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Dwarf pomegranate (*Punica granatum* var. nana), characteristics, generalities and preclinical studies of an ornamental plant with potential health benefits.

Granada enana (Punica granatum var. nana), características, generalidades y estudios preclínicos de una planta ornamental con potencial para la salud.

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Abstract:

Punica granatum has been extensively studied in recent years in different fields of science, especially in health, where we can find thousands of studies on its beneficial effects; however, most of these studies have been carried out on commercial varieties, leaving aside exotic varieties such as dwarf pomegranate (*P. granatum* var. nana), which is a variety known throughout the world for its ornamental use. This peculiarity has reduced the possibility of being studied, especially in health. The objective of this narrative review focuses on showing the characteristics, generalities and preclinical studies that have been found on this inedible ornamental pomegranate. The characteristics, uses of the pomegranate in traditional medicine, and *in vivo* and *in vitro* studies of biological anticancer, antidiabetic, hepatoprotective, antibacterial, antifungal, anthelmintic, and anti-inflammatory activities were found in various parts of this fruit, as well as important phytochemical components that support these biological activities. The information obtained indicates that it is necessary to deepen the study of this variety because the studies that have been carried out are still scarce despite being an easy plant to grow. It is still unknown if the biological activities that they possess have an effect on human health, since there are no clinical studies in this regard, and it is also unknown if these are of lesser or greater magnitude compared to edible varieties.

Keywords:

Pomegranate, punica granatum, punica granatum var. nana, dwarf pomegranate, health benefits, ornamental, antidiabetic activity

Resumen:

Punica granatum ha sido ampliamente estudiada en los últimos años en diferentes campos de la ciencia, especialmente en el de la salud, donde podemos encontrar miles de estudios sobre sus efectos beneficiosos, sin embargo, la mayoría de estos estudios se han realizado sobre variedades comerciales, dejando de lado variedades exóticas como la granada enana *(P. granatum* var. nana), la cual es una variedad conocida en todo el mundo por su uso ornamental. Esta peculiaridad ha reducido la posibilidad de ser estudiada, especialmente en salud. El objetivo de la presente revisión narrativa se centra en mostrar las características, generalidades y los estudios preclínicos que se han encontrado de esta granada ornamental no comestible. Se encontraron características, usos de la granada en la medicina tradicional, así como en estudios *in vivo* e *in vitro* actividades biológicas anticancerígena, antidiabética, hepatoprotectora, antibacteriana, antifúngica, antihelmíntica, antiinflamatorias encontradas en diversas partes de este fruto, así como componentes fitoquímicos importantes que respaldan dichas actividades biológicas. La información obtenida indica que es necesario profundizar en el estudio de esta variedad debido a que los estudios realizados aún son escasos y a pesar de ser una variedad fácil de cultivar aún se desconoce si las actividades biológicas que poseen tengan efecto en la salud humana pues no existen estudios clínicos al respecto, además se desconoce si estos son de menor o mayor magnitud en comparación con las variedades comestibles.

Palabras Clave:

Granada, punica granatum, punica granatum var. nana, granada enana, beneficios a la salud, granada ornamental, actividad antidiabética

INTRODUCTION

The pomegranate is an ancient fruit known in various cultures worldwide.[1] It was first cultivated in ancient Persia (today Iran and its surroundings) where it comes from. This fruit managed to be distributed and cultivated in various parts of the world including: China, Spain, Russia, Greece, U.S.A., and Mexico.[2,3] This plant with the scientific name *Punica granatum* belongs to

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the order of the *Myrtales* and the family *Lythraceae*, with two known species of the *Punica* genus: *Punica granatum* L., adapted to tropical and subtropical regions worldwide and *Punica protopunica* Balf., that is only found in Socotra archipelago, so it is considered endemic.[4,5]

