Review Article

RECENT UPDATES ON ANTICANCER ACTIVITIES OF POMEGRANATE

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ABSTRACT

Natural and some synthetic compounds can prevent, suppress, or reverse the progression of cancer. Natural products have proven to be the most effective in terms of their ability to alter the function of proteins relevant to cancer. Pomegranate (*Punica granatum* L.) is considered as an ancient, mystical, unique known edible fruit borne on a small, long-living tree cultivated throughout the whole globe and is the symbolic of abundance and prosperity. For thousands of years, many cultures have believed that pomegranate have beneficiary effects on health, fertility, longevity and rebirth. The synergistic action of the pomegranate constituents appears to be superior to that of single constituents. In the past decade, numerous studies on the various properties of pomegranate constituents have been published, focusing on treatment and prevention of cancer, cardiovascular disease, diabetes, dental conditions, erectile dysfunction, bacterial infections and antibiotic resistance, and ultraviolet radiation-induced skin damage, infant brain ischemia, Alzheimer's disease, arthritis, and obesity. Present review article highlights current and updates on the use and application of pomegranate for prevention and treatment of various types of cancer.

Keywords: Anti-inflammatory activity, cancer, pomegranate, prevention.

INTRODUCTION

Pomegranate, *Punica granatum* L., an ancient, mystical and highly distinctive fruit, is the predominant member of two species comprising the Punicaceae family.[1] Pomegranate is a widely used plant having medicinal properties. It is a nutrient dense fruit rich in phytochemical compounds.[2] Pomegranate has been used for thousands of years to cure a wide range of diseases across different cultures and civilizations. It has great nutritional values and numerous health benefits. The pomegranate has been used in natural and holistic medicine to treat sore throats, coughs, urinary infections, digestive disorders, skin disorders, arthritis and to expel tapeworms. However, modern research suggests that pomegranates might be useful in treating such serious conditions as prostate cancer, skin cancer, osteoarthritis, and diabetes. Studies also show that pomegranate seeds might help get rid of the fats of the digestive system. Clinical research shows that pomegranates, when part of a healthy diet, might help prevent heart disease, heart attacks and strokes. This is because pomegranates have the potential to thin the blood, increase blood flow to the heart, reduce blood pressure, reduce plaque in the arteries, and reduce bad cholesterol while increasing good cholesterol. A decoction of seed is used to treat syphilis. Juice used to treat jaundice and diarrhoea. Juice of flower is used to treat nose bleeds. The fruit pulp and the seed are stomachic. Dried, pulverized flower buds are employed as a remedy for bronchitis.[3]

In preliminary laboratory research and clinical trials, juice of the pomegranate may be effective in reducing heart disease risk factors, including LDL oxidation, macrophage oxidative status and foam cell formation. In mice, "oxidation of LDL by peritoneal macrophages was reduced by up to 90% after pomegranate juice consumption. In December, 2010 scientists identified components in pomegranate juice that inhibit the movement of cancer cells. Researchers at the University of California found that these components also weaken cancer cells' attraction to a chemical signal that promotes the metastasis of prostate cancer to the bone and pomegranate juice helps fight prostate cancer.

In the ancient Ayurveda system of medicine, the pomegranate has extensively been used as a source of traditional remedies for thousands of years. The rind of the fruit and the bark of the pomegranate tree is used as a traditional remedy against diarrhoea, dysentery and intestinal parasites. The seeds and juice are considered a tonic for the heart, throat and eyes and for a variety of purposes, such as stopping nose bleeds and gum bleeds, toning skin, firming-up sagging breasts and treating haemorrhoids. In the past decade, numerous studies on the antioxidant, anti-carcinogenic and anti-inflammatory properties

of pomegranate constituents have been published, focusing on treatment and prevention of cancer, cardiovascular disease, diabetes, dental conditions, erectile dysfunction, bacterial infections and antibiotic resistance, and ultraviolet radiation-induced skin damage. Other potential applications include infant brain ischemia, male infertility, Alzheimer's disease, arthritis, obesity, in treating diarrhoea, dysentery and intestinal parasites. Pomegranate is well known for its antioxidant properties. It helps in preventing the formation of skin cancer by reducing the frequency of lesions. It provides relief from minor skin irritations, such as dry skin, eczema and psoriasis.[3]

The botanical name of pomegranate is *Punica granatum* (Puniacaceae) and is commonly known as pomegranate and anar. The various parts used include the seeds, fruits, peels, flowers, leaves, etc.

