



## EVIDENCE-BASED THERAPEUTIC ACTIVITY OF POMEGRANATE AND ITS ACTIVE CONSTITUENT ELLAGIC ACID

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### ABSTRACT

Presently pomegranate is used in traditional medicine for its pharmacological properties. Consumption of fresh vegetables and fruits can improve the human health mainly because of their high contents of beneficial phytochemicals and other micronutrients. Pomegranate has multiple pharmacological activities including anti-inflammatory, antioxidant, and anticancer actions. Ellagic acid is a major compound of pomegranate which is naturally existing in many kinds. It has also been found in raspberries, blackberries, cranberries, strawberries, pecans, walnuts, green tea, pomegranates, and blueberries. Recently, numerous studies have proven the effectiveness of ellagic acid and pomegranate juice in the treatment of prostate cancer, diabetes, melasma, ultraviolet radiation-induced skin damage, endotoxemia, rheumatoid arthritis and osteoarthritis, cardiovascular diseases, blood pressure, hyperlipidemia, erectile dysfunction, dental disorders, diabetes, and idiopathic central precocious puberty. The therapeutic effect of ellagic acid and pomegranate juice could be due to the clinically evidenced antioxidant activities. In conclusion, ellagic acid may be used as a therapy or adjuvant therapy for the treatment of many illnesses.

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### Introduction

Globally, there is a growing concern in natural medicines which are associated with the huge number of research studies about pharmacological activities of the bioactive constituents and their power to manage different illnesses [1]. Most medicines have joined the universal market through investigation of ethnopharmacology and folk medicine [2]. Even though, scientific research studies are done on a great number of herbs, only little numbers of marketable medicines and phytochemicals have been included in the evidence-based therapeutics [3].

Pomegranate (*Punica granatum* L.) possess a great value across history. From centuries, the pomegranate was utilized in management of diarrhea [4], parasitic infection [5], diabetes mellitus [6], sore throat, inflammation, and rheumatism [7]. It possesses multiple pharmacological activities including anti-inflammatory, antioxidant, and anticancer actions. These activities are attributed to pomegranate active constituents mainly hydrolysable tannins including ellagitannins and gallotannins [8–11].

Ellagic acid is one of the naturally occurring phenolic active constituents of numerous flowering plants species. Hydrolysable tannins in plants are called ellagitannins. Ellagitannins are hexahydroxydiphenic acid esters; they produce dilactone ellagic acid after hydrolysis [8]. The ellagic acid concentration in sets of fruits and nuts was measured, and the largest quantities were found in raspberries, blackberries, walnuts, strawberries, pecans, cranberries [12], pomegranates [13], blueberries [14], and oak species like North America white oak (*Quercus alba*) and European red oak (*Quercus robur*) [15]. The green alga *Myriophyllum spicatum* also produces ellagic acid [16]. Ellagic acid established also in the *Phellinus linteus* medicinal mushroom [17].

In the previous few decades, there has been great attention to the probable health advantages of natural plant polyphenols as antioxidants. Epidemiological research and accompanied meta-analyses powerfully proposed that chronic administration of polyphenols of rich herbs provide preservation against the injury with diabetes, cancers, cardiovascular, osteoporosis, and neurodegenerative diseases [18]. This article pursues to review the evidenced therapeutic benefits of the polyphenols, ellagic acid either in its pure form or present in pomegranates juice. The review will focus only on the clinical researches.

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### Antioxidant activity

Ellagic acid is a broad-spectrum antioxidant [19]. Ellagic acid plays an important role as a scavenger of reactive oxygen species (ROS), reactive nitrogen species (RNS), hydroxyl radicals, peroxy radicals, nitrogen oxide radicals, and peroxynitrite. Furthermore, ellagic acid inhibits ROS generation, and chelates metal ions [20, 21]. A previous investigation done by Mertens-Talcott *et al.* [22] confirmed that acute administration of 800 mg standardized pomegranate extract to healthy human volunteers resulted in increased antioxidant capacity with a maximum effect of 32% reached after 30, 60 and 120 min. Ellagic acid from the pomegranate extract is bioavailable, with C<sub>max</sub> equal to 33 ng/mL reached after 60 min.

Recently, Belcaro *et al.* [23] evaluated the effect of Robuvit® (a wood extract of the French oak *Quercus robur* that is known to reduce the oxidative stress) on oxidative stress level in 40 patients with high oxidative stress levels. The subjects in the Robuvit® group were administered 3 doses of Robuvit® (100 mg)/day for about 2 months. Oxidative stress levels were lowered significantly with Robuvit® administration after 1 and 2 months.

