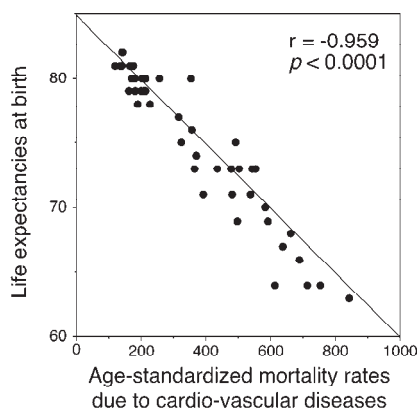
Polyamines - The Principal Candidate Substance of Soybean-Induced Health

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1. Introduction

In countries with sufficient medical and public health resources, cardiovascular diseases (CVDs), cancers, and other chronic metabolic diseases are major killers. The incidence of these diseases increases with aging and, therefore, they are called age-associated diseases. Importantly, the rate of mortality from these diseases ranges widely, even in countries with similar social and economic conditions. And, life expectancy at birth is greatly affected by the incidence of age-associated diseases, especially CVDs (Figure 1). The close inverse correlation between these two variables indicates that prevention of chronic age-associated diseases is the most effective way to improve health and prolong lifespan.



Close inverse correlation was found between life expectancy at birth in 2006 and age-standardized mortality rates due to CVDs per 100,000 population in 2002 (available date close to 2006) in 49 European and Western countries. Data are collected from World Health Organization (WHO).

Fig. 1. The relationship between CVD mortality and longevity.

Variation in the rates of mortality from age-associated diseases is considered to be largely due to lifestyle differences, especially differences in eating pattern. There is clear epidemiological evidence indicating that soybeans have beneficial effects on health and delay the onset of age-associated diseases, especially CVDs. However, in spite of numerous and extensive studies, the substance(s) in soybeans and mechanism(s) by which soybeans improve health are still obscured.

In our studies, we have shown that polyamines contained abundantly in soybeans inhibit the progression of age-associated pathological changes and prolong mouse lifespan.

Importantly, we found that the favorable effects of food polyamines on murine health and longevity were not due to differences in food intake or changes in body weight, but rather considered due to the polyamine-mediated suppression of inflammatory mediators (Soda et al., 2005, 2009a, 2009b).

In this chapter, I discuss the possible contributions to human health of polyamines present in dietary soybeans.

2. Foods that prolong life

Epidemiologic studies have suggested the relationship between intake of several foods and prolonged longevity, and numerous interventional studies have been done to test the effect of food on human health. The beneficial effects of soybean consumption on human health are well recognized. For instance, epidemiological studies have shown that consumption of soybean products is closely correlated with lower incidence of CVDs, type 2 diabetes, and decreased risk of certain types of cancers such as breast and prostate cancers as well as with better bone health and relief of menopausal symptoms. Human and animal intervention trials have also shown that consumption of soybean products has beneficial impacts on the risk factors for cardiovascular diseases (Anthony et al., 1998; Lin et al., 2004).

At one time, isoflavones were considered one of the most promising health-promoting nutritional factors in soybeans. Isoflavones are polyphenols found in many plants. They are antioxidants (i.e., chemicals that inhibit the transfer of electrons from a substance to an oxidizing agent). Because oxidative stress is involved in many age-associated diseases, isoflavones were previously considered to help decrease the incidence of age-associated diseases and help increase longevity. However, recent studies in animals as well as humans have shown that isoflavones are not responsible for the favorable effects of soy products, such as improvement of lipid metabolism, blood pressure, etc (Balmir et al., 1996; Sacks et al., 2006; Song et al., 2003). The US Food and Drug Administration (FDA) and the American Heart Association (AHA) Nutrition Committee have concluded from the findings of numerous intervention studies that isoflavones have no efficacy for preventing or treating age-associated diseases, despite the demonstration that consumption of soybeans and soy products does have efficacy (US Food and Drug Administration (FDA), 1999; Sacks et al., 2006).

