

Potential Antitumor Effects of Pomegranates and Its Ingredients

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ABSTRACT

The treatment based on plant or plant derivatives is a promising strategy in the killing of cancers cells. Moreover, wide-ranging finding has established that medicinal plant and its ingredient modulate several cells signaling pathways or inhibiting the carcinogenesis process. In this vista, pomegranates fruits, seeds and peels illustrate cancer preventive role seems to be due to rich source of antioxidant and other valuable ingredients. Furthermore, anti-tumour activities of pomegranates have been evidences through the modulation of cell signaling pathways including transcription factor, apoptosis and angiogenesis. In this review article, anti-tumor activity of pomegranates and its components or its different type of extracts are described to understand the mechanism of action of pomegranates in cancer therapy.

Key words: Antioxidant, anti-tumor, bioavailability, cell signaling pathways, pomegranates

INTRODUCTION

Cancer is multifactorial diseases and is rapidly becoming a global pandemic. Its incidence and prevalence is increasing rapidly and is a major culprit in health issues. It was estimated that there were approximately 12.7 million new cancer cases and 7.6 million cancer death cases occurred worldwide in year of 2008.^[1] Tobacco use, alcohol consumption, radiation exposure, chemicals exposure and microorganisms are the main culprit cancer formation. The treatment such as chemotherapy, hormone therapy and radiotherapy is very expensive and toxic to tumor cells and normal cells. Moreover, the common side effects of radiotherapy are mucositis and loss of taste that may be permanent due to the destructive effect of radiation on the salivary glands.^[2] Previous researches have established that the treatment based on natural products and derivatives of medicinal plants is very effective and causes less or no side effects on health and normal cells. Furthermore, studies have proven plant and derivatives of plants' effects in the tumor prevention.^[3-5]

Pomegranate's fruits, seeds, and peels illustrate cancer preventive role due to the antioxidants property and presence of numerous ingredients. Pomegranate fruit arils contain huge amounts of organic acids, sugars, minerals, vitamins and polyphenols and that show antioxidant effect.^[6] The ingredients of pomegranate show chemopreventive role through the inactivation and activation of cell signaling pathways including tumor suppressor gene, angiogenesis and apoptotic pathways.

In this regards, a study finding confirmed that pomegranate's fruits extract treatment to cells causes inhibition of nuclear factor kappa B (NF- κ B) DNA-binding activity.^[7] Pomegranate juice showed significant

role in the suppression of tumor necrosis factor-alpha (TNF- α)-induced cyclooxygenase (COX-2) protein expression and decreased the phosphorylation of the p65 subunit.^[8] In this review, we summarize the pharmacological activities of pomegranates and its components' health management.

ACTION OF POMEGRANATES AND ITS CONSTITUENTS ON TUMOR

Action of pomegranate's fruits, peels, and seeds against cancer cells has been confirmed by several earlier findings. Extract of pomegranate demonstrated its effect in inhibition of the proliferation of cells and extract-treated cells demonstrated an increase in caspase-3 enzyme activity.^[9] Earlier investigator demonstrated that fruit extract and dually sulfide alone slowed onset and incidence of tumor whereas combination of both synergistically decreased tumor incidence more effectively.^[10] Investigators reported that proapoptotic gene including Bax expression was increased, and antiapoptotic gene such as Bcl-2 was decreased after fruit extract treatment.^[11] Anticancerous effect of pomegranate extract was evaluated, and results confirmed that extract showed significant cytotoxic and growth inhibition effects on cancer cells.^[12] The Recent finding revealed that fruit extracts showed role in the enhancement of tamoxifen action through inhibition of cell viability.^[13] In this regards, another study? reported that pomegranate emulsion treatment showed chemopreventive activity through reduced incidence, number, multiplicity, size and volume of hepatic nodules, and precursors of hepatocellular carcinoma,^[14] and significant inhibition of prostate cancer development was noted through drinking water supplemented with fruit extract.^[15] Finding studies reported that pomegranate constituents include luteolin, ellagic acid (EA), and puniceic acid effectual in inhibiting growth of prostate cancer as well as metastasis than simply drinking the juice.^[16] Antitumor effect of pomegranate and harmal was evaluated

