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Pharmacognostical And Pharmacological Activity of Punica Granatum (Pomegranate): An Overview

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Abstract

Received on: 20 Apr 2020 Revised on: 10 May 2020 Accepted on: 18 May 2020 *Keywords:*

Punica granatum, Punicaceae, Pomegranate, Pharmacological activities, Traditional uses Punica granatum (PG) Linn (Family Punicaceae) is also known as pomegranate in English and commonly known as Anar in Hindi, it is found in the nearby region of Iran and very often found in the Himalayas and northern region of India and also cultivated since the ancient times, all over the region of Africa, Europe, and Asia. The various parts of pomegranate plants like seeds, leaf, root, and rind, in the traditional medicine system, used to treat multiple disease ailments such as wound healing, antioxidant, anti-inflammatory, decreases cancer risks, anti-arthritic, anti-proliferative and many more diseases. Punica granatum Linn. f. has an excellent level of pharmacological action, which very important according to the medicinal point of view. An enormous variety of phytochemicals such as alkaloids, flavonoids, saponin, carbohydrates, steroids, triterpenoids, carotenoids, amino acids, tannins, phenolics, and coumarins. This plant (PG) is very rich in phenolic compounds, due to the presence of such a wide variety of phytoconstituents. The whole plant was extensively used during the holistic medicine system in the treatment of the number of disease treatment. This review mainly focused on the large variety of essential pharmacognostic and pharmacological profile that is necessary to exhibit the crucial therapeutic activity and phytopharmacological properties of different parts of Punica granatum.

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INTRODUCTION

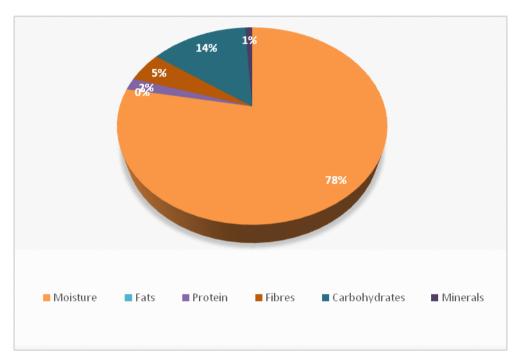
Plants have always been used for medicinal purposes since the prehistoric period, and the herbal medicinal plants (whole parts) play a significant role

in developing countries for influential therapeutic agents. Representation of rich customs, traditional and herbal biodiversity offers a unique opportunity to the researchers of drug discovery in India. Our country, India, is a massive repository to the medicinal plant and medical treatments, and about 22,000 medicinal plant species are in record nowadays. More than 400 traditional cultures, however, use about 800 plant species to treat different diseases, and at present, about 25% pharmaceutical prescriptions in the United States have at least one plantderived ingredient (Garach et al., 2012). According to WHO estimation, about 80% of the population still depends on historic medicine based mostly on plant species and animals for their primary health care.

Punica granatum L. (Pomegranate or Anar) is a

Plant Parts	Constituents
Seeds	Gallic acid, punicic acid (95%), ellagic acid, other fatty acids, and sterols.
Peel and rind	Gallic acid, Phenolic punicalagin, and other fatty acids, quercetin, anthocyanidins, rutin, catechin, and flavonols.
Juice	Glucose (excess), Anthocyanins, ellagic as well as gallic acid, quercetin, iron, amino acids and various minerals.
Flower	Triterpenoids, ursolic and Gallic acid, including maslinic and Asiatic acid, etc.
Leaves	Flavones glycosides, Tannins, apgenin, luteolin and Puni- calin.

Table 1: Active constituents



Graph 1: Nutritive value (percentage) of Punica granatum

deciduous shrub or small tree, growth of 1.8-4.6m tall, belonging to the family Punicaceae. The fruits of pomegranate itself possess various therapeutically relevant constituents and, many of these constituents are effective in treatments of various diseases.

The leaves are around 7.6cm long and shiny. It has orange-red, trumpet-shaped flowers with disarranged petals and about 5 cm long. The fruits are globose, bright berry types, and 5–7.6 cm in diameter, but when get matured, the colour is reddish or yellowish-green. The seeds are crunchy having acidic pulp enclosed in a membranous skin (Qnais *et al.*, 2007).

