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## Polyamines of Plant Origin – An Important Dietary Consideration for Human Health

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### 1. Introduction

Ubiquitous in nature, polyamines are a group of aliphatic amines, cationic at neutral pH, that are essential for cell growth and viability. Because of their positive charge, polyamines are able to bind by electrostatic linkages to many cellular macromolecules, including DNA, RNA, and proteins (Kusano et al. 2008). Polyamines are involved in the regulation of a diverse range of vital cellular processes in both eukaryotic and prokaryotic cells, including cell proliferation, signal transduction and membrane stabilization (Wang et al. 2003; Kusano et al. 2008). They are also involved in the regulation of gene expression and translation (Igarashi & Kashiwagi, 2000; Kusano et al., 2008), and control programmed cell death in some organisms (Seiler & Raul, 2005). The diamine putrescine and the triamine spermidine are found in nearly all organisms and are the most abundant polyamines in prokaryotic cells, such as bacteria, while the tetraamine spermine is mainly found in eukaryotic cells. In plants the most common polyamines are putrescine, spermidine and spermine (Tiburcio et al., 1993; Grimes et al. 1986), which are present as free amines, conjugated to small molecules such as hydroxycinnamic acid, or bound to larger macromolecules such as proteins or nucleic acids. Less common polyamines found in plants are cadaverine, and the spermidine- and spermine-related compounds, homospermidine, norspermidine, homospermine, norspermine and thermospermine (Martin-Tanguy, 2001). The structures of the common and less common polyamines found in plants are shown in Table 1. Polyamines are involved in many aspects of plant development (Martin-Tanguy, 2001; Li & Burritt, 2003; Hunter & Burritt, 2005; Baron & Stasolla, 2008) and are important molecules associated with both abiotic and biotic stress tolerance (Burritt, 2008). Because of their roles in a diverse array of fundamental processes, polyamines are found within all the compartments that make up the plant cell, including mitochondria, chloroplasts and the nucleus (Martin-Tanguy, 2001).

In recent years there has been considerable interest in the influence of ingested polyamines from plant-based foods on human health (Lima et al., 2011). In a recent study comparing several vegetable crops cultivated using organic or conventional procedures, Lima et al. (2011) reported that organic vegetables contained higher concentrations of polyamines than those produced by conventional cultivation, and suggested that this could be due to plants

cultivated organically being subjected to stress from pests and/or diseases. Hence an understanding of the factors regulating polyamine metabolism in plants could be of great value when considering the importance of polyamines of plant origin on human health. Polyamines are important to human health, particularly because they are involved in an array of specific roles that are essential to cell growth and proliferation (Kalač & Krausová, 2005). Therefore, polyamines may be considered especially important in the young. However, it is well established that the capacity for polyamine synthesis decreases with age (Larqué, 2007). Considering the array of specific roles that polyamines fulfil, a decrease in polyamines could contribute to the ageing process. Therefore, this chapter examines the content of polyamines in plants and plant-based foods, the role of polyamines in human health throughout the ageing process, and the benefit that might be achieved with consumption of high polyamine plant-based foods by older people.

Name	Structure
<b>Diamines</b>	
1,3-Diaminopropane	$\text{NH}_2(\text{CH}_2)_3\text{NH}_2$
Putrescine	$\text{NH}_2(\text{CH}_2)_4\text{NH}_2$
Cadaverine	$\text{NH}_2(\text{CH}_2)_5\text{NH}_2$
<b>Triamines</b>	
Spermidine	$\text{NH}_2(\text{CH}_2)_3 \text{NH}(\text{CH}_2)_4\text{NH}_2$
Homospermidine	$\text{NH}_2(\text{CH}_2)_4 \text{NH}(\text{CH}_2)_4\text{NH}_2$
Norspermidine	$\text{NH}_2(\text{CH}_2)_3 \text{NH}(\text{CH}_2)_3\text{NH}_2$
<b>Tetraamines</b>	
Spermine	$\text{NH}_2(\text{CH}_2)_3\text{NH}(\text{CH}_2)_4 \text{NH}(\text{CH}_2)_3\text{NH}_2$
Homospermine	$\text{NH}_2(\text{CH}_2)_3\text{NH}(\text{CH}_2)_4 \text{NH}(\text{CH}_2)_4\text{NH}_2$
Norspermine	$\text{NH}_2(\text{CH}_2)_3\text{NH}(\text{CH}_2)_3 \text{NH}(\text{CH}_2)_3\text{NH}_2$
Thermospermine	$\text{NH}_2(\text{CH}_2)_3\text{NH}(\text{CH}_2)_3 \text{NH}(\text{CH}_2)_4\text{NH}_2$

Table 1. Common and uncommon diamines and polyamines found in plants

## 2. Polyamines and plants

### 2.1 Polyamine biosynthesis and catabolism

In animals and most plants, with the notable exception of *Arabidopsis thaliana*, putrescine can be synthesized directly by decarboxylation of ornithine via the enzyme ornithine decarboxylase (ODC; EC 4.1.1.17) (Figure 1). However, unlike in animal cells, where the existence of the enzyme arginine decarboxylase (ADC; EC 4.1.1.19) is debatable, plants can synthesise putrescine from arginine, via ADC, agmatine iminohydrolase (EC 3.5.3.12) and N-carbamoylputrescine amidohydrolase (EC 3.5.1.53) (Alcázar et al. 2006; Slocum, 1991). Interestingly, plants also contain the enzyme arginase that allows the inter-conversion of ornithine and arginine, although in most plants the concentration of arginine is generally much higher than that of ornithine suggesting that the formation of arginine is generally favoured. In plants that contain both ADC and ODC the two pathways for putrescine biosynthesis appear to be physically separated within the cell, with ADC mostly found

