

Accepted Manuscript

Title: Possible use of *Punica granatum* (Pomegranate) in cancer therapy

Authors: Amrita Devi Khwairakpam, Devivasha Bordoloi, Krishan Kumar Thakur, Javadi Monisha, Frank Arfuso, Gautam Sethi, Srishti Mishra, Alan P. Kumar, Ajaikumar B. Kunnumakkara



PII: S1043-6618(18)30050-1
DOI: <https://doi.org/10.1016/j.phrs.2018.04.021>
Reference: YPHRS 3887

To appear in: *Pharmacological Research*

Received date: 11-1-2018
Revised date: 25-4-2018
Accepted date: 25-4-2018

Please cite this article as: Khwairakpam Amrita Devi, Bordoloi Devivasha, Thakur Krishan Kumar, Monisha Javadi, Arfuso Frank, Sethi Gautam, Mishra Srishti, Kumar Alan P, Kunnumakkara Ajaikumar B. Possible use of *Punica granatum* (Pomegranate) in cancer therapy. *Pharmacological Research* <https://doi.org/10.1016/j.phrs.2018.04.021>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Possible use of *Punica granatum* (Pomegranate) in cancer therapy

Amrita Devi Khwairakpam¹, Devivasha Bordoloi¹, Krishan Kumar Thakur¹, Javadi Monisha¹, Frank Arfuso², Gautam Sethi^{3,4,5*}, Srishti Mishra⁵, Alan P Kumar^{5,6,7,8,9}, Ajaikumar B. Kunnumakkara^{1*}

¹Cancer Biology Laboratory & DBT-AIST International Laboratory for Advanced Biomedicine (DAILAB), Department of Biosciences & Bioengineering, Indian Institute of Technology Guwahati, Assam 781039, India, ²Stem Cell and Cancer Biology Laboratory, School of Biomedical Sciences, Curtin Health Innovation Research Institute, Curtin University, Perth WA, 6009 Australia, ³Department for Management of Science and Technology Development, Ton Duc Thang University, Ho Chi Minh City 700000, Vietnam, ⁴Faculty of Pharmacy, Ton Duc Thang University, Ho Chi Minh City 700000, Vietnam, ⁵Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, 117600, Singapore, ⁶Cancer Science Institute of Singapore, National University of Singapore, Singapore, ⁷Medical Science Cluster, Yong Loo Lin School of Medicine, National University of Singapore, ⁸Curtin Medical School, Faculty of Health Sciences, Curtin University, Perth WA, Australia, ⁹National University Cancer Institute, National University Health System, Singapore.

* Authors for correspondence

Dr. Ajaikumar B. Kunnumakkara, Ph.D, Associate Professor, Department of Biosciences and Bioengineering Indian Institute of Technology Guwahati, Guwahati, Assam-781039, India

Email: kunnumakkara@iitg.ernet.in; ajai78@gmail.com

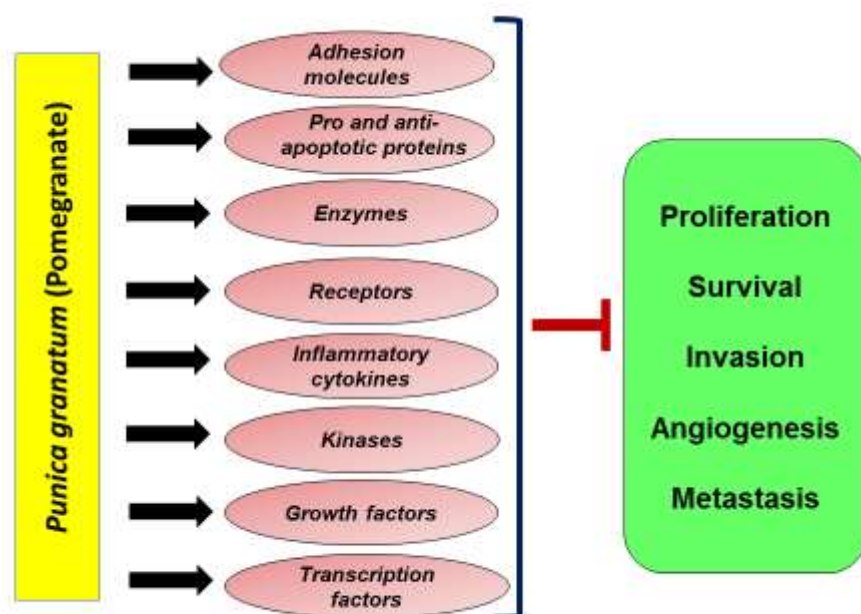
Phone: +91 361 258 2231 (Office); +91 789 600 5326 (Mobile)

Fax : +91 361 258 2249 (Office)

Dr. Gautam Sethi, Department for Management of Science and Technology Development, Ton Duc Thang University, Ho Chi Minh City 700000, Vietnam, Faculty of Pharmacy, Ton Duc Thang University, Ho Chi Minh City 700000, Vietnam, Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117600. Phone: (65) 65163267; Fax: (65) 68737690; Email:

gautam.sethi@tdt.edu.vn; phcgs@nus.edu.sg

Graphical abstract



Abstract

The intake of fruits has proven to reduce the risk and incidence of cancer worldwide and plays a crucial role in cancer prevention. Pomegranate (*Punica granatum*), which belongs to the Punicaceae family, is one such plant that contains beneficial nutrients as well as many bioactive components and important phytochemicals that can be attributed to cancer-related therapeutic purposes. Pomegranate possesses antioxidant, anti-inflammatory, anti-proliferative, anti-angiogenic, anti-invasive, and anti-metastatic properties, and induces apoptosis. It also down-regulates various signalling pathways such as NF- κ B, PI3K/AKT/mTOR, and Wnt, and down-regulates the expression of genes that are responsible in cancer development, such as anti-apoptotic genes, MMPs, VEGF, c-met, cyclins, Cdks, and pro-inflammatory cytokines. Therefore, inclusion of the fruit in one's diet would assist in a healthy life protected from cancer and also act as an effective chemotherapeutic with no toxic side effects.

Key words: Pomegranate, *Punica granatum*, punicalagin, cancer therapy, phytochemicals

1. Introduction

The ever increasing incidence of cancer has become the major health concern and is the second leading cause of death worldwide [1]. According to, GLOBOCAN 2012, 14.1 million new cancer cases are diagnosed annually and 8.2 million people are dying every year worldwide, while 32.6 million people are living and afflicted with cancer [2]. The common chemotherapeutic drugs available for the treatment of cancer to date are associated with inconsistent clinical responses, adverse side effects, and the development of resistance, which ultimately leads to cancer progression and recurrence [3, 4]. These limitations demand

the development of non-toxic, affordable, readily accessible, and highly effective regimens to combat this dreadful disease [5]. Extensive research over the past few years has revealed that an intake of a diet rich in fruits and vegetables is strongly linked with reduced cancer risk since they contain an abundance of phytochemicals with potent anti-cancerous properties [6]. Additionally, natural products generally have multi-targeted actions with minimal side-effects, making them ideal candidates for cancer therapeutics [7]. The polyphenols and flavonoid compounds present in fruits and vegetables have evinced the ability to downregulate the expression of various genes, proteins, and signalling cascades that are responsible for tumor growth and progression, making them potential therapeutic agents for cancer patients.[1, 8-10]. Pomegranate (*Punica granatum*), commonly known as grenade, granats, and punica apple, is a fruit belonging to the Punicaceae family and has been reported to possess profound anti-cancer properties [1, 11, 12]. It is indigenous to the Himalayas in northern India through to Iran, parts of Southeast Asia, the East Indies, and tropical Africa, and grows in almost all parts of the Mediterranean region [12].

The fruit is often freshly consumed and also eaten as juice, jam, and wine [1].

Pharmacologically, *Punica granatum* has been found to possess many active components that are antioxidant, anti-inflammatory, and neuroprotective in nature [13]. Researchers have found that the flavonoids obtained from pomegranate juice possess antioxidant activity similar to green tea and which is significantly higher than red wine [14]. Interestingly, the therapeutic potential of pomegranate has captivated the interest of many researchers worldwide. Furthermore, pomegranate has been shown to exhibit antibacterial, anti-proliferative, anti-invasive, anti-metastatic, and apoptotic properties [1, 15] The seed oil of pomegranate (PSO) and pomegranate peel contain many polyphenols and flavonoids that possess antioxidant and wound healing properties [8, 11, 16]. To understand the diverse beneficial properties of this plant, an extensive literature survey was conducted using Pubmed, Scopus and Google Scholar followed by bibliographic evaluation of the related articles published in the last sixteen years. This review focuses mainly on the traditional uses of the fruit, its different bioactive components, and its effect on various types of cancer such as bladder, breast, colon, liver, lung, prostate, skin, and leukemia, in order to provide a summary of research conducted to date and also to serve as criteria for further research on pomegranate.

2. Traditional uses and bioactive components of pomegranate

Pomegranate is regarded as “a Pharmacy unto itself” in Ayurveda [17]. Over the years, the seed extract, fruit, flower, and leaves of *Punica granatum* have been known to prevent thyroid disorders and thickening of arteries due to their potent anti-inflammatory, antioxidant, and cardioprotective function, and to prevent degenerative diseases [17, 18]. In traditional medicine, the seed of the plant has been found to improve urination and prevent urinary diseases [17]. In Unani and Chinese medicine, pomegranate has been documented for the management of diabetes [19]. Numerous findings have also reported the use of pomegranate as the herbal medicine of choice for the treatment of diabetes and renal disorders [20, 21]. Different plant parts of pomegranate have been outlined for their application in various folklore medicines

for their therapeutic ability in the treatment of diverse pathological diseases [22]. The pomegranate fruit has been used for the treatment of acidosis, dysentery, microbial infections, diarrhea, helminthiasis, hemorrhage, and respiratory diseases.

It is also known to exhibit anti-viral activity against herpes virus and influenza virus [23]. It has been used extensively as an astringent, hemostatic, and antimicrobial agent in Iranian traditional medicine [24]. The rind powder helped in the treatment of periodontitis and possesses antihelmintic properties [25, 26]. In traditional medicine, pomegranate seed has been reported to regulate urine discharge and control the burning sensation of urine, and been used for the treatment of bronchitis, diarrhea, digestive problems, infected wounds, and diabetes [17, 24]. In Mauritian folklore, bark extracts of the plant have been used to cure asthma, chronic diarrhea, chronic dysentery, and intestinal worms [22]. Moreover, the peel of pomegranate fruit is known for its strong astringent and anti-inflammatory properties as well as being a therapy for traumatic hemorrhage, ulcers and infections, diarrhea, dysentery, dental plaque, and as a douche and enema agent [25, 27]. The water decoction of the fruit has been used for the treatment of aphthae and ulcers in India, Tunisia, and Guatemala [27]. The peel has also found enormous application in traditional Chinese medicine for its efficacy in promoting hemostasis, killing parasites, and overcoming hyperacidity, along with potent wound healing abilities, therapy of diabetes, cancer, and blood pressure control [11, 25, 28]. In addition, studies have found that pomegranate peel impeded the release of toxins by bacteria and aided in their reduced growth [24].

Punica granatum has been considered to be pharmacologically active due to the presence of abundant phytochemicals [29, 30]. The different parts of the plant consist of various chemical compounds that impart crucial roles in the prevention of many diseases [25]. Different classes of phytochemicals have been identified from pomegranate, such as ellagitannins, gallotannins and derivatives, flavonoids, lignins, triterpenoids and phytosterols, fatty acids and lipids, organic acid and phenolic acids [30]. The fruit parts such as peel, aril, seeds, and juice are rich in phenolic acids, flavanols, flavones, flavonones, anthocyanidins, and anthocyanin [25, 30]. Glycated anthocyanins such as pelargonidin 3, 5-diglucoside and pelargonidin 3-glucoside are present in the pomegranate flower, while the leaves, roots, and stem contain apigenin, punicalin, punicalagin, and luteolin [25]. The fruit and its pericarp contain phenolic compounds, tannins, and hydrolysable tannins [24]. Pomegranate is a rich source of polyphenols [31, 32]. Especially, the pomegranate peel contains a larger amount of the polyphenol known as punicalagin, which is an ellagitannin with antioxidant efficacy and is unique to pomegranate [1].

Furthermore, compounds such as corilagin and pseudopelletierine have been obtained from the pomegranate peel and have been found to exert anti-tumor properties [28]. Large amounts of polyphenols such as ellagic acid (EA), gallotannins, anthocyanins (3-glucosides and 3, 5-glucosides of delphinidin, cyanidin, and pelargonidin), catechins, and other flavonoids (quercetin, kaempferol, and luteolin glycosides), gallo catechins, phenolic acids, tannins (punicalin and punicafolin), and punicalagin (PC), flavone glycosides, apigenin, sitosterol, fatty acids, and volatile compounds have also been found to be

present in pomegranate juice [Figure 1] [1, 12, 33-37]. Punicic acid (PuA) is a conjugated linolenic acid (C18:3 Δ 9c, 11t, 13c) with a wide range of nutraceutical effects and is the main component of seed oil from *Punica granatum* [38]. The conjugated fatty acid (cis(c)9, trans(t)11) and polysaccharide (PSP001) were obtained from seed oils and fruit rind of pomegranate respectively [39, 40]. Galactomannan (PSP001) obtained from the fruit rind of *Punica granatum* has been reported as an excellent antioxidant, immunomodulatory, and anti-cancer agent [41]. Therefore, it would be important to discuss the potent effectiveness of the different therapeutic compounds isolated from the plant in the treatment and prevention of various cancer types.

