Review Report

Potent health effects of pomegranate

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Abstract

Accumulating data clearly claimed that *Punica granatum* L. (pomegranate) has several health benefits. Pomegranates can help prevent or treat various disease risk factors including high blood pressure, high cholesterol, oxidative stress, hyperglycemia, and inflammatory activities. It is demonstrated that certain components of pomegranate such as polyphenols have potential antioxidant, anti-inflammatory, and anticarcinogenic effects. The antioxidant potential of pomegranate juice is more than that of red wine and green tea, which is induced through ellagitannins and hydrosable tannins. Pomegranate juice can reduce macrophage oxidative stress, free radicals, and lipid peroxidation. Moreover, pomegranate fruit extract prevents cell growth and induces apoptosis, which can lead to its anticarcinogenic effects. In addition, promoter inhibition of some inflammatory markers and their production are blocked via ellagitannins. In this article, we highlight different studies on the therapeutic effects of pomegranate and their suggested mechanisms of actions.

Key Words: Antioxidant, inflammatory activities, pomegranate

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INTRODUCTION

Punica granatum L. (Pomegranate) is a long-lived and drought-tolerant plant. Arid and semiarid zones are popular for growing pomegranate trees. They are widely cultivated in Iran, India, and the Mediterranean countries such as Turkey, Egypt, Tunisia, Spain, and Morocco.[1] However, pomegranate is categorized as a berry but it belongs to its own botanical family, *Punicaceae*. The only genus is *Punica,* with one predominant species called *P. granatum*.[2]

The trees can grow up to 30 feet in height. The leaves are opposite, narrow, oblong with 3-7 cm long and 2 cm broad. It has bright red, orange, or pink flowers, which are 3 cm in diameter with four to five petals. Edible fruit has a rounded hexagonal shape, with 5-12 cm in diameter and weighing 200 g. The thick skin surrounds around 600 arils, which encapsulates the seeds.[3]

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CHEMICAL COMPOSITION

Seed

About 18% of dried and cleaned white seeds are oil. The oil is rich in punicic acid (65%), which is a triple conjugated 18-carbon fatty acid [Figure 1]. There are some phytoestrogen compounds in pomegranate seeds

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that have sex steroid hormones similar to those in humankind. The 17-alpha-estradiol is a mirror-image version of estrogen.[3]

Juice and peel

Pomegranate juice is a good source of fructose, sucrose, and glucose. It also has some of the simple organic acids such as ascorbic acid, citric acid, fumaric acid, and malic acid. In addition, it contains small amounts of all amino acids, specifically proline, methionine, and valine. Both the juice and peel are rich in polyphenols. The largest classes include tannins and flavonoids [Figure 2] that indicate pharmacological potential of pomegranate due to their strange antioxidative and preservative activities.[3]

Ellagitannin is a type of tannins; it can be broken down into hydroxybenzoic acid such as ellagic acid. It is widely used in plastic surgeries, which prevents skin flap's death due to its antioxidant activity. Two other ellagitannins that are found in both pomegranate juice and peel are punicalagin and punicalin. Several classes of pomegranate flavonoids include anthocyanins, flavan 3-ols, and flavonols. Pomegranate juice and peel have catechins with a high antioxidant activity. They are essential compounds of anthocyanin's production with antioxidant and inflammatory role. Anthocyanins cause the red color of juice, which is not found in the peel. All pomegranate flavonoids show antioxidant activity with indirect inhibition of inflammatory markers such as tumor necrosis factor-alpha (TNF-α).[3]

Bark and roots

The pomegranate tree's bark and roots are rich sources of chemicals called alkaloids. They are carbon-based substances; they were used to treat worms in the human gastrointestinal tract in traditional medicine.[3]

Table 1 Shows pomegranate's nutrient values for 100 g of raw edible portion[4]

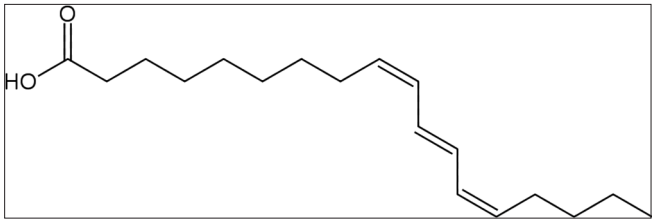

Figure 1: Chemical structure of punicic acid (9Z,11E,13Z-octadeca-9,11,13-trienoic acid)