Punica granatum L., has been used in traditional medicine, because in different parts of the tree, mainly in the fruit, various medicinal effects have been found, in addition to having good nutritional value. As a consequence, there is a greater demand generated by the informed consumer, causing there to be more producers.[6] In this sense, the distribution of pomegranate in the world implies a large number of varieties adaptable to the different climatic and soil conditions of each region, which are classified or named mainly by their citric acid content in the juice (sweet, bittersweet and acid).[7,8] There are more than 500 varieties of pomegranate crops distributed throughout the world. Among them there may be great differences or similarities in terms of color, peel, size, among other differences according to the different regions where it is grown (this fruit grows in arid climates and, in turn, is better harvested in somewhat more humid climates, besides being very resistant to salinity and cultivated in a wide variety of soils).[9] Additionally, one of the varieties presents a great difference in terms of size compared to the others, this exotic variety is *Punica granatum* var. nana (*P. granatum* var. nana), commonly known as "Dwarf pomegranate".[10] *P. granatum* var. nana is a non-edible pomegranate considered ornamental because it is a bushy, dwarf, evergreen tree, which produces very small fruits. Despite being known worldwide, this variant is not produced on a large scale and has no commercial value as a food product, as it is not edible. People use it as an ornamental plant, due to its aesthetic qualities. No compendium of information about *P. granatum* var. nana were found, so the objective of this review is to learn more about the characteristics of this variety, its uses in traditional medicine and particularly its uses in human health.

TAXONOMY POSITION AND DISTRIBUTION

Punica granatum is native from the Balkans region to the Himalayas; however, it is cultivated throughout the Mediterranean basin, and recently in North and South America.[11] The "dwarf pomegranate" variety (*P. granatum* var. nana*)*, belongs to the order *Myrtales*, to the family *Lythraceae*, to the genus *Punica* and specifically to the species *Punica granatum* and is known by various names (Dwarf pomegranate, *Punica granatum* nana, *Punica* nana L, *P. granatum* var. nana Pers., and *Punica granatum* "Nana").[12,14.15] This variety is best known for its ornamental use due to the decoration offered by its flowers and its fruits, which are not edible because its fruits are not edible. These ornamental trees grow in East Asia, southeastern Europe and are distributed especially in countries with a subtropical climate and in warm areas.[12,13] The taxonomic position of *P. granatum* var. nana is described in Table 1.

Table 1. Taxonomic positioning of *P. granatum* var. *nana*

Classification	Denomination	Common name
Order	Myrtales	-
Family	Lythraceae	Loosestrife
Genus	Punica	-
Species	*Punica granatum*	*Punica granatum* L., pomegranate
Variety	*Punica granatum* var. nana	Dwarf pomegranate, *Punica granatum* "Nana", *Punica granatum* nana, *P. granatum* var. nana Pers., and *Punica* nana L

Adapted from several authors[12,14,15]

MORPHOLOGY AND CULTIVATION

P. granatum var. nana is a rounded, compact and deciduous shrub, with a maximum height of 0.5 to 1 meter that takes approximately between 10 and 20 years to reach. It has elongated, narrow and shiny evergreen leaves that are lost in winter, turning yellow during autumn, while its flowers are bright orange-red, funnel-shaped, 4 cm thick with a flowering depending on the climate where it develops, it blooms from the end of April to the beginning of May. The fruit develops in autumn and is usually spherical, red or brown in color, and the pulp is edible. The taste of the fruit is very acidic, the peel is leathery with a thickness of 5 mm. Humans do not usually consider this fruit as food, because of both its taste and its small size. Easily grown in moist, deep, well-drained soils, it is drought tolerant as well as resistant to full sun exposure.[16,17,18] This type of plant has fruit – bearing characteristics and its main attribute is its showy flowers, in addition to being resistant to a variety of temperatures <15° and it supports direct exposure to the sun.[19,20] Table 2 lists some crops characteristics of the *P. granatum* var. nana.

Table 2. Crops characteristics of *P. granatum* var. nana

Punica granatum var. nana	Crop characteristics
Plant Type	Fruit
Plant Family	Lythraceae – Punica
Flower Attribute	showy flowers, shrubs
Height	60 cm – 1 meter
Spread	1.2 – 1.5 meter
Exposure	Full sun
Water Needs	Low, average
Soil Type	Well drained / sandy / loam
Growth Habit	Round
Bloom Time	Summer

Winter Hardiness	<15°

Adapted from several authors:[19,20,21]

MAIN PHYTOCHEMICAL COMPOUNDS

Different authors have found that *Punica granatum* has multiple phytochemical compounds, since various parts of the fruit as well as various parts of the tree have been studied.[22,23,24,25] However, edible pomegranates stand out for having a large number of polyphenols (flavonoids and tannins), in addition to containing sterols, fatty acids, and triglycerides. The most predominant tannin in *Punica granatum* is punicalagin. Some authors consider the pomegranate as one of the fruits with the highest antioxidant capacity.[26]

