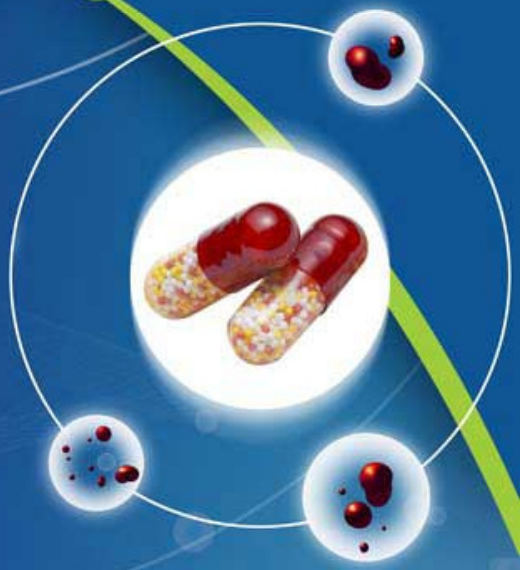
ISSN : 2320 4850

BI MONTHLY

Asian Journal of Pharmaceutical Research And Development

(An International Peer Reviewed Journal of Pharmaceutical Research and Development)

AJPRD



Volume - 01 Issue - 02 MAR-APR 2013

website: www.ajprd.com
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Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Review Article

CHEMICAL CONSTITUENTS OF VARIOUS PARTS OF *PUNICA GRANATUM* AND THEIR ANTI-INFLAMMATORY ACTIVITY: A REVIEW

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Received: 10 March 2013, Revised and Accepted: 20 March 2013

ABSTRACT

Punica granatum L. (Punicaceae), commonly called pomegranate, recently described as nature's power fruit, is a plant used in folkloric medicine for the treatment of various diseases widely cultivated in the Mediterranean region.The pomegranate has been traditionally used as medicines in many countries. The pomegranate tree can be divided into several anatomical compartments like seed, peel, juice, flower, leaf, bark, roots, etc. each of which has anti-inflammatory activitiy. The chemical composition of fruits differs depending on the cultivar, growing region, climate, maturity, cultural practice and storage. The anti-inflammatory properties of extracts of various (peels, rind, seeds, leaves, flowers, fruits) parts of pomegranate is reported in the present work.

Keywords: *Punicaceae, Punica granatum, Pomegranate,*

INTRODUCTION

Inflammation: The inflammatory process is the response to an injurious stimulus. It can be evoked by a wide variety of noxious agents (*e.g.,* infections, antibodies, or physical injuries). The ability to mount an inflammatory response is essential for survival in the face of environmental pathogens and injury; in some situations and diseases, the inflammatory response may be exaggerated and sustained without apparent benefit and even with severe adverse consequences. No matter what the initiating stimulus, the classic inflammatory response includes calor (warmth), dolor (pain), rubor (redness), and tumor (swelling).[1]

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Punica granatum L. (*Punicaceae*), commonly called pomegranate, recently described as nature's power fruit, is a plant used in folkloric medicine for the treatment of various diseases widely cultivated in the Mediterranean region.[2]

The genus name, Punica, was the Roman name for Carthage, where the best pomegranates were known to grow. Pomegranate is known by the French as grenade, the Spanish as granada, and literally translates to seeded ("granatus") apple ("pomum"). The pomegranate tree typically grows 12-16 feet, has many spiny branches, and can be extremely long lived, as evidenced by trees at Versailles, France, known to be over 200 years old. The leaves are glossy and lanceshaped, and the bark of the tree turns gray as the tree ages. The flowers are large, red, white, or variegated and have a tubular calyx that eventually becomes the fruit. The ripe pomegranate fruit can be up to five inches wide with a deep red, leathery skin, is grenade-shaped, and crowned by the pointed calyx. The fruit contains many seeds (arils) separated by white, membranous pericarp, and each is surrounded by small amounts of tart, red juice. The

pomegranate is native from the Himalayas in northern India to Iran but has been cultivated and Naturalized since ancient times over the entire Mediterranean region. It is also found in India and more arid regions of Southeast Asia, the East Indies, and tropical Africa. The tree is also cultivated for its fruit in the drier regions of California and Arizona.[3]

The pomegranate is a symbol of life, longevity, health, fecundity, knowledge, morality, immortality and spirituality, if not Divinity. In the ancient Egyptian culture the pomegranate fruit was regarded as a symbol of prosperity and ambition, making it common practice to decorate.[4]