associated with the thylakoid membranes of chloroplasts and in the nucleus (Borrell et al., 1995; Bortolotti et al., 2004), and ODC localized in the cytosol (Borrell et al., 1995). Irrespective of the pathway of biosynthesis, the pool of cellular putrescine can be used for the synthesis of spermidine, spermine and other polyamines. Addition of an aminopropyl group from decarboxylated S-adenosyl-methionine (dcSAM), synthesized by the enzyme S-adenosyl-methionine decarboxylase (SAMDC; EC 4.1.1.50), to putrescine via the action of spermidine synthase (SPDS; EC 2.5.1.16), produces spermidine, while the addition of a second aminopropyl group to spermidine via the action of spermine synthase (SPMS; EC 2.5.1.22) produces spermine (Alcázar et al. 2006; Slocum, 1991). While the tetraamine found at the highest concentration in most flowering plants is spermine, recent studies have shown that in non-flowering plants, thermospermine may be synthesized in preference to spermine. In this reaction, catalyzed by thermospermine synthase (tSPMS; EC 2.5.1.79), the aminopropyl group is added to the opposite end of the spermidine molecule to that used by SPMS. While most of the pool of cellular putrescine is used to synthesize other polyamines, in some plant species putrescine can be used to initiate the synthesis of alkaloids, via the activity of putrescine N-methyltransferase, or to generate H<sub>2</sub>O<sub>2</sub> in a reaction catalyzed by diamine oxidase (DAO; EC 1.4.3.22), a copper-containing enzyme (Figure 1). This reaction plays an important role in plant pathogen interactions (Martin-Tanguy, 2001). In addition to DAO, the flavin-containing polyamine oxidases (PAOs) found in plants can also generate H<sub>2</sub>O<sub>2</sub>. Unlike DAOs, which display a high affinity for putrescine, PAOs oxidize the secondary amine groups of spermidine and spermine (Medda et al., 1995). Both DAO and PAO are cell wall-associated enzymes (Slocum, 1991).

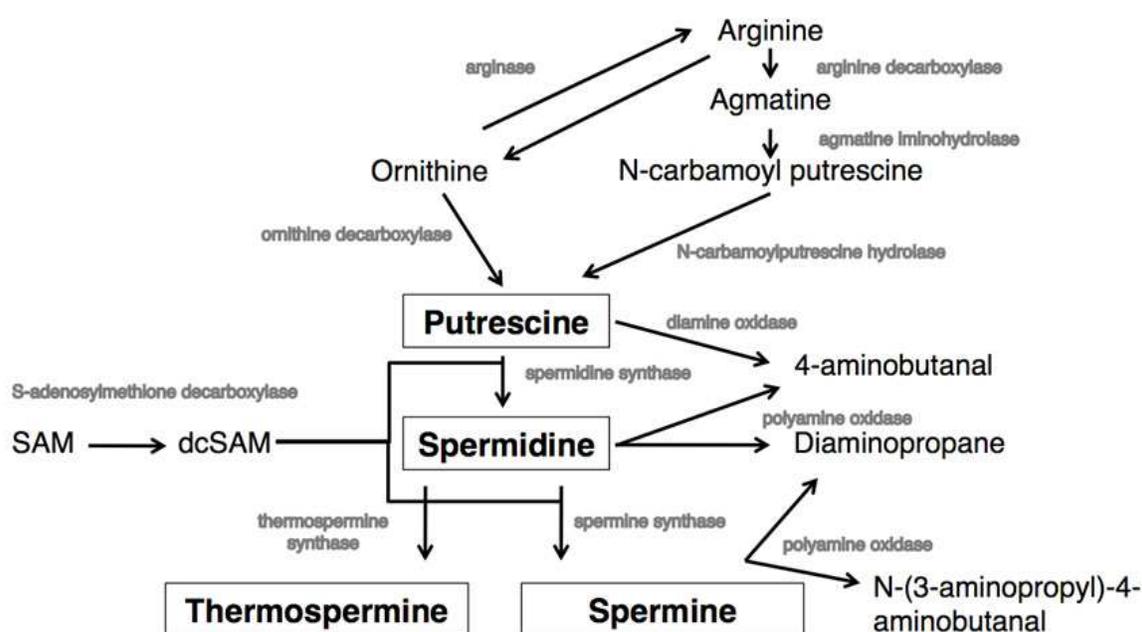


Fig. 1. Polyamine synthesis and breakdown in plants

## 2.2 Polyamine conjugation

While the bulk of cellular polyamines found in plants usually exist as free forms, polyamines can also be conjugated to small molecules like phenolic acids and various macromolecules such as DNA, RNA and proteins. Conjugation to phenolic acids is common in plants with

polyamines often covalently bonded to phenolic acids, such as hydroxycinnamic acids by the formation of an amide linkage (Martin-Tanguy, 2001). The formation of this linkage is catalyzed by a group of enzymes known as transferases and uses activated carboxyl groups provided by esters of coenzyme A (CoA) (Negrel, 1989). Conjugates occur as basic or as neutral forms (Martin-Tanguy, 1985); with the former, a single amine group of an aliphatic amine is linked to cinnamic acid with the resulting conjugate being basic, while if each terminal amine group is bound to a cinnamic acid, a neutral conjugate is formed (Martin-Tanguy, 1985). Polyamines conjugated to hydroxycinnamic acids are also referred to as hydroxycinnamic acid amides (HCAAs). HCAAs are found in many families of higher plants (Martin-Tanguy, 1985). The most common hydroxycinnamoyl substituents of spermidine include the coumaroyl, caffeoyl, feruloyl, hydroxyferuloyl, and sinapoyl acyl groups (Bienz et al., 2005). Mono-, di-, and trisubstituted hydroxycinnamoyl spermidine conjugates have also been reported (Bienz et al., 2005). Other HCAAs found in crop plants include diferuloylputrescine, diferuloylspermidine, and feruloyltyramine in *Oryza sativa* (rice) (Bonneau et al., 1994), hydroxycinnamoyl agmatine in *Hordeum vulgare* (barley) (Smith & Best, 1978), and 4-coumaroyltryptamine and feruloyltryptamine in *Zea mays* (maize) (Collins, 1989). Polyamines can also be post-translationally linked to proteins via covalent bonds. These reactions are catalyzed by transglutaminases (TGases; EC 2.3.2.13), a group of enzymes able to modify proteins post-translationally (Lorand & Graham, 2003). TGases are found in both intra- and extra-cellular locations in plants (Folk, 1980) and can modify protein substrates by “cationisation” or by forming inter- or intra-molecular bridges, using polyamines of different lengths (Serafini-Fracassini et al., 2009).

