

REVIEW ARTICLE

Anti-cancer activity of Pomegranate and Its Constituents: An Overview

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ABSTRACT

Cancer is the second leading cause of death and is becoming the leading one in the old age. Vegetable and fruit consumption are inversely associated with reduced cancer incidence and mortality. Antioxidants from fruits have been extensively studied for their free radical scavenging activities to prevent the occurrence of chronic degenerative diseases. The fruits which are high in polyphenols are reported to have antioxidant and chemo preventive and/or chemotherapeutic potential. There is a major need for less toxic but yet effective therapies to treat cancer. Pomegranate has been shown to exert anticancer and antioxidant activity, which is generally attributed to its high content of polyphenols due to their effects of neutralising free radicals. This review provides up to date info on how pomegranate and their biophenols can target a broad spectrum of genes and proteins to suppress cancer growth and progression. Pomegranate induces apoptosis and evokes anti-proliferative, anti-invasive, and anti-metastatic effects. Furthermore, pomegranate blocks the activation of inflammatory pathways. Thus, it was shown that pomegranate juice (PJ) and/or pomegranate extracts (PE) including genistein, significantly inhibit the growth of prostate cancer cells in culture and also inhibit cell proliferation and induce apoptosis in human breast cancer cells (MCF-7), human pancreatic cancer cells, colon cancer (CACO) and in Hepato-cellular carcinoma (HepGII) cell lines. The aim of this review is to investigate the effect of pomegranate and its biophenols in the prevention and potential treatment of various types of cancers.

Keyword: Pomegranate constituents, skin Cancer, Breast Cancer, Colon Cancer, Hepato-Cellular Carcinoma, Lung Cancer, Prostate Cancer, Thyroid cancer.

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INTRODUCTION

Cancer is considered to be the major cause of death all over the world. This disease is characterized by continuous replication of cells with the capability to invade other normal cells of the body. As reported by Usha et al., 1 in every 6 death is majorly caused by cancer. The major trigger of cancer results from the epigenetic and genetic changes, which cause alteration in essential biological-mechanisms like the cell cycle differentiation and genesis, which causes normal cells to transform into pre-neoplastic lesions, resulting in the conversion to invasive carcinomas. The signs and symptoms of cancer appear after a long period because the precursor lesion is in the intermediary state and grows slowly into a malignant cell. Pancreatic cancer marks the fourth leading cause of death in the US. Colon cancer is considered to be the fourth deadliest form of cancer that claims 9,00,000 deaths annually [1]. The death rate of cancer can be reduced by early diagnosis, intervention, and preventive measures. Allopathy offers a reliable source of treatment, but it can also render some serious side effects, as observed-in cases of cancer patients. Moreover, these chemotherapeutic agents themselves may act as candidates for cancer generation, as they kill normal cells. This has led the researchers to look for some other sources of treatment. As reported by an epidemiological investigation, administering natural products like fruits and vegetables-diminish the chances of cancer in an individual. Furthermore, databases also show that there are low incidences of cancer in patients who regularly consume antioxidant-rich fruits and vegetables. Herbal

medications, due to their safety profile and cost effectiveness, have been increasingly used in treating cancer patients. In the last two decades, multiple varieties of anticancer drugs have been identified and isolated from natural sources, which include plants, microorganisms, and marine sources [2]. Pomegranate (*Punica granatum* L.), belonging to the family Punicaceae, is a deciduous shrub that is native to the Middle East area and cultivated in the Mediterranean, eastward to China and India, American Southwest, California and Mexico . India is the largest producer of Pomegranate. This plant has been in medicinal use for a long time. In China, it is known as a traditional Chinese medicine for its wound healing property, treatment of bleeding and gastrointestinal infections. It also shows its beneficial effect-on the cardiovascular system, metabolic disorders along with its use in the treatment of cancer. Because of these medicinal and valuable properties, it is preferred to as “superfood” and “fruit of paradise”. Pomegranate fruit juice (PJ) is majorly obtained from the arils or the whole fruit, however, few researchers believe that the peel of the fruit possesses more medicinal value due to the presence of minerals, such as magnesium, potassium, sodium, phosphorous and nitrogen. Furthermore, pomegranate peel is also rich in high molecular weight polyphenols, which shows high antioxidant-properties. These antioxidants act as a scavenger eliminating free radicals overproduced in the body and can cause oxidative stress and other degenerative diseases. Other phytochemicals, such as terpenoids, alkaloids, flavonoids, and tannins, are also found to be present in the peel [3]. A rich pool of phytochemical is also found to be present in the fruit, leaves, stem, seed, juice, flower, bark, root, and peel.



