Pomegranate: constituents, biological properties, therapeutic applications and its safety – A Review

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Abstract

The pomegranate, Punica granatum L., is an ancient, mystical, unique fruit borne on a small, long-living tree cultivated throughout the Mediterranean region, as far north as the Himalayas, in Southeast Asia, and in California and Arizona in the United States. The pomegranate tree can be divided into several anatomical compartments like seed, peel, juice, flower, leaf, bark, roots, etc. each of which has interesting pharmacologic activities. Pomegranates contain high levels of a diverse range of phytochemicals including polyphenols, sugars, fatty acids (conjugated and non-conjugated), aromatic compounds, amino acids, tocopherols, sterols, terpenoids, alkaloids, etc. The synergistic action of the pomegranate constituents appears to be superior to that of single constituents. The biological properties of extracts (antimicrobial, antioxidant, anticancer, anti-inflammatory, among other properties) obtained from several parts of the pomegranate is reported in the review.

Keywords: Pomegranate, phytochemicals, constituents, Biological activities and Therapeutic applications.

Introduction

The pomegranate, Punica granatum L., an ancient, mystical, and highly distinctive fruit, is the predominant member of two species comprising the Punicaceae family (Fig. 1). It was lauded in ancient times in the Old Testament of the Bible, the Jewish Torah, and the Babylonian Talmud as a sacred fruit conferring powers of fertility, abundance, and good luck. It also features prominently in the ceremonies, art, and mythology of the Egyptians and Greeks and was the personal emblem of the Holy Roman Emperor, Maximilian. The genus name, Punica, was the Roman name for Carthage, where the best pomegranates were known to grow. Pomegranate is known by the French as grenade, the Spanish as granada, and literally translates to seeded (“granatus”) apple (“pomum”). Punicais a small genus of fruit-bearing deciduous shrub or small trees (Fig. 2). Its better-known species is the Pomegranate (Punica granatum L.). P. granatum is a member of the Punicaceae family which shares its botanical family only with Punica protopunica, the latter restricted in occurrence to Socotra, an island of the Yemeni coast. P. protopunica differs in having pink unlike the red flowers of P. granatum and smaller, less sweet fruit. The leaves are glossy and lance shaped, and the bark of the tree turns gray as the tree ages (Fig. 3). The flowers are large, red, white, or variegated and have a tubular calyx that eventually becomes the fruit (Fig. 4). The ripe pomegranate fruit can be up to five inches wide with a deep red,
Fig. 1: Pomegranate Fruit

Fig. 2: Pomegranate Tree and Seed

Fig. 3: Pomegranate Leaves

Fig. 4: Pomegranate Flower
leathery skin, is grenade-shaped, and crowned by the pointed calyx. The fruit contains many seeds (arils) separated by white, membranous pericarp, and each is surrounded by small amounts of tart, red juice. Over 1000 cultivars of *P. granatum* exist (Levin, 1994), originating from the Middle East, extending throughout the Mediterranean, eastward to China and India, and on to the American South-west, California and Mexico. The pomegranate is a symbol of life, longevity, health, femininity, fecundity, knowledge, morality, immortality and spirituality, if not Divinity (Mahdihassan, 1984). Pomegranate (*Punica granatum* L.) is considered one of the oldest known edible fruits and is the symbolic of abundance and prosperity.

In addition to its ancient historical uses, pomegranate is used in several systems of medicine for a variety of ailments. In Ayurvedic medicine the pomegranate is considered “a pharmacy unto itself” and is used as an antiparasitic agent, a blood tonic (Naqvi *et al*., 1991), and to heal aphthae (Lad and Frawley, 1986), diarrhea, and ulcers (Caceres *et al*., 1987). The edible part of the fruits contains acids, sugars, vitamins, polysaccharides, polyphenols and minerals, however, several factors may contribute to the chemical changes, including cultivars, environmental conditions, ripening, storage and postharvest treatments, which may affect fruit quality and health beneficial compounds (Schwartz *et al*., 2009a).