### 2.3 The functions of polyamines in plants

Polyamines appear to have numerous physiological functions in plants. They are associated with plant growth and development, playing roles in embryogenesis, root and shoot formation, floral initiation and fruit development (Evans & Malmberg, 1989; Galston & Kaur-Sawhney, 1990). In recent years there has been an increasing interest in the roles polyamines play as molecules that help to protect plants against environmental stresses. Research has clearly demonstrated that cellular polyamines show significant fluctuations in both composition and concentrations in response to environmental conditions (Bouchereau et al., 1999; Smith et al., 2001; Groppa & Benavides; 2008, Burritt, 2008). While it is clear that polyamines play an important role in protecting plant cells from adverse environmental conditions, their precise mode of action remains largely a matter of speculation. However, stress-driven fluctuations in polyamine metabolism could significantly influence the concentrations of bioavailable polyamines in plant-based foods.

## 3. Polyamines as cytoprotective molecules

### 3.1 Polyamines as antioxidants

Reactive oxygen species (ROS) are produced within cells as a consequence of normal metabolic processes. When cells are under stress, the production of ROS often increases (Halliwell & Gutteridge, 1999). When ROS are produced at high enough concentrations to overcome the antioxidant defences that normally keep an organism's ROS concentrations in check, oxidation of DNA, proteins and membrane fatty acids occurs, the latter resulting in

lipid peroxidation and a loss of membrane function (Halliwell & Gutteridge, 1999). Such damage is commonly referred to as oxidative stress and is considered a very sensitive biomarker of many important environmental stressors (Lesser, 2006; Burritt & MacKenzie 2003; Burritt, 2008). Numerous studies have shown that cells with reduced concentrations of polyamines are more sensitive to oxidative damage (Chattopadhyay et al., 2002; Rider et al., 2007; Burritt, 2008), which suggests that polyamines may play a role in protecting the cells of a wide range of organisms from oxidative damage caused by elevated ROS concentrations. Hence one of the potential modes of action by which polyamines could protect cells is to act as antioxidants. While several studies have tested the ability of polyamines to act as antioxidants, whether they can be classified as cellular antioxidants is still a matter of debate (Chattopadhyay et al., 2002; Kakkar & Sawhney, 2002; Groppa & Benavides, 2008). Bors et al. (1989) proposed that polyamines could act as antioxidants as their anion- and cation-binding properties involve radical scavenging and they have been shown to inhibit both lipid peroxidation and metal-catalyzed induction of oxidative stress (Kitada et al., 1979; Tadolini, 1988). However, other studies have shown that polyamines lack antioxidant activity and could even act as pro-oxidants (Groppa & Benavides, 2008).

### 3.2 Polyamines and DNA protection

Several studies have shown that both natural and synthetic polyamines can enhance the stability of DNA, and protect DNA from damage caused by oxidative stress and ionizing radiation, and from endonuclease digestion (Nayvelt et al., 2010). Two protective mechanisms have been proposed by which polyamines could protect DNA. It has been suggested that polyamines can directly scavenge ROS, in particular hydroxyl radicals that readily target DNA, and/or promote DNA packaging into nanoparticles (Nayvelt et al., 2010). Because of their positive charge, polyamines can interact electrostatically with DNA that has a negative charge, and spectroscopic evidence has shown that polyamine analogues can bind to guanine bases and the backbone phosphate groups of DNA, while spermidine and spermine bind to both the major and minor grooves of DNA, as well as to the phosphate groups. When 89-90% of the charges associated with DNA have been neutralised by the binding of polyamines, DNA compaction is induced, limiting the accessibility of hydroxyl radicals to target sites within the DNA and hence protecting against oxidative damage (Vijayanathan et al., 2002).

## 4. Polyamines and human health

### 4.1 Polyamines and healthy ageing

As in plants, polyamines (putrescine, spermidine and spermine) are also ubiquitous amongst mammalian cells, including human cells. Their diversity of roles in cellular metabolism and growth requires them to be available in large amounts in rapidly growing tissues (Bardócz et al., 1993), but they are also active in the control of various biological processes, such as mediating the action of hormones and growth factors (Bardócz et al., 1995), modifying the immune response, blocking calcium ion channels and regulating apoptosis (Larqué et al., 2007). Polyamines are, therefore, essential to maintaining health at all life stages. It was originally thought that polyamines were synthesised *in situ* within cells when they were required (Bardócz et al., 1996). However, it is now recognised that there are three sources of polyamines in humans: intracellular *de novo* synthesis of polyamines,

dietary polyamines, and polyamines produced as metabolites from gut microbiota. As humans age, the capacity for *in situ* polyamine biosynthesis reduces, because the activity of one of the key polyamine biosynthetic enzymes, ODC, decreases (Larqué et al., 2007; Das & Kanungo, 1982). Therefore, the importance of dietary polyamines may become elevated with age. Unfortunately, there are a limited number of studies examining the importance of polyamines in human health and ageing, and therefore the influence of polyamines on health is mostly extrapolated from *in vitro* and small animal studies.

As a result of unprecedented public health advances and successes in many parts of the world, the proportion of people aged 60 and over is growing faster than any other age group (Henry, 2002). Ageing is a multi-faceted process, and is the result of the combination of genetic and environmental factors, but a healthy diet and lifestyle are key components to healthy ageing. Undernutrition is most prevalent in developing countries, but it is also present in some elderly people of developed countries (Calder & Kew, 2002). The benefits of good nutrition can only be realised if the integrity and function of the gastrointestinal tract is maintained with age, making gut health an important health target in the elderly. Nutritional status is an important factor for maintaining optimal immune function, and one process that is central to ageing is immunosenescence. Age-associated changes affecting the immune system contribute to increased morbidity and mortality in the elderly as a result of higher incidence of infections, and possibly autoimmune diseases and cancer (Kalula & Ross, 2008; Pawelec, 1999). Immunosenescence not only results in an increase in infections, but is considered a contributor to systemic low-level inflammation (Fulop et al., 2010), termed 'inflammageing', an underlying cause of many common chronic diseases and frailty in elderly. It appears, therefore, that nutrition is a key aspect in achieving healthy ageing, and given the function of polyamines outlined above, it is reasonable to assume that polyamines play a part in maintaining health as people age.

