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Review Article

Bioactive Compounds, Pharmacological Properties, and Utilization of Pomegranate (*Punica granatum* L.): A Comprehensive Review

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ABSTRACT

Abstract: The pomegranate, or *Punica granatum L.*, is well known for its extensive historical background and wide range of bioactive chemicals, which underlie its powerful pharmacological effects. Notably, hydrolysable tannins, including punicalagin, punicalin, gallic acid, and derivatives of ellagic acid, constitute pivotal agents driving antioxidant potential. Anthocyanins, exemplified by delphinidin derivatives, contribute to its vibrant pigmentation. This review navigates through the intricate interplay of pomegranate's bioactive constituents and their pharmacological impacts. With a focus on antioxidative, anti-inflammatory, and anticancer attributes, pomegranate's diverse therapeutic potential is underscored. The distinctive presence of ellagic acid lends anti-inflammatory and antioxidant capabilities, while punicalagin's multifaceted effects include cardio protection and antimicrobial activity. Exploration of extraction methods highlights avenues for preserving these compounds. Conventional and non-conventional techniques, including ultrasound-assisted and microwave-assisted extraction, extract maximum benefits while minimizing environmental impact. Pomegranate's influence extends to enriching a plethora of food products. It elevates dairy, meat, and bakery items by infusing them with nutritional robustness and potent antioxidants. Furthermore, the integration of pomegranate-derived extracts into edible coatings and films augments food preservation and safety in a natural manner. As a nexus of tradition and innovation, pomegranate emerges as a source of natural wellness, rooted in ancient reverence, and validated by modern science. The current review provides a comprehensive understanding of pomegranate's exclusive bioactive compounds and their pivotal role in pharmacological activities, along with the methods of extraction and utilization in the development of value-added products.

Keywords: pomegranate, bioactive compounds, pharmacological properties, applications, value-added products.

Introduction

Pomegranate (*Punica granatum L.*) belongs to the family Punicaceae, which also includes *Punica protopunica* (endogenic to the Socotra islands) and *Punica granatum* (native to the Mediterranean areas and Iran).[1] Pomegranate cultivation as well as ingestion may be traced back to at least 3000 BC.[2] The fruit falls within the category of fleshy berry. Its calyx is formed like a crown and has a nearly spherical shape with a diameter of up to 10 cm. A fleshy mesocarp is housed inside the leathery exocarp (as shown in Figure 1) and is divided into chambers by membranes.

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The exocarp, or skin, makes up around 50% of the overall fruit, whereas the edible component of the pomegranate is made up of 10% seeds and 40% arils.[3] Table 1 represents the varying amount of nutrient composition in pomegranate and its by-products.

Punica granatum is known to contain primary active chemical components, predominantly hydrolysable tannins. These major compounds include punicalagin, punicalin, gallic acid, ellagic acid, and various derivatives of ellagic acid, often in methylated forms. Additionally, *Punica granatum* also contains secondary compounds like pedunculagin, punicacortein A–D, granatin A and B, punicafolin, punigluconin, and corilagin.[10] The anthocyanins found in pomegranates primarily consist of pelargonidin 3-glucoside, cyanidin 3-glucoside, delphinidin 3-glucoside, pelargonidin 2,5-diglucoside, cyanidin 3,5-diglucoside, and delphinidin 3,5-diglucoside. These compounds are responsible for the distinct hues of pomegranate fruits.[11]

Pomegranate fruit has health advantages that extend beyond just the edible portion (arils), particularly the peel, which has more biologically active elements as compared to the edible portion.[12] Pomegranate peels contain a diverse range of phytochemical compounds including gallic acid, gallotannins, ellagic acid, punicalagins, and punicalin. Among these, punicalagin exists in two forms - α and β anomeric forms and has been recognized as the antibacterial agent within pomegranate peel extracts.[13] Additionally,

ellagic acid exhibits properties such as antimutagenic, antiviral, antioxidant, and skin-lightening effects.[14] Pomegranate has a wide range of medicinal benefits, including antioxidant, antiviral, antibacterial, and anti-inflammatory attributes.[13] An extract derived from pomegranate, which includes Cyanidin, has demonstrated the ability to decrease levels of reactive oxygen species (ROS) in MCF-7 cell lines. Furthermore, this extract has exhibited the capability to impede the proliferation of MCF-7 cell lines.[15] Pomegranate was regarded in Traditional Indian Medicine as being a pharmacy by itself.[16] Strongly astringent fruit peel was used to treat diarrhoea, while the fruit was used as a tonic and anti-fever agent.[17] Pomegranate flowers were employed in traditional Greek Medicine to treat diabetes.[18]

The pomegranate fruit is often consumed in both raw and processed form, including juice, jelly, jam, wine, oil, vinegar, and dietary supplements. Pomegranate is used in a variety of items including teas, pharmaceutical and therapeutic products, colorants, and decoration.[19,20] The current review focuses on the bioactive compounds, pharmacological properties, methods of extraction, utilization, and application of pomegranate fruit.

Bioactive compounds

Phytochemicals, commonly referred to as bioactive substances, are secondary metabolites produced by plants. They can be thought of as chemical substances that might have an impact on health but are not necessary nutrients.[21] These bioactive substances are viewed as therapeutically useful chemicals because they possess the ability to influence calorie intake while reducing excessive oxidative stress, pro-inflammatory conditions, and metabolic disorders.[22] Climate, location, storage conditions, and cultivars all have an impact on the biochemical composition of fruit and other plant parts.[23] Flavonoids, ellagic acids, coniferyl, sinapyl, ferulic acids, anthocyanin, chlorogenic acid, quercetin, epicatechin, hydrolysable tannins, and rutin are some of the key bioactive components reported in pomegranates.[24]

Glycated anthocyanins such as pelargonidin 3,5-diglucoside and pelargonidin 3-glucoside are found in the pomegranate flower, while apigenin, punicallin, luteolin and punicalagin are found in the leaves, stem, and roots (Figure 2). There are phenolic substances, tannins together with hydrolysable tannins present within the fruit and its pericarp.[25] Table 2 represents the bioactive substances that have been found in various pomegranate fruit sections.

These findings provide a scientific basis for the traditional and modern uses of pomegranates in enhancing health and wellbeing by illustrating the intricate interplay of phytochemicals in various plant components. The influence of environmental factors also highlights how crucial it is to comprehend and manage these elements in order to maximize the bioactive potential of pomegranate products.

Pharmacological properties

The individual parts of pomegranate fruit have various chemical substances in varied concentrations such as minerals, polyphenols, vitamins, and carbohydrates. The presence of numerous chemicals with distinct chemical structures reveals several medicinal properties of pomegranate.[36] *Punica granatum* has numerous useful effects on overall health including antioxidant, anti-inflammatory, and antibacterial characteristics[13] (as shown in Figure 3). Additionally, it also exhibits anti-cancer as well as cardio-protective properties.[37] Table 3 represents the pharmacological properties of various parts of pomegranate and the bioactive compounds responsible for the health benefits.