Health effects

Prostate cancer

After lung cancer, the second leading cause of male cancer death is prostate cancer worldwide. Its progress before onset of symptoms is slow; therefore, pharmacological and nutritional interventions could affect the quality of patient's life by delaying its development.[5]

It was shown that pomegranate fruit could be used in the treatment of human prostate cancer because it could inhibit cell growth and induce apoptosis.[6] It leads to induction of pro-apoptotic proteins (Bax and Bak) and downregulation of anti-apoptotic proteins (Bcl-xL and Bcl-2).[6] Moreover, the presence of NFκB and cell viability of prostate cancer cell lines has been inhibited when using pomegranate fruit extract, because it blocks NFκB.[7] Polyphenols of fermented juice and pomegranate oil can inhibit the proliferation of LNCaP

Table 1: Pomegranate's nutrient values for 100 g of raw edible portion

Nutrients	Units	Value per 100 g
Water	g	77.93
Energy	Kcal	83
Protein	g	1.67
Total lipid (fat)	g	1.17
Ash	g	0.53
Carbohydrates	g	18.70
Fiber	g	4.0
Sugars, total	g	13.67
Calcium	Mg	10
Iron	Mg	0.3
Magnesium	Mg	12
Phosphorus	Mg	36
Potassium	Mg	236
Sodium	Mg	3
Ascorbic acid, total	Mg	10.2
Choline, total	Mg	7.6

Adapted from united states department of agriculture (USDA) National nutrient database for standard reference

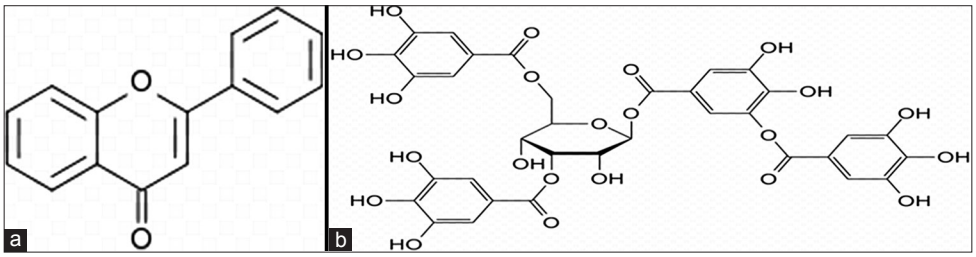

Figure 2: (a) Flavone backbone (2-phenyl-1, 4-benzopyrone). (b) Tannic acid

(epithelial cell line derived from a human prostate carcinoma), PC-3, and DU145 human prostate cancer cell lines. These effects were the result of changes in cell cycle distribution and apoptosis induction.[6] In addition, it is reported that pomegranate fruit extract oral administration in nude mice implanted with androgen-sensitive CWR22RV1 cells caused significant decrease in serum prostate-specific antigen (PSA) level and inhibited tumor growth.[7] Besides, the observed increase in NFκB activity during androgen dependence to androgen independence transition in the LAPC4 xenograft model was terminated.[8]

Breast cancer

Fermented pomegranate juice has double the antiproliferative effect compared to fresh pomegranate juice in human breast cancer cell lines MCF-7 (breast cancer cell line isolated in 1970 from a 69-year-old Caucasian woman) and MB-MDA-231. In addition, pomegranate seed oil caused 90% prevention of proliferation of MCF-7 cells.[9,10]

Lung cancer

Pomegranate fruit extract can inhibit several signaling pathways, which can be used in the treatment of human lung cancer. Pathways include Mitogen-activated protein kinases (MAPK) PI3K/Akt and NFκB. In addition, there was a 4 day delay in the appearance of tumors (from 15 to 19 days) in mice implanted with A549 cells.[10] These studies indicate the chemopreventive effects of pomegranate fruit extract.[3]

Colon cancer

Adams *et al*.[11] have reported the anti-inflammatory effects of pomegranate juice on the signaling proteins in HT-29 human colon cancer cell line. Reduction in phosphorylation of the p65 subunit of NFκB, its binding to the NFκB response, and 79% inhibition in TNF-α protein expression have been observed with 50 mg/L concentration of pomegranate extract.