Figure (1): pomegranate tree, fruits, juice.

Its extract from different-parts, such as flower, peel, juice, and seed, also possess the property to kill viruses and bacteria. Few researchers have identified its property to improve erectile dysfunction in rabbits and cure the gastric ulcer induced by ethanol in rat models. This wide array of medicinal advantages of pomegranate is the reason behind the vast availability of marketed preparations. The antioxidant activity observed in PJ is equivalent to that of green tea but more than that reported in red wine. The pomegranate juice, peel, and extracted oil possess anticancer activity, such as intrusion in angiogenesis and tumor cell proliferation [4]. Along with the antioxidant-property, it also suppresses inflammation, which help contribute to the chemopreventive and chemotherapeutic activity against cancer. Flavonoids possess the property to down regulate the expression of several genes and proteins that are found to escalate the process of tumor growth. PJ and its extract are also found to be beneficial in the case of prostate cancer inhibiting tumor growth. It also induces apoptosis in the case of breast cancer cells and colon and hepatocellular carcinoma cell lines. It targets various proteins present in their cell signaling pathways like matrix metalloproteinase, vascular endothelial growth factor, and lipoxygenase, etc. Pomegranate has successfully demonstrated anti-proliferative, anti-invasive, and antimetastatic activity in cancer lines through experimentation on animal models and human clinical trials [5]. This review will discuss the anticancer activity of pomegranate with a deep chemical elucidation of phytochemicals and how they are responsible for the said activity. This review also highlights various approaches of drug delivery along with its marketed preparations and ongoing clinical trials.

GEOGRAPHICAL SOURCE

Kingdom: Plantae

Division: Tracheophyta (Vascular plant)

Class: Magnoliopsida (Dicotyledon)

Order: Myrtales

Family: Lythraceae

Genus: *Punica*

Species: *Punica granatum* L.

CHEMICAL CONSTITUENTS AND COMPONENTS OF POMEGRANATES

The pomegranate is a very rich source of bioactive constituents, such as phenolics, flavonoids, ellagitannins, and proanthocyanidin compounds. Moreover, it also contains minerals including potassium (K), nitrogen (N), calcium (Ca), phosphorus (P), magnesium (Mg), zinc (Zn), Iron (Fe), cobalt (Co), and sodium (Na). The ripening of fruit is an important stage that determines the mineral content of the fruit. UHPLC-MSn revealed that 75 compounds are present in pomegranate juice. The seeds of pomegranate are a good source of antioxidants and anti-inflammatory properties due to the presence of tannins, including gallic acid, ellagic acid, and pedunculagin, punicalin, and anthocyanins, such as delphinidin-3-glucoside, cyanidin-3-glucoside, and pelargonidin-3-glucoside [6-8]. Ellagitannins are present in pericarp, seeds, bark, and flowers, while gallotannins are generally found to be present in leaves. Ellagitannins contain one or more hexahydroxydiphenic acid moieties esterified to a polyol, frequently glucose.

Among ellagitannins, the most plentiful moiety present is punicalagin, which possesses antioxidant, anti-fungal, and anti-proliferative properties. Ellagitannins undergo hydrolysis to form ellagic acid in the gut and prolong its release into the systemic circulation. Ellagic acid and urolithins, after reaching the blood circulation, reach and accumulates in its target organs, such as the prostate and colon, showing its reported effect. Punicic acid is present as a polyunsaturated fatty acid that is found to inhibit growth and induce apoptosis in cancerous cells [5]. The methoxy and hydroxyl groups present in the B ring of Flavylium cation are responsible for the coloured allied with the constituent. Moreover, anthocyanins also possess some biological properties, such as antioxidant, anti-inflammatory, and chemoprotective activities.

