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Potential of therapeutic antioxidant compounds from pomegranate as anti-cancer agent

Idris Aliyu Masaud[1], *Mohd Adzim Khalili Rohin[1,2], Atif Amin Baig[1] and Nasir Mohamad[1,3]

[1]Faculty of Medicine and Health Sciences, Universiti Sultan Zainal Abidin (UniSZA), City Campus, Jalan Sultan Mahmud, Kuala Terengganu, Terengganu, Malaysia
[2]Faculty of Medicine and Health Sciences, Universiti Sultan Zainal Abidin (UniSZA), Gong Badak Campus, Kuala Nerus, Terengganu, Malaysia
[3]UniSZA Medical Centre, Universiti Sultan Zainal Abidin (UniSZA), Gong Badak Campus, Kuala Nerus, Terengganu, Malaysia

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ABSTRACT

Antioxidants from fruits and vegetables have been extensively studied for their free radical scavenging activities to prevent the occurrence of chronic degenerative diseases. Pomegranate fruit extract possesses antioxidant capacity, superior to many fruits. The fruit extract has been investigated for its anticancer activity on in-vitro cancer cell models, preclinical laboratory animals and early phase clinical trials.The fruit extract has shown more anti-cancer prospect as compared to any of its individual constituents. The pharmacokinetics and mechanism of action of the extract have not been fully established. This may be due to its multiple components that work in tandem to produce its pharmacological activity. This review discusses on some literature that demonstrate the chemotherapeutic potential of pomegranate against some cancers.

Keywords: Antioxidants, Chemotherapy, Free radicals, *Punica granatum*, Ellagitannins

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INTRODUCTION

Punica granatum (PG) commonly called pomegranate is a fruit bearing deciduous shrub considered a native of Iran. It has featured virtually in all major religions and has been used for centuries as a folk medicine for the management and treatment of diverse ailments (4).The fruit has been mentioned twice in the Holy Quran as an example of God's good creations (1).The benefits of pomegranate are related to the phytochemicals it contains which are produced as a self defence mechanism for the plant (1, 3).The most abundant phytochemicals embedded in pomegranate are the phenolic compounds which have excellent antioxidant activity. They include flavonoids, anthocyanins and the hydrolysable tannins; ellagitannins.

Scientifically, pomegranates have been demonstrated to possess antioxidant, anti-inflammatory, antitumor, antidiarrhoeal, antimicrobial (antibacterial, antifungal and antiviral), anti-atherosclerotic effects, among others (4). All the anatomical parts of the plant have been studied and demonstrated to possess various pharmacological properties. In this research, the tremendous potential of pomegranate as a chemotherapeutic agent would be reviewed.

PHARMACOLOGY OF POMEGRANATE EXTRACTS

Looking at the trend of researches done on pomegranate, the outcome of *in-vitro* studies does not exactly give a reproducible result on *in-vivo* animal models and human trials. This has necessitated the need for research into the pharmacokinetics and pharmacodynamics of pomegranate extracts.

Pharmacokinetics

The high antioxidant capacity of pomegranate is largely attributed to the polyphenol ellagitannins (punicalagins and punicalins) it contains (6). Thus, emphasis would be on the pharmacokinetics of ellagitannins.Ellagitannins are hydrolysable tannins, which on hydrolysis yield ellagic acid and other small phenolics. A study has shown that, after oral consumption of pomegranate extract or juice, the phenolic components are available in increasing amounts during digestion, whereas the anthocyanins are largely metabolised to some non-coloured forms, oxidised or degraded into other chemicals. The major polyphenol ellagitannin was found to be neither hydrolysed nor degraded in the stomach. But they were slowly hydrolysed along the intestine to release ellagic acid, which is then metabolised by the intestinal microbiota to urolithins (7).