It was lauded in ancient times in the Old Testament of the Bible, the Jewish Torah and the Babylonian Talmud as a sacred fruit conferring powers of fertility, abundance, and good luck. It also features prominently in the ceremonies, art and mythology of the Egyptians and Greeks and was the personal emblem of the Holy Roman Emperor, Maximilian. Pomegranate is the symbol and heraldic device of the ancient city of Granada in Spain – from which the city gets its name. The genus name, *Punica*, was the Roman name for Carthage, where the best pomegranates were known to grow. Pomegranate is known by the French as grenade, the Spanish as granada, and literally translates to seeded ("granatus") apple ("pomum").[1]

The pomegranate tree typically grows 12-16 feet, has many spiny branches, and can be extremely long lived, as evidenced by trees at Versailles, France, known to be over 200 years old. The leaves are glossy and lance shaped and the bark of the tree turns grey as the tree ages. The flowers are large, red, white, or variegated and have a tubular calyx that eventually becomes the fruit. The ripe pomegranate fruit can be up to five inches wide with a deep red, leathery skin, is grenade-shaped and crowned by the pointed calyx. The fruit contains many seeds (arils) separated by white, membranous pericarp and each is surrounded by small amounts of tart, red juice. The pomegranate is native from the Himalayas in northern India to Iran but has been cultivated and naturalized since ancient times over the entire Mediterranean region. It is also found in India and more arid regions of Southeast Asia, the East Indies and tropical Africa. The tree is also cultivated for its fruit in the drier regions of California and Arizona.[4]

Chemical Constituents

The chemical composition of the fruits differs depending on the cultivar, growing region, maturity, cultivation practice, climate and storage circumstances.[5] The various chemical constituents present in the various parts of pomegranate are given in the table 1.

Table 1: Principle constituents of different parts of pomegranate tree and fruit

Pomegranate peel	Pomegranate juice	Pomegranate root & bark	Pomegranate flower	Pomegranate leaves	Pomegranate seed
Gallic acid	Simple sugars	Ellagitannins	Gallic acid	Carbohydrates	3,3'-Di-O-methylellagic acid
Ellagic acid	Aliphatic organic acids	Piperidine alkaloids	Ursolic acid	Reducing sugars	3,3',4'-Tri-O-methylellagic acid
Punicalin	Gallic acid	Pyrrolidine alkaloids	Triterpenoids	Sterols	Punicic acid
Punicalagin	Ellagic acid	Pelletierine alkaloids	Fatty acids	Saponins	Oleic acid
Caffeic acid	Quinic acid			Flavonoids	Palmitic acid
Ellagitannins	Flavanols			Tannins	Stearic acid
Pelletierine alkaloids	Amino acids			Piperidine alkaloids	Linoleic acid
Luteolin	Minerals			Flavone	Sterols
Kaempferol	EGCG			Glycoside	Tocopherols
Quercetin	Ascorbic acid			Ellagitannins	Sex steroids

Traditional uses of pomegranate

Heart Problems: Frequent intake of pomegranate juice can maintain good flow of the blood in the body. Along with this, it decreases the risk of heart attack and heart strokes.

Stomach Disorder: Pomegranates peel, bark and leaves are used to calm the stomach disorder or diarrhoea triggered due to any kind of digestive problems. Drinking tea made from the leaves of this fruit helps in curing digestive problems. Pomegranate juice is also used for handling problems of dysentery and cholera.

Dental Care: The best benefit of pomegranate is that its juice, along with its antibacterial and antiviral properties, helps to reduce the effects of dental plaque.

Cancer: Pomegranates consist of advanced level of antioxidants called flavonoids. These flavonoids are thought to be effective in counteracting various cancer radials. The individuals that face high risk of prostate and breast cancer should start drinking the juice of this fruit, as this will help them to reduce further risk of developing cancer. Regular consumption of pomegranates can reduce the PSA levels in the body and helps to fight the existing cancer cells in the body.

Osteoarthritis: Pomegranate minimizes the illness triggered in various forms, like atherosclerosis and osteoarthritis. The loss that is triggered due to the thickening and solidifying of the arterial walls and in cartilage and joints can be cured by consuming this fruit. Also, pomegranate is capable of preventing the creation of minerals that are liable for breaking down the connective tissues.