In the recent, Punica granatum (Anar) have been studied for various therapeutic and essential uses including, in bacterial infection, anti-arthritic, antiinflammatory, atherosclerosis or arteriosclerosis, immunomodulation, antioxidants, fungal infection, periodontal disease, parasitic infection, skin disorder and food poisoning, and gastro-intestinal infection. There have even been much preliminary toxicity studies and approved data in mice/rats (rodents) to report Punica granatum as non-toxic at all concentrations/doses, especially at a high dose (Braga *et al.*, 2005).

There are various compounds present in P.granatum fruits; among these compounds, the most therapeutic phytochemicals are polyphenolics, flavonoids, alkaloids, ellagic, as well as gallic acid. The peel contains punicalagin, alkaloids, tannins (approximately 20%), granatins A, granatins B, gallagyldilacton, tellimagrandin I, and corilagin, casuarinin, pedunculagin, having different

potential.

Compounds like granatins A and B, and punicalagin or punicalin are essential compounds having antimicrobial activities. The potential activities of compounds carried out in a study showed that phenolic compounds relatively at high dose contains the therapeutic potential for antifungal activity (Anibal *et al.*, 2013).

Scientific classifications

The Punica granatum belongs to the kingdom, Plantae, and clade is classified into four sub-categories as Tracheophytes, Angiosperms, Eudicots, Rosids, respectively. The genus is Punica, and it was originated from Iran to northern India and now widely cultivated throughout the world, especially, the fruits are in the northern hemisphere from September to February. The binomial name for it is Punica granatum Linn.

Phytochemicals of P. granatum

Punica granatum contains various phytochemicals constituents which are responsible for their therapeutic and potential activity against various disease. The plant parts with their phytochemical constituents are listed in the below Table 1 (Mena *et al.*, 2011).

Nutritive compositions

The fruits of pomegranate per 200gm serving 10-12% daily value of vitamin C and folate and 16% of vitamin K and 20% dietary fibres. The total carbo-hydrates present is about 9-14% and contains 8% of vitamin B6, and other nutritional values are in the given Graph 1 (Jasuja *et al.*, 2012).

Effects of Punica Granatum As An Antifungal Agent

The whole parts of Punica granatum (leaves, peel, flowers, and fruits) have been used for various diseases for centuries.

The whole parts of P. granatum have been extracted in ethanol to investigate the antifungal activity tested against Candida spp using microscopy and mass spectroscopy methods. The activity of these extracts and resistance to all strains shown after 24hours, pericarp extracts has more significant activity than the other extracts by displaying the lowest MIC (maximum inhibitory concentration) of 31.5μ g/ml and highest MIC of 125 or 250 μ g/ml against Candida species.

However, after 48 hours, both peel and pericarp have shown higher antifungal activity against C. parapsilosis and other Candida species (Anibal *et al.*, 2013). The phenolic peel extracts of P. granatum against the two strains of fungus, Aspergillus parasiticus NRRL 2999, and Aspergillus parasiticus NRRL 465 showed an antifungal activity by using disc diffusion methods. The potential activity of extracts depends upon the concentrations, as the extract concentration increases, the activity increases gradually (Oraki *et al.*, 2011).

The antifungal or anticandidal activity of plant P. granatum has been investigated in different solvents like ethanol, methanol, N, N-dimethyl formamide (DMF), propanol, acetone, benzyl alcohol and compared with commercial antibiotics like amphotericin B, clotrimazole and nystatins. These solvents extract of natural plant proved the more excellent potent activity than the existing commercially active compounds (Nair, 2005).

Punica granatum was used to test as antifungal agents against candidosis associated with denture stomatitis by preparing gel extraction of pomegranate to avoid fluctuations in the oral cavity's active principles concentration.

The investigation showed the therapeutic activity as antifungal agents by affecting bacterial membranes and disturbing bacterial co-aggregation with the help of salivary proteins and some oral bacterial enzymes (de Souza Vasconcelos *et al.*, 2003).

Effects of Punica Granatum As An Antioxidants Agent

In a human body, variable chemicals are created as free radicals through an oxidation process, and these free radicals can destroy cell membranes and other structures as their amount increases in the human body. Antioxidants work on these free radicals to remove and neutralize it from the body to make a correct balance.

The phenolic compounds and tocopherols present in Punica granatum have been studied for antioxidant activity by using various methods as differential pH methods, HPLC analysis. The hydrolysis of ellagitannins and gallotannins produced two hydroxybenzoic acids, i.e., ellagic acid and gallic acid, respectively, that are responsible for antioxidant activity. It was investigated that the seed oil contains a high volume of tocopherols having great activity as antioxidant using ORAC and FRAP assays (Elfalleh *et al.*, 2011).