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10.4103/phrev.phrev_25_17

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Cite this article as: Rahmani AH, Alsahli MA, Almatroodi SA. Potential antitumor effects of pomegranates and its ingredients. Phcog Rev 2017;11:136-40.

and finding revealed that extracts showed a significant reduction in cell proliferation.^[17] The study was made on breast cancer cells, and results demonstrated that fruit extract enhances the tamoxifen action in both sensitive and TAM-resistant breast cancer cells (MCF7) through the inhibition of cell viability through inducing cell death machinery.^[13] Result based on DNA microarray analysis confirmed that pomegranates extract showed role in the downregulation of genes associated with mitosis, chromosome organization, DNA repair, and upregulated genes involved in the regulation of apoptosis and cell proliferation.^[18] Extract of pericarp of pomegranate showed role in the inhibition of the binding of (3H) estradiol to ER and suppression of the growth and proliferation of ER-positive breast cancer cells.^[19] The role of pomegranates juice extract was examined, and it was noted that extract revealed a significant induction of apoptosis in all cell lines.^[20] Fruit extract causes the inhibition of the growth and progression of lung carcinoma.^[21] Other finding results demonstrated that juice concentrate showed the reduction of the volume and weight of xenografted tumors^[22] and pomegranate polyphenols showed cancer prevention effect.^[23]

MOLECULAR TARGET OF POMEGRANATES AND ITS CONSTITUENTS

The pomegranate including fruits, peels, and seed has demonstrated chemopreventive role through the modulation of a range of cell signaling pathways and Phase I and Phase II enzymes [Figure 1].

NUCLEAR FACTOR-KAPPA B

The NF- κ B is a family of transcription factors that control the genes' expression concerned in several physiological responses including inflammatory responses, proliferation, differentiation, as well as apoptosis.^[24] Activation/overexpression of NF- κ B have been observed in several types of tumors. *In vitro* study based on prostate cancer cell lines revealed that pomegranate extract inhibited NF- κ B and cell viability and maximal extract-induced apoptosis.^[25] The treatment of human lung carcinoma cells through pomegranate fruit extract showed arrest of cells in G0-G1 phase of the cell cycle. Moreover, study results also confirmed that extract treatment to cells demonstrated inhibition of NF- κ B DNA-binding activity.^[7] A recent study based on pomegranates illustrated that it considerably suppressed TNF- α -induced COX-2 protein expression^[8] and other study reported that fruit extract showed role in the inhibition of cell growth in prostate cancer cell lines.^[26]

APOPTOSIS

Altered expressions of proapoptotic protein such as Bax and antiapoptotic protein Bcl-2 shows role in carcinogenesis. The effect of EA in human neuroblastoma cells was evaluated, and results revealed that it induced cell detachment, decreased cell viability, and induced apoptosis.^[27] Results of the finding based on pomegranates extract demonstrated that treatment of prostate cancer cells established cell proliferation inhibition and induction of apoptosis.^[28]

Chemopreventive potential of a pomegranate emulsion against mammary carcinogenesis was carried out and study finding demonstrated that emulsion shows chemoprevention effect through suppressing cell proliferation and inducing apoptosis.^[29] Earlier finding result reported that drugs such as pomegranate extracts as well as genistein in single and in combination treatments showed role in the induction of apoptosis in MCF-7 cells.^[12] Pomegranate bioactive constituents showed role in the suppression of cell proliferation, regulation of cell cycle progression, as well as induction of apoptosis.^[30]

ANGIOGENESIS

Vascular endothelial growth factor (VEGF) is the chief angiogenic factors that stimulate the formation of new blood vessels and tumor growth.^[31] Natural products or herbs have proven their role in tumor inhibition through the inhibition of angiogenic factors.

A study finding reported that pomegranates extract showed role proliferation of prostate cancer cell inhibition and human umbilical vein endothelial cells significantly under both normoxic and hypoxic conditions. Furthermore, HIF-1 α and VEGF protein levels were reduced by extract under hypoxic conditions.^[32] Another study demonstrated that ingredient of pomegranate showed role in the inhibition of angiogenesis through downregulation VEGF in breast cancer MCF-7 as well as human umbilical vein endothelial cell lines.^[33]

