REVIEW
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The application of *Punica granatum* L. in traditional medicine and advances in modern pharmacological activity research

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Author contributions
Chen S conceived and designed the framework of this review, and wrote the initial draft of the manuscript. Che L conceived and designed the framework of this review. Cai A and Bao H provided guidance throughout the preparation of this manuscript. All authors have read and agreed to the final version of the manuscript.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
COX-2, cyclooxygenase-2; EA, ellagic acid; GA, gallic acid; MAPK, mitogen-activated protein kinase; Nrf2, nuclear factor erythroid 2-related factor 2; PPE, pomegranate peel extracts; TCM, traditional Chinese medicine; TMM, traditional Mongolian medicine.

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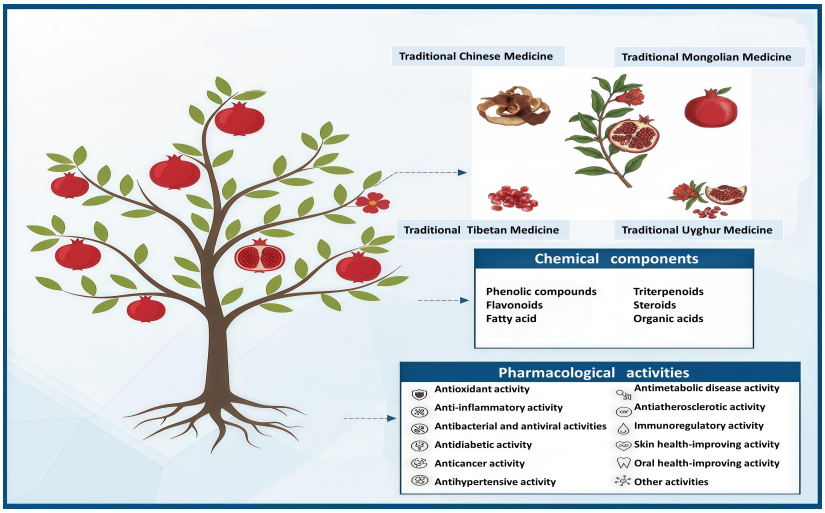
Abstract

Punica granatum L. is a deciduous shrub belonging to the family Punicaceae and the genus *Punica*, recognized as a plant with both medicinal and edible value. Its peel, seeds, juice, flowers, and leaves have long been used in traditional Chinese, Mongolian, Tibetan, and Uyghur medicine, illustrating the characteristic phenomenon of "different applications of the same drug". This article systematically reviews research progress from 2000 to 2025, focusing on chemical composition and pharmacological effects. Clinical practice and accumulated experience have led to distinct preferences across medical traditions: traditional Chinese medicine mainly uses dried peel to relieve diarrhea, stop bleeding, and expel parasites; traditional Mongolian medicine employs processed dried fruits to eliminate "Badgan", warm the stomach, and aid digestion; Tibetan medicine often applies the seeds to strengthen the stomach and warm the middle energizer; Uyghur medicine uses the flowers to treat diarrhea and trauma. Modern studies show that chemical composition varies significantly among plant parts: the peel is rich in tannins and phenolic acids, seeds contain mostly fatty acids, and flowers are high in flavonoids. These differences lead to varied pharmacological activities, such as antioxidant, anti-inflammatory, and antibacterial effects. Furthermore, studies reveal synergistic effects among active components from different parts, with whole fruit or multi-part combinations showing better efficacy than single components. It should be noted that such synergies were identified through modern pharmacological studies – not derived directly from traditional theories. Together, these findings provide a scientific basis for the traditional "different applications of the same drug" and support further development of pomegranate resources based on multi-component synergy.

Keywords: *Punica granatum* L.; medicinal plant parts; chemical components; pharmacological activities; traditional medicine



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Highlights

1. Recent studies have indicated that synergistic effects exist among the active constituents of different medicinal parts of pomegranate (such as the peel, seeds, and flowers). This "multi-component, multi-target" integrated mode of action results in superior efficacy in certain pharmacological activities compared to single constituents.
2. The "whole pomegranate fruit" application concept in traditional Mongolian medicine (TMM) closely corresponds to modern synergistic pharmacological mechanisms. However, current experimental evidence primarily derives from studies on isolated extracts. Therefore, elucidating the inherent synergistic mechanisms of the traditional whole-fruit application should be a key focus of future research, to establish a foundation for developing natural drugs based on synergistic principles.

