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Valorizing Pomegranate Peel Waste in Circular Economy: New Insights Into Biological Activities for Pharmaceutical Applications

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ABSTRACT

Pomegranate peel, a substantial byproduct of juice and food industries, represents an underused biomass rich in bioactive compounds with high relevance to pharmaceutics. Converting pomegranate peel into pharmaceutical ingredients offers a promising, sustainable pathway to fulfill circular bioeconomy objectives. This review summarizes recent insights into the biological activity of pomegranate peel. First, a brief analysis of green extraction methods shows how different techniques affect extract composition. Then, different biological activities of pomegranate peel extracts and constituents (punicalagin, ellagic acid, and more) are discussed, showing interesting pathway and target interactions. Finally, a critical acknowledgement of gaps and challenges is provided to guide research in translating future studies into effective pharmaceutical and nutraceutical solutions (antioxidants, anti-inflammatories, antimicrobials, adjunct cancer therapies, food supplements) aligned with standard and safety regulations.

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INTRODUCTION

A. Pomegranate: a 'Wonderful' Fruit Across Time and Cultures

Pomegranates (Punica granatum L.) are fruits popularly renowned for their nutritional and medicinal properties, with a rich history of use in traditional medicine across time and cultures. From ancient Mediterranean populations to traditional Chinese or Ayurvedic medicines, pomegranates represented a symbol of fertility, abundance, life, and death, and were used to treat ailments such as dysentery, diarrhea, bleeding, and parasitic infections, thanks to their astringent properties (Spagnoli et al., 2021). Even though ancient wisdom lacked scientific foundations (today we know astringency derives from tannins), traditional medicines demonstrated practical understanding of the therapeutic potential of pomegranates, and every part of the plant was used: arils, peels, seeds, flowers, barks, and roots. Indeed, scientific research has shed light on the potential of pomegranates as valuable sources of bioactive compounds with diverse biological activities (Valero-Mendoza et al., 2023). However, while the edible arils and juice of pomegranates have been extensively studied (Altieri et al., 2019; Di Sotto et al., 2019; Fraschetti et al., 2023; Cairone et al., 2025), the peel has often been overlooked and discarded as waste, even though it comprises roughly 49-55% of the fruit's weight (Magangana et al., 2020). Nowadays, pomegranates are widely cultivated globally, with the agricultural production generating substantial quantities of processing waste (Shahbazi et al., 2025). An accurate estimate of global production is difficult to quantify, due to lack of or outdated readily available data. Global pomegranate production remains concentrated in Asia and the Mediterranean, with India, Iran, and Türkiye among the largest growers. An approximate estimate, based on market imports/exports data, accounts for over 3 million tons annually. Therefore, peel waste generation could reach over 1.5 million tons. Among the different cultivations, the 'Wonderful' cultivar is the most prized, thanks to its sweet arils, high juice yield, and suitability for warm climates and commercial production. Therefore, pomegranate peel has emerged from a by-product to a critical resource in the paradigms of circular economy and green economy (Sadh et al., 2025). This shift represents a fundamental transformation in how we perceive and use agricultural waste, converting potential environmental burden into valuable scientific and industrial assets, with interesting implications (but not limited to) in pharmaceuticals (Noreen et al., 2025), cosmetics (Tumbarski et al., 2025), and nutraceuticals and functional foods *("Food Applications of Pomegranate Peel Bioactive Compounds," 2025)*. Indeed, the bioactive compounds found in pomegranate peels have been shown to modulate various cellular pathways, offering potential therapeutic applications in the prevention and treatment of chronic diseases such as cancer, cardiovascular diseases, and metabolic syndromes (Siddiqui et al., 2024). From a pharmaceutical perspective, extracted phytochemicals offer lead compounds for anti-inflammatory, antimicrobial, antioxidant, and metabolic-related therapies and could reduce drug development costs by supplying novel natural scaffolds (Balli et al., 2020). For nutraceuticals and functional foods, pomegranates provide concentrated sources of fibers, prebiotics, oligosaccharides, proteins and antioxidants that could improve gut health, glycemic control and oxidative stress when formulated into supplements (Buccato et al., 2025). For cosmetics, pomegranate peel provides new ingredients for sustainable cosmetic formulation (Dimitrijevic et al., 2024; Gomes et al., 2025).

B. The Peel Deal: Why Extraction Methods Affect Composition

Pomegranate peel, an agro-industrial by-product, requires targeted extraction and processing strategies to preserve and selectively recover high-value bioactive constituents. Among the main

Figure 1 Word cloud analysis of the main analytes found in pomegranate peels across different studies (Ain et al., 2023; Akhtar et al., 2015; Bakhti et al., 2024; Chen et al., 2021; Gosset-Erard et al., 2021; Omer et al., 2019; Suručić et al., 2025; Topkaya & Isik, 2019; Yulian Tumbarski et al., 2025; Zheng et al., 2025).

analytes found in pomegranate peels (Figure 1), hydrolyzable tannins (like punicalagins), ellagic acid and its glycosides, gallotannins, flavonoids (anthocyanins, catechins, rutin), phenolic acids (gallic, caffeic, chlorogenic), soluble polysaccharides, amino acids, and minerals were found (Mo et al., 2022; Singh et al., 2023).

In general, there is a great variability in nutritional content, which is affected by the maturity and the cultivar of pomegranates. The genotype of fruits affects both pomological and morphological variations, too (Khadivi et al., 2024). Therefore, the valorization and use of pomegranates must depend on predictable composition, and it is essential to understand how this variability is affected by cultivars. A standardization approach was employed by Zheng et al. (2025) to profile the quality of peels derived from 47 different cultivars. The experimental design is based on the prediction and assessment of fruit quality through quantitative analysis based on HPLC-PDA-MS/MS. The authors generated comprehensive fingerprints that captured variations in key bioactive compounds across peels from different origins. Multivariate analyses (PCA, HCA, PLS-DA) identified distinct sample clusters, demonstrating the ability of the method to discriminate peel quality and detect adulteration or changes induced by processing. The approach offered reproducible tools for quality control and standardization of by-products derived from pomegranates.

The extraction method critically determines yield, molecular weight distribution, and suitability for downstream applications. Conventional solvent-based extractions (maceration, digestion, Soxhlet, reflux) with polar organic solvents or aqueous ethanol (50-80% v/v) yield high total phenolic content but are time- and energy-intensive and may risk thermal degradation and solvent residues (Kupnik et al., 2022). Ultrasound-assisted (UAE) and microwave-assisted extraction (MAE) promote mass transfer and disrupt the plant matrix, shortening extraction time and lowering solvent consumption. When optimized for power, time, temperature, and solvent polarity, UAE and MAE generally increase recovery of punicalagins and ellagic acid, and enhance antioxidant activity while minimizing ellagitannin hydrolysis (Kaderides et al., 2019; Kyriakoudi et al., 2024). Pressurized liquid extraction operated at high temperature and pressure accelerates extraction kinetics and reproducibility with low solvent volumes, and is well suited for medium-polarity phenolics (*Recovery of Bioactive Compounds from Pomegranate (Punica Granatum L.) Peel Using Pressurized Liquid Extraction,* n.d.). Combining UAE with natural deep eutectic solvents (NaDES) enhances extraction via complementary physical and chemical mechanisms. Cavitation from ultrasounds produces intense local shear forces that rupture cell walls and membranes, improving the penetration of NaDES into the plant matrix and promoting mass transfer of phenolics. Concurrently, NaDES increase solubility and stabilize targeted bioactive compounds. The resulting synergy yields higher recovery and extraction efficiency than either conventional solvents or individual techniques alone (Oliveira et al., 2024). Subcritical water extraction exploits water's variable dielectric properties (100-220 °C) to extract phenolics without solvents, but often induces hydrolysis of polymeric tannins into ellagic and gallic acids, which can be an advantage or drawback depending on whether intact ellagitannins or hydrolysis products are the target (Yan et al., 2017). Supercritical CO_2, typically with polar cosolvents such as ethanol, is attractive for nonpolar-to-mid-polar fractions and for solvent-free processing but requires enhancements to recover high-molecular-weight ellagitannins effectively (Silva et al., 2021). Enzyme-assisted extraction using cellulases and pectinases improves release of bound phenolics under mild conditions and combines synergistically with other techniques to increase yield and selectivity (Alexandre et al., 2019; Mushtaq et al., 2015). Pre-treatments such as pulsed electric fields and high-voltage electrical discharges produce electroporation or cell disruption that shorten extraction times, and lower thermal loads and solvent consumption (Faria & Silva, 2024; Xi et al., 2017). Rapid solid-liquid dynamic extraction improves the extraction process by enabling fast and efficient extraction at low temperatures, which helps preserve sensitive bioactive compounds that might degrade under the harsher conditions of traditional methods (Polcaro et al., 2024). Solid-liquid dynamic extraction (executed via Naviglio extractors) employs cyclic pressure gradients at or near ambient temperature to accelerate transfer of compounds from a solid matrix into a solvent. Repeated application of a negative pressure differential forces solutes out of the matrix and, upon restoration of equilibrium, completes solvent refreshment and mass transfer. The method provides faster, more efficient extraction than many

conventional approaches and can be effective even when using solvents with relatively low affinity for the target analytes (Naviglio et al., 2019).