PHOSPHOINOSITIDE-3-KINASE/AKT PATHWAY

Altered expression of phosphoinositide-3-kinase (PI3K)/AKT has been observed in numerous tumors. Earlier study result confirmed that pomegranate juice showed role in the suppression of NF- κ B and VCAM-1 mRNA and it also showed role in the inhibition of phosphorylation of PI3K/AKT and mTOR expression as well as increased the expression of miR-126.^[34] Another study reported that

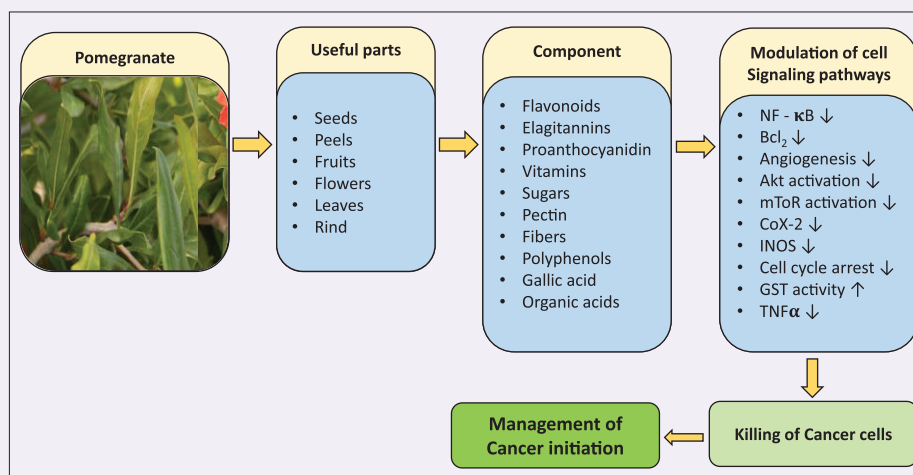


Figure 1: Role of Pomegranates and its ingredients in cancer management

pomegranates juice stop TNF- α -induced AKT activation and that is required for NF- κ B activity.^[8]

CYCLOOXYGENASE

Herbs and its derivatives show disease cure activity through inhibition of COX enzymes activity. Previous study results revealed that juice of pomegranates notably showed role in the suppression of TNF- α -induced COX-2 protein expression by 79%, total pomegranate tannin extract by 55%, and punicalagin by 48%. In addition, juice showed role in the reduction of phosphorylation of the p65 subunit and binding to the NF- κ B response element.^[8] In another study, our results advocate that topical application of fruit extract earlier to 12-O-tetradecanoylphorbol-13-acetate application to CD-1 mice resulted in a noteworthy decrease in skin edema, hyperplasia, and protein expression of epidermal ornithine decarboxylase and COX-2.^[35] The study was performed to evaluate the anti-inflammatory effects of EA and result demonstrated that, based on chronic ulcerative colitis model, EA showed role as mediators including COX-2 and iNOS were downregulated as well as the signaling pathways p38 MAPK, NF- κ B, and STAT3 were blocked.^[36]

CELL CYCLE ARREST

Cell cycle arrest is one of the essential steps in the prevention of cancer formation. In this issue, pomegranates and its ingredients show pivotal role in the management of cell cycle arrest at the G2/M phase. Peels extract of pomegranates showed role in the promotion of growth inhibition of K562 cells mainly through G2/M phase arrest.^[37] Result based on flow cytometry revealed that leaves extract affected H1299 cell survival through arresting cell cycle progression in G2/M phase and inducing apoptosis.^[38] Result based on multiple myeloma cells confirmed that cytotoxic and apoptotic effects of extracts of pomegranates through disruption of mitochondrial membrane potential and increasing cell cycle arrest.^[39]

ENHANCEMENT OF PHASE II ENZYMES

The effect of constituent of pomegranates including EA on the expression of glutathione S-transferase-Ya (GST-Ya) was evaluated, and results confirmed that rats fed EA significant increases in total hepatic GST activity, hepatic GST-Ya activity, and hepatic GST-Ya mRNA.^[40] Earlier study was performed to examine the effect of EA on the expression of the Phase II detoxification enzyme NAD(P)H:quinone reductase and finding of the study revealed that rats fed EA demonstrated increase in hepatic and pulmonary quinone reductase activity, associated with an increase in hepatic QRMrna.^[41] A previous study reported that leaf extract showed a protective effect against cyclophosphamide-induced DNA damage and inhibition of hepatic lipid peroxidation with related increase in reduced glutathione GST and superoxide dismutase in mice pretreated with leaf extract.^[42]