Medical history of objective

Punica granatum L. was introduced to China during the Western Han Dynasty via the Silk Road by Qian Zhang. It was first documented in Chinese agricultural literature *Qimin Yaoshu*, compiled by Sixie Jia in the 5th century CE. In traditional Chinese medicine, the dried peel of *Punica granatum* L. is commonly used medicinally, with its core efficacy focusing on arresting intestinal leakage to relieve diarrhea, stopping bleeding, and killing parasites. In TMM, the whole fruit is utilized primarily to eliminate "Badgan" (a specific imbalance in Mongolian medical theory characterized by cold and metabolic dysfunction). Modern research has confirmed that *Punica granatum* L. possesses pharmacological activities such as antioxidant, antibacterial, and anticancer effects.

Background

Punica granatum L. refers to the dried peel of the fruit from the plant *Punica granatum* L. of the family Punicaceae [1]. For thousands of years, pomegranate has been valued not only as a nutritious fruit but also utilized as a medicinal plant in various traditional medical systems [2]. In China, pomegranate is recognized as a plant with both medicinal and edible applications and has been incorporated into several traditional medical systems, including traditional Chinese medicine (TCM), traditional Mongolian medicine (TMM), traditional Tibetan medicine, and traditional Uyghur medicine. A notable phenomenon observed across these ethnic medical systems is "different applications of the same drug", which refers to the selective use of different anatomical parts of the pomegranate – such as the peel, seeds, juice, flowers, and leaves – to treat various diseases, based on distinct medical theories and accumulated clinical experience. For example, TCM primarily uses the dried peel for its astringent properties to treat diarrhea, bleeding, and parasites; TMM employs the processed dried ripe fruit to dispel "Badgan", warm the stomach, and aid digestion; Tibetan medicine often uses the seeds to warm the middle energizer and promote digestion; while traditional Uyghur medicine commonly applies the flowers to treat diarrhea and external injuries. These differences in application are influenced by geographical environment, theoretical systems, and cultural transmission.

Modern pharmacological research has begun to elucidate the scientific basis of these traditional uses, revealing significant differences in the chemical composition of different medicinal parts of pomegranate [3]. The peel is rich in hydrolyzable tannins (such as punicalagin and ellagic acid) and phenolic acids, which confer strong antioxidant and antimicrobial activities [4]. The seeds are characterized by conjugated fatty acids (including punicic acid), which are associated with anti-inflammatory and lipid-regulating effects [5]. The flowers primarily contain flavonoids, which exhibit notable antioxidant and anti-diabetic properties (Figure 1). These compositional differences underpin the distinct pharmacological activities observed in different plant parts.

Furthermore, recent studies indicate that synergistic interactions exist among the active components from different parts of pomegranate, with the whole fruit or multi-part combinations demonstrating superior efficacy compared to single components [6]. However, it should be noted that the discovery of such synergies stems from modern pharmacological studies on isolated components or combined extracts, rather than directly from traditional medical theories.

Given the extensive traditional uses, complex chemical composition, and broad medicinal potential of pomegranate, this review aims to systematically summarize and analyze research progress on pomegranate from 2000 to 2025, focusing on its chemical constituents, pharmacological activities, and quality control. By integrating modern scientific findings with traditional wisdom, this review seeks to provide a scientific basis for the phenomenon of "different applications of the same drug" and to establish a solid foundation for further development and utilization of pomegranate resources based on the principle of multi-component synergy.

Chemical components

Punica granatum L., a fruit with a long history of both medicinal and dietary use, has attracted increasing attention in recent years due to its rich array of bioactive compounds (Figure 2). Studies have shown that different parts of the *Punica granatum* L. – such as the peel, juice, seeds, flowers, and leaves – contain diverse chemical constituents with varied biological activities [7]. This review systematically summarizes the major chemical components of pomegranate based on their structural categories.

Phenolic compounds

Punica granatum L. are rich in polyphenolic compounds, primarily including phenolic acids, tannins, and phenolic glycosides, which are closely associated with medicinal properties such as antioxidant, antibacterial, antiviral, and anticancer activities. Among phenolic acids, gallic acid (GA) and ellagic acid (EA) are the most abundant and widely distributed in the peel, juice, and leaves. The peel also contains protocatechuic acid, chlorogenic acid, and caffeic acid. These compounds significantly contribute to the antioxidant and anti-inflammatory activities of *Punica granatum* L. Tannins are predominantly hydrolyzable and can be further divided into ellagitannins (e.g., punicalagin, corilagin, and pedunculagin) and gallotannins (e.g., galloyl glucose). Among these, punicalagin is recognized as the primary active component in pomegranate peel extracts (PPE), exhibiting effects such as blood-glucose-lowering, antioxidant, anti-inflammatory, antibacterial, and antiviral properties [8]. Gallotannins (e.g., galloyl glucose) are commonly found in the peel and flowers. Furthermore, phenolic glycosides (e.g., ellagic acid-4-O-glucoside), which are glycosidic derivatives of phenolic acids, are also primarily present in the peel [9].

