

Ancient Roots of Modern Medicines: Pomegranate

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ABSTRACT

Studies conducted over the past decades on plants mentioned in the literature or traditionally used for various ailments show that there has been exponential growth in the field of herbal medicine in recent years, resulting in Both of these drugs are in development, indicating their growing popularity. Their natural origin and fewer side effects, as well as in developed countries. I was. This review was conducted using the method of systematic narrative review of different parts of the pomegranate fruit. We are also looking at new research into the various uses and activities of pomegranate.

Key Words: Pomegranate, Primary Metabolites, Pomegranate Skin, Anthocyanins, Cancer

INTRODUCTION

In last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects medicinal importance of natural products those derived from plants and animals proceed human history by thousands of years. Pomegranate [punicagranatum] is an important and interesting fruit tree that cultivated in many parts of the world. [1], [3] The pomegranate fruit is fleshy berry with a nearly round shape, crowned by prominent calyx. The colour of the juicy layer can vary from white to deep red various parts used as a treatments against various ailments including stomachs and bacterial infections most of the therapeutic effects of the pomegranate fruit attributed to its secondary and primary metabolites, such as polyphenols, including flavonoids, anthocyanins, hydrolyzable tannins, fatty acids, and lipids. Pomegranate juice [PJS] are well known for their beneficial properties, they carry out antioxidant, antimicrobial, anticancer, cholesterol lowering, anti-atherosclerotic, and anti-diabetic activities as anthocyanin– rich food, pomegranate juice have been use at various concentration to enhance the colour, taste, and aroma properties; to increase the health – benefits properties and to improve shelf lives of the fortified foods. Numerous pharmacological studies have been associated with regular ingestion of PJS in fruit as a functional food. Anthocyanins, ellagic acid derivatives, and hydrolyzable tannins have been shown to be responsible for the antioxidant activity of pomegranate juice. Anthocyanins are important pigments in flowers and fruits. They fight pollinators and seed dispersal and protect plant tissues from photosynthetic photoinhibition and oxidation. In the case of pomegranate fruit, the skin in particular has been reported to have relatively higher antioxidant activity than the seeds and pulp. Antioxidants slow the development of serious degenerative diseases. Pomegranate was

mentioned by pharaohs and used to treat intestinal parasites. Pomegranate blossoms were used to treat stomach ulcers, to treat chronic diarrhea, and to treat cancer. Overall, pomegranates have been used for thousands of years as medicines for various ailments [2]

I. Early history of natural origin

The oldest medicinal manuscript, written in Mesopotamia, circa 2600 B, had documented thousands of clay tablets in cuneiform myrrha, and papaversomnifera which are still used in treatments of illness; extending from minor cough to sever inflammation and infections. The ancient Egyptian, eberspapyru, dated around 1500 Bc, documented thousands of complex medicinal prescription and the use of more than hundreds of natural products including aloe vera, boswelliacarteri, and ricinuscommunis .[31] over the same millennia, natural products derived medicines were already flourished in the orient. Ayurvedia- written on the holy pulp of betulautilis presumed to be the oldest written medicinal manuscript which described thousands of medicinal herb—précised in millions of poetic hymns. Simultaneously, sushruta [circa 600 BC] renowned Indian physician and surgeon of those millennia, apart from using surgical practices, also reported the medicinal importance of plants and animal species. Comparatively, these is very little known about any written earlist manuscripts of ancient Chinese herbal medicine but the most eminent encyclopedia of ‘chinese material medica’ listed around 6000 drugs , among them 4800 therapeutic agents are from plant origin. In herbal medicine, species such as Scutellaria baicalensis and Evodiartaecarpus, known as zoujinwan, have long been used to treat stomach ailments, but more recently, these activities have been enhanced by berberine, calistidine, limonene, rutecapine, and obacunone. It is suggested that it may be The most potent is Helicobacter pylori, an inhibitor of the intestinal flora. More importantly, these plant species are still used as antibiotics and frontline anti-ulcer agents. It has been used in ancient Chinese medicine for thousands of years, and although it has no antipyretic or anti-inflammatory properties, it treats Alzheimer's disease because it is a potent inhibitor of the enzyme acetylcholinesterase. [30]

