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BIOLOGICAL ACTIVITY AND THERAPEUTIC PROPERTIES OF PUNICA GRANATUM L

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The purpose of the study was to summarize the literature on the phytochemistry of the main molecular mechanisms of action and pharmacological properties of Punica granatum L, as well as the results of experimental and clinical studies of its use in clinical medicine. Punica granatum L. has been used for centuries in traditional medicine in the world to prevent and treat a wide range of health disorders. The pomegranate fruit is an important source of nutrients, including dietary fiber, polysaccharides, vitamins, fatty acids, and polyphenols. Biologically active compounds of Punica granatum L. provide a powerful potential and a wide spectrum of biological and pharmacological activity. The peel, seeds, and juice of pomegranate contain significant amounts of phenolic compounds and have antioxidant activity. It was found that pomegranate extract showed significant antibacterial (mainly bactericidal), antifungal effects and antiviral properties. Polyphenols such as punicalin, punicalagin, and ellagic acid are just some of the many compounds responsible for the anticancer activity of pomegranate. Punica granatum L. and its derivatives, such as ellagic acid, can regulate the expression and activity of several molecular targets related to oxidative stress, inflammation, cell cycle, apoptosis, angiogenesis, invasion, and metastasis, which makes it promising for further research in various pathological conditions.

Key words: phytotherapy, Punica granatum L, antioxidant effect, anti-inflammatory activity, antimicrobial activity, antiviral properties, anticarcinogenic properties.

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БІОЛОГІЧНА АКТИВНІСТЬ І ТЕРАПЕВТИЧНІ ВЛАСТИВОСТІ PUNICA GTANATUM L

Метою дослідження було узагальнення літературних джерел щодо фітохімії основних молекулярних механізмів дії та фармакологічних властивостей Punica granatum L, а також результатів експериментальних та клінічних досліджень його використання у клінічній медицині. Punica granatum L., століттями використовувався в традиційній медицині різних регіонів світу для профілактики та лікування широкого кола розладів здоров'я. Плід граната є визначним джерелом поживних речовин, включаючи харчові волокна, полісахариди, вітаміни, жирні кислоти та поліфеноли. Біологічно активні сполуки Punica granatum обумовлюють потужний потенціал та широкий спектр біологічної та фармакологічної активності. Шкірка, насіння та сік граната містять значну кількість фенольних сполук і мають антиоксидантну активність. Продемонстровано, що екстракт граната містить фенольні біоактивні компоненти, синергична дія яких проти вільних радикалів ймовірно пояснює встановлену антиоксидантну здатність екстракту. Продемонстровано, що кожна частина граната Punica gtanatum L. з величезною кількістю біохімічних властивостей пов'язана з протизапальною активністю. Встановлено, що екстракт граната виявив значну антибактеріальну (переважно бактерицидну), противірусну та протигрибкову дію. Поліфеноли, такі як пунікалін, пунікалагін та елагова кислота, є лише деякими з багатьох сполук, відповідальних за протиракову активність граната. Punica granatum та його похідні, такі як елагова кислота, можуть регулювати експресію та активність кількох молекулярних мішеней, пов'язаних з оксидативним стресом, запаленням, клітинним циклом, апоптозом, ангіогенезом, інвазією та метастазуванням, що робить перспективним продовження досліджень при різних патологічних станах.

Ключові слова: фітотерапія, Punica gtanatum L, антиоксидантна дія, протизапальна активність, антимікробна дія, противірусні властивості, антиканцерогенні властивості.

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The current trend is the rapid growth in the world of new infections resistant to antimicrobial drugs [33], as well as non-communicable diseases, including arterial hypertension, diabetes mellitus [8], bronchopulmonary pathology [49], oncological diseases [30], etc. Therefore, an important direction of modern medicine is the search for more effective and affordable methods of treatment of both acute and chronic diseases.

The frequency of using herbal substances as therapeutic agents for various health conditions is increasing every year. Traditional herbal medicines have significant advantages over new chemical compounds, as they have been used by humanity for hundreds or thousands of years. Indeed, many Ayurvedic medicines have been traditionally used to treat type 2 diabetes, and systematic reviews have demonstrated the efficacy and safety of certain Ayurvedic medicines [8]. Due to the long history of using herbal ingredients, potentially toxic compounds and plant parts are well known, and important safety concerns have come to the fore when using these medicines [47]. In recent years, significant progress has

been made in the research and application of natural herbal ingredients for the treatment of various pathological conditions. However, better methods are needed to prioritize herbal medicines for clinical trials to maximize the chances of selecting effective drugs.

The pomegranate (Punica granatum L.) is a large shrub or small tree belonging to the family Punicaceae [40]. Since ancient times, Punica granatum L. has been widely used as a folk medicine in many cultures, as documented in the Egyptian papyrus (c. 1550 BC) [16]. Punica granatum L. has been used for centuries in traditional medicine in China and other regions of the world to prevent and treat a wide range of health disorders, such as inflammation, malaria, diabetes, oral diseases, etc. [26]. The pericarp of the pomegranate fruit has been used to treat dysentery and intestinal disorders [23]. In China and Mexico, the bark of the pomegranate has been used to treat gastrointestinal diseases, such as diarrhea, dysentery, and abdominal pain. In India, the fruit juice is traditionally used to treat dysentery, mixed with warm water and taken twice daily, and as a tonic for anemia [5]. In Pakistan, the fruit is used to treat iron deficiency and is also used to treat nasal congestion [5].

It has been established that the Punica granatum L. biologically active substances have many effects, including anti-inflammatory, antimalarial, antifibrotic, antidiabetic, antitumor, antifungal and antibacterial properties, etc [26].

The purpose of the study was to summarize the literature on the phytochemistry of the main molecular mechanisms of action and pharmacological properties of Punica granatum L, as well as the results of experimental and clinical studies of its use in clinical medicine.

Chemical composition. The plant Punica granatum L. consists of sap, leaves, seeds, rind (pericarp), bark, roots, and flowers. The pericarp (rind or peel) of the pomegranate is the hard, and when ripe, almost dry, outer covering of the pomegranate fruit. The pericarp accounts for almost half of the fresh fruit weight; the seeds account for 10 %, and the pericarp accounts for 40 % [11].

The pomegranate fruit is an important source of nutrients, including dietary fiber, polysaccharides, vitamins, fatty acids, and polyphenols.

To date, active compounds have been isolated from pomegranate, namely: tannins (punicalagin and other ellagitannins), flavonoids (flavonols, proanthocyanidins and anthocyanidins), alkaloids, anthocyanidins, phenolic acids (gallic, ellagic, caffeic, ferulic and cinnamic acids), sterols, terpenes, terpenoids, amino acids, carbohydrates (sucrose, fructose, glucose and maltose), xanthonoids, fatty acids, a number of minerals (potassium, phosphorus, magnesium, iron, calcium, manganese, etc.), high content of vitamin C, etc.