Antioxidant property

Numerous chronic diseases are thought to be caused by reactive oxygen species (ROS), which are believed to be produced as a result of exposure to ionizing or xenobiotic radiation or as a result of normal cellular activities.[38] The potential of ROS to harm vital biological substrates including RNA, DNA, proteins, and membrane lipids gives them their hazardous properties.[39] By giving free radicals electrons and stabilizing them, antioxidants redirect this damage and protect cell components from the scavenging effects of free radicals.[40]

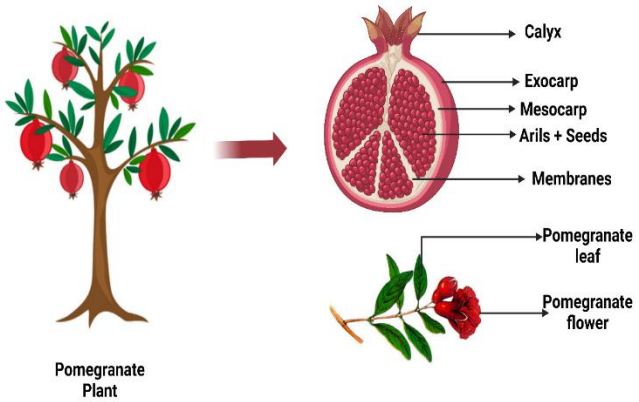

Figure 1: Different parts of Punica granatum L

Table 1: Proximate, nutritional, and mineral composition of pomegranate and its by-products

Parameters	Units	Pomegranate fruit (raw)	Pomegranate peel powder	Pomegranate seed powder	Reference
Moisture	g/100 g	-	8.43	-	4-9
Protein		1.67	3.26	13.66	
Fat		1.17	0.55	29.60	
Fiber		4	35.19	39.3	
Ash		0.53	3.35	-	
Carbohydrates		18.7	-	13.12	
Calcium	mg/ 100g	10	342	229.20	
Phosphorus		36	120	481.10	
Potassium		236	150	434.40	
Zinc		0.35	1.08	5.54	
Iron		0.3	6.11	10.88	
Vitamin C		10.2	12.90	3.02	
Vitamin E		0.6	3.99	1.35	

Vitamin B1	0.067	0.123	0.930

Table 2: Bioactive compounds found in different parts of plant *(Punica granatum L.)*

Plant part	Cultivar	Method of extraction	Compound	Pharmacological attribute	Reference
Leaves	Gabsi	Maceration	Ellagitannins, gallic acid, caffeic acid, coumaric acid derivatives, phlorizin, cyanidin, delphinidin, and pelargonidin derivatives.	Antioxidant activity.	[26]
	Gabsi	Soxhlet extraction (hexane, chloroform, ethyl acetate, and ethanol) Decoction (aqueous extract) Maceration (extract enriched with total oligomer flavonoids)	Phenolic acids (gallic acid & ellagic acid), flavonoids (luteolin & rutin), hydrolysable tannins, and other undetermined substances.	Antimicrobial activity and antibiotic modulation (synergistic effect).	[27]
	Big full and Wonderful	Maceration, ultrasound-assisted extraction, and microwave-assisted extraction	Phenolic acids (gallic acid, O-caffeoylquinic acid, methyl gallate hexoside, glucaric acid, ferulic acid hexoside, methyl ellagic acid hexoside, and ellagic acid penstoside) Flavonoids (catechin, epicatechin, Quercetin-3-O-rutinoside, quercetin-3-O-glucoside, and luteolin derivatives) Ellagitannins (punicalagin, granatin B, and pedunculagin)	Demonstrated wide-ranging antimicrobial activity against both clinical and food borne pathogens. Exhibited promising results as antioxidant and showed cytotoxic potential.	[28]
Seeds	Manfalouty seeds variety	Ultrasound assisted method	Catechin, quercetin, rutin, caffeic, chlorogenic, and gallic acid.	Pomegranate seed oil reduced aflatoxin as well as zearalenone secretion, therefore, regulating the process of fungal secondary metabolites.	[29]
	--	Ultrasonicated water bath	Vanillic acid, gallic acid, trans p-coumaric acid, p-hydroxybenzoic hexoside, catechin, quercetin hexoside, kaempferol-3-O-glucoside, ellagic acid, and anthocyanins.	The potential of phenolic compounds derived from pomegranate seeds was shown in their ability to inhibit DNA damage, oxidation of LDL-cholesterol, alpha-glucosidase activity, and lipase activity.	[30]
Peel	Gabsi	Solvent extraction	Punicalagin, pedunculagin, and ellagic acid -O- hexoside.	Pomegranate peel extracts possess promising pharmacological properties including potent antioxidant activity as well as significant antimicrobial effects.	[31]
	Wonderful	Solvent extraction	gallic acid, ferulic acid, p-coumaric acid or trans-4-hydroxycinnamic acid, syringic acid, and sinapic acid.	Pharmacological attributes include antioxidant protection, mitigation of	[32]

				oxidative damage, and potential metabolic regulation.	
Flower	Wonderful, Mollar de Elche, G1 pomegranate, and Parfianka.	Ultrasonic bath	Punicalins, punicalagin B and A, ellagic acid, gallic acid, cyanidin 3,5-diglucoside, pelargonidin 3,5-diglucoisde, and pelargonidin 3-glucoside.	Exhibited antioxidant, antimicrobial, and cytocompatibility properties, making them attractive contenders for cosmetic formulations.	[33]
Arils	--	Soxhlet extraction	Phenols, tannins, flavonoids, quinones, coumarins, triterpenoids, anthocyanins, alkaloids, and gallic acid.	The extracts could serve as valuable sources for antioxidants, antidiabetic agents, and potentially novel antibacterial compounds.	[34]
	--	Solvent extraction	Delphinidin, cyanidin, ellagitannins, Gallo tannins, ellagic acid.	Exhibited effective antimicrobial activity	[35]

Aloqbi *et al.*[41] examined the antioxidant effects of a polyphenolic tannin compound found in pomegranates, punicalagin, as well as the antioxidant properties of pomegranate juice. Different concentrations (0.05, 0.1 & 0.15 mg/mL) of punicalagin and pomegranate juice were used. DPPH scavenging revealed dose-dependent effects, with pomegranate juice exhibiting more pronounced radical scavenging compared to punicalagin at concentration of 0.1 and 0.15 mg/mL. Additionally, the investigation into the mechanisms by which punicalagin and pomegranate juice scavenge H2O2 revealed that their scavenging activity varies based on the dosage. Pomegranate juice exhibited a noteworthy ability to scavenge H2O2, outperforming punicalagin at a concentration of 0.15 mg/mL (statistically significant with $p < 0.001$). The inhibition percentages were 30% for pomegranate juice and 18% for punicalagin, respectively. Furthermore, the potential of punicalagin and pomegranate juice to serve as agents for chelating ferrous ions was also examined. Both substances demonstrated a dose-dependent reduction in the Fe2+-ferrozin complex within the concentration range of 0.05 to 0.15 mg/mL. Notably, at a concentration of 0.15 mg/mL, punicalagin exhibited significantly greater ferrous chelating activity compared to pomegranate juice (statistically significant with $p \leq 0.05$). The assessment of reducing power, which measures the ability of bioactive compounds to donate electrons, demonstrated a gradual enhancement in reducing activity for both punicalagin and pomegranate juice as the dosage increased. Notably, punicalagin displayed notably superior reducing power compared to pomegranate juice. These findings provide a valuable insight into the distinct antioxidant mechanisms of punicalagin and pomegranate juice.