Similarly, the effects of fruit polyphenols are not established yet. Red wine consumption is purported to underlie the “French paradox”, which refers to the relatively lower mortality from CVDs in France and among individuals who consume much more wine, especially red wine, despite their high intake of animal products rich in saturated fat. A large number of *in vitro* studies have shown the favorable effects of fruit polyphenols on human health. Moreover, animal experiments have shown many favorable effects of increased intake of polyphenols, such as decrease in carcinogenesis and attenuation of cerebro- and cardiovascular deterioration. However, in most of these experiments, the concentrations vastly exceed those physiologically achievable by diet, and therefore it is considered to be impossible for humans to benefit from fruit intake. The evidence from human intervention studies is limited, mostly inconsistent, and inconclusive. Most studies fail to show any effects leading to the prevention of CVDs. In addition, the strongest anti-oxidants, vitamin E and beta-carotene, even increased mortality, including mortality from CVDs (Miller et al., 2005; Vivekananthan et al., 2003).

These findings suggest that substance(s) other than isoflavones or fruit polyphenols help prevent age-associated diseases. Consequently, our focus since 2005 has been on the

polyamines in soybeans. In 2005, we first noticed that they have biological activities capable of delaying the onset of age-associated diseases (Soda et al., 2005).

3. What are polyamines

Polyamines (spermine, spermidine, and putrescine) are organic compounds having two or more primary amino groups $-NH_2$. Polyamines are synthesized from arginine and contained in almost all cells (Figure 2). They are indispensable for cell growth and differentiation, and are involved in diverse functions such as DNA synthesis and stability, regulation of transcription, ion channel regulation, and protein phosphorylation. With aging, the enzymatic activities required for polyamine synthesis decrease gradually.

Ornithine decarboxylase (ODC) and S-adenosylmethionine decarboxylase (3) but not spermine/spermidine synthases (which catalyze the synthesis of spermine from spermidine and spermidine from putrescine) (1) and (2) in Figure 2) are rate-limiting enzymes and under regulatory control. Intracellular *de novo* synthesis and concentrations of polyamines in cells and tissues, especially those of spermine and spermidine, decrease with aging (Das & Kanungo, 1982).

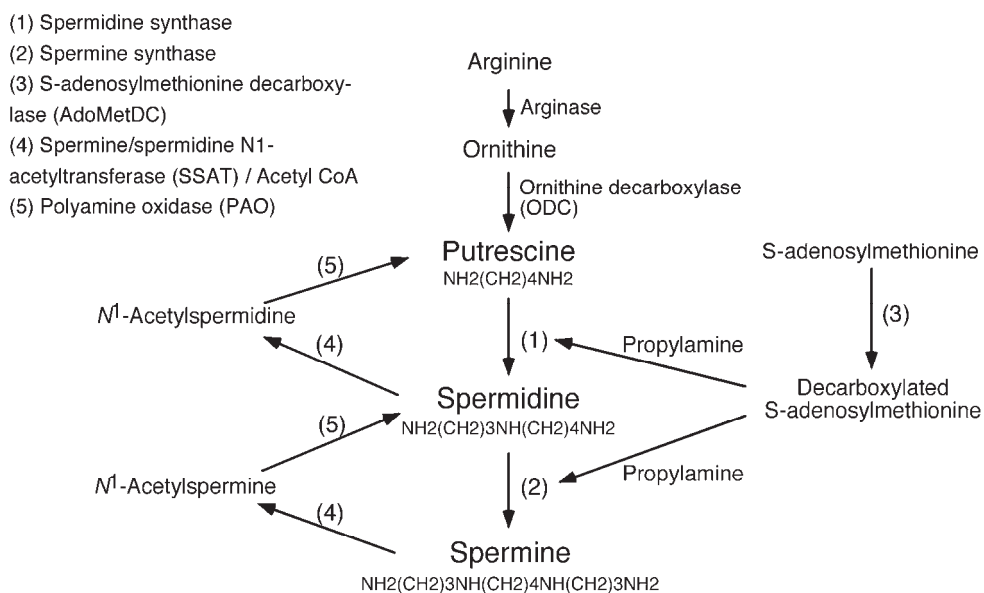


Fig. 2. Polyamine biosynthesis and catabolism.