The aqueous and ethyl acetate extracts of P. granatum evaluated for antioxidant activity using reagents and methods like DDPH test, chemiluminescence assay, and 5-lipoxygenase assay and this study investigated that the peel, juice, and extracts of pomegranate possess a significant antioxidant activity (Ricci *et al.*, 2006). The ethanolic, methanolic and aqueous extracts of peel and seed of pomegranate exhibited a various degree

of antioxidant activity that is determined with the bleaching of β -carotene and DDPH methods. The methanolic extracts of pomegranate peel possess the highest potential as antioxidants (Singh *et al.*, 2002).

The antioxidant action of Egyptian Punica granatum peel extracts was studied using HPCL modified analysis and standardization, ellagic acid, and gallic acid was considered as markers or positive control. The peel extraction with 70% ethanol showed the highest capacity to scavenge DDPH free radicals to exhibit a pronounced antioxidant activity (Motaal, 2011).

Effects of Punica Granatum As An Antidiarrheal Agent

The most common and known condition that affects all age group people is Diarrhoea and recognized by a frequent loose, watery bowel motion. The acute or brief diarrhoea is mainly caused by a parasitic, bacterial, and viral infection of the bowels and chronic might be caused by some disorder and conditions associated with gastroenteritis.

The aqueous and alcoholic extract of fruits rind of pomegranate was investigated on Albino rats to evaluate the antidiarrheal activity and compared with the most effective commercially available Loperamide hydrochloride. The aqueous extract was observed with the 86.6% effectiveness at 500mg/kg than alcohol extract for significant antidiarrheal activity (Pillai, 1992).

A study that was carried on the gastrointestinal motility in vivo, isolated rats ileum, and on castor oil-induced in rodents have revealed the extract contains many substances that inhibit intestinal motility and intestinal fluid accumulation and hence reduced diarrhoea. The potency of that extract showed similar effects to commercial drugs like loperamide (Qnais *et al.*, 2007) and its inhibitory percentage of defaecation was 71.25% for castor induced diarrhoea (Akter *et al.*, 2013). Punica granatum seeds that were extracted with methanol have shown inhibitory action against PGE₂ induced enteropooling in rats and castor-induced diarrhoea.

It has also shown a notable decrease in gastrointestinal movement (motility) in the charcoal meal test in rats (Das *et al.*, 1999). In castor oil-induced diarrhoea, extract inhibitory percentage of defaecation at a concentration/dose of 200mg/kg was 31.25%, and at the dose of 400mg/kg was 53.75%. The extract inhibitory percentage of defaecation has found to be 45.71% and 57.14% at the dose of 200mg/kg and 400mg/kg, respectively, in magnesium sulfate-induced diarrhoea (Akter *et al.*, 2013).

Effects of Punica Granatum As An Anti-Inflammatory Agent

Inflammation is the reaction of the body's immune system to injury, wound, or other damage to start the healing processes and to eliminate harmful stimuli. Anti-inflammatory is the agents that reduce the inflammation and relieve the pain due to inflammation.

Punica granatum contains various chemical constituents that significantly works on the inflammation by inhibiting the pro-inflammatory cytokines and reduces inflammation.

The ethyl acetate, phenolic and tannin extracts of Punica granatum strongly inhibited the lipoxygenase (LOX) and cyclooxygenase (COX) stimulation and activity during inflammation. It also inhibited the phosphorylation process of various cytokines in the UV-B irradiated keratinocytes, having mitogenactivated protein kinases (MAPK) (Lansky and Newman, 2007).

The study was done with the help of carrageenaninduced inflammation model for determining the inhibition of COX and LOX enzymes (Sarkar, 2012). Pomegranate extracts (pre-ether, dichloromethane, and methanol) were investigated for the antiinflammatory effect at the dose of 100mg/kg body weight using the carrageenan-induced acute inflammatory model and compared with diclofenac as a standard drug. This study has shown 27.97% inhibition of paw oedema and other inhibitory action on prostaglandin synthesis and pro-inflammatory mediators (Mastrogiovanni *et al.*, 2019).