Sun *et al.*[42] investigated the antioxidative characteristics of punicalin, punicalagin, and ellagic acid derived from pomegranate peel. through various *in vitro* assays, evaluating their potential to scavenge free radicals, exhibit reducing powers, inhibit lipid peroxidation, and counteract oxidative stress-induced damage. Additionally, the research examined their *in vivo* effects against oxidative injury, focusing on their ability to mitigate oxidative stress. A comprehensive measure (lipid peroxides) and three different categories of free radicals, encompassing DPPH, a form of reactive nitrogen species, O2-, a variety of reactive oxygen species, and Fe3+, a type of extremely reactive metallic ion, were employed for assessment to assess the in vitro antioxidant activity of three major polyphenols in pomegranate peel. Ellagic acid, punicalin, and punicalagin showed stronger activities compared to Trolox in both DPPH scavenging and FRAP assays. Punicalagin and punicalin demonstrated significantly higher activities against superoxide anion compared to Trolox and ellagic acid. However, Trolox outperformed all three compounds in inhibiting lipid peroxidation. On the other hand, BALB/c mice (in vivo) subjected to oxidative stress induced by oxidized fish oil were administered punicalagin, punicalin, or ellagic acid at a dosage of 10 mg/kg/day for a period of 21 days. Administration of ellagic acid to oxidatively stressed mice resulted in improved total antioxidant capacity levels in intestine, plasma, and liver. It also raised superoxide dismutase (SOD) activity in the liver and intestine, while increase glutathione peroxidase (GSH-Px) activity in intestine. Additionally, ellagic acid effectively reduced malondialdehyde (MDA) levels in plasma, liver, and intestine as well as downregulated the mRNA expression of pro-inflammatory markers (TNF-α, IFN-γ, and IL-6). Punicalin and punicalagin treatment enhanced the SOD and GSH-Px activities in intestine, accompanied by reduced MDA content and decreased mRNA expression of TNF-α and IL-6 in the intestine.

Chaabna *et al.*[43] studied the phenolic compound content and assess the potential antioxidant, anticholinesterase, and antibacterial activities of pomegranate peels collected from the eastern region of Algeria. The process involved the separation of pomegranate peel's hydro-ethanolic extract into different fractions, with subsequent evaluation of the biological functions of the ethyl acetate and n-butanol fractions. Multiple assays, including DPPH, ABTS, CUPRAC, phenanthroline, and reducing power tests, were employed to gauge the antioxidant prowess. The outcomes indicated that the ethyl acetate and n-butanol fractions exhibited noteworthy concentrations of phenolics, flavonoids, flavonols, and tannins. Furthermore, these fractions showcased impressive capabilities in mitigating oxidation even at low concentrations, surpassing the performance of standard antioxidants like ascorbic acid and trolox. The fractions obtained from pomegranate peels were subjected to testing to assess their capacity for inhibiting acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), with a comparison made to galantamine. Among these fractions, ethyl acetate exhibited the most substantial inhibitory effect against AChE, yielding an IC50 value of 76.51±3.32 µg/mL, in contrast to n-butanol with an IC50 of 150.17±5.00 µg/mL. Both ethyl acetate and n-butanol fractions demonstrated inhibition of BChE, with n-butanol proving to be more potent (IC50: 119.15±5.87 µg/mL) than ethyl acetate (IC50: 143.30±24.18 µg/mL).

The comparative analysis among the cited authors provides valuable insights into the antioxidant properties of pomegranate-derived compounds. Aloqbi *et al.*[41] emphasize the ROS-scavenging and metal-chelating abilities of punicalagin and pomegranate juice, while Sun *et al.*[42] expand on this, showcasing ellagic acid, punicalin, and punicalagin's potent scavenging activities and lipid peroxidation inhibition. Additionally, the *in vivo* study highlights their protective potential. Chaabna *et al.*[43] offer a neuroprotective perspective,

exploring inhibitory effects on key enzymes. Collectively, these studies unveil a multifaceted antioxidant potential, paving the way for therapeutic applications in combating oxidative stress-related ailments.

Anti-inflammatory property

It is well recognized that inflammation serves as the host's defence mechanism against infection and tissue damage, helping either to stop the spread of infection or speed up the healing process. The inflammatory process involves various cell kinds and mediators that have highly programmed abilities to control cell chemotaxes, migration, and proliferation.[44] Urolithins are the most significant constituent present in pomegranates that have anti-inflammatory actions[45]. Ellagitannins and ellagic acid are converted by the gut microbiota into urolithins.[46] Flavonoids such as procyanidin found in the juice as well as kaempferol & luteolin found in the peel are known to have considerable anti-inflammatory activities, as reported by several pharmacokinetic studies.[47] Houston *et al.*[48] showed the *Punica granatum L.* rind extracts have anti-inflammatory activity when applied topically to ex vivo skin. Different test solutions were used, and each was subjected to a different molecular biology technique in order to evaluate the anti-inflammatory effects in *ex vivo* skin. The test solution included Total pomegranate tannins (TPT), tannin-free fraction (TFF), pomegranate rind extract (PRE), zinc sulphate ($ZnSO_4$). For each experiment, 1 mL of these solutions were given at a dose of 0.1 mg/mL in phthalate buffer at 4.5 pH. Immunohistochemistry and western blotting were the molecular biology techniques used to evaluate anti-inflammatory effects. In general, cyclooxygenase-2 (COX-2) is only expressed in cells where prostaglandins are increased, such as inflammation. Western blot analysis measured the COX-2 expression. Comparing the application of pomegranate rind extract and zinc sulphate combined to the application of pomegranate rind extract alone, statistically similar downregulation of COX-2 was seen; the application of zinc sulphate alone had no effect. The absence of reduction with TFF suggests that the primary anti-inflammatory effects stem from tannins. TPT notably lowered COX-2 expression by 40.5%, surpassing PRE by a substantial 26%, whether ZnSO4 was present or not. The most significant reduction was seen when PRE remained an intact extract, whereas TPT displayed some anti-inflammatory activity, albeit not as pronounced. This further underscores the significance of tannins, especially punicalagin, in regulating inflammation in the ex vivo skin model. According to the results of immunohistochemistry, topically administering TPT and PRE reduced COX-2 expression, which had an effect on the inflammation pathway involving arachidonic acid. This decrease became statistically significant after 6 hours and remained so for 24 hours, showing that despite their large molecular sizes, PRE and TPT both successfully entered the skin. Interestingly, combining PRE with ZnSO4 produced findings that were equivalent, proving that zinc did not affect the outcome, in line with earlier studies.