The leaves of Punica granatum L. contain tannins (punicafolin and punicalin) and flavone glycosides (in particular, apgenin and luteolin), etc. [10].

Pomegranate seeds contain mainly water (85 %), sugars (10 %), and pectin (1.5 %), but are also a source of phenols, flavonoids, and anthocyanins. They contain 7–27 % oil, which is a rich source of polyunsaturated fatty acids, including linoleic and linoleic acids, as well as other lipids such as oleic, stearic, and palmitic acids. Ellagic acid, sterols, and punicic acid have also been found in the seed oil of Punica granatum L. [45].

The components of the peel of Punica granatum L. include gallic acid, phenolic punicalagins, rutin, flavonols (flavonones, flavones and anthocyanidins), quercetin and fatty acids (catechin), etc. The content of tannins ranges from 193 to 420 mg/g dry matter in pomegranate peel, while flavonoids range from 84 to 134 mg [29]. In an Italian study [36], a comparative qualitative and quantitative study of peel extracts of eight Punica granatum cultivars obtained from different areas of Southern Italy was conducted with the aim of evaluating them as by-products with health benefits. It was shown that all samples contained 45 ellagitannins, consisting mainly of polyhydroxyphenols; 10 flavonoids belonging to the flavonol, flavones and catechin classes; and 2 anthocyanins.

The bark and roots of Punica gtanatum L. contain piperidine alkaloids and ellagitannins (punicalagin and punicalin), etc. [26].

Pomegranate juice, known for its high vitamin C content, contains phenolic compounds such as punicalagin, as well as significant amounts of potassium, calcium, and antioxidants, etc. [7]. The juice is mainly composed of sugars, organic acids, polyphenols, and tannins, which contribute to its strong antioxidant properties [26]. Higher levels of total tannins, phenolic compounds, and antioxidant activity were found in pomegranate juice, while the peel had higher total flavonoids, anthocyanins, and ascorbic acid contents [11]. Anthocyanins, tannins, fatty acids, and phytochemicals such as lignans and sterols have been identified in pomegranate seeds [39].

Pomegranate (Punica gtanatum L.) has been shown to be rich in minerals such as sodium (3 mg/100 g), which is important for cellular homeostasis and helps maintain physiology; potassium (236 mg/100 g),

which is responsible for fluid balance; phosphorus (70 mg/100 g), iron (3 mg/100 g), calcium (10 mg/100 g) with its numerous functions in the human body as a major component of bones and teeth; and magnesium (12 mg/100 g), which helps maintain a steady metabolism and bone health. In addition, the fruit contains protein (1.67 g/100 g) and fat (1.17 g/100 g). Ascorbic acid (16.0 mg) has been determined in the plant Punica gtanatum L. The caloric value of Punica gtanatum L. is 65 mg/100 g [16].

Antioxidant effect. Numerous studies have shown that oxidative stress is a key link in the development of cancer, inflammation, cardiovascular and neurodegenerative diseases, and aging [3]. The toxicity of reactive oxygen species depends on the associated and sensitive biological substrates, such as nucleic acids, proteins, and membrane lipids. Biologically significant reactive oxygen species include superoxide anion radicals, lipid peroxides, hydrogen peroxide, and hydroxyl radicals [10].

The peel, seeds, and juice of pomegranate contain significant amounts of phenolic compounds and have antioxidant activity. Pomegranate seed oil has been shown to contain phytoestrogenic compounds, and the fruit is rich in phenolic compounds with strong antioxidant activity. Ellagic acid is one of the main components of pomegranate with potent antioxidant activity [40].

It has been established that the polyphenolic complex of the peel of Punica granatum L has more pronounced antioxidant and anti-inflammatory properties than other parts. And the most important active components of pomegranate peel, which are found only in this plant, are punicalagin, followed by ellagic acid and gallic acid [7]. It has been demonstrated that pomegranate extract contains phenolic bioactive components, the synergistic action of which against free radicals probably explains the established antioxidant capacity of the extract. One possible mode of action is related to the hydroxyl groups present in the phenolic aromatic rings, and natural polyphenolic compounds found in pomegranate extracts demonstrate their antioxidant properties [7]. These polyphenols demonstrate their antioxidant effect by neutralizing free radicals, dissolving peroxides, and due to their redox properties, they serve as antioxidants against singlet and triplet oxygen, [12]. These polyphenolic compounds of pomegranate peel are reported to have the most pronounced therapeutic effect [39].

More than two-thirds of the antioxidant activity of pomegranate juice has been shown to be due to its high content of punicalagin and its hydrolyzed tannins [10]. Several studies have shown the protective effect of ellagic acid, a punicalagin, against oxidative stress damage caused by free radicals [12].

In the study of Milošević M. et al. [28], the bioactivity of different parts (juice and peel extracts) of cultivated and wild pomegranate fruits was determined and compared. It was found that the total phenolic content was the highest in the wild pomegranate peel extract, expressed in gallic acid equivalents (340.92 mg/g, $p<0.05$), while the total flavonoid content was the highest in the cultivated pomegranate peel extract, expressed in quercetin equivalents (31.84 mg/g, $p<0.05$). It was shown that the highest antioxidant activity against free radicals DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2′-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid)) was found in the wild pomegranate peel extract. It was determined that the peel and membrane extract of cultivated pomegranate gave almost identical and strongest effects on hydroxyl radical suppression (41.24 and 41.23 μg/ml, respectively). It was also found that the highest levels of DPPH and ABTS free radical scavenging activity were found in the peel, followed by the pulp, and then the seeds [20].

According to the study by Yang Y. et al., pomegranate peel extract showed higher antioxidant activity compared to seeds and juice. The total content of phenols, flavonoids and flavonols in pomegranate peel was estimated to be much higher than that in seeds and juice. A significant positive correlation was also found between antioxidant activity and total phenolic content [22].

In another study [9], unlike the juice of the peel of Punica granatum L, the extracts of the outer and inner peel of pomegranate demonstrated significant and dose-dependent antioxidant and radical scavenging potential in vitro. Supplementation of Punica granatum L extracts significantly extended the lifespan of C. elegans. The protective effect of Punica granatum L. was also observed against oxidative stress in C. elegans. Therefore, an important role of Punica granatum L, especially the outer peel extracts, in the life-saving mechanisms of C. elegans was established due to their antioxidant activity and lifespan extension through the daf-16-dependent insulin signaling pathway.

Compared to red wine, green tea, apple, vitamins E and C, Punica granatum L, demonstrates significantly higher antioxidant activity, therefore, due to its antioxidant and anti-inflammatory properties, pomegranate may help prevent or improve the course of many chronic diseases, such as cardiovascular diseases, diabetes, neurodegenerative diseases, and cancer [24].

Morvaridzadeh M. et al. [32] conducted a meta-analysis of 11 randomized clinical trials with 484 participants, examining the effects of pomegranate on oxidative stress parameters. They found no convincing evidence of a significant increase in the effect of pomegranate consumption on TAC (SMD:

0.43; 95 % CI: -0.19, 1.06), Gpx (SMD: 0.18, 95 % CI: -0.25, 0.62, p=0.4) and paraxonase (SMD: 0.36, 95 % CI: -0.50, 1.22, p=0.41), and a slight decrease in malondialdehyde (MDA) levels (SMD: -0.81, 95 % CI: -1.79, 0.09, P=0.08).