Diabetes: Consuming of pomegranate fruit juice by a diabetic patient can prevent coronary illnesses. Along with this, there is a slowdown in solidifying of the bloodstream, which can fuel non-occurrence of various heart diseases.

Anaemia: Healthy blood flow can be maintained in the body by consuming this fruit in any form. Pomegranate seed extract supplies iron to blood and thus, help to decrease the anaemic symptoms including fatigue, wooziness and weakness and hear loss.[6]

Therapeutic uses of pomegranate

Pomegranate fruit juice is known as a delicacy and is made into excellent sherbet with the addition of water, sugar and taken internally, and some people use it in preparing ice-creams, jellies and marmalades. Such juice of pomegranate fruits possesses diuretic, cooling effect, glucose, fructose, tannins, oxalic acid, and reduces thirst in cases of fevers, supplies the required minerals and helps the liver to preserve vitamin A. from the food, increases the body's resistance to T.B. infection, and acts as a tonic for heart and kidney. According to Indian Herbal System, all parts of pomegranate including roots, leaves, flowers, rind, seeds and the reddish brown bark are used medicinally. Pomegranate bark and root contains several alkaloids including isopelletierine that fights against tapeworms. Pomegranate bark, leaves, immature fruit and fruit rind extracts is given to combat diarrhoea, dysentery and hemorrhages, whilst powdered flower buds acts as a remedy for nose bleeding.

For bleeding piles: the bark decoction is very effective, and if combined with Holarrhena's bark with a sip of honey it treats blood motions.

For threatened abortion: pomegranate leaves, sandal wood powder, curd and a sip of honey are useful.

For gum bleeding and bleeding of the teeth: the fruit rind powder mixed with black pepper, common salt, and applied. Such preparation whitens teeth, strengthens gum and said to prevent pyorrhea.

For urinary calculus: a teaspoonful of ground seeds along with a cup of gram soup taken internally

For diarrhoea, dysentery, nose bleeding, prolapsed rectum, leucorrhea, etc.: powdered dried rind with fenugreek decoction and a sip of honey are beneficial. The flower bud can also be snuffed in case nose bleeding.

For conjunctivitis: a paste of the leaves is applied on the red part of the eye. This is also beneficial in healing scabies, eczema, itchiness and ringworm.

Other uses: It has immuno-stimulantory, anti-oxidant, anti-inflammatory anti-diabetic and anticancer. It is widely used in treating certain types of cancer including leukemia, breast, prostate and colon cancer, dysentery, diarrhoea, excessive bleeding, intestinal worms and parasites.[3]