3. Molecular targets modulated by *Punica granatum*

The rich content of phytochemicals in the plant has assisted in the treatment of various cancer types. Numerous studies have reported the potent chemotherapeutic properties of *Punica granatum* that has targeted many molecular pathways and gene expression [Figure 2 & Table1]. EA and PSO extracts induced cell cycle arrest in the G0/G1 phase, the PLE induced G2/M phase arrest, and the acetonitrile fraction obtained from the pomegranate juice induced S phase arrest in several types of cancers. [42-45]. Different studies have found that treatment with pomegranate extract led to regulation in the expression of cyclin-dependent kinase (cdk) inhibitors WAF1/p21 and KIP1/p27 [46-48]. Moreover, it was found to be associated with the significant down-regulation of cyclins D1, D2, E, cyclin-dependant kinase (cdk)2, cdk4, and cdk6 that are noted to be the important regulators of the cell cycle [46, 49-51]. The expression of pro-inflammatory cytokines such as Interleukin (IL)-1 β , IL-2, IL-6, IL-8, IL-12, IL-17, induced protein 10 (IP-10), Macrophage Inflammatory Protein (MIP)-1 α , MIP-1 β , monocyte chemoattractant protein (MCP)-1, Tumor necrosis factor (TNF)- α , and Regulated on Activation, Normal T Expressed and Secreted (RANTES) was considerably reduced with the treatment of PSO extract in breast cancer in a dose-dependent manner [45, 52, 53]. These pro-inflammatory cytokines are produced predominantly by activated macrophages and are involved in the up-regulation of inflammatory reactions [54]. Additionally, the intake of pomegranate juice (PJ) leads to inhibition of the expression of α -induced Cyclooxygenase-2 (COX-2) in colon tumorigenesis [55].

Pomegranate extract has been found to down-regulate the increased expression of inflammatory markers such as inducible nitric oxide synthase (iNOS), 3-nitrotyrosine, heat shock protein 70 (HSP70) and 90, and Nuclear Factor Kappa Beta (NF- κ B) in a dose-dependent manner [56]. It also decreased the phosphorylation of PI3K/AKT (i.e. halted the phosphorylation of Akt at Thr(308)), suppressed the mechanistic target of rapamycin (mTOR) signaling pathway, and up-regulated Jun N-terminal Kinase (JNK) phosphorylation [50, 57-61]. Moreover, in *in vivo* studies, pomegranate emulsion (PE) reduced the expression of COX-2 and HSP90, and halted I κ B α degradation; thereby inhibiting the translocation of NF- κ B from the cytosol to nucleus. However, a rise in nuclear factor erythroid 2p45 (NF-E2)-related factor 2 (Nrf2) expression and nuclear translocation was observed in 7, 12-dimethylbenz[a]anthracene (DMBA)-

induced mammary tumorigenesis [62, 63]. In addition, the up-regulation in expression of growth factors such as vascular endothelial growth factor (VEGF) and c-met was reduced, and it also modulated the transforming growth factor beta (TGF- β)/Smads pathway [45, 64]. Chen HS *et al.*, reported the TGF- β /Smad signaling pathway as the molecular target of Ellagic acid (EA), which promoted cell cycle arrest in breast cancer cells *in vitro* [44]. TGF- β 1-induced arrest occurs during G1 and is mediated by Smad proteins, which regulate transcriptional targets, including c-myc [44]. The inhibition in the expression of c-myc led to the suppression of Cdk4-cyclin D [44].

Dong Y *et al.*, have revealed that the combined over-expression of cyclin D1 and Cdk4 in cancer patients indicates the poorest overall survival [65]. It has been demonstrated that treatment with pomegranate extracts caused a reduction in oxidative stress and regulated the expression of miR-126 [57, 58]. Also, a study carried on prostate cancer cells reported that microRNAs such as miR-335, miR-205, and miR-200 (that are anti-invasive) were increasingly expressed, while miR-21 and miR-373 (that are pro-invasive in nature) were suppressed following treatment with pomegranate extracts [53]. The β -catenin pathway was also inhibited via the suppression of β -catenin and its downstream factors cyclin D1 and survivin [66]. Moreover, punicalagin treatment led to the up-regulation of tissue inhibitor of metalloproteinase (TIMP)-2 and TIMP-3, and lessened the activities of matrix metalloproteinase (MMP)-2 and MMP-9, thereby retarding the migration of ovarian cancer cells [66]. It has also been shown in 2-dimethylhydrazine-induced colon cancer that treatment with standardized pomegranate extract reduced the Wnt pathway activity by down-regulating Wnt5a, FRZ-8, b-catenin, Lef1, Tcf4, c-myc, and cyclin D1. Remarkable up-regulation in the expression of APC and axin1 in the tissue occurred with diminution in the level of carcinoembryonic antigen (CEA) in the serum [49].

Studies with DNA microarrays have found that pomegranate extract suppresses the genes related to chromosome architecture, mitosis, DNA replication, processing of RNA, and repairing of damaged DNA; however, increased expression of apoptotic genes was observed in several types of cancer. Decreased expression of genes such as MRE11, RAD50, NBS1, RAD51, BRCA1, BRCA2, and BRCC3 that are responsible for the double strand break (DSB) repair via homologous recombination (HR) was also seen [67]. It also raised the levels of p21 and p53 and increased the expression of caspases and cytochrome c, thereby leading to apoptosis [68]. The proteolytic activity of collagenase IV, which plays a main role in proteolysis of tumor cell-mediated extracellular matrix, was found to be considerably decreased by treatment with EA [52, 69]. Other reports have indicated that pomegranate extract can reduce the expression of MMP-2 and MMP-9 and lowered the levels of reactive oxygen species (ROS) and the mitochondrial membrane potential [43, 50, 59]. Experimental studies on DU145 and PC3 prostate cancer cells have shown that PJ increased the expression of E-cadherin and intercellular adhesion molecule 1 (ICAM-1) that took part in cell adhesion, while genes such as hyaluranan-mediated motility receptor (HMMR) and type I collagen involved in cell migration were poorly expressed [53]. Also, mRNA and protein expression of vascular cell adhesion molecule 1 (VCAM-1) was found to be down-regulated by the polyphenolic compounds of pomegranate

[58]. Wang L *et al.*, have reported that PE suppressed the migration and chemotaxis of prostate tumor cells towards stromal cell-derived factor 1 α (SDF1 α), a chemokine crucial for metastasis of tumor cells to bone [70]. The PJ effectively impeded the activity of SDF1 α , a chemokine whose receptor is CXCR4, and inhibited cancer cell metastasis towards the bones [53]. Further, Sahebkar and group performed two meta-analyses of randomized controlled trials to evaluate the effect of PJ on plasma C-reactive protein (CRP) concentrations and lipid profile. The results indicate that consumption of PJ did not cause any notable effect on plasma CRP levels as well as lipid profile in human [71, 72]

4. The effect of pomegranate on different types of cancer

An abundance of studies has clearly demonstrated pomegranate to exert anti-cancer properties against diverse cancer types.

4.1 Pomegranate and bladder cancer

Bladder cancer is one of the widespread lethal malignancies of the urinary tract, with poor outcomes for patients with advanced stages of disease [73, 74]. Pomegranate is known to be a functional food of great significance, owing to its numerous health benefits in humans, and has been found to play a crucial role in the treatment of bladder cancer [18, 75]. Lee ST *et al.*, reported that pomegranate fruit ethanol extract (PEE) suppressed the proliferation of UBUC tumor cells via cell cycle arrest at S phase due to up-regulation of cyclin A and down-regulation of cdk-1 [75]. Further, it was seen that PEE triggered pro-caspase-3, -8, and -9, and elevated the Bax/Bcl-2 ratio. Above all, it was also found that PEE stimulated the expression of procaspase-12, with increased expression of CHOP and Bip, which are endoplasmic reticulum (ER) stress markers [75]. Additionally, Wu TF *et al.*, demonstrated that ethanol extract possesses anti-proliferative and apoptotic activities by down-regulating the PTEN/AKT/mTORC1 pathway through increased expression of profilin 1 [73].

4.2 Pomegranate and breast cancer

Breast tumor-associated mortality ranks second among women in the world and is found to be more prevalent in less developed regions [44]. In the year 2012, around 1.67 million new cases were diagnosed, i.e. 25% of all cancers [2]. Pomegranate has been proven to be a promising therapeutic agent against breast tumors [76]. Experimental studies have found that PJ and its components such as luteolin, EA, and punicic acid (PA) enhance the adhesion of tumor cells by up-regulation of E-cadherin and diminished tumor cell migration, without affecting the normal cells. It also suppressed the expression of pro-inflammatory cytokines IL-8, RANTES, and PDGFB, and obstructed chemotaxis of tumor cells to the chemokine SDF1 α [76]. EA exhibited growth inhibitory effects against breast cancer cells by inducing cell cycle arrest in the G0/G1 phase via the TGF- β /Smads pathway [44]. Resveratrol, a phytoestrogen present in pomegranate, has been found to be an effective agent against breast tumor progression and metastasis, and helped in the

chemosensitization of breast tumor cells to different chemotherapeutic drugs by inducing apoptosis and inhibiting aromatase activity [77]. Ellagitannins obtained from pomegranate have also shown estrogen-responsive breast tumor preventive characteristics via anti-aromatase activity, thereby inhibiting testosterone-induced proliferation of MCF-7 cells. This aromatase enzyme has been found to play a crucial role in tumorigenesis and takes part in the conversion of androgen to estrogen [78, 79]. 27-hydroxycholesterol (27HC), an endogenous selective estrogen receptor (ER) modulator (SERM), which is a primary metabolite of cholesterol and an ER and liver X receptor (LXR) ligand, has been found to be responsible for ER-dependent growth in breast cancer [80, 81]. The methanolic extract of the pomegranate pericarp (PME) down-regulated the activity of 27HC and led to reduced cell growth and proliferation of breast cancer cells.

Furthermore, PME was found to be associated with the ER and caused abrupt expression of estrogen response elements (ERE) [81]. It has also been reported that PME suppressed ER-positive breast tumor growth and proliferation via SERMs [82]. PSP001, a polysaccharide obtained from the pomegranate fruit rind, inhibited the rate of cell growth and proliferation, and the PPE extract caused apoptosis in MCF-7 cells [31, 40, 83, 84]. Treatment with 40 μ M punicalic acid has been found to cause cell death by 86 and 91% in MDA-MB-231 and MDA-ER α 7 cells respectively [85]. In MCF-10A and MCF-7 cells, inhibition of VEGF and increased expression of migration inhibitory factor (MIF) was seen when treated with PSO and fermented pomegranate juice [86]. Kim ND *et al.*, reported that the PSO extract suppressed MCF-7 cell proliferation of by 90% at 100 μ g/ml and cell invasion by 75% at 10 μ g/ml. Also, it was found to induce 54% apoptosis at 50 μ g/ml in MDA-MB-435 cells, which are estrogen receptor negative metastatic breast cancer cells [87]. It has been evidenced that PE showed cytotoxicity, suppressed proliferation, and elevated caspase-3 enzyme expression of WA4 cells *in vitro* [88]. Another study showed that the hydrophilic fraction of 80% aqueous methanol extract obtained from PSO led to significant reduction in cell growth, with cell cycle arrest at G0/G1 phase in two breast cancer cell lines- MCF-7 and MDA MB-231. Also, an increased expression of growth factors and pro-inflammatory cytokines was considerably reduced in a dose-dependent manner [45].

Moreover, experimental studies have shown that pomegranate fruit extracts (PFEs) down-regulated the expression of NF- κ B-dependent reporter gene and reduced the levels of RhoC and RhoA, thereby inhibiting metastasis of breast tumor cells [89]. In DMBA-induced mammary tumorigenesis in rats, pomegranate phytochemicals showed remarkable anti-proliferative and pro-apoptotic activities, thereby inducing a chemopreventive effect. A decreased expression of the intra-tumor ER- α , ER- β , and ER- α : ER- β ratio was also observed following treatment with a pomegranate emulsion. It also down-regulated β -catenin expression (a transcriptional cofactor for Wnt signaling), and cyclin D1, which is involved in the regulation of cell growth [90]. Further *in vivo* studies showed a decreased development of cancerous lesions by 47% following treatment with the polyphenols obtained from pomegranate fermented juice in DMBA-induced tumor lesions in the murine mammary gland [87, 91]. Interestingly, the nanoencapsulation of PC and EA

inhibited cell proliferation by 2- to 12-fold in MCF-7 and Hs578T breast cancer cells and increased the anti-tumor activity of the compounds [92]. The PSO extract showed a synergistic effect with trans-resveratrol in a self-nanoemulsifying drug delivery system (RES SNEDDS). *In vitro* studies have found that RES SNEDDS-PSO has a remarkable inhibitory effect against MCF-7 breast cancer cells [93]. It has also been found that the mono-dispersed gold nanoparticles synthesized with pomegranate fruit peel extract (PAuNPs) improved the therapeutic potential of Fluorouracil and targeted drug delivery [94].

4.3 Pomegranate and colon cancer

Colorectal cancer (CRC) is the leading cause of death globally. Approximately 70% of CRC cases are known to be sporadic and almost all are associated with a sedentary lifestyle [95]. Epidemiological studies have indicated that the intake of pomegranate has an inverse correlation with colon cancer incidence [95]. Pomegranate has been noted for its anti-tumorigenic properties in the colon [89]. Experimental studies on the HT-29 human colon cancer cell line have shown that the intake of PJ at a concentration of 50 mg/L resulted in 79% inhibition of TNF α -induced COX-2 protein expression [55]. *In vitro* studies have shown that PC, EA, and total pomegranate tannin extract possessed antioxidative properties and were found to induce apoptosis and reduce cell growth in HT-29 and HCT116 colon cancer cells [96].

Also, it has been reported that the ellagitannins obtained from pomegranate are hydrolyzed to form EA and are transformed to urolithin by gut microbiota. These components were found to impede Wnt signaling [97]. It has been evidenced that EA caused cell death in Caco-2 colon cancer cells but not in CCD-112CoN normal colon cancer cells [98]. *In vivo* studies have shown that treatment of azoxymethane (AOM)-induced tumorigenesis in rat colon with PPE mitigated cytotoxic activities [99]. The PSO inhibited AOM-induced colon tumorigenesis due to the up-regulation of PPAR γ protein expression [100]. Additionally, there are evidences that PJ, PPE, and PSO induced anti-tumorigenic activity against colon malignancies and reduced the number of aberrant crypt foci (ACF) and premalignant lesions developed in AOM-induced colon cancer [57, 58, 101].