Process variables (solvent type and polarity, solvent-solid ratio, particle size, pH, temperature, time, and use of chelators or antioxidants) influence solubility, diffusion and stability (*e.g.,* higher temperatures and more polar solvents favor ellagitannin solubility but accelerate hydrolysis; smaller particle sizes and higher solvent ratios increase mass transfer but raise solvent recovery costs) (Sood & Gupta, 2015). Therefore, design must reconcile yield, selectivity, compound integrity, and techno-economic and sustainability constraints. On this last matter, Santana et al. (2024) proposed a sustainable and efficient way to extract phenolic compounds from pomegranate peels using dynamic maceration with water at room temperature. The study looks at how factors like extraction time, temperature, acidity, and purification affect the yield and the antioxidant and antimicrobial activities of the extracts. The findings show that simple water extraction at room temperature gives good chemical content and bioactivity while being cost-effective and environmentally friendly. Additionally, it enables a one-step extraction that skips purification, improving scalability for industrial use. The approach is potentially well-suited to high-volume production and can be tailored to specific extraction targets. Minimizing organic solvent use, using water as the extraction solvent, and conducting extractions at room temperature all align with sustainability practices and environmental safety. Similarly, D'Agostino et al. (2025) focused on single-step extraction with the assistance of bicarbonate and achieved a higher yield (compared to simple decoction) in phenolics with low molecular weight, and in total phenol content in general. Downstream analytical workflows (solid-phase extraction, membrane ultrafiltration and nanofiltration, preparative chromatography) are essential to separate tannins with high molecular weight from phenolics with small and medium molecular weight, with targeted quantification typically performed by RP-HPLC-DAD and LC-MS/MS, and by NMR for definitive structural assignments and isomer discrimination. Reported compositional ranges are cultivar-, maturity- and extraction-dependent but often show punicalagins and ellagitannins as the dominant analytes, and significant interstudy variability in total phenolic content. This variability suggests the need for standardized reporting of extraction parameters to allow reproducible benchmarking of (i) cultivar- and season-driven compositional mapping; (ii) kinetic studies of tannin hydrolysis across novel extraction techniques; and (iii) techno-economic assessment comparing green extraction technologies for commercial production and regulatory compliance.

The suitability of one extraction method compared to another depends on the desired analytes and the final applications. For pharmaceuticals, supercritical fluid extraction or pressurized liquid extraction are the best choices: they achieve high purity yields without toxic or impurity residues, therefore respecting safety and contamination limits from current Good Manufacturing Practices (cGMPs). Cosmetics focus on aroma and formulation compatibility: solvent- and hydro-based extractions are suitable for preparing balms and lotions, while hydrodistillation is more suitable for extracting essential oils. Food industry prioritizes taste, preservation, and safety, choosing from green and scalable options such as high-pressure processing, ultrasound-, and microwave-assisted extractions.

C. Peelonomics: Rethinking Waste in Green Economy

In the context of circular economy, green economy, and renewable economy, the utilization of pomegranate peel as a sustainable resource aligns with the principles of waste reduction, resource efficiency, and environmental sustainability. The valorization of pomegranate peel represents a paradigmatic example of sustainable resource management within circular economy principles, transforming what was traditionally considered agricultural waste into a multifunctional biomaterial with significant economic and environmental potential. Pomegranate processing generates substantial by-products, with peels constituting up to 50% of the fruit's fresh weight (Mohlamonyane et al., 2024). Scientific investigations have demonstrated diverse applications spanning multiple domains: pharmaceutical industries can leverage the peel's potent antioxidant and antimicrobial properties for developing nutraceuticals and therapeutic compounds (Radan et al., 2024); food technology researchers have explored its potential as a functional ingredient in value-added products like fortified yogurts and novel gelling agents (Abid et al., 2018;

Jany et al., 2024); materials science perspectives reveal promising avenues for developing sustainable biomaterials through extraction and processing techniques that minimize environmental impact (Wan Ismail, 2025). Life cycle assessment (LCA) is a standardized methodology (ISO 14040/14044) for quantifying the environmental burdens of a product or process from raw material to use and disposal (Jensen, 1998; *Life Cycle Assessment (LCA) - A Guide to Approaches, Experiences and Information Sources,* 1998). The environmental impact assessed by LCA on pomegranate biorefinery, for example, found the pectin extraction step (using ethanol precipitation) to be critical in environmental indicators (Shinde et al., 2020). To circumvent the impact of this extraction step, ethanol use could be reduced in favor of enzyme-assisted extractions, as proposed by Maggiore and Setti (2025) to deconstruct pomegranate pomace into bioactive cosmetic ingredients and develop a prototype of face serum.

The strategic upcycling of pomegranate peels outlines circular economy principles by simultaneously addressing waste reduction, resource efficiency, and value creation, transforming a potential landfill burden into a high-value resource that contributes to more sustainable production systems across agricultural, food, and biotechnological sectors.

LITERATURE SURVEY

This review addresses recent insights into the main biological activities of pomegranate peel and its components. The aim is to explore new biological activities of this agro-industrial by-product, offering a pharmaceutical and nutraceutical perspective to value it, thereby generating novel economic opportunities. The literature search was conducted in November 2025 searching in two official scientific databases, PubMed and Scopus, and using combination of keywords 'pomegranate', and 'peel'. The search was limited to articles/chapters/reviews from the past two years, without applying additional filters. To ensure a comprehensive and unbiased selection, all retrieved records were screened regardless of subject areas (agricultural and biological sciences, biochemistry, chemistry, medicine, or pharmaceutics). Studies were included based on relevance to pathways and mechanisms, novelty to the topics, and potentially feasible translation into real use applications in waste management and circular economy. Selected papers were then categorized thematically to provide a clear summary of current trends.

A. Antioxidant Activity

Pomegranate peel, often overlooked in favor of the fruit's succulent arils, has emerged as a significant source of potent antioxidant phytochemicals (not limited to hydrolyzable tannins such as well-known punicalagins) that together confer potent free-radical scavenging, metal-chelating, and redox-modulating properties. Mechanistically, the antioxidants contained in pomegranate peel neutralize reactive oxygen species via electron-donation, interrupt radical chain reactions, chelate pro-oxidant transition metals (Fe^{2+}/Cu^{2+}), upregulate endogenous antioxidant defenses (superoxide dismutase, catalase, or glutathione peroxidase), and downregulate signaling linked to oxidative stress, such as NF-κB and NADPH oxidase (Andrés et al., 2023). Assay-wise, pomegranate peel extracts consistently show high activity across complementary *in vitro* methods (DPPH, ABTS, FRAP, and ORAC). These assays provide quantitative measurement of the antioxidant capacity and help elucidate the specific compounds responsible for the observed effects (Shahidi & Samarasinghe, 2025). *In vivo* and *ex vivo* studies corroborate protective effects against oxidative damage in models of metabolic syndrome, hepatic and renal injury, neurodegeneration, and cardiovascular dysfunction, demonstrating reduced lipid peroxidation (Al-Gubory et al., 2016), improved antioxidant enzyme profiles (Ayubi et al., 2025), mitigation of DNA oxidative damage (Danjolli-Hashani & Selen Isbilir, 2025), and attenuation of inflammation-driven oxidative cascades (Mehdi et al., 2022). Nevertheless, bioavailability constraints, the transformation of ellagitannins to urolithins mediated by gut microbiota, and metabolic conjugation modulate systemic exposure and biological outcomes. Dietary supplementation with pomegranate peel powder or aqueous extracts in rodents showed attenuation of oxidative biomarkers in plasma and target organs (Giménez-Bastida et al., 2021). Still, standardization in safety and clinically relevant dosage requires further controlled human trials to translate *in vitro*/*in vivo* antioxidant findings into validated health claims. As the demand for natural antioxidant sources increases (not limited to pharmaceutics and nutraceuticals, but also to food preservation (Mohlamonyane et al., 2024)), the exploration of pomegranate peel demonstrates

