

Punica granatum (Pomegranate) activity in health promotion and cancer prevention

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Abstract

Cancer has become one of the most fatal diseases in most countries. In spite of the medical care developing, cancer still remains a significant problem. The majority of the cancers are resistant to treatment. Thus, the research for novel, more efficient and less side effect treatment methods continues. Pomegranate contains strong antioxidant activity, with potential health interests. Research concern in pomegranate is increasing because of their anticancer potential due to possess rich in polyphenols. We highlight the pomegranate potential health benefits and mechanism of cancer progression inhibition. Pomegranate has indicated anti-proliferative, anti-metastatic and anti-invasive effects on different cancer cell line *in vitro*, *in vivo* and clinical trial. The aim of this review is to evaluate functional properties and the medical benefits of pomegranate against various cancer diseases. In addition, pomegranate properties in *in vitro* and *in vivo* experimental human and animal clinical trials and its future use are explored. The available data suggest that *Punica granatum* (pomegranate) might be used in the control and potential therapeutic for some disease conditions and benefits human health status. This review summarizes *in vitro*, *in vivo* and clinical trial studies highlighting the pomegranate role in prevent and treatment of breast, prostate, lung, colon, skin and hepatocellular cell cancers.

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Introduction

Pomegranates (*Punica granatum* L.) have prominent medical history, and possess remarkable medicinal properties.¹ Pomegranate is native in Asian countries including Iran to Northern India. It has been cultivated and naturalized over the whole Mediterranean region since ancient times.² Pomegranate has been the subject of current attractive as a medicinal agent with wide variety therapeutic indications.

Studies have demonstrated that pomegranates may use as natural remedy to chemical treatment due to their capability against a wide range of pathogens. Approximately every part of the pomegranate, including the fruit juice, peel, arils, flowers, and bark has been tested for antimicrobial activities. There are wide ranges of phytochemical properties have demonstrated antimicrobial activities in pomegranate. Ellagic acid and hydrolysable tannins, such as punicalagin, have the most activities.³

The use of the pomegranate juice, peel and oil has been indicated that pomegranate have anticancer activities, including interference with tumor cell proliferation, cell cycle, invasion and angiogenesis. These may be related to anti-inflammatory effects of pomegranate. The phytochemistry and pharmacological actions of pomegranate properties indicate a wide variety of clinical usage for the cancer prevention and treatment, also other diseases where chronic inflammation is reliable to play a main etiologic role.⁴

In the past decade, numerous studies on pomegranate constituents have been published.

The results suggest that pomegranate components have antioxidant, anti-carcinogenic and anti-inflammatory components, which is effective on prevention and treatment of cancer and other chronic and infection diseases.⁵⁻⁷

The aim of this systematic review was to summarize the present data on the medical-activity of pomegranate products from *in vitro* and *in vivo* experiments animal and human clinical trials in prevention and treatment of breast, lung, prostate, colon, skin and hepatocellular cell cancers.

Punica granatum L. compound

Pomegranate is an important source of bioactive properties and has been shown anticancer activities. Pomegranate contains strong antioxidant activity and has a high source of ellagitannins, anthocyanins, and hydrolysable tannins.⁸

The most components of the pomegranates are tannin and polyphenolics.⁹ Phytochemical analyses indicated that pomegranate peels possess active inhibitors, including phenolics and flavonoids.¹⁰

Pomegranate peel has ellagitannins, ellagic acid, gallic acid,¹¹ hydroxybenzoic acids such as ellagic acid, gallagic acid, and ellagic acid glycosides.¹² Punicalagin is the major bioactive com-

ponent of pomegranate peel.¹³ Anthocyanidins are mainly contained cyanidin, pelargonidin and delphinidin¹⁴ and flavonoids such as kaempferol, luteolin, and quercetin.¹⁵

Ozbay *et al.*¹⁶ reported that delphinidin presents growth inhibitory activity in breast cancer cells of different molecular subtypes, but elevate potential drug antagonism when used in combination with existing targeted therapies in HER2-overexpressing breast cancer.

Murthy *et al.*¹⁷ quantified methanolic extract of pomegranate peel by used chromatographic method (*i.e.* HPLC) and reported gallic acid (34.03%) and catechin (3.31%) presented.