4.4 Pomegranate and leukemia

Leukemia, a cancer of the blood and bone marrow, has been divided into four types on the basis of cell type and growth rate to give the categories of acute lymphocytic, chronic lymphocytic, acute myeloid, and chronic myeloid leukemia [102]. Pomegranate has been found to exert anti-cancer properties against leukemia. Treatment with PPE caused growth inhibitory effects and apoptosis in K562 cells, which were mediated by G2/M cell cycle arrest. It also raised the levels of p21 and p53 and increased the expression of caspases and cytochrome c, thereby leading to apoptosis [68]. The acetonitrile fraction obtained from PJ has been found to lower the levels of ATP in leukemia, with considerable up-regulation of caspase-3 and morphological alterations in the nucleus [42]. Another study has shown that a polysaccharide, PSP001,

separated from pomegranate, reduced the proliferative rate of chronic myeloid leukemic cells [40]. The compound has also been found to be non-toxic and augmented the growth of normal lymphocytes *in vitro* [40]. Moreover, the fermented juice and PME lowered the rate of tumor growth and proliferation of HL-60 cells *in vitro* [103]. Contrastingly, nanoparticles synthesized from partially purified pomegranate ellagitannins with gelatin were found to exert no impact on the apoptosis of HL-60 leukemia cells [104].

4.5 Pomegranate and liver cancer

Globally, hepatocellular carcinoma (HCC) has been noted as the fifth commonly widespread cancer and third foremost reason for cancer associated deaths, with limited treatment modalities [105]. Oxidative stress has been identified as the main driving force behind the occurrence of this cancer type [63]. Pomegranate is known to possess potent antioxidant and anti-inflammatory properties due to the presence of diverse beneficial phytochemicals [56, 63]. In the study conducted by Bishayee A *et al.*, 2011, it was observed that when pomegranate emulsion was used to treat dietary carcinogen diethylnitrosamine (DENa)-induced rat carcinogenesis in the liver, it resulted in marked diminution in the incidence, number, multiplicity, size, and volume of hepatic nodules, which are known to be the potent precursors of hepatic carcinoma [63]. This inhibition of hepatocarcinogenesis was found to be mediated through modulation of the NF- κ B signaling pathway [56].

It has been experimentally proven that treatment with pomegranate hull extract on DENa-induced HCC reduces the size of the tumor. In addition, it has been found to down-regulate the expression of cyclin D1 and β -catenin, which suggested that pomegranate could be a potent anti-cancerous therapeutic agent [105]. Pomegranate peel polyphenols (PPPs) induced cell arrest at the S-phase, increased the number of apoptotic cells, the levels of ROS and Cyt-c, and Caspase-3/9 activity. In addition, the Bax/Bcl-2 ratio and the protein expression of p53 were also up-regulated [106]. Celik I *et al.*, have reported that the beverage of pomegranate has antioxidant and protective effects against carcinogenic chemical (trichloroacetic acid) induced oxidative injury in rats [107]. Studies have also found that silver nanoparticles (AgNPs) using a *Punica granatum* leaf extract (PGE) reduced cell growth and proliferation of HepG2 cells. Additionally, PGE-AgNPs showed *in vitro* free radical-scavenging and antioxidant activity [108].

4.6 Pomegranate and lung cancer

Lung cancer has been noted as the most prevalent cancer worldwide, with around 1.8 million new cases in the year 2012 [2]. It has been demonstrated that PPE and seed extract possessed antioxidant properties and inhibited the growth and proliferation of A549 cells *in vitro* [31, 109]. The treatment of a non-small cell lung carcinoma cell line with pomegranate leaf extract (PLE) inhibited cell invasion and migration via cell cycle arrest at the G2/M phase, reduced the expression of matrix metalloproteinase, and lowered ROS and the mitochondrial membrane potential [43, 50, 59]. Both *in vitro* and *in vivo* studies have found that treatment

with PFE led to the down-regulation of NF- κ B expression and suppressed the degradation and phosphorylation of I- κ B α kinase. It also suppressed MAPK phosphorylation, and inhibited PI3K activity and phosphorylation of Akt at Thr(308). Moreover, it inactivated the mTOR pathway, inhibited c-met phosphorylation, and lowered the expression of CD31 and VEGF [50, 59]. PSO has also been found to be cytotoxic and reduced the rate of cell proliferation of A549 cells [109]. DNA cell cycle analysis found that PFE treatment caused cell cycle arrest at the G0-G1 phase, regulated the expression of cdk 2, cdk4, cdk6, WAF1/p21, and KIP1/p27, and reduced the expression of cyclins D1, D2, and E [50]. Altogether, these studies suggest that pomegranate has potent chemotherapeutic properties that exert anti-cancerous activities on lung carcinoma by inducing apoptosis, inhibiting cell growth and proliferation, and thereby impeding the migration and progression of lung cancer.

4.7 Pomegranate and prostate cancer

Prostate cancer is the second leading cause of death among men [110]. *In vitro* studies have found that PFE and EA regulated the expression of pro-apoptotic genes Bax and Bak in prostate tumor cells, thereby inducing apoptosis via an increase in the Bax/Bcl-2 ratio. Furthermore, the expression of WAF1/p21 and KIP1/p27 was found to be up-regulated while the anti-apoptotic genes Bcl-X (L) and Bcl-2 were down-regulated. Moreover, it also reduced the expression of cyclins D1, D2, and E, and cyclin-dependent kinases cdk2, cdk4, and cdk6 [46-48]. An *in vivo* study using the transgenic rat for adenocarcinoma of prostate (TRAP) model showed that both PJ and EA inhibited the growth, proliferation, and progression of prostate tumor, thereby promoting apoptosis via increased caspase 3 expression [46]. PJ and its components EA, L, and PA have been found to significantly suppress the growth of prostate tumor [46, 70]. The combined administration of L, EA, and PA suppressed hormone-dependent and -independent tumor cell proliferation and migration. It also inhibited metastasis by down-regulating chemotaxis towards the chemokine CXCL12. The components altogether controlled angiogenesis in *in vivo* conditions, down-regulated IL-8 and VEGF expression, and hindered the progression as well as metastasis of PCa cells [64]. In another study, pomegranate extract has found to minimize the protein levels of HIF-1 α and VEGF, thereby reducing the tumor size and vessel density *in vivo* [111]. EA suppressed the level of MMP-2, reduced cell viability, and halted tumor cell invasion of nearby tissues [52].

Further experimental studies on prostate cancer cells have reported the remarkable inhibition of cancer progression due to the reduced expression of IL-6, IL-12p40, IL-1 β , and RANTES [53]. PE enhanced the phosphorylation of JNK, down-regulated the Akt and mTOR pathways, and inhibited NF- κ B activation [60, 61]. Upon treatment with punicalic acid, a decreased growth rate of the androgen-dependent LNCaP cells was observed, together with increased apoptosis [112]. In addition, PC remarkably scavenged 2, 2-diphenyl-1-picrylhydrazyl (DPPH) and inhibited lipid peroxidation (LPO) in PC-3 and LNCaP cells in a concentration-dependent manner. Also, up-regulation in the expression of caspases-3 and -8 was observed in PC-3 [113]. Seeram NP *et al.*, have reported that the bioactive metabolites urolithins and ellagic acid,

obtained from pomegranate, were found to suppress tumor growth *in vitro*. Moreover, an *in vivo* study has reported high levels of metabolites in the prostate gland and proved that PE considerably suppressed LAPC-4 xenograft growth in SCID mice [114]. Additional reports have shown that EA and urolithin A (UA) promoted cell cycle arrest in the S and G2/M phase respectively, accompanied by a decline in the levels of cyclin B1 and D1, and induced apoptosis in EA treated prostate tumor cells. However, UA treatment showed dysregulation of the cyclin B1/cdc2 kinase complex via elevation of cyclin B1 and phosphorylated cdc2 [115]. Ming DS *et al.*, showed that the treatment of prostate tumor cells with 0-12 μ g/mL of pomegranate extract lessened the synthesis of testosterone, DHT, DHEA, androstenedione, androsterone, and pregnenolone [116]. Further, *in vivo* studies found a diminution of serum steroid levels [116].

In another study, Hong MY *et al.*, found that pomegranate polyphenols retarded the expression of genes linked with the enzymes producing androgen and the androgen receptors (AR), which are up-regulated in androgen-independent prostate tumor cells [117]. Wang Y *et al.*, reported the efficacy of pomegranate extract in inducing cytotoxicity and suppressing survival of metastatic castration-resistant PCa cells [118]. Studies have revealed survivin as a novel molecular target that regulated the anti-tumor activity of pomegranate extract via suppression of STAT3 [118]. *In vivo* studies have also found that pomegranate extract suppressed the expression of survivin, induced apoptosis, retarded C4-2 tumor growth in the skeleton, and significantly improved the effect of docetaxel in athymic nude mice [118]. Pomegranate peel extract (PoPx) showed inhibition of migration and invasion of the prostate cancer cells via a reduced level of MMP2/MMP9 and increased TIMP2 expression [119].

Furthermore, loss of mitochondrial transmembrane potential ($\Delta\psi$), an increase in ROS and Bax/Bcl2 ratio, and activation of caspase-3 occurred, leading to apoptosis of the prostate tumor cells [119]. Moreover, pomegranate whole seed ethanolic extract (PSEE) contains puniic, α -linoleic, and α -linolenic acids, which increased the inhibition of cell growth in the hormone dependent LNCaP prostate tumor cell line [120]. Overall, the different compounds obtained from pomegranate were found to exert anti-proliferative activity and anti-angiogenic effects, and induced apoptosis in prostate cancer. Hence, pomegranate can be regarded as an effective chemotherapeutic agent for the treatment of prostate cancer.

4.8 Pomegranate and skin cancer

Skin cancer is a widespread cancer, as skin serves as the first line of defence against heat, sunlight, injury, and infection [121]. Several *in vivo* studies have revealed that pomegranate possess anti-skin tumor promoting properties in various animal models [122, 123]. PFE has been observed to suppress UVB radiation-induced carcinogenesis in SKH-1 hairless mouse epidermis [124]. It has been found to inhibit skin edema, hyperplasia, lipid peroxidation, hydrogen peroxide generation, ornithine decarboxylase (ODC) activity, COX-2 expression, and expression of proliferating cell nuclear antigen. In addition, repair of UVB-mediated development of cyclobutane pyrimidine dimers and 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) was enhanced considerably [124]. Studies have found that PFE and diallyl sulfide synergistically

reduced the tumor incidence and caused regression in tumor volume in a 2-stage mouse skin tumorigenesis model due to down-regulation in the expression of ERK1/2 and JNK1, and a decrease in NF- κ B/p65 expression [125]. Moreover, increased expression of the tumor suppressor p53 and cyclin kinase inhibitor p21 was observed along with the down-regulation of NF- κ B and IKK α , together with inhibition of the phosphorylation and degradation of I κ B α [124, 126]. PFE also suppressed UVB-mediated phosphorylation of MAPK and inhibited p38 protein expression [126]. Another *in vivo* study by Hora JJ *et al.*, has shown that 5% pomegranate seed oil considerably reduced the expression of 12-O-tetradecanoylphorbol 13-acetate (TPA)-induced ODC activity that assists in skin cancer promotion [122]. Overall, pomegranate has been found to possess potent, efficacious chemopreventive properties against skin cancer while demonstrating no adverse side effects.

4.9 Pomegranate and other cancers

Pomegranate is known for its multiple health benefits and the possession of anti-cancerous properties. It has been shown that the polyphenolic-rich extracts of the non-edible parts of *Punica granatum*, such as leaves, stem, and flower extract, elicit anti-proliferative and apoptotic effects, with a rise in loss of mitochondrial membrane potential and cell cycle arrest, and reduced expression of MMP in U266 multiple myeloma cells [127]. Moreover, PJ showed anti-proliferative and anti-angiogenic properties and induced cell cycle arrest at the G0/G1 phase in multiple myeloma cells [128]. Ellagic acid obtained from the pomegranate peel extract was found to inhibit Hela cell invasion via suppression of the AKT/mTOR signaling pathway due to augmentation in the level of IGFBP7 expression [129]. Experimental studies have shown that PPE and the seed extract also inhibit the growth and proliferation of SKOV3 ovarian cancer cells [31, 109]. In addition, punicalagin has been found to inhibit cell proliferation and induce cell cycle arrest at the G1/S phase, thereby promoting apoptosis via up-regulation of Bax and down-regulation of Bcl-2 expression [66]. Nair V *et al.*, demonstrated that PE altered the cell phenotype by elevating the proportion of cells deficient in the expression of CD44 and CD24. PE was also found to be highly efficacious in suppressing the rate of cell proliferation of PANC-1 and AsPC-1 pancreatic cells, as compared to the dose of paclitaxel prescribed clinically [130]. Further investigations concluded that ellagic acid, luteolin, and ursolic acid are the compounds that were responsible for the decreased cell proliferation of PANC-1 cells in a dose-dependent manner [130].