Skin cancer

It has been demonstrated that pomegranate oil has chemopreventive efficacy in mice. Reduced tumor incidence (7%), decrease in tumor numbers, reduction in ornithine decarboxylase (ODC) activity (17%), significant inhibition in elevated Tissue plasminogen activator (TPA)-mediated skin edema and hyperplasia, protein expression of ODC and COX-2, and epidermal ODC activity have been reported with pomegranate oil treatments.[12,13] Pomegranate extract in various concentrations (5-60 mg/L) was effective against UVA- and UVB-induced damage in SKU-1064 fibroblast cells of human, which was relevant in reducing NFκB transcription, downregulating proapoptotic caspase-3, and elevating the G0/G1 phase associated with deoxyribonucleic acid (DNA) repair.[14]

Cardiovascular diseases

Pomegranate juice is an affluent source of polyphenols with high antioxidative potential. Moreover, its antiatherogenic, antihypertensive, and anti-inflammatory effects have been shown in limited studies in human and murine models.[15]

Hypertension is the most common disease in primary care of patients. It is found in comorbidity with diabetes and cardiovascular disease, and the majority of patients do not tend to be medicated. Pomegranate juice prevents the activity of serum angiotensin-converting enzyme and reduces systolic blood pressure.[16] Angiotensin II acute subcutaneous administration causes increased blood pressure in diabetic Wistar rats. It has been shown that pomegranate juice administration (100 mg/kg) for 4 weeks could reduce the mean arterial blood pressure.[17] Pomegranate juice consumption resulted in 30% decrease in carotid intima-media thickness after 1 year. The patient's serum paraoxonase 1 (PON 1) activity showed 83% increase, whereas both serum low dwnsity lipoprotein (LDL) basal oxidative state and LDL susceptibility to copper ion significantly decreased by 90% and 95%, respectively.[18]

Punicic acid, which is the main constituent of pomegranate seed oil, has antiatherogenic effects. In a study on 51 hyperlipidemic patients, pomegranate seed oil was administered twice a day (800 mg/day) for 4 weeks. There was a significant decrease in triglycerides (TG) and TG: High density lipoprotein (HDL) cholesterol ratio by 2.75 mmol/L and 5.7 mmol/L, respectively, whereas serum cholesterol, LDL-C, and glucose concentration remained unchanged.[19]

High plasma LDL concentration is the major risk factor for atherosclerosis. Therefore, LDL modifications, including oxidation, retention, and aggregation, play a key role in atherosclerosis as well. Studies have shown that consuming pomegranate juice for 2 weeks resulted in declined retention and aggregation of LDL susceptibility and increased activity of serum paraoxonase (a protective lipid peroxidation esterase related to HDL) by 20% in humans. Pomegranate juice administration in mice for 14 weeks showed reduced LDL oxidation by peritoneal macrophages by more than 90%, which was because of reduced cellular lipid peroxidation and superoxide release. The uptake of oxidized LDL showed 20% reduction in mice. The size of atherosclerotic lesions reduced by 44% after pomegranate juice supplementation.[20] Moreover, pomegranate juice administration to apolipoprotein

E-deficient mice with advanced atherosclerosis for 2 months reduced oxidized LDL (31%) and increased macrophage cholesterol efflux (39%).[21]

In cultured human endothelial cells and hypercholesterolemic mice, both pomegranate juice and fruit extract reduced the activation of ELK-1 and p-CREB (oxidation-sensitive responsive genes) and elevated the expression of endothelial nitric oxide synthase. It is suggested that polyphenolic antioxidant compounds in pomegranate juice are responsible for the reduction of oxidative stress and atherogenesis.[22]

In another study,[23] concentrated pomegranate juice was shown to reduce heart disease risk factors. Administration of concentrated pomegranate juice to 22 diabetic type 2 patients with hyperlipidemia could significantly reduce TC, LDL-C, LDL-C: HDL-C ratio, and TC: HDL-C ratio. However, it was unable to decrease serum TG and HDL-C concentrations.

