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A SYSTEMATIC REVIEW ON PHYTOCHEMISTRY AND PHARMACOLOGICAL ACTIVITIES OF *PUNICA GRANATUM*

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ABSTRACT

Punica granatum L. (Pomegranate) belonging to the family *Punicaceae* known to have several medicinal uses in different systems of medicine. The parts of *Punica granatum* plant such as seeds, peels, flowers, juice and leaves contain potent bioactive compounds which are useful in numerous diseases including gastrointestinal, cardiovascular and endocrine diseases. The juice and seed of *Punica granatum* has potential role in hepatoprotective injury. It has potent antioxidant, anti-inflammatory, antifungal, anticancer, antiviral, antimicrobial, antidiabetic and biopharmaceutical properties. It also has protective role in skin damage, male infertility and in various neurodegenerative diseases. The Present review outlines about different therapeutic uses and phytochemistry of Pomegranate (*Punica granatum*) based on the reported research studies and it involves summarized current research using various phytoconstituents and pharmacological approaches.

Keywords: Phytochemistry, Polyphenols, Pharmacological applications

INTRODUCTION-

India has a rich culture of medicinal herbs including ayurvedic and traditional uses of herbal medicines. The World Health Organization reports that the majority of people still use traditional medicines to treat their mental and physical health issues **[1]**. In Sanskrit, *Punica granatum* is known as 'dadima' and Pomegranate in English. Pomegranate is belonging to the family *Punicaceae*. Pomegranate is long living tree which grows 12-15 feet and live about 200 years. Flowers of *Punica granatum* are trumpet-shaped, orange-red, and have ruffled petals. The roughly 5 cm long,

sometimes double, and protractedly formed blooms are produced in the summer. When fully grown, the fruit is globose, 5-7.6 cm in diameter, and bright reddish or yellowish green. It is stuffed with crunchy seeds that are individually covered in a delicious, acidic pulp that is coated in a membranous shell **[2]**. Each part of *Punica granatum* is utilized in traditional medicinal systems due to the presence of potent phytoconstituents, which confer potent biological activity. It is widely consumed as a fruits or juice as it is biologically rich in various active substances like acids, sugars, vitamins, minerals **[3]**. The peels and fruits extract of *Punica granatum* has reported for different potent pharmacological activities including Antioxidant, Anti-inflammatory, Anticancer activities **[4]**. As Pomegranate has potent antioxidant activity, there has been great interest involved in accordance with the role of dietary antioxidant in various neurodegenerative diseases. Fruits of *Punica granatum* are rich source of vitamins and minerals which are widely used in the dietary supplement industry and peels are rich in Tannins, flavonoids and phenols so it is useful for various research purposes in growing field of herbal research **[5]**.

PHYTOCHEMISTRY OF P. GRANATUM FRUIT –

Punica granatum is recognised to contain a variety of phytochemicals, the majority of which have been found to have potent medicinal effects. Numerous substances, including tannins, punicalagin, ellagic acid, hydroquinone pyridinium, delphinidin, and cyanidin, have been identified from *Punica granatum*. Each part of *Punica granatum* contain different phytoconstituents that have effective pharmacological activity. The main phytoconstituents includes Polyphenols, Anthocynosides and other components **[6]**.

The Reported phytoconstituents of different parts of pomegranate is described in following **Table 1**.

Table 1: Phytoconstituents

Sr. No.	Parts of *Punica granatum*	Reported Phytoconstituents
1.	Root	Piperidine alkaloids, ellagitannins including punicalin and punicagalin [7].
2.	Bark	Ellagitannins including punicalin, punicagalin, punicacortein, pelletierine alkaloids [8].
3.	Leaves	Flavonols: quercetin, flavones, apigenin, flavones glycosides: luteolin, ellgitannins: punicalin, punicalagin corilagin, punicafolin, piperidine alkaloids [9].
4.	Flowers	Flavonoids, gallic acid, ellagic acids linoleic acid, palmitic acid, sterols , triterpenoides [10].
5.	Peels	Flavonoids: Anthocyanins such as pelargonidin, delphinidin, cyanidin and anthoxanthins such as catechin, epicatechin and quercetin. Tannins: ellagitannins and ellagic acid derivatives such as punicalagin, punicalin. Phenolic acids: chlorogenic acid, caffeic acid, ellagic acid, gallic acid [11].
6.	Juice	Anthocyanins, glucose, fructose, ascorbic acid, ellagic acid, Gallic acid, caffeic acid, catechin, quercetin, rutin, various minerals like iron and amino acids [12].

