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Pomegranate (*Punica granatum*) derived phytochemical actions towards prostate cancer

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ABSTRACT

Punica granatum, also known as pomegranate, is a super fruit. Prostate cancer is the most common cancer among men with 30,000 reported deaths. Due to the detrimental effects of aggressive treatment regimens, research on finding natural cancer therapeutics has been ongoing for the past decades. This is intended to repurpose plant-based therapeutics in conjunction with the existing treatment with the hope of reducing the need for synthetic medications. This review provided an overview of the evidence on the promising chemopreventive effects of phenolic compounds derived from pomegranate and their action to inhibit, arrest or reverse the progression of prostate cancer through analyzing findings from *in vitro*, *in vivo*, and clinical studies. The major beneficial phenolic constituents of pomegranate are punicalagin, ellagic acid, and gallic acid. *In vitro* studies have shown the reduction of prostate cancer cell growth along with increased apoptosis-inducing proteins. Clinical trials among patients intervened with pomegranate extracts showed lowered oxidative stress tissue biomarker. Further studies should include pharmacological studies with prolonged and larger clinical trials to fully identify the extent of pomegranate as a cancer intervention.

Keywords: chemopreventive agent; pomegranate; prostate cancer; polyphenols; phytochemical

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1. INTRODUCTION

Cancer, among other diseases, is the predominant cause of death and reduction of life expectancy among patients around the world. Prostate cancer affected around 1.3 million men worldwide and killed almost 359,000 patients in 2018. Cancer is the second disease that caused death among males in North America despite aggressive treatment regimens such as radiotherapy, surgery, and chemotherapy (Jaglanian et al., 2020). Androgen deprivation therapy (ADT) has been highly successful in treating advanced and metastatic cases of prostate cancer. However, it is also associated with serious complications such as lower libido, impotence, fatigue, osteoporosis, hot flushes, and muscle mass loss (Chi et al., 2020). These adverse side effects may affect the quality of life among prostate cancer patients. Decreasing the use of synthetic drugs for cancer treatment can positively impact patient outcomes, therefore, research on cancer therapeutics derived from natural sources has been ongoing for these past decades. However, the challenge arises in finding the right plant materials or compounds that can target specific cancer mechanisms to stop its proliferation, growth, and metastasis.

Around 3000 plant species have shown their potential to be utilized in cancer treatment, and scientists around the world are becoming more interested in gathering its evidence (Kuruppu et al., 2019). For instance, *Camellia sinensis* has shown a positive relationship in decreasing the risk of breast cancer by 15% (Gianfredi et al., 2018). Besides, pomegranate, which is grown all over Asia, is one of the most researched plants for its chemopreventive properties.

Ellagitannins, gallotannins, ellagic acid and flavonoids, including kaempferol and luteolin glycosides, are present in pomegranate contributing to their potent antioxidant activity (Mahesar et al., 2019). Phenolic compounds and their derivatives found in pomegranate were discovered to be able to inhibit the final step of both metastasis and tumorigenesis in various cancers (Panth et al., 2017). The purpose of this review is to present various study designs used to investigate and explore the chemopreventive mechanism of pomegranate toward prostate cancer and discuss several further improvements that can be made to improve its potential.

2. BOTANY OF POMEGRANATE

Two species of pomegranate namely *Punica granatu* and *Punica protopunica* come from the *Punicaceae* family. Previously, it was called "pomuni granatum" in which *pomum* is apple and *granatus* is grainy, and it is also called "seeded apple" (Kushwaha et al., 2020). According to Greek mythology, Proserpina (Persephone) believed pomegranate was once thought to be a symbol of revival, beauty, abundance, harmony, and many more (Gumus et al., 2020). It is grown largely in Mediterranean countries but also tropical and subtropical regions around the world (Uzuner, 2020). The largest supplier of pomegranate is India followed by Iran (Patel et al., 2018). Parts of pomegranate including the roots, bark, leaves, flowers, rinds (peels), and seeds have been reported to have medicinal purposes for thousands of years due to their rich beneficial chemical compositions (Venkitasamy et al., 2019). There are several health-related benefits of pomegranate including the ability to reduce inflammation, antihypertensive, and anti-diabetic (Kandylis and Kokkinomagoulos, 2020). The fruit part of the pomegranate is edible. Figure 1 shows the part of pomegranate consisting of aril, seed, albedo, and rind (peel). The pomegranate tree is small, ranging from 5 to 10 meters in height (Pande and Akoh, 2016).