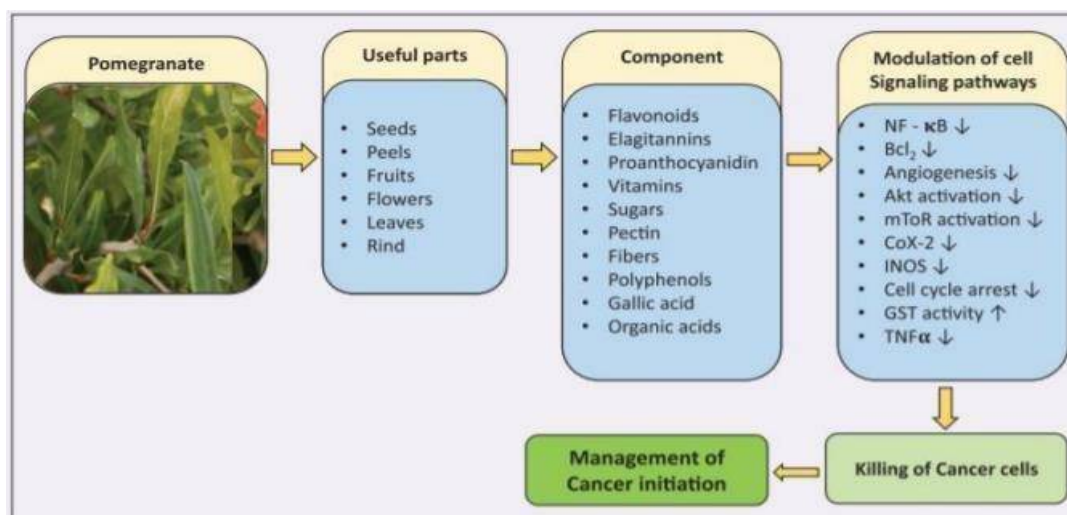


Fig.(2) depicts various chemical constituent present in pomegranate.

MOLECULAR TARGET OF POMEGRANATES AND ITS CONSTITUENTS (MECHANISM)

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

NUCLEAR FACTOR-KAPPA B.

The NF-κB 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.[6] Activation/over-expression 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. 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 and other study reported that fruit extract showed Role in the inhibition of cell growth in prostate cancer cell lines.

APOPTOSIS

Altered expressions of proapoptotic protein such as Wax and antiapoptotic Protein Mcl-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.[8] Results of the finding based on pomegranates extract demonstrated that Treatment of prostate cancer cells established cell proliferation inhibition And induction of apoptosis 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.[9] 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.

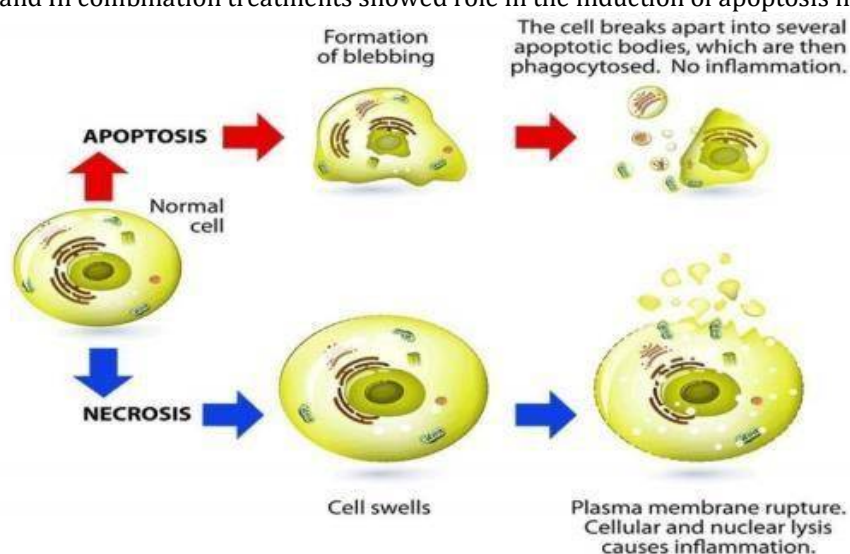


Figure (3) Comparison of apoptosis and necrosis

ANGIOGENESIS

Vascular endothelial growth factor (VEGF) is the chief angiogenic Factors that stimulate the formation of new blood vessels and tumor Growth.[10] 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.[11] Another Study demonstrated that ingredient of pomegranate showed role in the inhibition of angiogenesis through down regulation VEGF in Breast cancer MCF-7 as well as human umbilical vein endothelial Cell lines.

