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Role of Pomegranate in the Management of Cancer

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Abstract

Pomegranate (*Punica granatum*) has been used since ages as a folk medicine. Studies have shown that pomegranate extracts have a role in various signaling pathways involved in inflammation, cellular transformation, hyperproliferation, angiogenesis, initiation of tumorigenesis, and eventually suppressing the final steps of tumorigenesis and metastasis. In this chapter, we have discussed some of the polyphenolic constituents present in pomegranate and their medical value, and we then discussed studies on chemopreventive/chemotherapeutic properties of pomegranate against various types of cancer, such as skin, prostate, colon, head and neck and lung cancers in cell culture systems, animal models and humans.

Keywords: Pomegranate, cancer, antioxidants

1. Introduction

The Pomegranate fruit (*Punica granatum* L.) is a perineal fruit of the family puniceae, the fruit comprises of white to deep purple seeds covered in a spongy membrane which is further covered by the pericarp. It is available across the globe as a well-established folklore medicine owing to its anti-oxidant and anti-inflammatory properties. Various useful medicinally active components are present in the peel, seed, flower and even the leaves. The phenolic components comprise the major medicinally active part of the pomegranate extract along with minerals like magnesium, phosphorous, sodium and potassium [1–3]. There are four groups of phenolic compounds present in pomegranate namely the groups with anthocyanin pigments, hydrolysable tannins like punicalagin, ellagic acid and hydrolysable tannins. All of which contribute to the antioxidant activity. Moreover, it is rich in flavonoids and tannic acids which further adds to its the medicinal value. The antioxidant and anti-inflammatory potential of pomegranate juice and pomegranate extracts puts it apart from other fruits owing to the high concentrations of hydrolysable tannins and anthocyanins along with the polyphenols [4]. Among the various parts of the fruit, the peel and lamella which are the main on edible parts of the fruit has majority of the phenolic contents compared to the other edible parts. The peel accounts for more than half of the total antioxidative potential of the fruit and their anti-proliferative activity [5, 6]. The seed coat of the fruit also presents with numerous organic acids including citric acid

and ascorbic acid [7]. Among the major biomedical advantages of pomegranate is the anti-cancer activity since pomegranate and its various components has been prove to assist the treatment of cancer and show immunomodulatory activity [8]. This chapter will be discussing on the anti-cancer activity of pomegranate and its antioxidant activity.

Cancer is one of the most common disease conditions which is becoming the leading cause of death even when detected in its early stages. In the year of 2021, almost 2 million new cancer cases are expected to happen just in the united states. The cancer death is reducing with each decade comparing to the initial few decades since its peak. With each passing year, there is rapid improvement in the cancer treatment strategies [9]. Pomegranate components can be used for treatment of many ailments as such or as an adjuvant in the treatment. One of the common problems related to cancer therapy is the lack of specificity in differentiating the cancer cells from the normal cells which manifests problems in the oral cavities as mucositis or candidiasis. This shows the prospect of using pomegranate extracts as an adjuvant in normal cancer chemotherapy in order to improve the quality of life of the people undergoing treatment. Also, the rind extract rich in the tannin punicalagin when used in combination with zinc is shows healing activity in the oral cavity due to the anti-inflammatory activity [10, 11].

2. Pomegranate and prostate cancer

Prostate cancer is the most prevalent type of cancer in men with an incidence rate above 30 worldwide [12]. From the multicenter studies conducted in human prostate cancer using pomegranate extracts rich in polyphenols, the extracts were found to cause an inhibition in the proliferation of the cells in both in *vivo* and *in vitro* studies. Hence the study demonstrated a significant anticancer activity through the inhibition of invasion and proliferation of the cancer cells [13]. The initial stages of prostate cancer will be testosterone dependent and this can be treated with normal radiation or chemotherapy but not in the late stages which shows no dependence with testosterone. The Further studies on the extracts from different parts of pomegranate showed a synergic activity in the anti-proliferative activity of other components of pomegranate. The seed oil from pomegranate acts as a synergistic when used in conjunction with the juice rich in polyphenols in the prevention of proliferation even though it does not have any anti-proliferative effect alone [14].