A systematic review by Asgary S. et al. [3] evaluated the effects of pomegranate extract on reducing oxidative stress. Pomegranate was used in some studies in capsule form (250 mg to 250 g) and in some in liquid form (10 to 500 ml), and the duration of follow-up ranged from 3 weeks to 12 months. Pomegranate was shown to have a positive effect on oxidative stress biomarkers and reduced oxy-LDL and POX 1. Furthermore, the results showed that pomegranate consumption could significantly increase GPX and TAC. The combination result on TBRAS showed a significant effect of pomegranate consumption on reducing TBRAS. Since this review evaluated studies conducted mainly in Eastern countries, the authors concluded that pomegranate supplementation is effective in modifying oxidative stress in Eastern countries.

A review by Lorzadeh E. et al. [24], which examined the effects of pomegranate consumption on multiple biomarkers of oxidative stress, included 21 randomized clinical trials. It was found that pomegranate consumption compared with the control group was associated with significant increases in TAC [SMD = 0.72, 95 % confidence interval (CI): 0.42, 1.02, P < 0.001] and SOD [SMD = 0.72, 95 % CI: 0.25, 1.19, P = 0.002] and decreases in MDA [SMD = -0.98, 95 % CI: -1.49, -0.46, P < 0.001]. No statistically significant differences were reported in the effects of pomegranate on FRAP, GSH, GSH-Px, ox-LDL, and PON1 levels. Thus, pomegranate may be effective in improving some oxidative stress factors, but well-designed randomized controlled trials are needed.

Anti-inflammatory activity. Pomegranate has been used for centuries to treat inflammation due to its potential anti-inflammatory properties. Every part of the pomegranate, Punica granatum L., has been shown to contain a wide range of biochemical properties associated with anti-inflammatory activity [1]. Pomegranate peel exhibits anti-inflammatory properties due to phenolic components such as ellagic acid, punicalagin. Punicalagin is the main polyphenol of pomegranate, which is found in the fruit, leaves, and peel, where it is particularly abundant [26].

In a study by Li H.M. et al. [22], twenty polyphenols were isolated from the peel of Punica granatum L, nine of which were previously unknown, named punicagranins AI (1-9), along with eleven known isolates (10-20). The anti-inflammatory activity of pomegranate polyphenols in a lipopolysaccharide (LPS)-induced inflammatory macrophage model was demonstrated by the enhancement of nitric oxide (NO) production in response to inflammation stimulated in RAW 264.7 cells, which was controlled by compounds 1, 3, 5-8, 10, 11, 14 and 16-20 in a concentration-dependent manner. Structure-activity relationship studies for tannins 6-8 and 12-20 indicated that HHDP, flavogalonil and/or galagyl are the key groups for inhibiting NO production. Western blotting showed that compounds 6-8 could reduce the phosphorylation levels of p38 MAPK, IKKα/β, IκBα and NF-κB p65 proteins, and suppress the levels of cytokines and mediators related to inflammation, such as IL-6, TNF-α, iNOS and COX-2, at a concentration of 30 μM. The results obtained allowed us to conclude that polyphenols are considered as potential anti-inflammatory active ingredients in the peel of Punica granatum, and their molecular mechanism is likely related to the regulation of p38 MAPK and NF-κB signaling pathways.

Huang WC. et al. [17] studied the effect of punicalagin isolated from pomegranate peel (Punica granatum L.) and its anti-inflammatory mechanisms on inflammatory processes induced by pro-inflammatory cytokines (a mixture of tumor necrosis factor alpha, TNF-α and interferon-gamma, IFN-γ) on a model of human keratinocytes of the HaCaT line. It was found that punicalagin at a concentration of ≤100 μM did not reduce the viability of HaCaT cells, and a PUN concentration of ≥3 μM reduced the content of interleukin-6 (IL-6), IL-8, monocyte chemoattractant protein-1 (MCP-1), chemokine ligand 5 (CCL5), CCL17 and CCL20. Punicalagin concentrations ≥10 μM and ≥3 μM were shown to significantly upregulate sirtuin 1 (SIRT1) expression and inhibit signal transducer and activator of transcription 3 (STAT3) phosphorylation, respectively. Punicalagin mediated the Nrf2/HO-1 signaling pathway in TNF-α/IFN-γ-induced HaCaT cells via SIRT1. Thus, punicalagin was found to downregulate the expression of inflammation-related proteins cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), and to upregulate the expression of nuclear factor erythroid-related factor-2 (Nrf2) and heme oxygenase-1 (HO-1). Punicalagin was found to downregulate the expression of intercellular adhesion molecule-1 (ICAM-1) and inhibit monocyte adhesion to HaCaT cells induced by TNF-α/IFN-γ. Punicalagin blocked the STAT3/NF-κB (nuclear factor-kappa B) and MARK (mitogen-activated protein kinase) signaling pathways in HaCaT cells induced by TNF-α/IFN-γ. The results of this study confirmed that punicalagin concentrations of 25, 50, 75, 100, and 150 μM had no cytotoxic effects on the HaCaT cell model.

In a meta-analysis conducted by Jazinaki M.S. et al. [18], which included 11 studies (696 participants), the effect of pomegranate juice consumption on C-reactive protein (CRP) levels was studied.

It was found that pomegranate juice supplementation significantly reduced C-reactive protein levels compared to controls (WMD: 2.55 mg/L; 95 % CI: 3.44 to 1.66 mg/L; p<0.001). Subgroup analysis demonstrated a significant effect on C-reactive protein levels in studies that used a dose of pomegranate juice <250 ml/day. The subgroups included individuals of both sexes or only women of the Iranian population, individuals under 40 years of age, and patients with type 2 diabetes, polycystic ovary syndrome, etc. Meta-regression and dose-response analyses showed a weak linear and nonlinear relationship between intervention characteristics (duration and dose of pomegranate juice) and changes in C-reactive protein. The meta-analysis showed that pomegranate juice consumption has a positive effect on improving C-reactive protein levels. At the same time, the authors emphasized that it is necessary to better understand the effect, find the optimal dose and duration of pomegranate juice intake to reduce C-reactive protein levels in the blood, and then repeat the meta-analysis of randomized clinical trials. More detailed studies in humans are needed to definitively confirm these effects.