In a case study, 31.9 ng/mL of ellagic acid and its metabolites were detected in the plasma of an individual subject one hour after the ingestion of 180mL pomegranate (PG) juice. Plasma was cleared 4 hours after consumption, suggesting that ellagic acid from food is absorbed in humans (8). In a follow-up study, the rapid absorption and plasma clearance of ellagitannins was confirmed, as well as the persistent excretion of urolithin metabolites in the urine up until 48 hours after PG juice ingestion (9), which present significant antioxidant and anti-inflammatory properties *in vitro* (10, 11). Ellagitannin metabolites, urolithins were found in high amount accumulated in colon, prostate and other intestinal tissues after absorption. The metabolism of ellagitannin evaluated in rats showed that it was biotransformed by the rat microflora to 6H-dibenzo-6-one (urolithin B) derivatives. The study when expanded to 60 healthy human subjects revealed the absence of either ellagitannin (punicalagin) or ellagic acid in plasma or urine (7). Thus, it can be inferred from above, that PG ellagitannins are either directly absorbed into the plasma to exert their biological effect or indirectly as their active metabolites after microflora biotransformation. When absorbed, ellagitannins are also rapidly cleared from the plasma.

Pharmacodynamics (Mechanism of Action)

Local effects of PG can be hypothesised from its accumulation in prostate, colon and other intestinal tissues (12). The mechanism of action of PG on different cancer types is not very clear. This may be due to the different bioactive present in the extract that work synergistically or supra-additively. Nevertheless, scientific investigations have demonstrated their effect on cell cycle, angiogenesis, DNA repair, oxidation and inflammation, invasion and motility, apoptosis and some vital enzymes that are implicated in carcinogenesis.

These effects would be reviewed on the following cancers;

BREAST CANCER

Breast cancer is the most common cancer and the second leading cause of cancer death and morbidity among women in the western world (12).

A PG juice extract or a combination of its components luteolin + ellagic acid + punicic acid have been demonstrated to increase cancer cell adhesion and decrease cancer cell migration of the breast cancer cell lines MDA-MB-231and MCF-7 without affecting the non-neoplastic cell line MCF-10A. The treatments also inhibit chemotaxis of the cancer cell lines to SDF1α, a chemokine that attracts breast cancer cells to the bone. The treatments also significantly reduced pro-inflammatory cytokines/chemokines, thereby having the potential to decrease inflammation and its impact on cancer progression (12).

Toi *et al.* (13)hasevaluated the anti-angiogenic potential of PG by measuring vascular endothelial growth factor (VEGF), IL-4, and migration inhibitory factor (MIF) in the conditioned media of oestrogen sensitive (MCF-7) or oestrogen resistant (MDA-MB-231) human breast cancer cells, and immortalized normal human breast epithelial cells (MCF-10A). VEGF was strongly decreased in MCF-10A and MCF-7, however, MIF was increased in MDA-MB-231, showing significant potential for the inhibitory effects of angiogenesis by PG fractions of human umbilical vein endothelial cells (HUVEC) (13).

PG has shown dose-dependent inhibition effect on NF-kB-dependent reporter gene expression which is associated with proliferation, invasion, and motility in aggressive breast cancer phenotypes. This effect is behind to decrease RhoC and RhoA protein expression, suggests a role for these extracts in lowering the metastatic potential of aggressive breast cancer species (14).

Previous studies have suggested several mechanisms for these effects, such as modulation of cell signalling molecules in the cell cycle machinery. PGextract (PE) inhibited the proliferation of mouse mammary cancer cell line (WA4), derived from mouse MMTV-Wnt-1 mammary tumours in a time and concentration-dependent manner through an arrest of cell cycle progression in the G0/G1 phase (15).

In addition, PG extracts and punicic acid, an omega-5 long chain polyunsaturated fatty acid derived from PG, have been shown to induce apoptosis in both an oestrogen insensitive breast cancer cell line (MDA-MB-231) and an oestrogen sensitive cell line developed from MDA-MB-231 cells (MDA-ERalpha7) through lipid peroxidation and the PKC (Protein kinase C) signalling pathway. They also cause disruption to the cellular mitochondrial membrane (16).

Aromatase is the enzyme responsible for a key step in the biosynthesis of estrogens and catalyses the formation of estrone and estradiol, which is inhibited by PG (17). One of the possible mechanisms in which PG can inhibit breast cancer is its inhibitory effect on aromatase and 17 beta-hydroxysteroid dehydrogenase enzymes (17β-HSDs), as well as its anti-estrogenic activity (18). Furthermore, ellagitannins (ET) and urolithin B (UB), which are found in relatively high quantities in PG, have been shown to most effectively inhibit aromatase activity in a live cell assay (16).