II. History, naming of pomegranate

Botanically, the pomegranate [p. grantum] is the subclass rosidae, order fruit such as the guva [psidium sp.] and feijoa [feijoasp.] however, pomegranate is unusual in being one of only two species in its genus, punica which is the sole genus in the family punicaceae. Recent molecular studies suggest a taxonomic reconsideration might place punica within the lythraceae[Graham et al., 2005] . the second species in punica, p. protopunica, is found only on the island of Socotra ,of the Arabian peninsula, and is considered an ancestral species or an independent evolutionary path. The name punica is the feminized roman name for carthage, the ancient city in northern Tunisia from which the best pomegranate came to Italy.[4]

The pomegranate is one of the ‘seven kinds’ mentioned in the bible, the Koran, and in Buddhist and Chinese arts. It is estimated that pomegranate might have been introduced into culture about 5000 years ago. In different regions of the natural habitat of wild pomegranate, the period time between the first appearance of the modern type of human and the transition of their different populations to agricultural activities is anywhere between 2000 and 6000 Bp. [6]

According to the available records, seafaring in the ancient Mediterranean began more than 10,000 years ago and evidence of the depends on ship to transport merchandise is reflected in texts dating from the end of the 4th millennium B.P. a ship carrying the finest luxury goods of the late bronze age sank off the

coast of uluburum, turkey, in the late 1400 B.P. its discovery yielded great insight into cultural life during egypt's 18th dynasty and the LH IIB period in Greece. The ship contained ceramic containers in which more than 1000 archaeo botanical evidence from military sites shows that it was brought to central Europe by roman solders during their occupation of this areas and thus, it remained an important luxury item. In addition to the symbolic nature of pomegranate, its chemical properties made it useful for a no. of widely disparate purposes, ranging from perfume ingredients from pliny's natural history included pomegranate rind, while its juice was used as an astringent to prepare oil to get a scent. It was highly valued fruit during the late bronze age Ironically however, pomegranate peels rinds were included in recipes for different medicinal purposes during classical and medieval times. Use of pomegranate as a medicine is mentioned in ancient Greek medical papyrus by Rbers, which represents a complied reference book of the 16th century Bc. Even plinii emphasized that it had been considered a universal therapeutic agent and used by the prominent medical healers of the ancient world and middle ages viz. hypocrite, galen, oribasii, pauleginski, jovendamaskin, er-razi,joven-iben-mausa IBN sinn. In folk medicines of the orient, Mediterranean and Africa, it is included in 32 out of 56 groups of pharmacological and therapeutic treatments, 14 out of 17 pharmaco therapeutic groups of plants, used to treat diseases related to 15 out of 16 classes diseases according to the international. Classification.[5], [7],[8]

IV. Material and methods

Pomegranate fruits of Kurdistan cultivates were selected from halabja garden. Sweet pomegranate [punicagranatum cv assaria] were harvested in a commercial orchard in esternalgrave fruits were transported on the same day to the laboratory at the university of algrave. The selected plant material were harvested during nov.2018 at the field located in noto.

The harvest was performed according the riping stage, about 180 days after full bloom samples were taken from 12:00h to 14:30h after picking fruits were immediately transported to the laboratory. Each fruit was carefully cut at the equatorial zone with a sharpened knife, and then intact arils were manually obtained from whole fruits and the juices (1mg accuracy on balance), weight of the arils per fruit, juice yield (%) and the colour of juices by colorimeter Minolta CR 400 (Konica Minolta, Milan, Italy) were determined .

STANDARD REAGENTS AND CHEMICALS

Various chemicals present in different parts of pomegranate plant like peel, root, bark, flower, leaves and so fourth exhibit different phytochemicals are as follows:

A) Pomegranate peels

- 1) Gallic acid
- 2) Ellagic acid
- 3) Punicalin
- 4) Punicalagin
- 5) Caffeic acid
- 6) Ellagitannis
- 7) Pelletierine alkaloids
- 8) Luteolin