5. Clinicopathological studies of pomegranate on cancer

Several clinical trials have been performed in recent years on the anti-cancerous properties of pomegranate in colon and prostate cancer [97, 131]. Studies have shown that pomegranate juice possesses protective properties against prostate cancer [131]. A 14.7% rise in the median levels has been observed for prostate-specific antigen (PSA) in the patients who received a food supplement consisting of pomegranate, which is rich in polyphenol [132]. Pomegranate juice, extracts, and whole fruit powder were usually given for the

treatment of patients suffering from prostate cancer [131, 133-135]. Pantuck *et al.*, first reported on clinical trials in prostate cancer patients where elongation in the PSA doubling time (PSADT) was observed after treatment with PJ [133]. PSA has been reported to be the earliest biomarker of serum for the diagnosis of prostate cancer [136]. In a randomized phase II study, patients with prostate cancer were given 1 or 3 g of PE, which caused a reduction in PSA in 13% of the patients, while in 43% of patients, an elevated PSADT was observed in the two arms, with no significant side effects. Although little toxicity was observed, some patients were found to suffer from diarrhea [137]. On the contrary, Pantuck *et al.*, reported that PJ did not show any significant increase in PSADT as compared to placebo, as suggested by their placebo-controlled study [134]. A study using PE on colorectal cancer patients also found the presence of urolithin bioactive metabolites at a dose of 900 mg/day for 15 days [97]. These metabolites are synthesized by the gut microbiota and have been found to exert anti-cancer properties [138]. However, in a clinical study of 70 patients before radical prostatectomy, the oral administration of two tablets of PE or placebo for four weeks showed no dissimilarities between both arms of the study [135]. 21 of the 33 patients in the PE treated group and 12 of the 35 in placebo group showed the presence of UA glucuronide. In addition, no differences in the regulation of pS6 kinase, NF- κ B, Ki67, and PSA levels were observed in the two cohorts [135]. [Table 2]

6. Conclusion

Traditionally, pomegranate has been used by people worldwide for various medicinal applications. It has been found to be a potent anti-cancer agent that contains many bioactive components such as ellagic acid, punicalagin, and punicalgin. The extracts obtained from this plant have been found to suppress tumor cell proliferation, and induce cell cycle arrest and apoptosis through modulation of various transcription factors, signaling pathways, and the expression of various genes in both *in vitro* and *in vivo* settings. Clinical studies reported pomegranate juice intake aids in the control and stabilization of prostate and colon cancer. However, very few clinical studies have been undertaken. Therefore, more clinical studies are required to elucidate the diverse therapeutic properties of pomegranate and to establish it as an effective therapeutic strategy for the successful prevention and treatment of cancer.

Abbreviations

27HC, 27-hydroxycholesterol; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; 8-oxodG, 8-oxo-7,8-dihydro-2'-deoxyguanosine; APC, Adenomatous Polyposis Coli; AR, androgen receptors; AOM, Azoxymethane; ATP; Adenosine triphosphate ; B(a)P, Benzo(a)pyrene; Bad, Bcl-2-associated death promoter; Bax, BCL2 Associated X Protein; Bcl-2, B-cell lymphoma 2; Bcl-X(L), B-cell lymphoma-extra large; Bip, Binding immunoglobulin protein; CD31, Cluster of differentiation 31; CEA, Carcinoembryonic antigen; COX-2, Cyclooxygenase-2; CRC, Colorectal cancer; CXCL12, Chemokine (C-X-C Motif) Ligand 12; cdk, Cyclin-dependent kinase; DENA, Diethylnitrosamine; DHEA, Dehydroepiandrosterone; DHT, Dihydrotestosterone;

DMBA, 7,12-dimethylbenz[a]anthracene; DMH, 1,2-dimethylhydrazine; DSB, Double strand break; EA, Ellagic acid; ER, Estrogen receptor; ERE, Estrogen response elements; ERK1/2, Extracellular signal-regulated protein kinases 1 and 2; HIF-1, Hypoxia-inducible factor 1; HMMR, Hyaluronan-mediated motility receptor; ICAM-1, Intercellular adhesion molecule 1; IL, Interleukins; iNOS, Inducible nitric oxide synthase; $\text{I}\kappa\text{B}\alpha$ -Inhibitory kappa B alpha; JNK, c-Jun N-terminal kinases; L, luteolin; LXR, Liver X receptor; MAPK, Mitogen-activated protein kinases; MIF, Migration inhibitory factor; MMP, Matrix metalloproteinase; mTOR, Mammalian target of rapamycin; NF- κ B, Nuclear factor- κ B; Nrf2, Nuclear factor E2-related factor 2; NTCU, N-nitroso-tris-chloroethylurea; ODC, Ornithine decarboxylase; P, Punicic acid; PC, Punicalagin; PDGFB, Platelet Derived Growth Factor Subunit B; PE, Pomegranate extract; PEE, Pomegranate fruit ethanol extract; PFE, Pomegranate fruit extract; PI3K, Phosphatidylinositol-3-kinase; PJ, Pomegranate juice; PLE, Pomegranate leaves extract; PME, Pericarp of pomegranate; PPE, Pomegranate peel extract; PRE, Pomegranate rind extract; PR, Progesterone receptor; PSA, Prostate-specific antigen; PSADT, Prostate-specific antigen doubling time; PSEE, Pomegranate whole seed ethanolic extract; PSO, Pomegranate seed oil; RANTES, Regulated on Activation, Normal T cell Expressed and Secreted; RES SNEDDS, Trans-resveratrol in a self-nanoemulsifying drug delivery system; Rho, Ras homolog gene family; ROS, Reactive oxygen species; SCID, Severe combined immunodeficiency; SDF1 α , Stromal cell-derived factor 1 α ; SERMs, Selective estrogen receptor modulators; STAT3, Signal transducer and activator of transcription 3; TGF- β , Transforming growth factor- β ; Thr, Threonine; TNF- α , tumor necrosis factor alpha; TPA, 12-O-tetradecanoylphorbol 13-acetate; TRAP, Transgenic rat for adenocarcinoma of prostate; UA, Urolithin A; UB, Urolithin B; UVB, Ultraviolet B; VCAM-1, Vascular cell adhesion molecule 1; VEGF, Vascular endothelial growth factor.

Conflict of interest:

The authors expressed no conflict of interest.

Conflict of interest statement

The authors declare no conflict of interests related to this study.

Acknowledgement:

This work was supported by BT/P/ABK/03, awarded to Dr. Ajaikumar B. Kunnumakkara, by Department of Biotechnology, Government of India.

References

- [1] E. Turrini, L. Ferruzzi, C. Fimognari, Potential Effects of Pomegranate Polyphenols in Cancer Prevention and Therapy, *Oxidative medicine and cellular longevity* 2015 (2015) 938475.
- [2] J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D.M. Parkin, D. Forman, F. Bray, Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012, *International journal of cancer* 136(5) (2015) E359-86.
- [3] L. Zhang, Z. Yang, L. Granieri, A. Pasculescu, A. Datti, S.L. Asa, Z. Xu, S. Ezzat, High-throughput drug library screening identifies colchicine as a thyroid cancer inhibitor, *Oncotarget* (2016).
- [4] J. Monisha, G. Padmavathi, N.K. Roy, A. Deka, D. Bordoloi, A. Anip, A.B. Kunnumakkara, NF-kappaB Blockers Gifted by Mother Nature: Prospectives in Cancer Cell Chemosensitization, *Current pharmaceutical design* 22(27) (2016) 4173-200.
- [5] D. Bordoloi, N.K. Roy, J. Monisha, G. Padmavathi, A.B. Kunnumakkara, Multi-Targeted Agents in Cancer Cell Chemosensitization: What We Learnt from Curcumin Thus Far, *Recent patents on anti-cancer drug discovery* 11(1) (2016) 67-97.
- [6] A.B. Kunnumakkara, *Anticancer Properties of Fruits and Vegetables. A Scientific Review*, World Scientific (2015).
- [7] M.K. Shanmugam, J.H. Lee, E.Z. Chai, M.M. Kanchi, S. Kar, F. Arfuso, A. Dharmarajan, A.P. Kumar, P.S. Ramar, C.Y. Looi, M.R. Mustafa, V. Tergaonkar, A. Bishayee, K.S. Ahn, G. Sethi, Cancer prevention and therapy through the modulation of transcription factors by bioactive natural compounds, *Seminars in cancer biology* 40-41 (2016) 35-47.
- [8] M.R. Shams Ardekani, M. Hajimahmoodi, M.R. Oveisi, N. Sadeghi, B. Jannat, A.M. Ranjbar, N. Gholam, T. Moridi, Comparative Antioxidant Activity and Total Flavonoid Content of Persian Pomegranate (*Punica granatum* L.) Cultivars, *Iranian journal of pharmaceutical research : IJPR* 10(3) (2011) 519-24.
- [9] F. Martel, M. Guedes, E. Keating, Effect of polyphenols on glucose and lactate transport by breast cancer cells, *Breast cancer research and treatment* 157(1) (2016) 1-11.
- [10] J.H. Ko, G. Sethi, J.Y. Um, M.K. Shanmugam, F. Arfuso, A.P. Kumar, A. Bishayee, K.S. Ahn, The Role of Resveratrol in Cancer Therapy, *International journal of molecular sciences* 18(12) (2017).
- [11] H. Yan, K.J. Peng, Q.L. Wang, Z.Y. Gu, Y.Q. Lu, J. Zhao, F. Xu, Y.L. Liu, Y. Tang, F.M. Deng, P. Zhou, J.G. Jin, X.C. Wang, Effect of pomegranate peel polyphenol gel on cutaneous wound healing in alloxan-induced diabetic rats, *Chinese medical journal* 126(9) (2013) 1700-6.
- [12] S. Das, S. Barman, Antidiabetic and antihyperlipidemic effects of ethanolic extract of leaves of *Punica granatum* in alloxan-induced non-insulin-dependent diabetes mellitus albino rats, *Indian journal of pharmacology* 44(2) (2012) 219-24.
- [13] F. Forouzanfar, A. Afkhami Goli, E. Asadpour, A. Ghorbani, H.R. Sadeghnia, Protective Effect of *Punica granatum* L. against Serum/Glucose Deprivation-Induced PC12 Cells Injury, *Evidence-based complementary and alternative medicine : eCAM* 2013 (2013) 716730.
- [14] V.M. Adhami, I.A. Siddiqui, D.N. Syed, R.K. Lall, H. Mukhtar, Oral infusion of pomegranate fruit extract inhibits prostate carcinogenesis in the TRAMP model, *Carcinogenesis* 33(3) (2012) 644-51.
- [15] S. Bassiri-Jahromi, *Punica granatum* (Pomegranate) activity in health promotion and cancer prevention, *Oncology reviews* 12(1) (2018) 345.
- [16] E. Shaygannia, M. Bahmani, B. Zamanzad, M. Rafieian-Kopaei, A Review Study on *Punica granatum* L., *Journal of evidence-based complementary & alternative medicine* 21(3) (2016) 221-7.
- [17] N.R. Rathod, D. Biswas, H.R. Chitme, S. Ratna, I.S. Muchandi, R. Chandra, Anti-urolithiatic effects of *Punica granatum* in male rats, *Journal of ethnopharmacology* 140(2) (2012) 234-8.
- [18] A. Masci, A. Coccia, E. Lendaro, L. Mosca, P. Paolicelli, S. Cesa, Evaluation of different extraction methods from pomegranate whole fruit or peels and the antioxidant and antiproliferative activity of the polyphenolic fraction, *Food chemistry* 202 (2016) 59-69.
- [19] A. Kam, K.M. Li, V. Razmovski-Naumovski, S. Nammi, J. Shi, K. Chan, G.Q. Li, A comparative study on the inhibitory effects of different parts and chemical constituents of pomegranate on alpha-amylase and alpha-glucosidase, *Phytotherapy research : PTR* 27(11) (2013) 1614-20.

- [20] K.J. Salwe, D.O. Sachdev, Y. Bahurupi, M. Kumarappan, Evaluation of antidiabetic, hypolipidemic and antioxidant activity of hydroalcoholic extract of leaves and fruit peel of *Punica granatum* in male Wistar albino rats, *Journal of natural science, biology, and medicine* 6(1) (2015) 56-62.
- [21] P. Ankita, B. Deepti, M. Nilam, Flavonoid rich fraction of *Punica granatum* improves early diabetic nephropathy by ameliorating proteinuria and disturbed glucose homeostasis in experimental animals, *Pharmaceutical biology* 53(1) (2015) 61-71.
- [22] N. Rummun, J. Somanah, S. Ramsaha, T. Bahorun, V.S. Neergheen-Bhujun, Bioactivity of Nonedible Parts of *Punica granatum* L.: A Potential Source of Functional Ingredients, *International journal of food science* 2013 (2013) 602312.
- [23] A. Vidal, A. Fallarero, B.R. Pena, M.E. Medina, B. Gra, F. Rivera, Y. Gutierrez, P.M. Vuorela, Studies on the toxicity of *Punica granatum* L. (Punicaceae) whole fruit extracts, *Journal of ethnopharmacology* 89(2-3) (2003) 295-300.
- [24] A. Mahboubi, J. Asgarpanah, P.N. Sadaghiyani, M. Faizi, Total phenolic and flavonoid content and antibacterial activity of *Punica granatum* L. var. *pleniflora* flowers (Golnar) against bacterial strains causing foodborne diseases, *BMC complementary and alternative medicine* 15 (2015) 366.
- [25] T. Ismail, P. Sestili, S. Akhtar, Pomegranate peel and fruit extracts: a review of potential anti-inflammatory and anti-infective effects, *Journal of ethnopharmacology* 143(2) (2012) 397-405.
- [26] N. Ali, A. Jamil, S.W. Shah, I. Shah, G. Ahmed, M. Junaid, Z. Ahmed, Parasitocidal and brine shrimp cytotoxicity potential of crude methanolic extract of rind of *Punica granatum* Linn against round worms and tape worms, *Pakistan journal of pharmaceutical sciences* 28(3) (2015) 959-62.
- [27] J. Mo, P. Panichayupakaranant, N. Kaewnopparat, A. Nitruangjaras, W. Reanmongkol, Topical anti-inflammatory and analgesic activities of standardized pomegranate rind extract in comparison with its marker compound ellagic acid in vivo, *Journal of ethnopharmacology* 148(3) (2013) 901-8.
- [28] T. Usha, A.K. Goyal, S. Lubna, H. Prashanth, T.M. Mohan, V. Pande, S.K. Middha, Identification of anti-cancer targets of eco-friendly waste *Punica granatum* peel by dual reverse virtual screening and binding analysis, *Asian Pacific journal of cancer prevention : APJCP* 15(23) (2014) 10345-50.
- [29] R. Vini, S. Sreeja, *Punica granatum* and its therapeutic implications on breast carcinogenesis: A review, *BioFactors (Oxford, England)* 41(2) (2015) 78-89.
- [30] S. Wu, L. Tian, Diverse Phytochemicals and Bioactivities in the Ancient Fruit and Modern Functional Food Pomegranate (*Punica granatum*), *Molecules (Basel, Switzerland)* 22(10) (2017).
- [31] S. Modaeinama, M. Abasi, M.M. Abbasi, R. Jahanban-Esfahlan, Anti Tumoral Properties of *Punica Granatum* (Pomegranate) Peel Extract on Different Human Cancer Cells, *Asian Pacific journal of cancer prevention : APJCP* 16(14) (2015) 5697-701.
- [32] R. Kapoor, A. Ronnenberg, E. Puleo, R.T. Chatterton, Jr., J.F. Dorgan, N.P. Seeram, S.R. Sturgeon, Effects of Pomegranate Juice on Hormonal Biomarkers of Breast Cancer Risk, *Nutrition and cancer* 67(7) (2015) 1113-9.
- [33] S. Medjakovic, A. Jungbauer, Pomegranate: a fruit that ameliorates metabolic syndrome, *Food & function* 4(1) (2013) 19-39.
- [34] Y. Kumagai, S. Nakatani, H. Onodera, A. Nagatomo, N. Nishida, Y. Matsuura, K. Kobata, M. Wada, Anti-Glycation Effects of Pomegranate (*Punica granatum* L.) Fruit Extract and Its Components in Vivo and in Vitro, *Journal of agricultural and food chemistry* 63(35) (2015) 7760-4.
- [35] M. Mohan, P. Patankar, P. Ghadi, S. Kasture, Cardioprotective potential of *Punica granatum* extract in isoproterenol-induced myocardial infarction in Wistar rats, *Journal of pharmacology & pharmacotherapeutics* 1(1) (2010) 32-7.
- [36] D. Heber, Multitargeted therapy of cancer by ellagitannins, *Cancer letters* 269(2) (2008) 262-8.
- [37] J.G. Choi, O.H. Kang, Y.S. Lee, H.S. Chae, Y.C. Oh, O.O. Brice, M.S. Kim, D.H. Sohn, H.S. Kim, H. Park, D.W. Shin, J.R. Rho, D.Y. Kwon, In Vitro and In Vivo Antibacterial Activity of *Punica granatum* Peel Ethanol Extract against *Salmonella*, *Evidence-based complementary and alternative medicine : eCAM* 2011 (2011) 690518.
- [38] M. Garaiova, E. Mietkiewska, R.J. Weselake, R. Holic, Metabolic engineering of *Schizosaccharomyces pombe* to produce punicalic acid, a conjugated fatty acid with nutraceutical properties, *Applied microbiology and biotechnology* 101(21) (2017) 7913-7922.