On the other hand, few phytochemical studies were found in *P.granatum* var. nana; however, Amri et al.,[27] analyzed the leaves, flowers, peel and juice of *P. granatum* var. nana and found phenolic compounds (Ortho-diphenols, anthocyanins, flavonoids and tannins) and carotenoids. Especially in the peel it was found a high content of tannins, which indicates its high phytochemical value. Regarding anthocyanins, a high content was detected, these provide the color to the flowers and fruits (red) as well as the juice. It was also found that the juice is also a great source of polyphenols. They detected that the seed oil has unsaturated fatty acids, cis-linolenic acid, punicic acid, behenic acid, and conjugated linolenic acids. Sánchez-Hernandez et al. found that pomegranate arils contain a carbon percentage C = 43.15%, Hydrogen H = 6.41%, and Nitrogen N = 1.54% They also analyzed the extract of the whole fruit and found the following compounds (β-sitosterol, 5-hydroxymethylfurfural, pyrogallol and 2,3-dihydro-3,5-dihydroxy-6-methyl-(4H)-pyran-4-one) as well as the octadecadienoic and palmitic acids.[28] Janeczko and skoczowski identified *P. granatum* var. nana estrone only in the leaves, root and flower.[29]

Wafa et al., studied the phenolic composition of peel extract of *P. granatum* var. nana and they found 21 phenolic compounds such as anthocyanins (Pelargonidin-3,5-diglycoside, Delphinidin-3-glycoside, Cyanidin-3-glycoside), ellagitanins and flavanols ((+)-Catechin, Granatin A, (+)-Gallocatechin, Ellagic acid, HHDP-hexoside) among others.[30] Finally, El Mogahzy et al., discovered nine compounds isolated from the ethanolic extract of the leaves (β-amyrin, β-sitosterol, ursolic acid, corosolic acid, friedelin, 2-Methyl-pyran-4-one-3-O-β-dglucopyranoside, luteolin -4'-O-β-d-glucoside and luteolin-7-O-(6``-O-galloyl)-βd-glucoside. Figure 1 shows the chemical structure of some important phytochemicals in *P. granatum* var. nana.[31]

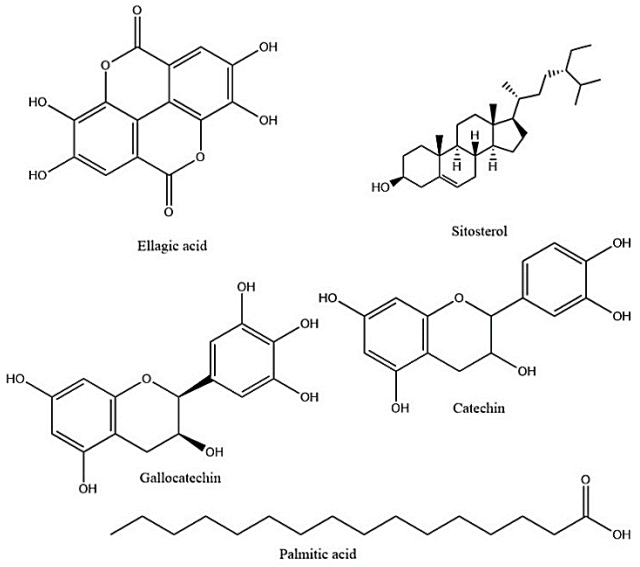

Figure 1. Chemical structure of some important phytochemicals in P. granatum var. nana. Source: self-made

USES IN TRADITIONAL MEDICINE

It has been reported that young roots, bark, leaves, flowers, fruit peel as well as juice have been used in traditional medicine. The fruit contains "strong tannins" and is considered as nutritionally bitter. Its decoction seems to be useful for the treatment of dysentery and stomach disorders.[32]

In the Charaka-Samhita (the oldest known medical work in the world), the medicinal properties of pomegranate root and peel were already mentioned as a taenicide; the Chinese, Romans, and the Arabs also knew this property. In India, the root of the pomegranate tree has been used to treat intestinal parasite infestations. There are reports that pomegranate macerates in ethanol are used as antibacterial and for the resolution of inflammatory diseases.[33,34] Another common use of the fruit and flower is as a powerful astringent agent (substance that has the property of retracting tissues and producing a healing, anti-inflammatory and anti-hemorrhagic action), thus, it is used for dysentery, diarrhea, stomatitis, ulcers, bleeding, and enemas.[34,35] It is also known that oral or vaginal extracts of the fruit or root have been used to prevent fertility and to induce abortion.[36,37]

In traditional Chinese medicine it is also used as a treatment for burns and it is documented that it has been used as a treatment for snake bites.[38,39] In traditional Mexican medicine, the fruit, seeds and peel, as well as the root and leaf (in tea or infusion) are used for the following ailments: parasites, hardening of teeth, bronchitis, blisters in the mouth, milkweed, diarrhea, cough, sore throat, and indigestion.[40] Some of these properties have been found in various varieties of pomegranate, including *P. granatum* var. nana.