PG has been shown to inhibit breast cancer cell lines MCF-7 and MB-MDA-231 by hindering angiogenesis, tumour growth, invasiveness, proliferation, and induction of apoptosis (13, 19-21). Pomegranate seed linolenic acid isomers were found to modulate oestrogen receptor activity in a concentration dependent manner (22).

In order to study breast tumorigenesis beyond antioxidation, shirode et al tested pomegranate extract on MCF-7 cell lines. Cell growth was inhibited by inducing cell cycle arrest in G2/M followed by the induction of apoptosis. In contrast, antioxidants N-acetylcysteine and Trolox did not affect cell growth at doses containing equivalent antioxidant capacity as PE, suggesting that growth inhibition by PE cannot solely be attributed to its high antioxidant potential. DNA microarray analysis revealed that PE downregulated genes associated with mitosis, chromosome organization, RNA processing, DNA replication and DNA repair, and upregulated genes involved in regulation of apoptosis and cell proliferation.

Both microarray and quantitative RT-PCR indicated that PE downregulated important genes involved in DNA double strand break (DSB) repair by homologous recombination (HR), such as MRE11, RAD50, NBS1, RAD51, BRCA1, BRCA2, and BRCC3. Downregulation of HR genes correlated with increased levels of their predicted microRNAs (miRNAs), miR-183 (predicted target RAD50) and miR-24 (predicted target BRCA1), suggesting that PE may regulate miRNAs involved in DNA repair processes. Further, PE treatment increased the frequency of DSBs.These data suggest that PE downregulates HR which sensitizes cells to DSBs, growth inhibition and apoptosis. Because HR represents a novel target for cancer therapy, down regulation of HR by PE may be exploited for sensitization of tumours to anticancer drugs (23).

PROSTATE CANCER

Cellular model (*in-vitro*), the animal model (*in-vivo*) and clinical trials (phase II) have been conducted with various extracts of pomegranates on prostate cancer.Pomegranate commercial extract (POM) 0-12µg/ml reduced the production of testosterone, DHT, DHEA, androstenedione and pregnolone in PCa cell lines (22RV1 and LNCaP) in vitro. In an in vivo study (PTEN knockout mouse), POM (0.17g/L in drinking water) treatment showed a reduction in serum steroid after 20weeks. There was also an increase in AKR1C3 and AR levels in both cell lines, perhaps as a negative feedback effect in response to steroid stimulation (24).

In another study on the androgen-independent cell line, DU 145, there was a significant increase from 11% to 22% in G2/M cells ($p < 0.05$) when treated with (35µg/mL) pomegranate cold-pressed oil (25). Pomegranate polyphenols inhibited gene expression involved in androgen-synthesizing enzymes and AR (Androgen receptor). This may be of particular importance in androgen-independent prostate cancer cells and the subset of human prostate cancers where

AR is up-regulated (5). Pomegranate polyphenols, ellagitannin-rich extract and whole juice extract inhibited gene expression of HSD3B2 (3-β-hydroxysteroid dehydrogenase-2), AKR1C3 (Aldo-ketoreductase family 1 member C3) and SRD5A1 (steroid 5-α-reductase-1), which are key androgen-synthesizing enzymes in LNCaP, LNCaP-AR, and DU-145 human prostate cancer cells (26).

Four pure chemicals, ellagic acid, caffeic acid, luteolin, and punicic acid, obtained from pomegranate fruit were presented as potential inhibitors of *in-vitro* invasion of human PC-3 prostate cancer cells in an assay employing Matrigel artificial membranes (27). The relationship between pomegranate-induced apoptosis in human prostate cancer cells (LAPC4) and the IGF/IGFBP system have been investigated (28). Recently, the PG inhibition of cell growth, followed by apoptosis of highly aggressive human prostate carcinoma PC3 cells through modulations in the cyclin kinase inhibitor-cyclin-dependent kinase machinery have been shown by Malik *et al.*