#### 4.2 Polyamines derived from dietary sources

In 1995, Bardócz and colleagues estimated that the average total polyamine daily intake by an adult in Britain was 388  $\mu\text{mol}$ , represented by 220  $\mu\text{mol}$  of putrescine, 99  $\mu\text{mol}$  of spermidine and 69  $\mu\text{mol}$  of spermine (Bardócz et al., 1995). However, until recently there were a limited number of reports detailing the polyamine content of food, but with the increased availability of high-throughput analysis techniques, specifically high performance liquid chromatography, information on the polyamine content in food is accumulating. As detailed in section 1, polyamines exist in free, conjugated and bound forms, but unfortunately reports examining the polyamine content in foods do not tend to examine the form in which polyamines are present within the foods. What also is not clear at this stage is whether the form of polyamine present in foodstuffs influences the bioavailability and/or bioactivity of diet-derived polyamines.

A wide variation in the concentration of polyamines in different foods is reported. Meat, fish and meat products tend to be high in putrescine and spermine, and low in spermidine, which is in contrast to plant-derived foods, which tend to be high in putrescine and spermidine (Kalač & Krausová, 2005). Fermentation of food enhances the polyamine content of some products. For example, the putrescine content of cooked cabbage was reported to be 5.6 mg kg<sup>-1</sup> (Eliassen et al., 2002, as cited by Kalač & Krausová, 2005), and that of sauerkraut was 146 mg kg<sup>-1</sup> (Kalač et al., 1999, as cited by Kalač & Krausová, 2005). The polyamine content

in cheese is reportedly high, particularly in mature cheddar, but is relatively low in yoghurt (Eliassen et al., 2002). Interestingly, cooking appears to have little effect on the composition and concentration of polyamines in most foods tested (e.g. carrot and potato), but does influence content in others (Eliassen et al., 2002). For example, mean putrescine content decreases slightly in broccoli after cooking, but spermidine decreases quite considerably (Eliassen et al., 2002). A decrease in polyamine content tends to occur as fruits and vegetables ripen (Valero, 2010; La Vizzari et al., 2007; Simon-Sarkadi et al., 1994, as cited by Kalač & Krausová, 2005), indicating that ripeness and length of time from harvesting to consumption may also influence the polyamine content of plant-derived foods.

An early study reporting the polyamine content of specific foods reported that green vegetables were high in spermidine, whereas other vegetables, fruits and fish were high in putrescine, and red meat and poultry were high in spermine (Bardócz et al., 1995). More detailed studies of the polyamine content of food have since been completed, and have revealed that corn, peas and potatoes are particularly rich vegetable sources of putrescine and spermidine; peas are also rich in spermine compared with the other foods of plant origin tested (with the exception of cashews); oranges are the richest fruit source of polyamines, particularly putrescine; and pears are a relatively rich source of putrescine and spermidine (Farriol et al., 2004, as cited in Larqué et al., 2007). In a recent study, Binh et al. (2010a) reported the polyamine content of Asian foods. The highest putrescine concentrations were found in maize, citrus fruits, peas, soybeans, and other beans; soybeans, other beans, and vegetables were the richest sources of spermidine; and edible offal, molluscs, meats, soybeans and other beans were rich sources of spermine (Binh et al., 2010a). Furthermore, an examination of the polyamine content of 227 foods, with a focus on Japanese foods, was reported by Nishimura et al. (2006). High polyamine plant-based foods included rice bran, wheat germ, green pepper, Japanese pumpkin, soybean, fermented soybeans (natto), pistachio nut, shimeji and dried agaricus (mushrooms), nukazuke (fermented cucumber), orange, Philippine mango, and green leaf tea.

Metabolites from intestinal microbiota are also considered an important source of polyamines (Bardócz et al., 1996). For example, *Bacteroides* spp. and *Fusobacterium* spp. produce polyamines when cultured *in vitro* in the absence of polyamines (Noack et al., 1998), and the administration of probiotics, e.g. *Bifidobacterium lactis* LKM512, has been shown to enhance faecal polyamine concentration (Matsumoto & Benno, 2004). The fibre and polyphenol compounds within plant foods are also capable of modulating growth and proliferation of gut microflora species (Parkar et al., 2008; Noack et al., 2000; Noack et al., 1998). Furthermore, purified fibre derived from plant material (pectin) stimulated proliferation of microflora species that promote polyamine production, thereby enhancing polyamine in the caecal contents (Noack et al., 2000). Interestingly, there was a decline of polyamines from caecum to faeces in all treatments and controls, suggesting that the polyamines synthesized by intestinal microbes are absorbed in the caecum and colon. Whether different plant foods or plant-derived ingredients stimulate the proliferation of different gut microflora, both *in vitro* and *in vivo*, continues to be investigated, and it would also be interesting to examine their effect on polyamine synthesis, to determine the extent to which plant foods might also indirectly contribute to the total body polyamine pool.

The polyamine content of a large range of different foods has recently been reported by Binh et al. (2010a, 2010b) and polyamine intake was correlated with gross domestic product (GDP) and longevity. In a study of 49 European and other Western countries, differences in

dietary intake were detected according to GDP (Binh et al., 2010b). The dietary profile of those countries with a higher GDP (>20,000 current international dollars) included higher amounts of animal products, seafood, and fruits, which was associated with increased supply of spermine and putrescine per total calorie intake. The dietary profile of countries with a lower GDP (<20,000 current international dollars) included higher amounts of whole milk, and crops, resulting in slightly higher supply of spermidine compared with the profile of higher GDP countries, although not significantly so. Overall, there was a significantly higher supply of total polyamines in higher GDP countries, and it was suggested that increased polyamine intake may have some role in the difference in the prevalence of diseases associated with socioeconomic disparity (Binh et al. 2010b). Although the daily amount of polyamine availability from foods in Asian countries was considerably lower than that reported in European countries, GDP of Asian countries was also positively correlated with polyamine content per energy (Binh et al. 2010a). Furthermore, increased life expectancy was also associated with greater polyamine content per energy in Asian countries. However, it was recognised that there may be other confounding factors contributing to increased life expectancy.