Flavonoids

Various flavonoids are distributed throughout different parts of the pomegranate. Major flavonoids include flavones and flavonols such as luteolin, apigenin, quercetin, and kaempferol, along with their glycosidic derivatives (e.g., rutin). Additionally , flavanols like catechin and epicatechin are also abundant. Collectively, these flavonoids contribute to the strong free radical scavenging capacity of pomegranate. Anthocyanins, such as cyanidin-3-glucoside, delphinidin-3,5-diglucoside, and pelargonidin derivatives, are responsible for the vivid red color of pomegranate juice and also possess notable antioxidant properties [10].

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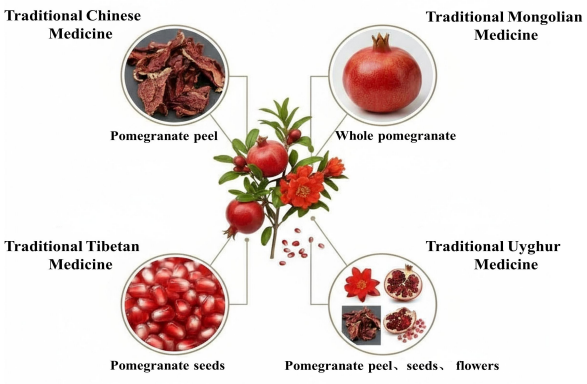

Figure 1 Utilization of different medicinal parts of *Punica granatum* L.in various traditional medical systems

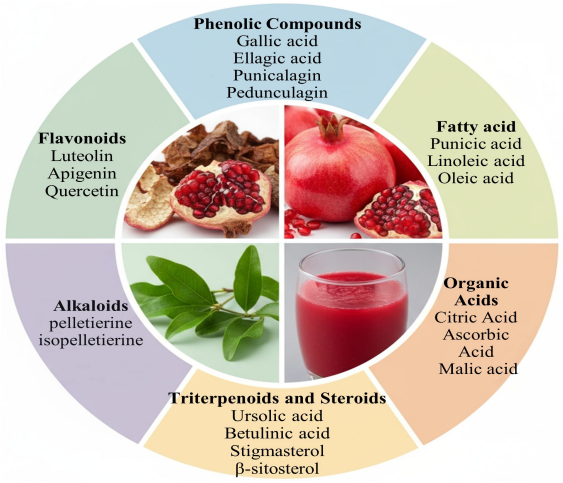

Figure 2 Classification of main bioactive chemical components in *Punica granatum* L.

Fatty acids

Punica granatum L. seeds are the main repository of fatty acids. The principal component is punicic acid, a unique conjugated trienoic acid with demonstrated anti-inflammatory and anticancer activities. Other fatty acids include oleic acid, linoleic acid, and α-linolenic acid [11].

Triterpenoids and sterols

The peel of pomegranate contains pentacyclic triterpenoids such as ursolic acid and betulinic acid, which exhibit antitumor and antibacterial activities. Meanwhile, pomegranate seed oil is rich in sterols, with β-sitosterol being the most abundant; other sterols include stigmasterol and campesterol [12].

Alkaloids

Punica granatum L. peel contains piperidine alkaloids, including pelletierine, pseudopelletierine, and isopelletierine. These compounds have been shown to possess anthelmintic and antimicrobial properties.

Other components

The juice contains various organic acids, such as citric acid, malic acid, and ascorbic acid (vitamin C), as well as multiple amino acids. The peel contains other organic acids including oxalic acid and succinic acid, and its polysaccharides are known to exhibit immunomodulatory functions (Table 1) (3, 9, 10, 12–24).

Pharmacological activities

Antioxidant activity

Punica granatum L.'s potent antioxidant properties are primarily attributed to its rich and diverse polyphenolic compounds, which are widely distributed in the peel, juice, seeds, flowers, and leaves . Specifically, PPE effectively scavenge various free radicals including DPPH (2,2-Diphenyl-1-picrylhydrazyl), OH, O_2^-, and $ABTS^+$ (2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)), with their scavenging capacity showing a positive correlation with concentration within a certain range [25]. Aqueous PPEs demonstrate higher total phenolic and flavonoid content along with stronger free radical scavenging capacity compared to ethanolic extracts [26]. Similarly, pomegranate juice, abundant in phenolic compounds, exhibits significant antioxidant activity wherein anthocyanins and neutral phenols synergistically contribute to 27% of the oxygen radical absorbance capacity, while added ascorbic acid shows dose-dependent synergistic effects in the ferric reducing antioxidant power assay [27]. Additionally, pomegranate seed ethanol extracts and flower extracts effectively neutralize reactive oxygen and nitrogen species [28, 29]. *Punica granatum* L.'s leaf extract also exhibits potent activity, functioning both by directly scavenging free radicals and by upregulating the endogenous antioxidant defense system [30] (Figure 3).