These events were associated with alterations in the levels of Bax and Bcl-2, shifting the Bax: Bcl-2 ratio in favour of apoptosis (29). Induction of Bax and Bak (proapoptotic), down-regulation of Bcl-X (L) and Bcl-2 (anti-apoptotic), induction of WAF1/p21 and KIP1/p27, a decrease in cyclins D1, D2, and E, and a decrease in cdk2, cdk4, and cdk6 expression have been shown to occur in prostate cancer PC3 cells, following PG treatment (30). Studies have shown that PG inhibits prostate cancer cell growth, induces apoptosis in PC-3 cells (highly aggressive prostate carcinoma cells), suppresses invasion of PC-3 cells and decreases proliferation of DU-145 prostate cancer cells *in-vitro* (30).

In a phase II clinical trial, Pantuck *et al.* (31) recruited patients with rising PSA and gave them 8 ounces of pomegranate juice daily until disease progression. PSA doubling time significantly increased with treatment from a mean of 15 mo at baseline to 54 mo post treatment ($P < 0.001$). A major drawback of this study was the absence of a proper placebo control; however, statistically significant prolongation of PSA doubling time suggested a potential of pomegranate for prevention of human PCa (31). This initial clinical trial bears evidence in support of PFE because it suggests that pomegranate consumption may retard PCa progression, which may not only prolong the survival but also improve the quality of life of patients.

Pomegranate juice reduced the levels of secreted pro-inflammatory cytokines/chemokines known to promote tumour growth (IL-6, -12p40, -1β and RANTES) suggesting that the inhibitory effect of pomegranate on prostate cancer cell metastasis is in part mediated through reducing inflammation (1).

González-Sarrías *et al.*(32) assessed whether ellagitanins or their metabolites ellagic acid and urolithins reach the human prostate upon consumption of pomegranate and evaluated the effect on the expression of proliferation biomarkers. Sixty-three patients with BPH or prostate cancer were divided into the controls and consumers of walnuts (35 g/day) or pomegranate juice (200 mL/day) for 3 days before surgery. The main metabolite detected was written-A-glucuronide together with the traces of urolithin-B-glucuronide and dimethyl ellagic acid. These studies were repeated and the findings corroborated in a parallel rodent study. The fact that metabolites were present in only a small number of prostates was probably due to clearance of the compounds. No apparent changes in the expression of CDKN1A, MKi-67 or c-Myc were found after consumption of the walnuts or pomegranate juice (32). The prevention of pro-carcinogen activation mediated through the inhibition of CYP enzyme activity may play an important role in pomegranate juice's effect on tumour promotion, and progression (33, 34, 35).

Seventy men were randomized to two tablets, POMx or placebo, daily up to four weeks before radical prostatectomy. Tissue was analysed for intraprostatic urolithin A, a pomegranate metabolite, benign and malignant 8-OHdG (an oxidative stress biomarker), and cancer pS6 kinase, NF-κB, and Ki67. The primary endpoint was differences in 8-OHdG, and the study was powered to detect 35% reduction. POMx was associated with 16% lower benign tissue 8-OHdG (P = 0.095), which was not statistically significant (36).

COLON CANCER

Ellagitannins, derived from PG juice, and their metabolites, urolithins exhibit dose and time-dependent decreases in cell proliferation and clonogenic efficiency of HT-29 cells through cell cycle arrest in the G0/G1 and G2/M stages of the cell cycle followed by induction of apoptosis (37).Ellagitannins (ETs) and its hydrolysed product, ellagic acid (EA), have been reported to induce apoptosis in human colon cancer Caco-2 cells through down-regulation of cyclins A and B1, upregulation of cyclin E, cell-cycle arrest in the S phase, induction of apoptosis via intrinsic

pathways (FAS-independent, caspase-8 independent) through bcl-XL down-regulation with mitochondrial release of cytochrome c into the cytosol as well as activation of initiator caspase-9 and effector caspase-3 (38).