- [39] R. Suzuki, R. Noguchi, T. Ota, M. Abe, K. Miyashita, T. Kawada, Cytotoxic effect of conjugated trienoic fatty acids on mouse tumor and human monocytic leukemia cells, *Lipids* 36(5) (2001) 477-82.
- [40] M.M. Joseph, S.R. Aravind, S. Varghese, S. Mini, T.T. Sreelekha, Evaluation of antioxidant, antitumor and immunomodulatory properties of polysaccharide isolated from fruit rind of *Punica granatum*, *Molecular medicine reports* 5(2) (2012) 489-96.
- [41] S. Varghese, M.M. Joseph, R.A. S, S.U. B, T.T. Sreelekha, The inhibitory effect of anti-tumor polysaccharide from *Punica granatum* on metastasis, *International journal of biological macromolecules* 103 (2017) 1000-1010.
- [42] H. Dahlawi, N. Jordan-Mahy, M. Clench, G.J. McDougall, C.L. Maitre, Polyphenols are responsible for the proapoptotic properties of pomegranate juice on leukemia cell lines, *Food science & nutrition* 1(2) (2013) 196-208.
- [43] Y. Li, F. Yang, W. Zheng, M. Hu, J. Wang, S. Ma, Y. Deng, Y. Luo, T. Ye, W. Yin, *Punica granatum* (pomegranate) leaves extract induces apoptosis through mitochondrial intrinsic pathway and inhibits migration and invasion in non-small cell lung cancer in vitro, *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* 80 (2016) 227-35.
- [44] H.S. Chen, M.H. Bai, T. Zhang, G.D. Li, M. Liu, Ellagic acid induces cell cycle arrest and apoptosis through TGF-beta/Smad3 signaling pathway in human breast cancer MCF-7 cells, *International journal of oncology* 46(4) (2015) 1730-8.
- [45] S. Costantini, F. Rusolo, V. De Vito, S. Moccia, G. Picariello, F. Capone, E. Guerriero, G. Castello, M.G. Volpe, Potential anti-inflammatory effects of the hydrophilic fraction of pomegranate (*Punica granatum* L.) seed oil on breast cancer cell lines, *Molecules (Basel, Switzerland)* 19(6) (2014) 8644-60.
- [46] A. Naiki-Ito, T. Chewonarin, M. Tang, P. Pitchakarn, T. Kuno, K. Ogawa, M. Asamoto, T. Shirai, S. Takahashi, Ellagic acid, a component of pomegranate fruit juice, suppresses androgen-dependent prostate carcinogenesis via induction of apoptosis, *The Prostate* 75(2) (2015) 151-60.
- [47] A. Malik, F. Afaq, S. Sarfaraz, V.M. Adhami, D.N. Syed, H. Mukhtar, Pomegranate fruit juice for chemoprevention and chemotherapy of prostate cancer, *Proceedings of the National Academy of Sciences of the United States of America* 102(41) (2005) 14813-8.
- [48] A. Malik, H. Mukhtar, Prostate cancer prevention through pomegranate fruit, *Cell cycle (Georgetown, Tex.)* 5(4) (2006) 371-3.
- [49] N.A. Sadik, O.G. Shaker, Inhibitory effect of a standardized pomegranate fruit extract on Wnt signalling in 1, 2-dimethylhydrazine induced rat colon carcinogenesis, *Digestive diseases and sciences* 58(9) (2013) 2507-17.
- [50] N. Khan, N. Hadi, F. Afaq, D.N. Syed, M.H. Kweon, H. Mukhtar, Pomegranate fruit extract inhibits prosurvival pathways in human A549 lung carcinoma cells and tumor growth in athymic nude mice, *Carcinogenesis* 28(1) (2007) 163-73.
- [51] X. Li, X. Gong, J. Chen, J. Zhang, J. Sun, M. Guo, miR-340 inhibits glioblastoma cell proliferation by suppressing CDK6, cyclin-D1 and cyclin-D2, *Biochemical and biophysical research communications* 460(3) (2015) 670-7.
- [52] P. Pitchakarn, T. Chewonarin, K. Ogawa, S. Suzuki, M. Asamoto, S. Takahashi, T. Shirai, P. Limtrakul, Ellagic acid inhibits migration and invasion by prostate cancer cell lines, *Asian Pacific journal of cancer prevention : APJCP* 14(5) (2013) 2859-63.
- [53] L. Wang, A. Alcon, H. Yuan, J. Ho, Q.J. Li, M. Martins-Green, Cellular and molecular mechanisms of pomegranate juice-induced anti-metastatic effect on prostate cancer cells, *Integrative biology : quantitative biosciences from nano to macro* 3(7) (2011) 742-54.
- [54] J.M. Zhang, J. An, Cytokines, inflammation, and pain, *International anesthesiology clinics* 45(2) (2007) 27-37.
- [55] L.S. Adams, N.P. Seeram, B.B. Aggarwal, Y. Takada, D. Sand, D. Heber, Pomegranate juice, total pomegranate ellagitannins, and punicalagin suppress inflammatory cell signaling in colon cancer cells, *Journal of agricultural and food chemistry* 54(3) (2006) 980-5.
- [56] A. Bishayee, R.J. Thoppil, A.S. Darvesh, V. Ohanyan, J.G. Meszaros, D. Bhatia, Pomegranate phytoconstituents blunt the inflammatory cascade in a chemically induced rodent model of hepatocellular carcinogenesis, *The Journal of nutritional biochemistry* 24(1) (2013) 178-87.

- [57] M.I. Waly, A. Ali, N. Guizani, A.S. Al-Rawahi, S.A. Farooq, M.S. Rahman, Pomegranate (*Punica granatum*) peel extract efficacy as a dietary antioxidant against azoxymethane-induced colon cancer in rat, *Asian Pacific journal of cancer prevention* : APJCP 13(8) (2012) 4051-5.
- [58] N. Banerjee, H. Kim, S. Talcott, S. Mertens-Talcott, Pomegranate polyphenolics suppressed azoxymethane-induced colorectal aberrant crypt foci and inflammation: possible role of miR-126/VCAM-1 and miR-126/PI3K/AKT/mTOR, *Carcinogenesis* 34(12) (2013) 2814-22.
- [59] N. Khan, F. Afaq, M.H. Kweon, K. Kim, H. Mukhtar, Oral consumption of pomegranate fruit extract inhibits growth and progression of primary lung tumors in mice, *Cancer research* 67(7) (2007) 3475-82.
- [60] S. Koyama, L.J. Cobb, H.H. Mehta, N.P. Seeram, D. Heber, A.J. Pantuck, P. Cohen, Pomegranate extract induces apoptosis in human prostate cancer cells by modulation of the IGF-IGFBP axis, *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society* 20(1) (2010) 55-62.
- [61] M.B. Rettig, D. Heber, J. An, N.P. Seeram, J.Y. Rao, H. Liu, T. Klatter, A. Beldegrun, A. Moro, S.M. Henning, D. Mo, W.J. Aronson, A. Pantuck, Pomegranate extract inhibits androgen-independent prostate cancer growth through a nuclear factor-kappaB-dependent mechanism, *Molecular cancer therapeutics* 7(9) (2008) 2662-71.
- [62] A. Mandal, D. Bhatia, A. Bishayee, Anti-Inflammatory Mechanism Involved in Pomegranate-Mediated Prevention of Breast Cancer: the Role of NF-kappaB and Nrf2 Signaling Pathways, *Nutrients* 9(5) (2017).
- [63] A. Bishayee, D. Bhatia, R.J. Thoppil, A.S. Darvesh, E. Nevo, E.P. Lansky, Pomegranate-mediated chemoprevention of experimental hepatocarcinogenesis involves Nrf2-regulated antioxidant mechanisms, *Carcinogenesis* 32(6) (2011) 888-96.
- [64] L. Wang, W. Li, M. Lin, M. Garcia, D. Mulholland, M. Lilly, M. Martins-Green, Luteolin, ellagic acid and punicic acid are natural products that inhibit prostate cancer metastasis, *Carcinogenesis* 35(10) (2014) 2321-30.
- [65] Y. Dong, L. Sui, K. Sugimoto, Y. Tai, M. Tokuda, Cyclin D1-CDK4 complex, a possible critical factor for cell proliferation and prognosis in laryngeal squamous cell carcinomas, *International journal of cancer* 95(4) (2001) 209-15.
- [66] J.M. Tang, J. Min, B.S. Li, S.S. Hong, C. Liu, M. Hu, Y. Li, J. Yang, L. Hong, Therapeutic Effects of Punicalagin Against Ovarian Carcinoma Cells in Association With beta-Catenin Signaling Inhibition, *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* 26(9) (2016) 1557-1563.
- [67] A.B. Shirode, P. Kovvuru, S.V. Chittur, S.M. Henning, D. Heber, R. Reliene, Antiproliferative effects of pomegranate extract in MCF-7 breast cancer cells are associated with reduced DNA repair gene expression and induction of double strand breaks, *Molecular carcinogenesis* 53(6) (2014) 458-70.
- [68] M.J. Asmaa, A.J. Ali, J.M. Farid, S. Azman, Growth inhibitory effects of crude pomegranate peel extract on chronic myeloid leukemia, K562 cells, *International journal of applied & basic medical research* 5(2) (2015) 100-5.
- [69] W.G. Stetler-Stevenson, Type IV collagenases in tumor invasion and metastasis, *Cancer metastasis reviews* 9(4) (1990) 289-303.
- [70] L. Wang, J. Ho, C. Glackin, M. Martins-Green, Specific pomegranate juice components as potential inhibitors of prostate cancer metastasis, *Translational oncology* 5(5) (2012) 344-55.
- [71] A. Sahebkar, C. Gurban, A. Serban, F. Andrica, M.C. Serban, Effects of supplementation with pomegranate juice on plasma C-reactive protein concentrations: A systematic review and meta-analysis of randomized controlled trials, *Phytomedicine : international journal of phytotherapy and phytopharmacology* 23(11) (2016) 1095-102.
- [72] A. Sahebkar, L.E. Simental-Mendia, P. Giorgini, C. Ferri, D. Grassi, Lipid profile changes after pomegranate consumption: A systematic review and meta-analysis of randomized controlled trials, *Phytomedicine : international journal of phytotherapy and phytopharmacology* 23(11) (2016) 1103-12.
- [73] T.F. Wu, L.T. Hsu, B.X. Tsang, L.C. Huang, W.Y. Shih, L.Y. Chen, Clarification of the molecular pathway of Taiwan local pomegranate fruit juice underlying the inhibition of urinary bladder urothelial carcinoma cell by proteomics strategy, *BMC complementary and alternative medicine* 16 (2016) 96.
- [74] O. Fahmy, M.G. Khairul-Asri, A. Stenzl, G. Gakis, The current status of checkpoint inhibitors in metastatic bladder cancer, *Clinical & experimental metastasis* 33(7) (2016) 629-35.