In addition to polyamines from *de novo* synthesis, polyamines are obtained from the environment (Bardocz, 1990a; Colombatto et al., 1990). White blood cells and red blood cells, because they circulate in all tissues and organs, should reflect, at least somewhat, the amount of polyamines in the body. However, the interindividual variation in polyamine concentration in human blood cells ranges widely and does not appear to decrease in an age-related manner (Elworthy & Hitchcock, 1989; Soda et al., 2005). Although the factors underlying this difference are not fully understood, one is considered to be the amount of

polyamine intake from food and/or the diversity of intestinal microflora (which serve as a source of endogenous polyamines). In fact, increasing polyamine intake increases blood polyamine concentrations in animals and humans (Soda et al., 2009a, 2009b).

4. Food is an important source of polyamines

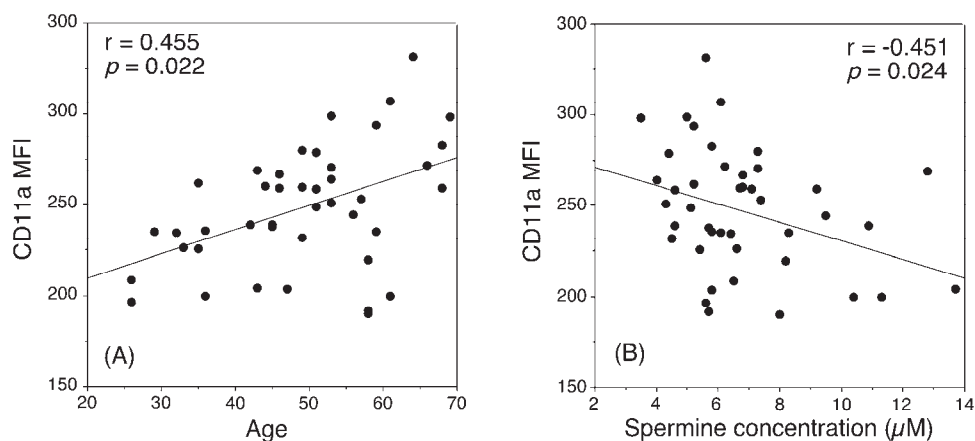
Because most foods originate from microorganisms, plants, or animals, almost all foods contain polyamines, but in widely varying concentrations. Of all foods, beans, especially soybeans, have the highest amount of the polyamines, especially spermine and spermidine. Spermine and spermidine are not enzymatically degraded in the alimentary tract, and they are absorbed quickly from the intestinal lumen and distributed to all organs and tissues (Bardocz, 1990b; Uda et al., 2003). In animals, polyamine restriction in conjunction with elimination of intestinal bacteria by antibiotics successfully decreases blood polyamine levels, suggesting the importance of polyamines from foods and microbes in the intestinal lumen.

However, short-term ingestion of polyamine rich foods fails to increase blood polyamine levels (Brodal et al., 1999; Soda et al., 2009a, 2009b). Cells contain polyamines, and erythrocytes and leukocytes contain almost all the polyamines in blood. Intracellular polyamine concentration is regulated very tightly by mechanisms such as synthesis, degradation, and transmembrane transport; therefore polyamine concentration can be stable. However, long-term intake of polyamine-rich chow gradually increases blood polyamine levels in mice, and continuous intake of the polyamine-rich food called "Natto" (a traditional Japanese dish made from fermented soybeans) gradually increases blood polyamine concentration in humans (Soda et al., 2009a). The slow increase in blood polyamine concentrations after long term increased polyamine intake suggests that the process is an adaptative response to polyamine influx from extracellular sources.

5. Polyamines as anti-inflammatory substances

We have found that polyamines, especially spermine and spermidine, suppress the expression of lymphocyte function-associated antigen-1 (LFA-1) on the surface of peripheral blood mononuclear cells (PBMCs), i.e., monocytes and lymphocytes in humans (Figure 3), and inhibit LFA-1 associated cellular functions (Kano et al., 2007; Soda et al., 2005). LFA-1 consists of two membrane molecules, CD11a and CD18. Among the many membrane molecules (i.e., membrane proteins) whose expression we studied on human PBMCs, only CD11a and CD18 were suppressed by spermine and spermidine. More than 300 membrane proteins with independent cellular functions were identified. LFA-1 is crucial for immune cell activation. Without this protein, immune cells are not activated and pathogens cannot be eliminated. In addition, spermine and spermidine have been shown to suppress the production of pro-inflammatory cytokines, both *in vitro* and *in vivo*. (M. Zhang et al., 1997; Zhu et al., 2009)

The suppressions of LFA-1 expression and of cytokine production was not due to decreases in cell activity and viability. Polyamines even enhance the mitogenic activities of immune cells responding to lectins, such as concanavalin A and phytohaemagglutinin (Soda et al., 2005). Both LFA-1 (a leukocyte cell surface protein) and pro-inflammatory cytokines promote systemic inflammation. Thus, polyamines, especially spermine and spermidine, are natural anti-inflammatory substances.