promising potential in health and nutrition, warranting further investigation into its bioactive compounds and its mechanisms of action. Truly, the antioxidant activity always occurs in a cross-talking and open context involving antimicrobial, anticancer, and anti-inflammatory properties. Antioxidant capacity is a physicochemical property and a descriptor of redox-scavenging potential, and antioxidant assays can quantify radical scavenging or reducing power, but not target engagement (Danet, 2021), yet reactive oxygen species are pleiotropic signaling molecules that aptly switch context dependence in cell biology (Sies & Jones, 2020). In cancer, low concentration of reactive oxygen species can promote proliferation and survival, while high concentration cause cytotoxicity (Ju et al., 2024). Similarly, in immune responses, reactive oxygen species participate in microbial killing, but indiscriminate antioxidant activity could blunt host defense (Bellanti et al., 2025). In conclusion, antioxidant capability is a means to achieve different other important biological activities.

B. Antimicrobial Activity

The global surge of antimicrobial resistance urgently requires the discovery of new, effective, and sustainable antimicrobial agents. Over the past decade, a growing body of *in vitro* and *in vivo* studies has consistently demonstrated antimicrobial activity of pomegranate peel extracts and isolated constituents against gram-positive and gram-negative bacteria, and fungi, stimulating interest in the use as alternative antimicrobials (Abu-Niaaj et al., 2024; Abutayeh et al., 2024), food preservatives (Kandylis & Kokkinomagoulos, 2020), and adjuvants in conventional therapies (Grandinetti et al., 2025; Rahman et al., 2023). Mechanistically, the antimicrobial activity is multifactorial and may involve: (i) disruption of microbial cell wall and membranes (Silva et al., 2025); (ii) interference with quorum sensing and biofilm formation (Carradori et al., 2020; Salim et al., 2023; Sateriale et al., 2025); (iii) modulation of host-microbe interactions (Buccato et al., 2025); and (iv) protein precipitation and enzyme inhibition mediated by tannins and polyphenols (Suručić et al., 2025). Both spectrum of activity and potency depend on the extract composition, which is determined by cultivar, geographic origin, fruit maturity, and extraction solvent and method. This makes standardization a central challenge for translational development. Therefore, reported minimal inhibitory concentrations vary widely between studies. In addition, the zone of inhibition (ZOI) diameter and the MIC allow a prediction of therapeutic success. While the MIC is a direct measurement of a concentration needed at the site of infection, ZOI is some sort of surrogate, which needs to be carefully determined before being assigned due to the different diffusion of the antibacterial substances present in a complex mixture (*e.g.,* extract). However, antibacterial activity against clinically relevant pathogens, including ESKAPEE bacteria, has been observed (Scaglione et al., 2024), and synergistic interaction of pomegranate peel and antibiotics has been reported (Kabbashi et al., 2024).

Starting from the antibacterial activity, the ethanolic (80% v/v) extract of pomegranate peel exhibited inhibition against strains of *Escherichia coli*, sampled from clinical cases of urinary infection and producing beta-lactamases (Alghamdi et al., 2024). Beta-lactamases are enzymes that hydrolyze the beta-lactam ring required for the antibacterial activity of widely prescribed beta-lactam antibiotics, such as penicillins, cephalosporins, and carbapenems. The production of beta-lactamases represents a critical molecular strategy of bacterial drug resistance and poses a major challenge in the treatment of bacterial infections (Huang & Zhou, 2025). Using well diffusion assay, the strains of *E. coli* showed resistance (no visible inhibition zone) at 100 mg/mL of peel extract and dose-dependent susceptibility in range 200-500 mg/mL. At the highest concentration tested, inhibition zones ranged from 9.0 mm to 18.3 mm among the different strains. For comparison, the assay on strains of *E. coli* using clinically employed antibiotics showed resistance to ampicillin (10 µg), amoxicillin with clavulanic acid (30 µg), ceftazidime (30 µg), while susceptibility to amikacin (5 to 58 mm at 30 µg) and netilmicin (15 to 25 mm at 30 µg). These results are in line with amikacin and netilmicin being aminoglycoside antibiotics, therefore unaffected by β-lactamases. On the contrary, ampicillin, amoxycillin and ceftazidime (a third-generation cephalosporin) all possess the β-lactam ring inactivated by beta-lactamases. However, it is interesting to note that the resistance to amoxicillin occurred even in the presence of clavulanic acid, an inhibitor of beta-lactamases often combined with penicillins. The rising ineffectiveness of this combination in tackling antibiotic resistance

has been recently highlighted by a comparative study on post-market pharmacovigilance and drug safety (Ammendolia et al., 2025). The analysis of the chemical composition of ethanolic extracts was not evaluated in the study.

Staying on the topic of antibiotic resistance, Kiran et al. (2024) reported that the methanolic (80% v/v) extract of pomegranate peel exhibited better antimicrobial activity than the ethanolic (70% v/v) extract on multidrug-resistant Enterobacteriaceae (Table 1).

Electrospray ionization mass spectrometry identified the presence of punicalagin, ellagic acid, and their metabolic derivatives, along with quinic acid and cryptochlorogenic acid (a cinnamate ester obtained by condensation of caffeic acid and quinic acid). Also, the synergistic activity of punicalagin and clinically used antibiotics (resisted by selected Enterobacteriaceae) was evaluated. The most relevant combination in overcoming drug resistance was punicalagin (30 µg/disk) and ciprofloxacin (5 µg/disk), which exhibited 55.3 mm and 65.3 mm inhibition zones against *S. typhimurium* and *E. coli*, respectively.

Shleghm et al. (2024) reported 13.7 mm and 12.5 mm zones of inhibition for *E. coli* and *Staphylococcus aureus*, respectively, at 200 mg/mL of ethanolic (50% v/v) extract of pomegranate peel (compared to 15.2 mm and 14.6 for chloramphenicol 0.03 mg/disk). *In vivo* administration (5 mg) of peel extract in mice infected by *E. coli* showed an average 1.79 log reduction in colony-forming unit after 3 days (by analyzing and observing feces). At day 6, all mice in the infected control group died, while all mice undergoing treatment survived with residual 10^{2-3} cfu/g in their feces.

Similarly, Suručić et al. (2025) reported the *in vitro* activity of the methanolic peel extract against *E. coli* and *S. aureus*. Interestingly, the inhibition of gram-negative *E. coli* required a higher concentration of peel extract compared to gram-positive *S. aureus* (250.00 µg/mL and 31.25 µg/mL, respectively). Punicalagin, ellagic acid and gallic acid were identified as major bioactive phytocompounds. Molecular docking of these compounds was performed against important targets in the biosynthesis of cell walls and in division processes: cell division protein FtsZ (*ftsZ*), UDP-N-acetylglucosamine 1-carboxyvinyltransferase (*murA*), penicillin-binding protein 2 (*mecA*), and peptidoglycan D,D-transpeptidase FtsI (*ftsI*). Results showed that punicalagin interacted with all targets in both strains but exhibited lower affinity in *E. coli*. Conversely, ellagic acid and gallic acid (which possess smaller structures than punicalagin) exhibited weaker predicted binding in *S. aureus* than *E. coli*. This behavior was correlated to the limited permeability of punicalagin through porins (typically located in the outer membrane of gram-negative bacteria).

Focusing on punicalagin from peel extract, Yin et al. (2024) showed that punicalagin administration (50 µM) in mice enhanced the clearance of *Pseudomonas aeruginosa* in lungs and *Escherichia coli* in the peritoneum. The augmented phagocytosis of macrophages occurred following the remodeling of f-actin polymerization. KEGG enrichment and

Table 1 Zone of inhibition (ZOI, in mm) and minimal inhibitory concentration (MIC, in mg/mL) of pomegranate peel extracts against Enterobacteriaceae.