Oral administration of pomegranate flower aqueous extract in streptozotocin (STZ)-induced albino Wistar rats in both 250 mg/kg and 500 mg/kg doses for 21 days could significantly reduce fibrinogen (FBG), TC, TG, LDL-C, and tissue lipid peroxidation level and increased the level of HDL-C and glutathione content.[24]

Heart fibrosis increases among diabetics, which results in impairing cardiac function. Endothelin (ET)-1 and NFκB are interactive fibroblast growth regulators. It is suggested that pomegranate flower extract (500 mg/kg/day) in Zucker diabetic fatty rats could reduce the ratios of van Gieson-stained interstitial collagen deposit area to a total left ventricular area and perivascular collagen deposit areas to coronary artery media area in the heart and diminishes cardiac fibrosis in these rats. In addition, overexpressed cardiac fibronectin and collagen I and II messenger RNAs (mRNAs) were inhibited. It also decreased the upregulated cardiac mRNA expression of ET-1, ETA, inhibitor-κBβ, and c-jun. Pomegranate flower extract is a dual activator of peroxisome proliferator-activated receptor (PPAR)-α and γ and improves hyperlipidemia, hyperglycemia, and fatty heart in diabetic fatty Zucker rats.[25,26]

Punicic acid caused a dose-dependent increase in PPAR alpha and gamma reporter activity in 3T3-L1 cells. Dietary punicic acid reduced plasma glucose, suppressed NFκB activation and unregulated TNF-α expression and PPAR-α/γ responsive genes in adipose tissue and skeletal muscle.[27]

Pomegranate leaf extract was administered (400 and 800 mg/kg/day) to high-fat-diet-induced obese and hyperlipidemic mouse models for 5 weeks. The results indicated significant reduction in body weight, energy intake (based on food intake), serum total cholesterol (TC), TG, FBG, and TC/HDL-C ratio. Intestinal fat absorption was inhibited as well.[28]

The high fat diet (HFD) with 1% pomegranate seed oil (rich source of punicic acid) was administered for 12 weeks to induce obesity and insulin resistance in mice. The pomegranate seed oil-fed group exhibited lower body weight (4%) and body fat mass (3.1%) compared with only HFD-fed mice. A clear improvement was observed in peripheral insulin sensitivity (70%) in pomegranate seed oil-administered rats.[29]

Fatty liver is the most common abnormal liver function among diabetics. Pomegranate flower was examined for its antidiabetic effects on diabetic type II and obese Zucker rats. Rats fed with 500 mg/kg/day of pomegranate flower extract for 6 weeks showed decreased ratio of liver weight to tibia length, lipid droplets, and hepatic TG contents. In addition, it increased PPRA-α and Acyl-COA oxidase mRNA levels in HepG2 cells.[30]

In a study by de Nigris *et al*.,[31] they compared the influence of pomegranate fruit extract with pomegranate juice on nitric oxide and arterial function in obese Zucker rats. They have demonstrated that both pomegranate fruit extract and juice significantly reduced the vascular inflammatory markers expression, thrombospondin, and cytokine TGFP 1. Increased plasma nitrite and nitrate were observed with administration of either pomegranate fruit or juice.

Many studies have reported the anti-inflammatory potential of pomegranate extract. In a study on 30 Sprague-Dawley rats with acute inflammation due to myringotomy, it was observed that 100 μl/day of pomegranate extract could significantly reduce reactive-oxygen species (ROS) levels. The extract was administered 1 day before and 2 days after surgery. Reduced thickness of lamina propria and vessel density was reported as well.[32] Both ellagitannins and ellagic acid are the main components of pomegranate extract, which have anti-inflammatory properties. They are metabolized by gut microbiota to yield urolithins. It is suggested that urolithins are the main components responsible for the anti-inflammation properties of pomegranate. It is suggested that NFκB activation, MAPK downregulation of COX-2, and mPGES-1 expression were inhibited through a decrease in PGE2 production.[33] Neutrophils play key roles in inflammatory processes by releasing great amounts of ROS generated by NADPH-oxidase and myeloperoxidase. It is indicated that punicic

acid exhibited a potent anti-inflammatory effect via prevention of TNF-α-induced priming of NADPH oxidase by targeting the p38MAPKinase/Ser 345-p 47 phox-axis and releasing MPO.[34] Hyperglycemia results in oxidative stress in diabetes mellitus, which is a major factor in the pathogenesis of cardiovascular disease. Results suggested that pomegranate extract, owing to its polyphenol-rich antioxidants (oleanolic, ursolic, and gallic acids), could prevent cardiovascular complications through decrease in LDL, increase in HDL, serum paraoxonase 1 stability and activity, and nitric oxide production.[35-37]

Osteoarthritis

The most common forms of arthritis are osteoarthritis and its major progressive degenerative joint disease, which could affect joint functions and quality of life in patients. It is mediated by proinflammatory cytokines such as IL-1 and TNF-α. MAPKs are important due to their inflammatory and cartilage damage regulation.[38] P38-MAPKs are responsible for regulating cytokine production, neutrophils activation, apoptosis, and nitric oxide synthesis. The MAPK family phosphorylates a number of transcription factors such as runt-related transcription factor-2 (RUNX-2).[39-41]

