

# POMEGRANATE JUICE GROW IN SPAIN

*Antioxidant punicalagin in pomegranate juice and pomegranate extract, for the functional diet of the future.*



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## The Food quality and safety group and the pomegranate

The Food Quality and Safety Group (FQS) research team at the Miguel Hernández University of Elche Department of Food Technology has conducted several studies on the organoleptic quality and functional properties of pomegranate juice and pomegranate-derived products (peel extract, dehydrated pomegranate, etc.).

One of the research projects undertaken was funded by the company Antioxidantes Naturales del Mediterráneo S.L. (Natural Mediterranean Antioxidants L.L.C.), and research focused on comparing the functional properties and acceptance by Spanish consumers of commercial pomegranate juices available on the domestic market. Moreover, in conjunction with the University of Kansas (United States of America), the FQS research team has conducted a study on the worldwide acceptance of different types of pomegranate juice. Within this study, Granatum Plus juice was selected as a benchmark for 100% natural juice.



## Research results

The results obtained following an analysis of commercial pomegranate juices in Spain in 2010 indicate that products from the Granatum Plus range contained a higher concentration of polyphenols, the pomegranate's natural antioxidant, than any of the other products analysed. Furthermore, an analysis of the prices of the different pomegranate products on the market also established that of all the products analysed, Granatum Plus products presented the best value for money.

Granatum Plus juices obtained the lowest scores in undesirable attributes and high scores in attributes such as sweetness, pomegranate aroma and colour.



The indication given on the product label of the geographic origin of the pomegranates and the variety used was considered highly commendable. Granatum Plus products excelled in the list of national products analysed, Granatum Plus is the only commercial brand that informs consumers of the geographic origin of the pomegranates (Spain) and the variety

The same study showed that Granatum Plus capsules contains around 30% punicalagins and a total percentage of polyphenols of nearly 50%.

Furthermore, this product also contains about 84% pomegranate extract. Taking a “Granatum Plus” capsule is the equivalent of drinking about 250 ml of juice squeezed from arils of the same variety. This study, together with others conducted in recent years by prestigious universities worldwide, has demonstrated that the antioxidant power of pomegranate peel is 10 times stronger than the edible parts.

## 1. Introduction

In order to move forwards towards the future, we often need to look first at our past. A clear example of this is one of the first crops to be domesticated by humans, the pomegranate. The presence of this fruit in Spanish culture and history is so ubiquitous that it even appears in coats of arms such as that of the Kingdom of Granada during the time of the Catholic Kings.

Another example highlighting the relationship between the pomegranate, Spain and research is the emblem of the Spanish National Research Council (CSIC), which incorporates a pomegranate tree (**Figure 1**).



**Figure 1.** A pomegranate orchard and the emblem of the Spanish National Research Council.

The aim of the present document is to highlight the importance of this crop in Spain, which is due both to the high volume of production and the benefits for human nutrition provided by this fruit and its derived products.

## 1.1. The origins of the pomegranate

The pomegranate (*Punica granatum* L.) has been cultivated since antiquity. It is one of the biblical crops, together with grapes, olives and dates. According to Nikolai Vavilov, the pomegranate evolved in the 4th Centre of Origin, the Middle East (Asia Minor, Transcaucasia, Iran and the highlands of Turkmenistan).

Its systematic classification is as follows:

**Division:** Magnoliophyta

**Class:** Magnoliopsida.

**Subclass:** Rosidae.

**Order:** Myrtales.

**Family:** Lythraceae

**Genus:** *Punica*.

**Specie:** *P. granatum*.

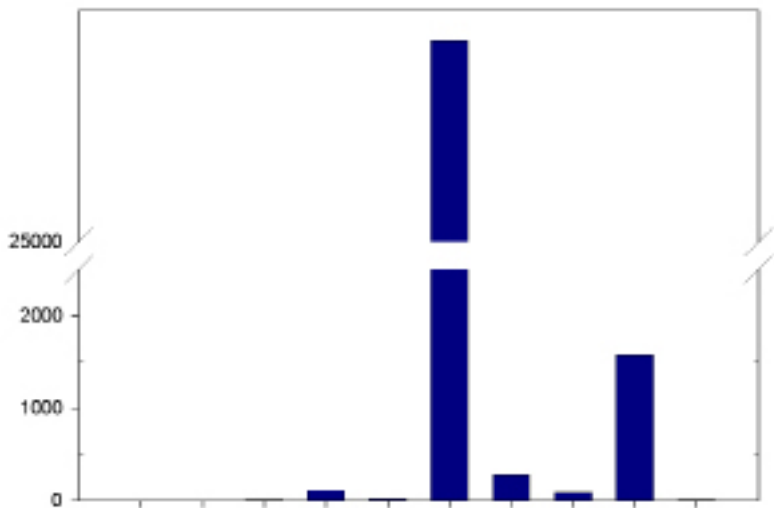


The pomegranate (*Punica granatum* L.) is a small deciduous tree that grows to a maximum of 8 metres high in the wild. It is a very valuable fruit tree in many regions of the world, especially those which are arid and semiarid, since it is capable of adapting to different areas where other, currently more widely grown fruit trees would not yield a profitable crop (Melgarejo and Salazar, 2003).

## 1.2. The Economic Importance of the pomegranate

The pomegranate is currently cultivated in a variety of countries, including Spain, the United States, Iran, Turkey, India, Israel, China and countries along the north coast of Africa, among others. Spain ranks as the largest producer in Europe, with an annual production of 22,311 tons (Spanish Ministry of the Environment and Rural and Marine Affairs, 2010).

Production is centred in Valencia, Andalusia and Murcia (**Figure 1**), although 90% of this is in the province of Alicante. In turn, production in Alicante is mainly concentrated in three municipalities, Elche, Albatera and Crevillente, in order of importance. This high level of concentration clearly indicates the enormous socio-economic importance of the pomegranate for these three municipalities and their surroundings.



**Graph 1.** Pomegranate producing communities in Spain.



### 1.3. The Mollar de Elche pomegranate

The pomegranate has traditionally been a highly prized and esteemed fruit in many civilizations. Together with the palm tree, the pomegranate tree is the most characteristic tree in Campo de Elche, and has been known from time immemorial. In Spain, the Mollar de Elche pomegranate (Figure 2) is by far the most popular variety and is unquestionably the most widely grown in this country.



**Figure 2**

The most important characteristics of the Mollar de Elche pomegranate are as follows:

- Large or very large sized fruit.
- Vigorous, fast growing tree.
- Large, dark red seed casings (arils) with very small and soft seeds.
- Maturing between October and November.
- It is more productive and of better quality and higher calibre than the Valencian group pomegranates, which rank second in Spanish production.

## 2. Functional products derived from the pomegranate and integral use of the fruit.

The study of the pomegranate's bio-active components and their benefits for human health is a highly topical and important field of research. Numerous scientific studies have shown that both the pomegranate and its derived products contain many components that contribute to preventing disease and maintaining health (Larrosa et al., 2006; Sartippour et al., 2008; Koyama et al., 2010).