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 miR-126.[12] Another study reported that pomegranates juice stops TNF- α -induced AKT activation and that I required for NF κ B activity.

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-Otetradecanoylphorbol-13-acetate application to CD-1 mice Resulted in a noteworthy decrease in skin edema, hyperplasia, and Protein expression of epidermal ornithine decarboxylase and COX2.[13] 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 COX2 and iNOS were Down regulated as well as the signaling pathways p38 MAPK, NFκB, and STAT3 were blocked.

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.[14] 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. 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.[15]

ENHANCEMENT OF PHASE II ENZYMES

The effect of constituent of pomegranates including EA on the expression Of glutathione Stransferase Ya (GST-Ya) was evaluated, and that rats fed EA significant increases in total hepatic GST Activity, hepatic GST-Ya activity, and hepatic GST-Ya mRNA.[16] 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.[17] 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.

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.[18] 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 behavioural or biochemical parameters.[19] 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.[20] The Toxicology and safety of pomegranate seed oil (PSO) was evaluated and the result showed no observable adverse effect level of PSO.[21] 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.[22] 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.

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,[5] antimicrobial,[6] anti-fungal by in vitro and in vivo evidence,[7,8] and antiviral,[28] It has also been effective in-treatment of cardiovascular disease in Wistar rats,[9] diabetes in hyperglycemic rats, denture stomatitis and mouth lesions in cultured cells[10] and in clinical trial,[11] and protective activity from ultraviolet radiation in ultraviolet-irradiated human skin fibroblasts and other potential usage include Alzheimer's disease in Transgenic Mouse Model,[12] cerebral ischemia in rat model and in human[13] arthritis in human chondrocytes,[14] skin lesions in rats,[15] obesity and lipid lowering effect in rats malaria by in vitro[16] prostate cancer in clinical trial,[17] atherosclerosis in mice,[18] hypertension in Wistar rats.[19] 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.[20]. 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 contain a lot of phytochemicals and considerable antioxidant activity, to be due to ellagic acid activity, which is the main pomegranate polyphenol.[21] Singh et al.[22] explained the first report on antioxidant pomegranate peel extract property. The pomegranate peel extract antioxidant activity is 10 times higher than the pulp extract. Peel extractability in cleaning hydroxyl and superoxide anion radical was also very high. 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. 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.[20] The other study demonstrated that rats feeding with pomegranate peel enabled protective activity against carbon tetra chloride (CCl₄) toxicity .pomegranate pulp extract has a-wide inhibitory activity on matrix metalloproteinases (MMPs) expression and IL-1 β induced tissue destruction .

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. [1,5,17,21] Pomegranate extract has indicated promising anti-tumor activities in various organs. Pomegranate contain polyphenols that they showed anti carcinogenic activities by in vitro and in vivo investigations. [1,13] 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. Study by Adhami et al.[5] has indicated that pomegranate extracts prevented the breast, prostate, colon and lung cancer cells growth in in vitro. Pomegranate extract has capability to inhibited lung, skin, colon and prostate tumors growth in preclinical animal studies. 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 types and skin carcinogenesis reduction in mice and carcinogenesis in a mouse mammary organ culture model. The pomegranate juice activity indicates of synergistic or additive effects from the other phytochemicals present in pomegranate juice. Pomegranate peel extracts have been illustrated to delay proliferation of cells in different cancer cell lines. Anti-carcinogenic properties of different combinations of the phytochemicals in pomegranate were studied. showed that punicalagin have chemotherapy preventive and chemotherapeutic activities against cervical cancer in humans through inhibition of the β -catenin signaling pathway. 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. 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.[12] Pomegranate juice also stimulated apoptosis when concentrations of isolated tannins that were equalized to amounts found in pomegranate juice had no effect. The juice also contains phytochemicals such as anthocyanins and flavonoids, which possess antioxidant and anti-proliferative activity. The synergistic action of the pomegranate constituents appears to be superior to that of single constituents.

