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in

Melgarejo P. (ed.), Martínez-Nicolás J.J. (ed.), Martínez-Tomé J. (ed.).
Production, processing and marketing of pomegranate in the Mediterranean region:
Advances in research and technology

Zaragoza : CIHEAM

Options Méditerranéennes : Série A. Séminaires Méditerranéens; n. 42

2000

pages 231-235

Article available on line / Article disponible en ligne à l'adresse :

<http://om.ciheam.org/article.php?IDPDF=600277>

To cite this article / Pour citer cet article

Lansky E., Shubert S., Neeman I. **Pharmacological and therapeutic properties of pomegranate.** In : Melgarejo P. (ed.), Martínez-Nicolás J.J. (ed.), Martínez-Tomé J. (ed.). *Production, processing and marketing of pomegranate in the Mediterranean region: Advances in research and technology.* Zaragoza : CIHEAM, 2000. p. 231-235 (Options Méditerranéennes : Série A. Séminaires Méditerranéens; n. 42)



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Pharmacological and therapeutic properties of pomegranate

E. Lansky*, S. Shubert** and I. Neeman**

*Rimoni Corporation, Science Park, Nesher, Israel

**Laboratories of Food Engineering and Biotechnology,
Technion - Israel Institute of Technology, Haifa, Israel

SUMMARY – The cross-cultural and ethnobotanical embodiments of pomegranate (*Punica granatum*) are reviewed. A symbol of fecundity and divine femininity emerges, whose fruit rinds, bark and roots are used worldwide as taenicides, owing to alkaloids, and treatment of diarrhea and oral and genital lesions, owing to tannins and astringency. The seeds contain an oil which contains not only the steroidal estrogen, estrone, in the highest concentration found in any botanical species, but also a full range of non-steroidal phytoestrogens including the comesten, coumestrol, and the isoflavones, genistein and daidzein. Both the juice and the oil contain numerous and diverse bioflavonoids, which have been shown to be both potently antioxidant and inhibitory of one or both of the enzymes cyclooxygenase (catalyzing arachidonic acid to prostaglandins) and lipoxygenase (catalyzing arachidonic acid to leukotrienes). Extracts of the rinds have been shown to be bactericidal, antiviral and antitumor. A 1998 medical monograph recommends the use of pomegranates in the treatment of Acquired Immune Deficiency Syndrome (AIDS) owing to their antioxidant properties and botanical uniqueness. The potential toxicity of pomegranate is also considered.

Key words: Pomegranate, phytoestrogens, taenicide, genistein, antioxidant, cyclooxygenase, lipoxygenase.

RESUME – "Propriétés pharmacologiques et thérapeutiques du grenadier". Cet article présente une révision des aspects culturels et ethnobotaniques du grenadier (*Punica granatum*). Symbole de fécondité et de féminité divine, dont l'écorce des fruits et des arbres et les racines sont utilisées dans le monde entier comme ténicides, grâce aux alcaloïdes, et dans le traitement de la diarrhée et des lésions orales et génitales, grâce à ses tannins et à son astringence. Les graines renferment une huile qui contient non seulement un œstrogène stéroïdal, l'estrone, selon la plus forte concentration trouvée chez les espèces botaniques, mais aussi une pleine gamme de phyto-œstrogènes non stéroïdaux y compris comesten, coumestrol, et les isoflavones, génistéine et daidzéine. Le jus ainsi que l'huile contiennent de nombreux et divers bioflavonoïdes, que l'on a démontré être puissamment antioxydants et inhibiteurs de l'une ou des deux enzymes cyclooxygénase (catalysant l'acide arachidonique en prostaglandines) et lipoxygénase (catalysant l'acide arachidonique en leucotriènes). Des extraits d'écorce se sont avérés être bactéricides, antiviraux et antitumoraux. Une monographie médicale de 1998 recommande d'utiliser les grenades dans le traitement du Syndrome Immunodéficient Acquis (SIDA) dû à leurs propriétés antioxydantes et à leur caractère botanique unique. La toxicité potentielle des grenades est également considérée.

Mots-clés : Grenade, phytoestrogènes, ténicide, génistéine, antioxydant, cyclooxygénase, lipoxygénase.

Introduction

In ancient Greek mythology, pomegranates are known as the "fruit of the dead", the sustenance available in Hades for its residents. Hades himself, the master, benefitted amorously when six pomegranate seeds from his realm sealed for him the betrothal of the beautiful daughter of Zeus and Demeter, fair Persephone.