The pomegranate is usually consumed fresh. However, a large proportion of the crop does not present sufficient visual quality to be destined for fresh consumption, since its acceptance by consumers is very low. However, the quality of the edible part, the arils, is similar to that of those specimens with good acceptance for fresh consumption. It is therefore necessary to find an alternative commercial use for this proportion of the crop unsuitable for fresh consumption, based on industrial processing.

The most important industrial products derived from the pomegranate are:



- Pomegranate juice: widely marketed in the USA, and with great potential in Spain
- Ready to eat arils
- Jams.
- Wines, vinegars and liqueurs.
- Dehydrated arils
- Nutraceuticals made from peel extract
- Food condiments.
- Cosmetics: creams, oils, gels, etc.

## 2.1. Chemical composition of the pomegranates

The peel, white pulp membrane, arils and seeds of the pomegranate all contain many chemical compounds of high biological value (Figure 3). The most important product derived from the pomegranate is its juice, which is unquestionably the most research element, with many articles published in both the Spanish and international scientific literature.



**Figure 3.** The different parts of the pomegranate.

About 50% of the total weight of the pomegranate corresponds to the peel and white pulp membranes, which are a major source of bio-active compounds such as polyphenols, flavonoids, ellagitannins, proanthocyanidins and minerals, mainly potassium, nitrogen, calcium, phosphorus, magnesium and sodium. Consequently, if processed correctly, nutraceutical products and food condiments made from peel and membrane extracts may provide an important source of these compounds.



The edible part of the pomegranate represents about 50% of the total weight of the fruit, of which the fleshy pulp of the arils accounts for 80% and the woody seeds contain 20%.

Pomegranate arils are composed of 85% water, 10% sugar (mainly fructose and glucose), 1.5% organic acids (principally ascorbic, citric and malic acids) and bioactive compounds such as polyphenols and flavonoids (mainly anthocyanins).

Pomegranate arils are also a major source of lipids, since fatty acids comprise between 12% and 20% of the total dry weight of the seeds.



The fatty acid profile is characterised by a high content in unsaturated fatty acids, including linolenic, linoleic, punctic, oleic, stearic and palmitic acids.

**Table 1.** Nutritional composition of the edible part (USDA, 2007).

Nutrient	Unit	Value per 100 g
<b>BASIC FOOD SUBSTANCES</b>		
Water	g	80.97
Energy	kcal	68
Protein	g	0.95
Fat	g	0.30
Carbohydrates	g	17.17
Dietary fibre	g	0.6
Total sugars	g	16.57
<b>VITAMINS</b>		
Vitamin C (ascorbic acid)	mg	6.1
Vitamin A	IU	108
Vitamin E ( $\alpha$ -tocopherol)	mg	0.60
Vitamin K (phyloquinone)	$\mu$ g	4.6
<b>OTHER</b>		
Phytosterols	mg	17
Cholesterol	mg	0
$\alpha$ -Carotene	$\mu$ g	50
$\beta$ -Carotene	$\mu$ g	40

**Table 2.** Mineral content of the edible part (USDA, 2007) and in pomegranate juice with pulp (Andreu-Sevilla et al., 2008).

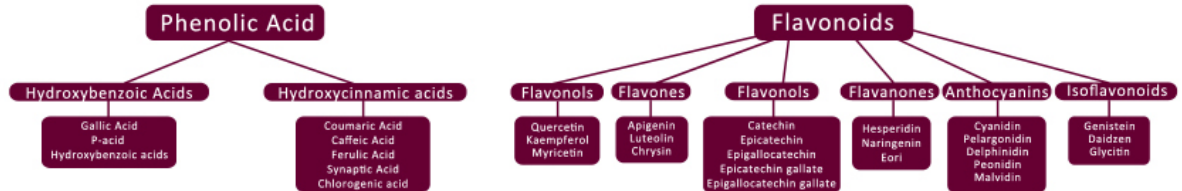
		(mg/L)		(mg/kg)
<b>Calcium</b>	4.6	18014	74.7	30
<b>Magnesium</b>	65.8	57	65.7	30
<b>Potassium</b>	933	3093	940	2590
<b>Sodium</b>	25.9	0	25.8	30
<b>Iron</b>	3.0	1499	8.8	3.0
<b>Copper</b>	2.1	661	4.7	0.7
<b>Manganese</b>	1.9	47	2.1	-
<b>Zinc</b>	4.4	0	4.4	1.2

The beneficial effects of fruit and vegetables arising from their high content in bioactive compounds are now widely accepted. The presence of the compounds listed above (**Table 2**) indicates the important nutritional value of the pomegranate.

## 2.2. Phenolic compounds

### 2.2.1. Low molecular weight phenolic compounds

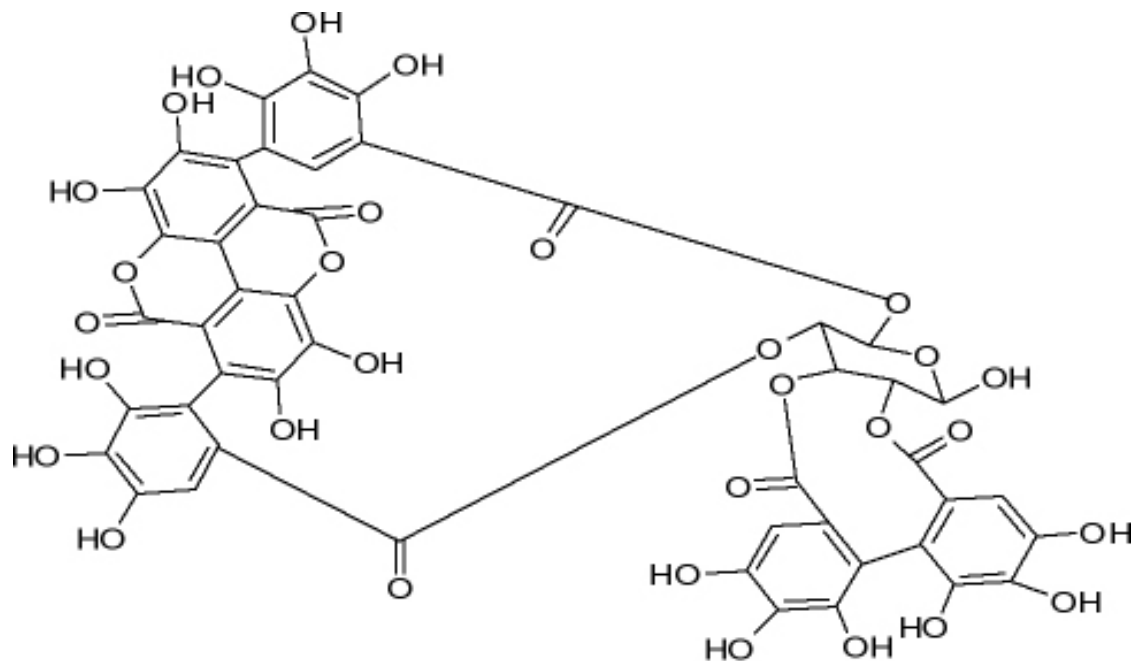
Phenolic compounds can be divided into simple molecules and polymers of these with a higher molecular weight. The flavonoids are the most numerous compounds in the first subgroup, mainly represented by anthocyanins, which are responsible for the characteristic colour of the pomegranate. The principal low molecular weight phenolic compounds are the phenolic acids, which include gallic acid and ellagic acid (**Figure 4**).