Middha *et al.*¹⁸ revealed antioxidant activity, polyphenolic, nutritive content, and phenolic specifications of methanol and aqueous extracts of *P. granatum* peel extract.

Botanical antioxidants usages have gained considerable attention as photochemopreventive agents.¹⁹

Investigation by HPLC method on the phenolic specification of the methanolic extracts showed about 5 different flavonoids, phenolic acids, and their derivatives including quercetin rutin, gallic acid, ellagic acid, and punicalagin as a major ellagitannin have been specified.

In study by Akbarpour *et al.*²⁰ were analyzed physical and chemical properties of twelve pomegranate (*P. granatum* L.) cultivars from different regions of Iran. Results of HPLC showed, ellagic acid content of juice and peel ranged were between 1-2.38 mg/100 mL and 10-50.00 mg/100 g, respectively. Total antioxidant activity in peel and juice measured by FRAP assay with a range of 225.17-705.50 (mmol/100 g) and 157.33-419.33 (mmol/100 mL), respectively.

Summary of evidence on prevention effectiveness

Pomegranate has been used to therapeutic the several diseases among various cultures and civilizations. The potential therapeutic of *P. granatum* peel covering an extensive range,

including cancer treatment and prevention by laboratory and clinical evidence,^{21,22} antimicrobial,^{23,24} antifungal by *in vitro* and *in vivo* evidence,²⁵⁻²⁷ and antiviral,²⁸ It has also been effective in treatment of cardiovascular disease in Wistar rats,²⁹ diabetes in hyperglycemic rats,³⁰ denture stomatitis and mouth lesions in cultured cells³¹ and in clinical trial,³² and protective activity from ultraviolet radiation in ultraviolet-irradiated human skin fibroblasts,³³ and other potential usage include Alzheimer's disease in Transgenic Mouse Model,³⁴ cerebral ischemia ischemia in rat model and in human,^{35,36} arthritis in human chondrocytes,³⁷ skin lesions in rats,³⁸ obesity and lipid lowering effect in rats,³⁹ malaria by *in vitro*,⁴⁰ prostate cancer in clinical trial,^{41,42} atherosclerosis in mice,⁴³ hypertension in Wistar rats.⁴⁴ Many researchers have focused on the biological activity of pomegranate peels. They found that the poly phenols have been demonstrated to have promoting health and preventive disease activity. The free radicals are demonstrated to stimulate and aggravate many diseases like arthritis, cancer, Alzheimer's disease, diabetic complications and Parkinson's disease.⁴⁵ These results indicated that pomegranate peel could be used as a possible source of natural antioxidant agents and tyrosinase inhibitors.

Antioxidant activity

Pomegranate peel extracts contains a lots of phytochemicals and considerable antioxidant activity, to be due to ellagic acid activity, which is the main pomegranate polyphenol.⁴⁶

Singh *et al.*⁴⁷ explained the first report on antioxidant pomegranate peel extract property. The pomegranate peel extract antioxidant activity is 10 times higher than the pulp extract.⁴⁸ Peel extract ability in cleaning hydroxyl and superoxide anion radical was also very high.⁴⁹ So pomegranate extracts are offered as two functional agents combining aldose reductase repressive activity with antioxidant actions.

Polyphenolic compounds source is in pomegranate seed oil; peel and juice have anti-oxidant action and inhibit pro-inflammatory enzymes including the cyclooxygenases and lipoxygenases.^{47,50-53}

Studies in rats with CCl₄-induced liver damage showed pomegranate peel pretreatment evaluate the free radical inhibitory effect of superoxide dismutase, the hepatic enzymes catalase, and peroxidase resulted in 54% lowering of lipid peroxidation values in compare to control group confirming the antioxidant content of the pomegranate peel.⁵⁴ The other study demonstrated that rats feeding with pomegranate peel enabled protective activity against carbon tetra chloride (CCl₄) toxicity.⁵⁵ Pomegranate pulp extract has a wide inhibitory activity on matrix metalloproteinases (MMPs) expression and IL-1 β induced tissue destruction.⁵⁶

Anti-cancer activity

Due to current chemotherapeutic regimens problems, there is a shifting to finding natural compounds currently that may be useful in preventing and to treat cancers.