9) Kaempferol

10) Quercetin

B) Pomegranate juice

1) Simple sugars

2) Aliphatic organic acid

3) Gallic acid

4) Quinic acid

5) Flavonols

6) Amino acid

7) Minerals

8) EGCG

9) Ascorbic acid

C) Pomegranate root and bark

1) ellagitannins

2) piperidine alkaloids

3) pyrrolidine alkaloids

4) pelletierine alkaloids

D) Pomegranate flower

1) Gallic acid

2) Ursolic acids

3) Triterpenoids

4) Fatty acids

E) Pomegranate leaves

1) Carbohydrate

2) Reducing sugars

3) Sterols

4) Saponins

- 5) Flavonoids
- 6) Tannins
- 7) Piperidine alkaloids
- 8) Flavones
- 9) Glycosides
- 10) Ellagitannins

F) Pomegranate seeds

- 1) 3,3' di-o methylellagic acid
- 2) 3'3',4'- tri-o methyallagic acids
- 3) Punicic acids
- 4) Oleic acids
- 5) Palmitic acids
- 6) Steric acids
- 7) Linolic acids
- 8) Sterols
- 9) Tocopherols
- 10) Sex steroids

Reagents like- delphinidin 3,5 diglucosides, delphinidine 3- glucosides, cyanidin 3,5 diglucose, cyanidine 3- glucoside, pterocyanidin 3,5- diglucoside standards were purchased from apin chemicals ltd,uk. Methanol was purchased from sigma-aldrichquimica, SA (spain). Formic, oxalic, tartaric, pyruvic, malic, ascorbic, maleic citric, fumaric and sulphuric acids glucose and fructose were purchased from *riedel-de-haen* (germany). The ultrapure water was purified with the millq system.

PRIMARY METABOLITES AND ANTHOCYANNIS

Pomegranate contains primary and secondary metabolites such as polyphenols, fatty acids and lipids such as flavonoids, anthocyanins and hydrolyzable tannins.

Sugars

Pomegranate fruit is rich in sugar. The sugar content of pomegranate juice is strongly correlated with its content in the juice and ranges from 4.2 to 8.5 g/100 g depending on the variety, climatic conditions and cultivation techniques. Pomegranate juice contains high amounts of polyphenols such as flavonoids, erigeron, and the pigment molecules anthocyanins found in the skin of the fruit. These are sugars that have been the subject of controversy in several studies from different

countries. Note that these studies were performed with different objectives and therefore followed different extraction and detection procedures.

Organic acids

Analyses of the organic acids of pomegranate aril juice have shown that citric acid is generally the predominant organic acid and its content can reach up to 3.76 g/100g in the juice in addition, it contains significantly lower levels of malic, oxalic, succinic, and tartaric acid ascorbic acids in the fruit peel, citric acid is the predominant organic acid and its content can reach up to 1.68/100g smaller amounts of mallic, succinic, and oxalic acid were detected in peels.[27]

Amino acids

Amino acids have an important role in protein biosynthesis and secondary metabolites syntheses addition to their role as building blocks of protein, amino acids functions as precursors or intermediates in biosynthetic pathways such as production of colour molecules and volatiles in fruits, energy release through degradation, signaling and plant stress response there are very limited data and only a handful of research publication concerning amino acids in the pomegranate fruit.[22],[23]

Proteins

The data on proteins in pomegranate fruits are limited and mainly concern total protein content in various tissues most of the studies do not report specific protein functions with the exception of storage proteins in the seeds and lipids transfer protein in the arils in general, the percent of total proteins in pomegranate juice is usually low, from < 1.0 to 1.1, which is quite a narrow range diversely, percent of total proteins in pomegranate seeds varirs from 4.1 to 16.9% which is quite a wide range.[24]

Lipids

The lipids are a group of small hydrophobic molecules that include fatty acids, waxes, sterols, fat soluble vitamins, phospholipids, mono-di and triglycerides primary and secondary lipids have diverse functions in living organisms, including energy storage, cell signaling, nutrition, hormones, transport and structural components of cell membranes. the most lipid rich fraction in pomegranate is the seed, which contribute 10% to fruit weight generally, seed oil constituents 6-20% of seed weight and contains a large quantity of lipid.[17]