PHARMACOLOGICAL ACTIVITIES OF *PUNICA GRANATUM* –

Pomegranate contain effective phytoconstituents which are having potent

pharmacological activities. The various Pharmacological activities of *Punica granatum* are explained in depth in this review.

These Pharmacological activities of Pomegranate are summarised in following **Figure 1**.

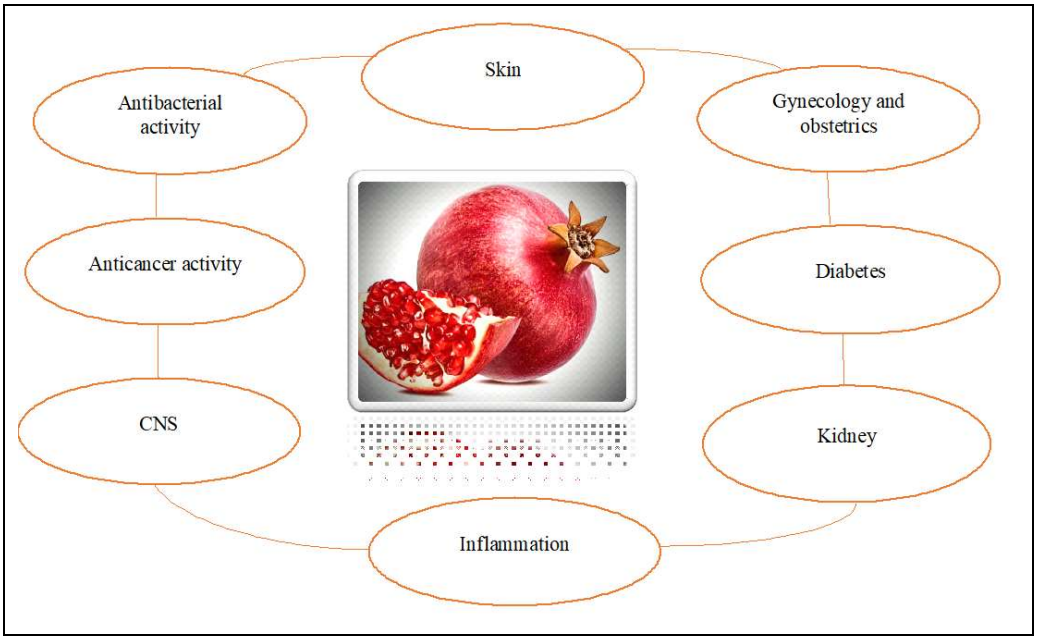

Figure 1: Pharmacological activities of Pomegranate

1. Anti-inflammatory Action [13, 14] -

Punica granatum is known to have a wide range of biochemical characteristics, including anti-inflammatory action. The *P. granatum* plant has been extensively employed for cosmetic applications in addition to traditional usage and pharmacological uses. Punicagranine 1, which is known to have anti-inflammatory activities, is found in dried *Punica granatum* peel extracts prepared in methanol, water and ethanol. Another study has been conducted by using aqueous and alcoholic extract of leaves and it is investigated that potential of pomegranate leaf extracts to stimulate hair development in albino mice by treating animals with alopecia diseases. Another observation was that oral treatment of Punica fruit extract (100 mg/kg) decreased paw edoema in carrageenan-induced mice paw edoema by lowering prostaglandin E2 synthesis. *Punica granatum* has been recognized for its effectiveness in treating a wide range of inflammatory diseases. For the treatment and prevention of arthritis and other autoimmune disorders, dietary supplements

containing pomegranate extract have attracted attention.

