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A COMPREHENSIVE REVIEW OF *PUNICA GRANATUM* (POMEGRANATE) PROPERTIES IN ETHNOPHARMACOLOGY

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ABSTRACT

Because of its rich content of bioactive chemicals, such as polyphenols, flavonoids, tannins, and anthocyanins, pomegranate (*Punica granatum*) has drawn a lot of attention for its various therapeutic uses. Its pharmacological potential is examined in this review, with a focus on its anti-obesity, anti-diabetic, anti-inflammatory, anti-emetic, anti-malarial, anti-cancer, and wound healing properties. The fruit's antioxidant qualities are essential for lowering oxidative stress and, consequently, the risk of developing chronic illnesses like heart disease and neurological disorders. Pomegranate's capacity to decrease tumor angiogenesis, induce apoptosis, and inhibit cell proliferation is associated with its anticancer potential. Its cardioprotective advantages also include improved lipid profiles, improved endothelial function, and blood pressure management. Although these results demonstrate the pomegranate's therapeutic potential, more clinical research is necessary to confirm its effectiveness, determine the best dosages, and investigate its incorporation into pharmacological and nutritional uses. The promising function of pomegranates in disease prevention and therapeutic interventions is highlighted in this review, indicating the need for further study to support its clinical translation.

INTRODUCTION

Knowledge about pharmaceutical herbs adds novel horizons to the world of medicine. Herbal medicines are cost-benefit and safer in comparison to synthetic medicines. Much of the data is limited to traditional healers or passed to the next generation orally, so it is important to preserve this valuable knowledge before it disappears [1,2]. A diet rich in antioxidant-rich fruits and vegetables might reduce your risk of developing oxidative stress-related chronic illnesses including diabetes, heart disease, and cancer. As a result, fruits are naturally high in bioactive chemicals associated with a wide range of biological functions, including as reducing inflammation, preventing cell death, and lowering blood sugar levels [2, 3]. Among these fruits, pomegranate (*Punica granatum* Linn.) has been discovered to be high in biologically active chemicals. The plant is a member of the Punicaceae family, found in Mediterranean countries. Because of its adaptability, the plant is now commonly thrived in warm, humid climate's locations on all continents. The pomegranate fruit is enjoyed both raw and cooked, and its many uses include juice, jam, molasses, and a variety of salad dressings, meats, and cheeses. Due to its high demand and great nutritional profile, pomegranate and its derivatives are widely accessible in global food markets [3-5].

Utilization:

Indeed, pomegranate has a long history of usage as a "healing food" in traditional medicine, with uses ranging from lowering fevers and parasites to treating a

variety of gastrointestinal issues, respiratory diseases, microbiological infections, and ulcers. Dental issues, sun-induced skin damage, male infertility, obesity, Alzheimer's, arthritis, cancer, new-born brain ischaemia, diabetes, and obesity are among the many additional ailments that traditional medicine has utilised it to cure.

Figure 1: *Punica granatum*plant

Table 1: Taxonomy

Kingdom	Plantae
Division	Magnoliophyta (Angiosperm)
Class	Magnoliopsida (Dicotyledon)
Subclass	Rosidae
Order	Myrtales
Family	Lythraceae
Genus	*Punica*
Species	*P. granatum*

Recent review publications have provided recent findings in the fields of ethnomedicine, pharmacology, phytochemistry, and molecular biology regarding the pomegranate. Additional research was undertaken on the health advantages of specific pomegranate parts and products. Furthermore, some believe that the health advantages of the Mediterranean diet are enhanced by pomegranate and its derivatives, including pomegranate molasses [6, 7].

Cultivation: Pomegranates are exported and produced by a large number of nations due to their distinctive flavour and possible health benefits. India ships its delicious pomegranate seeds to several countries, including the United States, Iran, and China. Russia, Iraq, and the UAE are among the nations that get Iran's pomegranates because of their reputation for producing high-quality fruit, especially the Malas variety. Pomegranates, a delicacy from Turkey, are exported to Europe and the Middle East, where they delight customers with their vibrant colour and flavour. Countries in the European Union, such as Germany and the United Kingdom, buy pomegranates from Egypt. The countries bordering Spain, such as France and Germany, receive the majority of the pomegranates produced by the Spanish fruit orchard. A growing number of people are looking for ways to improve their health, and pomegranate-based products are capitalising on this trend [8,9].