Nagaraju and Rao (1990), Boukef *et al*.(1982) and Caceres *et al*. (1987) reported that the dried pomegranate peels are decocted in water and employed both internally and externally for numerous problems demanding astringents and/or germicides, especially for aphthae, diarrhea and ulcers. Mixtures of pomegranate seed, juice and peel products, paradoxically have been reported to not only prevent abortion (Ramirez *et al*., 1988) but also conception (Gujral *et al*., 1960), Jochle (1971) and Zhan (1995).

In Unani medicine, a Middle Eastern traditional medical system that later took root in India (Izhar, 1989), pomegranate flowers serve as a remedy for diabetes mellitus (Saxena and Vikram, 2004). Modern uses of pomegranate derived products now include treatment of acquired immune deficiency syndrome (AIDS) Lee and Watson (1998), in addition to use for cosmetic beautification (Kawamada and Shimada, 2002; Moayadi, 2004) and enhancement (Curry, 2004), hormone replacement therapy (Lansky, 2000), resolution of allergic symptoms (Watanabe and Hatakoshi, 2002), cardiovascular protection (Shiraishi *et al*., 2002 ; Aviram *et al*., 2002), oral hygiene (Kim and Kim, 2002), opthalmic ointment (Bruijn *et al*., 2003), weight loss soap (Guojian, 1995), and as an adjunct therapy to increase bioavailability of radioactive dyes during diagnostic imaging (Il'iasov, 1975 and Amorim *et al*., 2003).

The current explosion of interest in pomegranate as a medicinal and nutritional product is evidenced by a MedLine search from 2000 to present, revealing over 130 new scientific papers pertaining to its health effects. Between 1950 and 1999 only 25 such publications appear on MedLine (Lansky and Newman, 2007). A recent review reported the chemical constituents of diverse parts of *P. granatumas* well as their potential for prevention and treatment of inflammation and cancer. The authors refer that in the pericarp, leaf and flower can be detected phenols (flavonoids and tannins) being some of them unique. Complex polysaccharides have also been detected and characterized in the peels. In seeds, triacylglycerols constituted the oil, with a high content of punicic acid. In this oil, the authors also reported the presence of sterols, steroids and cerebroside in very small amounts. In addition to the seed oil, lignin and their derivatives have also been reported to possess remarkable antioxidant activities (Lansky and
Newman, 2007). In the same review article, the authors highlighted the major components of pomegranate seeds, juice, pericarp, bark and leaf as well as their pharmacological activity in mammalian cells relevant to the prevention and/or treatment of malignant cell growth, from 2000 to 2006. The mechanisms claimed by the authors referred in that review article included increased apoptosis, decreased inflammation, decreased metastasis and invasion, as well as a decrease in drug resistance (Lansky and Newman, 2007). Antioxidant activities associated with different pomegranate components were also summarized by the authors.

One year later, other review article (Julie, 2008) revealed that pomegranate juice may be fruitful as a therapy for prostate cancer, particularly recurrent type of cells; in atherosclerosis by inhibiting the lipid peroxidation in plasma and in lipoproteins as well as the collagen induced platelet aggregation in human platelets ex vivo; in hyperlipidemia owing to the decrease absorption and increased faecal excretion of cholesterol as well as possible effects on HMG-CoA reductase and sterol Oacyltransferase, two enzymes key to cholesterol metabolism. Over the past few decades, scientific investigations have laid a credible basis for some of the traditional ethnomedical uses of the pomegranate (Julie, 2008). These studies, most completed in the past 7 years, may be divided into several general areas. For example, pomegranate mediated antioxidant activity can be considered a means of lowering the threshold for inflammation.

Pomegranate juice was also reported effective in hypertension by decreasing Angiotensin- Converting Enzyme (ACE) activity; reducing myocardial ischemia and improving myocardial perfusion; in diabetes through a significant effect on atherogenesis through reduced oxidative stress; in periodontal disease and denture stomatitis. Other benefits include the combat to some bacterial infections, erectile dysfunction, male infertility, Alzheimer’s disease, obesity. The authors also refer those works concerning the pharmacokinetic- (metabolism and availability) of ellagitannins present in pomegranate juice as well as the potential drug interactions and safety of pomegranate extracts. As a crop, pomegranate is extensively cultivated in Iran, India, Afghanistan and Mediterranean countries, and to some extent in the USA, China, Japan and Russia (Narzary et al., 2010a). It is one of the most valuable fruits and is grown on a commercial scale also in Iran (Ramezanian et al., 2009). Pomegranate fruit is consumed directly as fresh seeds, but can also be used for making juice, jelly, grenadine or as flavouring and colouringagents. In addition, this species has been proved to possess therapeutic properties, therefore with an economic and ecological importance (Al-Said et al., 2009 and Akbarpour et al., 2010).