	Escherichia coli		***Salmonella enterica* serovar Typhi**		***Salmonella enterica* serovar Typhimurium**	
	ZOI	MIC	ZOI	MIC	ZOI	MIC
Methanol 80% v/v	20.0	7.8	20.0	3.9	18.0	7.8
Ethanol 70% v/v	17.0	NA	17.0	NA	16.0	NA
Punicalagin (20 mg/mL)	13.0	>10	17.0	>10	14.0	>10

NA = Data Not Available.

transcriptome analysis revealed that the activation of NF-κB by the cascade of MAP kinases triggered the upregulation of C-type lectin domain family 4 member E (alternatively named Mincle), a calcium-dependent receptor that recognizes molecular patterns associated with pathogen infections or abnormal self-damages (Miyake & Yamasaki, 2020). Indeed, the correlation between Mincle and actin polymerization has been previously reported in neutrophils during sepsis (Lee et al., 2017), but further studies are needed to validate the implications for macrophages.

Following a prolific trend concerning pomegranate and oral health (Marrone et al., 2024; Potra Cicalău et al., 2024), Syahputra et al. (2025) reported dose-dependent inhibition of *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, and *Porphyromonas gingivalis* (species associated with periodontal disease) by treating with pomegranate peel extracts at concentrations ranging from 0.8% to 25%. The ethanolic extract (70% v/v) exhibited better inhibition for all species compared to the ethyl acetate and *n*-hexane extracts (Table 2).

Similarly, Silla et al. (2025) reported dose-dependent inhibition of *Streptococcus mutans* and *Streptococcus sanguinis*, two native species of the oral microbiota that colonize both saliva and dental plaque and are associated with tooth caries. Peel water extract (22.5% w/v, developed by Phenbiox Srl, Calderara di Reno, Bologna, Italy) inhibited the growth of *S. mutans* and *S. sanguinis* at 10% v/v and 5% v/v dilutions, respectively.

Table 2 Zone of inhibition (in mm) of oral bacteria treated with ethanolic 70% peel extract.

Concentration	*A. actinomycetemcomitans*	*F. nucleatum*	*P. gingivalis*
25.0%	16.90±0.12	16.35±0.55	16.8±0.35
12.5%	12.25±0.19	11.35±0.1	12.6±0.6
6.3%	9.30±0.22	7.8±0.38	8.35±0.53
3.1%	7.47±0.26	6.75±0.75	6.6±0.3
1.6%	7.30±0.20	0±0	0±0
0.8%	6.00±0.09	0±0	0±0

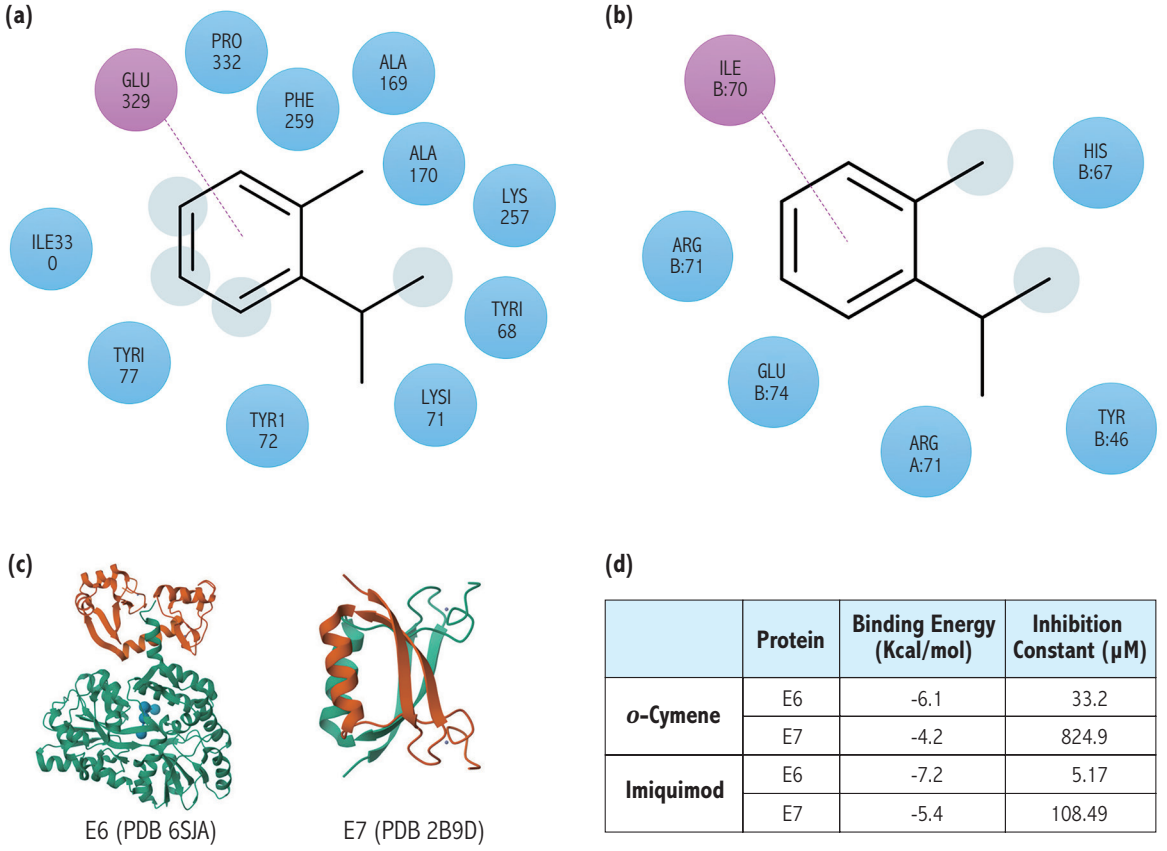
On the antifungal activity, Ferreira et al. (2025) investigated the efficacy of the ethanolic (92.8% w/w) peel extract against *Candida* species (*C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*). The exposure over 4 hours with 1×MIC (10 mg/mL) demonstrated the reduction in biofilm formation by 35-60%. Surprisingly, the reduction was not related to the biosynthesis of ergosterol (an important component of the fungal cell membrane), nor to the disruption of membranes or walls, suggesting different mechanisms in the regulation of biofilms.

C. Anticancer activity

Pomegranate peel contains bioactive compounds with promising anticancer potential, making it an intriguing subject of scientific investigation (Rauf et al., 2025). While not a cure, research has explored several interesting aspects of how pomegranate peel extracts might interact with cancer processes. *In vitro* studies have demonstrated that extracts from pomegranate peel exhibit antiproliferative activities against different cancer cell lines, including breast (Bagheri et al., 2018), colon (Ahmed et al., 2017), and prostate (Chaves et al., 2020) cancer cells. At molecular level, peel-derived phytochemicals modulate key signaling cascades including Akt/mTOR/S6K (Chaves et al., 2020), MAPK and JAK/STAT3 (Elbakry et al., 2023), and Wnt/β-catenin (Ahmed et al., 2017), leading to the arrest of the cell-division cycle (commonly at G0/G1 and G2/M phases) through the upregulation of cyclin-dependent kinase inhibitors 1 and 1B (p21 and p27 respectively). Apoptosis induction is consistently observed and involves both intrinsic (mitochondrial) and extrinsic pathways: balance alterations in the Bcl-2 family (downregulation of *BCL2* and *BCL2L1,* upregulation of *BAX* and *BAK1*) (Li et al., 2014), loss of mitochondrial membrane potential (Deng et al., 2017), release of cytochrome c (Abdul Ghani et al., 2018), activation of caspase-3 (Kusmardi et al., 2021), cleavage of poly [ADP-ribose] polymerase 1 (Tamborlin et al., 2020), and, in some contexts, activation of caspase-8 mediated by tumor necrosis factor receptor superfamily members 10A and 10B (alternatively named DR4 and DR5 respectively) (Chang et al., 2018). Autophagy modulation has also been reported (Čolić et al., 2022), showing that apoptosis and autophagy may cooperate or oppose each other, reflecting complex cross-talk across multiple signaling pathways. Antimetastatic effects derive from the