**Figure 4.** Low molecular weight phenolic compounds

### 2.2.2. High molecular weight phenolic compounds

Tannins are the most characteristic high molecular weight polyphenols. Pomegranate peel is rich in hydrolysable tannins, mainly punicalin, pedunculagin and punicalagin (**Figure 5**).



**Figure 5.** Molecular structure of punicalagin



### 2.3. The pomegranate as a functional food

The concept of functional food is complex and can refer to whether or not the components are nutrients, whether they have a positive effect on the body, or whether they have a physiological or psychological effect beyond the purely nutritional (Viuda-Martos et al., 2011a).



Functional foods include: (i) those containing certain minerals, vitamins, fatty acids or dietary fibre, (ii) foods to which biologically active substances, such as phytochemicals or other antioxidants, have been added, and (iii) probiotic foods containing beneficial live microorganisms.

Thus, given the results of various studies on the chemical composition of the pomegranate and more recently on its health benefits, the pomegranate can be considered a functional food (Melgarejo, 2010).

Anthocyanins are the compounds considered responsible for the red colour of pomegranate arils. The importance of these phenolic compounds lies in their antioxidant action, which protects against free radicals and retards the cell aging process.

The free radical scavenging activity of these flavonoids has been demonstrated in various studies, such as that conducted by Espín et al. (2000). An estimated 10% of the antioxidant action of pomegranate juice is due to the presence of these polyphenols, the anthocyanins (Gil et al., 2000).

The antioxidant capacity of pomegranate juice is three times that of red wine or green tea (Gil et al., 2000).



Its content in essential fatty acids (linoleic, linolenic and arachidonic acids) is of great importance, particularly due to the content in polyunsaturated fatty acids. These play an important role in the prevention of cardiovascular disease and some other heart problems, because this type of fatty acid significantly reduces HDL-cholesterol levels (bad cholesterol). Punicic acid has anti-atherogenic effects.

The ellagitannins can be transformed into urolithins; urolithin A may be the most active anti-inflammatory compound related to consumption of the pomegranate. Anti-inflammatory processes in the colon may be due to the unmetabolised fraction of ellagitannins (Larrosa et al., 2010).

Punicalagin, the polyphenol with the highest known molecular weight, is hydrolysed into ellagic acid and metabolised in the intestinal tract to generate urolithins. Punicalagin compounds present very high antioxidant or free radical scavenger capacity and are responsible for approximately 50% of this activity in pomegranate juice, followed by other hydrolysable tannins (33% of total activity) and, to a lesser extent, ellagic acid (3%) (Gil et al., 2000; García-Viguera et al., 2004).

The main functional properties of the punicalagins are: (Sánchez et al., 2009)



- Powerfull antioxidant effect.
- Anticancer action.
- Protective effect on the cardiovascular system.

## 2.4. Oxidation versus Antioxidation

Living organisms need energy, and this is provided by the basic food substances (carbohydrates, lipids and proteins).

This energy is obtained through chemical reactions which may or may not involve oxygen. Thus, we distinguish between anaerobic and aerobic metabolism.

Cells obtain more energy from aerobic metabolism. With oxygen, cells obtain more ATP from the basic nutrients (carbohydrates, lipids and proteins). Without oxygen, they obtain 20% less ATP (energy).



These oxidation reactions take place in the mitochondria, structures which are present in the cell cytoplasm. Basically, the glucose molecule (6 carbon atoms) splits into two pyruvic acid molecules (3 carbon atoms) which oxidise and release electrons and protons. These are eventually absorbed by the oxygen, converting it into water and carbon dioxide and storing energy in the form of tri-phosphate bonds (ATP).



The molecules derived from the oxidation of glucose continue to be oxidised and oxygen is reduced as it absorbs the electrons and protons; each oxygen molecule absorbs four electrons and four protons, thereby forming two water molecules. This is what is known as tetra-reduction.

However, the reaction does not always occur in exactly this way, and it has been calculated that an estimated five percent of reactions are mono- and bi-reductions that instead of generating water and CO<sub>2</sub>, which are easily and naturally eliminated by the excretory organs (kidneys, lungs, skin), generate harmful reactive species derived from oxygen (Reactive Oxygen Species, ROS) that are detrimental to our health because they perpetuate the oxidation of healthy tissue, leading to pathologies.

This 5% could be likened to the “soot” from a “metabolic chimney”; if it is not eliminated or neutralised, over time we become ill or age faster. Those body systems most vulnerable to attack are the circulatory, nervous and immune, or defensive, systems.

The reactive oxygen species produced in cells include hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), hydroxyl radical ( $-\text{OH}$ ) and superoxide ( $\text{O}_2^{\bullet-}$ ).

With the emergence of oxygen on the Earth, those species that were not equipped for oxidation disappeared, whilst those that could withstand the impact of oxygen survived, because they managed to develop a system that would protect them: the antioxidant system.

Oxidation is defined as the “theft” of electrons from the outer electron layers of atoms or molecules, converting them into charged ions. The substances that remove these electrons are called oxidising agents, and when oxidised, they are reduced. If these “oxidised” ions are not neutralised by another element (a reducing agent) that offers its own electrons or protons ( $\text{H}^+$ ), they are converted into free radicals and continue moving through the body until they can replace these electrons by removing them from other elements, the most vulnerable of which are the membranes that make up cells.

“Uncontrolled” oxidation in our body tissues is responsible for aging, degeneration and, of course, disease. We must fight against it if we want to survive.

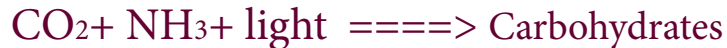
The normal function of our cellular antioxidant enzyme system is to control this excess of free radicals or reactive oxygen species produced by our own bodies:

- Superoxido dismutasa (SOD)
- Catalasa (CAT)
- Glutathione peroxides... and others

These three enzymes form our strongest anti-radical defence in cells. We should bear in mind that the consequence of an excess of free radicals (oxidising agents) or the inability on the part of our enzymatic defences to counter such an excess, is the risk of developing a multitude of pathological processes, and in particular, of degenerative diseases, such as Alzheimer's, Parkinson's, arthritis, etc.

Aging is no more than an imbalance in favour of oxidation mechanisms due to weak or inefficient antioxidant defence systems.

However, due to the pace of modern life, we must add many more “oxidative” attacks from our environment, which overwhelm our aforementioned innate antioxidative enzyme defence system: pollution, tobacco, radiation, countless preservatives in our food etc. But we can protect ourselves with substances that help us fight against oxidation: hydro-soluble vitamins (vitamins B1, B6, B12 and C), fat-soluble vitamins (Vitamins E and A), bio-carotenoids and polyphenols. Reactive oxygen species are also produced in plants during photosynthesis, the process whereby plants obtain energy from the sun.



Like us, plants also need to defend themselves in order to be able to survive the intense light which produces oxidation. This is the function of carotenoids, bioflavonoids and other substances that protect plants from the oxidation generated.