Anti-inflammatory activity

Punica granatum L. and its key bioactive constituents, such as punicalagin and ellagic acid, alleviate inflammation primarily by inhibiting critical signaling pathways including NF-κB and mitogen-activated protein kinase (MAPK), resulting in significant downregulation of pro-inflammatory enzymes and cytokines such as inducible nitric oxide synthase, cyclooxygenase-2 (COX-2), prostaglandin E2, interleukin-1 beta, interleukin-6, interleukin-8, and

tumor necrosis factor-α (TNF-α) [31–33]. Punicalagin inhibits NF-κB activation by blocking inhibitor of nuclear factor kappa B alpha phosphorylation and p65 nuclear translocation, while also modulating the aryl hydrocarbon receptor pathway to enhance anti-inflammatory and anti-sepsis responses [34, 35]. Extracts from different parts of pomegranate exhibit notable anti-inflammatory activities across various models: fruit extract or juice reduces vascular inflammation by decreasing thrombospondin, transforming growth factor beta 1, and C-reactive protein, while increasing endothelial nitric oxide synthase expression [36, 37]. Punicic acid from seed oil inhibits neutrophil activation, Reactive oxygen species production, and myeloperoxidase release [38]. Flower extract attenuates swelling by lowering IL-6 and TNF-α levels and reducing inflammatory cell infiltration [30]. And leaf extract suppresses pulmonary secretion of IL-1β and interleukin-5, reduces expression of iNOS and COX2, and inhibits NO release (Figure 4) [30, 39].

Table 1 The main chemical components isolated from *Punica granatum* L.

Phytochemical type	Chemical component	Species from plant parts	Reference(s)
Phenolic compounds	Gallic acid	P, J, S, F, L	[12–14]
	Ellagic acid	P, J, S, F, L	[14–16]
	Caffeic acid	P	[17]
	Chlorogenic acid	P, J	[17]
	P-coumaric acid	P, J, S	[17]
	Ellagic acid rhamnoside	J	[18]
	Ellagic acid-hexoside	P, J, S, L	[9, 13, 16]
	Ellagic acid-pentoside	P, J, F, S	[15–16, 18]
	Ferulic acid	P, J	[17–18]
	Protocatechuic acid	P, J, S	[9, 16]
	Vanillic acid	P, J, S	[10, 16, 17, 19]
	Punicalagin	P, J, F, L	[9, 12, 14, 20]
	Pedunculagin	P, J, L	[9, 13, 20]
	Corilagin	P, J, F	[21]
	Granatin A/B	P, J, F, L	[9, 12, 14, 22]
Flavonoids	Apigenin	P, F, L	[12, 17, 23]
	Epicatechin gallate	P	[17]
	Catechin	P, J, S	[12, 16]
	Kaempferol	P, F	[12, 23]
	Kaempferol-3-O-glucoside	P, J, S	[16, 22]
	Isoquercetin	F	[23]
	Luteolin	P, S, F, L	[3, 14, 22, 23]
	Quercetin	P, J, F	[17, 23]
	Rutin	P, J, S, L	[3, 12, 21, 22]
	Cyanidin-3-O-glucoside	P, J, S, F	[16, 23, 24]
	Cyanidin-3,5-O-diglucoside	P, J, S, F	[9, 15, 16, 23, 24]
	Delphinidin-3,5-O-diglucoside	P, J, S, F, L	[9, 15, 16]
	Delphinidin-3-O-glucoside	P, J, S, F	[9, 15, 16, 23, 24]
	Pelargonidin-3,5-O-diglucoside	P, J, F	[23, 24]
	Pelargonidin-3-O-glucoside	P, J, S, F	[16, 23]
Fatty acid	Linoleic acid	S	[12]
	Oleic acid	S	[12]
	Palmitic acid	S	[12]
	Punicic acid	S	[12]
	Stearic acid	S	[12]
Triterpenoids	Oleanolic acid	P, F	[12]
	Betulinic acid	P, F	[12]
	Ursolic acid	J, S, F	[12, 21]
Steroids	Stigmasterol	S	[12]
	β-sitosterol	S	[12]
	Camesterol	S	[12]
Organic acids	Ascorbic acid	J	[15]
	Citric acid	J, S	[15]
	Malic acid	J, S	[23]

P, peel; J, juice; S, seeds; F, flower; L, leaf.