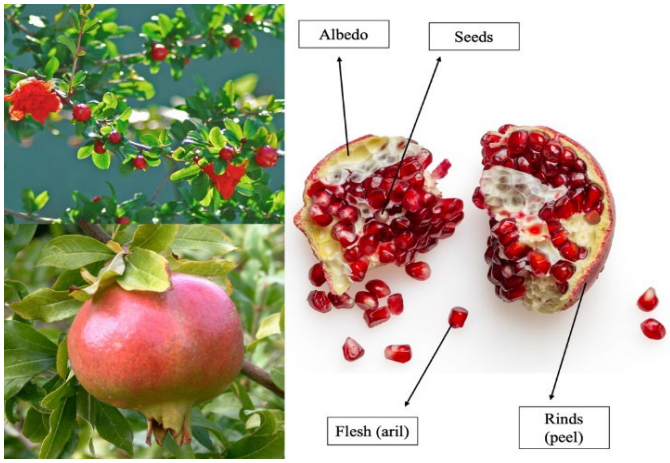


Figure 1. Parts of pomegranate

3. PHYTOCHEMISTRY OF POMEGRANATE

Pomegranate contains phytochemical compounds (Figure 2), which are the non-nutritive part of plants that were believed to have protective and disease-preventing properties towards the plant itself (Arendt and Zannini, 2013). On the other hand, phenolic compounds are powerful antioxidants that are classified as flavonoids and non-flavonoids found as secondary metabolites in plants (Gupta et al., 2020). These metabolites are produced when plants undergo physiological changes in response to environmental stress, which stabilizes their growth and increases their survival rate (Ashraf et al., 2018). Phenolic compounds are more than just an antioxidant. Due to variations in environmental stress, phenolic compounds are also associated with the ability to exhibit anti-inflammatory, anti-cancer, anti-allergic, anti-viral, anti-thrombotic, and anti-bacterial effects, as well as their application as a food additive (Kumar et al., 2019). Furthermore, the concentrations may be altered due to the environmental stress that the plant is exposed to. For example, the total phenolic compounds in the pomegranate peels collected from Southern Arava was higher, compared to the peel collected from Newe Ya'ar. The reason is due to the variation of temperature and radiation of the location where the tree was grown. Besides, higher production of punicalagin content is also observed in response to the higher level of temperature and radiation in the southern Arava region (Schwartz et al., 2009).

Gallic acid, ellagic acid and punicalagin

Gallic acid is a tri-phenolic acid that is found largely in plants. It has a low molecular weight and exists freely or is found as part of tannins (Al Zahrani et al., 2020). In contrast, punicalagin (α and β) has a high molecular weight and is a form of hydrolyzable tannin (Rongai et al., 2019). Punicalagin is largely found in pomegranate and berries. Pomegranate peel is usually high in punicalagin while its seed oil is high in punicic acid, which both are associated with its health benefits (Görgüç et al., 2022). Moreover, it is in agreement that 98% of phenolic acid found in pomegranate peel is punicalagin (El-Hadary and Ramadan, 2019). On the other hand, ellagic acid is a derivative of gallic acid that comes from the family of hydrolyzable ellagitannins. The chemical structure of ellagic acid, which comprises of four hydroxyl groups (Table 1), enables it to scavenge a huge amount of reactive oxygen species (ROS)

and nitrogen species (Bai et al., 2021). However, these compounds are not directly absorbed by the stomach but it is broken down by gut microbiota and turned into gut metabolites, which are then absorbed into the bloodstream.