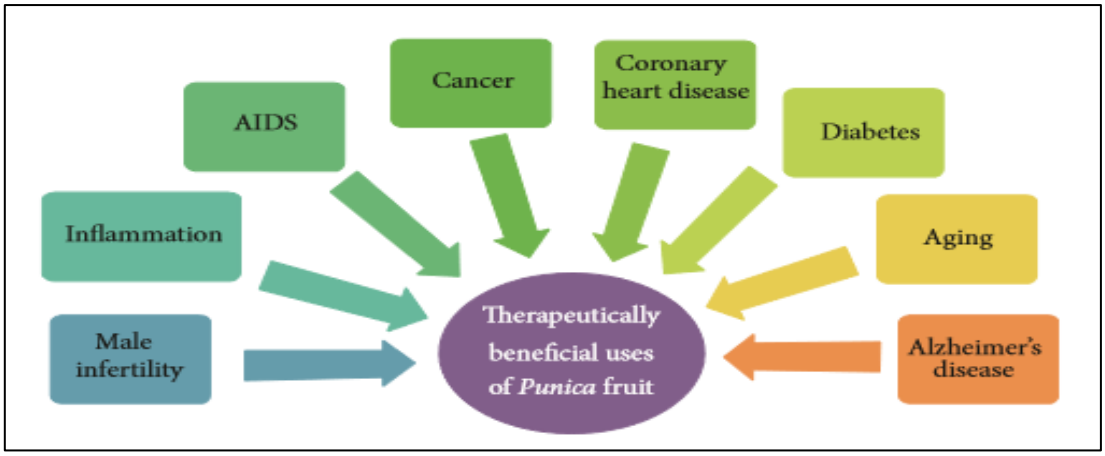

Fig. 1: Therapeutically beneficial uses of pomegranate

Table 2: Various activities of different parts of pomegranate

Part used	Activity
Peels	Antioxidant, nephrotoxicity protection
Peel powder	Hepatoprotective
Peel extract	Anti-diarrheal, antioxidant, anti-diabetic, hypolipidemic
Seed	Antioxidant
Seed extract	Anti-diabetic
Juice	Antioxidant, hormone elevation, enhancement of sperm motility, improvement of erectile dysfunction, oral health management
Juice extract	Cardiovascular complications management
Leaves	Antioxidant, anti-inflammatory, analgesic, anti-diabetic
Leaves extract	Antioxidant, anti-diabetic, hypolipidemic, anti-obesity
Fruit	Anti-inflammatory
Fruit extract	Oral health management, skin health management
Rind	Anti-inflammatory, analgesic
Rind extract	Anti-diabetic
Pomegranate supplementation	Neuro-protective
Pomegranate derived products	Skin health management

Anticancer property of pomegranat

The juice, peel, and seed oil of Pomegranate have been found to have anti-cancer properties that inhibit proliferation, cell cycle, and angiogenesis.[7]

It has been reported that pomegranate fruit, pomegranate juice, seed and seed oil are effective in prostate, breast, skin, colon, lung, oral and leukaemia cancers,[8] due to its antioxidant and antiproliferation (growth inhibition, cell cycle disruption and apoptosis).[8,9]

In a separate study it has been seen that **pomegranate seed oil** incorporated in the diet, markedly reduced the incidence and multiplicity of colonic carcinoma (measured as number of tumours/rat) induced by azoxymethane. In this experiment, pomegranate seed oil was added to AIN-76A diet. Increasing concentration of 0.01%, 0.1% and 1% (w/w), of pomegranate seed oil did not exhibit a dose response effect but anti-carcinogenic effects were observed at all the doses used in the study.[10]

It has also been found that **pomegranate seed oil and fermented juice** polyphenols tend to inhibit breast cancer cell proliferation, invasion, and promotes apoptosis of breast cancer cells[11] Reports on fermented pomegranate juice polyphenols consistently showed twice higher anti-proliferative effect as compared to fresh pomegranate juice polyphenols.[12] Research on lung cancer revealed that PFE (Pomegranate fruit extract) is effective treatment of lung cancer.[13] The results suggested that PFE can be used as a chemo-preventative agent against lung cancer. The effects of **pomegranate oil**, seed oil, fermented juice polyphenols, and pericarp polyphenols on human prostate cancer cell growth in vivo have shown significant antitumour activity against human prostate cancer.[14] Also activity of pomegranate fruit extract showed that cell growth was inhibited and was followed by apoptosis of extremely aggressive human prostate carcinoma PC-3 cells.

The **fermented pomegranate juice** polyphenols were also tested in combination

with pericarp polyphenols on the proliferation of DU 145 human prostate cancer cell lines in vitro. Supra-additive and synergistic effects were experimentally proven.[15] These studies provide evidence, suggesting that consuming pomegranate may delay prostate cancer progression.[16]

Prevention of skin cancer

There is an urgent need to develop mechanism-based approaches for the prevention/therapy of lethal skin cancer (non-melanoma). Skin is the organ most accessible to sunlight, and directly suffers from the deleterious effects of ultraviolet (UV)1 radiation, that is known to accelerate aging changes, causing fine and coarse wrinkling, rough skin texture, dryness, telangiectasia and dyspigmentation, resulting in skin cell DNA damage.[17] The increase in incidences of skin cancer is due to constant exposure of skin to environmental carcinogens, such as chemical agents and ultraviolet radiation, provides a strong basis for chemoprevention.[18] There is a considerable attention on the use of naturally occurring botanicals for their potential preventive effect against UV-mediated damages referred to as photochemopreventive effects.[19] In general, skin carcinogenesis, being a stepwise process of all three distinct stages, is an effective model for cancer chemoprevention.[20]

Pomegranate seed oil (PSO) was investigated for anticancer activity and the results stated that PSO appears to be a natural product with potential as a topical chemopreventive agent against skin cancer, through inhibition of PG biosynthesis and ornithine decarboxylase. PSO treatment did not delay the appearance of tumours, but significantly decreased the rate of tumour development, skin tumour multiplicity, and ornithine decarboxylase activity during 20 weeks of promotion. They stated that PSO, being rich in punicic acid, has inhibitory effect on PG biosynthesis, as well as inhibiting upstream eicosanoid enzyme, phospholipase A2.[21]