Furthermore, Plaza *et al.* [24] examined the effect of Brazilian berries, *Myrciaria jaboticaba* (*Jaboticaba*) peel consumption on antioxidant activity in a single-blind placebo-controlled crossover study. Anthocyanins, gallotannins, ellagic acid, ellagitannins, and flavonols were detected in *Jaboticaba*. The phenolics which were found in higher levels were anthocyanins. Although the main cause of total antioxidant action was ellagitannins. The study was conducted on 10 healthy human volunteers (5 males and 5 females). The results showed that subjects consuming the test meal, which containing *Jaboticaba* peel powder (27.6 g), markedly increased serum antioxidant capacity.

A randomized clinical trial was done to examine the impact of pomegranate juice ingesting on oxidative stress in diabetic patients type two. The study was conducted on 60 diabetic subjects. Patients administered pomegranate juice (200 ml)/ day for 6 weeks showed a significant increase in total serum antioxidant capacity [25]. Ammar *et al.* [26] tested the theory that pomegranate juice administration could reduce immediate and late oxidative stress reaction after weightlifting exercise. The study was carried out on 9 elite weightlifters doing two Olympic-Weightlifting periods post pomegranate juice consuming. Pomegranate juice possesses the potency to reduce oxidative stress by boosting antioxidant mechanisms determined shortly and 2 days after the weightlifting period.

A randomized clinical trial on 55 rheumatoid arthritis patients was conducted. They were divided into 2 groups. Treatment group administered pomegranate extract (500 mg/day) while the placebo group administered cellulose (500 mg/day). The treatment continued for 8 weeks. Administration of pomegranate extract significantly increased glutathione peroxidase enzyme activity [27]. Similarly, in a pilot open-labeled trial, 8 rheumatoid arthritis patients administered pomegranate extract (10 ml/day) for 3 months exhibited a significant decrease in oxidative stress markers [28]. Research in 65 people with non-alcoholic fatty liver disease has shown a significant increase in total antioxidant capacity following ingestion of two hundred-and fifty-ml pomegranate juice/day for three months [29].

Gouda *et al.* [30] concluded that administration of pomegranate juice (250 g/day) to 35 healthy adults' volunteers for 3 weeks significantly increased the urinary and blood antioxidant activity. Another study revealed that the consumption of pomegranate juice by 38 patients with knee osteoarthritis has a beneficial effect on the patients antioxidants activity as it increased the serum glutathione peroxidase enzymes activity [31]. A randomized double-blind, multicenter study was accomplished on 31 athletes. Treatment groups consumed either pomegranate juice (200 ml/day) or watered pomegranate juice (1:1). Pomegranate juice preserves while watered pomegranate juice reduces the levels of oxidative stress markers, protein carbonyls and lipid peroxidation [32].

Pomegranate juice administered in a randomized, double-blind, placebo- controlled study to 44 type 2 diabetic patients significantly decreased the oxidative stress marker, malondialdehyde [33]. Shema-Didi *et al.* [34] clearly demonstrated that administration of pomegranate juice to 27 haemodialysis subjects through one dialysis sitting accompanied by IV iron administration significantly maintained oxidative stress biomarkers compared to the placebo regimen. Furthermore, a randomized clinical study examined the impact of pomegranate juice ingestion for six weeks on plasma lipid peroxidation concentration. The study was performed on 23 women with the metabolic disorder. The participants consumed 300 ml of pomegranate juice daily. The results showed that pomegranate juice induced a positive impact on lipid peroxidation [35].

### Melasma

Melasma is acquired hyperpigmentation of sun-risky areas. A randomized, prospective, open-label study carried out on 30 melasma patients. The study aimed to compare the therapeutic effect of a gel formula containing natural ellagic acid (plant extracts) with another gel formula containing synthetic ellagic acid (arbutin) in treating melasma. The result showed that the two formula are equally effective in treating melisma, and hence the authors concluded that ellagic acid could be an alternative therapy in treating melasma [36].

### Prostate cancer

A study aimed to estimate if ellagitannins or their hydrolysis products ellagic acid and urolithins are present in the human prostate after 3 days of ingestion of ellagitannins-plantifol diet (35 g/day Walnuts and 200 ml/day pomegranate juice), and to evaluate the effect on the expression of three proliferation biomarkers. The ellagitannins-rich foods were administered 3 days before surgery to 63 patients with prostate cancer. The results proposed that dimethyl ellagic acid and urolithin glucuronides are probably the compounds accountable for the useful impacts of pomegranate juice in fighting prostate cancer [37]. Another study was conducted to investigate the impact of adjuvant ellagic acid therapy on chemotherapy toxicity, overall survival, objective response, biochemical response and individual clinical response in hormone-refractory prostate cancer

patients. Patients were randomly separated to two groups: 1- group A, who received chemotherapy (Vinorelbine and Estramustine phosphate) and 2- group B, who received chemotherapy (Vinorelbine and Estramustine phosphate) + ellagic acid. The results proposed that ellagic acid used as adjuvant treatment minimized the toxicity associated with chemotherapy, especially neutropenia, in hormone-refractory prostate cancer. Patients in the ellagic acid group showed better results in term of objective response, individual clinical response, and biochemical response [38].