suppression of epithelial-mesenchymal transition markers (decreased N-cadherin, vimentin; increased E-cadherin) (Bagheri et al., 2018), inhibition of matrix metalloproteinases (MMP-2, MMP-9) (Tang et al., 2016), and downregulation of focal adhesion kinase 1 (encoded by *FAK*) and integrin signaling (Chiablaem et al., 2025). Collectively, these effects help to reduce migration and invasiveness in multiple cancer cell lines. Anti-angiogenic activity is mediated via decreased VEGF expression (Zamani Esmati et al., 2020) and modulation of hypoxia-inducible factor 1-alpha C under hypoxic conditions (Tornese et al., 2024). Indeed, peel extracts and isolated compounds exert antioxidant effects that contribute to anticancer mechanisms: direct radical scavenging limits oxidative DNA damage and inflammation-driven tumorigenesis. Related *in vivo* studies using xenograft and syngeneic tumor models report modulation of systemic and intratumoral biomarkers (Ahmadiankia et al., 2018), reduced metastatic burden (Deng et al., 2017), and tumor growth inhibition (Luís et al., 2023). Finally, *in silico* approaches complement experimental data: molecular docking and dynamics simulations show favorable binding of punicalagin and ellagic acid to active sites of kinases (such as phosphoinositide 3-kinases or RAC-alpha serine/threonine-protein kinase), matrix metalloproteinases, topoisomerases, and anti-apoptotic Bcl-2 family proteins (Hatolkar et al., 2025; Majhi et al., 2025; Priosoeryanto et al., 2025). Still, preclinical evidence supporting anticancer effects of pomegranate peel does not always directly translate into clinical data, as human clinical trials are scarce and limited in scope. While toxicology and pharmacokinetics studies have been conducted (Andishmand et al., 2025), long-term safety need to be addressed in the future.

Regarding *in silico* studies, Veerabahu et al. (2024) identified *o*-cymene by GC-MS analysis of



	Protein	Binding Energy (Kcal/mol)	Inhibition Constant (μM)
***o*-Cymene**	E6	-6.1	33.2
	E7	-4.2	824.9
Imiquimod	E6	-7.2	5.17
	E7	-5.4	108.49

Figure 2 a) Interactions with E6; b) interactions with E7; c) 3D modeling of E6 (Suarez et al., 2019) and E7 (Liu et al., 2005), refined by Phenix and Refmac software, respectively; d) docking results of *o*-cymene, calculated by Auto dock Vina using its own hybrid scoring function (empirical plus knowledge-based).

pomegranate peel extracts and performed molecular docking against E6 and E7 proteins, derived from two major oncogenes of the human papillomavirus, the main cause of cervical cancer. The binding energy of *o*-cymene (Figure 2) showed affinity comparable to that of imiquimod, used as reference.

Instead, Majhi et al. (2025) performed a comprehensive database screening of known compounds identified in pomegranate peels to explore new treatments for pancreatic cancer. Figure 3 summarizes the compounds and the genes investigated.

The in silico analysis revealed that bioactive compounds from pomegranate peels, including 1-O-galloyl-β-D-glucose, epicatechin, phloridzin, and epicatechin gallate, exhibit strong binding affinities with key proteins implicated in pancreatic cancer progression, notably RAC-alpha serine/threonine-protein kinase *(AKT1)*, epidermal growth factor receptor *(EGFR)*, heat shock protein HSP 90-alpha *(HSP90AA1)*, and prostaglandin G/H synthase 2 *(PTGS2)*. Molecular docking results showed that these compounds achieved binding energies less than -6 kcal/mol, indicative of stable interactions, which were further corroborated by molecular dynamics simulations demonstrating minimal fluctuations in root mean square deviation and sustained hydrogen bonding over a 100 ns period. The stabilization of these protein-ligand complexes suggests the potential of pomegranate peel compounds to modulate cancer-related pathways, thereby supporting their candidature as natural therapeutic agents against pancreatic cancer.

Hamdulay et al. (2025) reported the antiproliferative activity of pomegranate peel extract

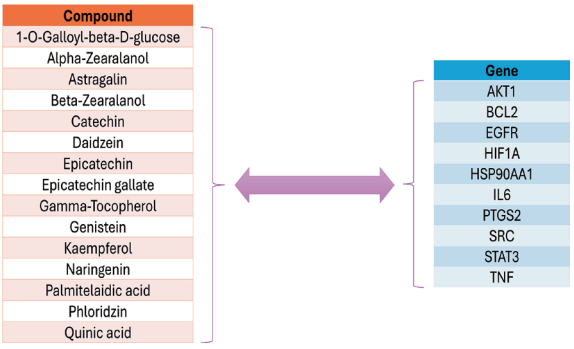


Figure 3 Scheme of the molecular docking against pancreatic cancer targets.

(produced by WonderLand Herbs, Bellingham, Washington, USA) against MCF-7 and MDA-MB-231 cells, the latter being a triple negative breast cancer cell line and therefore lacking receptors for estrogen, progesterone, and HER2 proteins. The highest reduction in cell metabolic activity for MDA-MB-231 (52.73%) and MCF-7 (81.92%) cells was induced at 79.95 mg/L and 25 mg/L, respectively. Hamdulay et al. (2025) speculated that MDA-MB-231 cells require higher concentration because they are estrogen-independent, whereas MCF-7 are estrogen-dependent. Therefore, MDA-MB-231 cells may exhibit a different mechanism involved in cancer resistance.

Focusing on breast cancer, Riaz et al. (2025) reported that methanolic (100% v/v) peel extract inhibited 6-phosphogluconate dehydrogenase (6PGD) with dose-dependent trend (IC_{50} = 0.090 µg/mL, K_i constant value = 12.72 ng/mL). 6PGD is a central enzyme of the oxidative pentose phosphate pathway and generates NADPH and ribulose 5-phosphate. In breast cancer, elevated 6PGD activity supports anabolic metabolism, maintains redox homeostasis, and fuels biosynthetic pathways that promote cell proliferation and survival. Moreover, 6PGD is markedly overexpressed in the MCF-7 breast cancer cell line. Similarly, peel extract inhibited the growth of MCF-7 cancer cells with dose-dependent trend (IC_{50} = 3.138 µg/mL). Molecular docking identified cyanidin, delphinidin, and procyanidin as phytochemicals exhibiting the best affinity for 6PGD. These compounds (Figure 4) are known antioxidants found in the plant kingdom (Qi et al., 2023) and their antitumoral activity could possibly be related to the modulation of redox states.

Hnit et al. (2025) reported that *in vitro* administration (9.4 mg) of peel water extract could inhibit the synthesis of DNA in dormant lung cancer cells (A549 and H460) awakened by serum exposure or dilution of contact inhibition. Results showed a dose-dependent inhibition over 72 hours, with a GI_{50} of 144 µg/mL and 85.5 µg/mL for A549 and H460, respectively. The treatment upregulated cyclin-dependent kinase inhibitor 1B (*CDKN1B*, involved in tumor development (Bencivenga et al., 2025)) and downregulated aurora kinase A (*AURKA*), myc proto-oncogene protein (*MYC*), and S-phase kinase-associated protein 2 (*SKP2*). Moreover, FACT complex subunit SPT16 (*SUPT16H*) and FACT complex subunit SSRP1 (*SSRP1*) levels

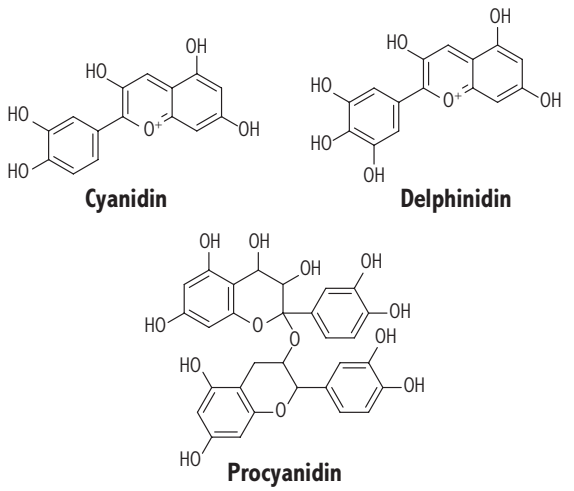
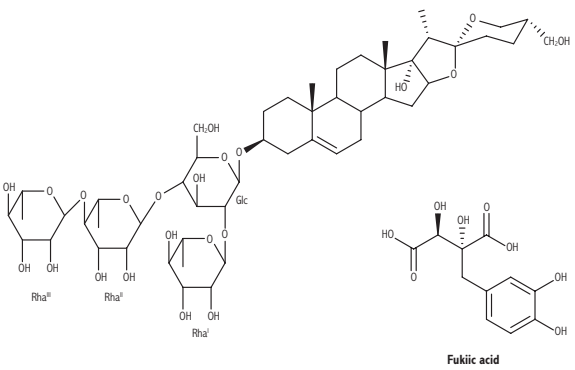


Figure 4 Structures of metabolites active against 6PGD.

were lowered following extract treatment. The modulation of these markers kept cells in the G0 phase. *In vivo* administration (9.4 mg/day) using a H460 cell xenograft model showed a 36% reduction in weight and a 26% reduction in tumor size. Finally, chemical profiling identified common analytes of pomegranates, such as ellagic acid and punicalagin, gallic acid, corilagin, and brevifolincarboxylic acid. Moreover, new analytes such as polyphylloside III and fukiic acid were found (Figure 5).