The chemopreventive efficacy of **pomegranate fruit extract (PFE)** and diallyl sulfide (DAS) was examined, alone and in combination, using 2-stage mouse skin tumourigenesis model. PFE alone delayed onset and tumour incidence by 55%, while in PFE+DAS combination at low doses synergistically decreased tumour incidence more potentially (84%). In addition, regression in tumour volume was seen with continuous combinatorial treatment ($p < 0.01$). Mechanistic studies revealed that this inhibition was associated with decreased expression of phosphorylated ERK1/2, JNK1 and activated NFκB/p65, IKKα, IκBα phosphorylation and degradation in skin tissue/tumour. Histological and cell death analysis also confirmed that combined PFE and DAS inhibit cellular proliferation and markedly induce apoptosis than the single agents.[22]

Prevention of prostate cancer

Prostate cancer is the second-leading cause of cancer-related deaths in men in the world. In vitro studies stated several pomegranate products inhibit prostate cancer cell growth, induce apoptosis of several prostate cancer cell lines, suppress invasive potential of PC-3 cells, and decrease proliferation of DU-145 prostate cancer cells.[23, 24]

It was seen that **pomegranate seed oil (PSO)** as well as polyphenols present in the pericarp and fermented juice suppress proliferation and invasion of several human prostate cancer cells, LNCaP, PC-3 and DU-145 across the matrigel matrix. Supraadditive, complementary and synergistic effects were proven in all models.[25]

It was also found that equally combined amounts of **pomegranate fermented juice, pomegranate pulp juice and cold-pressed pomegranate seed oil extracts** resulted in a 99% suppression of DU-145 prostate cancer cell invasion across a matrigel matrix. Ellagic acid, caffeic acid, luteolin and punicic acid, important components of pomegranate significantly inhibited in vitro invasion of human PC-3 prostate cancer cells when employed individually.[26]

It was seen that **pomegranate fruit extract** exhibited significant antiproliferative and pro-apoptotic activity against highly aggressive human PC-3 cells. The cell growth inhibition was dose-dependent, and alterations were in the regulatory molecules responsible in the G1 phase of the cell cycle. Another molecular mechanism through which pomegranate fruit extract is capable of inducing apoptosis in prostate cancer cells may be up-regulation of Bax and down-modulation of Bcl-2. PFE intake was observed to significantly slow the progression of tumour growth in athymic nude mice implanted with androgen-responsive CWR22R-1 cells. Importantly, this tumour growth inhibition followed a significant decrease in the serum levels of prostate specific antigen (PSA).[27]

Prostate cancer is dependent on circulating testosterone in its early stages and is treatable with surgery, radiation therapy, stereotactic radiosurgery, and proton therapy. Both

androgen and androgen receptor (AR) are recognized risk factors in the development of prostate cancer.[28] Reduction of circulating levels of androgens and suppression of AR are crucial for the treatment of prostate cancer as an elevated level of androgen causes enhancement of prostate cancer.[29] Pomegranate extracts has been shown to inhibit both androgen-dependent and androgen-independent prostate cancer cell growth. Since androgen and AR play central roles throughout prostate cancer development. The effects of pomegranate polyphenols, ellagitannin-rich extract and whole juice extract were examined on the expression of genes for key androgen-synthesizing enzymes [HSD3B2 (3β-hydroxysteroid dehydrogenase type 2), AKR1C3 (aldo-keto reductase family 1 member C3) and SRD5A1 (steroid 5α reductase type 1)] and AR in LNCaP, LNCaP–AR and DU-145 human prostate cancer cells. Pomegranate polyphenols inhibited gene expression and AR most consistently in the LNCaP–AR cell line. Therefore, inhibition by pomegranate polyphenols of gene expression involved in androgen synthesizing enzymes and the AR may be of particular importance in androgen independent prostate cancer cells and the subset of human prostate cancers where AR is upregulated.[30]

Prevention of breast cancer

Along with enthusiastic efforts in early diagnosis, aggressive surgical treatment and application of additional non-operative modalities, the prognosis of breast cancer is still chaotic. The antiangiogenic potential of pomegranate was evaluated where VEGF, interleukin-4 and migration inhibitory factor (MIF) were measured. Polyphenols from fermented pomegranate juice, pericarp and oil were shown to inhibit endogenous active estrogen biosynthesis with subsequent inhibition of aromatase activity. VEGF was strongly down regulated and MIF up regulated, representing a marked potential for down regulation of angiogenesis by pomegranate fractions.[31]