Wang P. and sang [46] conducted a meta-analysis that included 16 randomized controlled trials with 572 subjects to evaluate the effects of pomegranate juice on biomarkers of inflammation and endothelial function. It was found that pomegranate juice consumption significantly reduced the levels of high-sensitivity C-reactive protein (hs-CRP), IL-6, and TNF-α (weighted mean (WMD): -6.57 mg/L, 95 % CI: -10.04 to -3.10, P=0.000; WMD: -1.68 pg/mL, 95 % CI: -3.52, 0.157, P=0.000; WMD: -2.37 pg/mL, 95 % CI: -3.67, -1.07, P=0.00, respectively), compared with placebo. There was no significant reduction in C-reactive protein (WMD: 2.19 mg/dL, 95 % CI: -3.28, 7.67, P=0.61), E-selectin (WMD: 8.42 ng/mL, 95 % CI: -22.9, 39.8, P=0.599), ICAM (WMD=-17.38 ng/mL, 95 % CI: -53.43, 18.66, P=0.107), VCAM (WMD=-69.32 ng/mL, 95 % CI: -229.26, 90.61, P=0.396) or MDA (WMD=0.031 μmol/L, 95 % CI: -1.56, 0.218, P=0.746) levels when comparing pomegranate supplementation with with placebo.

A randomized, controlled, parallel study [14] examined the effects of pomegranate extract on inflammatory markers and cardiometabolic risk factors in healthy adults aged 55 to 70 years. Participants received either pomegranate extract (740 mg) or placebo capsules daily for 12 weeks. The pomegranate extract group showed significant decreases in IL-6 (p=0.02) and IL1-β (p=0.05) and a trend toward lower C-reactive protein and TNF-α compared with placebo. The pomegranate extract group showed a decrease in systolic blood pressure (by 5.22±1.26 mmHg, p=0.04) and a trend toward lower diastolic blood pressure (2.94±1.08 mmHg, p=0.3). Additionally, despite the absence of complaints or diagnosed diseases, a significant number of participants had elevated levels of inflammatory markers and systolic blood pressure. The authors concluded that pomegranate extract has the potential to affect inflammatory markers and blood pressure when elevated in normal and overweight older adults. This makes pomegranate extract a cost-effective intervention in healthy aging, but further long-term studies with larger numbers of participants are needed.

In inflammatory bowel diseases, the anti-inflammatory, antioxidant and immunomodulatory properties of Punica granatum L. can reduce the severity and frequency of symptoms. It has been found that different parts of Punica granatum L. mainly suppress inflammation in the intestinal wall by regulating key proteins of various inflammatory pathways, such as nuclear factor kappa B (NF-kB), mitogen-activated protein kinase (MAPK) signaling pathways, etc. [26]. At the same time, they also reduce the effects of oxidative stress on intestinal cells, maintain the integrity of its epithelial cells and the diversity of the intestinal microbiota [21].

Antimicrobial activity. According to the study [23] of pomegranate pericarp for antibacterial activity against diarrhea-causing microorganisms such as Staphylococcus aureus, Vibrio cholera, and Vibrio parahaemolyticus, it was found that, with the exception of Vibrio cholera, all the bacterial pathogens tested demonstrated inhibitory zones (6.3-14.8 mm) in response to Punica granatum L. extracts (ethanol and water). Other studies have shown that pomegranate has bactericidal activity against pathogenic bacteria, including Salmonella Typhi, Vibrio cholera, Yersinia enterocolitica, Shigella spp., and Listeria monocytogenes [1, 13, 25, 27].

In a study by Abutayeh R.F. et al. [1], the antimicrobial activity of pomegranate skin extracts alone and/or in combination with antibacterial agents against four bacterial strains was studied. It was found that the antibacterial activity of pomegranate skin extracts varied depending on the extraction method and the solvent used. Thus, the aqueous macerate and the extract obtained by microwave treatment showed high efficiency and similar activity against Staphylococcus aureus (S. aureus), Escherichia coli (E. coli) and Pseudomonas aeruginosa (MIC 12.5 and 25 μg/μl, respectively, for both aqueous extracts). In contrast, Proteus mirabilis was more sensitive to the inhibitory activity of organic pomegranate skin extracts with an MIC of 25 μg/μl recorded using ethanolic solvents. Bacterial antagonistic activity was observed against gentamicin-resistant Pseudomonas aeruginosa, especially when lower concentrations (3.125; 1.562; 0.781

and 0.39 μg/μl) of aqueous pomegranate skin extracts were evaluated in combination with different concentrations of gentamicin. Thus, the antimicrobial potential of pomegranate skin extracts was demonstrated, and the combination of the latter with antibiotics is a promising direction for the prevention of antibiotic resistance and highlights their potential role in the treatment of infectious diseases.

Farhat G. et al. [13] studied the antibacterial and antifungal effects of standardized pomegranate and lemon extracts on various types of gram-negative and gram-positive bacteria, as well as two types of yeast. In addition, the antimicrobial activity of common antibiotics (ciprofloxacin, imipenem, gentamicin and ceftazidime), both individually and in combination with pomegranate and lemon extracts against S. aureus and E. coli, was evaluated. It was found that pomegranate extract showed significant antibacterial (mainly bactericidal) and antifungal effects against most pathogenic microorganisms, while lemon extract showed antibacterial (mainly bacteriostatic) and antifungal properties to a lesser extent. When comparing the effects with antibiotics, it was found that pomegranate extract showed a larger zone of inhibition than ciprofloxacin and ceftazidime ($p<0.01$), and a comparable zone of inhibition with gentamicin ($p=0.4$) against S. aureus. However, combinations of pomegranate and lemon extracts with antibiotics had either neutral or antagonistic effects on antibiotic activity against S. aureus and E. Coli.

A Brazilian study [25] investigated the antibacterial activity of Punica granatum L. peel extract against the enterobacteria Escherichia coli (E. coli), Salmonella Typhimurium (S. Typhimurium) and Shigella Dysenteriae (S. Dysenteriae) and the Gram-positive bacteria Staphylococcus aureus (S. aureus). It was found that the methanolic peel extract (50 ml) of yellow Punica granatum L. showed 26, 10, 10 and 9 mm zones of inhibition (IZ) against S. aureus, S. Typhimurium, S. Dysenteriae and E. coli, respectively. It was found that the methanolic extract of red Punica granatum L. (100 ml) showed 27, 8, 12 and 15 mm zones of inhibition (IZ) against S. aureus, S. Typhimurium, S. Dysenteriae and E. coli, respectively. It was also found that methanolic extract of peel (50 ml) of yellow Punica granatum L. showed 26, 10, 10 and 9 mm zones of inhibition (ZI) against S. aureus, S. Typhimurium, S. Dysenteriae and E. coli, respectively. Furthermore, methanolic extract of red Punica granatum L. (100 ml) showed 27, 8, 12 and 15 mm IZ against S. aureus, S. Typhimurium, S. Dysenteriae and E. coli, respectively. The highest IZ was observed against Staphylococcus aureus. The authors of the study emphasized that many of the bacteria studied are capable of causing serious gastrointestinal infections that can lead to hemorrhagic diarrhea in children. These infections can be life-threatening for young children and the elderly. There is an incentive to find alternative control measures such as plant and herbal extracts, especially in less developed countries where traditional antibiotics may not be available.

