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R E V I E W A R T I C L E

Plant Polyamines as Therapeutic Agents: A Review

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A B S T R A C T

Polyamines are aliphatic amines, synthesized in all eukaryotic cell in minutes quantities. Their roles are critical for survival and increase in the conditions of stress. Various studies revealed that, they have significant roles in the health and disease. They are found in high quantities in ischemia, malignancy and other pathological states. But it was not clearly evaluated that elevated levels of polyamines causing the disease or they increase due to negative feedback mechanisms. But their external supplementation improved the conditions of wound healing, proliferation, anti-oxidant, and regulated gene expression andinflammation.Synthetic polyamines (putrescine, spermine and spermidine) are evaluated for their role in health disease. In the same way,Polyamine plant extracts can produce significant quantities of polyamine with the principle molecules of PUT, SPDM and SPM besides the other polyamines. Such extracts need to be tested in various disease conditions to study and to quantification of each polyamine with respect to the other one would be useful in understanding the roles of the polyamines in health and disease. This review describes how a plant derived polyamine extract can be used in treatment for diseases.

Key words: Polyamines, Putrescine, Spermidine, Spermine.

A R T I C L E I N F O

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1. Introduction

Polyamines are aliphatic amines present in all the eukaryotic cells. The polyamines are present in minute quantities but they play a central role in regulating the various cellular activities. Polyamines regulate the growth and proliferation of the cells and synthesized high quantities in the growing tissues. Endogenous polyamines are Putrescine (diamine), Spermidine(tri-amine) and Spermine (tetra-amine) are mostly synthesized polyamines in the mammals. These are synthesized by the regular pathway (in presence of Ornithine) by Ornithine decarboxylase (ODC). And from L-arginine by arginase decarboxylase to Agmatine (a diamine) and then to Putrescine.

Biosynthesis: The ODC converts the ornithine to putrescine which converted to Spermidine by the

spermidine synthase. Then the spermine synthase converts the spermidine to spermine.

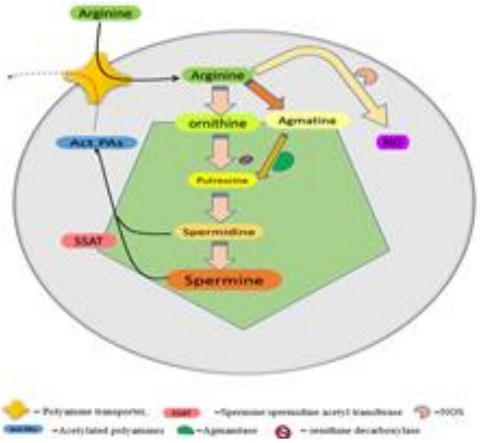

Fig 1: Biosynthesis of Polyamines

Metabolism:

These polyamines are metabolized by the Polyamine Oxidase (PAO) and N-acetyl transferase.

Polyamine transport:

Cellular polyamine contents are regulated by its biosynthetic, metabolic and transport mechanisms. If the biosynthetic pathway fails to produce adequate quantities of polyamines, the uptake mechanisms restores the normal values [L A Hongisto et al; 1980]. If the polyamine levels increase in the cell due to bio synthesis, the polyamine metabolism and the transport system eliminates the excess polyamines [Takeshi Uemura et, al; 2008]. So, polyamine transport system plays a key regulatory role in a cell.

Biological roles:

In cell cultural observations, the polyamines showed proliferation of the epithelial cells ofmucosal and retina and sealed the wounds[D.A.Jobnson et al;2002]. They also have significant effects on embryonic development, plantation, angiogenesis and foetal development [T. Hussain et al; 2017].They regulate the functioning of the various ion channels.As these are cations with specific transporting mechanisms, they bind with the nucleic acids, RNAs, and DNAs and regulate their function [Uriel Bachrach;2010]. They regulate the cytoskeletal transformation, restitution [IlianaNedeva et al; 2013] and play a role in cell migration by stimulating the Rac-1 [Ramesh M. Ray et, al; 2003] pathway and prompting the mucosal healing.Recently found that polyamines block the voltage-dependent potassium channels and have found that they inhibit the gastric acid secretion [Tushar K. Ray et al; 1982].Though the exact role of polyamines in regulating gastric acid secretion still has to be evaluated.The possible mechanism of polyamines in regulating the acid secretion through ion channels (K. v or K.i.r) is shown in the image1.0. Exogenous application of polyamines led to preserved membrane integrity and enhanced growth during stress, reduced accumulation of ROS and increased activity of antioxidant enzymes [Nadège Minois et al; 2011]. The triamine, Spermine was found toinhibite the pro-inflammatory cytokines IL-1, IL-2, IL6, and TNF-α, especially spermine has been implicated in macrophage cytokine synthesis inhibition [Minghuang Zhang et al; 1997]. Besides these activities, spermine also enhances, mucus production [WP Wang et al;2000].

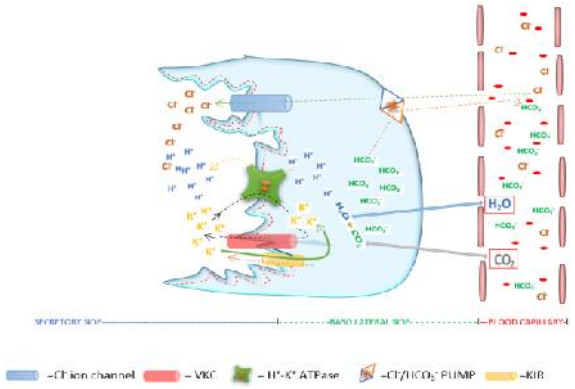

Fig 2: Secretion of HCl by Parietal cell and involvement of Kir and Kv channels

Polyamines in disease

Though polyamines are present in every cell, the contents of 3 polyamines (PUT, SPDM and SPM) are not same in all the type of tissues, it depends on the age and physiology of the cells. Due to their consecutive synthesis from (PUT<=> SPDM<=>SPM) one to another in any condition it is not easy to predict their exact role. The food supplements rich in polyamines (especially spermidine) improve from various age-related disease conditions [Frank Madeo et, al; 2019].

Age:

Polyamine especially spermidine increased the life span of organisms [Frank Madeo et, al; 2018 & Anthony E. Pegg; 2018]. Spermidine trigger its beneficial effects on life span and aging by promoting the autophagy [Nadège Minoiset al; 2011].

On GIT:

Polyamines play an important role in the GIT health and homeostasis. As these regulate the functions of ion channel and so regulate the secretagogues. The spermine and spermidine inhibit the H+ ion secretion into the gastric lumen. This was found not by affecting the H+-K+-ATPase but K+ ion dependent [Tushar K. Ray et al; 1982]. On increasing the K+ ion concentration in the secretory side, the effect of Polyamines on the H+ ions secretion was found decreased. Polyamines stimulate the mucosal recovery from the damages by the rapid process, restitution in all over the membrane of GIT tract [J.-H. GAO et al; 2013]. The polyamines are needed in restitution for polymerization and organization of microtubules immediately after mucosal injury [Ali Banan et al; 1998]. Spermine enhances the intestinal epithelial restitution through TRPC1 mediated Ca+ signalling by differentially modulating STIM1 and STIM2[Jaladanki N. Rao et, al; 2012] and mucosal healing [Wang and Johnson; 1992]. Besides these, spermine also increases the mucus secretion in the GIT and protects the epithelium[WP Wang et al; 2000]. As these molecules also regulate the inflammatory mediators, they could have possible roles in inflammation dependent diseases of the GIT.