Table 3: Pharmacological properties exhibited by various parts of pomegranate (*Punica granatum L.*)

Pharmacological properties	Plant part	Bioactive compound	Results/Findings	Reference
Antioxidant	Pomegranate juice and punicalagin	Punicalagin Pomegranate juice (anthocyanins, gallic acid, ellagic acid)	DPPH and H_2O_2 scavenging showed a dose-dependent trend. Dose-dependent reduction in Fe^{2+}-ferozzin complex as well as increase in reducing activity was observed.	[41]
	Pomegranate peel	Ellagic acid, Punicalin, and Punicalagin	The three compounds exhibited highest activity in DPPH scavenging assay and FRAP assay. In superoxide anion scavenging assay punicalagin and punicalin exhibited highest activity. *In vivo* results demonstrated that the compounds increased SOD and GSH-Px activity and decreased MDA levels along with mRNA expression of proinflammatory factors in liver, plasma, and intestine.	[42]
	Pomegranate peel	Flavonoids, phenolics, tannins, and flavonols.	Pomegranate peel fractions demonstrated potent antioxidant activity surpassing standard compounds (Trolox & Ascorbic acid) in various assays (ABTS, CUPRAC, reducing power, phenanthroline assay, DPPH) indicating their potential in oxidative stress mitigation and health promotion.	[43]
Anti-inflammatory	Pomegranate rind extract	Tannins (punicalagin)	Modulate the expression of cyclooxygenase 2 (COX-2), thereby, exerting anti-inflammatory properties	[47]
	Pomegranate juice	Ellagic acid, punicalagin, punicalagin isomer, ferulic acid hexoside, phlorizin anthocyanins (Cyanidin 3,5-diglucoside and	Pomegranate juice polyphenolic extract reduces proinflammatory cytokines, inhibits COX-2 expression, reduced nitro tyrosine formation, enhances the expression of	[48]

		pelargonidin 3-glucoside)	adhesion protein, counteracts oxidative stress, reduced apoptosis (induced by 5-FU), promotes wound healing.	
Anti-cancer	Pomegranate peel extract	Punicalagin and ellagic acid	Inhibition of cell proliferation, promotion of apoptosis together with nuclear fragmentation and cell shrinkage was observed. Reduced invasion and motility were observed due to reduced expression of matrix metalloprotein 9	[54]
	Pomegranate extract	Punicalagin, punicalin, and ellagic acid	Antiproliferation, DNA damage, mitochondrial dysfunction, apoptosis, and oxidative stress against cancer cells were observed. Additionally, downregulation of Mito tracker-detected mitochondrial mass was seen.	[56]
Cardio-protective	Pomegranate juice	Ellagic acid, gallic acid, punicalagin, punicalin, and gallagic acid	Increase in antioxidant activity was observed which resulted in decrease in MDA levels. A decrease in serum troponin levels was observed. Enhanced protection against ischemia-reperfusion injury was seen.	[59]
	Pomegranate peel extract	Gallic acid and punicalagin	Reduction in inflammatory cytokine TNF and increase in anti-inflammatory interleukin 6 was observed. Increase in lesion collagen and efferocytosis was observed.	[61]
Antidiabetic	Pomegranate peel, leaf, and juice	Polyphenols, flavonoids, and anthocyanins	Decreased fasting blood glucose levels, increased insulin sensitivity, decreased the activity of alpha amylase, enhanced the activity of antioxidant enzymes SOD and GPx. Reduced lipid peroxidation and protein carbonylation.	[62]
Antimicrobial	Pomegranate juice and peel extract	Caffeic acid, quercetin, epigallocatechin-3-gallate, and ellagic acid	Inhibits the expression of DNA gyrase in gram negative bacteria which leads to inhibition of microbial growth	[64]
	Pomegranate peel	Phenols	Phenolic toxicity interacts with sulfhydryl group of microbial proteins cause functional/structural alteration and eventually resulting in growth inhibition.	[65]
	Pomegranate peel	Flavonols, tannins, phenolics, and flavonoids.	Punica granatum peel fractions displayed variable antibacterial activity against Gram-positive and Gram-negative bacteria. Tannins and flavonoids may contribute to their antimicrobial potential.	[43]

Pepe *et al.*[49] studied the impact of pomegranate juice extract on Intestinal epithelia cells (IEC-6) cells both under inflammatory conditions and after receiving the antibiotic 5-fluorouracil. Intestinal epithelia cells-6 (IEC-6) were initially exposed to pomegranate juice polyphenolic extract (PPJE; 10–1.25 µg/mL) for one-hour post-adhesion. Following this, the cells underwent concurrent exposure to the examined extract, lipopolysaccharides from Escherichia coli (E. coli), and interferon-gamma (IFN-γ; 10 units/mL), with durations varying according to the specific mediator studied. Additionally, to explore the potential onconutraceutical effects of PPJE (10–1.25 µg/mL), the extract was administered to IEC-6 cells for one hour, succeeded by the addition of 5-Fluorouracil (5-FU; 10 µg/mL) for different time frames, contingent on the particular mediator under scrutiny. Nitro tyrosine has been identified as an indicator of cellular harm, inflammatory processes, and the generation of nitric oxide. The assessment of pomegranate juice extract's effects on IEC-6 cells

revealed a noteworthy reduction in the release of proinflammatory agents like cytokines, as well as the expression of cyclooxygenase-2 and inducible nitric oxide synthase. Additionally, the formation of nitro tyrosine was inhibited. Pomegranate extract also demonstrated the ability to counteract oxidative stress and enhanced the expression of adhesion proteins. In IEC-6 cells treated with 5-FU, pomegranate extract displayed inhibitory effects on both inflammatory and oxidative stress markers, along with apoptosis. The extract facilitated the mending of wounds and the expression of tight junctions.

In the context of inflammation, Houston *et al.*[48] investigated the anti-inflammatory potential of Punica granatum L. rind extracts in a skin model, underscoring the significance of tannins, particularly punicalagin, in downregulating inflammation through cyclooxygenase-2 (COX-2) expression inhibition. This aligns with Pepe *et al.*[49] who explored pomegranate juice extract's impact on intestinal epithelial cells (IEC-6). Their study demonstrated reduced proinflammatory agent release, suppressed cyclooxygenase-2 expression, and alleviation of oxidative stress. These parallel findings, observed across distinct cellular models, emphasize the consistent anti-inflammatory capacity of pomegranate compounds, thus suggesting their potential therapeutic utility in managing inflammatory responses effectively.

Anti-cancer property

According to scientific research, pomegranates may be useful in the prevention and treatment of several cancers, including breast cancer, prostate cancer, lung cancer, and skin cancer.[15,50-52] Pomegranate reduces the blood flow to tumours, starving them and shrinking them.[53] It also decreases the reproduction of cancer cells and may accelerate the process of apoptosis.[54] Li *et al.*[55] revealed that pomegranate peel extract has strong anticancer and anti-metastatic effects on thyroid cancer. The thyroid cancer cell lines BCPAP and TPC-1 were employed to assess the impact of pomegranate peel extract on thyroid cancer. For experiments conducted in a controlled laboratory environment (*in vitro* studies), the cells were exposed to various amounts of PPE (Pomegranate peel extract) at different concentrations: 0 µg/mL, 12.5 µg/mL, 25 µg/mL, 50 µg/mL, 100 µg/mL, and 200 µg/mL. For experiments carried out in living organisms *(in vivo* studies), PPE was mixed with normal saline and administered at doses corresponding to 125 mg per kilogram of body weight and 62.5 mg per kilogram of body weight. Punicalagin and ellagic acid were identified using the optimized high performance liquid chromatography (HPLC). TPC-1 cell line proliferation was inhibited by treatment of 100-200 µg/mL pomegranate peel extract (PPE), and BCPAP proliferation was noticeably decreased by 200 µg/mL PPE. Pomegranate peel extract promoted programmed cell death in thyroid cancer cells. PPE treatment caused nuclear fragmentation, cell shrinkage, and the development of reduced nuclei with bright-blue fluorescence. Furthermore, PPE considerably reduced the expression of matrix metalloproteinase-9 which resulted in reduced motility and invasion of thyroid cancer cells.[56]