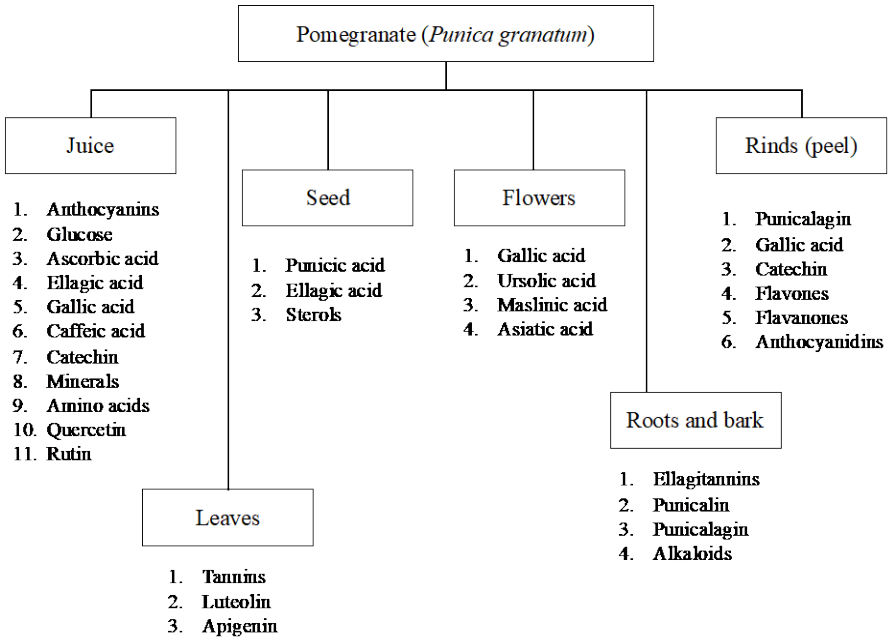
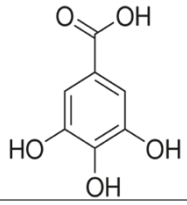
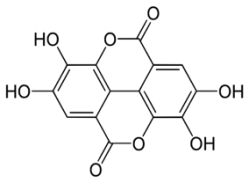
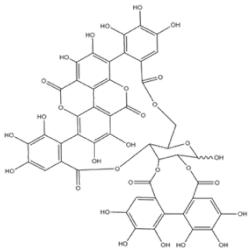


Figure 2. Chemical compositions of pomegranate (modified from Venkitasamy et al., 2019)

Table 1. Major phenolic compounds discussed for their chemopreventive activity toward prostate cancer

Compound	Chemical class	References
Gallic acid 	Phenolic acid	(Chaves et al., 2020; Fan et al., 2020; Ma et al., 2015)
Ellagic acid 	Hydrolysable tannin	(Chaves et al., 2020; Ma et al., 2015; Mohammed Saleem and Selim, 2020)
Punicalagin 	Ellagitannin	(Adaramoye et al., 2017; Chaves et al., 2020; Ma et al., 2015)

Urolithins

Urolithins are the main metabolism product of punicalagin and ellagic acid (Les et al., 2018). Once they enter the large intestines, microbial inhabitants perform biochemical processes such as hydrolysis, cleavage, and reduction that convert phenolic compounds to metabolite derivatives with increased bioavailability, compared to their original form (Al-Harbi et al., 2021; Espín et al., 2017). Bacterial inhabitants of *Gordonibacter urolithinfaciens* and *Gordonibacter pamelaeae* are reported to use catechol dehydroxylase to convert phenolic compounds to urolithins (García-Villalba et al., 2020). Urolithins are then divided into two major types of urolithin A and urolithin B that exist freely in the tissues and blood circulation after being absorbed by the stomach (Abdulrahman et al., 2020). Furthermore, these compounds are usually used in monitoring the treatment compliance of patients in clinical trials as it can be detected and quantified from the urine and blood samples. A metabolic profile of urolithins in the colorectal cancer tissues revealed a significant level of urolithins after the consumption of punicalagin derived from pomegranates (NuÒez-S·nchez et al., 2014). However, there is no studies reported on the physiology of urolithins in human prostate cancer tissues.