Table: 1 Chemical Constituent [3]

Plant Part	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 ellagic acid, other fatty acids, sterols.
Pericarp (Fruit and 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 flavone glycosides, including luteolin and apigenin.
Flower	Gallic acid, ursolic acid,triterpenoids, including maslinic and asiatic acid,
Root and Bark	Ellagitannins, including punicalin and punicalagin, numerous piperidine alkaloids

ANTI-INFLAMMATORY ACTIVITY

- **Ouachrif *et al*** (2012) have reported the analgesic and anti-inflammatory activities of the methanol extract (MoE) obtained from fruit peels of two varieties of Pomegranate: Amrouz (MoEA) and Sefri (MoES). Antinociceptive activity of MoEA and MoES was examined using four models of pain. The extracts were administered by the intraperitoneal route (i.p.) in writhing (50, 100 and 150 mg/kg) and formalin tests (25, 50 and 100 mg/kg) and by intra-cerebroventricular injection (i.c.v.) in hotplate and tail-immersion tests (10, 25 and 50 µg/3 µl/rat). Anti-inflammatory activity was studied using the hind paw egg albumin test (50, 100 and 150 mg/kg, i.p.). In the writhing test, the index of pain inhibition (IPI) was 52% for MoEA (150 mg/kg, i.p.) and 29% for MoES (150 mg/kg, i.p.). In the formalin test, the IPI of early and late phase were, respectively, 75% and 82% for MoEA (100 mg/kg, i.p.) and 8% and 63% for MoES (100 mg/kg, i.p.). In the hotplate and tail-immersion test, MoEA and MoES increased in a dosedependent manner the reaction latency to the thermal stimuli [5]

- **Sarker *et al*** (2012) have chosed the Pet-ether, dichloromethane and methanol fractions of flower part for pharmacological screening and analgesic and anti-inflammatory activities in animal model. The anti-inflammatory activity was assessed using the carrageenan-induced rat paw edema model. The analgesic effect was measured in mice using the acetic acid-induced writhing test. In the acetic acid-induced writhing test in mice, pet-ether, dichloromethane and methanol fractions at 200 mg/kg doses level showed 75.77% , 68.56%, 54.64% inhibition of writhing, respectively. In rat

paw edema model induced by carrageenan, pet-ether, dichloromethane and methanol fractions were found to reduce significantly the formation of edema at the 100 mg/kg dose level and showed 26.92%, 27.97%, 21.85% inhibition respectively of edema volume at the end of 4 h. *Punica granatum* possesses evident analgesic and anti-inflammatory activities.[6]

- **Gupta *et al*** (2011) have reported the anti-inflammatory activitis of *Punica granatum* seed extract. The aqueous extract explored its potency by tail immersion and carrageena induced paw edema models. The oral administration of the extract 100mg and 200mg/kg body weight showed significant pharmacological action.[7]

- **Nain *et al*** (2011) have studied for the anti-inflammatory andanalgesic activity methanolic extract of *Punica granatum* leaves by using t using carrageenan induced paw edema in rat with plethysmometer and analgesic activity on mice by Eddy's hot plate & tail immersion method. A preliminary phytochemical screening of leaves extract revealed the presence of alkaloids, tannins, flavonoids, and steroids. Among all the doses (200mg/kg, 400mg/kg, 600mg/kg, 800mg/kg) of methanolic extract 600mg/kg orally showed maximum significant anti-inflammatory and analgesic activity. The results showed that the leaves of Punica granatum linn contain flavonoids that posses anti-inflammatory and analgesic activity through inhibiting the prostaglandin biosynthesis. [8]

- **Das *et al*** (2011) have evaluated the analgesic and anti-inflammatory activity of the ethanolic extracts of leaves of *Punica granatum* Linn. (EEPG). The central analgesic activity was assessed using tail-flick method. The peripheral analgesic activity was assessed using acetic acid induced writhing method. Anti-inflammatory activity was assessed using carrageenan induced paw edema. It has been shown that EEPG (500 mg/kg s.c) and pethidine (5 mg/kg s.c) significantly increased the pain threshold as assessed by increase in the latency period or basal reaction time. Naloxone (1mg/kg s.c) was used to find the central mechanism of action. EEPG (500 mg/kg s.c) combined with naloxone (1 mg/kg s.c) significantly decreased the latency period indicating some agonistic activity of EEPG for the opioid receptors as the probable mechanism of action. EEPG(500 mg/kg p.o) and aspirin(100 mg/kg p.o) also significantly reduced acetic acid induced writhing response showing peripheral analgesic activity.It has also been shown that EEPG (500 mg/kg orally) and aspirin (100 mg/kg p.o) significantly reduced carrageenan induced paw edema. The resuts Have been justified that the traditional use of Punica granatum in inflammatory and painful conditions.[9]