- [75] S.T. Lee, M.H. Lu, L.H. Chien, T.F. Wu, L.C. Huang, G.I. Liao, Suppression of urinary bladder urothelial carcinoma cell by the ethanol extract of pomegranate fruit through cell cycle arrest and apoptosis, *BMC complementary and alternative medicine* 13 (2013) 364.
- [76] A. Rocha, L. Wang, M. Penichet, M. Martins-Green, Pomegranate juice and specific components inhibit cell and molecular processes critical for metastasis of breast cancer, *Breast cancer research and treatment* 136(3) (2012) 647-58.
- [77] D. Sinha, N. Sarkar, J. Biswas, A. Bishayee, Resveratrol for breast cancer prevention and therapy: Preclinical evidence and molecular mechanisms, *Seminars in cancer biology* 40-41 (2016) 209-232.
- [78] L.S. Adams, Y. Zhang, N.P. Seeram, D. Heber, S. Chen, Pomegranate ellagitannin-derived compounds exhibit antiproliferative and antiaromatase activity in breast cancer cells in vitro, *Cancer prevention research (Philadelphia, Pa.)* 3(1) (2010) 108-13.
- [79] S.R. Sturgeon, A.G. Ronnenberg, Pomegranate and breast cancer: possible mechanisms of prevention, *Nutrition reviews* 68(2) (2010) 122-8.
- [80] E.R. Nelson, S.E. Wardell, J.S. Jasper, S. Park, S. Suchindran, M.K. Howe, N.J. Carver, R.V. Pillai, P.M. Sullivan, V. Sondhi, M. Umetani, J. Geradts, D.P. McDonnell, 27-Hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology, *Science (New York, N.Y.)* 342(6162) (2013) 1094-8.
- [81] R. Vini, A.M. Juberiya, S. Sreeja, Evidence of pomegranate methanolic extract in antagonizing the endogenous SERM, 27-hydroxycholesterol, *IUBMB life* 68(2) (2016) 116-21.
- [82] S. Sreeja, T.R. Santhosh Kumar, B.S. Lakshmi, S. Sreeja, Pomegranate extract demonstrate a selective estrogen receptor modulator profile in human tumor cell lines and in vivo models of estrogen deprivation, *The Journal of nutritional biochemistry* 23(7) (2012) 725-32.
- [83] M. Dikmen, N. Ozturk, Y. Ozturk, The antioxidant potency of *Punica granatum* L. Fruit peel reduces cell proliferation and induces apoptosis on breast cancer, *Journal of medicinal food* 14(12) (2011) 1638-46.
- [84] M.A. Jeune, J. Kumi-Diaka, J. Brown, Anticancer activities of pomegranate extracts and genistein in human breast cancer cells, *Journal of medicinal food* 8(4) (2005) 469-75.
- [85] M.E. Grossmann, N.K. Mizuno, T. Schuster, M.P. Cleary, Punicic acid is an omega-5 fatty acid capable of inhibiting breast cancer proliferation, *International journal of oncology* 36(2) (2010) 421-6.
- [86] M. Toi, H. Bando, C. Ramachandran, S.J. Melnick, A. Imai, R.S. Fife, R.E. Carr, T. Oikawa, E.P. Lansky, Preliminary studies on the anti-angiogenic potential of pomegranate fractions in vitro and in vivo, *Angiogenesis* 6(2) (2003) 121-8.
- [87] N.D. Kim, 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, E. Lansky, Chemopreventive and adjuvant therapeutic potential of pomegranate (*Punica granatum*) for human breast cancer, *Breast cancer research and treatment* 71(3) (2002) 203-17.
- [88] Z. Dai, V. Nair, M. Khan, H.P. Ciolino, Pomegranate extract inhibits the proliferation and viability of MMTV-Wnt-1 mouse mammary cancer stem cells in vitro, *Oncology reports* 24(4) (2010) 1087-91.
- [89] G.N. Khan, M.A. Gorin, D. Rosenthal, Q. Pan, L.W. Bao, Z.F. Wu, R.A. Newman, A.D. Pawlus, P. Yang, E.P. Lansky, S.D. Merajver, Pomegranate fruit extract impairs invasion and motility in human breast cancer, *Integrative cancer therapies* 8(3) (2009) 242-53.
- [90] A. Mandal, A. Bishayee, Mechanism of Breast Cancer Preventive Action of Pomegranate: Disruption of Estrogen Receptor and Wnt/beta-Catenin Signaling Pathways, *Molecules (Basel, Switzerland)* 20(12) (2015) 22315-28.
- [91] R. Mehta, E.P. Lansky, Breast cancer chemopreventive properties of pomegranate (*Punica granatum*) fruit extracts in a mouse mammary organ culture, *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)* 13(4) (2004) 345-8.
- [92] A.B. Shirode, D.J. Bharali, S. Nallanthighal, J.K. Coon, S.A. Mousa, R. Reliene, Nanoencapsulation of pomegranate bioactive compounds for breast cancer chemoprevention, *International journal of nanomedicine* 10 (2015) 475-84.
- [93] L.Y. Lu, Y. Liu, Z.F. Zhang, X.J. Gou, J.H. Jiang, J.Z. Zhang, Q. Yao, Pomegranate Seed Oil Exerts Synergistic Effects with trans-Resveratrol in a Self-nanoemulsifying Drug Delivery System, *Biological & pharmaceutical bulletin* 38(10) (2015) 1658-62.

- [94] M. Ganeshkumar, M. Sathishkumar, T. Ponrasu, M.G. Dinesh, L. Suguna, Spontaneous ultra fast synthesis of gold nanoparticles using *Punica granatum* for cancer targeted drug delivery, *Colloids and surfaces. B, Biointerfaces* 106 (2013) 208-16.
- [95] M.A. Nunez-Sanchez, A. Gonzalez-Sarrias, M. Romo-Vaquero, R. Garcia-Villalba, M.V. Selma, F.A. Tomas-Barberan, M.T. Garcia-Conesa, J.C. Espin, Dietary phenolics against colorectal cancer--From promising preclinical results to poor translation into clinical trials: Pitfalls and future needs, *Molecular nutrition & food research* 59(7) (2015) 1274-91.
- [96] N.P. Seeram, L.S. Adams, S.M. Henning, Y. Niu, Y. Zhang, M.G. Nair, D. Heber, 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 Journal of nutritional biochemistry* 16(6) (2005) 360-7.
- [97] M.A. Nunez-Sanchez, R. Garcia-Villalba, T. Monedero-Saiz, N.V. Garcia-Talavera, M.B. Gomez-Sanchez, C. Sanchez-Alvarez, A.M. Garcia-Albert, F.J. Rodriguez-Gil, M. Ruiz-Marin, F.A. Pastor-Quirante, F. Martinez-Diaz, M.J. Yanez-Gascon, A. Gonzalez-Sarrias, F.A. Tomas-Barberan, J.C. Espin, Targeted metabolic profiling of pomegranate polyphenols and urolithins in plasma, urine and colon tissues from colorectal cancer patients, *Molecular nutrition & food research* 58(6) (2014) 1199-211.
- [98] M. Larrosa, F.A. Tomas-Barberan, J.C. Espin, The dietary hydrolysable tannin punicalagin releases ellagic acid that induces apoptosis in human colon adenocarcinoma Caco-2 cells by using the mitochondrial pathway, *The Journal of nutritional biochemistry* 17(9) (2006) 611-25.
- [99] M.I. Waly, A.S. Al-Rawahi, M. Al Riyami, M.A. Al-Kindi, H.K. Al-Issaei, S.A. Farooq, A. Al-Alawi, M.S. Rahman, Amelioration of azoxymethane induced-carcinogenesis by reducing oxidative stress in rat colon by natural extracts, *BMC complementary and alternative medicine* 14 (2014) 60.
- [100] H. Kohno, R. Suzuki, Y. Yasui, M. Hosokawa, K. Miyashita, T. Tanaka, Pomegranate seed oil rich in conjugated linolenic acid suppresses chemically induced colon carcinogenesis in rats, *Cancer science* 95(6) (2004) 481-6.
- [101] J. Boateng, M. Verghese, L. Shackelford, L.T. Walker, J. Khatiwada, S. Ogutu, D.S. Williams, J. Jones, M. Guyton, D. Asiamah, F. Henderson, L. Grant, M. DeBruce, A. Johnson, S. Washington, C.B. Chawan, Selected fruits reduce azoxymethane (AOM)-induced aberrant crypt foci (ACF) in Fisher 344 male rats, *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association* 45(5) (2007) 725-32.
- [102] American Cancer Society, *Cancer Facts & Figures*, (2013).
- [103] S. Kawaii, E.P. Lansky, Differentiation-promoting activity of pomegranate (*Punica granatum*) fruit extracts in HL-60 human promyelocytic leukemia cells, *Journal of medicinal food* 7(1) (2004) 13-8.
- [104] Z. Li, S.S. Percival, S. Bonard, L. Gu, Fabrication of nanoparticles using partially purified pomegranate ellagitannins and gelatin and their apoptotic effects, *Molecular nutrition & food research* 55(7) (2011) 1096-103.
- [105] N.E. El-Ashmawy, E.G. Khedr, H.A. El-Bahrawy, E.E. Abd El-Fattah, Effect of Pomegranate Hull Extract on Liver Neoplastic Changes in Rats: More than an Antioxidant, *Nutrition and cancer* 68(6) (2016) 1044-51.
- [106] B. Song, J. Li, J. Li, Pomegranate peel extract polyphenols induced apoptosis in human hepatoma cells by mitochondrial pathway, *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association* 93 (2016) 158-66.
- [107] I. Celik, A. Temur, I. Isik, Hepatoprotective role and antioxidant capacity of pomegranate (*Punica granatum*) flowers infusion against trichloroacetic acid-exposed in rats, *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association* 47(1) (2009) 145-9.
- [108] R.G. Saratale, H.S. Shin, G. Kumar, G. Benelli, D.S. Kim, G.D. Saratale, Exploiting antidiabetic activity of silver nanoparticles synthesized using *Punica granatum* leaves and anticancer potential against human liver cancer cells (HepG2), *Artificial cells, nanomedicine, and biotechnology* (2017) 1-12.
- [109] K. Seidi, R. Jahanban-Esfahlan, M. Abasi, M.M. Abbasi, Anti Tumoral Properties of *Punica granatum* (Pomegranate) Seed Extract in Different Human Cancer Cells, *Asian Pacific journal of cancer prevention : APJCP* 17(3) (2016) 1119-22.

- [110] S.T. Lee, Y.L. Wu, L.H. Chien, S.T. Chen, Y.K. Tzeng, T.F. Wu, Proteomic exploration of the impacts of pomegranate fruit juice on the global gene expression of prostate cancer cell, *Proteomics* 12(21) (2012) 3251-62.
- [111] M.R. Sartippour, N.P. Seeram, J.Y. Rao, A. Moro, D.M. Harris, S.M. Henning, A. Firouzi, M.B. Rettig, W.J. Aronson, A.J. Pantuck, D. Heber, Ellagitannin-rich pomegranate extract inhibits angiogenesis in prostate cancer in vitro and in vivo, *International journal of oncology* 32(2) (2008) 475-80.
- [112] J. Gasmi, J.T. Sanderson, Growth inhibitory, antiandrogenic, and pro-apoptotic effects of punicalic acid in LNCaP human prostate cancer cells, *Journal of agricultural and food chemistry* 58(23) (2010) 12149-56.
- [113] O. Adaramoye, B. Erguen, B. Nitzsche, M. Hopfner, K. Jung, A. Rabien, Punicalagin, a polyphenol from pomegranate fruit, induces growth inhibition and apoptosis in human PC-3 and LNCaP cells, *Chemico-biological interactions* 274 (2017) 100-106.
- [114] N.P. Seeram, W.J. Aronson, Y. Zhang, S.M. Henning, A. Moro, R.P. Lee, M. Sartippour, D.M. Harris, M. Rettig, M.A. Suchard, A.J. Pantuck, A. Beldegrun, D. Heber, Pomegranate ellagitannin-derived metabolites inhibit prostate cancer growth and localize to the mouse prostate gland, *Journal of agricultural and food chemistry* 55(19) (2007) 7732-7.
- [115] R. Vicinanza, Y. Zhang, S.M. Henning, D. Heber, Pomegranate Juice Metabolites, Ellagic Acid and Urolithin A, Synergistically Inhibit Androgen-Independent Prostate Cancer Cell Growth via Distinct Effects on Cell Cycle Control and Apoptosis, *Evidence-based complementary and alternative medicine : eCAM* 2013 (2013) 247504.
- [116] D.S. Ming, S. Pham, S. Deb, M.Y. Chin, G. Kharmate, H. Adomat, E.H. Beheshti, J. Locke, E.T. Guns, Pomegranate extracts impact the androgen biosynthesis pathways in prostate cancer models in vitro and in vivo, *The Journal of steroid biochemistry and molecular biology* 143 (2014) 19-28.
- [117] M.Y. Hong, N.P. Seeram, D. Heber, Pomegranate polyphenols down-regulate expression of androgen-synthesizing genes in human prostate cancer cells overexpressing the androgen receptor, *The Journal of nutritional biochemistry* 19(12) (2008) 848-55.
- [118] Y. Wang, S. Zhang, S. Iqbal, Z. Chen, X. Wang, Y.A. Wang, D. Liu, K. Bai, C. Ritenour, O. Kucuk, D. Wu, Pomegranate extract inhibits the bone metastatic growth of human prostate cancer cells and enhances the in vivo efficacy of docetaxel chemotherapy, *The Prostate* (2013).
- [119] Y. Deng, Y. Li, F. Yang, A. Zeng, S. Yang, Y. Luo, Y. Zhang, Y. Xie, T. Ye, Y. Xia, W. Yin, The extract from *Punica granatum* (pomegranate) peel induces apoptosis and impairs metastasis in prostate cancer cells, *Biomedicine & pharmacotherapy* 93 (2017) 976-984.
- [120] P. Lucci, D. Pacetti, M.R. Loizzo, N.G. Frega, *Punica granatum* cv. Dente di Cavallo seed ethanolic extract: antioxidant and antiproliferative activities, *Food chemistry* 167 (2015) 475-83.
- [121] M. Tonk, A. Vilcinskis, M. Rahnamaeian, Insect antimicrobial peptides: potential tools for the prevention of skin cancer, *Applied microbiology and biotechnology* 100(17) (2016) 7397-405.
- [122] J.J. Hora, E.R. Maydew, E.P. Lansky, C. Dwivedi, Chemopreventive effects of pomegranate seed oil on skin tumor development in CD1 mice, *Journal of medicinal food* 6(3) (2003) 157-61.
- [123] F. Afaq, M. Saleem, C.G. Krueger, J.D. Reed, H. Mukhtar, Anthocyanin- and hydrolyzable tannin-rich pomegranate fruit extract modulates MAPK and NF-kappaB pathways and inhibits skin tumorigenesis in CD-1 mice, *International journal of cancer* 113(3) (2005) 423-33.
- [124] F. Afaq, N. Khan, D.N. Syed, H. Mukhtar, Oral feeding of pomegranate fruit extract inhibits early biomarkers of UVB radiation-induced carcinogenesis in SKH-1 hairless mouse epidermis, *Photochemistry and photobiology* 86(6) (2010) 1318-26.
- [125] J. George, M. Singh, A.K. Srivastava, K. Bhui, Y. Shukla, Synergistic growth inhibition of mouse skin tumors by pomegranate fruit extract and diallyl sulfide: evidence for inhibition of activated MAPKs/NF-kappaB and reduced cell proliferation, *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association* 49(7) (2011) 1511-20.
- [126] F. Afaq, A. Malik, D. Syed, D. Maes, M.S. Matsui, H. Mukhtar, Pomegranate fruit extract modulates UV-B-mediated phosphorylation of mitogen-activated protein kinases and activation of nuclear factor kappa B in normal human epidermal keratinocytes paragraph sign, *Photochemistry and photobiology* 81(1) (2005) 38-45.