Anti-breast cancer

Pomegranate extract indicated anti-inflammatory and cytotoxic activities as in vitro and in vivo in breast cancer cells. The anticancer 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, [7,8] and reduce mammary carcinogenesis in the mouse mammary organ. Pomegranate extracts inhibit the growth of MCF-7 breast cancer cells through induction of apoptosis. 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. 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.[6] illustrated that encapsulation of pomegranate polyphenols enhances their bio efficacy inhibited cancer cell growth in MCF-7 and Hs578T breast cancer cells.

Anti-prostate cancer:

Pomegranate activity has been assessed on prostate cancer in the cell culture, animal models.[17] Also patients with prostate cancer in an initial phase II clinical trial, pomegranate juice has shown considerable prolongation doubling time of prostate specific antigen. Preclinical animal investigations showed the oral pomegranate extract administration inhibited growth of prostate tumors.[5] The first pomegranate juice clinical trial in patients with prostate cancer 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.

Anti-lung cancer:

The effects of pomegranate extract on lung tumor genesis were investigated both in vitro and in vivo by authors, these investigations showed that pomegranate extract could be useful chemo preventive and chemo-therapeutic agent against human lung cancer. It has 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. showed that pomegranate extract remarkably inhibits lung carcinogenesis in the mice model and able to investigate as a chemo preventive agent for human lung cancer. [19] 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. 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 adenocarcinomas. 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,[13] the effects could be due to the non-metabolised ellagitannin-related fraction. indicated that pomegranate seed oil can inhibit 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, anthocyanin, and tannins and possesses powerful antioxidant activity. Tannins compound, have remarkable activity in cancer prevention.[14] Tannin stimulated release of an interleukin 1 (IL-1) and IL-1 beta from the cells in the mice and humans' macrophages in vitro. These results suggest that tannins apply its antitumor effect via activation of macrophages. There are some observations showing evidence that pomegranate pulp extract contains anti-skin tumor promoting activity in CD1 mouse by preventing prevalent also new biomarkers of tetra decanoyl phorbol 13-acetate (TPA)-induced tumor promotion. Pomegranate seed oil has been exhibited in experimental studies to inhibit proliferation of various tumor cell types and to decrease skin carcinogenesis in mice. These primary remarks indicated that pomegranate seed oil is a safe and effective agent against skin cancer. Apoptosis is the most potent defence mechanism against cancer. in Balb/c mice showed significant induction of apoptosis by pomegranate extract. Percent increase in apoptotic population in pomegranate extract was [1,18]

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. The effect of pomegranate extract on DENA-

induced hepato-cell carcinogenesis, like hepatocellular carcinoma in humans, was examined in vivo. Considerable chemo-preventive potential was 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, 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. Investigations in rats with carbon tetra chloride toxicity induced liver damage showed pomegranate pre-treatment 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. demonstrated that pomegranate bioactive compounds apply a chemo preventive effect against diethyl nitrosamine 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.[23]

Anti Thyroid Cancer :

The most common endocrine malignancy is thyroid cancer. Thyroid malignancy can be classified into 4 types, papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), medullary thyroid cancer (MTC), and anaplastic thyroid cancer (ATC), of which the lowest mortality rate is observed in PTC.[16] The major treatment approach for these malignancies is surgical procedures. A recent study showed that pomegranate peel extract (PoPx) can inhibit the proliferation of cancer cells invasion and induce apoptosis via mitochondria led intrinsic pathway. PoPx has shown a strong inclination towards thyroid cancer, as evident by the inhibitory action on the replication of xenograft thyroid tumours without causing any harmful impact on the visceral organ[10]. The evaluation of extract was done on BCPAP and TPC-1 cell lines . The contents of punicalagin and ellagic acid found in PoPx were 83.9 mg g⁻¹ and 7.3 mg g⁻¹, respectively. Another study conducted elucidated that the possible mechanism of action of punicalagin, i.e., its induction of autophagic cell death, does not show any conjugation with apoptosis in PTC. showed that punicalagin causes the damage of DNA, which is independent of conformational DNA alterations along with reactive oxygen species induction. The data about the anticancer activity of pomegranate and its compound is still meagre and thus warrants further research in this area.[23]