- **Bachoual *et al*** (2011) have investigated the effect of *Punica granatum* peel aqueous extract (PGE) on human neutrophil reactive oxygen species (ROS) production in vitro and on LPS-induced lung inflammation in vivo in mice. PGE had no effect on superoxide anion generation, suggesting that it does not directly inhibit NADPH oxidase activity or activation pathways, or scavenge superoxide anions. PGE did not scavenge H(2)O(2) but directly inhibited myeloperoxidase activity in vitro. In vivo studies showed that PGE also attenuated LPS-induced lung inflammation in mice. So this study reveals that PGE inhibits neutrophil MPO activity and attenuates LPS-induced lung inflammation in mice. Inhibition of MPO activity by PGE could explain its anti-inflammatory action.[10]

- **Lee *et al*** (2010) have studied that Pomegranate has shown potential nitric oxide (NO) inhibition in LPS-induced RAW 264.7 macrophage cells. Pomegranate (100 mg/kg) significantly decreased carrageenan-induced mice paw edema for 1, 3, 4, and 5 h. the active anti-inflammatory components from the pomegranate are Punicalagin (1), punicalin (2), strictinin A (3), and granatin B (4) were obtained with yields of 0.093%, 0.015%, 0.003%, and 0.013%, respectively. All these hydrolysable tannins inhibited NO production and iNOS expression in RAW 264.7 cells.[11]

- **Yoganandam and Sucharita *et al*** (2010) have evaluated the efficiency of various extracts (Water, ethanol, methanol and ethyl acetate) of fruit peel of *Punica granatum.*L for anti-inflammatory activity by HRBC membrane stabilization method. Theresults showed that the methanol and ethyl acetate extracts exhibited better activity than the other two extracts which may be due to the

presence of higher phenolic content estimated by Folin-ciocalteu reagent.[12]

- **Olapour and Najafzadeh *et al*** (2010) have evaluated have analgesic and anti-inflammatory effect of Pomegranate Peel Extract (PPE) in mice. Hydro alcoholic peel extract of pomegranate was prepared by maceration method. The extract was intraperitoneally administrated at dose 400 mg/kg The results of study showed that pomegranate peel extract was considerably decreased licking and writhing Thus, PPE has analgesic and anti-inflammatory.[13]

- **Bagria *et al*** (2010) have studied the anti-inflammatory and analgesic activities of aqueous-ethanolic (50%) extracts of fruit rind (PGR), flower (PGF), and leaves (PGL) of *Punica granatum* at the doses of 150, 250 and 500 mg/kg body weight. Oral pretreatment with the dried extracts of *PG* produced statistically significant and dose dependent inhibition of edema induced by carrageenan at all doses when compared to the control groups. The highest activity was shown in the PGR that at 500 mg/kg p.o. inhibited inflammation by 82.14%. (79 % for indomethacin at 10 mg/kg). On the contrary, the aqueous-ethanolic (50 %) extracts of PGF and PGL exhibited 71.42% and 67.85% inhibition, respectively, at 500 mg/kg dose. The extracts at tested doses were found to possess analgesic activity in mice against tail-flick method. These results indicated that extracts of P. granatum possessed significant anti-inflammatory and analgesic activities suggesting its potential as an anti-inflammatory agent for use in the treatment of various inflammatory diseases in traditional medicine.[14]

- **Panichayupakaranant *et al*** (2010) have reported the antibacterial activity of standardised Pomegranate rind extract (SPRE). The antibacterial activity of SPRE was determined using the disc diffusion and broth microdilution methods. SPRE exhibited a potent bacteriostatic against *Propionibacterium acnes*, a Gram-positive anaerobe with a MIC of 15.6 lg/ml, and Grampositive facultative anaerobic bacteria, Staphylococcus aureus and *Staphylococcus epidermidis*, with MICs of 7.8–15.6 lg/ml. 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 NO inhibitory effect, with an IC50 of 10.7 lg/ml. Evaluation of the anti-allergic activity showed that SPRE inhibited the release of b-hexosaminidase from antigen-stimulated rat basophilic leukemia (RBL-2H3) cells with an IC50 of 20.9 lg/ml.[15]