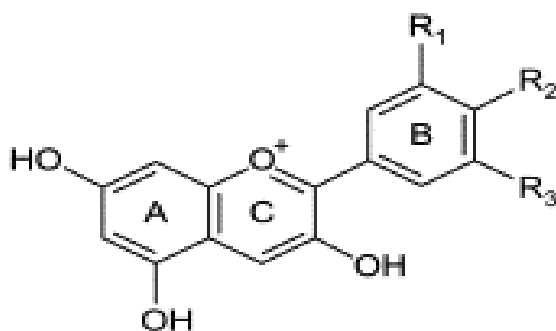
The chain length of the lipids is divided to three classes; medium- (C6-C12), long – (C14-C20), and very long (C22 and C24). The total lipid (the term refers to primary and secondary lipids) percentage in seeds varies from 4.4 to 27.2% [9],[13],[10],[25]

ANTHOCYNNIS

Anthocyanins is a secondary metabolites in pomegranate juice anthocyanins (ACNS) are the largest and most important groups of flavonoids present in pomegranate juice and together with hydrolysable tannis (HTS) they constitute the most valuable bioactive compounds chemically, ACNS are glycosides of polyhydroxy and polymethoxy derivatives of 2-phenylbenzopyrylium or flavyium salts. It is the key colour molecules of pomegranate present in various parts of the pomegranate trees, including leaves, flowers, and fruits. The pomegranate fruit is a rich source of anthocyanins and produces several

derivatives of anthocyanins these secondary metabolites accumulate in all fruits tissues and mainly in the edible part of the fruit, the arils and in the fruit peel all six anthocyanin pigments were detected in pomegranate cultivates from different geographical regions, which include israeli, turkish, Spanish, Californian, Tunisian, Italian and Chinese pomegranate.[26] The function of anthocyanin in the biology of the pomegranate tree is not yet fully understood the tree of the 'white' phenotype pomegranate varieties, which do not produce any anthocyanin, in vigorous and fertile. It seems, however, that the white flowers anthocyanins less fruits are more susceptible to browning and radiation damages. [19] Composition of anthocyanins in peels It an attempt to determine the colour variability among pomegranate varieties, 29 varieties that represent most of the phenotypic variability in the Israeli pomegranate collection were assayed. Total anthocyanin content was measured for both skin and Arilus extracts. The total anthocyanin content of the peel varied between 0.2 and 8.0 x 10 mg/l, and the anthocyanin content in the juice of the arils varied between 0.2 and 3.5 x 10 mg/l. [15], [16].

Composition of Anthocyanins in Juice Sap. We analyzed the anthocyanin content of 30 fruit juices grown in Tunisia



Basic chemical structure of anthocyanins

1. Use of peels

Pomegranate peel are useful for various disease. Pomegranate peels are typically discarded and thought of as inedible, but they're used regularly for various health and beauty benefits in ayurvedic medicines an alternative practice with roots in Indian culture pomegranate peels are high in antioxidant and polyphenols and they have been shown to treat hyperpigmentation, a condition characterized by dark patches of skin [11].

Pomegranate peels may protect may against UVB rays and improve hyperpigmentation, acne, signs of aging and wound healing. Pomegranate peels contains high amounts of punicalagin a polyphenol that has been shown to have anti-cancer properties in some test-tube studies. In one such study, pomegranate peel extract was found to be a promising treatment for prostate cancer because of its ability to induce the death of cancer cells [12][14].

Background – The health promoting activities are attributed to the high concentration of polyphenols found mainly in the fruits peels, which possess about 300-fold more polyphenols and 40-fold higher antioxidant activities than arils, the edible section these polyphenols act as scavengers of reactive oxygen species (ROS), and

are associated with a reduction in stress related chronic diseases and age related disorders. Previous studies showed that hydrolysable tannins (HTS) and anthocyanins (ATS) are predominant polyphenols present in outer fruits peels. These compounds are also produced in vegetative tissues during osmotic stress, drought, UV exposure, and cold temperatures. ATS and HTS biosynthesis are related to the shikimate pathway. ATS was formed from the phenylpropanoid pathway starting with phenylalanine, an aromatic amino acid produced by the shikimate pathway and thought to be produced by enzymes in the shikimate pathway. HTS biosynthesis begins with gallate (GA), which is thought to be produced by the shikimate dehydrogenase (SDH) reaction, an enzyme of the shikimate pathway. A previous study showed that 'Vitis vinifera' has four isoenzymes of DQD/SDH with different affinities for the cofactor NADPH+. shows that it can generate

