

## Punicalagins-A Large Polyphenol Compounds Found in Pomegranates: A Therapeutic Review

<sup>1</sup>Satyanand Tyagi, <sup>2</sup>Ajeet Singh, <sup>3</sup>Poonam Bhardwaj, <sup>4</sup>Sandeep Sahu, <sup>4</sup>A.P. Yadav and <sup>4</sup>M.L. Kori

<sup>1</sup>President, Tyagi Pharmacy Association & Scientific Writer, Chattarpur, New Delhi, India

<sup>2</sup>Dayanand Dinanath College, Institute of Pharmacy, Kanpur, Uttar Pradesh, India

<sup>3</sup>Department of Pharmaceutical Chemistry,

Shri R.N.S. College of Pharmacy, Gormi, Madhya Pradesh, India

<sup>4</sup>Vedica College of Pharmacy, Bhopal, Madhya Pradesh, India

**Abstract:** Punicalagins are tannins, large polyphenol compounds that are isomers of 2, 3-(S)-hexahydroxydiphenoyl-4, 6-(S, S)-gallagyl-D-glucose, hydrolysable tannins with a molecular weight of 1084. They are found in forms  $\alpha$  and  $\beta$  in pomegranates. Punicalagins are the largest molecule found intact in rat plasma after oral ingestion and were found to show no toxic effects in rats that were given a 6% diet of punicalagins for 37 days. Punicalagins are also found to be the major component responsible for pomegranate juice's antioxidant and health benefits. Punicalagins are water-soluble and have high bioavailability. They are known to hydrolyze into smaller polyphenols such as ellagic acid in vivo where one potential mechanism is hydrolysis across the mitochondrial membrane of cultured human colon cells. A study in Taiwan showed that  $\alpha$  punicalagin shows potential as strong cancer suppressors. Compounds found only in pomegranates called punicalagins are shown to benefit the heart and blood vessels. Punicalagins are the major component responsible for pomegranate's antioxidant and health benefits. They not only lower cholesterol, but also lower blood pressure and increase the speed at which heart blockages (atherosclerosis) melt away. The aim of present article is to provide in depth knowledge about Punicalagins, their clinical and biological profile as well as their role in prevention of certain dreadful disease such as cancer as well as various cardiac disorders.

**Key words:** Punicalagins • Punica granatum • Pomegranates • Polyphenol compounds.

### INTRODUCTION

One of the oldest known fruits, found in writings and artifacts of many cultures and religions, the pomegranate (*Punica granatum* L.) is an original native of Persia. This nutrient dense, antioxidant rich fruit has been revered as a symbol of health, fertility and eternal life. Pomegranate is a delicious fruit with many beneficial compounds. Pomegranate has substances, such as polyphenols, that have antioxidant, anti-viral and anti-tumor activity. Pomegranate may also be helpful in maintaining healthy cholesterol and triglyceride levels and a recent study indicates that pomegranate has compounds, which play a role in osteoarthritis and prostate health. Pomegranates contain high levels of flavonoids and polyphenols, potent antioxidants offering protection

against heart disease and cancer. The benefits related to the pomegranate are derived from its punicosides content. Specifically to punicalagins  $\alpha + \beta$ , ellagic acid and some glycosides, polyphenolic compounds with a high antioxidant power. A glass of pomegranate juice has more antioxidants than red wine, green tea, blueberries and cranberries. Pomegranate is available, of course, as a fruit, as fruit juice, in extract form as a supplement, jam, jelly, juice concentrate, molasses and even wine and martini. Pomegranate pills are available and are a good option in order to avoid the calories. Some of the prominent features of Pomegranate may be listed as follows:

- Most powerful anti-oxidant of all fruits
- Potent anti-cancer and immune supporting effects

- Inhibits abnormal platelet aggregation that could cause heart attacks, strokes and embolic disease
- Lowers cholesterol and other cardiac risk factors
- Lowers blood pressure
- Shown to promote reversal of atherosclerotic plaque in human studies
- May have benefits to relieve or protect against depression and osteoporosis.

Many studies show that the pomegranate is one of the most powerful, nutrient dense foods for overall good health. These clinical findings clearly show a correlation between pomegranate compounds and their positive effect on both human and animal cardiovascular, nervous and skeletal health. This is one fruit that person can't afford to exclude from diet.