Another study [19] investigated the effect of bioactive polyphenols from Punica granatum against enterobacteria and the effects of polyphenols in combination with antibiotics against clinical isolates of Enterobacteriaceae, mainly prevalent in South Asian countries. Extracts of Kandhari Punica granatum (of Pakistani origin) were tested for antienterobacterial activity using agar diffusion assay against MDR Salmonella enterica serovar Typhi, serovar Typhimurium and E. coli. It was found that methanolic extract of Punica granatum showed the largest zones of inhibition of 25, 22 and 19 μm and minimum inhibitory concentrations (MICs) of 3.9, 7.8 and 7.8 mg/mL for S. typhi, S. typhimurium and E. coli, respectively. Punicalagin and ellagic acid were identified as the dominant compounds by mass spectrometry. In the plate test, punicalagin (10 mg/ml) was shown to be active with vague zones of inhibition of 17, 14 and 13 mm against S. typhi, S. typhimurium and E. coli, respectively. However, in the broth dilution assay, punicalagin did not show MIC up to 10 mg/ml. The synergistic effect of punicalagin in combination with antimicrobial drugs – aminoglycoside, β-lactam and fluoroquinolone against multi-resistant strains was established. It was demonstrated that the percentage increase in the zone of inhibition varied from 3.4 ± 2.7 % to 73.8 ± 8.4 %. The authors concluded that the methanolic extract of Punica granatum peel exhibits antimicrobial activity against pathogenic microorganisms of the Enterobacteriaceae family. The bacteriostatic flavonoid punicalagin acts as a concentration-dependent agent that enhances the effect of antimicrobial drugs against enterobacteria.

The antidiarrheal effects of the aqueous extract of Punica granatum were evaluated in a rat experiment under conditions of castor oil-induced diarrhea [35]. A dose-dependent inhibition of spontaneous motility of the isolated rat ileum and attenuation of acetylcholine-induced contractions were found. The extract (100, 200, 300 and 400 mg/kg) also caused a dose-dependent decrease in gastrointestinal transit and significantly protected rats from castor oil-induced diarrhea. Preliminary phytochemical screening of the aqueous extract of Punica granatum peel gave positive results for tannins, flavonoids and alkaloids. The results obtained showed that the aqueous extract of Punica granatum peel contains some biologically active elements effective against diarrhea. This may be the basis for its traditional use in gastrointestinal disorders. Therefore, pomegranate peel is used in the phytotherapeutic treatment of

diarrhea due to the tannins it contains. The antimicrobial and anti-inflammatory properties of pomegranate peel can help reduce intestinal infections and inflammation. In addition, the tannins of Punica granatum L. inhibit the motility of the digestive tract and increase the density of intestinal contents.

Fungal infections, especially those caused by Candida species, represent a significant global health problem, exacerbated by the increasing resistance to antifungal drugs [35]. This reduces the treatment options for fungal infections, increasing the risk of mortality and increasing the cost of treatment. Therefore, the search for biologically active compounds with therapeutic potential for the treatment of candidiasis continues [34].

In a study by Ferreira N.S. et al. [15], the efficacy of dry extract of Punica granatum peel as an antifungal agent against Candida infections (C. albicans, C. parapsilosis, C. krusei and C. glabrata) and its effect on fungal growth, disruption of biofilms and integrity of fungal cell membranes was studied, and its safety against hemolysis was assessed at different concentrations. Dry extract of Punica granatum peel demonstrated inhibitory activity against all tested Candida strains with a minimum inhibitory concentration (MIC) of 1 % (10 mg/ml). The authors attributed the obtained effect to the phenolic composition of the peel extract, namely the content of gallic acid, punicalagin A, punicalagin B and ellagic acid. It was shown that dry extract of pomegranate peel disrupted Candida biofilms and demonstrated safety against hemolysis at concentrations up to 60 mg/ml. However, no evidence of direct interaction with the fungal cell wall or ergosterol of the fungal membrane was found.

Punica granatum L. polyphenols (caffeic and ellagic acids, luteolin and punicalagin) have also been found to have antiviral properties [41]. In vitro, pomegranate extracts and ellagitannins interact and inhibit the infectivity of a number of viruses, including SARS-CoV-2. In silico studies show that ellagitannins bind to several proteins of human SARS-CoV-2, including a number of proteases. This warrants further investigation of polyphenol-virus and polyphenol-host interactions in vitro and in vivo studies [41]. Recently, an in silico molecular docking study demonstrated that Punica granatum L. extract is a potential inhibitor of the SARS-CoV-2 fusion protein and the angiotensin-converting enzyme 2 (ACE2) receptor [4]. Pomegranate extracts, ellagitannins, and ellagic acid are promising agents for combating the SARS-CoV-2 virus, limiting the body's inflammatory responses to viral infections, and also replenishing the body's depleted antioxidant levels during the recovery stage from COVID-19 [2].

A randomized, double-blind, placebo-controlled trial [44] examined the effects of pomegranate juice on inflammatory status and complete blood count in hospitalized COVID-19 patients. The duration of the study was 14 days. It was found that additional pomegranate juice consumption resulted in significant reductions in IL-6 (5.24; 95 % CI: 0.87–9.61), C-reactive protein (23.19; 95 % CI: 11.93–34.44), and erythrocyte sedimentation rate [10.52; 95 % CI: 1.54–19.50) compared to baseline. Also, in the group that was additionally administered pomegranate juice, significant changes were noted in neutrophils, lymphocytes, platelets, platelet to lymphocyte ratio, and neutrophil to lymphocyte ratio ($p<0.05$) compared to baseline values. It was demonstrated that changes in IL-6 [7.09 (1.96–12.21)], leukocytes [3.09 (0.05–6.14)], neutrophils [9.12 (0.15–18.08)], lymphocytes [7.05 (0.17–13.92)], platelets [94.54 (49.75–139.33)], platelet-to-lymphocyte ratio [15.99 (2.67–29.31)], blood oxygen saturation [1.75 (0.13–3.37)], and MCV [0.31 (0.25–0.88)] significantly differed between groups. The authors concluded that supplemental pomegranate juice consumption may improve inflammatory status and complete blood count results in patients with COVID-19.

A systematic review [6] found that pomegranate juice may be beneficial in SARS-CoV-2 infection, especially for patients with a history of chronic diseases such as hypertension, cardiovascular disease, diabetes, and cancer.

Anticarcinogenic properties. Punica granatum L. is a rich source of polyphenols, including flavonoids and ellagitannins, and numerous other biologically active compounds. Polyphenols such as punicalin, punicalagin, and ellagic acid are just some of the many compounds responsible for the anticancer activity of pomegranate. Many pomegranate preparations such as pomegranate juice, pomegranate seed oil, pomegranate peel extract, etc. have been used in various clinical studies. These polyphenols exhibit anticancer activity, either by arresting the cell cycle in the G2/M phase, inducing apoptosis, or damaging the DNA of tumor cells [37]. This makes the use of various extracts of Punica granatum L. very attractive for the prevention and treatment of cancer.

