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PUNICA GRANATUM: A REVIEW ON PHARMACOLOGICAL AND THERAPEUTIC PROPERTIES

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ABSTRACT

A wide range of medicinal plant parts is used as raw drugs and they possess varied medicinal properties. The different parts used as raw drugs include root, stem, flower, fruit, twigs exudates and modified plant organs. The *Punica granatum* is a native shrub of occidental Asia and Mediterranean Europe that has a rich history of traditional use in medicine. For centuries, the barks, leaves, flowers, fruits, and seeds of this plant have been used to treat various diseases. The aim of this present review is to throw light on the therapeutic utility of various parts of pomegranate.

INTRODUCTION: *Punica granutam* is popularly known as pomegranate (Anar). It is a member of Punicaceae family, which is a large deciduous shrub or small tree native to Asia [1, 2]. *Punica granutam* have been used in folk medicine for centuries in the Middle East, India, and China, and it has been used to treat ailments ranging from inflammation and rheumatism to the pain of a simple sore throat. The most famous usage worldwide has been as a vermifugal or taenicidal agent [3, 4] i.e., a killer and expeller of intestinal worms. The pericarp is used by Chinese and South Africans for the treatment of diarrhea, metrorrhagia, metrostaxia, and bellyachea. In Unani medicine its flower is used as a food supplement to treat diabetes mellitus.

Different part of pomegranate like bark, leaves, immature fruits, and fruit rind have some medicinal significance. According to Satomi *et al*., the pericarps of *Punica granutam* contains seven highly active inhibitors of carbonic anhydrase (CA) i.e., punicalin, punicalagin, granatin B, gallagyldilactone, punicalagin, pedunculagin and tellimagrandin.

The four weakly active inhibitors, gallic acid, granatin A, corilagin and ellagic acid, are known to exhibit antimicrobial, antifungal, antimutagenic activity, (Punicaceae) and are term as ellagitannins. The type of inhibition by punicalin and punicalagin against p-nitrophenyl acetate as a substrate is found to be noncompetitive [5].

Other traditional uses of these materials have included treatments for snakebite [6], diabetes [7], burns [8] and leprosy [9]. The fresh fruit itself has been used as a refrigerant to lower fever [10].

TABLE 1: PHYTOCHEMICALS OF POMEGRANATE[11]

Plant Component	Constituents
Juice	Anthocyanins, glucose, ascorbic acid, ellagic acid, gallic acid; caffeic acid; catechin, EGCG, quercetin, rutin; numerous minerals, particularly iron; amino acids.
Seed oil	95-percent punicic acid; other constituents, including ellagicacid; other fatty acids; sterols.
Pericarp (Peel, rind)	Phenolic punicalagins; gallic acid and other fatty acids; catechin, EGCG; quercetin, rutin and other flavonols; flavones, flavonones; anthocyanidins.
Leaves	Tannins (punicalin and punicafolin); and flavones glycosides, including luteolin and apgenin
Flower	Gallic acid, ursolic acid; triterpenoids, including maslinic and Asiatic acid; other unidentified constituents
Roots and bark	Ellagitannins, including punicalin and punicalagin; numerous piperidine alkaloids.

Antimicrobial activity by *Punica granatum*: Medicinal plants represent a rich source of antimicrobial agents. Plants are used medicinally in different countries and are a source of many potent and powerful drugs. Burapadaja *et al*., reported that pomegranate fruit peel compound punicalagin have antimicrobial activity against *S. aureus* and *P. aeruginosa* [12].

According to Perez *et al*., pericarp extract of *Punica granatum* possess strong antibacterial activity against the multiple resistance of *Salmonella typhi*. Boiling water extracts of 132 plants commonly used in Argentine folk medicine, were screened for antibacterial activity against *Salmonella typhi* using the agar-well diffusion method. A reference concentration-response curve for ampicillin was used to estimate the apparent activity of the samples, and they found good result in case of pericarp extract of *Punica granatum* [13].