Pomegranate has anti-proliferative effect and anti-cancer activities against prostate, colon, oral, and breast-cancer cell lines. Pomegranate identified in preventing and therapeutic activity of inflammation and cancer, and it has an efficient result against oxidative damage in diabetic rats.^{1,21,23,41,42,46,57} Pomegranate extract have indicated promising anti-tumor activities in various organs. Pomegranate contain polyphenols that they showed anti-carcinogenic activities by *in vitro* and *in vivo* investigations.^{1,9,35,58-61} Pomegranate extract induced apoptosis and inhibited proliferation in cancer cells, also pomegranate juice induced significant apoptosis in lymphoid and myeloid leukemia cell lines, associated with cell cycle arrest.⁶⁰ Study by Adhami *et al.*²¹ has indicated that pomegranate extracts prevented the breast, prostate, colon and lung cancer cells growth in *in vitro*. Pomegranate extract have capability to inhibited lung, skin, colon and prostate tumors growth in preclinical animal studies.²¹ Pomegranate juice showed significant prolongation of prostate specific antigen doubling time in patients with prostate cancer in an initial phase II clinical trial. In experimental studies pomegranate seed oil has been demonstrated proliferation prevention of various tumor cell types⁶¹⁻⁶⁴ and skin carcinogenesis reduction in mice⁶⁵ and carcinogenesis in a mouse mammary organ culture model.⁶⁶ The pomegranate juice activity indicates of synergistic or additive effects from the other phytochemicals present in pomegranate juice.⁶⁷

Pomegranate peel extracts have been illustrated to delay proliferation of cells in different cancer cell lines.^{63,68,69} Anti-carcinogenic properties of different combinations of the phytochemicals in pomegranate were studied by Adams *et al.*⁷⁰

Investigation by Tang *et al.* showed that punicalagin have chemo preventive and chemotherapeutic activities against cervical cancer in humans through inhibition of the β -catenin signaling pathway.¹³ Purified ellagic acid was compared with its precursor punicalagin, and the total pomegranate juice tannins. All of them reduced the viable cell number of human oral and colon tumor cells; pomegranate juice had more action and has the most effective antioxidant sample tested.

Naiki *et al.*⁷¹ reported that pomegranate juice and ellagic acid are potential chemo preventive agents for prostate cancer, and Ellagic acid may be the active component of pomegranate juice that perform these anti-cancer effects.

Pomegranate juice also stimulated apoptosis when concentrations of isolated tannins that were equalized to amounts found in pomegranate juice had no effect.⁷² The juice also contains phytochemicals such as anthocyanins and flavonoids, which possess antioxidant and anti-proliferative activity.⁷³ The synergistic action of the pomegranate constituents appears to be superior to that of single constituents.^{64,73}

Anti-breast cancer

Pomegranate extract indicated anti-inflammatory and cytotoxic activities as *in vitro* and *in vivo* in breast cancer cells. The anti-cancer potential of pomegranate extract in breast cancer cells is due to targeting microRNAs155 and 27a partly. Pathways play an important role in the proliferation and inflammation phenotype exhibited by these cell lines. Pomegranate seed oil has been demonstrated to prevent proliferation of different tumor cell types in experimental studies,^{61,74} and reduce mammary carcinogenesis in the mouse mammary organ.⁶⁶ Pomegranate extracts inhibit the growth of MCF-7 breast cancer cells through induction of apoptosis.⁷⁵ Mehta⁶⁶ showed increased breast cancer preventive potential for the purified compound and pomegranate seed oil, more than pomegranate fermented juice polyphenols. Pomegranates have the ability to suppress expansion of new blood vessels. Development of angiogenesis is necessary to supply oxygen and nutrients for growth and metastasis of tumor.

The investigation by Kim *et al.*⁶¹ indicated preventive effect of pomegranate components against different breast cancer, and it suggests a possible pomegranate role in suppress and treat of cancer.

Study by Shirode *et al.* illustrated that encapsulation of pomegranate polyphenols enhances their bio efficacy inhibited cancer cell growth in MCF-7 and Hs578T breast cancer cells.⁷⁴

Anti-prostate cancer

Pomegranate activity has been assessed on prostate cancer in the cell culture, animal models.^{41,62,64} Also patients with prostate cancer in an initial phase II clinical trial, pomegranate juice has shown considerable prolongation doubling time of prostate specific antigen.²¹

Preclinical animal investigations showed the oral pomegranate extract administration inhibited growth of prostate tumors.²¹ The first pomegranate juice clinical trial in patients with prostate cancer reported by Pantuck *et al.*⁷⁶ indicated that the statistically remarkable prolongation of prostate-specific antigen (PSA) doubling time.