D. Anti-inflammatory Activity

There is a convergent picture that implicates direct modulation of pro-inflammatory signaling cascades and suppression of redox sensitive pathways mediated by antioxidants (Alhaj Sulaiman & Katanaev, 2025). Mechanistically, *in vitro* studies demonstrated that pomegranate peel extract could attenuate NF-κB activation (Du et al., 2019) and suppress MAPK signaling (Du et al., 2018). Parallel *in vitro* evidence supported the activation of the NRF2 pathway by pomegranate peel components (punicalagin (Liu et al., 2019) and ellagic acid (Xiao et al., 2022)), leading to increased expression of heme oxygenase 1. *In vivo*, multiple rodent models (carrageenan-induced paw edema (Lee et al., 2010), DSS colitis (Mansour et al., 2025), arthritis (Ge et al., 2022), or ischemia-reperfusion injury (Salama & Faried, 2018)) reported dose-dependent reduction in edema, leukocyte infiltration, cytokine levels, histologic damage scores, and biochemical markers of oxidative stress. Pharmacokinetics and formulation studies highlighted that high-molecular-weight punicalagins undergo hydrolysis to ellagic acid and urolithins in the gut, and both parent compounds and metabolites exhibit anti-inflammatory effects; this is important for bioavailability and *in vivo* mechanism, since microbial metabolism can shift active species (Caballero et al., 2022; Leng et al., 2025). Molecular docking has been used to predict direct interactions of peel phenolics with targets such as COX-2 (Iqbal et al., 2023) and MAPK isoforms (Zhang et al., 2024), identifying favorable binding energies and plausible hydrogen bonding networks consistent with biochemical inhibition data. Although docking studies could fail in capturing the extensive biological dynamics of inflammation (due to scoring function inaccuracy, inadequate modeling of interactions, or limited tradeoff in computational costs), both preclinical evidence and mechanistic insights guide future standardization of targeted pharmacokinetics/pharmacodynamics and metabolite activity studies, to translate effective biomarkers into clinical trials, to define therapeutic windows and to causally link specific metabolites (including microbially derived urolithins) to observed anti-inflammatory effects.



Polyphylloside III

27-Hydroxyl-pennogenin-3-O-[α-L-rhamnopyranosyl-(1→2)]-[α-L-rhamnopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→4)]-β-D-glucopyranoside

Figure 5 new analytes found in pomegranate peel.

An interesting finding about new pathways involves the role of aryl hydrocarbon receptors (AhRs). AhRs are ligand-dependent transcription factors that detect both external and internal chemical signals and modulate a range of biological functions, including immune activity, metabolic pathways, and cell development. Upon activation, AhRs move into the nucleus to regulate target genes, commonly partnering with aryl hydrocarbon receptor nuclear translocators (Bahman et al., 2024). W. Dai

et al. (2024) proposed that punicalagin acts as a modulator of AhRs. In murine peritoneal macrophages activated by lipopolysaccharide (LPS) and in human THP-1 cells, punicalagin (50 μM) upregulated the cytoplasmic expression, but not the nuclear translocation of AhRs. However, molecular docking showed that punicalagin possesses a structure too large to bind to AhRs, therefore it does not act as a direct agonist. Rather, punicalagin promoted the phosphorylation of the ribosomal protein S6 kinase alpha family as a downstream consequence of the cooperative activity of the MAPK/ERK and the PDK1 pathways. In turn, the phosphorylation of S6K-α-1-5 activated AP-1 transcription factor.

Using the same THP-1 cells, Dutta et al. (2024) assayed the methanolic extract of pomegranate peel to describe cytotoxicity and anti-inflammatory activity. The peel extract did not show significant modulation of cell metabolic activity in range 25-200 μg/mL over 24 hours and only at 400 μg/mL a 16% reduction in viability was observed compared to untreated control. Pretreatment with the peel extract (25 μg/mL) before stimulation with lipopolysaccharide on THP-1 cells showed the reduction of prostaglandin G/H synthase 2, tumor necrosis factor, and interleukin-6 compared to LPS-treated control (Table 3).

Table 3 Effect of methanolic peel extract on inflammation markers. Data are expressed as % of cells expressing the markers.

	COX-2	TNF	IL-6
Untreated	21.20±4.53	11.2±1.76	8.70±3.13
LPS-treated	57.70±6.98	35.9±7.61	33.90±1.72
Quercetin	64.10±5.91	25.6±6.10	18.70±2.68
Peel extract	3.25±0.82	10.0±2.98	22.10±4.79

W. C. Huang et al. (2024) reported that treatment with punicalagin reduced inflammatory markers in HaCaT cells stimulated with interferon γ and tumor necrosis factor. The reduction occurred after punicalagin (≥10 μM) upregulated the expression of *SIRT1*, which encodes for NAD-dependent protein deacetylase sirtuin-1, involved in transcriptional regulation and energy metabolism. In turn, the upregulation of *SIRT1* inhibited the phosphorylation of signal transducer and activator of transcription 3, nuclear factor erythroid 2-related factor 2, and the NF-κB family. These results are consistent with previous studies highlighting the role of *SIRT1* in modulating inflammatory responses and feedback (Sethi et al., 2025; Sun et al., 2024; Yang et al., 2022).

Instead, Zhang et al. (2025) reported the synergistic combination of pomegranate peel and hawthorn in ameliorating ulcerative colitis. *In vivo* administration (1.5 kg/kg × day) in mice (affected by colitis induced by dextran sulfate sodium) showed reduction in phosphorylated mitogen-activated protein kinase 1 and 11 (significantly increased in inflammation). Therefore, the amelioration was attributed to the suppression of the MAPK/NF-κB axis. KEGG analysis indicated that pomegranate peel mainly influenced the AGE-RAGE, PI3K-AKT, and TNF pathways, whereas hawthorn primarily affected IL-17 and NF-κB signaling. Interestingly, the combined therapy shifted the gut microbial composition, enriching Lactobacillaceae and *Terrisporobacter*, while reducing *Gehongia* and *Rikenella* (associated with dysbiosis) (J. Dai et al., 2024). Similarly, Roychowdhury et al. (2025) concluded that pomegranate peel extract (alone, dose-dependent in range 50-200 μg/mL) could mitigate inflammation in murine ulcerative colitis by downregulating the IL-6/STAT3 axis. It is possible that by downregulating the IL-6/STAT3 pathway, the peel extract could have potentially shifted macrophage polarization away from the M1 phenotype (IL-6/STAT3 signaling promotes the M1 macrophage phenotype (Chen et al., 2022)), thereby reducing inflammation. This possibility suggests that the peel extract could exert its anti-inflammatory effects partly through the modulation of macrophage polarization towards the M2 phenotype, which is associated with anti-inflammatory and tissue repair functions (Yan et al., 2024). Hence, the downregulation of the IL-6/STAT3 inflammatory pathways could lead to a shift in macrophage balance from a pro-inflammatory M1 state toward a resolution-promoting M2 state (a trend recurring in a physiological process called efferocytosis (Vafadar et al., 2024)), contributing to its therapeutic efficacy in colitis, as already reported elsewhere (K. Zhang et al., 2023; M. Zhang et al., 2023). Indeed, Ikhsas et al. (2025) reported that pomegranate peel (macerated and extracted) encapsulated (480 mg/kg) in chitosan

nanoparticles reduced M1 macrophage prevalence while promoting M2 macrophage polarization. Collectively, Roychowdhury et al. (2025) provided the conceptual and molecular framework about immune dysregulation and macrophage roles in colitis, while Ikhsas et al. (2025) highlighted a potential therapeutic approach grounded in the mechanisms described.