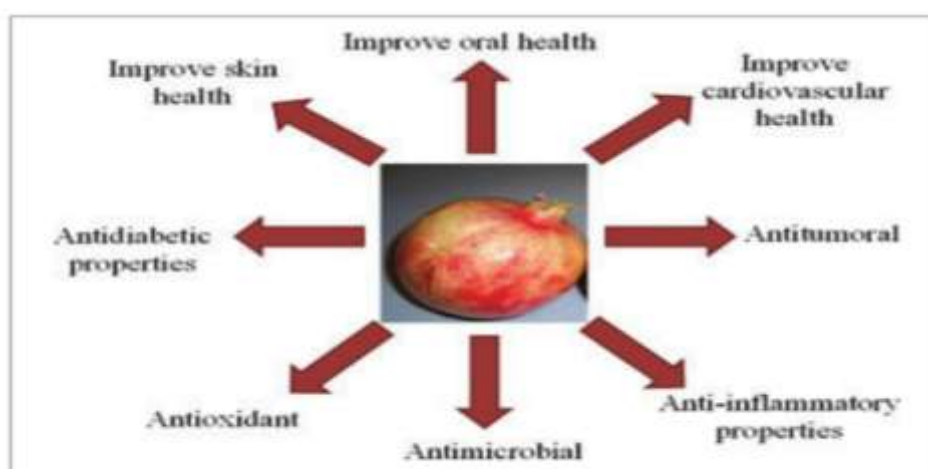


Figure 4–Principal functional and medicinal effects of pomegranate.

Oxidation / reduction mechanism of antioxidants

Antioxidants are one of the most important mechanisms for preventing or delaying the onset of serious degenerative diseases. Reactive oxygen species (hydroxyl, peroxy radical, and monooxygen) are highly toxic and one of the most potent causative agents of many diseases, including cancer and heart disease. Contracts and Cognitive Impairment. Antioxidants block the oxidative processes that contribute to these chronic diseases and delay the development of degenerative diseases in old age.[11]

Oxidation /reduction mechanism

- 1) Oxidative stress } endogenous source of ROS/RNA mitochondria poroxisomes
exogenous source of ROS/RNA radiation ozone
- 2) defense system - enzyamatic superoxide dismutase catalase
nOhon enzymatic vit.E, vit.C

Mechanisms of action of antioxidants

Two main mechanisms of action have been proposed for antioxidants. The first chain scission mechanism by which primary antioxidants donate electrons to free radicals (lipid radicals) present in the system. A second mechanism involves the removal of ROS, an RNA initiation catalyst.

Polyphenolic compounds have the ability to donate hydrogen atoms and act as chain-breaking antioxidants. It can also chelate transition metal ions to inhibit free radical formation.[34]

Pomegranate peel extract as an inhibitors of SARS-COV-2 (COVID -19)

Active substances in plant extracts are mainly secondary metabolites and can be divided into four main categories based on their different chemical properties and structures: terpenoids, polyphenols, nitrogen compounds and sulfate compounds. . [32].

Polyphenols are the largest and most widespread group of bioactive compounds in the plant kingdom. They possess a unique structural backbone composed of one or more aromatic phenyl rings attached to hydroxyl groups and exhibit a broad spectrum of health-related inflammatory, anti-allergic, anti-atherogenic, and anti-cancer properties. Additionally, several studies have demonstrated the antiviral potential of several classes of polyphenols against eptin barr virus, enteroviruses, herpes simplex virus (HSV), influenza virus, and other viruses that cause respiratory infections. It has been. The mechanisms underlying the antiviral activity of polyphenols are diverse and include inhibition of viral entry through permanent attachment to the virion envelope and inhibition of enzymes involved in viral replication. Severe acute respiratory syndrome coronavirus-2 (SARS-COV-2), a zoonotic virus first identified in December 2019, has caused one of the most severe pandemics in human history, coronavirus disease. 2019 (covid-19) cause. Covid-19 has over 60 million cases and more than 1.4 million deaths worldwide. SARS-CoV-2, like other coronaviruses, is an enveloped, positive-sense, single-canonical RNA virus that displays a highly glycosylated spike protein on its surface, allowing the virus to enter host cells. facilitates the intrusion of Entry depends on the binding of the surface unit S1 (part of the s protein) to cellular receptors, facilitating viral attachment to the surface of target cells. [33]

CANCER

Cancer is the second leading cause of death in the united states, and those who survive cancer may experience lasting difficulties, including treatment side effects, as well as physical, cognitive and pshychosocial struggles.