These activities were observed to be mediated by changes in cell cycle distribution and induction of apoptosis.⁷⁴

Anti-lung cancer

The effects of pomegranate extract on lung tumor genesis were investigated both *in vitro* and *in vivo* by authors.⁷⁶⁻⁷⁸ These investigations showed that pomegranate extract could be useful chemo preventive and chemo-therapeutic agent against human lung cancer.

Li *et al.*⁷⁹ have been shown that pomegranate leaves extract suppressed cell proliferation in non-small cell lung carcinoma cell line in a dose and time-dependent manner. Pomegranate leaves extract affected H1299 cell survival by arresting cell cycle progression in G2/M phase. These researchers suggested that pomegranate leaves extract could be an effective and safe chemotherapeutic agent in non-small cell lung carcinoma treatment by inhibiting proliferation, inducing apoptosis, cell cycle arrest and impairing cell migration and invasion. Pomegranate extract able to suppress pro survival pathways in human A549 lung carcinoma cells and tumor growth in the nude mice.⁷⁷

Khan *et al.* showed that pomegranate extract remarkably inhibits lung carcinogenesis in the mice model and able investigate as a chemo preventive agent for human lung cancer.⁸⁰

So, pomegranate extract can be a benefit chemo preventive and chemotherapeutic factor *versus* human lung cancer.

Anti-colon cancer

Inflammation has the main role in the growth of colon cancer, and different anti-inflammatory agents have indicated promise for prevention of colon cancer. Pomegranate seed oil exhibits chemo preventive activity against experimental colon carcinogenesis. Adams *et al.*⁷⁰ have reported the anti-inflammatory action of pomegranate juice on the signaling proteins in HT-29 human colon cancer cell line.

Administration of pomegranate seed oil enhanced peroxisome proliferator-activated receptor (PPAR) gamma protein expression in the non-tumor mucosa and remarkably prevented the incidence of colonic adeno-carcinomas.⁸¹

Investigation by Larrosa *et al.*⁸² in the colitis in the rat model and the effect of colon inflammation on phenolic metabolism, showed that Anti-inflammatory properties of a pomegranate extract and its metabolite urolithin-A could be the most active anti-inflammatory compound derived from pomegranate ingestion in healthy subjects, whereas in colon inflammation, the effects could be due to the non-metabolized ellagitannin-related fraction.

Results obtained by Kohno *et al.*⁸³ indicated that pomegranate seed oil can inhibits azoxymethane induced colon carcinogenesis, and the suppression is related partly with the increased content of conjugated linoleic acid in the colon and liver and elevated expression of PPAR gamma protein in the mucosa of colon.

Anti-skin cancer

Pomegranate extract is a high source of ellagitannins, anthocyanins, and tannins and possesses powerful antioxidant acting. Tannins compound, have remarkable activity in cancer prevention.⁸⁴ Tannin stimulated release of an interleukin 1 (IL-1) and IL-1 beta from the cells in the mice and humans macrophages in *in vitro*. These results suggest that tannins applies its antitumor effect via activation of macrophages.⁸⁵

There are some observations showing evidence that pomegranate pulp extract contains anti-skin tumor promoting activity in CD-1 mouse by preventing prevalent also new biomarkers of tetra decanoyl phorbol 13-acetate (TPA)-induced tumor promotion.⁸⁶⁻⁹⁰

Pomegranate seed oil has been exhibited in experimental studies to inhibit proliferation of various tumor cell types⁶¹⁻⁶⁴ and to decrease skin carcinogenesis in mice.⁶⁷

These primary remarks indicated that pomegranate seed oil is a safe and effective agent against skin cancer.⁸⁶

Apoptosis is the most potent defense mechanism against cancer.⁹¹ Results of investigation by George *et al.*⁹² in Balb/c mice showed significant induction of apoptosis by pomegranate extract. Percent increase in apoptotic population in pomegranate extract was 18.72±1.43.