The studies on LNCaP cell lines which are modified to over express androgen receptors so that a situation similar to that of androgen independent prostate cancer. By using the different pomegranate extracts rich in polyphenols, the study later on showed a decrease in expression of the gene for the androgen synthesizing enzymes. Since the down regulation of androgen receptors is evident from the study, pomegranate extracts can be of use in the treatment of prostate cancer with an up-regulation of androgen receptors [15]. In androgen independent prostate cancer, there is an observed activation of the nuclear factor NF- κ B. The activation of this nuclear factor is a common event in many types of cancer including breast cancer and cervical cancer [16]. In the molecular studies conducted using pomegranate extracts on the activity of NF- κ B. It was found that the pomegranate extracts were able inhibit the NF- κ B activity which was shown in the androgen independent cells, DU145 with increasing doses. Congruent results were obtained from the electro mobility shift assay conducted on the same cells using pomegranate extracts. In the DU145 and CL-1 cells which are the androgen independent cell lines, the activity of NF- κ B was found to be activated through the TNF- α . Pomegranate extracts showed

promising activity in the inhibition of NF- κ B cells activated in this way as well. In the LAPC4 xenograft induced model of cancer, the extracts from pomegranate was found to delay the initiation of prostate cancer through prevention of proliferation of the cells [17].

Punicalagin is an important polyphenol constituent of pomegranate and as discussed before, the antioxidant activity of which is very evident in the cancer cells. The antiproliferative activity of punicalagin was examined in previous studies using the DPPH assay and the lipid peroxidation inhibition assays. Along with this, the study checked the cytotoxic activity and viability effects were also determined using punicalagin. It was found that punicalagin inhibited proliferation of cancer cells in prostate cancer and that the prostate cancer cells remained intact in the presence of punicalagin which was further supported by evidences from cell viability assays. The antioxidant activity of the polyphenol was further shown in the DPPH free radical scavenging assay which showed that it scavenged the free radicals in a dose dependent manner. The lipid peroxidation was also inhibited in the presence of punicalagin. PC-3 is another major cell line which is involved in prostate cancer and the polyphenol was found to reduce the PC-3 cells through apoptosis with higher concentrations [18, 19].

Further, it was found that pomegranate extracts affect the bio synthesis of androgens from the studies conducted using prostate cancer models. In the in vivo study conducted on the animal model using PTEN (Phosphatase and tensin homolog) knockout mouse which represents prostate cancer, there was observable reduction in the levels of steroids in the serum and in the case of in vitro studies using prostate cancer cell lines LNCaP and 22RV1, pomegranate extracts were found to cause a fall in the production of androgens. The in vitro and in vivo data obtained from various studies further shows the possible activity of pomegranate extracts in the treatment of Prostate cancer [20].

3. Pomegranate and breast cancer

Breast cancer is the most common type of cancer diagnosed in women and the leading cause of death due to cancer in women with over 2 million cases being diagnosed from recent studies [21]. The major causative factor for the cancer proliferation in breast cancer proliferation is estrogen and the enzymes which catalyzes the production of estrogen. The enzyme aromatase aids in the conversion of androgen into estrogen. So, the inhibition of this enzyme can further aid in the treatment of breast cancer. In vitro studies conducted on one of the major constituents of the pomegranate namely extract ellagic acid and urolithins A and B showed promising results on the inhibition of aromatase enzyme. The placental microsome aromatase assay conducted on ellagitannin derived compounds from pomegranate extracts namely, methylated urolithin B, methylated urolithin A and urolithin A further showed the aromatase inhibiting activity of pomegranate extracts. Which in turn inhibits the proliferation of cancer cells [22].

From the in vivo studies conducted on mammary organ culture in mice using the pomegranate seed oil rich in punicalagin and the fermented fruit extracts, it was found that the extracts of pomegranate caused a reduction in the number of lesions obtained and supports the activity of pomegranate extracts in the treatment of breast cancer [23].

The in vitro studies conducted on cancer stem cells derived from MMTV-Wnt-1, pomegranate extract was found to inhibit the proliferation of cancer cell by arresting the cell cycle at an early phase and induced apoptosis of the cancer cells. Pomegranate extracts caused an elevation in the levels of the enzyme caspase 3 which

aids in the apoptosis. Among the various extracts, ellagic acid and ursolic acid along with luteolin were found to cause the inhibition of cell proliferation. Also, pomegranate extracts showed promising results in the molecular studies conducted on the MCF-7 cells of breast cancer through the inhibition of proliferation of the cancer cells. In the MCF-7 cells, the anti-cancer activity was found to be due to the cell cycle arrest, down regulation of genes which proliferate the cancer cells and also through the upregulation of the genes which aids in the regulation of proliferation and apoptosis. Hence, pomegranate extracts are relevant in the treatment of breast cancer therapy in the cases which are relatively resistant to the existing agents of treatment [24, 25].

