



Review

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

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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 signaling 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.

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; I κ B α , 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

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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 signaling 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), gallic acid, gallic acid, phenolic acids, tannins (punicalin and punicalagin), and punicalagin (PC), flavone glycosides, apigenin, sitosterol, fatty acids, and volatile compounds have also been found to be present in pomegranate juice [Fig. 1] [1,12,33–37]. Punicic acid (PuA) is a conjugated linolenic acid (C18:3Δ9c, 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.

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