Blood samples were collected from 42 healthy male volunteers. Concentration of polyamines in whole blood was measured by HPLC (High Performance Liquid Chromatography), and the expression of CD11a on peripheral mononuclear cells (lymphocytes and monocytes) was determined by flow cytometry.

(A) The positive correlation between age and CD11a MFI (mean fluorescence intensity).

(B) The inverse correlation between CD11a MFI and blood spermine concentration.

Fig. 3. Polyamine inhibits CD11a (i.e. LFA-1) expression.

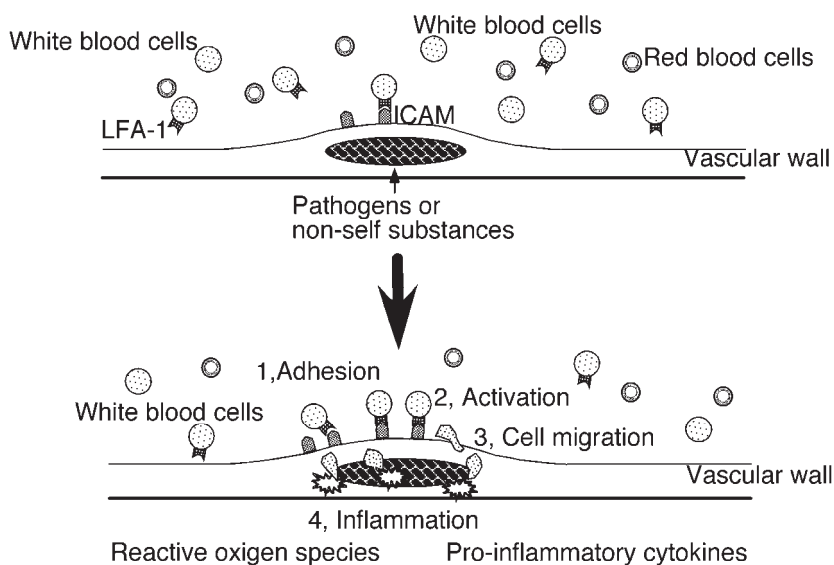
6. The role of inflammation in the pathogenesis and progression of age-associated diseases

Inflammation is a part of the biological response to harmful stimuli, such as pathogens, damaged cells, or irritants. Redness, swelling, heat, and pain are symptoms and signs of acute inflammation. Inflammation is the result of transmigration of immune cells from the blood into the inflamed site. Initially, leukocytes circulating in the bloodstream adhere to endothelial cells lining the blood vessels. Leukocyte adhesion is mediated by the binding of molecules, such as LFA-1 on the surface of immune cells and intercellular adhesion molecules (ICAMs) on the surface of endothelial cells. The adhesion stimulates immune cell activation, and the activated cells migrate to the sites of harmful stimuli and produce chemical substances, such as pro-inflammatory cytokines, to localize and eradicate such stimuli (Figure 4). Therefore, the primary objective of inflammation is to protect organisms from harmful stimuli.

Recent investigations have shown that chronic inflammation is involved in the pathogenesis of many age-associated diseases. Unlike acute inflammation, chronic inflammation manifests few symptoms and signs. Increased pro-inflammatory activities, such as age-dependent increase in the expression of LFA-1 on human PBMCs (Figure 3-A), are considered to be a factor accelerating the progression of age-associated pathologies, and “inflamm-aging” is a term coined to express the close association between inflammation and aging. For example, atherosclerosis, the underlying cause of CVDs, was formerly considered

to be merely a lipid storage disease. However, a fundamental role for inflammation in all stages of atherosclerosis and, ultimately, in thrombotic complications leading to CVD events has recently been established (Granger et al., 2004). Therefore, increased chronic inflammation in conjunction with impaired lipid metabolism is the principal factor contributing to initiation and progression of atherosclerosis (Figure 4).