Peng *et al*.[57] evaluated the pomegranate extract's ability to inhibit cell growth and its underlying mechanism in the context of human oral cancer cells (Ca9-22, HSC-3, and OC-2). Pomegranate extracts contain ellagitannins such as punicalagin and punicalin, in addition to ellagic acid. Different concentrations (0, 50, and 100 µg/mL) of the extract were used for experiments. Pomegranate polyphenolic extract exhibited antiproliferation, mitochondrial dysfunction, DNA damage, apoptosis, and oxidative stress mechanism against distinct kinds of oral cancer cells. The treatment resulted in the downregulation of the Mito tracker-detected mitochondrial mass. Alterations in mtDNA copy number may regulate apoptosis. Additionally, the treatment raised oxidative stress decreased the amount of mtDNA copies and caused apoptosis in cancer cells. Furthermore, pomegranate extract treatment resulted in mitochondrial fission and caused the oral cancer cells to die by apoptosis since pomegranate extract suppresses mitochondrial biogenesis and mass.

The authors present distinct yet complementary perspectives on the anticancer potential of pomegranate extracts. Li *et al.*[55] focus on thyroid cancer, demonstrating pomegranate peel extract's (PPE) ability to inhibit proliferation, induce apoptosis, and reduce invasion and motility of thyroid cancer cells. In contrast, Peng *et al.*[57] explore a broader range of oral cancer cells, emphasizing mitochondrial dysfunction, oxidative stress, and apoptosis induced by pomegranate polyphenolic extract. While Li *et al.*[55] highlight specific mechanisms within the context of thyroid cancer, Peng *et al*.[57] study provides a comprehensive understanding of the impact on various oral cancer cell types, revealing the potential of pomegranate extracts as a versatile anticancer agent with promising implications for cancer therapy.

Cardio-protective property

Cardiovascular disease (CVD) is a group of illnesses that affect the heart and blood arteries and is the leading cause of death worldwide.[58] The most significant risk factors for CVD include obesity, high blood pressure, elevated serum levels of total cholesterol & low-density lipoprotein cholesterol, and low serum levels of high-density lipoprotein cholesterol[59]. Razani *et al*.[60] investigated pomegranate juice's cardioprotective properties in ischemic heart disease patients. A hundred patients diagnosed with unstable angina or myocardial infarction were divided into test and control groups (50 patients each). During a 5-day hospital stay, the test group was given 220 mL of pomegranate juice daily along with standard treatment. Factors such as heart rate, blood pressure, angina severity, and serum markers (tumour necrosis factor alpha, interleukin 6, malondialdehyde) were observed. Additionally, troponin and high-sensitivity C-reactive protein (hs-CRP) levels were assessed in patients with myocardial infarction. As indicated by HPLC-mass analysis, the primary polyphenols present in the pomegranate juice were found to be ellagic acid, gallic acid, punicalagin, gallagic acid, and punicalin. In patients with unstable angina, pomegranate juice was found to have a protective effect against the occurrence, severity, and duration of angina. Patients with myocardial infarction (MI) who received pomegranate juice treatment saw a significant reduction in serum troponin levels. Pomegranate juice recipients had significantly reduced serum levels of malondialdehyde, indicating that its potent antioxidant properties may be responsible for some of the protective impact against damage brought on by ischemia and reperfusion.

Most clinical cardiovascular events have atherosclerosis as their underlying cause. It is a systematic disease process in which fatty deposits, inflammatory cells, and scar tissue accumulate within the walls of arteries. Pomegranate extract has been proven to be effective in reducing several coronary heart disease (CHD) risk factors, including the physiological and morphological consequences of atherosclerosis in CHD.[61] Manickam *et al.*[62] revealed that Apoe-/- mice fed a Western-style diet were protected from developing advanced atherosclerosis by a standardized hydroethanolic extract of pomegranate peel that is high in polyphenols. Experiment design involved Apoe-/- mice with atherosclerosis, both male and female mice were used at eight weeks of age. The mice were divided into two groups, with five mice per group for each sex. They were given a western diet rich in high fat and high cholesterol. Simultaneously, they were subjected to treatment for a duration of 12 weeks. One group received 200 mg/kg of Pomegranate Peel Extract (PPE) through daily oral administration, while the other group received a water-based solution as a control. Quantification of phenolic compounds revealed the presence of p-Coumaric acid, chlorogenic acid, gallic acid, caffeic acid, punicalagin A, and punicalagin B. of Pomegranate peel extract (PPE) treated mice had considerably lower blood glucose levels and better glucose tolerance than control mice. Furthermore, mice fed PPE showed considerably decreased plasma total cholesterol and triglyceride levels. Plaque necrosis, a crucial factor linked to plaque rupture and clinical signs and symptoms of myocardial infarction and stroke was markedly reduced in the PPE -fed mice. Additionally, PPE-fed mice showed enhanced lesion collagen content, which is linked to improved cardiovascular outcomes and plaque stability. Mice that were administered Pomegranate Peel Extract (PPE) showed a reduction in levels of the inflammatory cytokine TNF (Tumour Necrosis Factor) and an increase in the expression of the anti-inflammatory cytokine IL-10 (Interleukin-10). This indicates that PPE treatment led to a decrease in overall systemic inflammation. Furthermore, PPE-treated mice exhibited a noteworthy enhancement in the effectiveness of lesional efferocytosis, which pertains to the successful removal of apoptotic cells by phagocytosis. This

improvement suggests that PPE improved the macrophages' capability to clear apoptotic cells from atherosclerotic lesions. The heightened efficiency of efferocytosis observed in more advanced atherosclerotic lesions among the PPE-treated mice was linked to PPE's antioxidant properties. In particular, PPE was shown to inhibit the cleavage of Mertk, a critical molecule for efferocytosis, suggesting that the antioxidant attributes of PPE contributed to facilitating proficient macrophage-mediated removal of apoptotic cells.

The studies by Razani et al.[60] and Manickam *et al*.[61] offer distinct but interconnected perspectives on pomegranate's cardioprotective potential in ischemic heart disease. Razani *et al*.[60] focuses on clinical effects, demonstrating pomegranate juice's ability to reduce angina severity and inflammation markers in patients with unstable angina or myocardial infarction. This study underscores the antioxidant properties of pomegranate juice in countering ischemia-reperfusion damage. In contrast, Manickam *et al*.[61] delve into atherosclerosis mechanisms, using Apoe-/- mice models. Their study reveals that pomegranate peel extract rich in polyphenols inhibits advanced atherosclerosis progression, impacting glucose metabolism, lipid profiles, plaque stability, and inflammation. Together, these studies provide insights into pomegranate's potential in alleviating ischemic heart disease by targeting both clinical manifestations and underlying atherosclerosis mechanisms.