Punicalagins are tannins, large polyphenol compounds, which are isomers of 2, 3-(S)-hexahydroxydiphenoyl-4, 6-(S, S)-gallagyl-D-glucose, hydrolysable tannins with a molecular weight of 1084. They are found in  $\alpha + \beta$  forms in pomegranates. Punicalagins are the largest molecule found intact in rat plasma after oral ingestion [1] and were found to show no toxic effects in rats that were given a 6% diet of punicalagins for 37 days [2]. Punicalagins are also found to be the major component responsible for pomegranate juice's antioxidant and health benefits [3]. A study in Taiwan showed that punicalagin alpha shows potential as strong cancer suppressors. Punicalagins are water-soluble and have high bioavailability. They are known to hydrolyze into smaller polyphenols such as ellagic acid in vivo where one potential mechanism is hydrolysis across the mitochondrial membrane of cultured human colon cells [4-5]. Punicalagins are powerful antioxidants. They are present in a number of different plant species, with the pomegranate being the most prevalent. They are found in the inedible husk, rind and the inner yellow membranes surrounding the juice arils of the pomegranate fruit. Some punicalagins are found in the juice, but concentrations are lower and some processing methods can remove the benefits.

A few dietary supplements and nutritional ingredients are available that contain extracts of whole pomegranate and/or are standardized to punicalagins, the marker compound of pomegranate. Extracts of pomegranate are also 'Generally Recognized As Safe' (GRAS) by the United States. It has been recommended to look for pomegranate ingredients that mimic the polyphenol ratio of the fruit, as potent synergistic effects have been observed in 'natural spectrum' extracts,

especially pomegranate concentrate normalized to punicalagins [6]. A pomegranate extract standardized to punicalagins marketed under the name Pomella was found to absorb into the bloodstream after consumption in humans. A maximum 32% increase in plasma antioxidant status measured by ORAC was also noted in this study. Punicalagins (anomeric isomers of the punicalagin molecule) are the players behind the antioxidant properties of pomegranate. These pomegranate ellagitannins are 'polyphenol bombs' which extensively metabolize and are native in high concentrations unique to pomegranate fruit. Thus, they are the suitable biomarkers for a pomegranate extract whose natural phenolic profile is researched to offer tangible health benefits. Punicalagins are 100% water-soluble, highly bioavailable and supported by safety data. They are shown to possess a high absorption rate of up to 95%. And not only does punicalagins offer a powerful kick of antioxidant properties on their own; they can break-up into smaller polyphenols that are also absorbed into the body and extensively metabolized. In fact, metabolites of punicalagins have been detected in the body through 48 hours after consumption [7].

**Chemistry:** Punicalagins are tannins, large polyphenol compounds that are isomers of 2, 3-(S)-hexahydroxydiphenoyl-4, 6-(S, S)-gallagyl-D-glucose, hydrolysable tannins with a molecular weight of 1084. The chemical structure of punicalagin is shown in Fig.1.

**Potential Aspects of Punicalagins:** Punicalagins are shown to benefit the heart and blood vessels. Punicalagins are the major component responsible for pomegranate's antioxidant and health benefits. They not only lower cholesterol, but also lower blood pressure and increase the speed at which heart blockages (atherosclerosis) melt away. Recent medical research studied heart patients with severe carotid artery blockages. They were given an ounce of pomegranate juice each day for a year. Not only did study participants blood pressure lower by over 20%, but also there was a 30% reduction in atherosclerotic plaque. Just as astounding, participants who did not take the pomegranate juice saw their atherosclerotic plaque increase by 9% [8]. In other studies, potent antioxidant compounds found in pomegranates have shown to reduce platelet aggregation and naturally lower blood pressure, factors that prevent both heart attacks and strokes [9-10]. Not only are pomegranates good for heart and blood vessels but also they have been shown to inhibit breast