In addition, an association of chronic inflammation with several other age-associated metabolic disorders has been shown. For example, obesity is not merely a problem related to increased fat storage but also involves increased production of inflammatory mediators in fat tissues. Therefore, strategies for preventing or treating age-associated diseases must include suppression of inflammation.



1. LFA-1 is an adhesion molecule on the leukocyte surface that exclusively recognizes the intercellular adhesion molecule (ICAM).
2. Binding between LFA-1 and ICAM initiate activation of immune cells.
3. The activated immune cells transmigrate into the site where pathogens or non-self substances exist.
4. Interaction between migrated immune cells and pathogens provokes the production of chemical substances, resulting in inflammation.

In the pathogenesis of atherosclerosis, monocytes in the intima are transformed to macrophages, which take up oxidized-low density lipoprotein (LDL) to generate lipid-laden macrophages, also known as foam cells. Chronic inflammation disrupts endothelial and muscle cells and destroys the normal structure of the vessel wall.

Fig. 4. Role of inflammation in the pathogenesis of atherosclerosis.

7. Food, food nutrients, and chronic inflammation

Several foods, including soybeans, are confirmed to have favorable effects on human health. Foods and food components that inhibit the progression of age-associated diseases are shown to have anti-inflammatory properties. Examples are soybeans, mono-unsaturated fatty acids in olive oil, n-3 unsaturated fatty acids in fish oil, and components of the "Mediterranean diet" (MD) (Table 1).

● High olive oil consumption
● High consumption of legumes
● High consumption of fruits
● High consumption of vegetables
● Moderate consumption of dairy products (mostly as cheese and yogurt)
● Moderate to high consumption of fish plus low consumption of meat and meat products
● Moderate wine consumption
● High consumption of unrefined cereals
● Less sweets

Table 1. The principal aspects of a Mediterranean diet

The benefit of dietary soybeans has been attributed primarily to reducing serum cholesterol levels, especially low density lipoprotein (LDL) cholesterol level, which if high promotes atherosclerosis in humans and animals (Jenkins et al., 2002; McVeigh et al., 2006; Reynolds et al., 2006). However, studies have shown that atherosclerotic lesions are reduced in atherosclerosis-susceptible apolipoprotein E knockout (apoE^{-/-}) mice fed a soy-containing diet despite unchanged serum lipid levels (Adams et al., 2002; Nagarajan et al., 2008). Moreover, intervention studies in humans have shown that the favorable effects of soy protein on vascular function are independent of lipid and antioxidant effects (Steinberg et al., 2003). Soy protein has anti-inflammatory properties, and the mechanisms of soy-mediated inhibition of atherosclerosis are considered to be anti-inflammatory (Nagarajan et al., 2008). The importance of isoflavones has been disputed because the favorable effects of soy can be elicited by soy protein devoid of isoflavones (Balmir et al., 1996; Nagarajan et al., 2008; Song et al., 2003).

The effects of various fatty acids on inflammation are well established. Recent investigations have linked the health benefit of olive oil and fish oil to anti-inflammatory effects. Mono-unsaturated fatty acids in olive oil and n-3 polyunsaturated fatty acids in fish oil inhibit prostaglandin-mediated inflammation (Lee et al., 1985; Mehta et al., 1988).

The dietary patterns of several countries in the Mediterranean Basin are similar (Table 1) (Trichopoulou & Lagiou, 1997). In spite of the relatively high amount of fat consumed by individuals in Mediterranean countries, rates of CVDs are far lower in these individuals than in those living in the other European countries and the United States, where similar levels of fat are consumed. In addition to many epidemiological studies, several intervention studies have shown that the Mediterranean diet (MD) is closely associated with prolonged lifespan and decreased mortality from chronic age-associated diseases (Bamia et al., 2007; de Lorgeril et al., 1999; Tunstall-Pedoe et al., 1999). The mechanism underlying this favorable

effect on health has not been fully elucidated. However, the MD has been shown to attenuate inflammation (Esposito et al., 2004; Schulze et al., 2005).

On the other hand, food components that enhance inflammation seem to have deleterious effect on health. Examples are saturated fatty acids from animal fat and trans-fatty acids. Increased intake of these fatty acids is associated with increased incidence of age-associated diseases, especially CVDs (Forman & Bulwer, 2006; Howard et al., 2006).