Antioxidant activity, as well as suppression of inflammation, may contribute to chemotherapeutic and chemo-preventive utility against cancer. The other potential therapeutic properties of pomegranate are wide-ranging and include treatment and prevention cardiovascular disease, diabetes, dental conditions, erectile dysfunction, protection from ultraviolet (UV) radiation, infant brain ischemia, Alzheimer’s disease, male infertility, arthritis, obesity, etc. The last review about the therapeutic effects of pomegranate found in the ISI Web of Knowledge (Thomson Reuters) was that of Julie (2008). Therefore, the present work intends to make a review about this subject using the same database from 2009 up to 3rd October, 2010. Search keys used for the research were: P. granatum (topic) and 2009 to 2010 (year published).

The predominant theme was indubitably the biological properties of pomegranate, nevertheless other approaches were also found: pests and diseases...
in pomegranate crop (Bardas et al., 2009; Mondal and Mani, 2009; Qasen, 2009; Spadaro et al., 2010; Wohlfarter et al., 2010a; Wohlfarter et al., 2010b); pomegranate on the combat of microorganisms affecting plants (Guo et al., 2009; Hassan et al., 2009; Tayel et al., 2009a; Osorio et al., 2010), seeds during storage (Gandhi et al., 2010) or against Lymphocystis Disease Virus (LDV) in the fish olive flounder Paralichthys olivaceus (Harikrishnan et al., 2010). Being pomegranate for fresh consumption of arils or juice, the appearance and colour of the skin of the fruit or juice and freshness are very crucial. Therefore, preservation and shelf-life extension has been the major goal of many works over time. Spermidine and calcium chloride (Ramezanian et al., 2010); polyamide plastic (Sadeghi and Akbarpour, 2009); individual film wrapping of pomegranate in combination with fludioxonil (D’Aquino et al., 2010) were all valuable treatments for improving storability of pomegranate fruits. Biotechnology has been the tool for characterize pomegranate cultivars. There are many molecular marker systems available to characterize genetic resources and cultivars (Staub et al., 1996). Another aspect in biotechnology on pomegranate is the regeneration of this plant by in vitro techniques. Kanwar et al. (2010) concluded that cotyledons excised from in vitro germinated seedlings were the most responsive explants for callus induction and plant regeneration.

Chemical composition of pomegranates

The pomegranate tree can be divided into several anatomical compartments: seed, juice, peel, leaf, flower and root bark, each of which is widely used in therapeutic and food formulas, and cosmetics due in large part to the scientifically supported health benefits on arteriosclerosis, cholesterol levels and cancer prevention. The other parts are good source of tannins, dyes, and alkaloids (Khan, 2009; Viuda-Martos et al., 2010; Wang et al., 2010). The chemical composition of the pomegranate and its products depends on the cultivar, growing region, and climate, the fruit’s stage of maturity, cultural practices and manufacturing systems (Badenes et al., 1998; Dumas et al., 2003; Toor et al., 2006; Raffo et al., 2006, Borochov-Neori et al., 2009; Zarei et al., 2011). From Table 1 and 2 show the chemical composition of pomegranate fruit and phytochemicals in pomegranate and its parts.