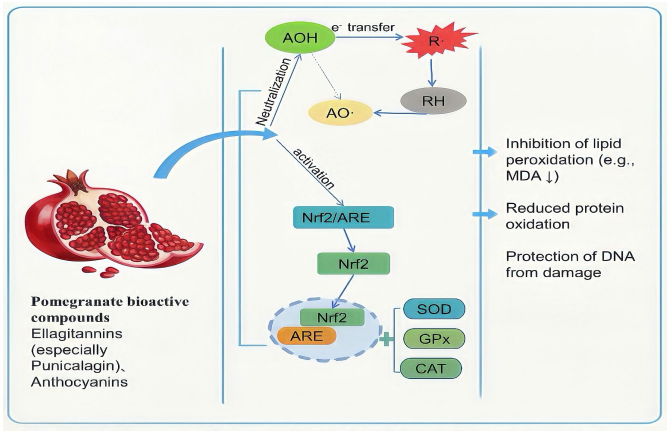

Figure 3 Activation of the Nrf2/ARE pathway and subsequent antioxidant defense by *Punica granatum* L. active components.
ARE, antioxidant response element; CAT, catalase; GPx, glutathione peroxidase; MDA, malondialdehyde; Nrf2, nuclear factor erythroid 2-related factor 2; SOD, superoxide dismutase.

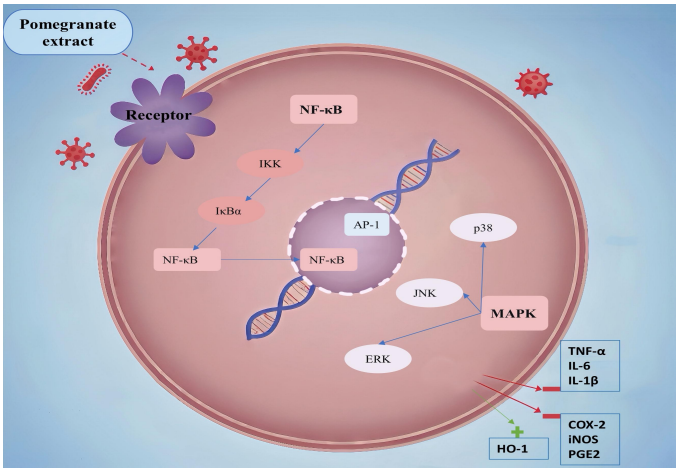

Figure 4 Core anti-inflammatory signaling pathways of *Punica granatum* L.
AP-1, activator protein 1; COX-2, cyclooxygenase-2; ERK, extracellular signal-regulated kinase; HO-1, heme oxygenase-1; IKK, IkB kinase; IL-1β, interleukin-1 beta; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; IkBα, inhibitor of kappa B alpha; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PGE2, prostaglandin E2; TNF-α, tumor necrosis factor alpha.

Antibacterial and antiviral activities

PPE and its key phenolic compounds (such as punicalagin, punicalin, EA, and GA) exhibit broad-spectrum antibacterial effects. They inhibit multidrug-resistant pathogens through time- and dose-dependent bactericidal mechanisms, effectively eliminating intracellular bacteria without host cell toxicity [40]. Additionally, silver nanoparticles synthesized using pomegranate leaf extract (PGL-AgNPs) enhance antibacterial and antibiofilm activity, particularly against Pseudomonas aeruginosa [41]. PPE also show strong antiviral activity by inhibiting the binding of Severe acute respiratory syndrome coronavirus 2 S-glycoprotein to Angiotensin-converting enzyme 2, with punicalin demonstrating the highest affinity [42].

Antidiabetic activity

Punica granatum L.'s peel, juice, seeds, and flowers have demonstrated antidiabetic effects. The main bioactive compounds responsible include GA, ellagitannins, flavonoids (such as tricetin), and triterpenoids (e.g., oleanolic acid and ursolic acid). These components exert hypoglycemic actions through multiple mechanisms, including enhancing insulin sensitivity, inhibiting carbohydrate-digesting enzymes, activating the peroxisome proliferator-activated receptor gamma signaling pathway, and exerting antioxidant effects. Specific mechanisms involve: improving insulin sensitivity via activation of PPAR-γ and upregulation of glucose transporter type 4 expression [43]; enhancing insulin signaling through modulation of the Protein Kinase B/Glycogen Synthase Kinase-3 Beta pathway (Akt/GSK-3β pathway) and suppression of the Inositol-requiring enzyme 1 alpha – X-box binding protein 1 pathway [44] and delaying carbohydrate digestion by inhibiting α-glucosidase and α-amylase activities [14]. Other mechanisms include binding to thioredoxin-interacting protein to modulate glucose metabolism [45], upregulating paraoxonase 1 expression to alleviate oxidative stress [46], and mitigating diabetic complications through antioxidant and antiglycation activities [47]. These multi-pathway mechanisms collectively contribute to the comprehensive antidiabetic effects of pomegranate.