Pomegranate extract, with its rich source of polyphenols, can inhibit IL-1 β-induced activation of MKK3, DNA-binding activity of RUNX-2 transcription factor, and p38 α-MAPK isoform.[38]

Rheumatoid arthritis

Rheumatoid arthritis is an autoimmune disease that affects 0.5-1% of people worldwide. Women are afflicted more than men. This inflammatory disease is characterized by inflammation and bone erosion.[38,39] Critical mediators in the pathogenesis of rheumatoid arthritis are TNF-α, IL-1 β, MCP1, Inducible nitric oxide synthase (iNOS), and COX-2-agents, which are stimulated by p38-MAPK and NFκB activation.[42,43]

It is shown that pomegranate extract could reduce the onset and incidence of collagen-induced arthritis in mice. Severity of arthritis, joint inflammation, and IL-6 level were significantly reduced in pomegranate extract-fed mice.[44]

Antimicrobial/fungal effect

Since bacterial resistance to antimicrobial drugs is increasing, medicinal plants have been considered as alternative agents. Pomegranate has been widely approved for its antimicrobial properties.[4,45,46] It has been shown that dried powder of pomegranate peel has a high inhibition of *Candida albicans*.[47] In addition, antimicrobial effects of both methanol and dichloromethane pomegranate extracts have been demonstrated on the *Candida* genus yeast as pathogen-causing disease in immunosuppressive host.[48] Methicillin-resistant *staphylococcus aureus* (MRSA) and methicillin-sensitive *staphylococcus aureus* (MSSA) (multiple antibiotics resistant) produce panta valentine leukocidin (PVL) toxin, which can lead to higher levels of morbidity and mortality.[49,50] It is indicated that a combination of pomegranate peel extract with Cu (II) ions exhibit enhanced antimicrobial effects against isolated MSSA, MRSA, and PVL.[51] One of the leading etiological bacteria of urinary tract infections is *Escherichia Coli.* Strong antibacterial activity of ethanol extract against *E. coli* has been shown.[52]

Skin

Solar ultraviolet radiations are the primary causes of many biological effects such as photoaging and skin cancer. These radiations resulted in DNA damage, protein oxidation, and matrix metalloproteinases induction. In one study, the effects of pomegranate juice, extract, and oil were examined against UVB-mediated damage. These products caused a decrease in UVB-induced protein expression of c-Fos and phosphorylation of c-Jun.[53] On the other hand, production of proinflammatory cytokines IL-1 β and IL-6 was decreased by topical application of 10 micromol/L of ellagic acid. The inflammatory macrophages infiltration was blocked in the integuments of SKH-1 hairless UVB-exposed mice for 8 weeks.[54]

Dental effects

The interbacterial coaggregations and these bacterial interactions with yeasts are related to the maintenance of oral microbiota. It is indicated that dried, powdered pomegranate peel shows a strong inhibition of *C. albicans* with a mean zone of 22 mm.[55] In another study, the antiplaque effect of pomegranate mouth rinse has been reported.[56] In addition, hydroalcoholic extract of pomegranate was very effective against dental plaque microorganisms (84% decrease (cfu/ml)).[57]

Reproductive system

One of the main constituents (16%) of the methanolic pomegranate seed extract is beta-sitosterol. It is suggested that the extract is a potent phasic activity stimulator in rat uterus, which happens due to the non-estrogenic effects of beta-sitosterol on inhibiting sarco-endoplasmic reticulum Ca^{2+}-ATPase (SERCA) and K channel, which resulted in contraction by calcium entry on L-type calcium channels and myosin light chain kinase (MLCK).[58] It is demonstrated that pomegranate fruit extract has an embryonic protective nature against adrianycin-induced oxidative stress (adrianycin is a chemotherapeutic drug used

in cancer treatment).[59] Moreover, pomegranate juice consumption could increase epididymal sperm concentration, motility, spermatogenic cell density, diameter of seminiferous tubules and germinal cell layer thickness.[60]

Alzheimer

Hartman *et al*.[61] showed that mice treated by pomegranate juice have 50% less soluble Abeta 42 accumulation and amyloid deposition in the hippocampus, which could be considered for Alzheimer's disease improvement.