Importantly, there is good evidence that dietary polyamines contribute directly to the total body polyamine pool. An early classical experiment using a rat model demonstrated that radio-labelled putrescine, spermidine, and spermine were taken up by the small intestine in a dose-dependent manner (Bardócz et al., 1995). However, the uptake and fate of the polyamines varied. One hour after the rats were given <sup>14</sup>C-labelled putrescine by intubation, only 29-39% of the label was recovered as polyamines, of which 11-15% was present as putrescine. In contrast, 79% and 72-74% of labelled spermidine and spermine, respectively, were recovered in the same form as given, and, if conversion to other polyamines was also included in the calculations, up to 96% and 82% of the radio-labelled spermidine and spermine were recovered, respectively. Bardócz et al. (1995) suggested therefore, that diet could provide polyamines for absorption and contribution to the total polyamine pool through the systemic circulation, thereby reaching every tissue of the body. Similarly, putrescine uptake and metabolism from the small intestinal lumen of healthy volunteers was demonstrated following perfusion with increasing concentrations of putrescine (Milovic et al., 1997, as cited in Milovic, 2001). Some 60-80% of the putrescine disappeared from the lumen linearly with time, although putrescine *per se* was not recovered in the blood. There was, however, a transitory increase in acetylated putrescine, and a steady increase in spermidine and spermine concentrations, suggesting the polyamines were absorbed from the intestinal lumen in humans and putrescine underwent extensive metabolism before reaching the systemic circulation (Milovic, 2001), although spermidine and spermine uptake was not examined in this study.

Long-term supplementation of diets with polyamines or polyamine rich foods has been shown to increase polyamine concentrations in the blood in animal models and humans. For example, mice fed experimental chow containing high concentrations of polyamines for 26 weeks had significantly higher concentrations of blood spermine and spermidine than mice fed chow containing low or normal concentrations of polyamines (Soda et al., 2009a). Soda et al. (2009a) noted that there was considerable blood spermine and spermidine variability between mice, which was exaggerated in mice fed the high polyamine diet. These findings are supported with human data. Healthy human male volunteers were asked to either exclude soybean products and fermented foods from their diet, or include 50-100 g of natto,

a fermented soybean product, in their diet for 2 months (Soda et al., 2009b). Following long-term daily consumption of natto, blood spermine concentrations significantly increased, but concentrations remained unchanged in those from the control (no natto) group. The blood spermidine concentrations did not change for either group. Interestingly, although not statistically significant ( $p=0.06$ ), age had a positive correlation ( $r=0.62$ ) with changes in blood spermine concentration. The findings from this study demonstrate that long-term intake of a polyamine-rich diet can increase blood polyamine concentrations, and the effect of dietary polyamines might be greater in older people.

#### 4.3 Effect of age on polyamine concentrations

Polyamines are present in all tissues, although their concentration and the ratio between polyamines vary between different tissues. For example, in rats aged 3 months the highest concentration of spermidine was detected in the thymus, and large amounts were also detected in the liver, spleen, lungs and different parts of the gastro-intestinal tract (Jänne et al., 1964). These tissues, as well as the kidneys, also contained relatively large amounts of spermine. In a more recent study, similar trends were reported for the polyamine content of mice, although the pancreas was found to contain the highest concentration of spermidine, and in this study the concentration of putrescine was also considered (Nishimura et al., 2006). The putrescine concentration of a range of tissues was typically low, below approximately 2 nmol/mg protein in all tissues of mice aged 3 weeks, compared with spermidine and spermine, which ranged from approximately 1.0 nmol/mg protein in muscle, heart and skin tissues, up to approximately 25 nmol of spermidine/mg protein in the pancreas and 5 nmol of spermine/mg protein in the thymus (Nishimura et al., 2006). These data tend to support the suggestion that putrescine undergoes extensive metabolism upon uptake, although the content of the relative polyamines in the mouse chow was not described.

The effect of age on polyamine concentrations in tissues was also examined by Jänne et al. (1964) and Nishimura et al. (2006). Overall, the concentration of polyamines (spermidine and spermine) decreased with increasing age (0-9 months) in all tissues examined from rats (Jänne et al., 1964). However, the decrease in spermidine was most marked during the first month of life, decreasing relatively slowly after one month, and the concentrations of spermine increased slightly during the first month in the liver, thymus, spleen and kidneys, and remained unchanged or decreased slightly after one month, and from birth in other tissues. Similar trends were observed in ageing mice (3 to 26 weeks), with a significant decrease of spermidine in the thymus, spleen, ovary, liver, stomach, lung, kidney, heart and muscle, as well as skin from the ear and abdomen (Nishimura et al., 2006). In contrast, however, the polyamine concentrations in the pancreas, brain and uterus were maintained in the ageing mice. It was suggested that stimulation of protein synthesis and modulation of the ion channels are the most important functions of polyamines, and these functions are necessary activities in these organs/tissues, therefore mechanisms exist in these tissues to maintain polyamine concentrations through ageing (Nishimura et al., 2006). Furthermore, Nishimura et al. (2006) recommended that since the decrease in spermidine was most marked, either foods containing putrescine, spermidine and spermine or foods particularly rich in spermidine should be consumed. As indicated above, green vegetables, corn, peas, beans and potatoes are particularly rich sources of spermidine, possibly suggesting that a

predominantly plant-based diet would provide the polyamines of most benefit as humans' age.

#### 4.4 Role of dietary polyamines in maintaining health during ageing

There is a consensus among the literature that polyamine concentrations within the body decrease with age, although this may be tissue specific. The effect that this has on health is still being understood; however, enhancing polyamine intake appears to have a positive effect on health as ageing progresses. For example, in a study where mice were fed a low, normal or high polyamine diet from 8 weeks of age, whole blood spermidine concentrations were significantly higher after 26 weeks of feeding with the high polyamine experimental chow, and mice fed the high polyamine chow lived significantly longer than mice fed the low or normal polyamine chow (Soda et al., 2009a). Furthermore, pathological changes associated with ageing were inhibited in mice consuming the high polyamine chow, specifically lower incidence of glomerulosclerosis and higher protein expression of SMP-30, a protein expressed in multiple organs and tissues that protects from oxidative stress during ageing.