Another clinical study estimated the effect of liquid pomegranate extract on serum levels of prostate-specific antigen (PSA) in prostate cancer patients with elevated PSA after primary treatment, and results revealed that there are no differences between PSA doubling time in pomegranate extract group and control group [39]. In addition, in a randomized, multi-center, double-blind, dose-investigating phase II study, 104 patients with rising PSA were incorporated and treated for up to 18 months with 1 or 3 g of pomegranate extract. This study was structured to determine a 6-month increase in PSADT in each group from the beginning. The consumption of pomegranate extract increased PSADT in both study groups approximately after 6 months without adverse events [40].

#### **Ultraviolet-induced pigmentation**

Placebo-controlled, a double-blind study carried out on female healthy volunteers (n=30) revealed that oral administration of ellagic acid-rich pomegranate extract (100 and 200 mg/d ellagic acid), ameliorates UV irradiation-induced slight skin pigmentation [41]. A double-blinded clinical trial investigated the skin-whitening action of a locally applied formulation composed of ellagic acid (0.5%) plus salicylic acid (0.1%). In addition, the effect of the new formulation was compared to a generic product containing hydroquinone (4%). Individuals (n=54) were instructed to apply the test product and the generic hydroquinone two times/day for 12 weeks. The test formulation provided skin depigmentation effect which is comparable to the commercial formula [42].

#### **Endotoxemia**

Microbiota dysbiosis in gut modifies the function of the intestinal barrier, increases the plasma concentration of lipopolysaccharide (LPS), which increases endotoxemia and contributes to the onset and progression of colorectal cancer. A recent clinical study newly notified lowering of plasma LPS-binding protein concentrations, an indicator of endotoxemia, post pomegranate administration in recently identified colorectal cancer patients [43]. In addition, a randomized cross-over study utilized 49 overweight-obese individuals, and it was concluded that daily administration of pomegranate extracts significantly reduced endotoxemia indicator LPS-binding protein by microbiota remodeling, mainly by modifying *Faecalibacterium*, *Odoribacter*, and *Parvimonas* [44].

#### **Rheumatoid arthritis and osteoarthritis**

In a randomized double-blind, placebo-controlled study which was performed on 30 rheumatoid arthritis patients, consumption of pomegranate extract capsules twice a day (250 mg) for 2 months ameliorated rheumatoid arthritis aggressiveness [27]. In a randomized clinical study carried on 38 subjects with knee osteoarthritis who consumed pomegranate extract for 6 weeks resulted in improvement in physical function, rigidity, reduced cartilage breakdown enzymes and improved antioxidant status in patients with knee osteoarthritis [31]. In a pilot open-labeled trial performed on 8 active rheumatoid arthritis individuals, administration of pomegranate extract (10 ml) daily for 12 weeks decreased disease activity index [28].

#### **Cardiovascular diseases**

A randomized clinical study was carried on 100 unstable angina and myocardial infarction individuals who administered 220 ml/day pomegranate juice together with the standard therapy. The treatment continued for 5 days. Pomegranate juice in participants with unstable angina resulted in a marked reduction in the severity, occurrence, and span of angina pectoris. In addition, the subjects showed a significant reduction in serum troponin concentration [45]. In a randomized double-blind, placebo-controlled study, which tested the effect of three months of daily consumption of pomegranate juice (240 ml) on myocardial perfusion in subjects (n=45) with coronary heart disease and myocardial ischemia, the consumption of pomegranate juice improved myocardial ischemia caused by stress in patients with cardiovascular disease [46].

#### **Blood pressure and hyperlipidemia**

A randomized, placebo-controlled crossover study conducted on 19 young, healthy men investigated whether a pomegranate extract drink ingested with a lipid-rich diet, can lower postprandial blood lipids level and ameliorate vascular function and blood pressure. The results revealed that drinking pomegranate extract produced no suppression of postprandial blood lipids. Furthermore, ingestion of pomegranate extract before high-fat meal (PE-BEF) caused a marked rise in the venous plasma triacylglycerols after 2 hours compared to placebo and pomegranate extract administered during high-fat meal (PE-DUR). In addition, both PE-PEF and PE-DUR regimens significantly lowered systolic blood pressure compared to the placebo group [47].