DRUG DELIVERY APPROACHES FOR TARGETED DELIVERY TO TUMORS

The polyphenols show poor bioavailability limiting their use despite cytotoxicity potential. These show poor intestinal absorption due to the presence of intestinal microbiota. They also show the difficulty in crossing the blood-brain barrier. There are many convention formulations available but faces some limitations, such as lack of targeting, poor absorption and bioavailability, nonspecific biodistribution, and low therapeutic indices. To minimise such limitations and utilize the useful properties of polyphenols, novel drug delivery systems are deeply studied by scientists to enhance the circulation efficiency and biodistribution, and tissue targeting, reduce the cytotoxic effect of anticancer drugs, and enhance permeability and retention, etc .[21] The various drug delivery, such as polymeric drug micelles, liposomes, dendrimer, carbon nanotubes, nano rods, nano structured lipid carrier, etc. can be used . Liang et al. developed a stimuli responsive drug delivery by using a multifunctional coating of polyphenol on zein nanoparticles. The formulation showed a drug release when exposed to an acidic medium with highly efficient internalisation and an apparent cytotoxic effect on HeLa cells. This system showed delayed release behaviour and a promising media for biomedical application for cancers. The nanoparticles of tea polyphenols showed a promising cancer treatment. It resulted in high drug loading, pH responsive drug release, high cancer cell inhibition rate, high accumulation and retention at the tumor site, etc. The polymeric nanoparticles showed high stability, homogeneous size distribution, controllable physicochemical properties, high drug payload, and controlled drug release. [16] *Callistemon citrinus* rich in polyphenols helps in the treatment of breast cancer. It was encapsulated in poly (lactic-co-glycolic acid) (PLGA) polymer, which proved to be effective against invasion of MDA-MB 231, MCF-10A, and MCF7 breast cancers. In this formulation, encapsulation was achieved at 80 % and effectively helped in treating breast cancer. Nanoparticles of tea polyphenols (epigallocatechin gallate (EGCG)) act as antioxidants and shows their beneficial effect for anti-cancer. A self-assembled nanoparticle is another approach utilized to improve the drug delivery of polyphenols. It controls the thickness, morphology, and functionality of the material, which enhances the drug delivery. Nano encapsulation of polyphenols helps in effective systemic circulation, increases stability, improves solubility and enhances bioavailability [22]. Moreover, the anticancer activity of polyphenols is increased by nano carriers. formulated a natural polysaccharide-

cloaked lipidic nano carrier loaded with natural polyphenol curcumin used for the treatment of small lung cancer. The formulation has easy scale-up, low cost, and has high safety. It also helped improve the bioavailability by showing the synergistic effect through improved cell penetration, and resistance to acidic degradation, etc.. formulated a stimulus-responsive tea polyphenol as a nanocarrier for selective intracellular drug delivery. The nano sized particles helped target the tumor site and inhibit the cancerous cell. formulated a Chitosan-PEG-folate-Fe(III) complexes as nanocarriers of epigallocatechin-3-gallate, showing its potential for cancer treatment with controlled-release [23].

CONCLUSION

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.