Table 2: Global production of pomegranate including top 8 countries (2008)

S. No.	Country	Production (in million tonnes)
1	Iran	0.600
2	India	0.500
3	China	0.260
4	US	0.110
5	Turkey	0.090
6	Spain	0.037
7	Tunisia	0.025
8	Israel	0.017

Pomegranate peels: Pomegranate peels are traditionally used to treat digestive issues, diarrhoea, and parasite infections. Pomegranate peels strong antioxidant content helps scavenge free radicals and protect cells from oxidative stress. Antioxidant activity may lower chronic disease risk and slow aging. Pomegranate peels possess powerful anti-inflammatory chemicals that can treat inflammation-related diseases. Pomegranate peels can replace synthetic preservatives in meat products, increasing shelf life while retaining quality. Adding pomegranate peel extracts can improve texture, extend shelf life, enhance colour stability, and boost antioxidant activity. These extracts are rich in polyphenols, such as ellagitannins and anthocyanins, which have been linked to many health advantages such as anti-oxidant, anti-inflammatory, and anti-bacterial characteristics. Incorporating pomegranate peel extracts into meat products can provide customers with a healthier and more appealing alternative.

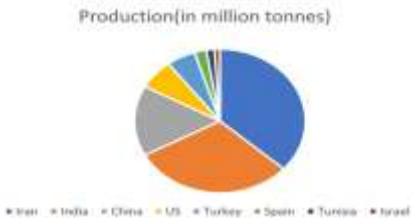

Figure 2: Pictorial graph representing the share of production of pomegranate as contributed by top 8 countries (2008)

Pomegranate peels contain a variety of polyphenols, including flavonoids, phenolic acids, and tannins, each having distinct structure and functional capabilities. Flavonoids and phenolic acids include hydroxyl groups and conjugated double bonds, which enhance their antioxidant and anti-inflammatory properties. Ellagitannins in pomegranate peels, including punicalagins and punicalins, have a complicated structure with ellagic acid moieties connected to glucose units. Pomegranate peels' high fiber content may improve gastrointestinal health and lower cholesterol levels. Overall, the structure-function relationship of pomegranate peels highlights how their particular components and structural traits contribute to their different biological activities, making them a significant source of naturally occurring bioactive chemicals with potential health advantages [10-12].

Figure 3: Dried pomegranate peel

Benefits of pomegranate fruit: Fruits are high antioxidant potential that have been linked to a variety of medical characteristics and health benefits. Fruits are a rich source of phytochemicals and antioxidants, such as flavonoids, tannins, and phenolic acids, which have been demonstrated to help prevent a number of serious illnesses, such as cancer and cardiovascular and cerebrovascular disease. Antioxidant-rich bioactive compounds eliminate free radicals from cells to prevent oxidative damage and lipid peroxidation processes, maintaining cell structure and function and halting food degradation.

Figure 4: Pomegranate fruit

Since it is connected to the genesis and evolution of diabetes mellitus, oxidative stress is the primary cause of many chronic illnesses. The most common kind of diabetes mellitus in the world is type 2, which is a metabolic disorder characterized primarily by hyperglycemia brought on by anomalies in insulin production and/or action. By 2040, there will likely be 642 million people worldwide with type 2 diabetes mellitus, up from 415 million in 2015. Because type 2 diabetes is mostly associated with poor dietary habits and obesity, eating more fruits and vegetables rich in natural bioactive components can help prevent its development. Pomegranate has been widely used as a "healing food" in many cultures since ancient times, as traditional remedy for parasites and alleviate worm infections, boils, ulcers, diarrhoea, acidosis, haemorrhage, aphthae, respiratory disorders, and microbiological infections. Additionally, it has a long history of usage as a folk remedy for cancer, gum disease, and bacterial infections, UV-induced issues with the skin, infertility in men, arthritis, obesity, and foetal brain ischaemia. Lebanese people have traditionally relied on pomegranate extract as a diabetic treatment [13-15].

Phytochemistry: Peel contains complex polysaccharides, minerals bioactive chemicals (including phenolics, flavonoids, ellagitannins, and proanthocyanidin compounds), and accounts for around half of a fruit's overall weight. Forty percent of a pomegranate's fruit is edible, including the arils and ten percent the seeds. In addition to pectin (1.5%), organic acids (ascorbic, citric, and malic acid) and bioactive chemicals (phenolics, flavonoids, and mostly anthocyanins), arils also include 85% water and 10% total sugars (primarily fructose and glucose).