Everyone knows that if tomatoes, broccoli, oranges or apples did not contain antioxidant substances, they would not keep, they would simply rot. If we include these nutrients in our diet, they stimulate our antioxidant system and reduce what is known as oxidative stress.

Anti-oxidant help is always necessary, especially when our metabolism has been weakened, for example, by physical over-exertion (pregnancy, growth, sports competitions, etc.), or when our bodies are trying to recover from an infection or an operation, or when we are simply entering a transitional stage (andro- and menopause).

This search for antioxidative nutrients may be why those fruits and vegetables which are most resistant to the impact of light energy from the Sun are also those to which we are most attracted.

The concentration of antioxidants provided by a fruit or vegetable is highest at maturity, which is when we should consume them. Their attractive colours are a clear sign of the high concentration of substances they contain with strong antioxidant properties such as carotenoids, polyphenols, resveratrols, etc.

Here, special mention should be made of the pomegranate, because it contains more antioxidants than other fruits which are thought to be antioxidant-rich, such as citrus fruits or bilberries, and more even than green tea or red wine.



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### 3. Pomegranate and health

The pomegranate (*Punica granatum* L.), an ancient, mystical and distinctive fruit, was praised in antiquity in various works, such as the Bible, the Jewish Torah and the Babylonian Talmud, as a sacred fruit which promoted fertility, abundance and good luck. It also appeared in Egyptian and Greek ceremonies, art and mythology, and was the personal emblem of the Roman Emperor Maximus.



In addition to these historical antecedents, the pomegranate is used by several types of medicine for the treatment of a variety of diseases. In Ayurvedic (traditional Indian) medicine, the pomegranate is used to treat parasites, diarrhoea and ulcers and is considered to have depurative properties. The pomegranate also serves as a remedy for diabetes in Unani medicine (also practiced in India).

The great interest shown nowadays in the medicinal and nutritional benefits of the pomegranate began in 2000, and since then, more than 200 articles have been written describing the beneficial health properties of the pomegranate and its derived products. In contrast, in the period between 1950 and 1999, only about 25 scientific papers were published on this topic.



The pomegranate has a broad range of potentially therapeutic uses, including treatment and prevention of cancer, cardiovascular disease, Alzheimer's disease, inflammatory disease, oral and skin disease, obesity, erectile dysfunction and diarrhoea.



Below, details are given of the main results of a review of the scientific literature until the year 2011, describing the various therapeutic applications of the pomegranate mentioned above.

### 3.1. Anti-cancer and anti-tumour properties

Numerous studies have been conducted to assess the efficacy of the pomegranate and its derived products, which have been shown to have a potent antioxidant action as an anti-proliferative, anti-invasive and pro-apoptotic agent in diseased cells and in animal models (Lansky and Newman, 2007; Syed et al., 2007; Hong et al., 2008; Hamad and Al-Momene 2009).

Hong et al. (2008) demonstrated that pomegranate juice and extracts are potent inhibitors of cell growth, even more potent than some polyphenols when considered in isolation, suggesting the existence of a synergistic effect with the phytochemicals present in the pomegranate and its extracts.

A pomegranate extract applied as a topical pre-treatment reduced the incidence of tumours in mice from 100% to 30%, and also increased the latency in tumour development from 9 to 14 weeks (Afaq et al., 2005). Albretch et al. (2004) studied the effects of pomegranate oil, the polyphenols in the peel and membranes and the polyphenols from fermented juice, on prostate cancer. All of these agents individually prohibited the proliferation in vitro of tumour cells in human LNCaP, PC-3 and DU 145 cells, demonstrating that pomegranate-derived products have a clear anti-tumour action in the case of prostate cancer.

Kohno et al. (2004) demonstrated that the administration of pomegranate seed oil in the diet inhibited the incidence and proliferation of colon adenocarcinomas in rats.

The inhibition of colon tumours by the seed oil is associated with an increase in conjugated linoleic acid in the colonic mucosa and liver. There is scientific evidence showing that pomegranate juice suppresses the expression of COX-2 induced by TNF- $\alpha$ , the NF-kB pathway and activation of Akt. Certain bioactive components present in pomegranate juice, such as anthocyanins and flavonols, may be responsible for reducing the proliferation of cancer cells (Adams et al., 2006). Seeram et al. (2005b) described the powerful anti-proliferative action of pomegranate juice against various tumour cell lines, with a large inhibition effect of between 30% and 100%.



Pomegranate juice, ellagic acid and punicalagin induced apoptosis (genetically regulated cell death) of HT-29 colon cells, but in HCT116 colon cells, only ellagic acid and punicalagins contributed to apoptosis whereas pomegranate juice did not (Seeram et al., 2005b).

Therefore, pomegranate peel extract, which is rich in these compounds (punicalagins and ellagic acid) may have potential for the treatment of colon cancer in the future. Lansky et al. (2005b) reported that certain components present in the pomegranate significantly inhibited cancer cell invasion of the prostate in vitro (PC-3 cells).

Fjaeraa and Nanberg (2009) showed that ellagic acid induced apoptosis by measuring DNA breakage and alteration in the cell cycle. González-Sarrías et al. (2009) suggested that ellagic acid and its metabolites, such as urolithins A and B, may contribute to the prevention of colon cancer. Hong et al. (2008) showed that pomegranate juice and its extracts have a potent ability to stop proliferation and stimulate apoptosis in prostate cancer cells. More recently, Koyama et al. (2010) demonstrated that the use of pomegranate extracts with stabilised ellagitannin content (punicalagin) to treat LAPC4 prostate cells inhibited proliferation by 37% and led to apoptosis. From the foregoing, we can conclude that the pomegranate and its derived products have a beneficial effect against cancer and tumours due to the high content of compounds such as anthocyanins, ellagic acid and punicalagins. Furthermore, the cases studied have demonstrated that pomegranate products and extracts have different effects, as has administration of the compounds responsible individually or in isolation. Therefore, the use of pomegranate and its derived products is highly dependent on the type of clinical condition. It is important to emphasise that all the cases mentioned above refer to the prevention and treatment of cancer, and never to a cure for cancer or tumours. Due to their phytochemical composition, the pomegranate and its derived products are highly recommended for the prevention and treatment of cancer.

A summary is given below of the main actions or anti-tumour effects of the pomegranate and its products against different cancers (breast, colon, prostate, etc.).

**Table 4.** Main antitumoral effects of pomegranate fruit.

- *Antiproliferative: Stopping tumor growth.*
- *Induces apoptosis: induced cell death (suicide).*
- *Inhibits NF- $\kappa$ B nuclear factor (NF- $\kappa$ B): regulates expression of more than 200 genes (immune system, cell proliferation, tumor invasion, metastasis).*
- *Anti-angiogenesis: new blood vessel formation.*
- *Inhibits tumor invasion (metalloproteinases).*

**Source:** Dr. Gilberto E. Chéchile Toniolo (2011). II Symposium Internacional sobre el Granado, Madrid, España.

### 3.2. Prevention of cardiovascular disease

One of the major risk factors for developing coronary heart disease is dyslipidemia, which is characterised by elevated levels of low-density cholesterol (LDL) and/or low levels of high density cholesterol (HDL) (Esmailzadeh and Azadbakht, 2008). Cholesterol is divided into two types: low density cholesterol (LDL), or bad cholesterol, and high density lipoprotein (HDL), or good cholesterol. Good cholesterol (HDL) is so called because it is thought to help reduce cholesterol levels in the blood; high density cholesterol is produced naturally by the body itself and removes cholesterol from the artery walls, returning it to the liver. Bad cholesterol (LDL) accumulates on the artery walls, forming plaques which hinder the flow of blood to the heart. Therefore, excessively high levels of LDL cholesterol will increase the risk of cardiovascular disease. It is thought that LDL oxidation contributes to atherosclerosis and cardiovascular diseases (Heinecke, 2006).