On CNS:

Polyamines were found to influence the physiology of the nervous tissue. Systemic polyamines can protect a wide variety of central and peripheral neurons from natural or induced degeneration [Gad M.Gilad et al; 1991]. As these molecules modulate the functions of various ion channels in CNS (NMDA,GABA), they also have significant roles in supressing the ischemia, and degeneration of neurons [Serguei Skatchkov et al;2014]. Spermidine prevents neuronal injury by inhibiting caspase 3-mediated Beclin 1 cleavage and thus it enhances the autophagy in neurons [Yi Yang et al;2017]. Spermine and spermidine shows neuroprotection by stabilization of chromatin, increasing mitochondrial Ca2+ buffering capacity in focal cerebral ischemic cells[Adibhatla RM et al; 2002]. Thus,polyamines may have therapeutic roles in neurodegenerative disorders like Alzheimer`s and Parkinson`s and other memory impaired diseases which has to be evaluated.

On CVS:

The spermidine increaseslife span of myocytes from aging by autophagy. Polyamines reversed previously existing age-associated myocardial morphology changes and myocardial fibrosis, and inhibited cell apoptosis in aging rat heart [Hao Zhang et al; 2017]. Thepolyamines improve the diastolic function and restores the contractility in heart failure and relieves the arterial stiffness[Frank Madeo et, al; 2019]. Polyamines also involve in the hypertrophy of the ventricles in the cardiac remodelling. In such conditions, their regulation should be important because the polyamine metabolism (especially spermine`s) produces the free radicles by which there will be a chance to enhancing the atrophy and ischemia.

In Inflammation:

Polyamines play a critical role in the process of inflammation but it is not yet clear that weather these moleculesinitiate the inflammation. They inhibit the pro-inflammatory cytokines (IL-1, IL-2, IL-6, and TNF-α and enhances the regulatory cytokines IL-10 and TGF-β [Minghuang Zhang et al; 1997].Besides these, the polyamines have role in the tissue regeneration and proliferation which was observed different due to the expression of the different type of amines (PUT or SPDM or SPM).

Sources of polyamines

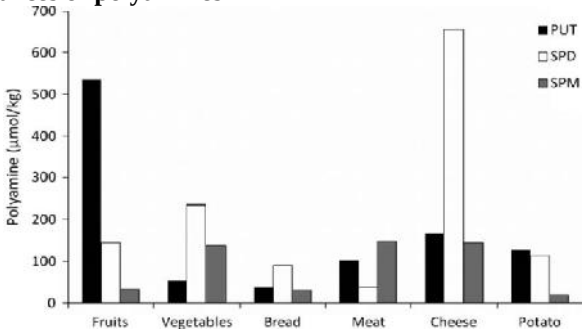

Fig 3: Polyamines in each food group. Source M A Ali et al; 2011, Food Nutr Res:55

Polyamines are ubiquitously expressed in all the eukaryotic cells so such every organism plants, animals and micro-organisms contain as secondary metabolites in minute quantities. Their levels increase in the conditions of stress. But different cells produce the different quantities of the polyamines. Some of the foodsfrom the various categories are given in the graph with their approximate contents of polyamines. They are actually present in high quantities in newly developing tissues and seed germs of the cereals.

2. Extraction of Polyamines

General method:

Polyamines can be extracted from any tissue by the only method performed by Mary A. Smith (1985). According to this method, the tissues are first lysed to homogenization in 5% perchloric acid (HClO¬4¬). Then the homogenates are centrifuged at 20000g for 10-20 min under 40C. The free polyamines are present in the supernatant liquid.

A non-scientific method:

The polyamines are soluble in aqueous solutions and their extraction increases upon adding an acid to the solvent until PHof the solution reaches 2 and below 6. Polyamines extract more in to the aqueous solvents than organic solvents like ethanol or methanol under acidic conditions. Besides this the extracts are more stable under acid conditions.For that inorganic acids perchloric acid(HClO¬4), hydrochloric acid(HCl) and sulphuric acid(H2SO4) can be used. The other natural active componentspresent in the extract include saccharides such as monosaccharides and oligosaccharides, peptides and proteins.