Anti-hepatocellular carcinoma

Hepatocellular carcinoma is a common and fatal cancer which is extremely stimulated by oxidative stress. The pomegranate peel, have hepato-protective activity.⁹³ The effect of pomegranate extract on DENA-induced hepato cell carcinogenesis, like hepatocellular carcinoma in humans, was examined *in vivo*. Considerable chemo-preventive potential were reported due to decrease in the incidence, size, volume and multiplicity of the hepatic nodules. Pomegranate extract also reduced in the liver lipid peroxidation and oxidation of proteins. Bishayee *et al.*⁹⁴ suggested and supported pomegranate administration derived agents in the treatment and prevention of hepatocellular in humans.

Nutrition of rats with pomegranate pulp provided protective potential against carbon tetra chloride toxicity.⁹⁵ Investigations in rats with carbon tetra chloride toxicity induced liver damage showed pomegranate pretreatment increased or retain the free radical inhibiting activity of the hepatic enzymes catalase, superoxide, peroxidase and dismutase, and resulted in 54% decrease of lipid per-oxidation values compared to control groups verifying the antioxidant property of the pomegranate pulp.⁹⁶

Bishayee *et al.*⁹⁷ demonstrated that pomegranate bioactive compounds apply a chemo preventive effect against diethylnitrosamine-induced rat liver carcinogenesis by inhibiting hepatic oxidative. The chemo-preventive of pomegranate possess potent against hepatic carcinoma, possibly through antioxidant signaling mechanisms without any toxic expression. Pomegranate bioactive properties inhibit cell proliferation, regulate cell cycle progression, and induce apoptosis in Sprague-Dawley rats.⁹⁸

Efficacy and safety of pomegranate

Studies have shown that the pomegranate have anti-inflammatory, anti-proliferative, antioxidant and anti-tumorigenic attribute by modulating multiple signaling pathways, that offer its use as a promising chemo preventive and chemotherapeutic food.⁸

All parts of pomegranate such as peel, juice and oil have been shown anticancer activities including interference with tumor cell proliferation, cell cycle, and angiogenesis.

The phytochemistry actions of punica granatum components capable for the treatment and prevention of cancer, as well as other diseases where chronic inflammation is believed to play an essential etiologic role.⁹⁹

Pomegranates have been used without adverse effects for centuries.¹⁰⁰ Animal Studies of pomegranate component did not indicate any toxic effects at concentrations commonly used in traditional medicine.²⁹ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4158581/?report=printable> - ref13 Pomegranate juice, oil or extracts can be used without high risk by healthy individuals. No adverse effects on liver or renal function were observed upon pomegranate administration of up to 1420 mg/day extract tablets in humans.¹⁰¹

Pomegranate extracts contain significant antioxidants; have been progressed as natural supplements in order to process an alternative suitable form for using the bioactive polyphenols.¹⁰² In

Recent study by Bassiri Jahromi *et al.*¹⁰³ have been shown that administration of 3 various doses of pomegranate peel extract in BALB/c mice produced no toxic effects in terms of food intake, weight gain, or behavioral or biochemical factors. Biochemical studies indicated no disturbances in glucose, cholesterol, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) following administration of 3 various doses of pomegranate peel extracts. *P. granatum* peel extract administered showed normal histopathological examinations with no inflammation at the supra therapeutic dose (7.5 mg/kg).

Conclusions

The therapeutic potential of pomegranate appears to be wide variety. So, leading to an enhance popularity as a natural compounds and functional food since centuries. The pomegranate polyphenol; punicalagin, is known to have potent anticancer activity in breast, lung, and cervical cells.

All parts of the fruit were reported to have therapeutic activity including anticancer, anti-inflammatory, anti-atherogenic, anti-diabetes, hepato protective, and antioxidant activity, *etc.*^{4,105-108} Antioxidant activity of the pomegranate components has been investigated in recent years. The current research contains excellent evidence relevant to anticancer, anti-inflammatory, anti-proliferative activities of pomegranate-derived products particularly relevance to their anticancer properties. In view of the different activities of pomegranate extracts, we believe that they are suitable further investigations as potential multiple target-oriented therapy and prevention and suppression for the wide variety of cancer and its pathological outcomes. It is hoped that the present review will provide some worthwhile clues for continues explorations of this most attractive botanical species.

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