Several in vitro studies have been conducted with animals and humans to analyse the effect of various pomegranate-related products on the prevention and mitigation of atherosclerosis and LDL oxidation (Aviram et al., 2000; Sezer et al., 2007; Basu and Penugonda 2009; Davidson et al., 2009; Fuhrman et al., 2010). Aviram et al. (2000) analysed the effect of pomegranate juice consumption in healthy men on LDL oxidation and found that LDL levels were reduced and HDL activity was increased by around 20%. Sezer et al. (2007) compared the total polyphenol content and antioxidant action of pomegranate wine and red wine.

Both polyphenol content and antioxidant action were higher in pomegranate wines than in red wines. Both wines produced a reduction in LDL; however, due to its higher antioxidant ability, the decrease induced by pomegranate wine was greater than that caused by red wine, namely by 24% for pomegranate wine and 14% for red wine. Esmailzadeh et al. (2006) administered 40 g of concentrated pomegranate juice to diabetic and hyperlipidemic (elevated cholesterol and triglyceride levels) patients for 8 weeks. By the end of the study, triglyceride and HDL levels had not changed. However, total cholesterol level was reduced by 5.43%, LDL by 9.24%, total cholesterol/HDL ratio by 7.27% and the LDL/HDL ratio by 11.76 %.

Basu and Penugonda (2009) summarised the main antiatherogenic mechanisms of pomegranate juice as follows:



- It increases the antioxidant action of blood serum, reducing plasma lipids and lipid peroxidation
- It reduces LDL oxidation
- It reduces the size of atherosclerosis lesions
- It reduces systolic blood pressure

Thus, pomegranate juice intake has a beneficial effect on the progression of atherosclerosis and consequently on the risk of developing coronary heart disease.

Dr. Aviram conducted numerous experiments with healthy and hypertensive patients, to whom he administered pomegranate juice for different periods of time. As a result of these studies, it was concluded that blood pressure was reduced by up to 36% after two weeks of treatment with pomegranate juice. This reduction has been attributed to the high antioxidant power of pomegranate polyphenols (Aviram and Dornfeld, 2001; Aviram et al. 2004).

### 3.3. Inflammatory properties

Inflammation, the human body's first physiological defence, can protect us from lesions caused by wounds and poisoning. This defence system can eliminate infectious microorganisms, eradicate irritations and maintain normal physiological functions. However, overexposure to inflammation can cause physiological dysfunctions such as asthma and arthritis (Lee et al. 2010). There is considerable scientific evidence demonstrating the anti-inflammatory action of the pomegranate and its derived products (Lansky and Newman, 2007; Shukla et al., 2008; Larrosa et al., 2010, Lee et al., 2010). Some pomegranate extracts, particularly the extract of cold-pressed seeds, inhibit the action of cyclooxygenase and lipoxygenase enzymes in vitro. Cyclooxygenase is an important enzyme in the conversion of arachidonic acid to prostaglandins, which are in turn important mediators of inflammation. This latter, therefore, is significantly inhibited by the ingestion of pomegranate extracts. Lipoxygenase mediates the transformation of arachidonic acid into leukotrienes, which also mediate inflammation, and thus inflammation is also inhibited by pomegranate seed extract (Thomas-Barberán, 2010).



Boussetta et al. (2009) showed that the punicalic acid and conjugated fatty acid present in pomegranate seed oil has a proven anti-inflammatory effect in vivo and therefore limits lipid peroxidation. Lee et al. (2010) analysed four hydrolysable tannins, among which were punicalagin and punicalin, all isolated from the pomegranate. Each of these compounds at different doses significantly inhibited the production of nitrogen monoxide (NO) in vitro, producing an anti-inflammatory effect.

De Nigris et al. (2007) demonstrated that administration of pomegranate juice and pomegranate extracts to obese rats significantly reduced the expression of certain genetic markers which influence cardiovascular inflammation.



Subsequently, Romier-Crouzet (2009) obtained similar results with pomegranate juice and pomegranate extracts, and observed inflammatory prevention due to high ellagic acid content. Lastly, Larrosa et al. (2010) found that administration of pomegranate extracts reduced prostaglandin levels in colonic mucosa, again due to the high levels of ellagic acid present in the pomegranate.



### 3.4. The anti-diabetic properties of the pomegranate



Diabetes is the most common metabolic disease in the world, affecting millions of people. According to the International Diabetes Federation, the estimate for 2025 is that this disease will affect about 333 million people. Diabetes ranks third in prevalence after cardiovascular disease and cancer.

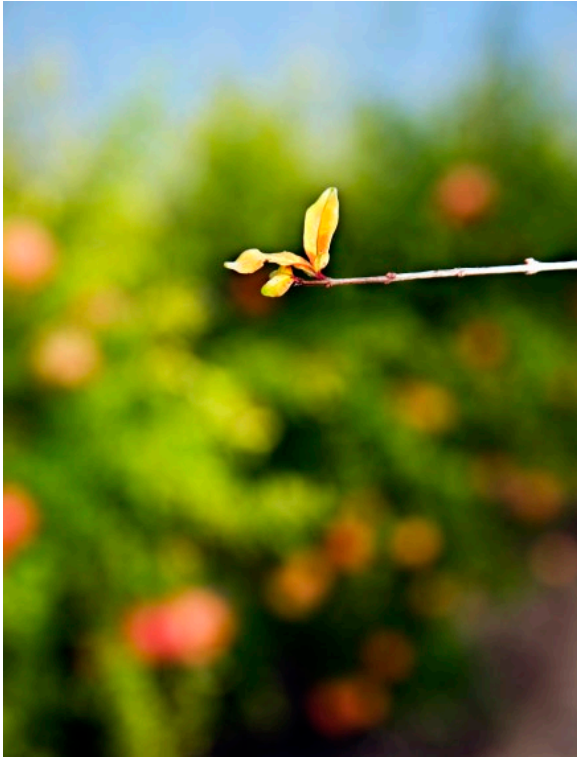
This is where the pomegranate and its derived products can play a key role, and there is a significant body of scientific evidence supporting

the anti-diabetic properties of this fruit (Huang et al., 2005; Li et al., 2005; Katz et al., 2007; Parmar and Kar, 2007; Li et al., 2008; Bagri et al., 2009).

Diabetes is associated with high levels of oxidative stress and the development of atherosclerosis. It seems clear that the antioxidant compounds present in the pomegranate can exert a significant effect on diabetes.