2. Antibacterial activity [15]–

Medicinal herbs, when taken as natural treatments, may provide an entirely different approach to the battle against antibiotic resistance. Initially, the disc diffusion method was used to assess the antibacterial effectiveness of 10 distinct *P. granatum* samples (fresh juice, lyophilized juice, EtOH peel extract, EtOH lyophilized peel extract, H2O peel extract, H2O lyophilized seed extract, EtOH seed extract, EtOH lyophilized seed extract) (DDM). The four most successful samples were also selected depending on DDM, where antibacterial effectiveness was measured. By using the broth microdilution technique (BMD) at five different sample concentrations, the microbial growth inhibition rate (MGIR) on Gram-negative (*E. coli, P. aeruginosa, and P. fluorescens*) and Gram-positive (B. cereus, S. aureus, and S. pyogenes) bacteria was assessed. According to the literature, Gram-positive bacteria is more susceptible to antimicrobial agents, while Gram-negative bacteria is more resistant due to their outer lipopolysaccharide membranes. As a result, in our investigation, *P.granatum* extracts were specifically evaluated against Gram-negative and Gram-positive bacteria, both of which are rapidly adaptable and well-known to develop resistance.

3. Anticancer Activity [16] –

Pomegranate is rich source of Polyphenolic compounds. The peels of Pomegranate which is biowaste of that fruit contain polyphenolic compounds that are beneficial for curing the various types of cancer such as breast cancer, colon cancer, colorectal cancer, cervical cancer, hepatocellular carcinoma, lung cancer, liver cancer, osteosarcoma, ovarian cancer, prostate cancer, skin cancer, thyroid cancer, urinary bladder cancer etc. Studies conducted in vitro and in vivo have demonstrated that polyphenol-rich Punica peel extract acts as potent antioxidants that help in the suppression of cancer cell proliferation **[16]**.

4. Antidiarrheal activity [17]-

The Antidiarrheal activity of aqueous extract of pomegranate peel was studied in rats. In vivo gastrointestinal motility, the isolated rat ileum, and rat castor oil-induced diarrhoea were all the subjects of research. The outcomes showed that the extract attenuated acetylcholine-induced contractions and inhibited the spontaneous movement of an isolated rat ileum in a concentration-dependent manner. Rats were significantly protected from castor oil-induced diarrhoea entero-pooling and the extract (100, 200, 300, and 400 mg=kg) also caused a dose-dependent reduction in gastrointestinal transit. It was discovered that the extract's LD50 after intraperitoneal administration in mice was 132115 mg/kg. Tannins, flavonoids, and alkaloids were detected

during a preliminary phytochemical screening of the aqueous *Punica granatum* peel extract. The results obtained showed that an aqueous extract of *Punica granatum* peels may contain some biologically active principles that may be active against diarrhea, and this may be the basis for its traditional use for gastrointestinal disorders.

5. Cardioprotective activity [18] -

Edible parts of pomegranate fruits (about 50% of total fruit weight) comprise 80% juice and 20% seeds. Fresh juice contains 85% moisture, 10% total sugars, 1.5% pectin, ascorbic acid, and polyphenols. Polyphenolic flavonoids are extensively found in the pomegranate fruits and they are effective in various cardiovascular diseases. The Pomegranate polyphenols which have antiatherogenic effect on serum lipoproteins and on artificial macrophages using in vivo and invitro human and animal models. Pomegranate juice and its byproducts diminished the deposition of cholesterol and oxidised lipids in macrophages as well as the production of foam cells, which is a sign of early atherogenesis. As a result, atherosclerosis and the subsequent cardiovascular events were decreased. Flavonoids are potent antioxidants, and their composition influences how effective they are. Plant flavonoids have the ability to efficiently prevent the oxidation of macrophages or low-density lipoprotein (LDL). The juice of pomegranate contain soluble polyphenols and mainly anthocyanins and anthoxanthins. They also contain Ellagic acids and Tannins which have potent Antioxidant action against cardiovascular diseases. The major ellagitannin present in the pomegranate juice is punicalgin which plays important role in the protection of heart against atheroschlerosis.