Inflammation plays a key role in the development of colon cancer. The anti-inflammatory properties of pomegranate, linked to its cancer protective effect have been attributed to the urolithins, in particular urolithin-A, and ellagic acid, found at relatively high concentrations in the colon. In one study, the colonic fibroblasts were exposed to urolithins and ellagic acid, at concentrations achievable after the consumption of pomegranate, with or without inflammatory cytokines, and the effects on fibroblast migration and monocyte adhesion were determined (39).

There was significant down-regulation of inflammatory markers such as PGE2, PAI-1, and IL-8, as well as other key regulators of cell migration and adhesion. Fibroblast migration and monocyte adhesion was inhibited suggesting that consumption of ellagitanin-containing foods has potential beneficial effects on gut inflammatory diseases (39). Treatment of HT-29 colon cancer cells has been indicated by PG juice through decreasing COX-2 expression and inhibiting inflammatory cell signalling processes which may cause cancer initiation and progression (40).

In one *in vivo* experiment, rats were daily gavaged with 0.5 ml of 2% pomegranate seed oil rich in punicic acid, for 10 days, before TNBS treatment. Oral administration of pomegranate seed oil prevented TNBS-induced colitis and lowered ROS-induced tissue damage in rats. The beneficial anti-inflammatory effects of pomegranate seed were attributed to punicic acid-mediated down regulation of neutrophil activation and lipid peroxidation (41). Pomegranate peel extract (6 mg/d) administered to mice over a period of 4 weeks counteracted the high fat-induced expression of inflammatory markers, both in the colon and the visceral adipose tissue (42).

Sprague-Dawley rats (n = 10 per group) received pomegranate juice (2504.74 mg Gallic acid equivalents/l) or a polyphenol free control beverage ad-libitum for 10 weeks and were injected with azoxymethane (AOM) subcutaneously (15mg/kg) at weeks 2 and 3. Consumption ofpomegranate juice suppressed the number of aberrant crypt foci (ACF) and dysplastic ACF by 29 and 53.5% (P = 0.05 and 0.04), respectively, and significantly lowered proliferation of mucous cells. Pomegranate juice significantly down-regulated pro-inflammatory enzymes nitric oxide synthase and cyclooxygenase-2 messenger RNA (mRNA) and protein expression. In addition, it suppressed nuclear factor-κB and VCAM-1 mRNA and protein expression in AOM-treated rats.

Pomegranate also inhibited phosphorylation of PI3K/AKT and mTOR expression and increased the expression of miR-126. The specific target and functions of miR-126 were investigated in HT-29 colon cancer cell lines. In vitro, the involvement of miR-126 was confirmed using the antagomiR for miR-126, where the pomegranate reversed the effects of the antagomiR on the expression of miR-126, VCAM-1 and PI3K p85β.

In summary, therapeutic potentials of pomegranate in colon tumorigenesis were due in part to targeting miR-126-regulated pathways, which contributes in the underlying anti-inflammatory mechanisms (43). There has been a correlation between inducible nitric oxide (iNOS) synthase and COX-2 expression in human colorectal adenocarcinoma. In fact, a possible link between advanced stages of this disease and higher expression of iNOS and COX-2 has been shown by Habibollahi *et al*. (44, 45).The standardized ellagitanin extracts obtained from pomegranate and berries have been shown to inhibit Wnt signalling (46), emphasizing further the inhibitory potential of ellagitanin-rich foods against colon carcinogenesis.

CONCLUSION

Pomegranate fruit is a powerful exogenous source of antioxidant that has been studied for several pharmacological effects. It has been extensively studied for its antitumor property. Conventional chemotherapeutic agents are expensive and have serious side effects. This has necessitated the need for exploring natural products as alternative chemotherapeutics or adjuvants to conventional anticancer drugs. Studies have demonstrated a great potential for pomegranate fruit extract as an anticancer agent. In this review, the chemotherapeutic potential of the fruit extract against breast cancer, prostate cancer and colon cancer were considered. Researches on the effect of the fruit extract on prostate cancer have reached advanced clinical trials. However, studies on other cancer types are lagging and require more scientific efforts. The constituents of the fruit extract when isolated and tested demonstrate inferior therapeutic potential as compared to the whole extract. The multicomponent nature of the fruit extract has made its pharmacokinetics and pharmacology to remain unclear.

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