Voravuthikunchai *et al*., used aqueous and ethanolic extracts of *Punica granatum* to test their antibacterial activity against different strains of *Escherichia coli*. Inhibition of growth was primarily tested by the paper disc agar diffusion method. Among the medicinal plants tested by dilution method in petri dishes with millipore filter, aqueous extract of *Punica granatum* was highly effective against *Escherichia coli* O157:H7 with the best MIC (minimum inhibitory concentration) and MBC(minimal bactericidal Concentration) values of 0.09, 0.78, and 0.19, 0.39 mg/ml, respectively [14].

According to Vasconcelos *et al*., *Punica granatum* extract can be used to control the adherence of different microorganisms in the oral cavity. They used various extract of *Punica granatum* against the streptococci strains, *S. mutans*, and *S. mitis* and *C. albicans* and the found good results against selected bacteria [15].

In a separate study, it was found that hydroalcoholic extract (HAE) from *Punica granatum* is very effective against dental plaque microorganisms (In vivo) and the number of colony forming units per milliliter (CFU/ml) was reduced by 84% as compared to the control group (11% decrease). These results indicated that the HAE may be a possible alternative for the treatment of dental plaque [16].

Braga *et al*., investigated the effects of pomegranate extract on *Staphylococcus aureus* FRI 722, the bacterial growth and subsequent enterotoxin production was studied by tube dilution method and production of enterotoxin was assessed by using membrane-over-agar (MOA) plates. At a low extract concentration (0.01%, v/v) bacterial growth was delayed, whereas a higher concentration (1%, v/v) of extract eliminated the bacterial growth. A 0.05% (v/v) concentration of extract was found to inhibit *Staphylococcal* enterotoxin (SE) production [17].

A study has demonstrated that tannin from the pericarp of *Punica granatum* is an effective component against genital herpes virus (HSV-2). The tannin not only inhibits HSV-2 replication, but also shows stronger effects on killing virus by blocking its adsorption on to cells.

Pomegranate extracts have been found to be effective against the herpes virus [18]. According to Haidari *et al*., purified polyphenol extract of pomegranate inhibited influenza virus and also showed a synergistic effect with oseltamivir [19]. Influenza virus causes epidemics and pandemics in human population. Hydroalcoholic extract of whole fruits exhibits high activity against the influenza virus [20, 21]. Such virus has several zoonite hosts, therefore cannot be eradicated from human populations. Influenza continues to be a major cause of mortality and morbidity, although the vaccines and antiviral therapies.

In vitro study by Neurath *et al*., indicated that an anti-HIV-1 microbiocide could potentially be made from *Punica granatum* that could be used as a topica microbiocide for HIV prevention [22].

In a study by *Dahham et al*., the antibacterial and antifungal activities of pomegranate peel extract (rind), seed extract, juice and whole fruit on the selected bacteria and fungi. The peel extract showed the highest antimicrobial activity compared to other extracts. Among the selected bacterial and fungal cultures, the highest antibacterial activity was recorded against *Staphylococcus aureus* and amongst the fungi the highest activity was recorded against *Aspergillus niger* [23].

In vitro studies of water extracts of plant *Punica granatum* was found to be detrimental to dermatophytes. The actone extract of *Punica granatum* was fungitoxic to *Puricularla oryzae* and *Colletotrichum falcatum* .The extracts of the bark, fruit, pulp, flower, and leaves of *Punica granatum* completely inhibited the spore germination of fungi viz., *Dreschlera rostrata* and *Curvularia lunata* [24].

Healing Activity: Gallic acid and catechin are the major components of *Punica granatum* which are responsible for the healing activity.

According to Murthy *et al*., The methanolic extract of dried pomegranate *(Punica granatum*) peels showed the presence of a high content of phenolic compounds (44.0%) along with other constituents. This extract was formulated as a 10% (w/w) water-soluble gel and was studied for its wound healing property against an excision wound on the skin of Wistar rats. The group of rats that received 5.0% gel showed complete healing after 10 days, whereas in rats treated with 2.5% gel, healing was observed on day 12, in contrast to the positive control animals receiving the blank gel, which took 16-18 days for complete healing [25].