The interest in the anti-inflammatory activity of peel compounds related to the gastrointestinal system continued with Guo et al., (2025) who employed a dual bioinformatics and network pharmacology approach to delineate the relationship between bioactive molecules (derived from literature analysis) and key targets implicated in irritable bowel syndrome (IBD) pathophysiology. A summary of the most interesting results is provided in Figure 6.

The targets affected are specific to IBD but also belong to common inflammatory pathways, further validating the potential of pomegranate peel and its bioactive compounds. Moreover, based on previous results (Ma et al., 2024), the binding affinity to NOS2 and PTGS2 was evaluated by molecular docking for pedunculagin (-9.3 kcal/mol and -8.4 kcal/mol, respectively) and punicalin (-9.4 kcal/mol and -9.2 kcal/mol, respectively). For reference, celecoxib and 1400W scored -8.4 kcal/mol and -7.3 kcal/mol against PTGS2 and NOS2, respectively. Thus, computational analysis supports the potential utility of these compounds in treating IBS. Finally, Wang et al. (2025) reported that punicalagin (50 mg/kg) protected neuronal cells in spinal cord injury (mouse model) by inhibiting ferroptosis via the upregulation of the NRF2-SLC7A11-GPX4 pathway and by suppressing neuroinflammation via the polarization of microglia towards a pro-resolving phenotype.

E. Metabolism

The effects of specific dietary components on metabolic disorders are critically important, as researchers aim to delineate the mechanistic relationships between dietary bioactive compounds and metabolic homeostasis (Leziak et al., 2025). In this context, pomegranate has gained a privileged role in scientific research, as its supplementation has been linked to the reduction of risk factors such as body weight, glycemia, blood pressure, high density

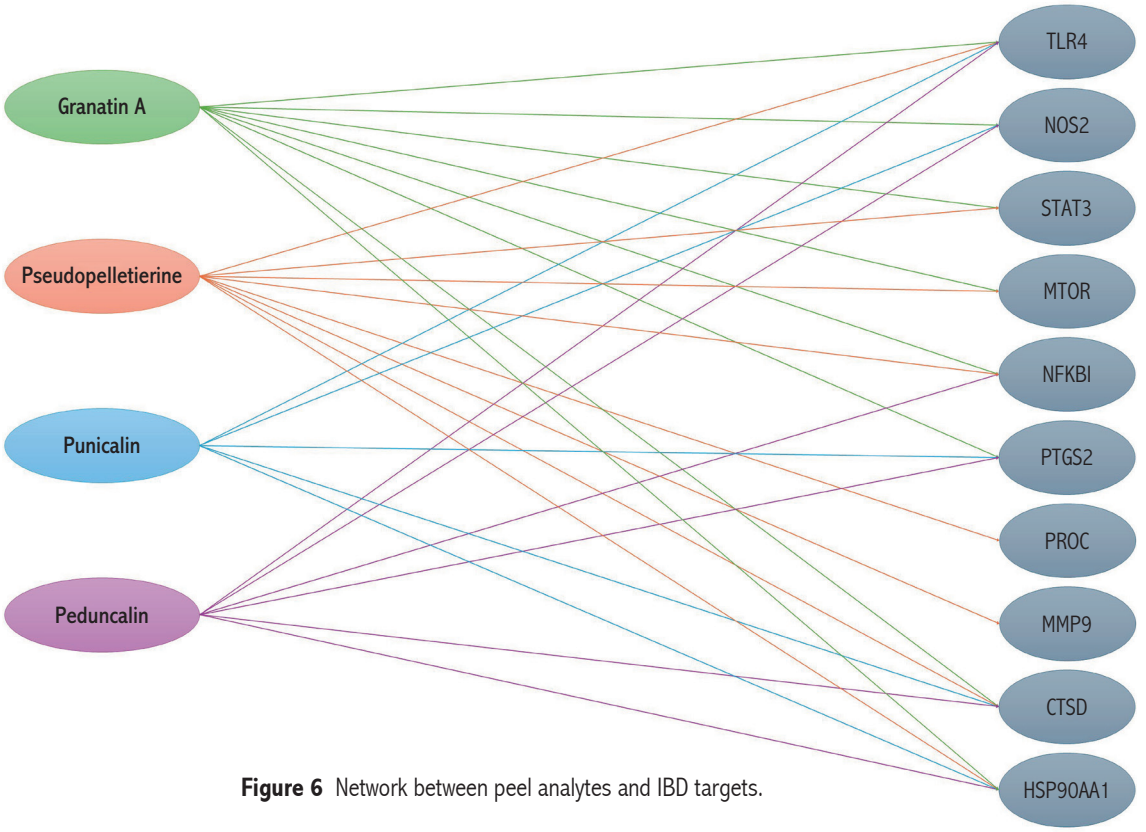


Figure 6 Network between peel analytes and IBD targets.

lipoproteins, and total cholesterol (Laurindo et al., 2022; Bahari et al., 2024; Mohammadi et al., 2025; Mohammadzaheri et al., 2025). Metabolic disorders (including metabolic syndrome, insulin resistance and type 2 diabetes, dyslipidemia, and obesity-related hepatic steatosis) arise from convergent biochemical and cellular perturbations. Pomegranate peel extracts (ultrasonication, ethanol 50-70% v/v) have demonstrated to modulate altered cellular pathways related to these disorders: impairment of insulin receptor substrate 1 and phosphoinositide 3-kinases signaling (Zhang et al., 2022), reduced AMPK activity (Reguero et al., 2022), dysregulated PPARα/γ-mediated lipid handling (Li et al., 2020), chronic NF-κB/NLRP3-driven inflammation (Chen et al., 2025), and mitochondrial dysfunction caused by reactive oxygen species (Rak-Pasikowska et al., 2024).

Focusing on cholesterol, Dehghani et al. (2024) compared the activity of punicalagin alone and pomegranate peel ethanolic extract (80% v/v) in reducing low-density lipoproteins (LDLs). When LDL-bound cholesterol is elevated, it promotes atherogenesis. Hepatocytes remove LDL via LDL receptors (LDLRs), but proprotein convertase subtilisin/kexin type 9 (PCSK9) binds LDLRs and targets them for lysosomal degradation, reducing the availability of receptors. Statins inhibit HMG-CoA reductase, lowering intracellular cholesterol and upregulating LDLRs expression; however, they also increase PCSK9 expression, which can partially offset LDL lowering. For greater LDL-C reduction and cardiovascular risk reduction, therapies that inhibit PCSK9 (such as monoclonal antibodies or siRNA agents (Kim, 2025)) are added to statins to preserve LDLRs levels and enhance LDL clearance. Dehghani et al., (2024) reported that both punicalagin and peel extract exhibited increasing dose-dependent uptake of LDLs after 24 and 48 hours on HepG2 cells (derived from liver hepatocellular carcinoma). The uptake after 24 hours was almost doubled compared to control at 50 µg/mL of punicalagin and 150 µg/mL of peel extract. However, after 48 hours the uptake decreased at higher concentrations. Moreover, both punicalagin (at 50 µg/mL) and peel extract (at 150 µg/mL) reduced the expression of PCSK9 by 69.59% and 68.70%, respectively. It is significant that the profile trend from the immunofluorescence analysis of punicalagin alone mirrored that of the peel extract, possibly implying the prominent role of punicalagin (previously linked to the modulation of LDL influx in macrophages (Atrahimovich et al., 2016)).