The effects of extracted polyphenols from **pomegranate fermented juice**, were examined, using the mouse mammary organ culture, an animal model of breast cancer having >75% accuracy to predict in vivo carcinogenesis. They showed that the purified chromatographic peak of pomegranate fermented juice polyphenols and pomegranate seed oil possesses greater chemopreventive potential. While fermented juice polyphenols effected a 42% reduction in the number of DMBA-induced cancerous lesions compared with control, purified compound, peak B, and pomegranate seed oil each effected an 87% reduction. Peak B is believed to be a phenolic compound with potent chemopreventative properties.[32] Combination treatment of MCF-7 breast cancer cells with both pomegranate extracts and genistein was found to be more effective on inhibition and cytotoxicity than with single treatments.[33]

Pomegranate seed linolenic acid isomers were evaluated as selective estrogen receptor modulators (SERMs) in vitro. Punicic acid and α-eleostearic acid present in seed oil of pomegranate inhibited the IC_{50} estrogen receptors ERα and ERβ depending on the dose. At lower doses of punicic acid acted as agonist for both receptors and antagonist at higher concentrations. Both acids were effective in producing effective inhibition of cancer cell proliferation: MCF-7 (ER-positive human breast cancer cells) and MDA-MB-231 (ER negative human breast cancer cells) and are SERMs.[34]

Prevention of colon cancer

Current treatment options in colorectal cancer such as surgical intervention and adjuvant chemotherapy have several limitations in counteracting the disease. Furthermore, at advanced stages the patients might be unresponsive to any form of treatment. In this regard, an optimal model for primary and secondary prevention in colon cancer, given the availability of effective screening procedures and a well-defined multi-step carcinogenic pathway, can be thought as the development of new cancer chemopreventive agents that could be employed to inhibit tumour development without causing systemic toxicity such as increasing the consumption of food containing anticarcinogenic compounds. Phytochemicals from pomegranate have been shown to inhibit colon cancer cell proliferation and apoptosis through the modulation of cellular transcription factors and signaling proteins.[35]

There is considerable evidence that the anticarcinogenic effect of **pomegranate ellagitannins** is mainly due to ellagic acid, which induces apoptosis in human colon cancer cell line via the intrinsic pathway with release of cytochrome c into the cytosol, activation of initiator caspase 9 and effector caspase 3 and down-regulation of B-cell lymphoma-extralarge (BclXL). In addition, pomegranate treated Caco-2 cells showed arrest in the S phase of the cell cycle, down-regulation of cyclins A and B1 and upregulation of cyclin E.[36]

The effects of **pomegranate juice** were examined on inflammatory cell signaling proteins in the HT-29 human colon cancer cell line. In HT-29 colon cancer cells, at a concentration of 50 mg/L pomegranate juice significantly suppressed TNFα-induced COX-2 protein expression by 79%, total pomegranate tannin extract (TPT, 55%), and punicalagin 48% Cyclooxygenase-2 (COX-2) expression is increased via activation of nuclear factor kappa-B (NFKB) by tumour necrosis factorα (TNF-Ot), an inflammatory cell signaling process that may be a cause of cancer initiation and progression.[37]
Additionally, **pomegranate juice** reduced phosphorylation of the p65 subunit and binding to the NFKB response element 6.4-fold. TPT suppressed NFK binding 10-fold, whereas punicalagin 3.6-fold. It was shown that inflammatory enzymes in colon cancer cells were inhibited by the pomegranate juice components. Ellagic acid, punicalagin and TPT failed to induce apoptosis in HT-29 and HCT-116 cells when treated at doses equivalent to found in pomegranate juice. They were only effective when treated at equivalent doses of 100 µg/mL.[38]

CONCLUSION

Punica granatum along with its other preventive activities has also shown prevention for four major cancers namely skin cancer, prostate cancer, breast cancer and colon cancer due to the various chemical constituents present in it. Future studies can be performed for the prevention of other cancers and can help in the betterment of the people.