4. STUDIES ON PROSTATE CANCER

Prostate cancer is the third most prevalent cancer among men (Giona, 2021). The activation of androgen receptors by testosterone and dihydrotestosterone plays a crucial part in carcinogenesis; ADT has been successful in reducing its occurrence (Alukal and Lepor, 2016). Prostate cancer cells are highly sensitive to androgens that depend on the hypothalamus-pituitary-gonadal signalling pathway (Hu et al., 2020). ADT is often used in advanced, progressive and relapse cases of prostate cancer, which is performed by surgery or chemical castration (Shore et al., 2020). Although ADT has been shown to reduce disease progression and symptoms, as well as increase survival rates, it is also linked to several secondary side effects, including an increased risk of developing cardiovascular diseases, diabetes, and impairment of cognitive functions (Shore et al., 2020). Plant-derived compounds are generally considered safe to be consumed. Thus, redirecting our focus on potential cancer therapeutics from plants could be a safer route for patients.

In vitro studies

In vitro study design is one of the preclinical study designs and is carried out in a laboratory setting to obtain preliminary evidence and data on the theoretical hypothesis. It is found that pomegranate extracts can inhibit cell migration. This is a crucial step of metastasis as the cancer cells move from the primary tumor and are dispersed to other organs through the bloodstream (Pijuan et al., 2019). Chaves et al. (2020) revealed that aqueous preparation of pomegranate juice and peel extracts can suppress cell migration at different concentrations of peel and juice extracts (23.9-136.3 μg/mL) for 24 and 48 h. Shortly after the cell proliferation assay was performed, it was found that the extracts exert anti-proliferative activity by modulating the metalloproteinases (MMP) gene expression impairment along with the downregulation of the mTOR/S6K pathway (Chaves et al., 2020). The major role of MMP in cell differentiation is cell invasion and angiogenesis, in which downregulating its expression may suppress new cell formation (Alaseem et al., 2019). Interestingly, seed oil extract of pomegranate has a significant anti-proliferative effect, compared to the juice and peel extract. It was observed that treatment with 0.25 mg/mL of the seed oil extract inhibits 80% of the DU-145 cell population after 48 h of exposure (Amri et al., 2020). On the other hand, the androgen castration-resistant variant of prostate cancer cells (C4-2B) is inhibited by 40% after the treatment with urolithin A (IC_{50} = 35 μM) (Dahiya et al., 2018).

Apoptosis is one of the chemopreventive mechanisms exerted by pomegranate toward prostate cancer cells. The same mechanism is also exerted by synthetic drugs, such as cisplatin, camptothecin, and oxaliplatin, but it also affects other healthy fast-growing cells (Jan and Chaudhry, 2019). Gallic acid extracted from pomegranate also induces apoptosis after exposing to a PC-3 cell line at different concentrations (5.0, 10.0, and 20.0 μmol/L). In the same study, the investigators quantified the level of proteins that influence the apoptosis rate for the cells and revealed the reduction of Akt and mTOR proteins, compared to an increased level of IGFBP7 (Fan et al., 2020). A study shows that ellagic acid could significantly stimulate apoptosis in PC-3 cells, compared to 22RV1 and androgen-sensitive-prostate-adenocarcinoma-cells (LNCaP) cells, however, the levels of p53 pro-apoptotic proteins are elevated in all three cancer cell lines (Mohammed Saleem and Selim, 2020). Finally, a high concentration of punicalagin (50 and 100 μM) from pomegranate can cause cell death in both PC-3 and LNCaP due to the increased expressions of caspase-3 and caspase-8, however, not in the normal BPH-1 cells (Adaramoye et al., 2017). Caspase-3 and 8 are proteins that interacts with each other and have been linked to apoptosis (Esteban-Fernández de Ávila et al., 2017; Fritsch et al., 2019) .

In vivo studies

Pomegranate extracts also show promising results in animal studies or *in vivo* studies, as shown in Table 2. A xenograft model (BALB/cA-nu) of nude mice model bearing PC-3 prostate cancer cell tumor supplemented with pomegranate extract showed a significant reduction of tumor weight and volume, which is associated with increased expression of TNF-α (Ma et al., 2015). This cytokine has been positively associated with its anti-tumor activity toward cancer cells that may induce blood vessel destruction and cell death (Josephs et al., 2018). On the other hand, angiogenesis is a crucial part of cancer metastasis whereby the formation of new blood vessels emerge from their original vasculature in response to tissue metabolism that requires nutrients and oxygen (Zuazo-Gaztelu and Casanovas, 2018). Treatment of punicalagin synthesized from pomegranate to chorioallantoic membrane model (CAM) was able to disrupt blood vessel vasculature and perfusion after 48 h of incubation (Adaramoye et al., 2017).