4. Pomegranate and colon cancer

Colorectal cancer is currently one of the most common diagnosed cancer in men and women and it manifests with the uncontrolled proliferating of the epithelial cells and the suppression of their apoptosis [26]. One of the major constituents of pomegranate, the ellagitannin urolithin A plays a key role in the inhibition of proliferation of colon cancer cells through cell cycle arrest and the inhibition of mitogen activated protein kinase signaling (MAPK) [27].

The action of ellagitannins and urolithin on the CYP1 enzymes is important as these enzymes lead to the activation of inactive carcinogens into active carcinogenic chemicals in colon cancer. In the cell line study using HT-29 colon cancer cells, the evaluation of activity of CYP1 enzyme by employing EROD assay (ethoxy resorufin-*O*-deethylase assay) showed a reduction of CYP1 enzymes which were induced in the cell line. The extracts were found to show selective inhibition of proliferation of the cells omitting the non-cancer cells in a dose dependent fashion. Further, ellagitannin and urolithin was found to cause an increase in the apoptosis of the cell lines resulting in a reduction of the cell colony [28].

From the animal studies conducted on rats which were induced with colon cancer using N-methylnitrosourea which caused an increase in antigens which were specific to colon cancer along with an increase in plasma levels of Bcl2 and TGF- β , it was found that pomegranate peel extracts caused a fall in the cancer specific parameters which were induced in the mice. The *in vivo* study further suggests the efficacy of pomegranate in the treatment of colon cancer through the inhibition of proliferation and increased apoptosis which was evident from the fall in CEA and CCSA-4 prostate cancer cell markers along with the down regulation of β -catenin genes which has a pivotal role in the advancement of colon cancer. The down regulation of the specific gene disrupts the signaling pathway involving Wnt/ β -catenin [29, 30].

From the cell line studies using HCT116 and HT-29 colon cancer cell lines, pomegranate extracts comprising of punicalagin, ellagic acid and tannins showed a drastic antiproliferative activity which led to complete inhibition of proliferation depending on the dose. The extract was found to cause apoptosis in the selected cell lines. Further, the extracts were found to have effect on the colon cancer cells which were not metastatic. The cell line studies further cement the role of punicalagin, ellagic acid and pomegranate tannins in the cancer protective activity in colon cancer [31].

5. Pomegranate and head and neck cancer

Head and neck cancers are one of the prevalent type of cancer which usually includes squamous cell carcinomas found in the epithelial cells of the pharynx,

larynx and the oral cavity [32]. Due to the underdeveloped methods of screening of the disease, the chances of predicting the cancer at an early stage is less. This condition further leads to the increase in number of people who are diagnosed at a late stage of disease progression. In the current scenario, the treatment strategy of the disease mainly involves chemoradiation and surgery. The therapeutic approach to head and neck cancer comes with the common side effects of mucositis and dermatitis. Pomegranate extracts were studied for its protective effect in ameliorating the side effects of the treatment. In the clinical setup of a cohort containing patients with head and neck cancer, it was found that the extracts reduced the extend of damage caused by radiation induced dermatitis as well as mucositis [33].

Radiation therapy is applied in the cancer therapy for a long time because of its ability to kill the tumor cells but this will also lead to the production of reactive oxygen species that will damage the normal adjacent cells. Pomegranate extract has been studied in the amelioration of cellular damage induced by these reactive oxidants. From a study conducted using the extracts from pomegranate fruit and seeds, it was found that the treatment with the extracts increased the levels of antioxidant and the enzymes which has antioxidant property. Further the extracts were found to cause a decline in the lipid peroxidation levels suggesting the protective effect of pomegranate extracts in the cancer treatment as an adjuvant to reduce the unwanted side effects [34].