The pomegranate peel extract (PPE) was studied for anti-inflammatory effects and has shown the concentration-dependent activity at 0, 1.0, 2.5, 5, 10, 25 μ g/ml by conquering the CXCL8 concentrations in the cell and tissue supernatants in both the in-vitro Caco-2 cell model and ex-vivo porcine colonic explant model (Lee *et al.*, 2010). The phenolic content of Pomegranate fruits had shown the potential nitric oxide (NO) inhibitory action in the LPS induced RAW 264.7 macrophages cells and significantly decreases paw oedema at the concentration/dose of 2.5 and 10.0 mg/kg (Houston *et al.*, 2017; BenSaad *et al.*, 2017).

It also showed important effects on COX-2 expression in ex vivo skin when investigated with total pomegranate tannins, and pomegranate rind extracts with or without zinc (Kota *et al.*, 2018). When the anti-inflammatory activity was evaluated using Ethyl phenylpropionate (EPP) induced ear oedema at the dose of 20μ l/ear, it has given a significant decrease in pain and oedema (Bhandary

et al., 2014).

ethanolic The and methanolic extracts of pomegranate when investigated by in vitro HRBC membrane-stabilizing method at the concentration of 50, 100, 200, 400, 800 and 1600 μ g/ml using UV spectrophotometer at 560nm, it showed the concentration-dependent potential with 81.76% protection as compared to diclofenac sodium as standard (Nainwani, 2014). The formalin-induced nociceptive behaviour in mice was evaluated for the anti-inflammatory activity and found an effective reduction in both phases of formalin tests (González-Trujano et al., 2015). The ethanolic extract of pomegranate showed the highest potent activity against control and standard drug, diclofenac sodium (Wang et al., 2019).

Effects of Punica Granatum As An Antibacterial Agent

Antibacterial agents are those that combat pathogenic bacteria by killing and reducing metabolic activity in the biological environment and its pathogenic effects. The agent may avoid accumulation of bacterial plaque in oral surrounding.

The antibacterial activity of Pomegranate with methanol, acetone, extracts were investigated by pour plate method against a gram-positive as well as gram-negative bacteria. A potent radical-scavenging activities has shown with all extracts at low concentrations, but acetone extract showed the best potential than the other two extracts (Negi and Jayaprakasha, 2003). The whole pomegranate parts were investigated for an antibacterial activity against four gram-positive (B. coagulants, B. cereus B. subtilis and, S. aureus) and three Gram-Negative bacteria (E. coli, K. pneumoniae, and, P. aeruginosa). The peel extract has shown the most effective action as an antibacterial against Staphylococcus aureus and fewer effects on E.coli bacteria (Dahham et al., 2010).

The chemical constituents, especially tannins and ellagic acid, were highly responsible for the antibacterial action against S. aureus and also accelerated blood clotting and control haemorrhage in animals (Akiyama, 2001). The peel ethanol extract of pomegranate against around 16 strains of salmonella has shown minimum inhibitory concentrations in the range of 62.5–1000x03BCgmL, and in vivo activity was determined in S. Typhimurium infection mouse model that showed potential effects on a number of viable S. Typhimurium improved from faeces and motility (Choi *et al.*, 2011).

The leaf of Punica granatum was extracted with several different solvents (with polarity) to determine its antibacterial activity against 6 strains (clinical) of S. paratyphl, S. aureus, E. aerogenes, S. epidermidis, P. aeruginosa, and, B. Subtilis by growth inhibition with the help of Agar ditch diffusion assay. However, aqueous extracts have shown maximum inhibition zone to 1.4 cm, and the next solvent was 1, 4-dioxane with 0.9cm (Nair and Chanda, 2005).

The effect of Punica granatum (pomegranate) on S. aureus FRI 722 growth and, enterotoxin production has determined by using the tube dilution technique and membrane-over-agar, respectively. The potential of extracts showed concentration-dependent activities, i.e., at low concentration, it showed 0.01-0.02% v/v delay of bacterial growth, and at high concentration, there was (1%v/v) elimination of bacterial growth (Braga *et al.*, 2005).

Effects of Punica Granatum As Neuroprotective Agent

The neuroprotective word itself defines the meaning or function in the human and animal body, i.e., 'Neuro' indicates neurons or nervous system and 'Protective' implies to protect. Thus, it is defined as the substances or agents that have mechanisms and strategies to protect the nervous system from any injury or damage and preserves the structural and functional characteristics of the neurons(brain) by inhibiting and intervening the pathogenetic cascade.