REFERENCES

1. http://en.wikipedia.org/wiki/Pomegranate. [Accessed September 25, 2007]
2. Miguel M, Neves M, Antunes M (2010) Pomegranate (*Punica granatum* L.): a medicinal plant with myriad biological properties—a short review. J Med Pl Res 4:2836–2847.
3. https://nutritiondata.self.com. [Accessed September 25, 2007]
4. http://www.crfg.org/pubs/ff/pomegranate.html. [Accessed September 25, 2007]
5. Fadavi A, Barzegar M, Azizi M, Bayat M (2005) Physicochemical composition of ten pomegranate cultivars (*Punica granatum* L.) grown in Iran. Food Sci Tech Int. 11:113–119.
6. Harborne S, Baxter H (1995) Phytochemical Dictionary A Handbook of Bioactive Compounds from Plants. Taylor and Francis, London.
7. Lansky E, Newman R (2007) *Punica granatum* (pomegranate) and its potential for prevention and treatment of inflammation and cancer. J Ethnopharmacology 109:177-206.
8. Amin A, Kucuk O, Khuri F, Shin D (2009) Perspectives for cancer prevention with natural compounds. J Clin Oncol 27:2712-2725.
9. Adhami V, Khan N, Mukhtar H (2009) Cancer chemoprevention by pomegranate: Laboratory and clinical evidence. Nutr. Cancer 6:811-815.
10. Kohno H, Suzuki R, Yasui Y, Hosokawa M, Miyashita K, Tanaka T (2004) Pomegranate seed oil rich in conjugated linolenic acid suppresses chemically induced colon carcinogenesis in rats. Cancer Sci 95:481-486.
11. Toi M, Bando H, Ramachandran C, Melnik SJ, Imai A, Fife RS, Carr RE, Oikawa T, Lansky EP (2003) Preliminary studies on the anti-angiogenic potential of pomegranate fractions *in vitro* and *in vivo*. Angiogenesis 6:121-128.
12. Kim N, Mehta R, W Yu, I Neeman, T Livney, A Amichay, D Poirier, P Nicholls, A Kirby, W Jiang, R Mansel, C Ramachandran, T Rabi, B Kaplan, E Lansky (2002) Chemopreventive and adjuvant therapeutic potential of pomegranate (*Punica granatum*) for human breast cancer. Breast Cancer Res and Treatment 71:203-17.
13. Khan N, Handi N, Afaq F, Syed DN, Kweon MH, Mukhtar H (2007) Pomegranate fruit extracts inhibits prosurvival pathways in human A549 lung carcinoma cells and tumour growth in athymic nude mice. Carcinogenesis 28:163-173.
14. Albrecht M, Jiang W, Kumi-Diaka J, Lansky EP, Gommersall LM, Patel A, Mansel RE, Neeman I, Geldof AA, Campbell MJ (2004) Pomegranate extracts potently suppress proliferation, xenograft growth, and invasion of human prostate cancer cells. J Med Food 7:274-283.
15. Lansky EP, Jiang W, Mo H, Bravo L, Froom P, Yu W, Harris NM, Neeman I, Campbell MJ (2005) Possible synergistic prostate cancer suppression by anatomically discrete pomegranate fractions. Invest New Drugs 23:11-20.