Switching to diabetes, Tan et al. (2024) reported that punicalagin administration in diabetic mice could ameliorate diabetic liver injury by inhibiting pyroptosis and upregulating autophagy. Following punicalagin administration (20 mg/kg), alanine transaminase and aspartate transaminase levels were lowered compared to control, and the expression of Caspase-1, gasdermin-D, interleukin-1β, and NLRP3 was reduced. Moreover, expression levels of microtubule-associated protein 1 light chain 3β (in its lipidated form) and beclin-1 in the punicalagin group were significantly increased ($p<0.05$ and $p<0.01$ respectively), and sequestosome-1 was significantly decreased ($p < 0.01$) too. These results were also confirmed on HepG2 cells under high glucose medium growth and were mechanistically linked to the upregulation of forkhead box protein O1 (a transcription factor that is the main target of insulin signaling (Teaney & Cyr, 2023)) and the downregulation of thioredoxin-interacting protein (a factor that modulates proliferation and apoptosis of pancreatic β-cells (Wondafrash et al., 2020)). Similarly, Apaydin Yildirim et al. (2025) reported that the ethanolic extract of pomegranate peel ameliorated diabetic nephropathy in mice. The amelioration occurred on three different fronts: (i) cell death modulation, by upregulating apoptosis regulator Bcl-2 and downregulating caspase-3 and bax protein; (ii) inflammation modulation, by downregulating NF-κB; and (iii) antioxidant response, by upregulating renal levels of nuclear factor erythroid 2-related factor 2 and heme oxygenase 1. Instead, Bustamante et al. (2025) reported that the ethanolic extract of pomegranate peel mitigated insulin resistance induced by palmitic acid in myotubes of differentiated C2C12 cells. Treatment with the peel extract (containing 100 µM of punicalagin) restored the phosphorylation of RAC-alpha serine/threonine-protein kinase (AKT) induced by insulin and impaired by palmitic acid. It is known that insulin induces phosphorylation of AKT at Thr308 and Ser473, a critical step for propagation of PI3K-dependent metabolic signaling (Tsuchiya et al., 2014). Exposure to the saturated fatty acid palmitic acid attenuates this response, reducing AKT phosphorylation and downstream signaling to targets such as TBC1 domain family

member 4 and Glycogen synthase kinase-3 beta (Mäkinen et al., 2017). In previous studies, palmitate has been shown to promote inflammatory kinase activation (c-Jun N-terminal kinases, IκB kinases) and accumulation of inhibitory lipid intermediates that impair insulin receptor substrate and PI3K, thereby limiting the activation of AKT mediated by PDK1/mTORC2 signaling (Blaustein et al., 2021). The impairment of the phosphorylation of AKT contributes to defective glucose uptake and glycogen synthesis in insulin-responsive tissues and is a key component of lipotoxic insulin resistance. Moreover, treatment with the peel extract increased the ratio between the lipidated form and the soluble unbound form of microtubule-associated protein 1 light chain 3β (LC3-II/LC3-I), thus promoting autophagy and reducing the overall oxidative stress. The LC3-II/LC3-I ratio is a biochemical readout used to assess autophagosome dynamics. Microtubule-associated protein light chain 3 exists as a cytosolic form (LC3-I) that is conjugated to phosphatidylethanolamine to generate LC3-II. An increase in LC3-II relative to LC3-I typically reflects enhanced autophagosome abundance. However, changes in this ratio can result from either stimulated autophagosome formation or impaired autophagosome turnover, so interpretation requires concurrent measures of autophagic flux (for example, monitoring sequestosome-1) (Klionsky et al., 2008). Bustamante et al. (2025) confirmed the augmented autophagy by observing decreased levels of dynamin-like GTPase OPA1, mitochondrial (long isoform). This result is also reported by Díaz-Castro et al. (2024) who observed that the cleavage of OPA1 is linked to the remodeling of mitochondria. By controlling mitochondrial inner membrane fusion and cristae organization, OPA1 preserves oxidative phosphorylation efficiency, stabilizes respiratory chain complexes, and limits cytochrome c release during stress (Quintana-Cabrera et al., 2021). Through these actions OPA1 supports ATP production, fatty acid and substrate oxidation, and mitochondrial quality control (including mitophagy), so that reductions in OPA1 impair bioenergetics, increase reactive oxygen species, and contribute to metabolic dysfunction in tissues with high energy demand. Finally, the decrease in p-IκBαSer32 indicates attenuated NF-κB activation, aligning with reduced inflammation and enhanced insulin sensitivity (Zanfardino et al., 2025).

The role of OPA1 returned in Duarte et al. (2024) who reported that the administration (150 mg/kg, containing 40% punicalagin) of pomegranate peel ethanolic (77% v/v) extract to C57BL/6J mice prevented the downregulation of *Opa1* and *Ppargc1a* induced by a high-fat diet. Moreover, the pomegranate peel extract modulated gut microbiota diversity: alpha-diversity (measuring the variety of microorganisms within a single sample) did not change from the control group, whereas beta-diversity (measuring the difference or similarity between two or more microbial communities) showed a significant difference. The observed increase in diversity suggests that pomegranate peel extract may promote a more resilient and balanced microbial community. The mechanisms underlying these changes possibly involve the activity of prebiotics such as ellagitannins, which are metabolized by gut microbiota into bioactive urolithins (postbiotic metabolites). Indeed, administration of pomegranate peel in mice fed with high-fat diet reduced Firmicutes and increased Proteobacteria phyla, while restoring Bacteroidetes to control level (Table 4).

Finally, S. Huang et al. (2024) investigated the interaction between punicalagin and targets of bacterial enteritis using *in silico* analysis. Of the 130 targets found in a preliminary study

Table 4 Changes in relative abundances of bacterial communities after high-fat diet (HFD) or HFD plus pomegranate peel extract (PPE) administration.

	Control	HFD	HFD+PPE
Bacteroidetes	0.354±0.047	0.161±0.103	0.389±0.098
Firmicutes	0.426±0.097	0.692±0.118	0.411±0.109
Proteobacteria	0.141±0.048	0.089±0.029	0.154±0.013

using the STRING database, 5 were deemed core targets and further selected for molecular docking (Table 5).

Table 5 Molecular docking against targets of bacterial enteritis.

GENE (PDB)	TP53 (6CGI)	IL6 (5FUC)	CASP3 (5AOM)	VEGFA (1NMS)	TNF (5DN2)
Energy (kcal/mol)	-9.2	-9.3	-10.2	-10.3	-10.9

Further *in vivo* studies on mice validated the interactions. Specifically, in the treated groups, mice showed: (i) reduction in pro-inflammatory cytokines TNFα and IL-6 in both serum and intestinal tissues; (ii) restoration of intestinal barrier integrity, evidenced by increased expression of tight junction protein 1; and (iii) modulation of gut microbiota composition (reduced proliferation of Bacteroidaceae, Bacteroidetes, and Muribaculaceae; increased proliferation of Firmicutes, Lachnospiraceae, *Lactobacillus*, and Ruminococcaceae).

CONCLUSIONS

In conclusion, pomegranate peel represents a high-value and underused by-product with pharmaceutical and nutraceutical potential. Exploring biological activities of agro-industrial products and waste is one approach to create or add value to them, thus developing new economic opportunities. Still, several gaps and challenges must be addressed to translate laboratory findings into scalable, safe, and economically viable green economy solutions.

Key gaps include: (i) inconsistent phytochemical characterization (variability by cultivar, geography, maturity, and processing) and lack of standardized extraction and analytical protocols that impair reproducibility and cross-study comparison; (ii) limited mechanistic and target-validated pharmacology, with most evidence confined to *in vitro* assays or acute animal models; and (iii) scarce clinical data and no consensus on effective, safe dosing regimens or formulations for human nutraceutical or therapeutic use.

From a technology and circular economy perspective, challenges include: (i) the development of cost-effective, green extraction and fractionation processes that can be integrated into existing agro-industrial chains; (ii) scale-up obstacles such as seasonal feedstock supply, preprocessing, storage and quality control; and (iii) limited industrial examples of value chain integration that ensure producer incentives and market uptake.

Future directions should therefore prioritize: (i) harmonized analytical and reporting standards, such as fingerprint metabolomics, validated bioassays, and reporting of cultivar/origin/processing, to enable meta-analysis; (ii) mechanistic pharmacology and translational pipelines, involving rigorous ADMET, interaction studies and early phase human trials focused on defined indications (like metabolic syndrome, topical antimicrobials, adjunctive cancer support); (iii) development and validation of scalable green extraction and valorization routes (aqueous, enzymatic, supercritical) with downstream fractionation for target enrichment and residuals used in low value streams (animal feed, compost, bioenergy) to maximize circularity; (iv) formulation research to improve stability and oral/percutaneous bioavailability (for example, using nano/microencapsulation or complexation with biopolymers) coupled with stability and shelf life studies; and (v) integrated techno-economic and lifecycle assessments and pilot demonstration projects that quantify environmental, social and economic impacts and inform policy incentives. All of the above points are crucial, not least their compliance with safety regulations and requirements set by Food and Drug Administration (FDA), European Medicines Agency (EMA), European Food Safety Authority (EFSA), and other national agencies.

Addressing these gaps through multidisciplinary and stakeholder driven research will be essential to unlock pomegranate peel's potential as a sustainable resource in the circular bioeconomy while ensuring safety, efficacy, and market feasibility.

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