The dietary intake of polyamines has been cautioned in the past because the increased requirement for polyamines by rapidly dividing cells and tissues, such as tumour cells, is well recognised. Interfering with the supply of polyamines with ODC inhibitors, polyamine structural analogues and derivatives, and deprivation of exogenous polyamines, are potential therapeutic targets for tumour growth (Kalač & Krausová, 2005). However, the study described above (Soda et al., 2009a) suggests that in the absence of a tumour, a high polyamine diet is beneficial to maintaining health through ageing. Further support for this is afforded with the use of transgenic mouse models. For example, a transgenic mouse line over-expressing human ODC gene was used to examine whether constitutively over-expressed ODC pre-disposes the animals to enhanced tumorigenesis (Alhonen et al., 1995). At 2 years of age, the tissue ODC activity in the transgenic animals was 20- to 50-fold that in their syngenic littermates, but the occurrences of spontaneous tumours between the two groups of animals was comparable.

Notwithstanding the requirement for polyamines in tumorigenic tissue, evidence suggests that enhanced endogenous polyamine concentrations promote health during ageing via a number of mechanisms. A recent study by Eisenberg et al. (2009) examined the influence of spermidine on a number of ageing models, and demonstrated extended lifespan with exogenous application of spermidine. Using a yeast cell model of chronologically ageing cells, exogenous supply of spermidine increased lifespan by up to four times that of untreated cells, and using a yeast model of replicative ageing (representing the lifespan of dividing cells in higher eukaryotes), spermidine caused a significant increase in the replicative lifespan of old cells. Furthermore, spermidine-treated cells were resistant to stress from heat shock or hydrogen peroxide treatment, which supports the theory that improved longevity often correlates with increased stress resistance (Eisenberg et al., 2009). Enhancement of lifespan in human cells was then demonstrated, using long-term culture of peripheral blood mononuclear cells (PBMCs), treated with or without exogenous spermidine in the culture medium, and measuring cell survival by flow cytometry. After 12 days, only 15% of the control cells had survived, whereas 50% of spermidine (20 nM)-treated cells survived (Eisenberg, et al. 2009). Staining indicated that enhanced cell survival by spermidine was not as a result of inhibition of apoptosis, but rather an inhibition of necrosis.

As discussed by Eisenberg et al. (2009), necrosis culminates in the leakage of intracellular compounds resulting in local inflammation, a suspected cause of 'inflammageing'. Following on from this, the effect of exogenous spermidine on oxidative stress was examined, given that, in the free radical theory, ageing is attributed to the accumulation of oxidative stress. Indeed, mice fed spermidine (3 mM added to drinking water) for 200 days had an increase in free thiol groups compared with control mice, suggesting a lower degree of oxidative stress and protein damage (Eisenberg et al., 2009). Furthermore, autophagy, the major lysosomal degradation pathway for recycling damaged and potentially harmful cellular material, is thought to be essential for healthy ageing and longevity and Eisenberg et al. (2009) also examined the involvement of spermidine in autophagy. Spermidine enhanced autophagy, as determined both directly and indirectly, in a number of cell types including cultured human cells, and it was suggested that spermidine-induced autophagy increased lifespan in the variety of model organisms used. Given that polyamines appear to increase lifespan, their involvement in preventing or delaying the onset of the major underlying pathologies that contribute to ageing is also worthy of consideration.

#### 4.4.1 Gut health

Whilst the growth of many organs ceases with adolescence, the integrity of the mucosa of the gastrointestinal (GI) tract is maintained by continuous cell renewal (Majumdar, 2003). Deviation in these replicative processes may result in the loss of structural and functional integrity of the gut; therefore maintenance of normal growth and general properties of the adult GI tract is a key aspect to healthy ageing. Polyamines have been implicated in the maintenance of gut integrity. The strongest evidence of the involvement of polyamines in the development, maturation and maintenance of gut integrity comes from studies using young animals. For example, suckling rats were either fed a polyamine-deficient diet, a polyamine-deficient diet plus antibiotics, a polyamine-deficient diet plus polyamine supplementation at normal concentrations, or normal standard laboratory chow for six months (Löser et al., 1999). Although after six months there were no differences in body weight gain, food consumption or general behaviour, consumption of a polyamine-deficient diet with or without antibiotics resulted in significant decreases in organ weight, protein content, and DNA content in the small intestinal and colonic mucosa. Interestingly, there was no significant difference in the intracellular polyamine metabolism between any of the treatment groups, indicating that intracellular *de novo* synthesis of polyamines was not activated to compensate for a deficiency in exogenous polyamines (Löser et al., 1999). Conversely, oral administration of polyamines to neonatal mice resulted in precocious maturation of the gut, as evidenced by increased villus and crypt length, changes of the activities of brush-border membrane hydrolases (Dorhout et al., 1997, as cited by Seiler and Raul, 2007), as well as precocious development of the intestinal immune system after spermine administration (ter Steege et al., 1997, as cited by Seiler and Raul, 2007). Importantly, the action of polyamines in gut development has been demonstrated using a human model, albeit *in vitro*. Caco-2 cells, derived from a colorectal adenocarcinoma, are commonly used for studies of the gastric mucosa, because they spontaneously express characteristics of enterocyte differentiation upon confluence, including the formation of tight junctions. Depletion of the putrescine and spermidine pools with the specific inhibitor  $\alpha$ -difluoromethylornithine (DFMO), prevented the growth of microvilli and differentiation of Caco-2 cells (Herold et al., 1993, and Duranton et al., 1998, as cited by Seiler and Raul, 2007). Whilst polyamines are clearly required for gut development and maturation in the

young, these studies also suggest implications of polyamines for gut integrity with ageing, because the continual renewal process in the gut is characterized by active proliferation of stem cells localized near the base of the crypts, progression of these cells up the crypt-villus axis with cessation of proliferation and subsequent differentiation and apoptosis (Zou et al., 2008).

Maintenance of gut integrity, such as through formation of tight junctions and production of mucus, is essential to good health because this helps to prevent a leaky gut, limiting the incidence of infection from pathogenic bacteria and food intolerance. An insult to the intestinal mucosa is repaired via two mechanisms: restitution and replacement. Restitution is a rapid process whereby existing viable cells from adjacent areas migrate to the lesion and cover denuded spots, and is therefore suitable for superficial mucosal damage (Seiler and Raul, 2007). Replacement of damaged cells occurs via cell division, and is a slower process than restitution. As reviewed by Seiler and Raul (2007), polyamines are involved in many aspects of these processes, including the production of cytoskeletal components, cell adhesion factors, and crypt reproduction. In addition to these functions, a novel function of polyamines within the gut was postulated by Bardócz et al. (1998). Radiolabelled putrescine was administered to fasted rats and 70% of the putrescine was converted to succinate, more than double the rate of rats fed *ad libitum*. Bardócz et al. (1998) suggested, therefore, that dietary polyamines may serve as a source of instantly metabolisable energy and further support the metabolic needs of the gut tissue.