Pomegranate fruit is a rich source of two types of polyphenolic compounds: anthocyanins and hydrolyzable tannins, which account for 92% of the antioxidant activity of the whole fruit (Gil et al., 2000). The soluble polyphenol content in pomegranate juice varies between 0.2 and 1.0%, depending on variety (Narr Ben et al., 1996). The seeds are a rich source of lipids; of which comprised of 12% to 20% of total seed weight and characterized by a high content of polyunsaturated (n-3) fatty acids such as linolenic, linoleic, and other lipids such as punicic acid, oleic acid, stearic acid, and palmitic acid (Ozgul-Yucel, 2005). Al-Maiman and Ahmad (2002) showed the amounts of potassium, calcium and sodium were higher in both juice and seeds followed by magnesium, phosphorous, zinc, iron and copper. The authors stated that pomegranate can be a good source of nutrients and variation could originate from the pomegranate cultivar, and agro-climatic. Akpinar-Bayizit (2010) reported that although processing steps include clarification and filtration, the pomegranate juices in Turkish market were a good source for minerals such as potassium (1283.30 mg/L), calcium (107.53 mg/L), sodium (96.02 mg/L), phosphorus (76.54 mg/L) and magnesium (67.22 mg/L). The high mineral content of pomegranate juices could contribute to the daily intake of these constituents in the human diet.
A large number of articles concerning antimicrobial, antioxidant, anti-inflammatory, anticancer and immune suppressive activities of pomegranate in the period of 2009 to 2010 (October) were found. Protective effects on hepatic function or on the glucose and lipid metabolism were also reported, among other biological properties summarized below.

### Table – 1. Chemical Composition of Pomegranate (Yilmaz, 2007)

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moisture</td>
<td>72.6-86.4%</td>
</tr>
<tr>
<td>Protein</td>
<td>0.05-1.6%</td>
</tr>
<tr>
<td>Fat</td>
<td>0.01-0.9%</td>
</tr>
<tr>
<td>Mineral elements</td>
<td>0.36-0.73%</td>
</tr>
<tr>
<td>Fibre</td>
<td>3.4-5.0%</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>15.4-19.6%</td>
</tr>
<tr>
<td>Calcium</td>
<td>3.0-12.0 mg</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>8.0-37.0 mg</td>
</tr>
<tr>
<td>Iron</td>
<td>0.3-1.2 mg</td>
</tr>
<tr>
<td>Sodium</td>
<td>3.0 mg</td>
</tr>
<tr>
<td>Magnesium</td>
<td>9.0 mg</td>
</tr>
<tr>
<td>Ascorbic acid (Vitamin C)</td>
<td>4.0-14.0 mg</td>
</tr>
<tr>
<td>Thiamine (Vitamin B1)</td>
<td>0.01 mg</td>
</tr>
<tr>
<td>Riboflavine (Vitamin B2)</td>
<td>0.012-0.03 mg</td>
</tr>
<tr>
<td>Niacine</td>
<td>0.18-0.3 mg</td>
</tr>
</tbody>
</table>

### Table – 2. Phytochemicals of Pomegranate (Jurenka, 2008)

<table>
<thead>
<tr>
<th>Plant Component</th>
<th>Constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pomegranate juice</td>
<td>Anthocyanins; glucose; ascorbic acid; phenolics such as ellagic acid, gallic acid, caffeic acid, catechin, epigallocatechin gallate (EGCG), quercetin, rutin; mineral elements; aminoacids</td>
</tr>
<tr>
<td>Pomegranate seed oil</td>
<td>Punicic acid; ellagic acid; fatty acids; sterols</td>
</tr>
<tr>
<td>Pomegranate pericarp (peel, rind)</td>
<td>Phenolic compounds like punicalagins, gallic acid, catechin, EGCG, quercetin, rutin, anthocyanidins, other flavonoids</td>
</tr>
<tr>
<td>Pomegranate leaves</td>
<td>Ellagitannins (punicalin and punicafolin); flavonols such as luteolin and apgenin</td>
</tr>
<tr>
<td>Pomegranate flower</td>
<td>Gallic acid, triterpenoids such as ursolic, maslinic and asiatic acid</td>
</tr>
<tr>
<td>Pomegranate roots and bark</td>
<td>Ellagitannins; pipe ride alkaloids</td>
</tr>
</tbody>
</table>

### Biological Properties and Therapeutic Applications

A large number of articles concerning antimicrobial, antioxidant, anti-inflammatory, anticancer and immune suppressive activities of pomegranate in the period of 2009 to 2010 (October) were found. Protective effects on hepatic function or on the glucose and lipid metabolism were also reported, among other biological properties summarized below.