6. Antidiabetic and Hypolipidemic activity [19, 20]-

Pomegranates and other fruits high in polyphenol and antioxidants have been demonstrated in animal experiments to activate beta cells to produce insulin. The anti-diabetic properties of pomegranates have also been examined in a number of human investigations. Punicic acid, methanolic seed, and pomegranate peel extracts may have a role in the pomegranate juice's (PJ) ability to assist diabetic individuals to lower their fasting blood glucose levels. Reduced oxidative stress, lipid peroxidation, and inhibition or activation of nuclear factor κB and peroxisome proliferator-activated receptor served as the underlying mechanisms for this function. 85 diabetic individuals who consumed fresh PJ (1.5 ml/kg) showed a substantial decrease in FBG and insulin resistance as well as an improvement in -cell function (p 0.05).

7. Antiviral activity [21]-

Pomegranate contain polyphenols mainly caffeic acid, ellagic acid, Punicalin, Punicalgin, Anthocyanins, flavonols that are effective in various viral diseases including food borne, pox, herpes and HIV following the mechanism of action by decreasing the viral binding, infectivity and structural damage of viruses. In order to cure or prevent foodborne norovirus infections, it is essential to investigate more thoroughly the efficacy of natural treatments such pomegranate juice and extracts. Recent research has demonstrated that the antiviral activities of pomegranate juice and polyphenols are considerable against the foodborne virus. Pomegranate juice and polyphenols were applied to the host cell monolayers for the respective viruses before or after infection in order to understand the mechanism of action. Pomegranate extracts have also shown antiviral effects against influenza virus, HIV-1 and poxviruses. According to reports from 2003, the AIDS epidemic claimed that lives of 30 million people and caused 14,000 new HIV-1 infections per day worldwide. Antiretroviral chemotherapeutics have been mostly utilised in developed nations to reduce HIV-1 symptoms in the absence of vaccines.

8. Antifungal activity [22] –

The pomegranate skin was removed, dried, and pulverised. *Candida albicance* was inoculated at 37 °C and then seeded on Sabouraud's agar medium. The seeded plates are covered with sterilised filter sheets that have been soaked with extracts, and these plates are infected at 24 and 48 hours. Using a vernier calliper, zones of inhibition were measured all the way around the filter paper. With a mean zone of inhibition of 22 mm, *Candida albicans* was inhibited at the maximum level. The findings suggested that this extract may be used as an affordable and practical adjuvant to prescription antifungal treatments.

9. Antioxidant and Analgesic activity [23]-

The most significant and widely investigated class of plant phenolics are polyphenolic flavonoids. The number of flavonoids known so far reaches 4000. Flavonoids are powerful antioxidants, and their activity is related to their chemical structure. Three pain models, the writhing, hot tail flick, and plantar tests, were used to evaluate the analgesic efficacy of pomegranate ethyl acetate fraction (EtOAc). For all experiments, EtOAc was given orally through gavage in dosages of 100, 150, and 200 mg/kg, p.o. It was compared to the usual medication, aspirin, which was given at a dose of 100 mg/kg, p.o. High performance liquid chromatography (HPLC) with ultraviolet (UV) detection and mass spectrometry were used to conduct phytochemical investigations of EtOAc (MS). The index of pain inhibition (IPI) during the writhing test was 41% for EtOAc

(200 mg/kg, p.o.) and 56% for aspirin. As opposed to aspirin, which had a maximum potential analgesia (MPA) of 43.8%, EtOAc (200 mg/kg, p.o.) demonstrated analgesia reaching its peak at 60 min. The plantar test demonstrated that EtOAc decreased pain in a dosage-dependent way and performed comparably to aspirin at a dose of 100 mg/kg, p.o. The withdrawal latency in the left hind paw was prolonged to 11.9 0.3 with the 200 mg/kg dosage, compared to 13.4 0.2 with aspirin (p 0.001). Gallic acid, ellagic acid, and punicalagins A & B were detected in EtOAc using HPLC analysis. They were able to confirm their achieved by mass spectroscopy.