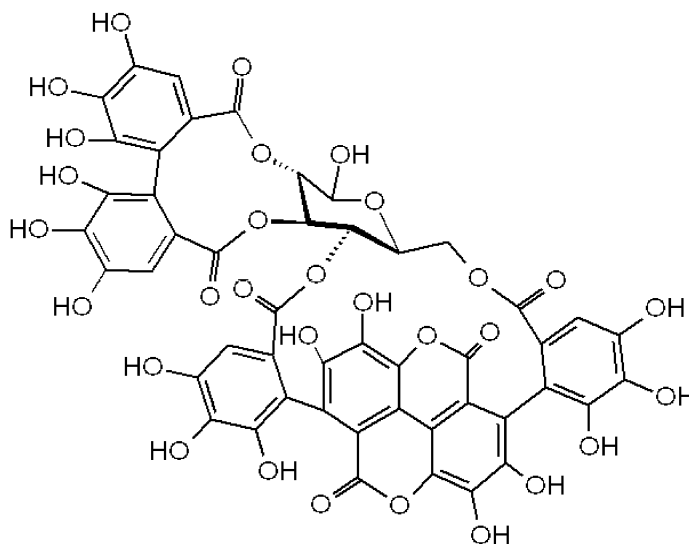


Fig. 1: Structure of Punicalagin

cancer, prostate cancer, colon cancer, leukemia and to prevent vascular changes that promote tumor growth in lab animals [11-14]. Several in vitro studies have shown this remarkable anti-cancer effect. Additional studies and clinical trials currently taking place are hopeful to reveal this fascinating effect on humans. Also of note, pomegranate juice contains phytochemical compounds that stimulate serotonin and estrogen receptors, improving symptoms of depression and increasing bone mass in lab animals. It is recommendable that all patients who have heart disease, high cholesterol, or high blood pressure as well as those who are looking to prevent these ailments incorporate the powerful components of pomegranates into their diet. Pomegranate extracts standardized for their primary active component, punicalagin, have received considerable attention for their role cardiovascular protection, weight management and cancer prevention. Punicalagins are the most important active component in the fresh pomegranate fruit; these are typically lost or in very low amounts when pomegranate juice is made. A new study shows that punicalagins have potent anti-fungal activity against *Candida albicans*. Punicalagins is considered generally safe with no known side effects [15].

#### Pharmacological Activity

**Antioxidant Activity:** The potent antioxidant capacity of pomegranate and its components has been reported by numerous scientists using multiple in vitro assay systems. This activity is largely due to the polyphenolic constituents. Punicalagins and other polyphenols in

pomegranate have higher total polyphenolic content and greater antioxidant activity than other commonly consumed fruit juices, including grape, cranberry, orange and apple juice among others. Pomegranate punicalagins with other polyphenols were found to be potent antioxidant in protecting nitric oxide then Concord grape juice, blue berry juice, red wine, vitamin C and vitamin E [16-17].

**Cardiovascular Health:** The primary health benefits of punicalagins have focused on the antioxidant actions and its potential to prevent atherosclerosis as well as slow progression of atherosclerotic plaques. Five small human clinical trials testing cardiovascular activities have evaluated punicalagins for effects on cholesterol, atherosclerosis, myocardial perfusion, hypertension and erectile dysfunction [18-19].

**Prostate Cancer:** A well designed phase-II clinical study suggest that Punicalagins and other pomegranate tannins may be potentially effective in slowing progression of prostate cancer and reducing recurrence rates of the disease [20].

#### CONCLUSIONS

The beneficial clinical effects of the *Punica granatum* L. for the treatment of malaria possibly include the direct anti-parasitic activity and the ability to limit the excess inflammatory response of the host, thus limiting the risk of progression to the more severe form of the disease,

including the onset of cerebral malaria. In coinclusion, various studies showed that pomegranate juice can demonstrate statistically significant improvements in intima-media thickness (IMT), end-diastolic volume, peak systolic velocity (PSV), systolic blood pressure, TBARS, lipid peroxides, serum ACE activity, summed stress and rest scores and the number of angina episodes. No improvements were seen in lipids, glucose, or HbA1c. The clinical relevance of these improvements varies, but in general they can be taken to represent positive trends in overall improvement of cardiovascular risk.

