

Research Article

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The Role of Punicalagin in Slowing Down the Decaying of Neurons

Dasika Sairam

Student Pursuing MSc in Biotechnology, Vellore Institute of Technology, Vellore, Tamil Nadu, **INDIA**

*Email: boltsairam@gmail.com

ABSTRACT

Punicalagin is an active compound found in the Pomegranate rind. The hallmark of the compound is its antioxidant properties which is more than most other sources such as Red wine. The poly-phenol donates hydrogen to free radicals like peroxynitrites and prevents it from oxidizing and destroying microglial cells in the brain. The compound has high bio-availability and is has reduced neuronal inflammation as well. The compound is useful for treating Alzheimer's, Parkinson's, Huntington's and many other Dementia's. Apart from its antioxidant properties, the compound is an antidermatophyte and antimicrobial. Punicalagin has also shown ability in down regulating virulent Quorum sensing genes in Salmonella.

Keywords: Punicalagin, microglial cells

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INTRODUCTION

Pomegranate (*Punica granatum-L*) is a fruit that has been used extensively in traditional medicine for the treatment and prevention of numerous diseases such as dysentery, diarrhoea, etc. Pomegranate comprises of four major plant-based compounds namely, Anthocyanins Ellagic Acid, Gallic Acid and Punicalagin.

Punicalagin is majorly found in the Pomegranate and gets its name from the fruit's scientific name. It is a much sought-after compound synthesized from Pomegranate. It is extracted from the Fruit peel of (*Punica granatum*) Pomegranate.

Punicalagin is a polyphenol formed by the oxidative linkages between galloyl or Gallic acid groups on the Penta Gallo L glucose. However, the hallmark of Punicalagin is its enormous Anti-Oxidant property. Its Anti-Oxidant content is three times higher than that found in Green Tea and Red Wine. It is this attribute that makes this compound a much sought-after one.

ROLE OF PUNICALAGIN IN ALZHEIMER'S

The presence of Peroxynitrite (ONOO⁻), a free radical is one of the causes for Alzheimer's. These free radicals inhibit the release and synthesis of neurotransmitters involved in short-term memory, sleep, mood, social recognition and alertness. Thus, they prevent regeneration of neurons and it leads to a substantial loss of neurons. But Anti-Oxidants such as Punicalagin inhibit the formation of Peroxynitrites or even delay the onset of Alzheimer's.

The inflammation of the *microglial* cells (in Brain) can be curbed by this biological compound obtained from Pomegranate. Apart from Alzheimer's, the inflammation found in Parkinson's and Rheumatoid Arthritis and other types of Dementias as well are said to be acted upon by Punicalagin. Globally, there are around 44.4 million

Dementia sufferers with the number only expected to increase in the coming years.[Olumayokun AO et al. 2014].

In another Experiment, the compound's efficiency in LPS- activated microglial cells of rats (Inflamed) were tested. Here, Punicalagin was inserted in an immunoassay comprising of TNF- α and IL-6 gene expression of LPS stimulated hippocampal slices. The result was amplified using PCR and then evaluated using Western Blotting. It showed that Punicalagin completely inhibited the gene expression and the concentration of microsomal prostaglandin E synthase 1 was shown to be lesser than earlier. Thus, it was concluded that this could be a possible remedy for Neuro-Degenerative Diseases. [Olumayokun AO et al. 2014].

ROLE OF PUNICALAGIN IN VARIOUS CANCERS

Pomegranate products (including Punicalagin) have showed remarkable efficiency in increasing "Prostate specific antigen", reveals a study.

The various polyphenol compounds (i.e. Ellagic Acid, Punicalagin and Anthocyanin) of Pomegranate were obtained using High Performance Liquid Chromatography (HPLC). Folin- Ciocalteu was used to for their determination with Gallic Acid as a reference. Another revelation by the same study is that the compounds showed far more reliability than the more fancied and preferred Pomegranate blend that is widely prescribed for medications.

Thus, the study offers a new approach to tackle Prostate Cancer.[Sigrun CH et al. 2014]

Gut microbiota produces a biological compound called "Urolithins" from Ellagic Acid and other Ellagitannins. They verified whether the compound is found in the Colon in Colorectal Cancer (CRC) patients after having ingested a Pomegranate extract (PE) diet.

The patients were given a diet of 900 mg for a fortnight. The Ellagic Acid ratio of PE-1(Pomegranate Extract)and PE-2 was calculated and monitored. Interestingly after surgical resection, Twenty three metabolites but not any Ellagitannins were found in the urine, plasma samples using Ultra Performance Liquid Chromatography (UPLC).

All in all, a substantial amount of EAs (Ellagitannins) and Urolithins was found in the colon in the Colorectal Cancer patients after consuming a decent amount of PE-rich diet. However, work needs to be done to identify their biological impact.[Saravana KJ et al. 2014]. One has also to assess and determine the dosage of the compound and also monitor its progress in the long run.