10. CNS related activities [24]-

The Pomegranate has potent pharmacological action on CNS including antidepressant, antiepileptic, Alzheimer's and dementia. Ellagic acid's potential antidepressant-like actions were examined in Swiss young male albino mice. To cause stress, mice were immobilised for 150 minutes. Ellagic acid (8.75, 17.5, and 35 mg/kg, po) and fluoxetine (20 mg/kg, ip) were given to both unstressed and stressed mice, and the length of time the mice remained immobile was determined using the forced swim test and tail suspension test. In both stressed and unstressed mice, plasma nitrite levels were also calculated. On the antidepressant-like action of ellagic acid, the effects of aminoguanidine (an iNOS inhibitor), 7-nitroindazole (an nNOS inhibitor), sulpiride (a selective D2-receptor antagonist), prazosin (an a1-adrenoceptor antagonist), and p-chlorophenylalanine. Ellagic acid significantly reduced immobility length when administered at two higher dosages (17.5 and 35 mg/kg, p.o.). Ellagic acid was discovered to be the mechanism of action that included the central monoaminergic system. *Punica granatum* hydroalcoholic extract was also tested for antiepileptic potential.

14. Effect on fertility [25]–

Male healthy rats were used to study the effects of pomegranate juice (PJ) intake on antioxidant activity, sperm quality, spermatogenic cell density, and serum testosterone levels. After receiving PJ therapy, a discernible decline in malondialdehyde (MDA) level was seen. Additionally, in rats given various dosages of PJ, a notable rise in the activities of glutathione peroxidase (GSHPx), glutathione (GSH), catalase (CAT), and vitamin C was seen. Increased epididymal sperm concentration, sperm motility, sperm cell density, seminiferous tubule diameter, and germinal cell layer thickness were seen after PJ treatment. In comparison to the control group, it also reduced the rate at which aberrant sperm were produced. These findings imply that PJ treatment enhances antioxidant activity and sperm quality in rats.

15. Hepatoprotective & Gastroprotective activity [26, 27]–

A disorder usually referred to as fatty liver is shown by abnormal liver function tests. The way that pomegranate flowers work (PGF), a conventional diabetes medication, on fatty liver was investigated. The results showed that this medication improves fatty liver disease linked to diabetes and obesity, at least in part, by promoting the hepatic gene expression that regulates fatty acid oxidation. using pomegranate as a pretreatment floral extract, given for seven days at a dosage of 50-150 mg/kg body weight, significantly increased the amount of Oxidative stress is dose-dependently brought on by decreased nitrilotriacetate (Fe-NTA). Protection from haptic harm was the effect of this. Up to 60% of the extract's protective action was visible. After extract administration, glutathione (GSH) levels and the activity of the antioxidant enzymes glutathione peroxidase (GPX), catalase (CAT), glutathione-S-transferase, and glutathione were all elevated.

Orally given pomegranate aqueous methanolic extract effectively decreased the ulcer index caused by alcohol, Rats receiving indomethacin and aspirin. Moreover, the extract considerably decreased the ulcerative lesions, stomach volume, and overall acidity in the rat pylorus-ligation model. By raising the pH of the stomach and secreting more mucus in pylorus-ligated rats, it avoided ulcers. Gastric ulcers are prevented by the tannins present in pomegranates

16. Effect on dental plaque [27]-

P. granatum fruits exerts a significant activity against microorganisms commonly present in the dental plaque. The effect was observed immediately after the mouth-rinse with HAE, when the number of CFU was reduced by 84%, as compared with the CFU number before mouth-rinse. A similar effect was observed with chlorhexidine. In contrast, in the control group, the reduction of the number of CFU was only 11%.

CONCLUSION-

Numerous phytochemical components, such as polyphenols, flavonoids, anthocyanosides, alkaloids, lignans, and triterpenes are reported for its potent pharmacological activities. Major Diabetes, cardiovascular illness, oral cavity problems, endocrine disorders, and cancer are among the conditions for which pomegranate has been shown to have positive pharmacological benefits in randomised clinical studies. *Punica granatum* and its components have multiple pharmacological effects and clinical applications. Large clinical trials have looked into its therapeutic activities against inflammation, cardiovascular diseases (e.g., hyperlipidemia and hypertension), endocrinopathies (e.g., diabetes), and cancer. Additionally, drinking pomegranate juice reduces obesity,

metabolic syndrome, and coronary heart disease (which is thought to be preventable because of its strong antioxidant qualities). Due to its anti-inflammatory, antioxidant, and antimicrobial properties, it probably has something to do with gingivitis and stomatitis.

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