For example, Katz et al. (2007) demonstrated the hypoglycemic action of pomegranate flowers, seeds and juice. The mechanisms by which the pomegranate and its derived products exert this effect remain unknown. However, although there are numerous hypotheses about these mechanisms, all seem to suggest the inhibition of certain genetic markers and certain compounds that induce oxidative stress. For example, Li et al. (2005) suggested that the anti-diabetes mechanism of pomegranate flower extract was inhibition of the  $\alpha$ -glucosidase enzyme. Pamar and Kar (2007) demonstrated that administration of pomegranate peel extract normalised the adverse effects of a compound that induces diabetes in mice.





Mcfarlin et al. (2009) studied the effect of pomegranate seed oil on fat accumulation in mice and observed an improvement in insulin sensitivity.

All these findings, together with those related to cardiovascular disease, suggest that the pomegranate and its derived products have a beneficial effect on diabetes and on cardiovascular disease in diabetic patients, since their effects on heart disease have also been established.

The main components with anti-diabetic properties are the polyphenols; these compounds affect blood glucose through numerous mechanisms, including the inhibition of glucose absorption through the gut or via peripheral tissues.

The most probable anti-diabetic mechanism is inhibition of the  $\alpha$ -glucosidase enzyme. Other mechanisms may include the reduction of blood sugar level due to absorption by peripheral tissues rather than through the intestine (Scalbert et al., 2005).

### 3.5. Prevention of oxidative deterioration

Oxidative deterioration is a very topical issue and a clear example of this is that the action of fruit and vegetables against oxidative deterioration (high content of antioxidant compounds) is one of the properties or characteristics most highly valued by consumers. Generally, an antioxidant can be defined as a natural or artificial substance with the ability to protect a biological system by neutralising free radicals such as oxygen, nitrogen and lipid radicals (Cano and Arnao, 2004).

These antioxidant properties endow fruit and vegetables with beneficial health properties, protecting against or reducing the risk of certain degenerative diseases (Brandt et al., 2004, Chen et al., 2007). Consequently, antioxidant content has become an important quality parameter of fruit and vegetables in recent years.

Compounds with antioxidant properties include anthocyanins and other phenols (Espin et al., 2007; Dorais et al., 2008), carotenoids (Perera and Yen, 2007) and vitamins A, C and E (Hoursome et al., 2008).

The compounds responsible for the potent antioxidant action of the pomegranate and its derived products have been studied by many researchers, using both in vitro and in vivo models. The antioxidant action in vitro of the pomegranate and its derived products has been assessed in several studies (Naveena et al., 2008; Cam et al., 2009; Mousavinejad et al., 2009; Tezcan et al., 2009).

Tzulker et al. (2007) determined that the high antioxidant capacity of the pomegranate and its derived products is due to the presence of punicalagins, and not of anthocyanins as previously thought.

The mechanisms of antioxidant action in vivo remain unclear, although it is known that these mechanisms act on biological matrices in a very complex way. Madrigal-Carballo et al. (2009) suggested that the pomegranate's phenolic compounds undergo a redox reaction, since the hydroxyl groups of the phenolic molecules donate a hydrogen molecule to reducing agents. Other researchers (Amarrowicz et al., 2004) have reported that the antioxidant action of phenolic compounds is due to their ability to capture free radicals and chelating metal cations.

### 3.6. Prevention of skin damage

The process of photoageing includes molecular and structural damage of the skin, such as inflammation, decreased collagen synthesis, thickening or proliferation of the epidermis (surface of the skin), incomplete degradation of collagen fragments and protein oxidation.

All these changes translate clinically into a thin skin with wrinkles, yellowish discolouration, round or oval white spots or irregular dark spots and telangiectasia (visible blood vessels), among others.

These are also accompanied by the appearance of benign lesions such as seborrheic keratoses or lentigines (coffee-coloured lumps or spots), sebaceous hyperplasia and premalignant lesions such as actinic keratoses.

Skin damage occurs as a result of natural aging. However, exposure to the sun also induces major damage to the skin. Prolonged exposure to ultraviolet rays can cause numerous problems, such as skin cancer.

Studies conducted with different pomegranate extracts (Aslam et al., 2006) suggest that pomegranate peel extracts promote regeneration of the dermis, while seed oil extracts regenerate the epidermis.



Pacheco-Palencia et al. (2008) described the protective properties of pomegranate extracts against UVA and UVB radiation due to a reduction in the generation of reactive oxygen species (ROS). Afaq et al. (2009) suggested that UVB radiation-induced skin damage can be reduced by the intake of products derived from pomegranate peel and seeds.

All these scientific results demonstrate the excellent ability of pomegranate peel and seed extracts to protect the skin.

### 3.7. Antimicrobial properties of the pomegranate and its derived products

Many food preservation technologies, some of which have been in use for a long time, protect food from alteration by microorganisms. Thus, microorganisms can be inhibited by refrigeration, reduced water activity, acidification, modified atmosphere packaging, by non-thermal treatments or by addition of antimicrobial compounds.

Antimicrobial products for food use consist of chemical compounds which are added or already present in food that kill or retard the growth of microorganisms, thus increasing resistance to alterations in quality or safety. The main targets of antimicrobial agents are the microorganisms that cause food poisoning (infectious agents and toxin producers) or that alter foods and whose metabolic end products (catabolites) or enzymes cause bad odours, unpleasant flavours, texture problems, changes in colour and/or health risks (Davidson and Zivanovic, 2003).



The use of synthetic and chemical agents with considerable antimicrobial properties as microbial growth inhibitors is one of the oldest techniques on earth for the control of microbial growth, and is therefore a suitable preservation technique (Viuda-Martos et al., 2008).

At present, there is a tendency to replace these chemicals with possible natural treatments by using agents present in fruits, vegetables and herbs. The principal natural antimicrobial agents are the essential oils obtained from herbs and spices. Essential oils derived from plants are known for their high antimicrobial action against a broad range of bacteria and fungi. In addition, they can enhance the antioxidant action of the treated products themselves (Ayala-Zavala et al., 2005).

The antimicrobial action of the pomegranate and its derived products has been demonstrated in numerous studies which have reported the inhibition of the activity of numerous microorganisms (Reddy et al., 2007; McCarrell, 2008; Al-Zoreky 2009; Choio et al., 2009; Gould et al., 2009).

Reddy et al. (2007) found that different pomegranate extracts in different solvents (water, ethanol, etc.) presented a significant antimicrobial action against *E. coli*, *Pseudomonas aeruginosa*, *Candida albicans*, *Cryptococcus neoformans* and *S. aureus*. Al-Zoreky (2009) showed that the growth of *Listeria monocytogenes*, *S. aureus*, *E. coli* and *Yersinia enterocolitica* is significantly inhibited by pomegranate peel extract. Choi et al. (2009) investigated the in vivo and in vitro effect of the application of different concentrations of pomegranate peel extract on skin to inhibit the growth of *Salmonella*, and found that the minimum dose was 62.5 mg/L.

In general, the potent inhibitory action of the pomegranate and its derived products is attributed to the high concentration of compounds such as polyphenols, tannins and anthocyanins. Very recent studies have found that the use of derivatives and by-products as food additives not only improves antioxidant capacity but also ensures total safety due to the considerable ability of the pomegranate and its extracts to inhibit the activity of microorganisms that cause food deterioration (Navarro et al., 2011; Viuda-Martos et al., 2011b).