Table 2. Chemopreventive potential of pomegranates toward prostate cancer in preclinical studies

Extract/derivative used	Study design	Mechanism of action	References
Gallic acid	*In vitro*	Cell proliferation was suppressed by the increased IGFBP7 protein expression and AKT/mTOR pathway inhibition	(Fan et al., 2020)
Pomegranate juice and peel extracts	*In vitro*	Cells colony formation was suppressed. MMP and Akt/mTOR/S6k expression was inhibited	(Chaves et al., 2020)
Pomegranate peel extract	*In vivo*	Significant reduction of PC-3 tumor weight and upregulation of TNF-α expression	(Ma et al., 2015)
Ellagic acid	*In vitro*	Stimulated the production of pro-apoptotic proteins (PUMA and NOXA0) and downregulates the P53/MDM2 pathway	(Mohammed Saleem and Selim, 2020)
Urolithin A	*In vitro* *In vivo*	Apoptosis was induced by the upregulation of caspase-3 and PARP-1 apoptotic proteins expression Significant reduction of tumor growth by the inhibition of Ar/pAKT expression	(Dahiya et al., 2018)
Punicalagin	*In vitro* *In vivo*	Apoptosis was stimulated in cancerous cells (PC-3 and LNCaP) by the upregulation of caspase-3 and caspase-8 expression Significant decrease of blood perfusion in blood vessel vasculature	(Adaramoye et al., 2017)
Juice, seed oil and peel extract of ornamental pomegranates	*In vitro*	Apoptosis was induced by all extracts with the reduction of COX-2 expression	(Amri et al., 2020)
Pomegranate fruit extract	*In vivo*	Extract was able to inhibit and reduce tumor growth in transgenic mouse models (TRAMP)	(Adhami et al., 2012)

The chemopreventive activity is demonstrated by a study that uses transgenic mice models. As the mice grow with the altered DNA, it is preferable to be used for monitoring tumor progression since there is no interference with the microenvironment, thus making it far more suitable for preventive studies. An older study revealed a significant reduction in tumor weight as the mice were fed with two doses of pomegranate extract, which is equivalent to about 250 mL and 500 mL of pomegranate juice (Adhami et al., 2012). Further analysis revealed the inhibition of PI3K/Akt/mTOR and IGF-1/IGFBP-3 ratio, which was similar to the *in vitro* studies mentioned. This may suggest a common mechanism of chemopreventive activity induced by pomegranate and its derivatives.

Clinical trials

Clinical trials are carried out among participants in a study design that subjects to interventions and placebo or other controls. It is also the gold standard to make sure that the evidence generated is reliable for a larger population (Demiris et al., 2019). Pomegranate, among curcumin and other natural interventions, has been extensively used as an intervention in human trials towards many diseases. The four clinical trials that used similar interventions are tabulated in Table 3. To summarize, the study by Jarrard et al. (2021) revealed the reduction of tissue biomarker 8-hydroxy-deoxyguanosine (8-OHdG) and the expression of androgen receptor in the pomegranate extract-treated group. The 8-OHdG is a tissue oxidative biomarker for DNA damage, which interprets as the measurement of oxidative stress. Similarly, Freedland et al. (2013) also reported a 16% reduction in 8-OHdG level although the data were not statistically significant. Both studies could not be directly compared, due to the differences in the study design and subjects. Jarrad's subjects were patients with low-grade prostate cancer, but Freeland's patients were diagnosed with prostate adenocarcinoma. Clinically, the level of 8-OHdG is significantly higher in prostate cancer tissue than those in benign prostatic hyperplasia (Ohtake et al., 2018). The reduction of this biomarker may be interpreted as the reduction of inflammation in the tissue, which is crucial to stopping the progression of cancer. Besides, there is a strong relationship between patients with a history of prostate inflammation that have progressed to prostate cancer in the general population (Cai et al., 2019).