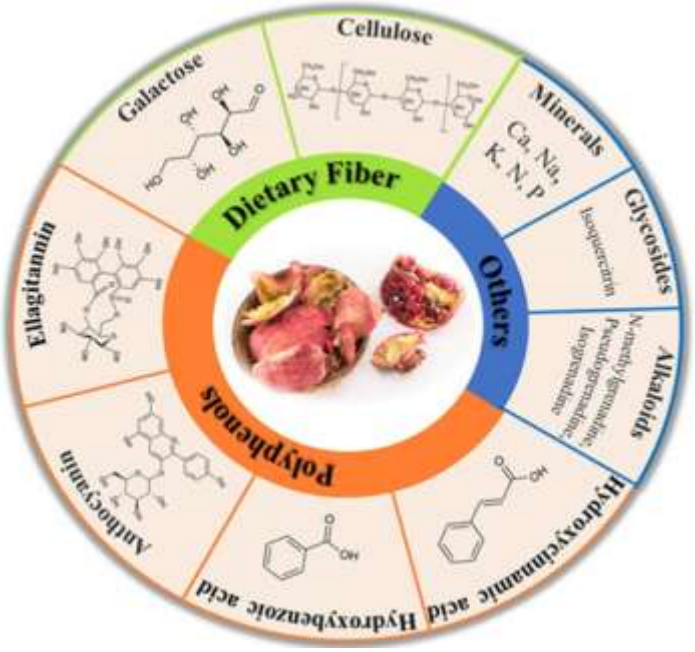

Figure 5: Chemical composition of *P. granatum* peels

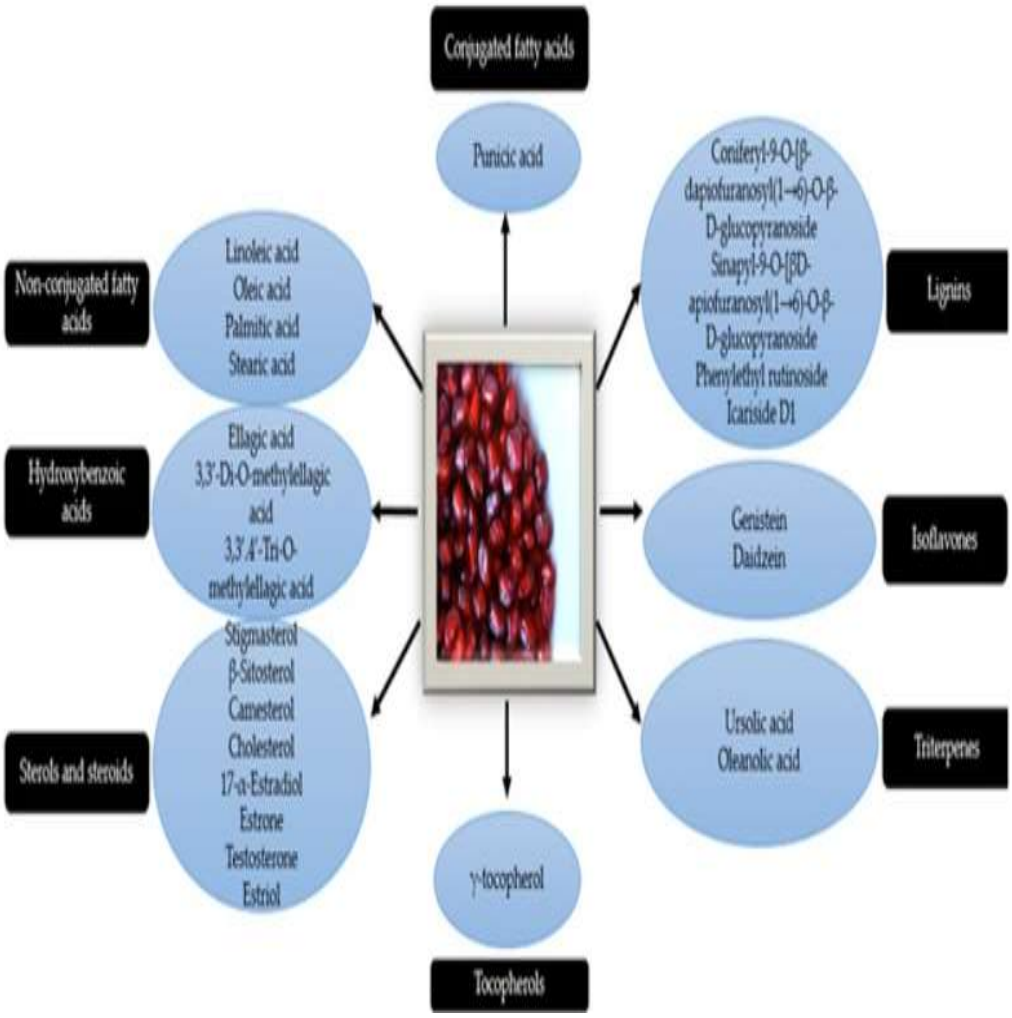

Figure 6: Chemical composition of the *P. granatum* seeds

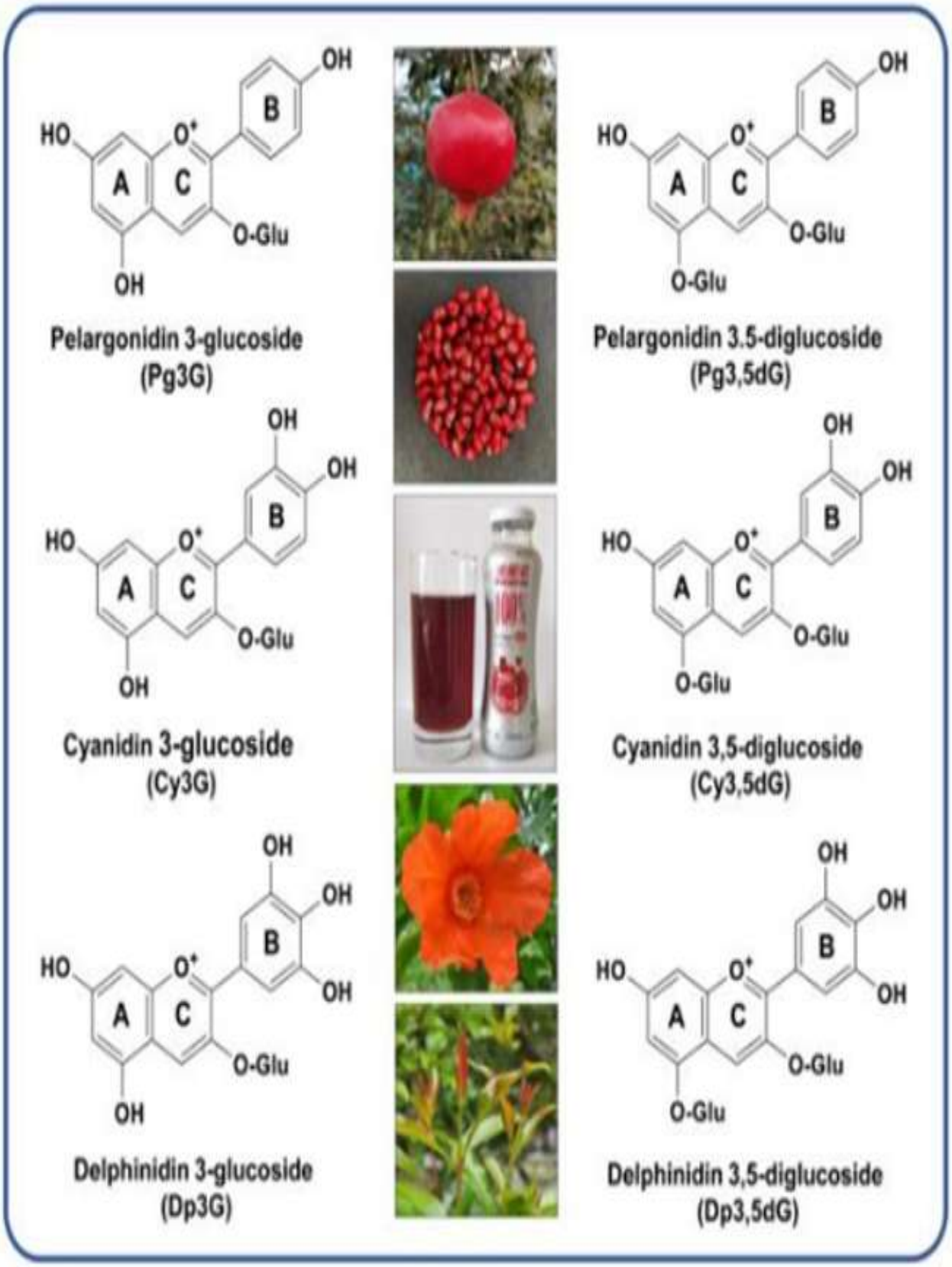

Figure 7: The important phenolic ingredients in *P. granatum*

Some of the anthocyanins found in pomegranate juice include delphinidin-3,5-diglucoside, cyanidin-3,5-diglucoside, pelargonidin-3,5-glucoside, and delphinidin-3,5-diglucoside, all of which are found in the fruit's seed coat. Some of the anthocyanins found in pomegranate juice include delphinidin-3,5-diglucoside, cyanidin-3,5-diglucoside, pelargonidin-3,5-glucoside, and delphinidin-3,5-diglucoside, all of which are found in the fruit's seed coat. There are several anthocyanins found in pomegranate juice, the most prominent of which being delphinidin-3,5-diglucoside. The fruit's seed coat also includes cyanidin-3-glucoside, pelargonidin-3,5-diglucoside, delphinidin-3,5-diglucoside, and cyanidin-3,5-diglucoside. 12–20% of total seed weight of pomegranate comprises seed oil and is self-possessed with more than 70% of the conjugated linolenic acids. The fatty acid component of pomegranate seed oil comprises over 95% of the oil, of which 99% is triacylglycerols. Minor components of the oil include sterols, steroids, and a key component of mammalian myelin sheaths, cerebroside. Seventy to seventy-six percent of the seed oil contains punicic acid, an interesting conjugated isomer found only in pomegranate