Anti-diabetic property

Fruits high in polyphenols and antioxidants, including pomegranates, have been proven to encourage beta cells to release insulin in investigations on animals. The pomegranate's antidiabetic properties have also been examined in a number of human research. Punicic acid, methanolic seed, and pomegranate peel extracts may have a role in the reduction of fasting blood glucose in diabetes individuals after pomegranate juice consumption.[1]

Amri *et al.*[63] investigated the potential effects of prolonged exposure spanning 12 weeks to extracts derived from pomegranate leaves (PL), pomegranate juice (PJ), and pomegranate peel (PP) on male Wistar rats subjected to a diet rich in high-fructose and high-fat content. The primary focus of the research was to evaluate changes in glucose tolerance, insulin sensitivity, oxidative stress markers in the liver, and the activity levels of key enzymes like α-amylase and lipase. The application of pomegranate juice, peel, and leaves yielded significant reductions in fasting plasma glucose and insulin levels. Consequently, the homeostatic index of insulin resistance (HOMA-IR) exhibited substantial declines, with a 50% decrease for juice and leaves extracts and a 39.1% reduction for peel extract, indicating a notable enhancement in insulin sensitivity facilitated by the three pomegranate extracts. Moreover, oral administration of pomegranate juice, peel, and leaves led to noteworthy decreases of 30%, 50%, and 49%, respectively, in α-amylase activity when compared to the group consuming the high fructose-high fat diet (HFD). Furthermore, the consumption of these pomegranate extracts demonstrated the ability to mitigate lipid peroxidation and protein carbonylation. Moreover, the extracts significantly enhanced the levels of hepatic antioxidant enzymes such as Superoxide dismutase (SOD) and glutathione peroxidase (GPx) in the treated groups. The study reveals the antidiabetic potential of pomegranate extracts and links ingestion of pomegranate leaf, juice, and peel extracts to improvements in glucose tolerance, insulin sensitivity, and oxidative stress markers. This study highlights the variety of bioactive chemicals found in pomegranates and how they may affect several aspects of diabetes management.

Anti-microbial property

Punica granatum L. stands out due to its notable antioxidant capability, with its antibacterial effects primarily attributed to tannins.[33] Likewise, the antibacterial potential of pomegranate peel flour juice extracts has shown favourable outcomes against various pathogenic bacteria, encompassing *Pseudomonas aeruginosa, Escherichia coli, listeria monocytogenes, salmonella spp., and staphylococcus aureus*[64]. The antimicrobial effectiveness of pomegranate juice, extracts from the inedible peel using methanol and water, as well as four specific polyphenolic compounds (caffeic acid, quercetin, epigallocatechin-3-gallate, and ellagic acid), was assessed by Dey *et al.*[65] against clinical isolates that display antibiotic resistance. The minimal inhibitory concentration (MIC) of the drinkable juice was 256 > 1024 g/mL, but the MIC of the peel extracts ranged from 64 to 1024 g/mL. While quercetin and epigallocatechin gallate were shown to be the most effective (MIC 64-256 g/mL), caffeic acid and ellagic acid were only moderately efficient (MIC 128-512 g/mL) against the ESBL (extended-spectrum -lactamase) and KPC-type carbapenemase-producing *K. pneumoniae* isolates. Pomegranate fruit pericarp extracts in methanol and water demonstrated stronger antitubercular action (MIC 64-512 and 64-1024 g/mL, respectively) when compared to lyophilized juice (MIC 256 >1024 mg/mL). In a study conducted by Ali *et al.*[66] starch-based films were created using pomegranate peel, which served as a reinforcing and antibacterial agent. Larger inhibitory zones against *S. aureus* than *Salmonella* were seen in starch-based film equipped with pomegranate peel. The phenolic toxicity that interacts with sulfhydryl groups of proteins in microbes may serve as the basis for the pomegranate peel particles' potential mode of action against germs. Chaabna *et al.*[43] unveiled the notable antibacterial potential of n-butanol and ethyl acetate fractions of pomegranate peel, showcasing promising effects against *Staphylococcus aureus*, *Bacillus cereus*, and *Pseudomonas aeruginosa*. In vitro experiments demonstrated that the aqueous-alcoholic extract derived from pomegranate peel effectively hindered the interaction between the SARS-CoV-2 S glycoprotein and ACE2, suggesting its potential in impeding the entry of SARS-CoV-2 into host cells.[67]

Dey *et al.*[65] explore antimicrobial efficacy of pomegranate constituents against antibiotic-resistant clinical isolates. Quercetin and epigallocatechin gallate show effectiveness, while caffeic and ellagic acids demonstrate moderate efficiency. Incorporating pomegranate peel into starch-based films reveals varying inhibitory zones against distinct bacteria. Phenolic interactions with microbial proteins potentially underlie the antibacterial mechanism. Chaabna *et al.*[43] underscore antibacterial potential of pomegranate peel fractions. Additionally, aqueous-alcoholic pomegranate peel extract hinders SARS-CoV-2 entry. These studies collectively underscore pomegranate's versatile antibacterial properties, implying broader applications.

Methods of extraction

Extraction stands as a key method for isolating components from plant-derived materials. Bioactive compounds, which are natural secondary metabolites found in different plant parts like leaves, stems, roots, seeds, flowers, and fruits, are extracted using various methods.[68] The effectiveness of bioactive compound extraction is influenced by factors like the extraction technique, source materials, and the solvent employed. These techniques can be categorized into either conventional or non-conventional methods. Conventional approaches typically involve organic solvents, temperature control, and mechanical agitation.[69] In recent times, there has been a growing emphasis on green technology, promoting the use of environmentally friendly methods for processing ingredients. Novel and environmentally conscious extraction techniques, such as microwave-assisted extraction (MAE) and ultrasound-assisted extraction (UAE), have emerged as alternatives. These techniques offer notable benefits, including rapid extraction, minimal solvent usage, utilization of environmentally friendly solvents, improved compound recovery rates, and enhanced selectivity.[70]

Maceration

Maceration is a process where crushed plant materials are soaked in a solvent while being regularly stirred over an extended period, often at room temperature.[71] Maceration is particularly useful for extracting bioactive compounds from discarded plant material thanks to its ability to handle compounds sensitive to heat[72]. Ranjha *et al.*[73] conducted a research study aiming to compare the efficiency of maceration and ultrasound-assisted extraction (UAE) methods in extracting polyphenols from apple and pomegranate peels. The goal was to determine the polyphenol content and antioxidant activity of the extracts and utilize them in creating nutritious date bars. Three distinct solvents, namely acetone, methanol, and ethanol, were

employed at two varying concentrations (50% and 75%) in the experimental process. Regarding pomegranate peel, the greatest yield was observed using methanol at 50% concentration (31.45%) in the ultrasound-assisted extraction (UAE) method. The findings from this study suggest that the sonication technique results in a higher quantity of polyphenols extracted compared to the maceration technique. While maceration proves suitable for extracting heat-sensitive components, its primary disadvantages include being time-intensive, energy-demanding, and exhibiting low extraction efficiency.[71]

Solvent extraction

The availability of polyphenols greatly depends on the extraction technique employed. The conventional approach for obtaining pomegranate peel extracts involves solvent extraction. However, conventional methods are typically characterized by slow processing and substantial solvent usage.[74] Magangana *et al.*[75] undertook an investigation aimed at identifying the most effective processing regimen for pomegranate peel residues. The study encompassed a systematic examination of distinct solvents (ethanol, methanol, and acetone) utilized at varying concentrations (50%, 70%, and 100%). It was observed that ethanol exhibited the highest efficacy in phytochemical extraction and antioxidant capacity, followed by methanol, with acetone yielding the least favourable results. Likewise, regarding concentrations, the sequence of superior yields was found to be 70%, succeeded by 50%, and finally, 100% concentration. Interestingly, the undiluted (100%) solvents exhibited relatively modest extraction capabilities, whereas blending pure solvents with water to attain concentrations of 70% and 50% respectively led to notable increments in phytochemical yields and antioxidant activity. This amplified extraction efficiency of aqueous solvents suggests that amalgamating less polar solvents with water might augment the solvent's polarity index, thereby enhancing the solubility and extraction potential of a specific solvent.