Additional two studies were focused on prostate-specific antigen (PSA) doubling time or PSDAT, which is defined as the time, in terms of months, taken for the PSA level to increase two-fold (Vickers and Brewster, 2012). PSADT level is also used to indicate tumor activity and the degree of prognosis among patients (Zharinov et al., 2017). A significant result of PSADT elongation was reported by Paller et al. (2013) whereby the PSADT level in the treatment group was extended up to six months. Although the finding sounds promising, the researchers did not implement a placebo-control group in the study design. On the other hand, an updated trial by Pantuck et al. (2015) reported an increase in the PSADT, although no statistically significant was achieved. In addition, preliminary genotyping studies of manganese superoxide dismutase (MnSOD) on 34 subjects revealed that the PSADT level is increased for the extract (13.6 months to 25.6 months), which was greater than in the non-MnSOD group. MnSOD exists in the mitochondria and it converts DNA damage caused by ROS to oxygen and hydrogen peroxide (Iguchi et al., 2015). Pantuck et al. (2015) hypothesized the correlation between this subpopulation that is much more susceptible to a high antioxidant diet, which may explain the prolongation of PSADT. Due to the absolute metabolism of phenolic compounds to gut metabolites, treatment

compliance of supplemented polyphenols was screened using urinary metabolites (urolithin A) in all clinical trials except the report by Freedland et al. (2013), which used tissue urolithin levels to monitor the level of the metabolites. It means that the subjects comply with the intervention given (Jin et al., 2008). The side effects reported by Paller et al. (2013) and Pantuck et al. (2015) were largely associated with gastrointestinal issues, such as bloating, acid reflux, loss of appetite, and constipation.

Table 3. Chemopreventive potential of pomegranate towards prostate cancer in clinical trials

Intervention design	Subjects	Assessment	References
Daily consumption of POMx for 52 weeks	Men diagnosed with low grade prostate cancer	Evaluate serum level of IGF-1 along with PSA, testosterone, IGFBP-3, and urinary metabolites for polyphenols (urolithin A and B)	(Jarrard et al., 2021)
Twice-daily consumption of POMx (1000 mg POMx powder containing ~600 mg polyphenols)	Men scheduled for radical prostatectomy	Assess the effect of pomegranate extract towards prostate cancer by measuring the level of 8-OHdG, urolithin A, pS6 kinase, NF-κB and Ki67	(Freedland et al., 2013)
Oral consumption of 8 oz pomegranate juice extract (POMx) everyday	Men diagnosed with prostate cancer with rising PSA level after undergoing treatment by surgery or radiation therapy	Comparing the effect of pomegranate juice extract towards PSADT level	(Pantuck et al., 2015)
Oral consumption of one or three POMx capsules everyday	Men diagnosed with prostate adenocarcinoma and had radical prostatectomy, radiation or cryotherapy	Determine the activity of double dose of POMx in recurrent cases of prostate cancer by looking at the PSADT changes	(Paller et al., 2013)

5. FUTURE PERSPECTIVES

Taken together, this review showcases the ability of phenolic compounds found in pomegranate extracts to target prostate cancer, which was demonstrated by various study designs including preclinical and clinical studies. The evidence presented in this review is insufficient. Therefore, future clinical trials with an elongated period and improved intervention and study design may assist in clarifying the full potential of pomegranate extracts in targeting prostate cancer. To demonstrate the chemopreventive activity of the compounds, participants in the pre-cancerous stage should be recruited instead of those who are diagnosed with end-stage tumors. Aside from that, metabolic profiling studies on urolithins in prostate cancer tissue should be carried out to see if the bioactive component is even present after the phenolic compounds have been digested. Precision oncology approach is making success in specialized targeted cancer therapy. Therefore, researchers may use this approach to target molecular profiles of cancer that may be susceptible to natural interventions, which concurrently reduces the need to use synthetic treatments that may be fatal to the patients. Lastly, extensive preclinical and clinical studies alongside a strong fundamental of pharmacological properties for the compounds can guarantee the use of these compounds for their chemopreventive activity towards prostate cancer in humans in the future.

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