Braga and his colleagues evaluated the interaction between *Punica granatum* (pomegranate) methanolic extract (PGME) and antibiotics against 30 clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA). Susceptibility testing of the isolates to PGME and antibiotics was performed by the broth dilution method.

Synergistic activity was detected between PGME and the five tested antibiotics i.e. chloramphenicol, gentamicin, ampicillin, tetracycline, and oxacillin [26]. For some isolates, PGME did not interfere with the action of any of the antibiotics tested. The bactericidal activity of PGME (0.1 x MIC) in combination with ampicillin (0.5 x MIC) was assessed using chosen isolates by time-kill assays, and that confirmed the synergic activity. Using this combination, cell viability was reduced by 99.9% and 72.5% in MSSA and MRSA populations, respectively. PGME increased the post-antibiotic effect (PAE) of ampicillin from 3 to 7 h. In addition, PGME demonstrated the potential to either inhibit the efflux pump NorA or to enhance the influx of the drug. The *in vitro* variant colonies of *S. aureus* resistant to PGME were low and they did not survive. In conclusion, PGME dramatically enhanced the activity of all antibiotics tested, and thus, offers an alternative for the extension of the useful lifetime of these antibiotics [26].

Anti-inflammatory Activity: The major ingredient of pomegranate fatty acids, punicic acid, is well known anti-inflammatory compound which inhibits the development of inflammation by suppressing the biosynthesis of prostaglandin [27].

The anti-inflammatory compounds were mainly obtained from the seeds. The results exhibited polyphenols and fatty acids were the major anti-inflammatory constituents. The extract from the cold pressed seed oil of pomegranate mainly comprised of polyphenols and fatty acids which showed 31-44% inhibition of sheep cyclooxygenase and 69-81% inhibition of soybean lipooxygenase, whereas the extract from fermented juice showed 21-30% inhibition of soy bean lipooxygenase [28].

According to Van De Walle *et al*., [29] the polyphenols in cold pressed seed oil were reported by another research group to suppress inflammatory cell signaling in colon cancer cells [30]. Pomegranate extract exhibited anti-inflammatory activity via inhibition of NF-κB (nuclear factor kappa-B) activity and Erk1/2 activation and decreased NO (nitric Oxide) and PGE_2 synthesis in human intestinal Caco-2 cells. In addition, ellagic acid was capable of decreasing NF-κB activation through a mechanism independent of Iκ-Bα phosphorylation

Panichayupakaranant *et al*., carried out *in vitro* studies on antibacterial, anti-inflammatory and anti-allergic activities of standardized pomegranate rind extract (SPRE) containing 13% (w/w) ellagic acid. Anti-inflammatory activity of SPRE was evaluated by measuring the inhibition of nitric oxide (NO) production by murine macrophage-like RAW264.7 cells. SPRE exhibited a potent inhibitory effect on NO production, with an IC- 50 of 10.7 l g/ml [31].

Anti-diabetic Activity: The current diabetes epidemic is a global concern with readily available effective therapies or preventative measures in demand. In traditional folk medicines of India, one natural product with such potential is the pomegranate (*Punica granatum*), with hypoglycemic activity a special attribute of its flowers, seeds, and juice. Pomegranate compounds associated with antidiabetic effects include oleanolic, ursolic, and gallic acids.

Flower of pomegranate have been used as an anti-diabetic medicine in Unani medicine and as a supplement in the diet therapy in many countries. The flowers can significantly lower the blood glucose level in case of type II diabetes with different possible mechanisms including enhancement of mRNA expression, improvement of insulin receptor sensitivity, increment of peripheral glucose utilization, etc.