PRECLINICAL STUDIES

There are few *in vitro* and *in vivo* studies where beneficial effects on health of *P. granatum* var. nana were found:

ANTI-PROLIFERATIVE EFFECT AND ANTI-CANCER ACTIVITIES

Amri et al.,[27] analyzed the antiproliferative activity of *P. granatum* var. nana at different concentrations: they used juice extract, seed oil, peel extract at doses of (0.05, 0-1, 0.25 and 0.5 mg/ml), the study was carried out in DU145 cell lines, which are prostate cancer cell lines. Treatments were applied from 24 to 48 hours, after that, antiproliferative activity and cell apoptosis were evaluated. The results obtained indicated that all the extracts had an antiproliferative effect; however, the one with the greatest effect was the seed oil and the most important effect in terms of cell apoptosis occurred with the peel extracts. Finally, they conclude that juice, leaves, oil and peel of the *P. granatum* var. nana has anticancer, antiproliferative and cytostatic activities on DU-145 cells, as well as cell apoptosis by inhibition of COX-2 expression and DNA fragmentation.

ANTI-DIABETIC ACTIVITY

Kadriya et al.[41] evaluated the antidiabetic effect of an ethanolic extract of P. granatum var. nana, evaluated acute toxicity and identified antidiabetic, antioxidant, and anti-inflammatory compounds. Diabetes was induced in adult male Sprague-Dawley rats by administering streptozotocin and nicotinamide for 14 days, the treatment was administered with the ethanolic extract of P. granatum var. nana in two doses (100 and 200 mg/kg intragastrical) for 4 weeks. They found that the administered doses significantly decreased the levels of glucose and glycosylated hemoglobin in the blood, in addition to detecting that gallic acid, rutin, tulipanin, and nictoflorin are responsible for the antidiabetic and anti-inflammatory effects.

HEPATOPROTECTIVE ACTIVITY

Diab et al.,[42] evaluated the hepatoprotective and curative effect of a methanolic extract from the leaves of *P. granatum* var. nana at doses of 60, 120 and 240 mg/kg intragastric in female albino rats. To determine the curative effect, carbon tetrachloride (CCl_4) was used at a dose of 2 ml/kg intraperitoneal weight for 10 days until hepatic failure occurred, subsequently CCl_4 was injected twice a week plus the administration of the extracts. To determine the hepatoprotective effect, the aforementioned doses of extract were administered daily together with CCl_4 for 10 days, to subsequently be injected twice a week while treatment with extracts was continued daily. Biochemical variables of liver function, lipid profile, oxidative stress and renal function determination were analyzed. The result obtained was that the methanolic extract of leaves of *P. granatum* var. nana attenuated the hepatotoxic effect of CCl_4, significantly improving most of the biochemical parameters in both the protective and curative treatments, concluding that this extract has preventive and curative activity against liver damage.

ANTI-BACTERIAL, ANTI-FUNGAL AND ANTI-HELMINTIC ACTIVITY

Wafa et al.[30] evaluated the bactericidal effect of the juice, aqueous, hydroethanolic, and hydromethanolic extracts from peel, leaves and flowers of *P. granatum* var. nana. They selected two strains: *Salmonella kentucky* and *Salmonella enteritidis* to inoculate them in chicken meat. They determined the antimicrobial resistance using agar well diffusion method, while the determination of the minimum inhibitory concentration was determined by tests in Mueller Hinton Broth medium and the minimum bactericidal concentration was determined as the lowest sample concentration 0.1% (MBC/MIC) for each tested strain. The results showed that the most important antibacterial activity against *S. enteritidis* was from the hydromethanolic extract of the pomegranate peel, while the most important antibacterial activity against *S. kentucky* was from the hydroethanolic and hydromethanolic extracts from the pomegranate peel. The MBC/MIC study shows that both extracts have bactericidal effects on these pathogens.