### REFERENCES

1. Cerda, B., R. Llorach, J.J. Ceron, J.C. Espin and F.A. Tomas-Barberan, 2003. Evaluation of the bioavailability and metabolism in the rat of punicalagin, an antioxidant polyphenol from pomegranate juice. *The Europ. J. Nutri.*, 42(1): 18-28.
2. Cerda, B., F.A. Tomas-Barberan and J.C. Espin, 2003. The repeated oral administration of high doses of the pomegranate ellagitannin punicalagin to rats for 37 days is not toxic. *J. Agric. Food Chem.*, 51: 3493-3501.
3. Gil, M.I., F.A. Tomas-Barberan, B. Hess-Pierce, D.M. Holcroft and A.A. Kader, 2000. Antioxidant activity of pomegranate juice and its relationship with phenolic composition and processing. *J. Agric. Food Chem.*, 48: 4581-4589.
4. Seeram, N.P., R. Lee and D. Heber, 2004. Bioavailability of ellagic acid in human plasma after consumption of ellagitannins from pomegranate (*Punica granatum L.*) juice. *Clinica Chimica Acta*, 348(1-2): 63-68.
5. Larrosa, M., F.A. Tomas-Barberan and J.C. Espin, 2006. The dietary hydrolysable tannin punicalagin releases ellagic acid that induces apoptosis in human colon adenocarcinoma Caco-2 cells by using the mitochondrial pathway. *The J. Nutrit. Biochem.*, 17(9): 611-625.
6. Seeram, N.P., L.S. Adams, S.M. Henning, Y. Niu, Y. Zhang, M.G. Nair and D. Heber, 2005. In vitro antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. *The J. Nutr. Biochem.*, 16(6): 360-367.
7. Mertens-Talcott, S.U., P. Jilma-Stohlawetz, J. Rios, L. Hingorani and H. Derendorf, 2006. Absorption, metabolism and antioxidant effects of pomegranate (*Punica granatum L.*) polyphenols after ingestion of a standardized extract in healthy human volunteers. *J. Agric. Food Chem.*, 54: 8956-8961.
8. Aviram, M., M. Rosenblat, D. Gaitini, S. Nitecki, A. Hoffman, L. Dornfeld, N. Volkova, D. Presser, J. Attias, H. Liker and T. Hayek, 2004. Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation. *Clinical Nutr.*, 23(3): 423-433.
9. Aviram, M., L. Dornfeld, M. Rosenblat, N. Volkova, M. Kaplan, R. Coleman, T. Hayek, D. Presser and B. Fuhrman, 2000. Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL and platelet aggregation: studies in humans and in atherosclerotic apolipoprotein E-deficient mice. *The American J. Clinical Nutr.*, 71(5): 1062-1076.
10. Aviram, M. and L. Dornfeld, 2001. Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. *Atherosclerosis*, 158(1): 195-198.
11. Kim, N.D., R. Mehta, W. Yu, I. Neeman, T. Livney, A. Amichay, D. Poirier, P. Nicholls, A. Kirby, W. Jiang, R. Mansel, C. Ramachandran, T. Rabi, B. Kaplan and E.P. Lansky, 2002. Chemopreventive and adjuvant therapeutic potential of pomegranate (*Punica granatum*) for human breast cancer. *Breast Cancer Res. Treat.*, 71(3): 203-217.
12. Kohno, H., R. Suzuki, Y. Yasui, M. Hosokawa, K. Miyashita and T. Tanaka, 2004. Pomegranate seed oil rich in conjugated linolenic acid suppresses chemically induced colon carcinogenesis in rats. *Cancer Sci.*, 95: 481-486.
13. Toi, M., H. Bando, C. Ramachandran, S.J. Melnick, A. Imai, R.S. Fife, R.E. Carr, T. Oikawa and E.P. Lansky, 2003. Preliminary studies on the anti-angiogenic potential of pomegranate fractions in vitro and in vivo. *Angiogenesis*, 6(2): 121-128.
14. Kawaii, S. and E.P. Lansky, 2004. Differentiation-promoting activity of pomegranate (*Punica granatum*) fruit extracts in HL-60 human promyelocytic leukemia cells. *J. Medicinal Food*, 7(1): 13-18.
15. Mori-Okamoto, J., Y. Otawara-Hamamoto, H. Yamato and H. Yoshimura, 2004. Pomegranate extract improves a depressive state and bone properties in menopausal syndrome model ovariectomized mice. *J. Ethnopharm.* 92(1): 93-101.

16. Noda, Y., T. Kaneyuki, A. Mori and L. Packer, 2002. Antioxidant activities of pomegranate fruit extract and its anthocyanidins: delphinidin, cyanidin and pelargonidin. *J. Agric. Food Chem.*, 50: 166-171.
17. Plumb, G.W., S. De Pascual-teresa, C. Santos-buelga, J.C. Rivas-gonzalo and G. Williamson, 2002. Antioxidant properties of gallicocatechin and prodelfinidins from pomegranate peel. *Redox Report*, 7: 41-46.
18. Rosenblat, M., T. Hayek and M. Aviram, 2006. Anti-oxidative effects of pomegranate juice (PJ) consumption by diabetic patients on serum and macrophages. *Atherosclerosis*, 187: 363-371.
19. Summer, M.D., M. Elliott-eller, G. Weidner, J.J. Daubenmier, M.H. Chew, R. Marlin, C.J. Raisin and D. Ornish, 2005. Effects of Pomegranate Juice Consumption on Myocardial Perfusion in Patients with Coronary Heart Disease. *American J. Cardiol.*, 96: 810-814.
20. Pantuck, A.J., J.T. Leppert, N. Zomorodian, W. Aronson, J. Hong, R.J. Barnard, N. Seeram, H. Liker, H. Wang, R. Elashoff, D. Heber, M. Aviram, L. Ignarro and A. Belldgrun, 2006. Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer. *Clinical Cancer Res.*, 12: 4018-4026.