- **Venktrao *et al*** (2007) have reported the antidiarrhoel and anti-inflammatory activity of the hot aqueous, cold aqueous and cold ethanolic extract of *Punica granatum* rind in different animal models like castor oil induced, gastro intestinal motility and prostaglandin E_2 induced diarrhoea and carregeenan induced paw edema in rats. Extract were used 288.68 mg/kg, 384.44 mg/kg, 275.76 mg/kg and 224.35 mg/kg respectiviey for the study. Antidiarrhoel potential of the extract was evidenced by a significant reduction in faceal output in castor oil induced diarrhoe and also a signigicant decrease propulsive movement of GIT content and significant reduction in fluid accumulation with PGE_2. All four extract had produced significant anti-inflammatory activity in carregeenan induced paw edema in rats.[16]

- **Yahya et al** (2005) has studied the anti-inflammatory activity of an ethanolic extract of Punica granatum (Pomegranate) rind on inflammation induced by carrageenan and cotton pellets implantation in rats; the effect of rind extract was also examined in aspirin and necrotizing agents-induced gastric mucosal damage in fasted rats. Oral administration of Pomegranate rind at a dose of 500 mg kg-' body weight showed a significant anti-inflammatory activity in rats.The findings suggested that the rind extract possesses an anti-inflammatory activity through the inhibiting the prostaglandin biosynthesis in laboratory animals.[17]

CONCLUSION

The pomegranate has been an in exhaustible source of research going from chemistry in the search for new compounds, techniques of production and conservation, biotechnology in search of more profitable varieties.[18]After extensive literature reports on the medicinal

properties of pomegranate it is easy to understand why researchers have referred to the pomegranate as "nature"s power fruit".[4]

Pomegranate is a potent anti-inflammatory activity. The anti-inflammatory activity of various parts of pomegranate is measured by the different methods. Based on the literature precedence, most of the important research about Pomegranate and its antioxidant activity has been performed during the past decade.

Table: 2 Reported research work onAnti-inflammatory activity of various parts of *punica granatum*

S.No	Plant Part	Type of Extract	Dose	Model	Author
1	Peel	Methanolic	50, 100 and 150 mg/kg	The hind paw egg albumin test	Ouachrif *et al* (2012)
2	Flower	Pet-ether, dichloromethane and methanol	100mg/kg	Carrageenan Induced Paw Oedema Method in Rats	Sarker (2012)
3	Seeds	*Aqueous*	100mg/kg and 200mg/kg	Carrageenan Induced Paw Oedema Method in Rats	Gupta (2011)
4	Leaves	Methanolic	200mg/kg. 400mg/kg, 600mg/kg and 800mg/kg	Carrageenan Induced Paw Oedema Method in Rats	Mamta (2011)
5	leaves	Ethanolic	500mg/kg	Carrageenan Induced Paw Oedema	Das (2011)
6	peel	*Aqueous*		LPS-induced lung inflammation in vivo in mice	Bachoual *et al* (2011)
7	Rind	Methanolic		inhibition of nitric oxide (NO)	Panichayupakaranant (2010)
8	Peel	Ethanol, methanol and ethyl acetate		HRBC membrane stabilization method	Yoganandam *et al* (2010
9	Peel	Hydroalcohlic	400 mg/kg	Formalin test	Olapour *et al* (2010)
10	Fruit	*Aqueous ethanolic*	200mg/kg and 400mg/kg	Carrageenan Induced Paw Oedema Method in Rats	Perumal (2010)
11	Flower, leaves and rind	*Aqueous ethanolic*	150, 250 and 500 mg/kg	Carrageenan Induced Paw Oedema	Bagria *et al* (2010)
12	Rind	Hot aqueous, cold aqueous and cold ethanolic extract	288.68mg/kg, 384.44 mg/kg, 275.76 mg/kg and 224.35mg/kg	Carregeenan induced paw edema	Venktrao *et al* (2007)
13	Rind	Ethanolic	500 mg/kg	*Carrageenan and cotton pellets implantation in rats*	Yahya *et al* (2005)

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