The involvement of polyamines in the maintenance of gut integrity would suggest that polyamines are essential for the process of healthy ageing, as opposed to pathological ageing. Evidence that this is the case in humans is limited, given the difficulty in obtaining suitable tissue samples. Nevertheless, faecal polyamine concentrations provide supporting evidence of higher polyamine concentrations within the gut in young and healthy adults compared with the elderly. For example, the concentration of spermidine in the faeces of the elderly was found to be significantly less than that in healthy young adults, and this was linked with changes to gut microbiota (Mäkivuokko et al., 2010). Further evidence suggests that hospitalised elderly subjects have significantly lower intestinal polyamine concentrations than healthy adults, and polyamine concentration was significantly influenced by the faecal microflora pattern present between the two groups (Matsumoto & Benno, 2007). It is possible that the difference in faecal microflora is indicative of different dietary habits, or the difference in faecal microflora results in variation between other microflora metabolites with health benefits, such as short chain fatty acids, but it is also possible that differences in polyamine uptake from diet and microflora directly influence health status through ageing. An interesting aspect that has not yet been examined, to our knowledge, is whether synergistic interactions between microflora metabolites, namely polyamines and short chain fatty acids, promote gut integrity and/or immune function (as detailed below).

#### 4.4.2 Immune function and inflammation

The decrease in polyamine concentrations with age has clearly been demonstrated in numerous tissues and blood. Given that the majority of circulating polyamines are contained in the erythrocytes and leukocytes (Cohen et al., 1976), and polyamines play a pivotal role in numerous cellular functions, it is natural to consider whether decreasing polyamine concentrations with ageing plays a role in immunosenescence and 'inflammaging'.

With age, increased expression of several adhesion molecules occurs, playing a crucial role in cell adhesion and mediating cell-cell interactions, resulting in augmented capability of cell adhesion and activation of immune cells, thereby mediating inflammation (Soda et al., 2005). Lymphocyte function-associated antigen-1 (LFA-1) is an adhesion molecule, and modulating its function can control cellular immunity and inflammation. Soda et al. (2005) demonstrated that exogenous application of spermine to cultured PBMCs suppressed LFA-1 expression, which was accompanied with a decrease in adhesion capacity of PBMCs to human umbilical vein endothelial cells. Similar, but weaker effects were also observed with the application of spermidine. These results suggest that elevated polyamine concentrations, in this case spermidine and spermine only, inhibit a very early and important event that is involved in invoking inflammation.

Further support for the positive effects that polyamines have on modulation of inflammation is given through examination of their effects on the production of inflammatory cytokines. For example, exogenously supplied spermine inhibited the synthesis of a number of pro-inflammatory cytokines from PBMCs stimulated with lipopolysaccharide, including tumour necrosis factor (TNF), interleukin (IL)-1, IL-6, macrophage inflammatory protein (MIP)-1 $\alpha$  and MIP-1 $\beta$  (Zhang et al., 1997). Whilst inhibition of MIP-1 $\alpha$  and MIP-1 $\beta$ , and IL-6 approached 100%, complete inhibition of TNF and IL-1 $\beta$  by spermine was not achieved. Coupled with an earlier report that administration of spermine failed to inhibit the production of transforming growth factor  $\beta$ , a potent anti-inflammatory cytokine (Tsunawaki et al., 1988), and the fact that TNF and IL-1 $\beta$  are involved in important antimicrobial and antiviral immune responses, spermine appears implicated in maintaining an appropriate inflammatory status. Importantly, these findings translate into a dampening down of the inflammatory response *in vivo*. For example, co-administration of spermine with carrageenan protected mice against the development of acute inflammation of the foot pad, using the carrageenan-induced paw edema model (Zhang et al., 1997). A mouse model for inflammation-mediated intestinal damage also showed that spermine exerted a protective effect, inhibiting the expression of inducible nitric oxide synthase and nitrotyrosine, and decreasing serum concentrations of pro-inflammatory mediators, including nitrate, nitrite and interferon- $\gamma$ , whilst enhancing the concentration of IL-10, an anti-inflammatory cytokine (ter Steege et al., 1999). Taken together, these findings suggest that although endogenous polyamine production decreases with age, enhancement of exogenous sources of polyamines might be useful in mitigating the loss of gut function and integrity, and regulation of inflammatory processes that occurs with ageing. The specific effects that exogenous sources of polyamines have on human health with ageing still largely remains to be investigated, but through understanding the effect of polyamines on processes of immune function and chronic inflammation, and the effect this has on non-communicable diseases that become more prevalent with ageing, the roles of polyamines in these diseases may be suggested. For example, Soda (2010) suggested that by considering the inhibition of cell adhesion through suppression of LFA-1 by dietary polyamines, and increased availability of arginine for nitric oxide synthesis (which is important for vascular physiology and function) in the presence of dietary polyamines, polyamines may inhibit cardiovascular disease.

#### 4.4.3 Other potential health benefits of polyamines

The causes of pathological ageing and frailty are complex and multidimensional, based on the interplay of genetics, biological, physical, psychological, social and environmental

factors (Fulop et al., 2010). Given the ubiquity of polyamines within the body, and their centrality in maintaining normal cell function, it might be expected that polyamines are integral to many processes in ageing. The use of transgenic animals has given some insight into what these might be (Alhonen et al., 2009).