### 3.8. Effects of the pomegranate on oral health

Maintaining optimal dental health is not only important to preserve the appearance and function of teeth, but also to protect against cardiovascular disease. Science now recognises that chronic inflammatory periodontal disease is closely related to the worsening of cardiovascular disease (Dumitrescu, 2005).

Di Silvestro et al. (2009) showed that a mouthwash based on pomegranate extracts effectively reduced the amount of dental plaque microorganisms. This beneficial effect is mainly attributed to the clear action of polyphenol and flavonoid compounds against the development of gingivitis. Gingivitis is a bacterial oral disease that produces inflammation and bleeding of the gums, and is caused by food debris caught between the teeth.

Menezes et al. (2006) studied the effect of a pomegranate extract on dental plaque microorganisms. They found that it was highly effective, reducing the number of microorganisms by 84%.

Sastravaha et al. (2005) demonstrated the effectiveness of a gel containing pomegranate extracts as an additional, complementary treatment for standard periodontal therapy. Badria and Zidan (2004) showed that pomegranate flavonoids possess an antibacterial action in vitro against the microorganisms responsible for gingivitis.

Fewer studies have been conducted on the effect of the pomegranate and its derived products on oral disease compared to research on diseases such as cancer or cardiovascular disease. The cases cited above are the most recent examples of research on this question.

Consumption of pomegranates, either as fresh fruit, derived products or even in extract form, is also enjoyable because of the delicious flavour, making the pomegranate a perfect solution for proper oral health.

**Table 5** summarises some of the most relevant studies.

Study model	Clinical condition	Part of the plant	Dose	Time (days)	Effect	Reference
In vivo	Diabetes	Flowers	250 mg/(kg d)	21	Reduces total cholesterol, triglycerides, LDL cholesterol and increases HDL cholesterol	Bagri <i>et al.</i> 2009
In vivo	Diabetes	Peel	20 mg/(kg d)	28	Increases activity of enzymes involved in diabetes, liver and kidney	Alyhunibat <i>et al.</i> 2010
In vivo	Healthy	Peel	50 mg/(kg d)	28	Antioxidant protection from numerous enzymes	Murthy <i>et al.</i> 2002
In vivo	Healthy	Juice	-	28	Antioxidant protection from numerous enzymes	Faria <i>et al.</i> 2007
In vivo	Healthy	Ellagic acid	60 mg/(kg d)	45	Reduces cholesterol, fatty acids, triglycerides, and phospholipids	Devipriya <i>et al.</i> 2008
Humans	Healthy	Juice	250 mL/d	28	Reduces lipid and LDL cholesterol oxidation	Guo <i>et al.</i> 2008
Humans	Healthy	Fruit	100 g	10	Increases the antioxidant capacity of plasma	Hajimahmoodi <i>et al.</i> 2009

**Table 5.** in vivo studies conducted to evaluate the beneficial effects of the pomegranate on laboratory animal and human health.

Study model	Clinical condition	Part of the plant	Dose	Time (days)	Effect	Reference
In vivo	Healthy	Peel	500 mg/kg	36 h	Anti-inflammatory properties against oedema and granulomas	Al Yahya (2005)
Humans	Healthy	Ellagic acid extract	100 mg/day	28	Inhibits ultraviolet radiation damage to pale skin	Kasai <i>et al.</i> , (2006)
Humans	Healthy	All Parts	-	-	Inhibits allergic reactions	Park <i>et al.</i> , (2008)
In vivo	Diabetes	Flowers	400 mg/kg	45	Reduces lipid oxidation and glucose levels	Manoharan <i>et al.</i> , (2009)
In vivo	Cancer	Fruit	-	240	Reduces carcinogenic lung tumours	Khan <i>et al.</i> , (2007)
In vivo and humans	Cancer	Fruit	50-150 µg/ml	3	Inhibits growth of lung tumours	Khan <i>et al.</i> , (2006)
Humans	Diabetes	Juice	40 g	56	Reduces LDL cholesterol levels	Esmailzadeh <i>et al.</i> , (2006)



Study model	Clinical condition	Part of the plant	Dose	Time (days)	Effect	Reference
In vivo	Healthy	Peel and leaves	20 mg/ml	16	Faster wound healing	Soni <i>et al.</i> , (2011)
In vivo	Cancer	Fermented juice	-	-	Retards metastasis of mammary cells	Khan <i>et al.</i> , (2007)
In vivo	Healthy	Juice	-	45	Inhibits damage to kidney cells and oxidative stress	Ilbey <i>et al.</i> , (2009)
In vivo	Diarrhoea	Peel	100-400 mg/kg	-	Reduces gastroenteritis	Qnais <i>et al.</i> , (2007)
Humans	Healthy	Fruit	-	1	Antibacterial activity against dental plaque microorganisms	Menezes <i>et al.</i> , (2006)
In vivo	Atherosclerosis	Juice	-	60	Powerful anti-atherosclerosis action	Kaplan <i>et al.</i> , (2001)
Humans	Healthy	Juice	-	2	Presence of urolithin in human urine	Seeram <i>et al.</i> , (2006)

Study model	Clinical condition	Part of the plant	Dose	Time (days)	Effect	Reference
In vivo	Diabetes	Seed oil	-	-	Weight loss and reduction in type 2 diabetes	McFarlin <i>et al.</i> , (2008)
Humans	Healthy	Juice	300 ml/d	14	Reduces systolic pressure	Carpenter <i>et al.</i> , (2009)
Humans	Metabolic syndrome	Juice	240 ml	30	Improves endothelial function	Hashemi <i>et al.</i> , (2010)
In vivo	Diabetes	Flowers	500 mg/kg	42	Reduces cardiac fibrosis	Huang <i>et al.</i> , (2005)
In vivo	Cancer	Seed oil and fermented juice	-	-	Seed oil is better than fermented juice against breast cancer	Mehta <i>et al.</i> , (2004)
In vivo	Cancer	Fruit	50-150 mg/ml	3	Inhibits cancer cell markers	Khan <i>et al.</i> , (2007)
In vivo	Cirrhosis	Peel	50 mg/kg	28	Prevents cirrhosis, has anti-oxidative properties and reduces gallbladder	Toklu <i>et al.</i> , (2007)

Study model	Clinical condition	Part of the plant	Dose	Time (days)	damage	Reference
					Effect	
In vivo	Diabetes	Peel	600 mg/kg	1	Beneficial effects against diabetes	Najafzadeh <i>et al.</i> , (2011)
In vivo	Cancer	Peel extract and arils	0.8 mg	1	Prevents multifocal development and survival of prostate cancer cells	Sartippour <i>et al.</i> , (2008)
In vivo	Influenza	Seed extract	175 mg/KG	28	Considerably reduces the concentration of the influenza virus	Figueroa <i>et al.</i> , (2006)
In vivo and humans	Cardiovascular disease	Juice	-	-	Inhibits the development of atherosclerotic lesions due to the protection of LDL against oxidation	Aviram <i>et al.</i> , (2002)
In vivo and humans	Healthy	Juice	-	98	Anti-atherogenic effects in humans and anti-atherosclerotic effects in mice	Aviram <i>et al.</i> , (2000)
Humans	Hypertension	Juice	50 ml/day	14	Inhibits oxidative stress	Aviram <i>et al.</i> , (2001)
In vivo	Diabetes	Peel and seed	200	14	Powerful anti-diabetic action	Das <i>et al.</i> , (2009)