A systematic review by Wong T.L et al. [48] presents an analysis of preclinical (in vitro, ex vivo and in vivo) and clinical studies of the anticancer effects of phytochemicals and molecular targets of Punica granatum L. in numerous types of cancer, such as breast cancer, gastrointestinal (oral cavity, colon, liver and pancreas), gynecological (uterine and ovarian), hematological (lymphoma, leukemia and myeloma), lung, neurological (glioma), urogenital (bladder and prostate) cancer.

Polyphenols and flavonoids in pomegranate juice may be important components responsible for the antitumor activity in hepatocellular carcinoma [50]. It has been experimentally shown that serum containing pomegranate juice inhibits the migration of hepatocellular carcinoma cells by regulating the balance of TIMP2/MMP2 and the expression of MMP9, and also promotes the apoptosis of hepatocellular carcinoma cells by inducing mitochondrial dysfunction and triggering the caspase cascade [50].

Polyphenols isolated from Punica granatum L. have demonstrated anticancer activity. In a review by Teniente S.L. et al. [42], studies investigating the anticancer activity of polyphenolic compounds from the peel of Punica granatum L. in cervical cancer were summarized. Biologically active compounds from the peel of Punica granatum L. have been shown to have anticancer activity in in vitro studies against cervical cancer [31], lung cancer [30], and colon cancer [42].

In a study by Teniente S.L. et al. [43], the antiproliferative and cytotoxic activities of pomegranate peel polyphenols, coffee pulp polyphenols, and a 50-50 % mixture of both substances were studied on HeLa, A549, MDA-MB, and Hek-293 cell lines. The antiproliferative and cytotoxic effects of pomegranate peel polyphenols and coffee pulp polyphenols were established when administered at different concentrations or mixtures on HeLa, A549, and MDA-MB cell lines. However, no significant antiproliferative effect was found on Hek-293 cells treated under similar conditions. The authors concluded that the results obtained indicate the potential of pomegranate peel polyphenols and coffee pulp polyphenols, individually or in combination, to modulate biological mechanisms that operate in cervical, breast, and lung cancer.

Punic acid is a long-chain omega-5 polyunsaturated fatty acid that constitutes approximately 65-80 % of pomegranate seed oil and has been shown to have anticancer activity in various types of cancer. A study by Quitmeyer B. et al. [37] examined the effects of punic acid on both the human breast cancer cell line MCF-7 and the non-cancerous breast epithelial cell line MCF-10A. According to the protocol, both cell types were treated with different concentrations of punicic acid and viable cell density, cytotoxicity and apoptosis, and expression of the antioxidant peroxiredoxin (Prdx) were measured. It was found that punicic acid exhibited cytotoxic effects for both lines, but the levels of cytotoxicity and sensitivity to MCF-10A cells were higher at lower concentrations. This indicated that cytotoxicity was associated with apoptosis in both cell lines. Using real-time PCR, the authors demonstrated induction of all six Prdx mRNAs in MCF-7 cells, ranging from a 1.4-fold increase at 2 μg/ml to a more than 5-fold increase at 10 μg/ml. The scientists showed that in the MCF-10A cell line model, significantly higher induction of all six Prdx mRNAs was detected at 10 μg/ml, exceeding the 30-fold induction of Prdx1, Prdx2, and Prdx5. Thus, the use of punicic acid demonstrated different cytotoxicity and regulation of Prdx in MCF-7 and MCF-10A cell lines, which allows to clarify the cell-specific mechanisms of its action in breast cancer.

However, it should be noted that the use of juice and extracts from various parts of Punica granatum L. may cause side effects [38]. According to a systematic review (2016), the most common side effects were gastrointestinal problems, flu-like symptoms, and urinary problems. In case studies, the most significant side effect reported was allergic reaction.

Further research into the health-promoting properties of Punica granatum L. will enable the effective use of this cost-effective remedy in healthy aging, prevention of infectious diseases, and cancer control. Planned randomized controlled long-term studies with a larger number of participants are needed to definitively confirm the therapeutic effects of Punica granatum L.

Conclusions

1. Punica granatum L. has been used for centuries in traditional medicine in the world to prevent and treat a wide range of health disorders. The pomegranate fruit is an important source of nutrients, including dietary fiber, polysaccharides, vitamins, fatty acids, and polyphenols. Biologically active compounds of Punica granatum L. provide a powerful potential and a wide spectrum of biological and pharmacological activity.

2. The peel, seeds, and juice of pomegranate contain significant amounts of phenolic compounds and have antioxidant activity. It was found that pomegranate extract showed significant antibacterial (mainly bactericidal), antifungal effects and antiviral properties. Polyphenols such as punicalin, punicalagin, and ellagic acid are just some of the many compounds responsible for the anticancer activity of pomegranate.

3. Punica granatum L. and its derivatives, such as ellagic acid, can regulate the expression and activity of several molecular targets related to oxidative stress, inflammation, cell cycle, apoptosis, angiogenesis, invasion, and metastasis, which makes it promising for further research in various pathological conditions.