Campos *et al.*[76] conducted a study on extracting bioactive elements from pomegranate by-products, peels, and seeds, sourced from Acco, Big Full, and Wonderful cultivars in Portugal. They investigated the impact of various ethanol concentrations in hydroalcoholic extraction solvents (ethanol/water blends) on extraction yields (EY), total phenolic compounds (TPC), total flavonoids (TF), and antioxidant activity (AA) in both peel and seed extracts. Four ethanol/water mixtures (0%, 25%, 50%, and 75% EtOH, v/v) were used to extract bioactive compounds from the powders. Pomegranate peels exhibited the highest extraction yield and notably higher TPC and TF quantities compared to seed extracts. The extraction solvent with a 50% EtOH concentration yielded the most favourable outcomes overall, showing the highest average extraction yield (45%), TPC content (0.34 mg GAE/mg), TF content (0.026 mg CATE/mg), and the most potent antioxidant activity (lowest IC50 of 0.12 mg/mL).

Overall, these results shed light on the influence of solvent composition on bioactive compound extraction and emphasize the significance of solvent selection in optimizing the extraction of valuable phytochemicals from plant materials. Further studies could delve into the specific types of bioactive compounds extracted and their potential bioavailability and health implications.

Soxhlet extraction

The Soxhlet extraction method combines the advantages of reflux extraction and percolation. It utilizes reflux principles to continuously extract plant material with fresh solvent, resembling a syphoning process.[77] Kaur *et al.*[78] prepared different pomegranate peel extracts using the Soxhlet extraction method, utilizing solvents such as hexane, dichloromethane, ethyl acetate, and methanol to assess the antioxidant and antimicrobial potential of pomegranate peel. Powdered peels were successively extracted with solvents of increasing polarity (hexane, dichloromethane, ethyl-acetate, methanol). Extracts were filtered, re-extracted, and concentrated via rotary evaporation. Maximum yield was from methanol (37.8%), and the minimum from hexane (2.1%). Antimicrobial activities against *Pseudomonas aeruginosa* were assessed using MIC values. Methanol extract exhibited highest activity, followed by 5-hydroxymethylfurfural, dichloromethane, furan-2,5-dicarbaldehyde, ethyl-acetate, 5-chloromethylfurfural, and hexane extracts. These results reveal a correlation between solvent polarity and yield, as well as antimicrobial potential. Methanol extract and its derivatives displayed the most potent antimicrobial activity. This study underscores the significance of solvent choice in extraction and underscores the potential of pomegranate peel extracts for antimicrobial applications.

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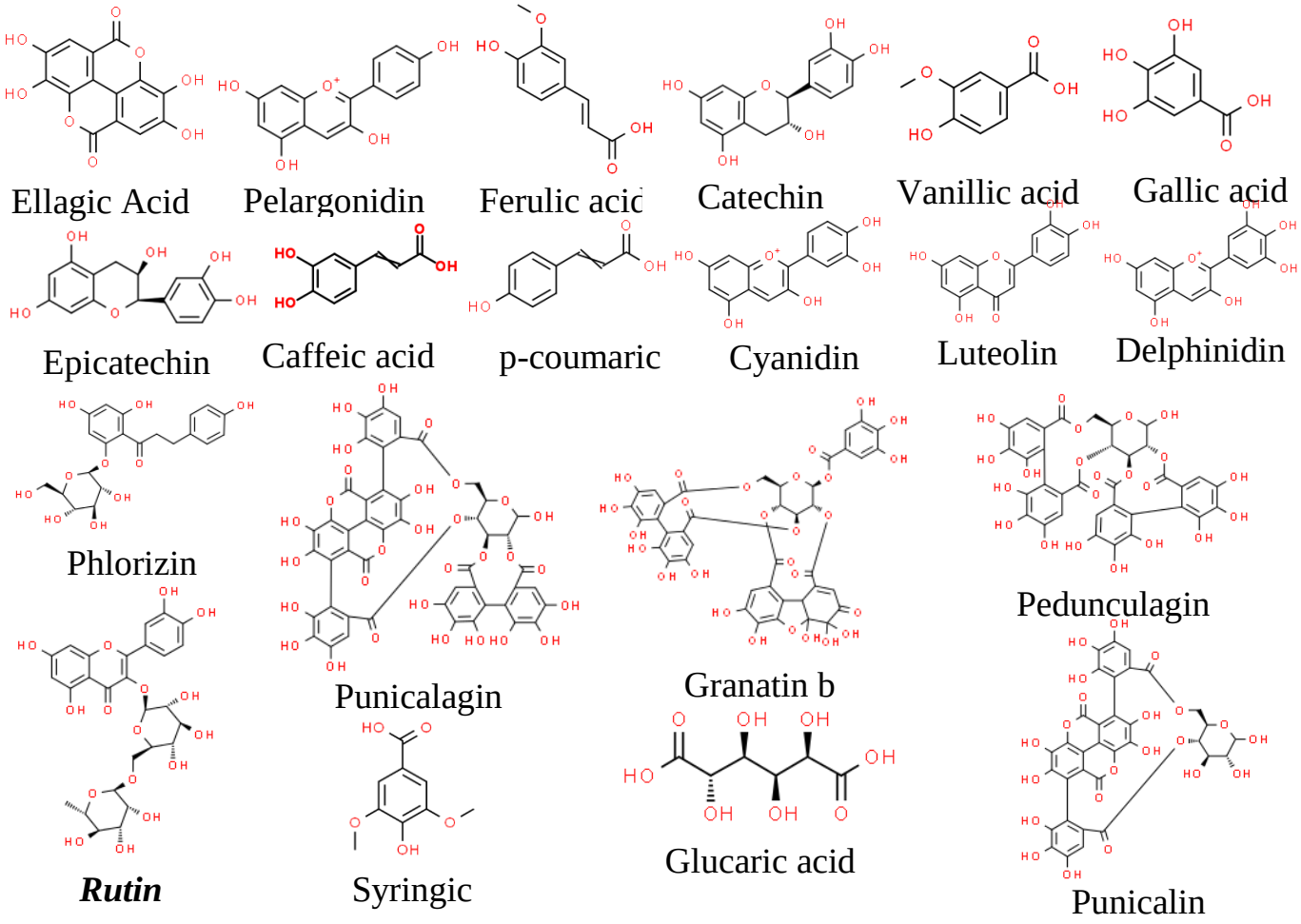

Figure 2: Major phytochemicals found in pomegranate (Punica granatum L.)