REFERENCES

1. Stavridi F, et al. (2010). "Targeted therapeutic approaches for hormone-refractory prostate cancer". *Cancer Treat Reviews* 36.2: 122-130
2. Donaldson, M.S. (2004). Nutrition and cancer: A review of the evidence For an anti-cancer diet. *Nutr. J.*, 3(1), 19.
3. Syed, N; Chamcheu, J.-C; Adhami, M; Mukhtar, H (2013). Pomegranate Extracts and cancer prevention: Molecular and cellular activities. *Anti-cancer agents in medicinal chemistry (formerly current medicinal Chemistry-anti-cancer agents.*, 13(8), 1149-1161.
4. Prajapati, S.K.; Mishra, G.; Malaiya, A.; Jain, A.; Mody, N.; Raichur, A.M. (2020). Antimicrobial application potential of phytoconstituents from turmeric and garlic. *Bioactive natural products for pharmaceutical applications*; Springer: Cham, 2020, pp. 409-435.
5. Ashtami VM, Khan N, Mukhtar H. (2009). Cancer chemoprevention By pomegranate: laboratory and clinical evidence. *Nutr Cancer*; 61:811-5.
6. Abdollahzadeh SH, Mashouf R, Mortazavi H, et al. (2011). Antibacterial and antifungal activities of *Punica granatum* Peel extracts against oral pathogens. *J Dent (Tehran)* 1;8:1-6.
7. Anibal PC, Peixoto IT, Foglio MA, Höfling JF. (2013). Antifungal Activity of the ethanolic extracts of *Punica granatum* L. and Evaluation of the morphological and structural modifications Of its compounds upon the cells of *Candida* spp. *Braz J Microbiol* ;44:839-48.
8. Bassiri-Jahromi S, Pourshafie MR, Mirabzade Ardakani E, Ehsani AH, Doostkam A, Katirae F, Mostafavi E PhD. (2018). In Vivo Comparative Evaluation of the Pomegranate (*Punica granatum*) Peel Extract as an Alternative Agent to Nystatin against Oral Candidiasis. *Iran J Med Sci*; 43(3):296-304. PMID: 29892147; PMCID: PMC5993896.
9. Mohan M, Patankar P, Ghadi P, Kasture S. (2010). Cardioprotective potential of *Punica granatum* extract in isoproterenol-induced myocardial infarction in Wistar rats. *J Pharmacol Pharmacother.* 1(1):32-7. doi: 10.4103/0976-500X.64533. PMID: 21808588; PMCID: PMC3142755.
10. Tavassoli-Hojjati S, Aliasghar E, Ahmadian Babaki F, et al. (2014). Pomegranate juice (*Punica granatum*): a new storage medium For avulsed teeth. *J Dent (Tehran)*; 11:225-32.
11. Bhadbhade SJ, Acharya AB, Rodrigues SV, Thakur SL. (2011). The Antiplaque efficacy of pomegranate mouthrinse. *Quintessence Int*; 42:29-36.
12. Subash S, Essa MM, Al-Asmi A, et al. Tradit. (2014). Pomegranate From Oman alleviates the brain oxidative damage in transgenic mouse model of Alzheimer's disease. *Complement Med*; 4:232-8.
13. West T, Atzeva M, Holtzman DM. (2007). Pomegranate polyphenols and resveratrol protect the neonatal brain against hypoxicischemic injury. *Dev Neurosci*; 29:363-72.
14. Rasheed Z, Akhtar N, Haqqi TM. (2010). Pomegranate extract Inhibits the interleukin-1 β -induced activation of MKK-3, P38 α -MAPK and transcription factor RUNX-2 in human Osteoarthritis chondrocytes. *Arthritis Res Ther* ;12:R195.
15. Mo J, Panichayupakaranant P, Kaewnopparat N, et al. (2014). Wound Healing activities of standardized pomegranate rind extract And its major antioxidant ellagic acid in rat dermal wounds. *J Nat Med*; 68:377-86.
16. Dell'agli M, Galli GV, Bulgari M, et al. (2010). Ellagitannins of the Fruit rind of pomegranate (*Punica granatum*) antagonize in Vitro the host inflammatory response mechanisms involved In the onset of malaria. *Malar J* ;9:208.

17. Malik A, Mukhtar H. (2006). Prostate cancer prevention through Pomegranate fruit. *Cell Cycle*;5:371-3.
18. Al-Jarallah A, Igdoura F, Zhang Y, et al. (2013). The effect of pomegranate extract on coronary artery atherosclerosis in SRBI APOE double knockout mice. *Atherosclerosis*; 228:80-9.
19. Mohan M, Waghulde H, Kasture S. (2010). Effect of pomegranate Juice on Angiotensin II-induced hypertension in diabetic Wistar rats. *Phytother ResSuppl* 2:S196-203.
20. Sen S, Chakraborty R, Sridhar C, et al. (2010). Free radicals, antioxidants, diseases and photo medicines: current status and future Prospect. *Int J Pharm Sci Rev Res*;3:91.
21. Syed DN, Chamcheu JC, Adhami VM, Mukhtar H. (2013). Pomegranate extracts and cancer prevention: molecular and Cellular activities. *Anticancer Agents Medchem* ;13:1149-61.
22. Singh R, Singh MK, Chandra LR, et al. (2012). In vitro antioxidant and free radical scavenging activity of *Macrotyloma uniflorum* (Gahat dal) from Kumauni region. *J Fundam Appl Sci*;1:7-10.
23. Kaplan M, Hayek T, Raz A, et al. (2001). Pomegranate juice supplementation to atherosclerotic mice reduces macrophage lipid Peroxidation, cellular cholesterol accumulation and development of atherosclerosis. *J Nutr* 131:2082-9

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