#### Antimicrobial activity

In the review article made by Julie (2008), the capacity of preventing infections of extracts of pomegranate was already well documented. Food-borne illnesses are still a major concern for consumers, the food industry and food safety authorities. In the addition, pomegranate purified polyphenol extract inhibited influenza virus having also a synergistic effect.
Influenza virus causes epidemics and pandemics in human population. Such virus has several zoonotic hosts, therefore, cannot be eradicated from human populations. Influenza continues to be a major cause of mortality and morbidity, although the vaccines and antiviral therapies (Haidari et al., 2009). Tayel and El-Tras (2009) demonstrated that methanol, ethanol and water extracts of pomegranate peels were effective against C. albicans growth. In addition, they also proved that pomegranate peel extract aerosol was an efficient method for complete sanitizing of semi-closed places against C. albicans growth, and thereby could contribute for preventing C. albicans contamination and growth in suspected places.

**Antioxidant activity**

Over the past few years, consumer demand-based research on functional foods gave a basis for traditional using of pomegranate, which lead to an increase in the number of scientific papers concerning pomegranate and its products with health-improving effects (Mehta and Lansky, 2004; Rettig et al., 2008; Turk et al., 2008; Alam et al., 2010; Dai et al., 2010; Jadeja et al., 2010; Park et al., 2010). The antioxidant activity was almost determined in vitro conditions and several methods could be used for its determination. Some works focus on the comparative studies of antioxidant activities of diverse fruits and vegetables (Stangeland et al., 2009). Generally, pomegranate possessed the best antioxidant activity, independent on the antioxidant test assayed and generally with significant linear correlation between phenolics concentration and antioxidant capacity (Elfalleh et al., 2009). Pomegranate could be expected to be suitable for food processing in which thermal devices are used, because of their heat resistance. Several works have demonstrated that peel, seeds, arils have antioxidant activity, nevertheless, after ingestion those antioxidant compounds, mainly tannin components, are metabolized by gut bacteria into urolithins, which readily enter systemic circulation. Bialonska et al. (2009a) studied the antioxidant activities of seven urolithins derivatives in a cell-based assay in order to reflect bioavailability of the test compound to the cells, and the antioxidant activity is evaluated in the cellular environment and in terms of inhibition of intracellular generation of reactive oxygen species. They found that urolithins exhibited a significant antioxidant activity correlated with the number of hydroxyl groups as well as lipophilicity of the molecules.

**Anti-inflammatory activity**

Pomegranate and the selected chemical constituents isolated from juice, peel, and seed have been found to have a large range of effects: (i) inhibition of Cyclooxygenase-2 (COX-2) expression and ultimately eicosanoid biosynthesis (Schubert et al., 1999; Shukla et al., 2008); (ii) synergistic suppression of inflammatory cytokine expression (Adams et al., 2006); (iii) inhibition of matrix MMPs (Okamoto et al., 2004; Ahmad et al., 2005; Aslam et al., 2006).

The NO production induced by lipopolysaccharide (LPS) in RAW 264.7 macrophage cells was inhibited by pomegranate aqueous extracts. The extracts used and in the concentrations tested did not present any cytotoxicity (Kumar-Roine et al., 2009). Lee et al., (2010) also demonstrated the capacity of pomegranate extracts for inhibiting NO production by RAW 264.7 macrophage cells.

Orissa Malaria Research Indigenous Attempt (OMARIA) in Orissa, India, used herbal formulation containing the sun-dried rind of the immature fruit of pomegranate for the therapy and prophylaxis of malaria. A complication of the infection by P. falciparum is an inflammatory cytokine-driven disease associated to an up-regulation and activity
of metalloproteinase-9 (MMP-9) and to the increase of TNF production. In addition to the anti-malarial activity of fruit rind of pomegranate, it can also act in the inhibition of the pro-inflammatory mechanisms involved in the onset of cerebral malaria (Dell’Agli et al., 2010).