References

1. Abutayeh RF, Ayyash MAK, Alwany RA, Abuodeh A, Jaber K, Al-Najjar MAA. Exploring the antimicrobial potential of pomegranate peel extracts (PPEs): Extraction techniques and bacterial susceptibility. PLoS One. 2024;19(12):e0315173. doi: 10.1371/journal.pone.0315173.
2. Alexova R, Alexandrova S, Dragomanova S, Kalfin R, Solak A, Mehan S, et al. Anti-COVID-19 Potential of Ellagic Acid and Polyphenols of Punica granatum L. Molecules. 2023;28(9):3772. doi: 10.3390/molecules28093772.
3. Asgary S, Karimi R, Pour PM, Heydarpour F, Mostafaei S, Farzaei MH, et al. Is Consumption of Pomegranate Supplementation Effective on Oxidative Stress Biomarkers Including MDA, ox-LDL, POX 1, GPX, TAC, and TBRAS? A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Curr Probl Cardiol. 2023;48(8):101198. doi: 10.1016/j.cpcardiol.2022.101198.
4. Ashfaq F, Barkat MA, Ahmad T, Hassan MZ, Ahmad R, Barkat H, et al Phytocompound screening, antioxidant activity and molecular docking studies of pomegranate seed: a preventive approach for SARS-CoV-2 pathogenesis. Sci Rep. 2023;13(1):17069. doi: 10.1038/s41598-023-43573-1.
5. Aziz MA, Khan AH, Pieroni A. Ethnoveterinary plants of Pakistan: a review. J Ethnobiol Ethnomed. 2020;16(1):25. doi: 10.1186/s13002-020-00369-1.
6. Banihani SA. Possible Beneficial Effects of Fresh Pomegranate Juice in SARS-CoV-2 Infection Conditions. J Nutr Metab. 2022;2022:5134560. doi: 10.1155/2022/5134560.
7. Benchagra L, Berrougui H, Islam MO, Ramchoun M, Boulbaroud S, Hajjaji A, et al. Antioxidant Effect of Moroccan Pomegranate (Punica granatum L. Sefri Variety) Extracts Rich in Punicalagin against the Oxidative Stress Process. Foods. 2021;10(9):2219. doi: 10.3390/foods10092219.
8. Chattopadhyay K, Wang H, Kaur J, Nalbant G, Almaqhawi A, Kundakci B, et al. Effectiveness and Safety of Ayurvedic Medicines in Type 2 Diabetes Mellitus Management: A Systematic Review and Meta-Analysis. Front Pharmacol. 2022;13:821810. doi: 10.3389/fphar.2022.821810.
9. Chaubey MG, Chauhan AP, Chokshi PR, Amin RS, Patel SN, Madamwar D, et al. Therapeutic potential of bioactive compounds from Punica granatum extracts against aging and complicity of FOXO orthologue DAF-16 in Caenorhabditis elegans. EXCLI J. 2021;20:80-98. doi: 10.17179/excli2020-3011.
10. Chen P, Guo Z, Zhou B. Neuroprotective Potential of Punicalagin, a Natural Component of Pomegranate Polyphenols: A Review. J Integr Neurosci. 2023;22(5):113. doi: 10.31083/j.jin2205113.
11. Cordiano R, Gammeri L, Di Salvo E, Gangemi S, Minciullo PL. Pomegranate (Punica granatum L.) Extract Effects on Inflammaging. Molecules. 2024;29(17):4174. doi: 10.3390/molecules29174174.
12. Dogara AM, Hama HA, Ozdemir D. Update on the Potential of Punica granatum L. Traditional Uses and Pharmacological Uses: A Review. Adv Pharmacol Pharm Sci. 2024;2024:6523809. doi: 10.1155/adpp/6523809.
13. Farhat G, Cheng L, Al-Dujaili EAS, Zubko M. Antimicrobial Potential of Pomegranate and Lemon Extracts Alone or in Combination with Antibiotics against Pathogens. Int J Mol Sci. 2024;25(13):6943. doi: 10.3390/ijms25136943.
14. Farhat G, Malla J, Vadher J, Al-Dujaili EAS. Effects of Pomegranate Extract on Inflammatory Markers and Cardiometabolic Risk Factors in Adults Aged 55-70 Years: A Randomised Controlled Parallel Trial. Nutrients. 2025;17(7):1235. doi: 10.3390/nu17071235.
15. Ferreira NS, Moreno TJC, Duarte CES, Moreira MG, Ucella-Filho JGM, Ferreira IM, et al. Exploring the antifungal potential and action mechanism of pomegranate peel extract against Candida species in planktonic and biofilm conditions. Microb Pathog. 2025;204:107596. doi: 10.1016/j.micpath.2025.107596.
16. Ge S, Duo L, Wang J, GegenZhula, Yang J, Li Z, et al. A unique understanding of traditional medicine of pomegranate, Punica granatum L. and its current research status. J Ethnopharmacol. 2021;271:113877. doi: 10.1016/j.jep.2021.113877.
17. Huang WC, Liou CJ, Shen SC, Hu S, Chao JC, Huang CH, et al. Punicalagin from pomegranate ameliorates TNF-α/IFN-γ-induced inflammatory responses in HaCaT cells via regulation of SIRT1/STAT3 axis and Nrf2/HO-1 signaling pathway. Int Immunopharmacol. 2024;130:111665. doi: 10.1016/j.intimp.2024.111665.
18. Jazinaki MS, Rashidmayvan M, Pahlavani N. The effect of pomegranate juice supplementation on C-reactive protein levels: GRADE-assessed systematic review and dose-response updated meta-analysis of data from randomized controlled trials. Phytother Res. 2024;38(6):2818-2831. doi: 10.1002/ptr.8188.
19. Kiran S, Tariq A, Iqbal S, Naseem Z, Siddique W, Jabeen S, et al. Punicalagin, a pomegranate polyphenol sensitizes the activity of antibiotics against three MDR pathogens of the Enterobacteriaceae. BMC Complement Med Ther. 2024;24(1):93. doi: 10.1186/s12906-024-04376-7.
20. Kupnik K, Primožič M, Vasić K, Knez Ž, Leitgeb M. A Comprehensive Study of the Antibacterial Activity of Bioactive Juice and Extracts from Pomegranate (Punica Granatum L.) Peels and Seeds, Plants. 2021; 10(8). https://doi.org/10.3390/plants10081554.
21. Larrosa MN, Benito N, Cantón R, Canut A, Cercenado E, Fernández-Cuenca F, et al. From CLSI to EUCAST, a necessary step in Spanish laboratories. Enferm Infecc Microbiol Clin (Engl Ed). 2020;38(2):79-83. doi: 10.1016/j.eimc.2018.09.014.
22. Li HM, Kouye O, Yang DS, Zhang YQ, Ruan JY, Han LF, et al. Polyphenols from the Peels of Punica granatum L. and Their Bioactivity of Suppressing Lipopolysaccharide-Stimulated Inflammatory Cytokines and Mediators in RAW 264.7 Cells via Activating p38 MAPK and NF-κB Signaling Pathways. Molecules. 2022;27(14):4622. doi: 10.3390/molecules27144622.
23. Limsuwan S, Jarukitsakul S, Issuriya A, Chusri S, Joycharat N, Jaisamut P, et al. Thai herbal formulation 'Ya-Pit-Samut-Noi': Its antibacterial activities, effects on bacterial virulence factors and in vivo acute toxicity. J Ethnopharmacol. 2020;259:112975. doi: 10.1016/j.jep.2020.112975.
24. Lorzadeh E, Heidary Z, Mohammadi M, Nadjarzadeh A, Ramezani-Jolfaie N, Salehi-Abargouei A. Does pomegranate consumption improve oxidative stress? A systematic review and meta-analysis of randomized controlled clinical trials. Clin Nutr ESPEN. 2022;47:117-127. doi: 10.1016/j.clnesp.2021.11.017.
25. Mahmood MS, Ashraf A, Ali S, Siddique AB, Asad F, Abbas RZ, et al. Portrayal of Punica granatum L. peel extract through High Performance Liquid Chromatography and antimicrobial activity evaluation. Braz J Biol. 2021;83:e244435. doi: 10.1590/1519-6984.244435.
26. Maphetu N, Unuofin JO, Masuku NP, Olisah C, Lebelo SL. Medicinal uses, pharmacological activities, phytochemistry, and the molecular mechanisms of Punica granatum L. (pomegranate) plant extracts: A review. Biomed Pharmacother. 2022;153:113256. doi: 10.1016/j.biopha.2022.113256.