OTHER NATURAL COMPOUNDS USED FOR SIMILAR PURPOSES

Apart from Punicalagin there have been several other phenolic compounds that have shown Anti-Inflammatory characters [Hsiao CW et al.]. According to a study done in South Korea, where the testing of 28 Herbal Extracts was carried out for their *Peroxy nitrite* scavenging activities using Fluorometric method. Results revealed that Hazel bark (*Hamamelis Virginiana*) showed the strongest Peroxynitrite scavenging property among the 28 extracts. Eugenol obtained from Rosemary had the second highest Peroxynitrite scavenging property. Others extracts included Lemon Balm Extract (Eugenol+ Ferulic Acid), Jasmine Tea, Ginseng (Ferulic Acid +Syringic Acid) [Choi HR et al. 2002]. Polyphenols are compounds that can donate multiple hydrogen atoms (such as Punicalagin) are potent Peroxynitrites scavengers. But likely even better are methoxyphenols because the methoxy group increases the hydrogen releasing capacity of the phenol groups. A study revealed that Eugenol (obtained from Rosemary), when ingested, can damage the Liver and other cells in our body. [Seiichiro F et al. 2002]... Another report stated that two people died after consuming Eugenol. [Hartnoll G et al. 1993]. A study in Germany revealed that Tumerone, an aromatic Turmeric-based compound can assist the Brain in self-repairing. Here, the research team injected it into brain cells of the rodents and noticed that the cells were active. In another Experiment, they placed the neuronal stem cells of the rodents into petri dishes having the compound and observed that 80% of the stem cells formed Neurons. Although no Human trials have been carried out, they concluded that this property of Tumerone can be used as the basis for treating Neuro-degenerative diseases such as Alzheimer's, Huntington's and Parkinson's. [Hucklenbroich J et al. 2014]. Curcumin, a methoxy phenol obtained from Ginger (*Zingiberaceae*) was believed to be a sure-shot remedy for Cancer and Alzheimer's. But according to recent studies the compound insufficiently enters the Blood Stream [Dills RL et al. 2001]. Add to this the numerous side effects that it has such as Mild Nausea or Diarrhoea [Chih Hung Tsu et al, 2007]. More recently it was found that Curcumin alters Iron Metabolism and suppresses the Hcpidin, the master regulation of Iron metabolism in the body. [Satomi HU et al. 1993]. Ferulic Acid (FA) is a natural monophenolic compound that is found in abundance in Plant cell walls, leaves and seeds. It is a widely sought-after compound due to its wide range of applications. The compound is also present in the outer covering of coffee beans, apple, peanut and orange. It can be extracted from wheat bran and maize bran. The compound links with polysaccharides and lignin and thus helps in providing rigidity to plant cells and also helps in

theformation of organic compounds such as coniferyl alcohol, vanillin, sinapic etc. The compound exhibits its antioxidant property in the presence of free radicals such as ROS i.e. Reactive Oxygen Species by donating a Hydrogen atom from its phenolic hydroxyl group. ^[16] Certain animal studies have the reveal the compound's remarkable ability to initiate antitumor activity against Breast and Lung Cancer. [MA Indap et al. 2006]. A research study also states that the compound can inhibit melanin production through competitive inhibition with tyrosine and thus may lead to whitening of the skin. [Tanimoto S et al. 2006]. However, perhaps the biggest hindrance is the cumbersome extraction of FA as it is mainly present in combined state in nature. Apart from this, its anti-cancerous activity is yet to be tested on human samples. A study in France conducted on the compound's bioavailability in rat intestines, and liver reveal the compounds' low bioavailability in cereals owing to its linking with lignin and arabinoxylans. [Adam A et al. 2002].

WHY PUNICALAGIN IS PREFERABLE?

Punicalagin is water soluble and has high bio availability. It implies that the body has little trouble in it breaking down. It is a potential inhibitor of Carbonic Anhydrase. [Aviram M et al. 2000] It has shown to reduce platelet aggregation and naturally lower blood pressure, factors that prevent both heart attacks and strokes. [Cerdeira B et al. 2003]. It has shown no Toxic effects. A study in 2003 revealed that when rats were administered 6% diet of Punicalagin for 37 days and the result obtained showed that it was not harmful. [Simone RF et al.] The compound has repeatedly shown anti-fungal and anti-bacterial properties as well. [Foss SR et al. 2014]