No less, in the ancient Hebrew tradition, pomegranates adorned the vestments of the high priest, were extolled by Solomon in his *Song of Songs*, the numbers of seeds were considered mystically equivalent to the number of virtues in even a simple person, and for the initiated, the pomegranate was understood to be symbolic of the female aspect of the Creator, i.e., the *Shekinah* (Wolfson, 1988).

The Babylonians regarded the seeds as an agent of resurrection, the Persians as conferring invincibility on the battlefield and for ancient Chinese alchemical adepts, the bright red juice was mythopoetically regarded as a "soul concentrate," homologous to human blood, and capable of conferring on a person longevity or even immortality (Maadihassan, 1984).

In all these cultures, red, glistening, juice-encapsulated pomegranate seeds were seen as a natural symbol for fertility and fecundity, and the shape of the fruit itself evoked a primeval image of the female human's breast. All of this is reflected in a rich tradition of sacred and erotic art worldwide involving the pomegranate (Muthmann, 1982).

The pomegranate tree, which is said to have flourished in the Garden of Eden, has also been extensively used as a folk medicine in many cultures, documented at least as far back as the Egyptian Papyrus of Ebers, *circa* 1550 B.C. (Wren, 1988). The most famous usage worldwide has been as a vermifugal or taenicidal agent (Zhicen, 1987; Kapoor, 1990), i.e., a killer and expeller of intestinal worms. According to one account, the alkaloids contained in the root, treebark, and to a lesser extent, fruit rind, cause the "tapeworm to relax its grip on the wall of the intestine" thus allowing the weakened parasites to be easily expelled by a second herbal drug, one which is cathartic (Wren, 1988).

The second major property of pomegranate hulls exploited in folk medicine is their strong astringency, making them a popular remedy throughout the world, in the form of an aqueous decoction (i.e., boiling the hulls in water for 10-40 minutes), for dysentary and diarrhea, and also for stomatitis (Boukef *et al.*, 1982; Caceres *et al.*, 1987; Nagaraju and Rao, 1990). The decoction can be drunk, used as a mouthwash, douche or enema.

Other ethnomedical explorations have documented pomegranate hull and/or root extract usage both orally and intravaginally to prevent fertility (Gujral *et al.*, 1960; Jochle, 1971; Razzack, 1980) and abortion (Ramirez *et al.*, 1988) and to ameliorate assorted gynecological problems (Singh *et al.*, 1980; Goh *et al.*, 1984). Other traditional uses of these materials have included treatments for snakebite (Jain and Puri, 1984), diabetes (Singh, 1986), burns (Siang, 1983) and leprosy (Singh *et al.*, 1980). The fresh fruit itself has been used as a refrigerant to lower fever (Arseculeratne *et al.*, 1985).

Pharmacological investigations

Investigations of various parts of the tree, including the hulls of the fruit but especially the roots, have clearly documented their anthelmintic properties (Caius and Mhaskar, 1923; Kim, 1974; Kaleysa-Raj, 1975; Prakash *et al.*, 1980; Kiuchi *et al.*, 1989; Naovi *et al.*, 1991). Several important alkaloids including the *pelletierines* have been characterized and shown to possess anthelmintic activity (Willaman and Schubert, 1961).

More recent studies have proven the simple extracts of the hulls to additionally have efficacy against the virulent intestinal bacteria *Salmonella typhi* (Perez and Anesini, 1994) and *Vibrio cholerae* (Guivara, 1994), the parasite *Giardia* (Ponce-Macotela, 1994), ameba (Segura *et al.*, 1990), and most recently, viruses including *Herpes simplex* (Zhang, 1995) poliovirus and human immunodeficiency virus (HIV) (Stewart, 1995) and tumors (Mavlyanov *et al.*, 1997).

It is also well known that the dried pomegranate seeds contain an oil, which has been shown to contain not only the steroidal estrogen estrone (Heftman *et al.*, 1966; Dean *et al.*, 1971), but also the isoflavonic phytoestrogens genistein and daidzein and the phytoestrogenic coumestrol, coumestrol (Moneam *et al.*, 1988). When injected, a hydrolyzed concentrate of the oil produced increased uterine weight in immature rabbits, and cornification of vaginal epithelium in ovariectomized adult mice, both indicative of estrogenic action *in vivo* (Sharaf and Nigm, 1964).