Tammam et al.[43] used a methanolic extract of *P. granatum* var. nana leaves at doses of 400, 800 and 1600 μg/ml to evaluate its nematicide and fungicidal effect in an *in vitro* and *in vivo* studies, as well as its antioxidant effect. They selected and isolated three nematodes (*Meloidagyne incognita, Rotylenchulu reniformis* and P*ratylenchus penetrans)*, also selected and isolated three phytopathogenic fungi (*Fusarium oxysporum* f. sp. *lycopersici*, *Rhizoctonia solani* and *Sclerotium rolfsi*), the *in vitro* studies were carried out with two techniques, which consisted of using a nutritive glucose agar medium and petri dishes, as well as inhibition of spore and sclerotia germination; *in vivo* studies were carried out on tomato transplants. Subsequently, the methanolic extract was isolated from its antioxidant components. They found that the extract has an antifungal effect against the fungus *R. solani*, while the most effective nematicide effect was against eggs and larvae, at a concentration of 400 to 1600 μg/ml; the higher the concentration, the better the nematocidal activity it had on *P. penetrans*. Finally, it was found that the methanolic extract of pomegranate leaves contains phenols (anthocyanins, flavonoids, tannins), saponins, sterols and triterpenoids and glycosides to which they attribute effects.

Yones et al.,[44] studied the anthelmintic effect of two ethanolic extracts of *P. granatum* var. nana (leaves and stem bark), at doses of 100, 300 and 500 μg/ml. They used mouse fibroblast cells for *in vitro* studies, while doses of 600 and 800 mg/kg were used for the *in vivo* assay in Swiss albino female mice. On the other hand, parasites *(Schistosoma mansoni)* were used, which were inoculated into the mice using the tail immersion

technique and analyzed 8 weeks after infection, while the *in vitro* study lasted 12 weeks. In addition, phytochemical screening was carried out to find the presence of the components of the extracts. The results indicated that the antiparasitic effect depends on the dose administered. A decrease in parasitic motility was observed. An increase in the death of 100% in parasites, in all doses, while at high doses the number of eggs in hepatic tissues decreased.

ANTI-INFLAMATORY ACTIVITY

El-Moghazy et al.,[31] evaluated the anti-inflammatory and antioxidant effect of two ethanolic extracts of pomegranate (stem bark and leaves) in male albino rats, in which inflammation was induced by an edema model to evaluate the anti-inflammatory activity while the antioxidant activity was determined by DPPH method. The results indicated that the stem bark extract considerably reduced the edema in the animal's paw than that of the leaves, and the ethanolic extract of the leaves presented a very important anti-inflammatory activity that can be compared with indomethacin.

CONCLUSIONS

Punica granatum has been extensively studied in recent years in different fields of science, especially in health, where we can find thousands of preclinical and clinical studies on its beneficial effects; however, there is a significant lack of information regarding the commercial varieties, leaving aside exotic varieties such as *P. granatum* var. nana which, being a variety known throughout the world for its ornamental use, this peculiarity has reduced the possibility of being studied, especially regarding its health benefits. Because it is an easy-to-grow tree, it has been distributed worldwide and although there are few studies that show us its phytochemical composition, we can conclude that it is similar to that of the *Punica granatum* species; however, it is important to detect what makes it unique, since it is believed that, being a tiny fruit, it does not contain the same amounts of phytochemical components as *Punica granatum*. As a result of knowing these components that are responsible for the beneficial health effects detected in various parts of this fruit, in vitro and in vivo studies have been carried out to detect biological activities, which are of clinical interest since today's society faces chronic degenerative diseases and the secondary effects generated by treatments to combat or control them. A very common pathology is diabetes, it was found that *P. granatum* var. nana has antidiabetic activity, although one study is insufficient to generalize these data, it is known that *Punica granatum* also has it; however, the important difference is that many studies have been carried out on this important effect of this species, but on the variety of dwarf pomegranate further studies are needed. The information obtained indicates that it is necessary to deepen the study of this variety because the studies carried out are still scarce despite being a plant that is easy to grow, and it is also unknown if the biological activities they possess have an effect on human health, since there is no clinical study in this regard, and it is also unknown if these are of a lesser or greater magnitude compared to the edible varieties and even with the *Punica granatum* species.

ETHICAL CLEARANCE

Not applicable.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest involved in the writing of this review.

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