The pomegranate constituents are shown to modulate transcription factors, pro-apoptotic proteins, anti-apoptotic proteins, cell cycle regulator molecules, protein kinase, cell adhesion molecule, pro-inflammatory mediators, and growth factors in various cancers.Pomegranate has also been shown in preclinical studies, to boost the effectiveness of certain chemotherapy drugs the while protecting against their harmful side effects. [18]

How pomegranate fights cancers in addition to preventing cancer from developing , in preclinical studies, pomegranate has shown multiple effects that help block the growth of existing cancer cells and prevent them from spreading these effects include 4,5 blocking the cells cycle. Pomegranate can shut off a cancer cells ability to divide, limiting its growth by affecting multiple genes related to the cell cycle however, it does not block healthy cells from dividing normally inducing cell death compound in pomegranate directly cause cancer cell to die by including apoptosis. Cancer cells require new blood vessels in order to support their growth with an ample blood supply pomegranate blocks growth factors related to angiogenesis, which limits the formation of new blood vessels in tumors. Cancer cells often separate from their cells, migrate through tissues, and eventually spread to distant organs in the body. Pomegranate has also been exported as an adjuvant to conventional cancer treatments such as

chemotherapy, where it has been shown to enhance the efficacy of such treatments, but it is also known to have harmful side effects.

POMEGRANATE AND BREAST CANCER

Breast cancer was the second leading cause of cancer-related deaths in women in 2016. An estimated 246,660 new cases of invasive breast cancer in the United States are expected to be diagnosed in a US woman, along with her 61,000 new cases of noninvasive breast cancer. Her one of the top cancers diagnosed occurs primarily in women in the United States. Breast cancer is a type of tissue cancer that primarily involves the lining of the breast glands or lobules and ducts. [35]. Breast cancer arises from cells in the breast. A malignant tumor is a group of cancer cells that invade and destroy nearby tissues. It may also spread to other parts of the body. Breast cells may change and stop growing and functioning normally. These changes can lead to noncancerous (early) breast diseases such as atypical hyperplasia and cysts. It can also lead to noncancerous tumors such as intraductal papilloma, but changes in breast cells can also lead to breast cancer. In most cases, breast cancer begins in the cells that line the ducts, the tubes that carry milk from the mammary glands to the nipple. This type of cancer is called lobular carcinoma. Both ductal and lobular carcinoma can be noninvasive. That is, the cancer is still where it started and has not grown into the surrounding tissue. They can also be invasive. This means that it has grown into the surrounding tissue. Less common types of breast cancer can also occur, such as inflammatory breast cancer, Paget's disease of the breast, and triple-negative breast cancer.[36],[37].

CONCLUSION

In this review, we observed various beneficial parts of pomegranate and pomegranates used for various ailments such as diabetes, heart disease and rheumatoid arthritis. It has antioxidant, antibacterial and anticancer properties. Various parts such as pomegranate skin, leaves, and juice are used. Pomegranate has been used since ancient times, so it is called Ayurvedic fruit and contains many metabolites. Primary and secondary metabolites serve our body, such as sugars, amino acids, lipids, proteins, organic acids, anthocyanins, etc. Pomegranate is also very useful against cancer, most breast cancer cells, It exhibits multiple anti-cancer cell effects and prevents spread. It also reduces the activity of the viral 3cl protease in vitro, possibly making the extract an adjuvant in the treatment of SARS-COV-2 (Covid-19) infection. indicates to use. The study presented here paves the way for longer-term, in-depth studies on the activity of pomegranate SARS-COV2 infection in vivo, reusing agricultural industry by-products for valuable and healthy uses. It can also foster new ideas.

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