- [127] Y. Kiraz, V.S. Neergheen-Bhujun, N. Rummun, Y. Baran, Apoptotic effects of non-edible parts of *Punica granatum* on human multiple myeloma cells, *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine* 37(2) (2016) 1803-15.
- [128] D. Tibullo, N. Caporarello, C. Giallongo, C.D. Anfuso, C. Genovese, C. Arlotta, F. Puglisi, N.L. Parrinello, V. Bramanti, A. Romano, G. Lupo, V. Toscano, R. Avola, M.V. Brundo, F. Di Raimondo, S.A. Raccuia, Antiproliferative and Antiangiogenic Effects of *Punica granatum* Juice (PGJ) in Multiple Myeloma (MM), *Nutrients* 8(10) (2016).
- [129] H. Guo, D. Zhang, Q. Fu, Inhibition of Cervical Cancer by Promoting IGFBP7 Expression Using Ellagic Acid from Pomegranate Peel, *Medical science monitor : international medical journal of experimental and clinical research* 22 (2016) 4881-4886.
- [130] V. Nair, Z. Dai, M. Khan, H.P. Ciolino, Pomegranate extract induces cell cycle arrest and alters cellular phenotype of human pancreatic cancer cells, *Anticancer research* 31(9) (2011) 2699-704.
- [131] A. Gonzalez-Sarrias, J.A. Gimenez-Bastida, M.T. Garcia-Conesa, M.B. Gomez-Sanchez, N.V. Garcia-Talavera, A. Gil-Izquierdo, C. Sanchez-Alvarez, L.O. Fontana-Compiano, J.P. Morga-Egea, F.A. Pastor-Quirante, F. Martinez-Diaz, F.A. Tomas-Barberan, J.C. Espin, Occurrence of urolithins, gut microbiota ellagic acid metabolites and proliferation markers expression response in the human prostate gland upon consumption of walnuts and pomegranate juice, *Molecular nutrition & food research* 54(3) (2010) 311-22.
- [132] R. Thomas, M. Williams, H. Sharma, A. Chaudry, P. Bellamy, A double-blind, placebo-controlled randomised trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer--the U.K. NCRN Pomi-T study, *Prostate cancer and prostatic diseases* 17(2) (2014) 180-6.
- [133] A.J. Pantuck, 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, A. Belldegrun, Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer, *Clinical cancer research : an official journal of the American Association for Cancer Research* 12(13) (2006) 4018-26.
- [134] A.J. Pantuck, C.A. Pettaway, R. Dreicer, J. Corman, A. Katz, A. Ho, W. Aronson, W. Clark, G. Simmons, D. Heber, A randomized, double-blind, placebo-controlled study of the effects of pomegranate extract on rising PSA levels in men following primary therapy for prostate cancer, *Prostate cancer and prostatic diseases* 18(3) (2015) 242-8.
- [135] S.J. Freedland, M. Carducci, N. Kroeger, A. Partin, J.Y. Rao, Y. Jin, S. Kerkoutian, H. Wu, Y. Li, P. Creel, K. Mundy, R. Gurganus, H. Fedor, S.A. King, Y. Zhang, D. Heber, A.J. Pantuck, A double-blind, randomized, neoadjuvant study of the tissue effects of POMx pills in men with prostate cancer before radical prostatectomy, *Cancer prevention research (Philadelphia, Pa.)* 6(10) (2013) 1120-7.
- [136] K. Ito, T. Yamamoto, M. Ohi, K. Kurokawa, K. Suzuki, H. Yamanaka, Free/total PSA ratio is a powerful predictor of future prostate cancer morbidity in men with initial PSA levels of 4.1 to 10.0 ng/mL, *Urology* 61(4) (2003) 760-4.
- [137] C.J. Paller, X. Ye, P.J. Wozniak, B.K. Gillespie, P.R. Sieber, R.H. Greengold, B.R. Stockton, B.L. Hertzman, M.D. Efron, R.P. Roper, H.R. Liker, M.A. Carducci, A randomized phase II study of pomegranate extract for men with rising PSA following initial therapy for localized prostate cancer, *Prostate cancer and prostatic diseases* 16(1) (2013) 50-5.
- [138] A. Gonzalez-Sarrias, M.A. Nunez-Sanchez, R. Garcia-Villalba, F.A. Tomas-Barberan, J.C. Espin, Antiproliferative activity of the ellagic acid-derived gut microbiota isourolithin A and comparison with its urolithin A isomer: the role of cell metabolism, *European journal of nutrition* 56(2) (2017) 831-841.
- [139] B. Zhou, H. Yi, J. Tan, Y. Wu, G. Liu, Z. Qiu, Anti-proliferative effects of polyphenols from pomegranate rind (*Punica granatum* L.) on EJ bladder cancer cells via regulation of p53/miR-34a axis, *Phytotherapy research : PTR* 29(3) (2015) 415-22.
- [140] A. Bishayee, A. Mandal, P. Bhattacharyya, D. Bhatia, Pomegranate exerts chemoprevention of experimentally induced mammary tumorigenesis by suppression of cell proliferation and induction of apoptosis, *Nutrition and cancer* 68(1) (2016) 120-30.
- [141] F. Aqil, R. Munagala, M.V. Vadhanam, H. Kausar, J. Jeyabalan, D.J. Schultz, R.C. Gupta, Anti-proliferative activity and protection against oxidative DNA damage by punicalagin isolated from pomegranate husk, *Food research international (Ottawa, Ont.)* 49(1) (2012) 345-353.

[142] T. Ozbay, R. Nahta, Delphinidin Inhibits HER2 and Erk1/2 Signaling and Suppresses Growth of HER2-Overexpressing and Triple Negative Breast Cancer Cell Lines, *Breast cancer : basic and clinical research* 5 (2011) 143-54.

[143] W. Zhao, Y. Wang, W. Hao, H. Yang, X. Song, M. Zhao, S. Peng, Preparative isolation and purification of urolithins from the intestinal metabolites of pomegranate ellagitannins by high-speed counter-current chromatography, *Journal of chromatography. B, Analytical technologies in the biomedical and life sciences* 990 (2015) 111-7.

[144] H. Dahlawi, N. Jordan-Mahy, M.R. Clench, C.L. Le Maitre, Bioactive actions of pomegranate fruit extracts on leukemia cell lines in vitro hold promise for new therapeutic agents for leukemia, *Nutrition and cancer* 64(1) (2012) 100-10.

[145] K. Sineh Sepmehr, B. Baradaran, M. Mazandarani, V. Khori, F.Z. Shahneh, Studies on the Cytotoxic Activities of *Punica granatum* L. var. *spinosa* (Apple Punice) Extract on Prostate Cell Line by Induction of Apoptosis, *ISRN pharmaceuticals* 2012 (2012) 547942.

[146] E.P. Lansky, G. Harrison, P. Froom, W.G. Jiang, Pomegranate (*Punica granatum*) pure chemicals show possible synergistic inhibition of human PC-3 prostate cancer cell invasion across Matrigel, *Investigational new drugs* 23(2) (2005) 121-2.

Figure legends:

Figure 1: Structures of different compounds isolated from *Punica granatum*

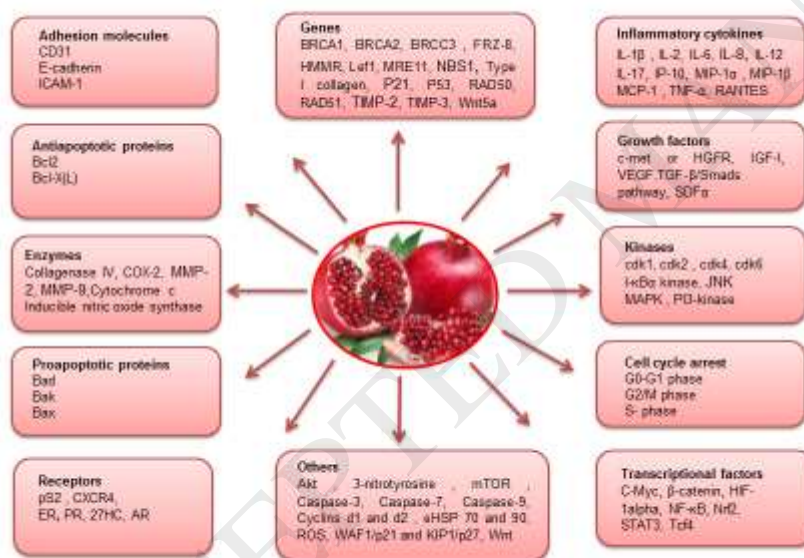
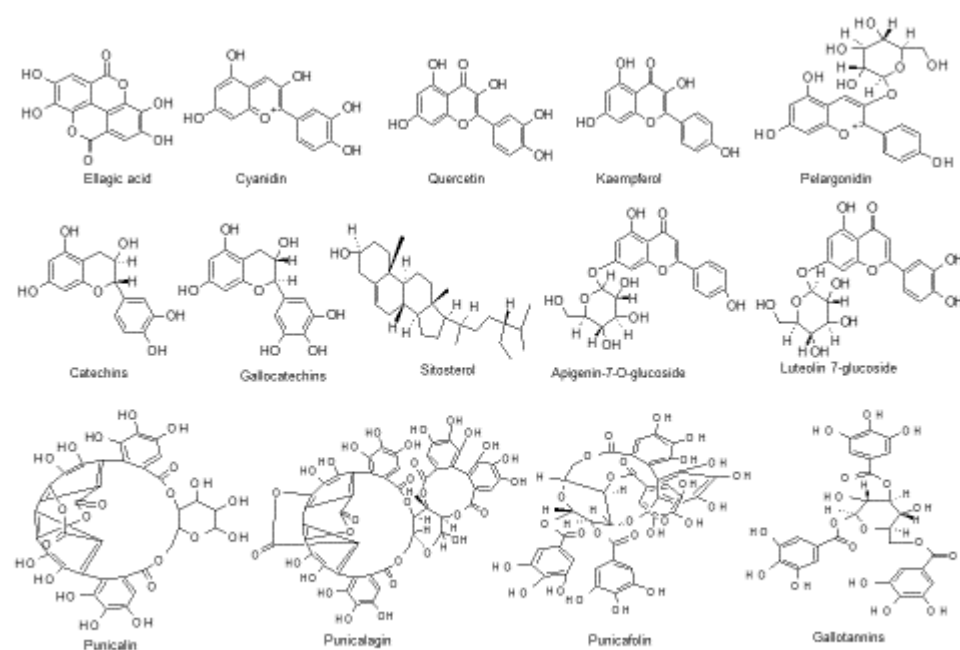


Figure 1: Molecular targets of *Punica granatum*

Figure 1: Molecular targets of *Punica granatum*

Figure 2: Molecular targets of *Punica granatum***Figure 2** Structures of different compounds isolated from pomegranate**Figure 2:** Structures of different compounds isolated from pomegranate**Table 1:** The effect of *Punica granatum* on different types of cancer (Preclinical studies)**Table 2:** Studies on the potential of *Punica granatum* in the prevention and treatment of cancer (clinical studies)**Table 1: The effect of *Punica granatum* on different types of cancer (Preclinical studies)**

Cancer	Model	<i>In vitro</i> / <i>In vivo</i> / Clinical	Effect	Reference
Bladder cancer				
	T24 cells	<i>In vitro</i>	Inactivated PTEN/AKT/mTORC1 pathway via profilin 1	[73]
	EJ cells	<i>In vitro</i>	Increased expression of p53 protein and miR-34a	[139]
	T24 and J82 cells	<i>In vitro</i>	Reduced cell growth via cell cycle arrest at S phase	[75]
	DMBA-initiated rat mammary tumor	<i>In vivo</i>	Reduced the expression of COX-2 and HSP90	[62]
	MCF-7, MDA-MB-231	<i>In vitro</i>	Reduced the ERE-mediated transcription	[81]
	MCF-7	<i>In vitro</i>	Inhibited cell proliferation	[109]
	DMBA-inflicted rat	<i>In vivo</i>	Reduced the expression of intra-tumor ER- α and ER- β , lowered	[90]
	DMBA-induced rat	<i>In vivo</i>	Up-regulation of Bad, caspase-3, caspase-7, caspase-9, poly (ADP ribose) polymerase, and cyt-c	[140]
	MCF-7	<i>In vitro</i>	Inhibited proliferation of tumor cells	[31]
	MCF-7	<i>In vitro</i>	Targeted TGF- β /Smads signaling pathway	[44]
	MCF-7	<i>In vitro</i>	Reduced the rate of proliferation of tumor cells	[120]
	MCF-7, MDA-MB-231	<i>In vitro</i>	Reduced VEGF and nine pro-inflammatory cytokines (IL-2, IL-6, IL-12, IL-17, IP-10, MIP-1 α , MIP-1 β , MCP-1, and TNF- α)	[45]
	MCF-7	<i>In vitro</i>	Inhibited tumor cell proliferation	[141]
	MCF-7	<i>In vitro</i>	Inhibited tumor growth via cell cycle arrest at G2/M	[67]
	MCF-7, MDA-MB-231	<i>In vitro</i>	Reduced pro-inflammatory cytokines/chemokines	[76]