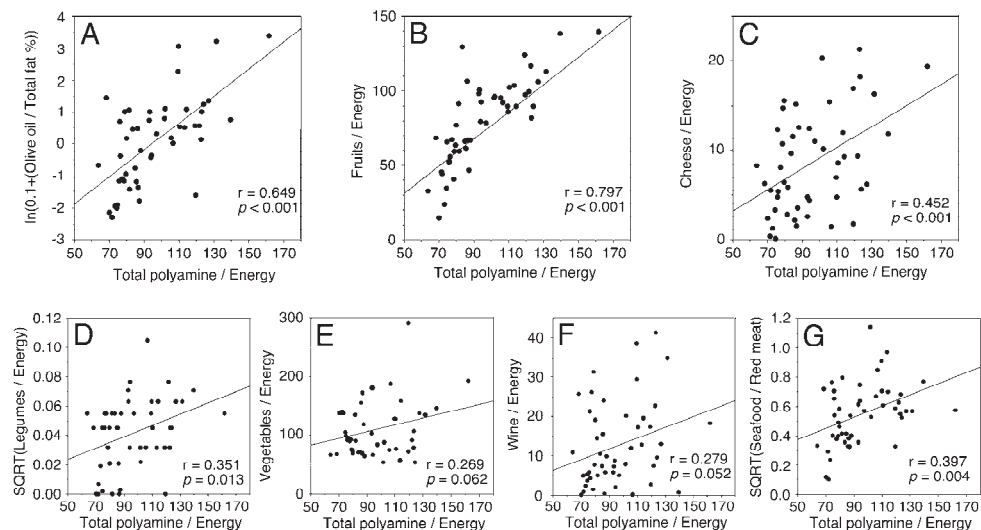
8. Epidemiological evidence showing a soybean diet improves human health

The results of basic and animal studies have indicated that polyamines are potential candidate molecules responsible for the beneficial effects of soybeans on human health. Epidemiological evidence other than that indicating an association between soybean intake and human health provides further support for the role of polyamines in human health.

The MD pattern has attracted considerable interest because of its association with a lower mortality from all causes in prospective studies (Lasheras et al., 2000; Trichopoulou et al., 2003) and also with lower incidence of coronary events in recent case-control studies (Martinez-Gonzalez et al., 2002; Panagiotakos et al., 2002). Although there is no one MD, the principal components of the MD pattern are shown in Table 1. Health benefits of the MD can be partially explained by the relatively high intake of mono- and n-3 poly-unsaturated fatty acids from olive oil and fish oil. The MD does not include many animal meats rich in saturated fatty acids and emphasizes foods rich in n-3 polyunsaturated fatty acids and monounsaturated fatty acids, including legumes, fresh fruits and vegetables, seafood, and olive oil. However, they do not sufficiently explain the beneficial effects of the MD. The "French paradox" shows that mortality from CVDs can be lower despite the high intake of animal products rich in saturated fatty acid.

To evaluate the association between the MD and increased polyamine intake, the amounts of food in 49 European and other Western countries were collected from the United Nations' database, and the amount of food polyamine was estimated using polyamine concentrations in foods from published sources. For all 49 countries and for foods such as olive oil (Figure 5-A), fruits (B), and cheese (C), the ratios of the amounts of these foods to total calories were all positively associated with the amount of polyamines per total food energy supplied (Figure 5). The amount of legumes (beans and nuts) per energy unit (1000 kcal/capita/day) (Figure 5-D), vegetables per energy unit (E), wine per energy unit (F), and the amount of seafood relative to red meat (G) tended to have a positive association with the amount of polyamines per energy unit, while several foods in the non-MD group tended to have no or negative association. Examples are the amounts of whole milk per energy unit ($r = -0.291$, $p = 0.043$), other alcohols per energy unit ($r = -0.181$, $p = 0.215$), and potato per energy unit ($r = -0.174$, $p = 0.234$) (Binh et al., 2011).