There is a various investigation performed for the determination of various parts of Punica granatum for their neuroprotective potential. The pomegranate was evaluated for its neuroprotective activities against methotrexate-induced toxicity in rats by giving 225 mg/kg extract on the first day through orogastric gavage once a day and 20mg/kg of methotrexate on second day intraperitoneally. The sciatic nerves were measured for the TAS (total antioxidant capacity), IL-1 β , and TNF- α , and it was found that there is a significant decrease in these levels when compared with the methotrexate group (Celik *et al.*, 2013).

Pomegranate extracts have also shown a dosedependent neuroprotective potential against the MPTP-Induced cytotoxicity and oxidative stress in human primary neurons (Braidy *et al.*, 2013). When the aqueous extract of the pomegranate(peel) was evaluated for the neuroprotective potential, it has shown antioxidant assay (DPPH assay) having IC50 values of $32.89\mu g$, $28.25\mu g$ and acetylcholinesterase inhibition analysis with IC50 values of $387.5\mu g$ and $201.3\mu g$ Vasudev *et al.* (2015).

It was investigated that the consumption of pomegranate peel extract helps to protect or prevent the progression and establishment of the neurodegenerative process through the reduction of amyloid plaque density, acetylcholinesterase enzyme, and lipid peroxidation when induced in mice by infusion with amyloid- β peptide (Morzelle *et al.*, 2016). The hydrolyzable polyphenol compound, Punicalagin, in Punica granatum when tested against the focal cerebral ischemia-reperfusion injury in rats at the constant dose of 15 and 30 mg/kg, showed the potential inhibitory effects due to potent antioxidant and neuroprotective (Yaidikar *et al.*, 2014).

Effects of Punica Granatum As An Anti-Arthritic Agent

A musculoskeletal, metabolic, autoimmune, inflammatory, and infectious condition that affects all of the joints protected by synovium leading to debilitating polyarthritis and other body organs and as the disease progresses, the inflamed synovium seizes and damages the cartilage and bone, weakening the surrounding muscles, ligaments and tendons.

When the aqueous and ethanolic extracts of Punica granatum were evaluated for the in vitro antiarthritic activity, it showed the concentrationdependent potential with the maximum inhibitory percentage of 99.18% at the dose of 800 μ g/ml when compared with diclofenac sodium as reference (Kamble and Nazia, 2017) by reducing the cartilage damage, lessen the inflammation, and fights with the enzymes that damage or destroy the cartilage (Bhowmik *et al.*, 2013).

The methanolic extract of the Punica granatum has the most potent and higher anti-arthritic potential as compared to the aqueous and ethanolic extracts because of high amounts of phytochemicals like flavonoids, sterols, etc (Gautam *et al.*, 2013; Jayakumar *et al.*, 2012).

The extracts of pomegranate were investigated for anti-arthritic activity using in vivo FCA induced arthritic rat models, and it was found to be most effective in the reduction of paw volume and increase body weight at the dose of 200mg/kg and 400mg/kg in both developing and developed arthritis (Kothari *et al.*, 2011) by reducing the altered level of interleukin 1β (IL- 1β) and TNF- α levels in rats (Wang *et al.*, 2019).

Effects of Punica Granatum As An Anticancer Agent

Cancer is a life-threatening disease for thousands of years because the cells present in the human body somehow get altered, multiplies, and spread out of control, and the treatment and prevention of cancer are still tough challenges throughout the world. There are many commercial as well as herbal drugs used in the treatment of cancer, and Punica granatum is one of the most effective natural plants that is used as anticancer agents.

Punica granatum rind extract when investigated against human lung cancer A549 cell lines using cell viability assay and DNA fragmentation analysis at the following concentration of 12.5, 25, 50,100 μ g/ml for 48 hours, it showed the dose-dependent inhibitory potential by inhibiting the growth of the cell and apoptosis (Jayakumar *et al.*, 2012).

Similarly, melanoma cell lines (A375) were also determined at the highest concentration of 2000mg/kg using MTT assay at the wavelength of 570nm using a microplate spectrophotometer, and Doxorubicin was used as a reference drug to compare the cell viability and percentage life span (Joseph *et al.*, 2013).

The leaf extract of Punica granatum was investigated against human liver cancer cells (HepG2) at the dose of IC₅₀ 70 μ g/ml using MTT assay and found to have a significant potential of killing cancerous cells and also indicated the free radical scavenging in vitro activity (Saratale *et al.*, 2018).