Other than in chemoradiation, pomegranate fruit extracts rich in punicalagin has been found useful in acting as a protective agent for the skin fibroblast cells namely the SKU-1064 from possible apoptosis due to UV-A and UV-B exposure. The extracts were found to suppress the NF- κ B activation and through the downregulation of caspase-3 which is proapoptotic. Further studies found an increase in DNA repair through the increase in G0/G1 phase [35]. All these findings further supports the fact that pomegranate extracts can be applied in the treatment of cancer as an adjuvant also as a protective for radiation induced cellular damage.

6. Pomegranate and lung cancer

Lung cancer is one of the leading causes of death related to cancer worldwide in both men and women. Cigarette smoking is attributed to e the major cause of the condition. Along with lung cancer, cigarette smoke causes an increase in oxidative stress and DNA damage. From the animal studies conducted on the formation of lung nodules associated with lung cancer and other cancer related factors like the attenuation of mitosis and the levels of hypoxia inducible factor-1 α or HIF1 α because of cigarette smoke, it was found that pomegranate juice supplements wee able to reduce the formation of lung nodules which is a common observation in the case of cigarette smoke exposure along with the reduction of mitosis and HIF-1 α [36].

Further, pomegranate fruit extract treatment in the cell line study using human carcinoma cell associated with lung cancer namely the A549 cells showed an inhibition of the markers of cell proliferation and angiogenesis such as MAPK, NIF-kappa B and PI3K/Akt. The treatment with the extracts further arrested the growth of tumor cells. Thus, pomegranate may be useful as a chemo preventive or as a chemotherapeutic agent against cancer affecting lungs [37]. Methotrexate is a widely used chemotherapeutic agent but it causes injuries in the lung cells due to oxidative stress. In the animal studies employed to study the effect of pomegranate extracts on the protective action against the lung injury caused

due to methotrexate, it was found that the use of pomegranate extracts as a prophylactic significantly reduced the total oxidant status and the oxidative stress index along with elevating the total antioxidant capacity. This in turn shows the application of pomegranate extracts as an adjuvant as well in the therapy of lung cancer [38, 39].

7. Pomegranate and skin cancer

Pomegranate extracts from seed, peel and the whole fruit have been proven to be beneficial in the treatment of many cancer treatments. Skin cancer is the most common cancer among the Caucasian population and it varies depending on the type of cells affected. UV radiation is the major cause of skin cancer since it initiates and promotes tumor [40]. The in vivo and in vitro studies has shown the efficacy of pomegranate as a protectant in the UVB radiation induced skin damage. The oral treatment of pomegranate juice and extract in the Fitzpatrick II-IV skin type showed the possibility of enhancement in the protective from UV damage since it is able to increase the threshold of the UV dose required to cause erythema of skin [41].

The oil extracted from seed of pomegranate fruit was studied on animals as a topical prophylactic in the mice which was induced with skin cancer using 12-*O*-tetradecanoylphorbol 13-acetate and 7,12-dimethylbenzanthracene and it was found that the pre-treated animals had a significant less incidence of skin cancer which tells the protective effect of pomegranate in skin cancer [42]. From the studies conducted on the human skin fibroblasts SKU-1064 which were irradiated with UV, it was found that the pomegranate extracts rich in punicalagin was able to prevent the skin cell death showing the effect of pomegranate as a topical protective agent against skin cancer [35].

8. Conclusion

Pomegranate and the products derived from it has been proven to show various medicinal properties. Even though it has been in use in various traditional medical folklore since ages, the medicinal property of pomegranate is not explored much to be of use in the current medical scenario. Pomegranate is still being used as just a fruit and from the studies which are conducted so far on the fruit, it is to be noted that the extracts of the fruit rather than the whole fruit as such possesses many medicinal properties.

The role of pomegranate in the therapy of cancer as such and as an adjuvant in therapy is explored very less as there are very few studies has been conducted on humans, even though there are a handful of studies which are conducted on animal models or cell line studies which deems the fruit and its extracts effective in the therapy of cancer. The studies conducted so far shows the potency of pomegranate and its components in the treatment of cancer relating to prostate, breast, head and neck, colon, lungs and skin or as an adjuvant in the treatment to minimize the unwanted side effects. The various components of pomegranates because of its antioxidant and anti-inflammatory property can be applied to various treatment strategies in numerous types of cancer in one way or the other.

Hence it can be concluded that pomegranate extracts can be made to much use for humans in improving the treatment strategies in turn improving the quality of life, for which there has to be more human, animal and cell line studies so that the complete potency of pomegranate can be uncovered.

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