The addition of polyphenol adsorbents {polyvinyl poly-pyrrolidone (PVPP), poly-vinyl pyrrolidone (PVP), polyethylene glycol (PEG)} and alcohols (ethanol or methanol)can suppress an entry of polyphenols to improve the quality of extract. Pre-treating the plant materials with alcohol solution, extracts the polyphenols from the plant tissue and it will be easy to extract polyamines with good quality. For the extraction of polyamines, the cellular contents are brought equally mixed so the tissues are desirably damaged by crushing, grinding by means of a blender or a homogenizer or a mortar. Then subject the homogenate to extract with acidand the liquid fraction is then subjected to separation from residues such as centrifugal separation or filtration separation.

To get highly purified extract, the supernatant solution is subject forion-exchange or a gel filtration method, or electrodialysis methods. Plantpolyamine extract is derived from a natural plant and hence is safer than chemically synthesized products and contains at least three polyamines of putrescine, spermidine, and spermine and hence the necessity of individually preparing these polyamines is eliminated. The acid extracts contain free acid groups which damage the tissues upon consumption.To avoid this the solution is neutralized with 30% solution of sodium hydroxide and then centrifuged.

Plant tissues used for the polyamine extraction:

The newly growing plant tissues, cereals and plant exudates are more preferable for the extraction. As mentioned above, different sources have different quantities of polyamines but to use the extract as herbal product,high levels of the

spermidine and spermine are desirable.If the extract high putrescine but low spermidine or spermine contents, the putrescine metabolized by di-amine oxidase (DAO) in the intestine and systemic circulation.

Fromthe below table, extracts of H_2SO_4 are having more spermidine and spermine contents than other solvents.

Safety of the polyamine supplements

[Claudia Schwarz et al; 2018] spermidine-rich plant extract was safe and well tolerated in mice and older adults with subjective cognitive decline (SCD) [Claudia Schwarz et al; 2018]. No significant changes in the vital signs of weight of organs, systolic & diastolic blood pressures, heart rate and blood parameters observed with spermidine rich extract in the mice and humans.

Table 1: Contents of polyamines in mg of plant tissues. Ref: kitazawa et al 2011. Google patent (US20110236512A1)

Plant tissue	Solvent	Putrescine	Spermidine	Spermine	Total polyamine
Soya bean Derived	**5% $HClO_4$**	**23.5**	**24.0**	**9.6**	**57.1**
	0.1N HCl	**217.9**	**163.5**	**34.7**	**461.1**
	0.5N HCl	**226.5**	**170.0**	**36.5**	**433.0**
	1.0N HCl	**232.4**	**174.4**	**39.96**	**446.76**
	0.1N H_2SO_4	**220.8**	**165.7**	**35.1**	**521.6**
	0.5N H_2SO_4	**223.7**	**167.9**	**35.5**	**427.1**
	1.0N H_2SO_4	**229.4**	**172.2**	**36.5**	**438.1**
Wheat Derived	**5% $HClO_4$**	**6.40**	**23.9**	**14.3**	**44.6**
	0.1N HCl	**48.4**	**201.6**	**46.0**	**296.0**
	0.5N HCl	**48.4**	**183.6**	**50.8**	**281.3**
	1.0N HCl	**51.3**	**204.4**	**56.6**	**312.2**
	0.1N H_2SO_4	**50.0**	**195.6**	**46.4**	**292.0**
	0.5N H_2SO_4	**50.0**	**201.6**	**56.6**	**308.2**
	1.0N H_2SO_4	**52.8**	**197.2**	**58.4**	**308.4**

3. Conclusions

From these observations, the polyamines have promising roles in curing diseases and correcting the homeostasis. From the knowledge of the polyamine research, it can be concluded that PUT, SPDM and SPM have significant scope to use as therapeutic agents, but their metabolic and biosynthetic changesneed adepth research in every health condition. Some of the polyamine preparations of specific polyamine extracts are being under clinical observations. Any polyamine extract contain definite quantity of the polyamines could have a clinical importance. And also,there is need to develop simple methods to isolate and quantify different polyamines from the plants.

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