Malaria

In the presence of pomegranate fruit rind, the induced MMP-9 mRNA levels by haemozoin or TNF was decreased, which may be attributed to the antiparasitic activity and the inhibition of the proinflammatory mechanisms responsible in the onset of cerebral malaria.[62,63]

HIV

The anti-HIV-1 microbicide of pomegranate juice blocks virus binding to CD4 and CXCR4/CCR5, thereby preventing infection by primary virus clades A to G and group O.[64]

Wound healing

Use of pomegranate extract and flower showed significant reduction in wound area and increased the well-organized bands of collagen, fibroblasts, and few inflammatory cells.[65,66] Properties of elevated wound contraction and the period of epithelialization, collagen, and protein synthesis were reported in hydroalcoholic pomegranate extract.[67]

Mechanisms of action

Pomegranate can induce its beneficial effects through its various metabolites. The antioxidant and antiatherosclerotic potentials of pomegranate are mainly relevant to the high polyphenol concentrations in pomegranate fruit such as ellagitannins and hydrolysable tannins.[68] COX-1 and COX-2 enzymes and IL-1 β activity can be inhibited by pomegranate fruit extract.[69]

It is suggested that pomegranate can antagonize the stimulation of mRNA of MMP-9 in THP-1/ monocytes. The whole fruit and compounds inhibit TNF-induced MMP-9 promoter activity.[41] Urolithins are metabolites that are metabolized by the human intestinal microflora. These compounds decreased MMP-9 sretion and mRNA levels induced by HZ or TNF. It is suggested that ellagitannins are responsible for the control of excessive production of MMP-9, which could result in decreased production of noxious cytokine TNF.[70] TNF cytokines promote NFκB binding to target sequences while inducing transcription of several genes such as the MMP-9 gene.[71] Ellagitannins prevent NFκB promoter activity by blocking NFκB-driven transcription and affecting the entire cytokine cascade. Ellagitannins inhibit the activation of inflammatory pathways such as MAPK.[40] In addition, pomegranate compounds could inhibit angiogenesis through the downregulation of vascular endothelial growth factor in cancers.[4]

Drug interactions involving pomegranate

Therapeutic benefits of pomegranate in various diseases would lead to an increase in its consumption.[72] It is important that pomegranate consumption does not affect the oral bioavailability of drugs.[73]

A study on human liver microsomes has shown the inhibitory effect of pomegranate juice on CYP2CP (a gene that codes for an enzyme to break down warfarin in the body) and increased bioavailability of tolbutamide (substrate for CYP2CP) in rats. Moreover, it is suggested that pomegranate may inhibit cytochrome P450-3A (CYP3A)-mediated carbamazepine metabolism.[4,74,75]

Pomegranate safety

Many studies have been carried out on the different components derived from pomegranate but no adverse effects have been reported in the examined dosage. Histopathological studies on both sexes of OF-1 mice confirmed the non-toxic effects of the polyphenol antioxidant punicalagin. Besides, in a study on 86 overweight human subjects who received 1420 mg/day of pomegranate fruit extract in tablet form for 28 days, no side effects or adverse changes in urine or blood of individuals were reported.[4,76]

Products and supplementation

Apart from fruit, pomegranate is available in various forms such as bottled juice (fresh or concentrated), powdered capsules, and tablets, which are derived from seed, fermented juice, peel, leaf and flower, gelatin capsules of seed oil extracts, dry or beverage tea from leaves or seeds, and other food productions such as jams, jellies, sauces, salad dressings, and vinegars. Anardana, which is the powdered form of pomegranate seed, is used as a form of spice.[3]

CONCLUSION

Pomegranate is a potent antioxidant. This fruit is rich in flavonoids, anthocyanins, punicic acid, ellagitannins, alkaloids, fructose, sucrose, glucose, simple organic acids, and other components and has antiatherogenic, antihypertensive, and anti-inflammatory properties. Pomegranate can be used in the prevention and

treatment of several types of cancer, cardiovascular disease, osteoarthritis, rheumatoid arthritis, and other diseases. In addition, it improves wound healing and is beneficial to the reproductive system. Pomegranate can induce its beneficial effects through the influence of its various bioavailable constituents and metabolites on gene expression. Although many *in vitro,* animal and clinical trials have been carried out to examine and prove the therapeutic effects of these compounds, further human trials and studies are necessary to understand the therapeutic potentials of pomegranate.

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