27. Mehta J, Rolta R, Dev K. Role of medicinal plants from North Western Himalayas as an efflux pump inhibitor against MDR AcrAB-TolC Salmonella enterica serovar typhimurium: In vitro and In silico studies. J Ethnopharmacol. 2022 Jan 10;282:114589. doi: 10.1016/j.jep.2021.114589.
28. Milošević M, Vulić J, Kukrić Z, Lazić B, Četojević-Simin D, Čanadanović-Brunet J. Polyphenolic Composition, Antioxidant and Antiproliferative Activity of Edible and Inedible Parts of Cultivated and Wild Pomegranate (Punica granatum L.). Food Technol Biotechnol. 2023;61(4):485-493. doi: 10.17113/ftb.61.04.23.8159.
29. Mo Y, Ma J, Gao W, Zhang L, Li J, Li J, et al. Pomegranate Peel as a Source of Bioactive Compounds: A Mini Review on Their Physiological Functions. Front. Nutr. 2022;9:887113. doi: 10.3389/fnut.2022.887113.
30. Moga MA, Dimienescu OG, Bălan A, Dima L, Toma SI, et al. Pharmacological and Therapeutic Properties of Punica granatum Phytochemicals: Possible Roles in Breast Cancer. Molecules. 2021;26(4):1054. doi: 10.3390/molecules26041054.
31. Mohan M, C A M, D P, V AG. Review of Pharmacological and Medicinal Uses of Punica granatum. Cureus. 2024;16(10):e71510. doi: 10.7759/cureus.71510.
32. Morvaridzadeh M, Sepidarkish M, Daneshzad E, Akbari A, Mobini GR, Heshmati J. The effect of pomegranate on oxidative stress parameters: A systematic review and meta-analysis. Complement Ther Med. 2020 Jan;48:102252. doi: 10.1016/j.ctim.2019.102252.
33. Murray CJL, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629-655. doi: 10.1016/S0140-6736(21)02724-0.
34. Nawaz M, Pan J, Liu H, Umer MJ, Liu J, Yang W, et al. Integrated evaluation of antifungal activity of pomegranate peel polyphenols against a diverse range of postharvest fruit pathogens. Bioresour Bioprocess. 2025;12(1):34. doi: 10.1186/s40643-025-00874-9.
35. Osset-Trénor P, Pascual-Ahuir A, Proft M. Fungal Drug Response and Antimicrobial Resistance. J Fungi (Basel). 2023;9(5):565. doi: 10.3390/jof9050565.
36. Parisi V, Santoro V, Donadio G, Bellone ML, Diretto G, Sandri C, et al. Comparative Chemical Analysis of Eight Punica granatum L. Peel Cultivars and Their Antioxidant and Anti-Inflammatory Activities. Antioxidants (Basel). 2022;11(11):2262. doi: 10.3390/antiox11112262.
37. Quitmeyer B, Emelife C, Klausner H, Gbayisomore O, Phelan S. Differential Effects of Punicic Acid on Cytotoxicity and Peroxiredoxin Expression in MCF-7 Breast Cancer and MCF-10A Normal Cells. Anticancer Res. 2024;44(11):4751-4759. doi: 10.21873/anticanres.17301.
38. Rani P, Petrulio F, Bacchelli A. On Refining the SZZ Algorithm with Bug Discussion Data. Empir Softw Eng. 2024;29(5):115. doi: 10.1007/s10664-024-10511-2.
39. Sweidan N, Abu Rayyan W, Mahmoud I, Ali L. Phytochemical analysis, antioxidant, and antimicrobial activities of Jordanian Pomegranate peels. PLoS One. 2023;18(11):e0295129. doi: 10.1371/journal.pone.0295129.
40. Salih AM, Alattas NM, Alsubaie QD, Anifowose SO. Bidah Pomegranate Landrace: Chemical Composition, Antioxidant, Antibacterial, and Anticancer Activity. Life (Basel). 2025 Mar 18;15(3):489. doi: 10.3390/life15030489.
41. Suručić R, Travar M, Petković M, Tubić B, Stojiljković MP, Grabež M, et al. Pomegranate peel extract polyphenols attenuate the SARS-CoV-2 S-glycoprotein binding ability to ACE2 Receptor: In silico and in vitro studies. Bioorg Chem. 2021 Sep;114:105145. doi: 10.1016/j.bioorg.2021.105145.
42. Teniente SL, Flores-Gallegos AC, Esparza-González SC, Campos-Múzquiz LG, Nery-Flores SD, Rodríguez-Herrera R. Anticancer Effect of Pomegranate Peel Polyphenols against Cervical Cancer. Antioxidants (Basel). 2023 Jan 5;12(1):127. doi: 10.3390/antiox12010127.
43. Teniente SL, Esparza-González SC, Ascacio-Valdés JA, Campos-Múzquiz LG, Nery-Flores SD, Onofre-Rentería K, et al. Antiproliferative and cytotoxic effects of polyphenols from pomegranate peel and coffee pulp on cancer cells. Nat Prod Res. 2024:1-7. doi: 10.1080/14786419.2024.2310669.
44. Yousefi M, Sadriirani M, Mahmoodi S, Samimi B, Pourmahmoudi A, Hosseinikia M, et al. Adjuvant pomegranate juice intake improves the inflammatory status of hospitalized COVID-19 patients: A randomized and placebo-controlled trial. Complement Ther Med. 2023;75:102958. doi: 10.1016/j.ctim.2023.102958.
45. Valero-Mendoza AG, Meléndez-Rentería NP, Chávez-González ML, Flores-Gallegos AC, Wong-Paz JE, Govea-Salas M, et al. The Whole Pomegranate (Punica granatum. L), Biological Properties and Important Findings: A Review. Food Chem. Adv. 2023;2:100153. doi: 10.1016/j.focha.2022.100153.
46. Wang P, Zhang Q, Hou H, Liu Z, Wang L, Rasekhmagham R, et al. The effects of pomegranate supplementation on biomarkers of inflammation and endothelial dysfunction: A meta-analysis and systematic review. Complement Ther Med. 2020;49:102358. doi: 10.1016/j.ctim.2020.102358.
47. Willcox ML, Tai CJ, Chattopadhyay K, Hu XY, Heinrich M. Editorial: Clinical phytopharmacology. Front Pharmacol. 2024;14:1353483. doi: 10.3389/fphar.2023.1353483.
48. Wong TL, Strandberg KR, Croley CR, Fraser SE, Nagulapalli Venkata KC, Fimognari C, et al. Pomegranate bioactive constituents target multiple oncogenic and oncosuppressive signaling for cancer prevention and intervention. Semin Cancer Biol. 2021;73:265-293. doi: 10.1016/j.semcancer.2021.01.006.
49. Zhou YM, Dong XR, Xu D, Tang J, Cui YL. Therapeutic potential of traditional Chinese medicine for interstitial lung disease. J Ethnopharmacol. 2024;318(Pt A):116952. doi: 10.1016/j.jep.2023.116952.
50. Zhou T, Zhou H, Tian L, Tang M, Wang L, Kang Y, et al. Pomegranate juice-containing serum inhibits migration of hepatocellular carcinoma cells and promotes apoptosis by induction of mitochondrial dysfunction. J Nutr Biochem. 2024;125:109557. doi: 10.1016/j.jnutbio.2023.109557.

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