According to Bagri *et al*., the oral administeration of aqueous extract of pomegranate flowers at doses of 250 and 500 mg/kg for 21 days resulted in a significant reduction in fasting blood glucose, TC(total cholesterol)., TG (Triglycerides), LDL-C (low-density-lipoprotein cholesterol), VLDL-C (very-low-density lipoprotein cholesterol) and tissue LPO (lipid peroxidation) level coupled with elevation of HDL-C (High- density- lipoprotein cholesterol), GSH (glutathione) content and antioxidant enzymes in comparison with diabetic control group.

Results suggested that the aqueous extract of flowers can be used as dietary supplement in treatment and prevention of chronic diseases characterized by hetrogenous lipoprotein profile, aggravated antioxidant status and impaired glucose metabolism [32]. The mechanisms for such effects are unknown, though recent researches suggest that pomegranate flowers and juice may prevent diabetic sequelae via peroxisome proliferator-activated receptor-gamma binding and nitric oxide production.

Esmaillzadeh *et al*., found that pomegranate juice significantly reduced total cholesterol, low-density lipoproteins (LDL), the ratio of LDL/ HDL (high- density lipoproteins), and the ratio of total cholesterol to HDL. These findings show that consumption of the pomegranate juice may modify heart disease risk factors in patients with hyperlipidemia [33].

Anti cancer Activity: The juice, peel, and seed oil of Pomegranate have been found to have anti-cancer properties that inhibit proliferation, cell cycle, and angiogenesis [34].

Amin *et al*., reported that pomegranate fruit, pomegranate juice, seed and seed oil are effective in prostate, breast, skin, colon, lung, oral and leukaemia cancers [35], due to its antioxidant and antiproliferation (growth inhibition, cell cycle disruption and apoptosis) [36, 35].

In a separate study by Kohno *et al*., pomegranate seed oil incorporated in the diet, markedly reduced the incidence and multiplicity of colonic carcinoma (measured as number of tumors/rat) induced by azoxymethane. In this experiment, pomegranate seed oil was added to AIN-76A diet. Increasing concentration of 0.01%, 0.1% and 1% (w/w), of pomegranate seed oil did not exhibit a dose response effect but anti-carcinogenic effects were observed at all the doses used in the study [37].

Toi *et al*., have found that pomegranate seed oil and fermented juice polyphenols tend to inhibit breast cancer cell proliferation, invasion, and promotes apoptosis of breast cancer cells [38]. Kim et al. reports that fermented pomegranate juice polyphenols consistently showed twice higher anti-proliferative effect as compared to fresh pomegranate juice polyphenols [39]. Research on lung cancer revealed that PFE(Pomegranate fruit extract) is effective treatment of lung cancer [40]. The results suggested that PFE can be used as a chemopreventative agent against lung cancer.

Albrecht *et al*., studied the effects of pomegranate oil, seed oil, fermented juice polyphenols, and pericarp polyphenols on human prostate cancer cell growth in vivo and found that it demonstrated significant antitumor activity against human prostate cancer [41]. Lansky *et al*., utilizing pomegranate fruit extract, showed that cell growth was inhibited and followed by apoptosis of extremely aggressive human prostate carcinoma PC-3 cells.

The fermented pomegranate juice polyphenols were also tested in combination with pericarp polyphenols on the proliferation of DU 145 human prostate cancer cell lines in vitro. Supra-additive and synergistic effects were experimentally proven [42]. These studies provide evidence, suggesting that consuming pomegranate may delay prostate cancer progression [43].

CONCLUSION: For a long period of time, the Pomegranate plant have been used as a natural source of medicine, and the use of plant compounds for pharmaceutical purpose has gradually increased in the world over. According to the WHO, this medicinal plant is the best source to obtain variety of drugs. About 80% of individuals from developed countries use them in traditional medicine. The plant part or the compounds derived from the plants are now established recipe of both pharmaceuticals and nutraceuticals. This review aims to highlight the medicinal importance of the plant and journey of this folk medicine to modern medicine.

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