Anticancer activity

Punica granatum L., particularly its peel, juice, and seed oil, is rich in a variety of potent bioactive compounds such as polyphenols (including EA and punicalagin) and polysaccharides. These components demonstrate broad-spectrum anticancer activity against various cancer types by inhibiting proliferation, inducing cell cycle arrest, apoptosis, and autophagy. The cancers affected include breast cancer [48, 49], prostate cancer [50], colon cancer, liver cancer [51], blood cancers [52], acute leukemia [53], oral cancer [54], neuroblastoma [55], and glioma [56]. The anticancer effects are mainly manifested as anti-proliferative, pro-apoptotic, and anti-metastatic activities, which are primarily achieved through the modulation of key signaling

pathways such as PI3K/Akt, NF-κB, and MAPK. Notably, combinations of different pomegranate fractions exhibit significant synergistic effects – for example, markedly enhancing anti-invasiveness and anti-proliferation efficacy in prostate cancer [57] – outperforming individual compounds. This synergistic interaction may be crucial to its anticancer mechanisms (Figure 5).

Antihypertensive activity

The polyphenolic compounds (such as ellagitannins and punicalagin) abundant in pomegranate juice contribute to its antihypertensive effects. Studies have demonstrated that pomegranate juice has potent antihypertensive effects. In a study involving 10 patients with hypertension, serum angiotensin-converting enzyme (ACE) activity significantly decreased by 36% in 7 of the 10 patients and systolic blood pressure decreased by an average of 5% after 2 weeks of pomegranate juice consumption [58]. A meta-analysis indicated that pomegranate juice significantly reduces systolic blood pressure in a dose-dependent manner [59]. These findings suggest that pomegranate juice can decrease blood pressure, and its mechanism may be related to the inhibition of ACE activity and Angiotensin II production.

Antimetabolic disease activity

Punica granatum L. and its bioactive components, such as punicalagin and EA, alleviate metabolic syndrome-related diseases primarily through antioxidant and anti-inflammatory activities. Specifically, they improve nonalcoholic steatohepatitis by reducing hepatic steatosis, inflammation, and oxidative stress [60]; help ameliorate dyslipidemia by lowering total cholesterol, triglycerides, and LDL-C while increasing HDL-C [61]; and enhance cardiac and hepatic function via modulation of Nrf2, NF-κB, and CPT1 [62]. Furthermore, PPE promote cholesterol metabolism by increasing bile acid content [63] and inhibits hepatic fibrosis through suppression of the p38MAPK/Nrf2 signaling pathway [64]. Additionally, pomegranate polyphenols and punicalagin upregulate LXRα and ABCA1 to enhance reverse cholesterol transport [65], and pomegranate juice has been shown to reduce oxidized LDL uptake in macrophages [66] and attenuate hepatic fibrosis by regulating the Nrf2 and NF-κB pathways [67]. Moreover, pomegranate flower extract activates PPAR-α, CPT-1, and acyl-CoA oxidase, thereby promoting fatty acid oxidation and reducing lipid accumulation [68].

Antiatherosclerotic activity

Atherosclerosis is the leading cause of vascular disease worldwide, with its major clinical manifestations being ischemic heart disease, ischemic stroke, and peripheral arterial disease [69]. The vascular protective effects of pomegranate are mainly attributed to hydrolyzable tannins, ellagitannins, EA, anthocyanins, and flavonoids [2].

These compounds act through multiple mechanisms such as enhancing antioxidant capacity and nitric oxide activity, reducing lipid levels and oxidative stress, inhibiting oxidized LDL uptake by macrophages, decreasing inflammatory responses, and improving cholesterol efflux [70]. Notably, pomegranate flowers exhibit the most potent antiatherogenic effects, significantly reducing atherosclerotic lesion area and improving serum lipid and glucose levels [71].

Immunoregulatory activity

PPE and its polysaccharides are key bioactive components that exert immunomodulatory effects through multiple pathways. PPE alleviate symptoms of atopic dermatitis by suppressing inflammation in skin models [72], and inhibits Interleukin-17 production in immune cells, thereby attenuating autoimmune responses [73]. *Punica granatum* L. peel polysaccharides enhance proliferation and immunoglobulin secretion in splenic lymphocytes, while boosting antioxidant activity in the liver [74]. Additionally, pomegranate seed oil production of immunoglobulins Immunoglobulin G and Immunoglobulin M [75]. Overall, pomegranate components modulate immunity by inhibiting inflammatory mediators, regulating cytokines, and enhancing immune cell function.