The pomegranate seed extracts against colon cancer (Caco cells) cell lines and Hepatocellular carcinoma (HepG2) showed the dose-dependent antiproliferating response at the dose concentration of 10-100 μ g/ml with the highest percentage 95.8% and 99% respectively (El-Awady *et al.*, 2015). When the pomegranate extracts were evaluated with similar methods as above against MCF-7, Breast cancer cells, at a significant dose of 40 μ g/ml, has shown the programmed cell death and apoptosis of cancerous cells (Jeune *et al.*, 2005).

Punica granatum has also shown potential inhibitory action against human PC-3 prostate cancer cells when three or more chemical constituents mixed in equal or same gross dosage $(4\mu g/ml)$ (Lansky *et al.*, 2005). The ethanolic peel extracts of pomegranate have shown the highest potential against the cancerous cell lines when compared to other extracts (Motaal, 2011).

Effects of Punica Granatum As A Radioprotective Agent

The term radioprotection is explained that the prevention from the ionizing radiation that can be planned or unplanned exposure of the radiation of the biological system. Acetone extract of the Punica granatum fruit rind showed the radioprotective effect on male Swiss albino mouse (mus musculus norvegicus) at the various concentration (5,10,15,20,30,40 and 50mg/kg body weight). The effect of the various concentrations was evaluated against the gamma radiation (8Gy) (Mathur and Sharma, 2013).

Effects of Punica Granatum As An Aphrodisiac Agent

The juice of the Punica granatum showed the reproductive effect against the carbon tetrachloride (CCl_4) induced testes toxicity on adult male Wistar albino rats (Al-Olayan *et al.*, 2014).

The ethanolic extracts of the pericarp of Punica granatum showed the reproductive effect at the dose of 500mg/kg body weight against the lead acetate induced toxic effect on adult male Holtzman rats sperm production (Leiva *et al.*, 2011) Iso-flavonoid extracted (Ethyl acetate fraction) from the fresh, dried rind powder of the plant Punica granatum has been shown the reproductive effect in male rabbits (Al-Saeed and Hadi, 2015).

The juice of pomegranate showed a significant increase in plasma gonadotropin and testosterone level at the dose of 8ml/kg, i.e., increase in reproductive capacity, as compared to control and standard (Riaz *et al.*, 2018).

Effects of Punica Granatum As An Trypsin And Protein Denaturation Inhibitory Agent

Methanolic and ethanolic extract of the plant Punica granatum showed the concentration-dependent trypsin (Proteinase) and protein denaturation inhibitory activity at the dose of 10, 50,100, 200, 400, 800, 1000 and 2000μ g/ml when compared with diclofenac as standard using UV visible spectrophotometer at 660nm and viscosities were measured using the Ostwald viscometer (Gautam *et al.*, 2013).

Effects of Punica Granatum As A Collagenase (Matrix Metalloproteinases) Inhibitory Agent

Ethanolic extract of the plant Punica granatum showed the potential Collagenase (Matrix metalloproteinases) inhibitory activity at the various concentration (100, 250, 500, and 1000μ g/ml) due to the presence of potential anti-inflammatory compounds. The diclofenac sodium was used as a standard reference drug with the same concentration variation (Patel and Zaveri, 2016).

Effects of Punica Granatum As A Hrbc Membrane Stabilization Agent

The aqueous, ethanol and methanol extracts of the Punica granatum has shown the concentrationdependent in-vitro membrane stabilization activity against the HRBC membrane stabilization assay at the different concentrations with 50, 100, 200, 400, 800 and 1600 μ g/ml using UV spectrophotometer at 560nm. The parameters were compared with diclofenac as a standard drug (Gautam *et al.*, 2013; Kota *et al.*, 2018).

CONCLUSIONS

The data of Punica Granatum has revealed its wide variety of activity which has been explored in recent years, but by reviewing this article, we are sure that this plant has immense potential, which can be further explored for different other activity which is untouched. There are a few behaviours which were previously investigated for their specific activities. There are still too many diseases in the lap of nature that remain unexplored and need to be studied. Like allopathic drugs, herbal medications have little or no side effects, and regular toxicity. This analysis is, therefore, merely an initiation to include herbal source choices for the treatment of diverse types of diseases.

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Conflict of Interest

The authors declared that they have no conflict of interests.

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