oil. The biological and free radical scavenging capabilities of phenolic compounds, flavonoids, anthocyanins, and tannins make them a significant class of antioxidant phytochemicals. Many studies showed that pomegranate extracts from diverse portions of the fruit worked better than a single extract, and this might be because different regions of the fruit contain varied amounts of phenolic acids, flavonoids, and tannins. A comparative investigation revealed that pomegranate anthocyanins had more antioxidant activity than α-tocopherol, β-carotene, and ascorbic acid, the three forms of vitamin E [1,4,16-19].

Pharmacology [4,16,18,20-25]

Anti-obesity attributes: The molecular effects of pomegranate on obesity have been examined in numerous studies. The capacity of pomegranate punicic acid (PUA) to activate PPAR-α and γ. The findings indicated that PUA can enhance the expression of PPAR-α and PPAR-γ in 3T3-L1 pre-adipocytes; however, PUA did not exhibit strong binding affinity to the human PPAR-γ ligand-binding domain.

Antidiabetic properties: Pomegranate flower extracts can prevent the onset of type 2 diabetes by lowering blood glucose levels and subsequently inhibiting the alpha-glucosidase enzyme, thereby reducing postprandial hyperglycemia in type 2 patients. Methanol leaf extracts of *Punica granatum* were examined for their efficacy in treating diabetic nephropathy, resulting in enhanced lipid metabolism, normalized serum albumin levels, and reduced hyperglycemia. A comparable investigation examining methanolic leaf extracts on diabetic rats revealed that the methanol leaf extract included antioxidants that exhibit antidiabetic properties.