**Anti-cancer**

Singh and Singh (2009) effectuated an ethno-botanical study of medicinal plants in Chandauli District, one of the less studied regions of India, using semi-structured interviews, field observations, preference and direct matrix ranking with traditional medicine practitioners. *P. granatum* was found to be an ingredient of a powder along with whole plant of *Vernonia cinerea* Less. Two recent review articles reported the laboratory and clinical evidence of cancer chemo prevention or treatment of pomegranate (Adhami et al., 2009; Amin et al., 2009). Amin et al. (2009) reported that pomegranate fruit, pomegranate juice, pomegranate seed and seed oil act in prostate, breast, skin, colon, lung, oral and leukaemia, cancers, through antioxidant, antiproliferation (growth inhibition, cell cycle disruption and apoptosis), anti-angiogenesis and anti-inflammatory mechanisms of action. Ellagic acid, one of the constituents of pomegranate juice and seed oils are reported as acting against cancer of skin, pancreas, breast, prostate, colon, intestine, oesophagus, bladder, oral, leukaemia, liver and neuro-blastoma, which mechanisms of action are similar to those described for pomegranate. Sharma et al. (2010) studied the effects of urolitinins, ellagic acid and ellagitannin-rich fruit extracts on Wntsignalling in a human 293T cell line using a luciferase reporter of the canonical Wnt pathway-mediated transcriptional activation. After this study, they concluded that urolithins produced in the colon from ellagitannins present in pomegranate are inhibitors of the canonical Wntsignalling pathway at physiologically relevant concentrations.

**Other biological activities**

Research findings indicated that apart from the potential benefits for antioxidant, anti-inflammatory, anticancer, etc., pomegranate may confer a multitude of other health promoting effects in the body. However, more conclusive studies are needed to confirm these effects, because, there are very few references present in the scientific literature to substantiate these findings. In addition to the biological activities of pomegranate reported so far in the present work, others were also found during our database research. They include for, example, the reversible inhibition of human plasma thrombin at physiological pH values by the pomegranate extracts (endocarp and mesocarp) which were mainly constituted by catechin along with gallic acid, epicatechin and ellagic acid (Cuccioloni et al., 2009). The effect of pomegranate juice and the polyphenol rich extracts from pomegranate fruit on platelet aggregation, calcium mobilisation production of thromboxan A2 induced by collagen and arachidonic acid revealed that both types of samples were able to reduce all platelet responses studied; polyphenol-rich extracts from pomegranate fruits showed a strong action in reducing platelet activation, being active at concentrations similar to those after ingested (Mattiello et al., 2009).

**Adverse effects and Safety of Pomegranate extracts**

Pomegranate and its constituents have safely- been consumed for centuries without adverse effects. Studies of pomegranate constituents in animals at concentrations and levels commonly used in folk and traditional medicine note no toxic effects (Vidal et al., 2003). Pomegranate and its products have a long history of use as food or ethnic medicine without adverse effects, and also it has GRAS (generally natural...
recognized as safe) status in the USA. The published safety data is limited and no clinical or laboratory adverse events were reported. However, there are some publications on the occurrence of allergic reactions when handling or ingestion of pomegranate fruit/seeds due to eliciting a type I hypersensitivity reaction, and thus it is crucial to advise consumers the side effects (McCutcheon et al., 2008).

**Conclusion**

Nowadays, it is widely accepted that the beneficial health effects of fruits and vegetables in the prevention of diseases are due to the bioactive compounds they contain.

The pomegranate has been an inexhaustible source of research going from a chemistry in the search for new compounds, techniques of production and conservation, biotechnology in search of more profitable varieties, to the biological effects as antimicrobial antioxidant, anti-inflammatory, anticancer, anti-diabetic, among other applications. However, many biological studies that are described are still performed in *in vitro* or in animals whose metabolic pathways are not exactly the same that those occurring in humans. Based on the explosion of interest in the numerous therapeutic properties over the last decade and *in vitro*, animal, and clinical trials pomegranate seems to be a promising food with well-defined therapeutic benefits. It is likely that much more will follow, as the medical community and the public continue to exhibit renewed interest in the pomegranate as a therapeutic source.

Based on the literature precedence, most of the important research about Pomegranate, and its biological activity has been performed during the past decade. It may be worth looking deeper into the chemical constituents of different parts of Pomegranate and their activity profiles either individually or in combination. In addition, the possible use of pomegranate extracts as a therapy or adjunct for prevention and treatment of several disease processes, such as diabetes, cardiovascular disease, atherosclerosis, inflammation, microbial infection, obesity, male infertility, Alzheimer underscores the need for more clinical research and developing some of the novel pomegranate derived products such as ready-to-eat pomegranate seeds, single-strength juices, juice concentrates, seeds in syrup, traditional products etc.,

**References**


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