Skin health-improving activity

Current studies affirm the significant potential of pomegranate in managing a wide range of dermatological conditions, including acne, psoriasis, photoaging, hyperpigmentation, and impaired wound healing [76]. Its efficacy is attributed to the diverse bioactive compounds found in different parts of the fruit. The polyphenol-rich extracts and specific compounds like punicalagin exhibit photoprotective, anti-inflammatory, and anti-microbial effects, modulating key cellular pathways to protect against UV damage and inflammatory skin conditions [77, 78]. In a randomized controlled trial, topical formulations containing peel extract (e.g., in microemulsions) were shown to effectively reduce melanin and erythema [79]. A separate clinical trial also found that pomegranate seed oil significantly enhances skin hydration, elasticity, and thickness, demonstrating benefits against striae distensae [80].

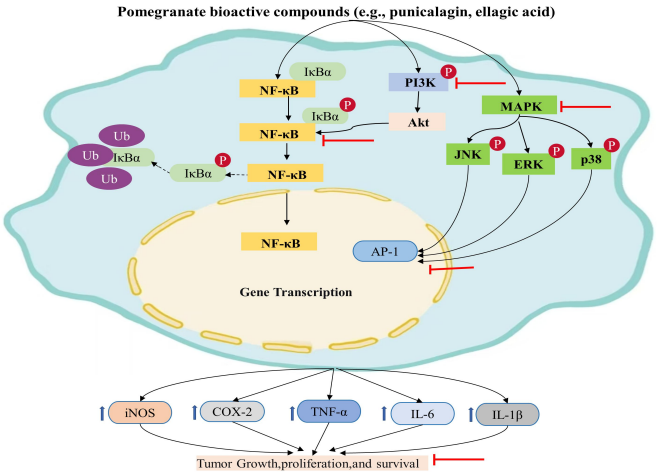

Figure 5 Schematic diagram of key anti-cancer signaling pathways regulated by *Punica granatum* L.extract.

AP-1, activator protein 1; Akt, protein kinase B; COX-2, cyclooxygenase-2; ERK, extracellular signal-regulated kinase; IL-1β, interleukin-1 beta; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; IkBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase; TNF-α, tumor necrosis factor-alpha.

Oral health-improving activity

Punica granatum L. extracts, primarily rich in polyphenols, flavonoids, and triterpenoids, exert anti-inflammatory, collagen-promoting, and antimicrobial effects. These bioactive components help reduce gingival inflammation more effectively than chlorhexidine in mouthwash applications [81], and show potential as endodontic irrigants due to their disinfecting properties and low cytotoxicity [82]. Additionally, pomegranate flower tablets accelerate the healing of aphthous ulcers by reducing pain and ulcer size [83]. Notably, PPE modulate osteogenic gene expression (e.g., RUNX2, BMP2, COL1A1) in gingival mesenchymal stromal cells under inflammatory conditions, particularly enhancing osteoblastic differentiation in periodontitis-derived cells [84].

Other activities

Polyphenols derived from pomegranate, particularly from its peel and juice, exhibit multifaceted protective effects through modulation of inflammatory and oxidative pathways. These compounds – such as punicalagin – inhibit key signaling pathways including NF-κB and NLRP3 inflammasome, reducing neuroinflammation, amyloid-beta amyloid accumulation, and oxidative stress, thereby alleviating cognitive dysfunction in Alzheimer's and Parkinson's diseases [85–87]. Additionally, pomegranate polyphenols improve cardiovascular health by diminishing angina symptoms and myocardial injury [88], support menopausal well-being [89], and demonstrate antimalarial properties [90]. In addition, it reduces the intensity, frequency, and duration of angina pectoris and alleviates oxidative stress and myocardial injury, thereby exerting cardioprotective effects in patients with ischemic heart disease [88].

Discussion

Punica granatum L. has a long history of medicinal use in various traditional systems. Interestingly, different traditions use distinct parts of the plant based on empirical knowledge: TCM primarily uses the peel, while TMM uses the whole fruit. These differences reflect diverse cultural backgrounds and the practical wisdom of applying different medicinal parts.