MDA-MB-231	<i>In vitro</i>	Lowered Sp proteins and Sp-regulated genes	[58]
BT474 xenograft mice	<i>In vivo</i>	Promoted expression of SHIP-1, reduced miRNA-155, and impeded PI3K-dependent phosphorylation of AKT	
MCF-7	<i>In vitro</i>	Reduced tumor cell proliferation	[40]
MCF-7	<i>In vitro</i>	Increased expression of Bax, decreased expression of Bcl-2	[83]
MCF-7, MDA MB-231	<i>In vitro</i>	Reduced the expression of selected estrogen-responsive genes	[82]
HCC1806, MDA231, MDA468, MDA453, SKBR3, BT474, MCF7	<i>In vitro</i>	Inhibited cell growth and reduced MAPK signaling	[142]
WA4	<i>In vitro</i>	Decreased cell growth and cell viability	[88]
MCF-7	<i>In vitro</i>	Inhibited testosterone-induced cell proliferation	[78]
MDA-MB-231	<i>In vitro</i>	Reduced cell growth, disrupted mitochondrial membrane potential	[85]
MDA-ERalpha7, MDA-MB-231	<i>In vitro</i>	Retarded NF-κB-dependent reporter gene expression and reduced expression of RhoC and RhoA protein	[89]
MCF-7	<i>In vitro</i>	Inhibited cell growth and induced apoptosis	[84]
MCF-7, MDA MB-231, MCF-10A	<i>In vitro</i>	Reduced VEGF, inhibited angiogenesis	[86]
Cervical cancer			
HeLa	<i>In vitro</i>	Up-regulated the expression of IGFBP7 and inhibited AKT/mTOR pathway	[129]
Colon cancer			
Caco-2	<i>In vitro</i>	Reduced the intracellular ROS and malondialdehyde levels, and elevated the SOD activity	[143]
HT29, HCT116	<i>In vitro</i>	Decreased the expression of VEGF and pro-inflammatory cytokines	[45]
AOM-induced ACF rats	<i>In vivo</i>	Reduced AOM-induced colon cancer in rats, through its potent antioxidant activities	[99]
HT29	<i>In vitro</i>	Inhibited phosphorylation of PI3K/AKT and mTOR, and promoted miR-126 expression.	[58]
AOM-induced ACF rats	<i>In vivo</i>	Suppressed mRNA and protein expression of NF-κB and VCAM-1	[58]
DMH-induced rats	<i>In vivo</i>	Suppressed Wnt signaling	[49]
Caco-2	<i>In vitro</i>	Reduced the expression of cyclins A and B1, bcl-XL and regulated caspase-9 and -3	[98]
HT-29	<i>In vitro</i>	Terminated TNF alpha-induced AKT activation	[55]
HT-29, HCT116, SW480, SW620	<i>In vitro</i>	Reduced proliferation of tumor cells	[96]
AOM-induced ACF rats	<i>In vivo</i>	Elevated the expression of PPAR gamma protein	[100]
Leukemia			
K562	<i>In vitro</i>	Inhibited tumor cell proliferation via cell cycle arrest	[68]
CCRF-CEM, MOLT-3, HL-60, THP-1	<i>In vitro</i>	Decreased ATP levels, activated caspase-3 and induced apoptosis	[42]
[42][42][42][42][42]			
Jurkat, SUP-B15, MOLT-3	<i>In vitro</i>	Reduced tumor cell growth and also induced apoptosis	[144]
CCRF-CEM, HL-60, THP-1, K562, KG1a			
K562	<i>In vitro</i>	Reduced tumor cell growth	[40]
HL-60	<i>In vitro</i>	Inhibited proliferation of tumor cells	[103]
Liver cancer			
HepG2	<i>In vitro</i>	Suppressed cell growth and antioxidative effects	[108]
HepG2	<i>In vitro</i>	Upregulated the level of Caspase-3/9 and cyt-c, and cell cycle arrest at S-phase	[106]
DENA induced-rat hepatocarcinoma	<i>In vivo</i>	Reduced the expression of heat shock protein 70 and 90, COX-2 and NF-κB	[56]
DENA induced-rat hepatocarcinoma	<i>In vivo</i>	Elevated nuclear factor E2-related factor 2 (Nrf2)	[63]

	TCA exposed rats		Antioxidant and protective effect against carcinogenic TPA induced oxidative injury	[107]
Lung cancer	A549	<i>In vitro</i>	Down-regulated VEGF, MMP-2 and MMP-9	[41]
	A549, H1299, LL/2	<i>In vitro</i>	Cell cycle arrest in G2/M phase, reduced ROS, MMP-2 and MMP-9	[43]
	A549	<i>In vitro</i>	Inhibited tumor cell proliferation	[109]
	A549	<i>In vitro</i>	Suppressed tumor growth	[31]
	[B(a)P], NTCU induced lung tumor	<i>In vivo</i>	Inhibited regulation of NF- κ B and, mTOR pathway	[59]
	A549	<i>In vitro</i>	Suppressed the phosphorylation of Akt, MAPK	[50]
	A549	<i>In vitro</i>	Suppressed the NF- κ B DNA-binding activity	[50]
Multiple myeloma	A375, B16F10	<i>In vitro</i>	Down-regulated VEGF, MMP-2 and MMP-9	[41]
	B16F10 - C57BL/6 mice	<i>In vivo</i>	Inhibited pulmonary lung metastasis	[41]
	KMS26, MM1S and U266	<i>In vitro</i>	Upregulated PPAR γ mRNA expression, blocked cell cycle in G0/G1 phase	[41]
	U266	<i>In vitro</i>	Increased loss of mitochondrial membrane potential, cell cycle arrest, and reduced expression of MMP	[127]
Ovarian cancer	A2780	<i>In vitro</i>	Inhibition of β -catenin signaling pathway	[66]
	SKOV3	<i>In vitro</i>	Inhibited tumor cell proliferation	[109]
	SKOV3	<i>In vitro</i>	Inhibited tumor cell proliferation	[31]
Pancreatic cancer	PANC-1, AsPC-1	<i>In vitro</i>	Suppressed the rate of cell proliferation	[130]
Prostate cancer	DU145, PC3, TRAMP-C1	<i>In vitro</i>	Upregulated the Bax/Bcl-2 expression ratio	[119]
	PC-3 LNCaP, and BPH-1	<i>In vitro</i>	Increased the expression of caspases-3 and -8	[113]
	PC-3	<i>In vitro</i>	Inhibited tumorous growth	[31]
	LNCaP, PC-3, DU145	<i>In vitro</i>	Elevated Bax/Bcl-2 ratio and also caspase 3, reduced cyclin D1, cdk1	[46]
	TRAP model	<i>In vivo</i>	Suppressed tumor progression and induced apoptosis by caspase 3 activation	[46]
	LNCaP	<i>In vitro</i>	Inhibited proliferation of tumor cells	[11]
	22RV1, LNCaP	<i>In vitro</i>	Reduced testosterone, DHT, DHEA, androstenedione, androsterone, and pregnenolone	[116]
	PTEN knockout mouse	<i>In vivo</i>	Reduced the level of serum steroids	[116]
	PC3, C4-2, ARCaPM	<i>In vitro</i>	Inactivated survivin and Stat3	[118]
		<i>In vivo</i>	Inhibited tissue expression of survivin and induced apoptosis	[118]
	LNCaP-AR, DU145, 22RV1	<i>In vitro</i>	Inhibited tumor cell growth	[114]
	SCID Mice	<i>In vivo</i>	Inhibited the growth of tumorous xenograft tissue	[114]
	T24	<i>In vitro</i>	Activated pro-caspase-3, -8 and -9, also increased Bax/Bcl-2 ratio	[75]
	DU-145, PC-3	<i>In vitro</i>	Induced cell cycle arrest and apoptosis	[115]
	PC-3, PLS10	<i>In vitro</i>	Decreased secretion of MMP-2, inhibited collagenase IV activity	[52]
	PC3	<i>In vitro</i>	Inhibited cell proliferation and induced apoptosis	[145]
	DU145, PC3, LNCaP	<i>In vitro</i>	Inhibited the CXCR4/SDF1 α chemotaxis axis and decreased oncogenic miRNAs	[70]
	DU145	<i>In vitro</i>	Dys-regulated proteins participated in cytoskeletal functions, anti-apoptosis, proteasome activity, NF- κ B signaling etc.	[110]
	TRAMP model	<i>In vivo</i>	Suppressed IGF-I/Akt/mTOR pathways	[14]
	LNCaP	<i>In vitro</i>	Promoted intrinsic apoptosis via a caspase-dependent pathway	[112]
	LAPC4, 22RV1	<i>In vitro</i>	Increased JNK phosphorylation, and reduced activation of Akt, mTOR	[60]
LAPC4 xenograft model	<i>In vivo</i>	Suppressed NF- κ B and cell viability of tumor cells	[61]	
LNCaP-AR, DU-145	<i>In vitro</i>	Down-regulated the gene expression involved in androgen synthesis	[117]	
LAPC4 xenograft SCID	<i>In vitro</i>	Inhibited cell growth and proliferation	[111]	

mice				
LNCaP, HUVEC	<i>In vivo</i>	VEGF peptide levels and HIF-1 α expression were decreased	[111]	
LAPC4, 22RV1	<i>In vitro</i>	Decreased Igf1 mRNA expression	[60]	
LAPC4 xenograft SCID mice	<i>In vivo</i>	Suppressed tumor growth	[114]	
PC3	<i>In vitro</i>	Inhibited proliferation of tumor cells	[48]	
CWR22Rnu1 xenograft athymic nude mice	<i>In vivo</i>	Reduced tumor growth	[48]	
PC-3	<i>In vitro</i>	Reduced tumor proliferation and invasion	[146]	
Skin cancer				
2-stage mouse skin cancer	<i>In vivo</i>	Reduced the levels of phosphorylated ERK1/2, JNK1 and decreased NF- κ B/p65, IKK α and I κ B α phosphorylation	[125]	
SKH-1 hairless mouse	<i>In vivo</i>	Suppressed UVB radiation-induced carcinogenesis and increased expression of p53 and p21	[124]	
NHEK	<i>In vitro</i>	Suppressed UV-B-mediated phosphorylation of MAPK and inhibited p38 protein	[126]	
TPA induced cancer in CD-I mice	<i>In vivo</i>	Inhibited TPA-induced phosphorylation of ERK1/2, p38, and JNK1/2, inactivated NF- κ B and IKK α , and inhibited phosphorylation of I κ B α	[123]	

ABBREVIATIONS

ACF, Aberrant crypt foci; ATP, Adenosine triphosphate; AOM, Azoxymethane ; [B(a)P], Benzo(a)pyrene; BAD, Bcl-2-associated death promoter *protein*; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; CDK1, Cyclin-Dependent Kinase 1; CXCR4, Chemokines receptor type 4; DENA, Diethylnitrosamine ; DHEA , Dehydroepiandrosterone; DHT, Dihydrotestosterone; DMH, 1,2-dimethylhydrazine dihydrochloride; ERE, Estrogen response elements; HIF-1, Hypoxia-inducible factor 1; IGF-1, Insulin-like growth factor 1; JNK , Jun amino-terminal kinases; MAPK, Mitogen-activated protein kinases; MCP-1, *Monocyte chemoattractant protein-1*; MIP, *Macrophage Inflammatory Proteins*; MMP, *Matrix metalloproteinase*; mTOR , *Mechanistic target of rapamycin*; Nrf2, Nuclear factor E2-related factor 2; NTCU, N-nitroso-tris-chloroethylurea; PI3K, Phosphatidylinositol 3,4,5-trisphosphate; PPAR, *Peroxisome proliferator-activated receptor*; RhoC, Ras homolog family member C; ROS, *Reactive oxygen species*; SCID, Severe combined immunodeficient mice; SHIP-1, Inositol 5'-phosphatase; Sp, Specificity protein; STAT3, *Signal transducer and activator of transcription 3*; TGF- β , Transforming growth factor- β ; TNF- α , Tumor necrosis factor- α ; TRAP, Transgenic rat for adenocarcinoma of prostate model; VCAM-1, Vascular cell adhesion molecule 1; VEGF, Vascular endothelial growth factor.

Table 2: Studies on the potential of pomegranate in the prevention and treatment of cancer (clinical studies)

Cancer type	Dose	Pts	Phase	Clinical outcome	Reference
Prostate cancer	-	183	-	No significant elongation in PSADT	[134]
Breast cancer	8 ounces/day 3 weeks	-	-	Decline in estrone and testosterone	[32]
Colorectal cancer	900 mg/day, 15 days	52	-	Significant levels of EA derivatives, urolithins were formed in colon tissues	[97]
Prostate cancer	100mg, thrice/ day, 3-6months	199	-	Rise in PSA	[132]
Prostate cancer	2 tablets/day, 4 weeks	70	-	Accumulation of urolithins, reduced oxidative stress	[135]

Prostate cancer	1 or 3 g, 18 months	144	II	PSADT increased in 43% of patients, 13% showed decline in PSA	[137]
Prostate cancer	200 mL/day, 3 days	63	-	Traces of urolithin A and B, glucuronide, dimethyl ellagic acid	[131]
Prostate cancer	-	48	II	Significant prolongation of PSADT	[133]

ACCEPTED MANUSCRIPT