16. Malik A. and Mukhtar H (2006) Prostate cancer prevention through pomegranate fruit. Cell Cycle 5:371-3.
17. Afaq F (2011) Natural Agents: Cellular and Molecular Mechanisms of Photoprotection. Arch Biochem Biophys, 508:144-151.
18. Gupta S, Mukhtar H (2002) Chemoprevention of Skin Cancer: Current Status and Future Prospects. Cancer Metastasis Rev 21:363-380.
19. Afaq F, Saleem M, Krueger CG, Reed JD, Mukhtar H (2005) Anthocyanin- and Hydrolyzable Tannin-rich Pomegranate Fruit Extract Modulates MAPK and NFkappaB Pathways and Inhibits Skin Tumourigenesis in CD-1 mice. Int J Cancer 113:423-333.
20. Richmond E, Viner JL (2003) Chemoprevention of Skin Cancer. Seminars in Oncology Nursing 19:62-69.
21. Hora JJ, Maydew ER, Lansky EP, Dwivedi C (2003) Chemopreventive Effects of Pomegranate Seed Oil on Skin Tumour Development in CD1 Mice. J Med Food 6:157-161.
22. George J, Singh M, Srivastava AK, Bhui K, Shukla Y (2011) Synergistic Growth Inhibition of Mouse Skin Tumours by Pomegranate Fruit Extract and Diallyl Sulfide: Evidence for Inhibition of Activated MAPKs/NF-κB and Reduced Cell Proliferation. Food Chem Toxicology 49:1511-1520.
23. Lansky EP, Harrison G, Froom P, Jiang WG (2005) Pomegranate (Punica granatum) Pure Chemicals Show Possible Synergistic Inhibition of Human PC-3 Prostate Cancer Cell Invasion Across Matrigel. Investigational New Drugs 23:121-122.
24. Pantuck AJ, Leppert JT, Zomorodian N, Aronson W, Hong J, Barnard RJ, Seeram N, Liker H, Wang H, Elashoff R, Heber D, Aviram M, Ignarro L, Belldegrun, A (2006) Phase II Study of Pomegranate Juice for Men with Rising Prostate-specific Antigen following Surgery or Radiation for Prostate Cancer. Clin Cancer Res 12:4018-4026.
25. Albrecht M, Jiang W, Kumi-Diaka J, Lansky EP, Gommersall LM, Patel A, Mansel RE, Neeman I, Geldof AA & Campbell MJ (2004) Pomegranate Extracts Potently Suppress Proliferation, Xenograft Growth, and Invasion of Human Prostate Cancer Cells. J Med Food 7:274-283.
26. Lansky EP, Jiang W, Mo H, Bravo L, Froom P, Yu W, Harris NM, Neeman I, Campbell MJ (2005) Possible Synergistic Prostate Cancer Suppression by Anatomically Discrete Pomegranate Fractions. Investigational New Drugs 23:11-20.
27. Malik A, Afaq F, Sarfaraz S, Adhami VM, Sved DN, Mukhtar H (2005) Pomegranate Fruit Juice for Chemoprevention and Chemotherapy of Prostate Cancer. Proceedings Nat Academy Sci USA 102:14813-14818.
28. Heinlein CA, Chang C (2004) Androgen Receptor in Prostate Cancer. Endocrine Rev 25:276-308.
29. Attard G, Sarker D, Reid A, Molife R, Parker C, de Bono JS (2006) Improving the Outcome of Patients with Castration-resistant Prostate Cancer through Rational Drug Development. Brit J Cancer 95:767-774.
30. Hong MY, Seeram NP, Heber D (2008) Pomegranate Polyphenols Down-regulate Expression of Androgen-synthesizing Genes in Human Prostate Cancer Cells over Expressing the Androgen Receptor. J Nutri Biochem 19:848-855.
31. Toi M, Bando H, Ramachandran C, Melnick SJ, Imai A, Fife RS, Carr RE, Oikawa T, Lansky EP (2003) Preliminary Studies on the Anti-angiogenic Potential of Pomegranate Fractions in vitro and in vivo. Angiogenesis 6:121-128.
32. Mehta R, Lansky EP (2004) Breast Cancer Chemopreventive Properties of Pomegranate (*Punica granatum*) Fruit Extracts in a Mouse Mammary Organ Culture. Euro J Cancer Prevention 13:345-355.
33. Jeune MA, Kumi-Diaka J, Brown J (2005) Anticancer Activities of Pomegranate Extracts and Genistein in Human Breast Cancer Cells. J Med Food 8:469-475.
34. Tran HNA, Bae SY, Song BH, Lee BH, Bae YS, Kim YH, Lansky EP, Newman RA (2010) Pomegranate (*Punica granatum*) Seed Linolenic Acid Isomers: Concentration-dependent Modulation of Estrogen Receptor Activity. Endocrine Res 35:1-16.
35. Mertens-Talcott SU, Percival SS (2005) Ellagic Acid and Quercetin Interact Synergistically with

Resveratrol in the Induction of Apoptosis and Cause Transient Cell Cycle Arrest in Human Leukemia Cells. Cancer Letters 218:14151.

36. Larrosa M, Tomas-Barberan FA, Espin JC (2006) The Dietary Hydrolysable Tanin Punicalagin Releases Ellagic Acid that Induces Apoptosis in Human Colon Adenocarcinoma Caco-2 cells by Using the Mitochondrial Pathway. J Nutri Biochem, 17:611-625.
37. Adams LS, Seeram NP, Aggarwal BB, Takada Y, Sand D, Heber D (2006) Pomegranate Juice, Total Pomegranate Ellagitannins, and Punicalagin Suppress Inflammatory Cell signaling in Colon Cancer Cells. J Agri Food Chem 54:980-985.
38. Seeram NP, Adams LS, Henning SM, Niu Y, Zhang Y, Nair MG, Heber D (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. J Nutri Biochem 16:360-367.
39.