Social factors play an important part in maintaining good health and physical functionality with age. Central to social interaction is the ability to communicate, and age-related hearing loss may prevent or reduce social interaction. Clinical studies have shown that DFMO, a specific inhibitor of putrescine synthesis, can cause hearing loss in some patients (Meyskins & Gerner, 1999). A transgenic mouse model has been developed that is completely deficient in spermine synthase, has reduced concentrations of spermine and increased spermidine in all cells examined, and is profoundly hearing impaired (Wang et al., 2009). The hearing loss was attributed to a large reduction in endocochlear potential, and it was reversed by breeding the deficient strain with a strain that ubiquitously expresses spermine synthase. The application of DFMO in the mice deficient in spermine synthase resulted in profound weight loss and death within a few days, from a severe loss of balance that prevented normal feeding and drinking (Wang et al., 2009). It was suggested that polyamines are important in auditory physiology because of their role as regulators of potassium channels, thereby influencing endocochlear potential. Although the importance of polyamines in maintaining hearing and balance has been highlighted, what is not clear is whether it is the absence of spermine or an altered spermidine:spermine ratio that causes the hearing loss. Given this study, it is possible that a greater body pool of polyamines could help to prevent hearing loss with ageing, although this study considered the effect of endogenous polyamine production and it is not known whether uptake of dietary polyamines would influence hearing. Furthermore, oxidative damage has also been implicated in age-related hearing loss (Someya & Prolla, 2010), which provides another potential mechanism by which polyamines may assist in the prevention of hearing loss. It should be noted that the involvement of polyamines in age-related hearing loss is, at this stage, largely speculative, and considering the difficulty in determining polyamine concentrations within the ear, at least in humans, it is not an issue that will be quickly resolved. Epidemiological studies correlating dietary habits and intake with the onset of age-related hearing loss may give some insights into the impact of diet on hearing loss.

Considering that the pancreas contains the highest concentration of spermidine (Nishimura et al., 2006), it might be expected that spermidine, or polyamines in general, play an important role in maintaining the function of the pancreas. A transgenic rat model has been used to demonstrate that a depletion of pancreatic spermidine and spermine, through over-expression of the catabolic polyamine enzyme spermidine/spermine *N*<sup>1</sup>-acetyltransferase (SSAT), leads to onset of acute pancreatitis (Alhonen et al., 2000), and this could be prevented with the application of 1-methylspermidine, a metabolically stable analogue of spermidine (Räsänen et al., 2002). It should be kept in mind that Nishimura et al. (2009) demonstrated a steady-state of polyamines were present in the pancreas even with ageing, but given that the total body pool of polyamines generally decreases with age, diet-derived polyamines could still be an important source to maintain pancreatic polyamine concentrations. Liver injury as a result of xenobiotic insult causes cell death, and requires quiescent hepatocytes to proliferate and restore liver mass and hepatic function, but the capacity to achieve this diminishes with age (Sanz et al., 1999). The main age-related changes in the process of recovery from liver injury are a delayed response in the

development of cell killing and regeneration, and decreased regenerative ability (Sanz et al., 1999). Using the transgenic rat model over-expressing SSAT, it was shown that a profound decrease in hepatic spermidine and spermine pools caused a failure to initiate liver regeneration (Räsänen et al., 2002). Furthermore, supplementation with 1-methylspermidine restored early liver regeneration. These results might suggest that, despite the capacity for endogenous polyamine production reducing with age, a diet high in polyamines, particularly spermidine, could support a higher total body polyamine pool and promote liver regeneration and function into old age.

## 5. Conclusions

Because of their ubiquity in human tissue and involvement in a wide range of vital cellular processes, the importance of polyamines to maintenance of human health is well recognised. Despite this, however, the specific mechanisms by which polyamines influence human health, particularly with increasing age, are less well understood. It is likely that the implication of polyamines in the growth of tumours has meant that research into the health benefits of polyamines has been largely overlooked. The evidence provided within this chapter indicates that polyamines are important molecules for maintaining good health into old age, and the total body polyamine pool may be influenced by diet. Polyamines are also ubiquitous in plant tissues, and they have similarly important functions in plants and animals, particularly as cytoprotective molecules. The production of polyamines in plants can be manipulated through cultivation practices and environmental stressors, and the polyamine content of plant-derived foods may also be influenced by postharvest practices and conditions. Plant-derived foods tend to be a rich source of putrescine and spermidine; however, research is lacking an examination of the form in which polyamines are present in plant-derived foods (free, conjugated or bound) and whether this influences the bioavailability and bioactivity of polyamines in humans. Nevertheless, plant-derived foods represent an important source of dietary polyamines. The evidence presented here, that maintaining endogenous polyamine concentrations with increasing age and in the absence of tumour tissue has a positive influence on sustaining good health, has largely been derived from the use of animal models. This is because demonstrating unequivocal cause and effect of polyamines in health or disease prevention requires determination of polyamine content within the tissues under consideration, and human tissue samples are usually not readily available. An alternative approach to this, as has been taken with other phytonutrients such as polyphenols and carotenoids, is the completion of epidemiological studies that could examine estimates of typical polyamine consumption from diet records, and correlate it with health status and disease prevalence in the elderly. Further strength could be provided by these studies, if blood samples were obtained and blood polyamine concentrations determined. Nevertheless, there is good evidence to suggest that polyamines assist with healthy ageing. However, more research is required before recommendations on optimal and safe polyamine intake can be made.

## 6. References

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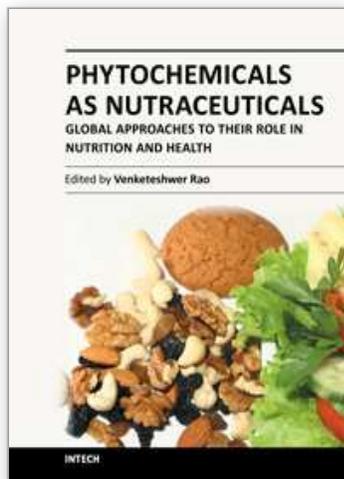
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## **Phytochemicals as Nutraceuticals - Global Approaches to Their Role in Nutrition and Health**

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Phytochemicals are biologically active compounds present in plants used for food and medicine. A great deal of interest has been generated recently in the isolation, characterization and biological activity of these phytochemicals. This book is in response to the need for more current and global scope of phytochemicals. It contains chapters written by internationally recognized authors. The topics covered in the book range from their occurrence, chemical and physical characteristics, analytical procedures, biological activity, safety and industrial applications. The book has been planned to meet the needs of the researchers, health professionals, government regulatory agencies and industries. This book will serve as a standard reference book in this important and fast growing area of phytochemicals, human nutrition and health.

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