Anticancer efficacy: In order to create natural medical treatments, several studies on cancer have been conducted. As a result, a number of anticancer agents, such as taxanes, vinca alkaloids, podophyllotoxin, and other natural-based medicines, are made from compounds present in a variety of medicinal plants. In contrast to colon cancer cell lines, the cytotoxicity of pomegranate seed oils was assessed using a 3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay against human lung cancer cell lines. Lung cancer cell lines (80.3 ± 1.2–25.4 ± 1.2%) and colon cancer cell lines (83.3 ± 1.2–28.4 ± 1.2%) showed negligible anti-cancer effects from the seed oil. Additionally, fruit peel extracts have been found to have anti-cancer properties that prevent the growth of tumour cells. The inhibition of COX-2 expression, cellular proliferation, and cellular growth has been investigated. The mitogen-activated protein kinase (MAPK) and phosphatidyl-inositol-3-kinase PI3K)/protein kinase B (Akt)/nuclear factor kappa B (NF-kB) pathways are linked to the expression of COX-2. Activation of PI3K triggers the phosphorylation of Akt, which activates NF-kB, ultimately resulting in elevated COX-2 expression in colon cancer. Activation of PI3K leads to the production of COX-2 and

enhanced proliferation of the human colorectal adenocarcinoma cell line (HT-29).