Modern research confirms that pomegranate's chemical composition varies significantly by part: the peel is rich in tannins and phenolic acids, the seeds are high in fatty acids, and the flowers contain abundant flavonoids. These unique profiles explain their specific pharmacological effects, such as antioxidant, anti-inflammatory, and antimicrobial activities. Importantly, evidence shows that combining different parts or compounds enhances the therapeutic effect through synergistic interactions.

The anti-inflammatory and anti-cancer activities of *Punica granatum* L. originate from the synergistic interactions among its multiple bioactive constituents, rather than the effect of any single compound. Studies demonstrate that polyphenols in *Punica granatum* L., such as punicalagin, ellagic acid, and gallic acid, can act together to synergistically inhibit the activation and nuclear translocation of NF-κB and modulate the MAPK signaling pathway. Consequently, they suppress the production of key inflammatory mediators, including IL-6, TNF-α, and COX-2, at multiple critical points. This multi-target synergistic mechanism is also significant in anti-cancer effects. For instance, the combination of luteolin, punicic acid, and ellagic acid from pomegranate juice exhibits a stronger synergistic effect in inhibiting the growth, adhesion, and migration of prostate cancer cells compared to individual components [91]. Therefore, the overall biological efficacy of pomegranate extract, as a multi-component system, benefits from the complementary and synergistic actions of its different constituents on signaling pathways.

In inhibiting tumor cell proliferation and inducing apoptosis, PJ outperforms its individual purified compounds. Punicalagin and EA inhibit the NF-κB pathway, while anthocyanins and quercetin in the juice concurrently target the PI3K/Akt or MAPK pathways, working together to induce cell cycle arrest and activate the mitochondrial apoptosis pathway [6]. Stronger evidence comes from combinations of extracts from different anatomical parts: when fermented pomegranate juice polyphenols, pomegranate peel polyphenols, and pomegranate seed oil were used together, they showed significantly superior inhibition of DU145 cell proliferation, PC-3 cell invasion, and secreted phospholipase A2 expression compared to any single extract [57]. Although the precise molecular mechanisms were not detailed, it can be inferred that these effects are achieved through cross-regulation of multiple targets (e.g., matrix metalloproteinases, NF-κB, STAT3) and pathways (e.g., apoptosis, inflammation, angiogenesis).

This "multi-component, multi-target, pathway network" mode of action showcases immense potential – unattainable by single constituents – for treating complex diseases like cancer and inflammation. It provides a solid scientific foundation for developing complex botanical drugs based on whole-fruit extracts.

These findings suggest that while bioactive compounds from different medicinal parts of pomegranate have clear synergistic potential, and while the whole-fruit application in TMM exhibits conceptual similarities to the modern "multi-component combination" strategy, it should be noted that current experimental models are based on reconstituted isolated compounds or purified extracts rather than being derived from or fully consistent with the traditional practice and theoretical framework of whole-fruit use in TMM. Therefore, although scientific studies have confirmed synergistic interactions among different chemical constituents of pomegranate, existing evidence does not directly demonstrate that the holistic application of the whole fruit in TMM follows the same mechanisms or produces equivalent effects. The use of the whole fruit in TMM constitutes a complex holistic system refined through long-term practice, and its mechanisms of action may extend beyond the scope of current reductionist research.

Future studies should more systematically explore the intersection between traditional holistic perspectives and modern synergy-based pharmacology. Doing so would not only help clarify the scientific basis of traditional knowledge but also support the development of novel natural multi-component drugs founded on synergistic principles.

Conclusion

Punica granatum L., as an important medicinal plant with a long history of therapeutic use, has been widely employed in various traditional medical systems such as TCM, TMM, traditional Tibetan medicine, and traditional Uyghur medicine, demonstrating significant clinical efficacy. Different ethnic medical systems have developed distinct application models – for example, TMM often uses the whole fruit, while TCM primarily utilizes the peel. Research shows that the chemical compositions of different medicinal parts of pomegranate (such as the peel, seeds, and flowers) vary significantly: the peel is rich in tannins and phenolic acids, the seeds are characterized by fatty acids, and the flowers contain abundant flavonoids. These distinct chemical profiles contribute to unique pharmacological activities, such as antioxidant, anti-inflammatory, and antibacterial effects. Modern research has confirmed the presence of synergistic effects among the bioactive components of different parts of the pomegranate, with the whole fruit demonstrating superior efficacy compared to any single constituent. While TMM employs the whole fruit, and pharmacological studies have revealed the cooperative potential among its parts, current experimental evidence is largely based on combinations of isolated extracts rather than being derived from or aligned with TMM's theoretical and practical framework. Therefore, future studies should integrate traditional theories with modern science to directly investigate the mechanisms of whole-fruit application, thereby advancing the development of natural multi-component drugs based on synergistic principles.

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