OTHER USES OF PUNICALAGIN

Apart from being a useful antioxidant, antimutagenic, antiproliferative compound, Punicalagin has many other applications. One of the most prominent ones is its Anti-Fungal attributes. A study conducted revealed its resistance towards Dermatophyte growth as well. Here, Punicalagin was isolated and identified by the spectroscopic analysis. Here, Punicalagin showed activity against the Hyphal stage in fungi. Interestingly, it showed toxicity towards Fungi and not mammalian cells. Further tests showed that the compound-specific inhibition towards *T. rubrum*. Thus, it was concluded that this could be a probable Anti-Dermatophyte medicine shortly. [Olumayokun AO et al. 2014]. An investigation in Naples, Italy revealed that Punicalagin can help in suppressing of oxidation sensitive genes such as ELK-1 and p-CREB. The study also stated that the compound can reverse pro-atherogenic effects that are induced by shear stress while increasing the levels of cGMP and nitrates. Interestingly, PFE (Pomegranate Fruit Extract i.e. rich in Punicalagin) and Pomegranate juice, which were administered on human endothelial cells (used as standard) and atherosclerosis prone areas of hypercholesterolemic mice, did not show any significant effects on the conversion of *L-arginine* to *L-citrulline*. [De Nigris et al. 2007]. *Salmonella* is one of the prominent bacterial families that are responsible for food-borne diseases such as Vomiting, Diarrhoea, and Fever, etc. It is already known that *Salmonella* uses Quorum Sensing (QS) for transmission of Virulence Factors. Here, MICs of Punicalagin was done for ten *Salmonella* strains, followed by Motility Assays and Reverse Transcription-PCR (RT-PCR) to investigate the virulent attributes and the QS-related genes in *Salmonella*. Results revealed that the Punicalagin (at 1/16 MIC and at 1/32 MIC) had significantly reduced the swimming of bacterial strains and also downgraded the expression of *Salmonella*'s QS related genes as well. Another assay indicated that Punicalagin inhibited the production of Violacein (now also used as a biosensor for Quorum Sensing) by *Chromobacterium violaceum* and reduced the expression of QS genes (SdiA and SrgE) found in *Salmonella*. Thus, the study reveals the potential of Punicalagin as an anti-QS agent. [Guanghui Li et al. 2014].

CHALLENGES FACED BY PUNICALAGIN

Punicalagin despite being an effective antimicrobial, anticancer, anti-inflammatory, antioxidant compound it is not yet ready for human use and treatment. One of the biggest problems with Punicalagin is that despite its high bio-availability only about 6% of the compound successfully enters the blood stream. Secondly, the compound has not been successfully treated on human samples. Thirdly, if it is found to be effective on humans, we need to finalise its dosage.

CONCLUSION

All in all, Punicalagin is a polyphenol compound that has tremendous potential in decelerating the Decaying of Neurons and although a one needs to iron out a few complications before they can be used as medicines or even as a therapy. Having said that, the compound's effectiveness comes as a welcome development.

REFERENCES

Adam A, Crespy V, Levrat-Verny MA, Leenhardt, Leuillet M, Demigne C, Remesy C; The bioavailability of Ferulic acid is governed primarily by the food matrix rather than its metabolism in intestine and liver in rats; Journal of Nutrition 2002 Jul; 132 Vol (Issue 7) 1962-68 pgs.