SAFETY AND TOXICITY LEVEL OF PUNICA GRANATUM

Pomegranate safety and toxicity was evaluated by earlier study based on animal model. Several studies based on animal models demonstrated that the consumption of pomegranate is safe and doesn't cause any severe side effects. Experiments were made to evaluate the toxic effect of punicalagin upon repeated oral administration of punicalagin-containing diet. Results based on histopathological analysis confirmed that liver and kidney confirm the absence of toxicity.^[43] Another study reported that different doses of extract; the repeated intranasal administration to rats produced no toxic effects in terms of food intake, weight gain, and behavioral or biochemical parameters.^[44] Finding of the study

revealed that, compared to the control group, administration of the pomegranate fruit extract did not affect in toxicologically significant treatment-related changes in clinical observations, body weights, body weight gains, clinical pathology evaluations, and organ weights.^[45] The toxicology and safety of pomegranate seed oil (PSO) was evaluated, and the result showed no observable adverse effect level of PSO.^[46] A pomegranate ellagitannin-enriched polyphenol extract was prepared for dietary supplement, and the study was carried out in clinical studies. The study was made for safety assessment in overweight individuals. The participants took either 1 or 2 extract capsules per day providing 710 or 1420 mg of extracts. Finding of the study concluded that there were no serious adverse events in any participant studied.^[47] Acute and subacute toxicity profile of ethanolic extracts of pomegranates whole fruit and seeds, and EA (EA) was examined and results demonstrated that whole fruit, seeds extract, and synthetic EA are safe up to 2000 mg/kg body weight oral administration and can be considered as nontoxic.^[48]

BIOAVAILABILITY OF POMEGRANATE

Numerous findings confirmed that medicinal plants or constituents of plants have low absorption and bioavailability. The reason for low bioavailability of any agent is low absorption, rapid elimination, and clearance from the body.^[49] In this regards, several studies revealed that pomegranates show poor absorption and bioavailability and required high doses to accomplish desired blood levels. Investigator reported that healthy volunteers were given 180 mL of juice concentrate was associated with maximum plasma concentrations of EA of 0.06 μ mol/L after 1 h and the EA metabolites, total urolithin A of 0.14 μ mol/L, and total urolithin B of 0.01 at 6 h. Moreover, EA metabolites were also present in plasma and urine in conjugated and free forms.^[50] Another study was performed on healthy men and women were placed on a polyphenol- and antioxidant-free diet earlier to consuming pomegranate extract. Capsule of pomegranate extract daily was given to participants that contains 330.4 mg punicalagins and 21.6 mg EA. Results of the study designate that EA from the extract is bioavailable, with an observed C(max) of 33 ng/mL at t(max) of 1 h. The plasma metabolites - urolithin A, urolithin B, hydroxyl-urolithin A, urolithin A glucuronide, and dimethyl EA-glucuronide were identified.^[51] Bioavailability and metabolism of punicalagin in the rat model were evaluated. Finding reported that, in plasma, punicalagin was detected at concentrations around 30 mg/mL, and glucuronides of methyl ether derivatives of EA were also detected.^[52]

CONCLUSION

Cancer is groups of diseases, and numerous factors involve in this process including alteration in cell signaling pathways. The current treatment module such as chemotherapy, hormone therapy, and radiotherapy is very expensive, toxic to tumor cells and normal cells, and also causes severe side effects. So far, research studies on animal model and clinical trials have established that treatment based on natural products and derivatives of plants is very effective in the cancer management. In this regards, pomegranate's fruits, seeds, and peels contain numerous components including organic acids, polyphenols, and minerals and those constituents show health management activity seems to be due to rich source of antioxidants. Pomegranates have come out as one of the most potent chemopreventive and anticancer agents by inhibiting carcinogenesis process including initiation, promotion, and progression. *In vivo* and *in vitro* and clinical studies have confirmed that ingredients of pomegranates, especially ellagitannins and gallotannins induce apoptosis, modulate numerous cell signaling pathways, and finally inhibit the tumor development and progression. In this review article, a study based on *in vivo* and *in vitro* and clinical studies linked to cancer development and progression through modulation of molecular pathways is addressed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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