Because polyamines content of wine is low, the positive correlation between the amount of wine and amount of polyamines can be interpreted as indicating that consumption of wine tends to accompany consumption of foods rich in polyamines. Many epidemiological studies have shown that milk consumption is positively correlated with CDV incidence, however several studies have indicated that such a positive correlation is attenuated or lost when the relationship is to dairy foods (including cheese) (Tholstrup, 2006). Epidemiological studies indicate that individuals who prefer whole milk prefer foods containing less polyamines and those who prefer cheese prefer foods rich in polyamines.



Energy = 1000 kcal/capita/day; Olive oil, and Wine = mL/capita/day; Fruit, Cheese, Legumes, Vegetables, Seafood, and Red meat = g/capita/day.

Total polyamines (Putrescine + Spermidine + Spermine) = $\mu\text{mol/capita/day}$.

Some data were transformed to approximate a normal distribution. In = natural logarithm, SQRT = Square root.

All data are obtained from the statistical database of the Food and Agriculture Organization (FAOSTAT) of the United Nations.

Fig. 5. Mediterranean diets and the amount of polyamine

In addition, two other elements of the MD in Table 1 (high consumption of unrefined cereals and less sweets) have a relationship with the amount of polyamines. Polyamines are abundant in cereal germ and bran; however, refined cereals and Western sweets (a combination of refined flour, sugar, milk, egg, and butter) contain only a small amount of polyamines (Cipolla et al., 2007; Nishimura et al., 2006).

9. Other background information concerning the health effects of polyamine

In addition to anti-inflammation, dietary polyamines play a role in the prevention of age-associated diseases, especially CVDs. Endothelium covers the inner surface of the vessel wall, and the status of endothelial function can be predictive of future cardiovascular events. Endothelium uses nitric oxide (NO) to signal the surrounding vascular smooth muscle to relax, thus resulting in vasodilation and increasing blood flow. Decreased bioavailability of NO is involved in the pathogenesis of various disorders (John & Schmieder, 2003). Conversely, increased NO synthesis by arginine administration restores vascular function (Cooke et al., 1992; Drexler et al., 1991).

Nitric oxide synthase (NOS) enzymes use only L-arginine to synthesize NO. Simultaneously and competitively, arginase catalyzes the first step of polyamine synthesis, which is the conversion of L-arginine to ornithine (Figure 2). Therefore, polyamines and their metabolic

and catabolic enzymes affect the synthesis of NO by increasing or decreasing the amount of L-arginine available. An increase in intracellular polyamines from extracellular sources suppresses polyamine synthesis and increases arginine availability for NO synthesis (Mendez et al., 2006; Stojanovic et al., 2010). Conversely, decrease in arginine availability as a consequence of increased arginase activity inhibits endothelial NO synthesis (Thengchaisri et al., 2006; C. Zhang et al., 2001). Therefore increased polyamine intake enhances the bioavailability NO, essential for normal vascular physiology.

10. Conclusion

Polyamines have many biological activities for the possible inhibition of age-associated diseases. And, recent studies have shown the contribution of polyamines on longevity of various living organisms including mammals. In addition, epidemiological studies show the close positive correlation between increased polyamine intake and increased components of healthy dietary pattern, Mediterranean diet. Soybean is one of the foods containing the largest amount of polyamines in nature. Therefore, I believe that soybean-induced inhibition of age-associated diseases is mainly produced by polyamines. Polyamines, in association with the appropriate amount of and ratios of various fatty acids, e.g. n-3 polyunsaturated fatty acids, saturated fatty acids, may be two major food components that help inhibit the progression of age-associated diseases and prolong human lifespan.

11. References

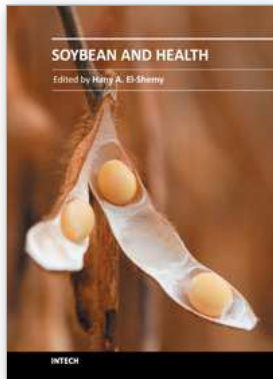
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Worldwide, soybean seed proteins represent a major source of amino acids for human and animal nutrition. Soybean seeds are an important and economical source of protein in the diet of many developed and developing countries. Soy is a complete protein, and soy-foods are rich in vitamins and minerals. Soybean protein provides all the essential amino acids in the amounts needed for human health. Recent research suggests that soy may also lower risk of prostate, colon and breast cancers as well as osteoporosis and other bone health problems, and alleviate hot flashes associated with menopause. This volume is expected to be useful for student, researchers and public who are interested in soybean.

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