- Aviram M, Dornfeld L, Rosenblat M, Volkova N, Kaplan M, Coleman R, Hayek T, Presser D, Fuhrman Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: studies in humans and in atherosclerotic apolipoprotein E-deficient mice; *American Journal of Clinical Nutrition*; 2000 May; 71(5) 1062-76pg
- Cerda B, Ceron JJ, Tomas-Barberan FA, Espin JC; Repeated oral administration of high doses of the pomegranate ellagitannin punicalagin to rats for 37 days is not toxic; *Journal Agriculture and Food Chemistry*; 2003 May 21; 51(11) 3493-501pg
- Chih Hung Hsu, Ann Lii Cheng; *Clinical studies with Curcumin* Vol 595 2007, pp 471-480
- Choi HR, Choi JS, Han YN, Bae SJ, Chung HY; Peroxynitrite scavenging activity of herb extracts; *Phytotherapy Research*; 2002 June 16(4) 364-7pg
- De Nigris F, Williams-Ignarro S, Sica V, Lerman LO, D'Armiento FP, Byrns RE, Casamassimi A, Carpentino D, Schiano C, Sumi D, Fiorito C, Ignarro LJ, Napoli C; Effects of a pomegranate fruit extract rich in Punicalagin on oxidation-sensitive genes and eNOS activity at sites of perturbed shear stress and atherogenesis; *Cardiovascular Research* 2007 Jan 15; 73 edition Issue 2; 414-423pgs
- Dills RL, Zhu X, Kalman DA; Measurement of urinary methoxyphenols and their use for biological monitoring of wood smoke exposure; *Environment Research*; 2001 Feb; 85(2); 145-58pgs.
- Foss SR, Nakamura CV, Ueda-Nakamura T, Cortez DA, Endo EH, Dias Filho BP; Antifungal activity of pomegranate peel extract and isolated compound punicalagin against dermatophytes; *Annals of Clinical Microbiology and Anti microbials*; 2014 Sept 5; 13 (1)
- G Hartnoll, D Moore, D Douek; near fatal ingestion of oil of cloves; *Archives of Disease in Childhood* 1993, 69 edition, 392-393pg
- Guanghai Li, Chunhong Yan, Yunfeng Xu, Yuqing Feng, Qian Wu, Xiaoying Lv, Baowei Yang, Xin Wang and Xiaodong Xia; Punicalagin Inhibits Salmonella Virulence Factors and Has Anti-Quorum-Sensing Potential; *Applied and Environmental Microbiology*; 80th Edition Issue 19; 6204-11pg
- Hsiao C Wang, Julia L Brumaghim; Polyphenol Compounds as Antioxidants for Disease Prevention: Reactive Oxygen Species Scavenging, Enzyme Regulation, and Metal Chelation Mechanisms in *E. coli* and Human Cells; *American Chemical Society*; Vol 1083; Chapter 5; 99-175pg
- Joerg Hucklenbroich, Rebecca Klein, Bernd Neumaier, Rudolf Graf, Gereon Rudolf Fink, Michael Schroeter and Maria Adele Rueger; Aromatic-turmerone induces neural stem cell proliferation in vitro and in vivo; *Journal of Stem cell research and Therapy*; Sept 2014;
- Kikuzaki H, Hisamoto M, Hirose K, Akimaya K, Taniguchi H; Antioxidant properties of Ferulic acid and its related compounds; *Journal of Agriculture and Food Chemistry*
- MA Indap, S Radhika, Leena Motiwale, KVK Rao; Anticancer activity of phenolic antioxidants against breast cancer cells and a spontaneous mammary tumour; *Indian Journal of Pharmaceutical Sciences* 2006 Vol 68 Issue 4; 470-474pgs.
- Olumayokun A. Olajide, Asit Kumar, Ravikanth Velagapudi, Uchechukwu P. Okorji1 and Bernd L. Fiebich; Punicalagin inhibits neuroinflammation in LPS-activated rat primary microglia; *Journal of Molecular Nutrition and Food Research*; Volume 58 Issue 9; 1843-51pg; September 2014
- Olumayokun A. Olajide, Asit Kumar, Ravikanth Velagapudi, Uchechukwu P. Okorji1 and Bernd L. Fiebich; Punicalagin inhibits neuroinflammation in LPS-activated rat primary microglia; *Journal of Molecular Nutrition and Food Research*; Volume 58 Issue 9; 1843-51pg; September 2014
- Olumayokun A. Olajide, Asit Kumar, Ravikanth Velagapudi, Uchechukwu P. Okorji1 and Bernd L. Fiebich; Punicalagin inhibits neuroinflammation in LPS-activated rat primary microglia; *Journal of Molecular Nutrition and Food Research*; Volume 58 Issue 9; 1843-51pg; September 2014
- Saravana Kumar Jaganathan, Muthu Vignesh Velayappan, Gayathri Narsimhan and Eko Supriyanto; Role of pomegranate and citrus fruit juices in colon cancer prevention; *World Journal of Gastroenterology* 2014 Apr 28; 20 (16): 4618-4625pgs.
- Satomi H, Umemura K, Ueno A, Hatano T, Okuda T, Noro T; Carbonic anhydrase inhibitors from the pericarps of *Punica granatum* L; *Biological and Pharmaceutical Bulletin*; 1993 Aug 16 (8); 787-90pg
- Seiichiro Fujisawa, Toshiko Atsumi, Yoshinori Kadoma, Hiroshi Sakagami; Antioxidant and prooxidant action of eugenol-related compounds and their cytotoxicity; *Journal of Toxicology*; Volume 177 Issue 1; August 2002, Pages 39-54
- Shinichi TANIMOTO, Hitoshi TOMINAGA, Yoshiharu OKADA and Masato NOMURA; Synthesis and Cosmetic Whitening Effect of Glycosides Derived from Several Phenylpropanoids; *the Pharmaceutical Society of Japan YAKUGAKU ZASSHI* 126 (3) 173-177 (2006)
- Sigrun Chrubasik-Hausmann, Christian Vlachojannis and Benno Zimmermann; Pomegranate Juice and Prostate Cancer: Importance of the Characterisation of the Active Principle; *Journal of Phytotherapy Research* Vol 28 Issue 11 1676-1678pg; Nov 2014
- Simone R Foss, Celso V Nakamura, Tania Ueda-Nakamura, Diogenes AG Cortez, Eliana H Endo and Benedito P Dias Filho; Antifungal activity of pomegranate peel extract and isolated compound Punicalagin against dermatophytes; *Annals of Clinical Microbiology and Antimicrobials*