A previous study tested the effect of ingestion of pomegranate juice on lipid profiles in diabetes patients type II with hyperlipidemic. The study was performed on 22 healthy diabetic individuals; they administered pomegranate juice (40 g/day) for 8 weeks. The administration of pomegranate juice, markedly reduced both total cholesterol and low-density lipoprotein-cholesterol. Although, there have been no changes in serum triacylglycerol and high-density lipoprotein-cholesterol [48]. In a randomized placebo-controlled parallel study the impact of pomegranate juice was tested on blood pressure, pulse wave velocity (PWV) and plasma antioxidant levels in healthy individuals (n=51). The study aimed to judge the effect of ingestion of pomegranate juice (330 ml) daily for 4 weeks. Variables were measured at the beginning and 4 weeks thereafter. Both

PWV and plasma antioxidant showed no alteration. Although, there was a significant decline in both diastolic and systolic blood pressures and mean arterial pressure [49].

In a randomized, double-blind, placebo-controlled clinical study, the effect of pomegranate seed oil consumption on serum lipid profiles was examined. The study was done on hyperlipidaemic individuals (n=51), they were either administered pomegranate seed oil (400 mg) or placebo betimes/day for 4 weeks. Serum levels of lipids and lipoproteins were determined at the baseline and 4 weeks after treatment. Pomegranate seed oil significantly lowered concentration of triacylglycerol and the triacylglycerol: high-density lipoprotein-cholesterol ratio compared with baseline values [50].

#### **Erectile dysfunction**

A randomized-controlled crossover study investigated the effect of pomegranate juice in ameliorating erections in 53 adult individuals with mild to moderate erectile dysfunction. The study composed of two 4-weeks therapeutic intervals. Despite the statistical insignificance results, this pilot trial proposed the probability that larger cohorts and longer medication intervals may fulfill statistical significance [51].

#### **Dental diseases**

A study was performed on 30 healthy volunteers, randomly allocated to either pomegranate, chlorhexidine, or distilled water mouthwash twice daily, and results revealed that the pomegranate mouthwash has an antiplaque activity [52]. A similar study was conducted on 60 healthy subjects, randomly divided to either hydroalcoholic extract of pomegranate, chlorhexidine, or distilled water mouthwash (15 ml). The hydroalcoholic extract of pomegranate offered an antimicrobial effect against certain bacteria and may provide a potential choice for treating dental plaque [53].

A double-blind randomized clinical trial was conducted on 80 diabetic patients suffering from gingivitis, that were set to either pomegranate or chlorhexidine (0.2%) mouthwash for 2 weeks to assess their safety and effectiveness in managing diabetic-induced gingivitis. Both regimens offered a significant amendment on all the gingival and plaque indices. Pomegranate mouthwash significantly ameliorates the gingival index compared to chlorhexidine. Furthermore, pomegranate mouthwash had no coloring action [54].

#### **Diabetes**

Two randomized, crossover, controlled, double-blinded trials of 16 healthy volunteers were conducted. The study examined if pomegranate polyphenols could reduce the blood glucose level induced by a high-glycemic index diet when administered concomitantly. Both studies investigated the acute influence of a pomegranate juice and a polyphenol-rich pomegranate extract on the bread-induced postprandial blood glucose levels. The results indicated that polyphenols in the pomegranate can reduce the postprandial glycemic response of bread by adding in a juice form but not in a form of supplements, although microbial metabolites from pomegranate polyphenols may adjust the delayed sugar level in the postprandial period. [55].

A clinical study was carried out on 85 type 2 diabetic subjects, which determined the acute (3 hours) consequences of pomegranate juice consumption (1.5 ml/kg) on various diabetic parameters measured in type 2 diabetic patients. The results revealed that pomegranate juice reduced fasting blood glucose, enhanced  $\beta$ -cell function, and lowered insulin resistance amongst type 2 patients. This hypoglycemic effect relies on baseline fasting glucose levels, as subjects with lower fasting glucose levels showed a better hypoglycemic action [54].

#### **Idiopathic central precocious puberty**

A trial aimed to evaluate the effects of adding pomegranate extract to gonadotropin-releasing hormone (GRH) analog on idiopathic central precocious puberty in 286 Chinese girls. Patients were randomized to administer a combination regimen of GRH analog, and pomegranate extract daily for 3 months. The results demonstrated that the daily administration of pomegranate extracts improved the treatment benefits of GTH analog therapy in idiopathic central precocious puberty in Chinese women [56].

#### **Conclusion**

Numerous human studies have revealed wide-spread therapeutic uses of pomegranate and its active constituent ellagic acid. These studies proposed its prospective applications as medicine or adjuvant medicine for managing of a vast variety of diseases. The therapeutic effect of ellagic acid and pomegranate juice could be attributed to the clinically evidenced antioxidant activities. This supposes the necessity for additional human studies, to prove or refute any therapeutic effects. Nowadays, many clinical studies are in proceed to inspect the therapeutic potency of pomegranate and ellagic acid. Although, before their application, pomegranate and ellagic acid should be compared with the present confirmed pharmacological medication. Moreover, large-scale, multicenter trials are pivotal to assess the efficacy of these precious nutraceuticals.

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