Study model	Clinical condition	extract	mg/kg/day		Effect	Reference
		Part of the plant	Dose	Time (days)		
Humans	Carotid artery stenosis	Juice	-	3 years	Reduces systolic blood pressure	<a href="#">Aviram et al., (2004)</a>
In vivo	Healthy	Peel	100-1000 mg/kg/day	35	Inhibits the proliferation of melanocytes and melanin	<a href="#">Yoshimura et al., (2005)</a>
In vivo	Healthy	Flowers	50 mg/kg	1 h	Powerful analgesic effect	<a href="#">Guno, C (2008)</a>
In vitro and In vivo	Salmonella	Peel	3.9-2000 mg/ml	4	Powerful anti-bacterial action of ethanol extracts	<a href="#">Choi et al., (2011)</a>
Humans	Healthy	Ellagic acid	100-200 mg/day	28	Oral administration lightens skin affected by UV radiation	<a href="#">Kasai et al., (2006)</a>
In vivo	Healthy	Peel	50 mg/kg/day	20	Powerful protective effect against radiation therapy	<a href="#">Toklu et al., (2009)</a>
In vivo	Healthy	Flowers	50-100	-	Powerful antihistamine action and	<a href="#">Barwal et al., (2009)</a>

Study model	Clinical condition	Part of the plant	mg/kg/day		potential role against asthma	
			Dose	Time (days)	Effect	Reference
In vivo	Diarrhoea	Peel	10-400 mg/kg/day	4 hours	Anti-diarrhoea effect and powerful cytotoxic action	<a href="#">Hasan et al., (2009)</a>
In vivo	Cancer	Seed oil	5%	140	Effective anti-cancer agent for skin	<a href="#">Hora et al., (2004)</a>
Humans	Cancer	Extract	-	-	Induces apoptosis when combined with genistein	<a href="#">Lous Jeune et al., (2005)</a>
Humans	Cancer	Juice	-	28	Prevents pro-carcinogenic activation	<a href="#">Faria et al., (2007)</a>
Humans	Cancer	Peel	25-300 µg/ml	3	Reduces the proliferation of breast cancer cells	<a href="#">Dikmen et al., (2011)</a>
Humans	Erectile dysfunction	Juice	-	28	Suggests that long-term treatment is effective	<a href="#">Forest et al., (2007)</a>
In vivo	Obesity	Leaf extract	800 mg/kg	35	Inhibits development of obesity	<a href="#">Lei et al., (2007)</a>

Study model	Clinical condition	Part of the plant	Dose	Time (days)	Effect	Reference
In vivo	Healthy	Seeds	250-500 mg/kg/day	21	Cognitive deficits induced by scopolamine	Kumar <i>et al.</i> , 2009
In vivo	Healthy	Polyphenol extract	4.8 mg/day	1	Visibly reduces neonatal brain damage	West <i>et al.</i> , 2007
In vivo	Myocardial Infarct	Juice	100-300 mg/kg/day	21	Alleviates cardiotoxic effects and may be valuable for the treatment of micro strokes	Mohan <i>et al.</i> , 2010
Humans	Heart disease	Juice	240 ml/day	90	Daily consumption of pomegranate juice improves acute myocardial ischaemia	Summer <i>et al.</i> , (2005)
In vivo	Menopause	Juice and extract	-	14	Anti-depressant action and less bone loss	Mori-Okamoto <i>et al.</i> , (2004)
In vivo	Healthy	Juice	1 ml	49	Significant improvement in the quality of semen	Türk <i>et al.</i> , (2008)

### 3.9. Other health-related properties of the pomegranate

#### 3.9.1. Effects of the pomegranate against diarrhoea

Only two studies have been conducted recently that demonstrated the effect of pomegranate peel extract in the prevention of diarrhoea. Both experiments were conducted on laboratory rats; after the administration of a pomegranate peel extract, it was observed that both the number of bowel movements and the mass of the same were reduced. The studies were conducted by Qnais et al. (2007) and Olapour et al. (2009). The dose proposed by the latter for the treatment of this condition was 400 mg per kg of body weight.

#### 3.9.2. Effects of the pomegranate on sperm quality and erectile dysfunction

The basic purpose of semen is reproduction, since it acts as a “vehicle” for transporting sperm to the female reproductive tract. Although orgasm and sexual pleasure accompany the ejaculation of semen, erection and orgasm are controlled by independent mechanisms, thus the emission of semen is not essential for the enjoyment of sex.

Türk et al. (2008) found that consumption of pomegranate juice produced an increase in the concentration of sperm in the epididymis, an increase in mobility and a greater density of spermatogenic cells; it also reduced the amount of poor quality semen compared to the reference or control group.

In a more recent study, this same research group suggested that ellagic acid has a protective effect on testicles and sperm. This effect may be related to the potent action of ellagic acid against oxidative stress (Türk et al., 2010).

Erectile dysfunction is the repeated inability to develop or maintain an erection which is firm enough for successful sexual intercourse. In a study carried out by Forest et al. (2007), it was found that after four weeks of consumption of pomegranate juice, patients showed better erectile function than other patients who had been given a placebo.

### 3.9.3 Effects of the pomegranate on obesity

Obesity is a chronic disease of multifactorial origin that is characterised by the excessive accumulation of fat or general hypertrophy of adipose tissue in the body. Obesity, therefore, refers to a situation where the natural energy reserve of humans and other mammals, stored as body fat, increases to a point where it is associated with multiple complications, such as certain health conditions or diseases and increased mortality.

The World Health Organisation's (WHO) definition of obesity is when the Body Mass Index (BMI), which is a calculation based on an individual's height and weight, is equal to or greater than 30 kg/m<sup>2</sup>. Another sign of obesity is an abdominal perimeter greater than or equal to 102 cm in men and 88 cm in women.

Obesity forms part of the metabolic syndrome, and is a known risk factor. In other words, it increases the risk of developing various diseases, particularly cardiovascular disease, type 2 diabetes mellitus, sleep apnoea, stroke, osteoarthritis, and some forms of cancer and dermatological and gastrointestinal ailments.

Although obesity is an individual clinical condition, it has become an increasingly serious public health problem, and the WHO believes that "obesity has reached epidemic proportions worldwide, and at least 2.6 million people die each year because of obesity or overweight. Although previously considered a problem confined to high income countries, obesity is now also prevalent in low and middle income countries".



<i>in vivo</i> studies	Part of the plant	Time (days)	Effect	Reference
<b>Rats</b>	20% pomegranate extract (6% punicalagin)	37	Weight loss at baseline	<u>Cerdá</u> <i>et al.</i> 2003
<b>Mice</b>	Leaves	-	On a high fat diet, leaf extract reduced the development of	Lei <i>et al.</i> 2007

**Table 6.** Studies to assess the effect in vivo of the pomegranate or its extracts on obesity.

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