Anti-inflammatory properties: Linked to anti-inflammatory activities, *Punica granatum* has many biochemical properties. Apart from its conventional and pharmacological applications, the *P. granatum* plant is also very much used in cosmetic compositions. The pomegranate plant and its fruits in skincare products, including anti-wrinkle products, pigment, colour agents for bathing products, and anti-inflammatory characteristics supporting UV-induced formulations. The effects of aqueous and alcoholic pomegranate leaf extracts on hair development in albino mice suffering from alopecia. Relatively to the control group, the aqueous and alcohol extracts showed a 3% increase in hair growth. The investigation came to the conclusion that in anti-dandruff and anti-lice properties, the alcohol leaf extracts are plentiful and successful.

Antimalarial properties: Natural chemicals originating from medicinal plants have been used in pomegranate research to enhance the treatment of malaria. An analysis showing that pomegranate peel extract has anti-malarial qualities and is effective against *Plasmodium vivax* and *Plasmodium falciparum,* two common parasites that cause malaria. Additionally, Swiss albino mice showed efficacy against the *Plasmodium chabaudi* parasite when exposed to a pomegranate peel methanol extract.

Antiviral and anti-COVID-19 efficacy: Alkaloids, polyphenols, and coumarins are among the chemicals found in *P. granatum* that have been connected to virucidal and viral replication inhibition. *P. granatum* fruit and plants are primarily composed of polyphenols. Caffeic acid, ellagic acid, luteolin, and punicalagin are the four unique chemicals that make up polyphenols and give *P. granatum* its antiviral properties. By reducing the agglutination of red blood cells in chicks, these polyphenols to hinder the reproduction of RNA viruses.

Antiemetic activity: The ethanol extracts of *Punica granatum* (200 mg/kg) have protective effect against copper sulphate induced-retching in young chickens, possibly by peripheral and central mechanisms. The potential of this extract as antiemetic activity may be due to the presence of phytoconstituents like alkaloids and terpenes and might be responsible for its activity.

Wound healing activity: Several research have proven *P. granatum* improve wound repairing process. In this study, a 95% decreasing wound area was reported on animals treated by the extract compared with 84% at control group. Skin epithelialization in pomegranate extract-treated group was faster than control group, and the content of hydroxyproline in pomegranate extract-treated group was remarkably greater than the control group. As a result, *P. granatum* significantly improved wound healing in rats.

Antioxidant activity: The presence of antioxidants has been reported in Pomegranate juice. Pomegranate contains some species of flavonoids and anthocyanidins (delphinidin, cyaniding and pelargonidin) in its seed oil and juice and shows antioxidant activity three times greater than green tea extract. Pomegranate fruit extracts exhibit scavenging activity against hydroxyl radicals and superoxide anions, which could be related to anthocyanidins. The antioxidant action of Pomegranate is observed, not only through its scavenging reactions, but also by its ability to form metal chelates.

CONCLUSION

Pomegranate, botanical name *Punica granatum* L., is a largely consumed fruit deriving from the deciduous tree of *Punica* L. genus, Punicaceae family. However, pomegranate has been known also for its medical use. Pomegranate constitutes an important source of a wide variety of bioactive compounds with beneficial properties. Pomegranate juice, fruit, and extracts have been used extensively in the folk medicine of ancient cultures for various medicinal properties. Pomegranate has been shown to possess phytochemicals which may hold pharmacological and toxicological properties. The information presented in this review article which was obtained from *in-*

vitro, *in-vivo* and clinical trial investigations has shown some of the pharmacological and toxicological mechanisms and properties of Pomegranate. These properties include anti-oxidative, anti-inflammatory, anticancer, and inhibitory effect on invasion/motility, cell cycle arrest, apoptosis, stimulation of cell differentiation and anti-mutagenic effects, and inhibitory effects. However, further investigations are required to elucidate the mechanisms of action and the synergistic effects of the phytochemicals contained in pomegranate. Moreover, future *in vivo* and *in vitro* studies should be undertaken in order to provide a better understanding of pomegranate potential in preventing a wide spectrum of pathological conditions and supporting therapeutic strategies.

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