Pre-publication findings from our own research have demonstrated antioxidant properties of pomegranate fermented juice and cold pressed pomegranate seed oil mixed polyphenol/flavonoid concentrates significantly superior to that of red wine and approaching that of premium green tea and the synthetic antioxidant, butyrate hydroxyanisole (BHA). Further, these fractions were shown to inhibit one or both of the eicosanoids pathways enzymes cyclooxygenase and lipoxygenase *in vitro* (Shubert *et al.*, in press).

In conclusion, a note on toxicity. One team proved a high incidence of esophageal cancer in a population of pregnant women in Western Iran being fed a traditional prenatal mixture, known as *majoweh* or *majum*, of crushed pomegranate seeds, black pepper, raisins and occasionally garlic, believed to be associated with the physically irritating effects of the crudely crushed seed (Ghadirian, 1987; Ghadirian *et al.*, 1992). Idiosyncratic allergic reactions to pomegranate fruit ingestion have been

noted including IgE mediated tongue angioedema in an elderly adult (Igea *et al.*, 1991) and an incidence of asthma in a child which responded to salbutamol inhalation (Gaig *et al.*, 1992). Finally, so-called "genotoxicity" has recently been reported in a study of aqueous pomegranate rind extract in two *in vitro* human tissue cell cultures (Settheetham and Ishida, 1995).

Clinical implications

An article in a monograph published during the past year recommends pomegranate as a medicinal article of food to be used in the treatment of Acquired Immune Deficiency Syndrome (AIDS) (Lee and Watson, 1998) owing to the fruits's rich concentration of diverse bioflavonoids and to their known free radical scavenging activity and inhibition of lipoxygenase, the enzyme which converts arachidonic acid to leukotrienes. The authors also emphasize the biological uniqueness of *Punica granatum*, having no close botanical relatives, and consequently being a potential source for many, perhaps yet undiscovered, physiological factors which could have significant effect on human health and disease. Further, pomegranate is one of 9 herbs included in a recent Japanese-patented formula for treating AIDS (Hozumi *et al.*, 1997). Certainly, in any future inquiries as to herbs possessing anti-viral properties, pomegranate must be considered.

For the treatment of diarrhea and dysentery, pomegranate rinds enjoy an illustrious history of use. Future research and development will focus on developing the rind extract into natural antidiarrheal drugs for over-the-counter or prescription use. Vermicidal properties may be exploited in remedies for both human and veterinary applications.

Our studies in Israel have clearly confirmed the suspicion that the flavonoids in pomegranate comprise a potent antioxidant with additional enzyme inhibition properties which make preparations of the juice and oil potential dietary supplements for promoting longevity and preventing heart disease and cancer. Also, the fact the extract of the oil was effective in inhibiting prostaglandin and leukotriene formation through inhibition of the eicosanoids enzymes cyclooxygenase and lipoxygenase respectively, raises the possibility of use of the oil or its derivatives as both internal and external anti-inflammatory preparations (Shubert *et al.*, in press).

Finally the tremendous recent explosion of interest in phytoestrogenic compounds in medicine for potential prophylaxis and treatment of menopausal vasomotor phenomena, osteoporosis, estrogen-depletion cardiovascular disease and cancer (Knight and Eden, 1996) raises the possibility that pomegranate seed oil and extracts might be employed in menopausal women as external and internal phytoestrogen medicaments, as a possible alternative or supplement to conventional hormone replacement therapy (HRT) (Lansky, in press).

Toxicity of pomegranate preparations from juice and seeds would appear to be very low, owing to the use of the these components as common items of dietary commerce. The reported association of seed ingestion with esophageal cancer is apparently related to the crude form used, and in preparations involving pressed oil or extracts this problem should not exist. The potential for allergic reactions to pomegranate, a fruit with virtually no botanical relatives and possessing a unique set of antigenic and chemical markers, should not be ignored, and potential users of pomegranate products should be routinely spot tested for sensitivities. The reported genotoxicity of peel preparations (Settheetham and Ishida, 1995) is more worrisome, and though the peels have been safely used in Ayurvedic, Chinese and other folk medicines for thousands of years, this finding should be the subject of further rigorous investigations, and the possible use of such peel concentrates in anticancer therapy (Mavlyanov *et al.*, 1997) is also suggested.

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