A key benefit of this extraction method is its ability to maintain continuous contact between the sample and fresh solvent through repetitive cycles. This prevents solvent saturation, facilitates analyte removal, and keeps the system temperature close to the solvent's boiling point. However, drawbacks include lengthy extraction times, the need for substantial solvent volume, and other limitations.[79]

Ultrasound-assisted extraction (UAE)

Ultrasound-assisted extraction (UAE) stands out as an exceptionally efficient method for retrieving polyphenols from a variety of sources such as fruits, vegetables, herbs, and spices. It serves as a prominent technology built upon the principle of utilizing ultrasonic cavitation to disintegrate plant materials. This technique is lauded for its simplicity, high efficacy, and cost-effectiveness.[80] Ultrasonic baths, while being economically advantageous and user-friendly, suffer from limited reproducibility, thereby constraining their applicability in extraction procedures. On the other hand, ultrasonic probes consist of a horn or probe connected to a transducer. When immersed in the extraction medium, the probe delivers ultrasound with minimal energy loss, enhancing its efficiency.[81]

Rajha *et al.*[82] investigated how ultrasound influences the kinetics of polyphenol extraction from pomegranate peels and seeds. The study aimed to optimize the process of aqueous extraction of polyphenols from these plant parts using ultrasound assistance. The extraction of polyphenols from both pomegranate peels and seeds was carried out at a temperature of 50°C within a thermal bath. The study compared extractions conducted with or without an ultrasonic pre-treatment, employing different pre-treatment durations. The results indicated that ultrasound pre-treatment significantly improved the recovery of phenolic compounds from both pomegranate seeds and peels when compared to traditional extraction methods. The use of ultrasound pre-treatment led to an increase in the quantity of extracted molecules from both peels and seeds, while maintaining their compositional diversity. Upon analysis, it was determined that the optimal duration for ultrasound pre-treatment was 10 minutes. This duration exhibited superior enhancement in polyphenol extraction in comparison to a 5-minute treatment, and it yielded similar results to a 20-minute treatment. This insight advances green and efficient extraction techniques, holding promise for various applications in nutraceuticals, food, and pharmaceutical industries.

Microwave-assisted extraction (MAE)

Microwaves are a type of electromagnetic radiation characterized by their higher frequency, occupying the region between radiofrequency and far infrared wavelengths in the electromagnetic spectrum. This corresponds to a frequency span ranging from 0.3 to 300 GHz and wavelengths spanning from 1 mm to 1 cm. Within the context of this extraction technique, the process involves the utilization of potent microwaves in conjunction with solvents to extract plant metabolites[83]. Kaderides *et al.*[84] conducted a study to establish an effective environmentally friendly technique for extracting phenolics from pomegranate peels. The research involved optimizing operational parameters and examining the mechanism underlying the improved extraction process through the observation of plant material cell disruption. Thirteen experimental runs were conducted, each utilizing five different solvents: water, 50% and 70% aqueous ethanol, and 50% and 70% aqueous methanol. The optimal conditions identified were the solvent type being 50% aqueous ethanol, a solvent-to-solid ratio of 60/1 mL/g, and a power level of 600 W. Comparative analysis was

performed between the proposed microwave extraction protocol and ultrasound-assisted extraction, another ecologically conscious extraction method previously studied by the researchers. The microwave method produced around 1.7 times the amount of product within a notably briefer processing duration of 4 minutes, in contrast to the ultrasound-assisted extraction procedure, which took 10 minutes. The discrepancies in yield and processing time were attributed to the significant cell damage observed in the plant material subjected to microwave treatment, as confirmed through SEM analysis. While UAE has shown efficacy, the prolonged exposure to lower-energy cavitation may account for the observed differences in extraction efficiency and time. These findings emphasize the potential of MAE for yielding enhanced bioactive compound extraction in a more time-efficient manner.

Utilization and applications

Pomegranate has been extensively used in the formulation of several value-added products owing to its nutrient as well as phytochemical characteristics. The incorporation of different parts of pomegranate either in the form of powder or extract serves as an enhancer of rheological, nutritional, sensorial, storage, microbial, and antioxidant attributes. Utilization of Pomegranate components in various formulations, including yogurt, cheese, pork sausages, meatballs, beef burgers, cupcakes, wheat bread, gluten-free bread, and other products (as shown in Table 4), has been the objective of diverse experiments and research.

Dairy products

Abd El Moneem *et al.*[85] examined the impact of incorporating pomegranate pomace powder (PPP) into low-fat probiotic yogurt as a supplement, with a focus on evaluating its rheological, microbiological, and sensory properties. A partition was made of low-fat buffalo milk, which contained 1% fat, into three equal portions. The first portion free from additive was designated as the control group (C1), while the remaining two segments were subjected to the addition of pomegranate pomace powder (PPP) at varying concentrations of 1% and 2%, respectively. The yogurt samples containing probiotics were subjected to storage at a temperature of 5 ± 1 ˚C. The samples were analysed at different time intervals, including immediately after preparation and after 5, 10, and 15 days of storage. By adding pomegranate pomace powder to low-fat yogurt, the viability of the probiotic starter culture saw an increase. The chemical composition of the final product underwent significant changes due to the fortification of reduced-fat milk for probiotic yogurt production. The observed changes encompassed increased amounts of protein, total solids, dietary fiber, phenolic compounds, ash, viscosity, and pH. The extent of these improvements was directly proportional to the supplementation ratio employed. Pomegranate pomace powder (PPP) added to low-fat yogurt enhanced its organoleptic properties and this enhancement was proportional to the supplementation ratio; low-fat yogurt enriched with 2% PPP received the highest score.

Ali[86] examined the impact of raw pomegranate juice as phytochemically rich components in comparison to more often utilized fruits like strawberries and mango on the properties of yogurt drinks. Four yogurt drink formulations were created by adding crude pomegranate juice at rates of 0, 10, 15, and 20%. Pomegranate juice was added to the yogurt beverage, which resulted in a rise in the amounts of ash, fat, protein, and total carbohydrates while a decrease in viscosity and pH. The 15% pomegranate juice treatment performed better than the control in terms of organoleptic properties. The findings made it clear that the overall bacterial counts in all yogurt drinks that contained pomegranate juice dropped in direct proportion to an increase in pomegranate juice. The decline in overall bacterial populations could potentially be attributed to the abundant phytochemical content present in *Punica granatum.* Additionally, all yogurt beverages were found to be free of coliform bacteria, mold, and yeast.

El-Shafei *et al.*[87] studied the effects of varying pomegranate peel extract concentrations as natural antioxidants on the physicochemical, oxidative stability, microbial, antioxidant activity, and sensory characteristics of goat's cream cheese. Shelf-life analysis was performed at 4±1 ℃ over 45 days. Cream cheese was produced from goat's milk, supplemented with varied amounts of pomegranate peel extracts (PPE) (0.5%, 1%, and 2%). The addition of increased PPE content led to noteworthy increases in moisture, protein, and acidity within the experimental cheese. Conversely, higher PPE content resulted in significant reductions in fat, salt, and pH values across all experimental cheeses. Notably, cheese with 2% PPE exhibited elevated values in terms of radical scavenging activity, total phenolic content, and total flavonoid content. The results revealed that overall bacterial counts significantly increased in the control group after storage but counts decreased in the other treatments as extract concentration increased. The proteolytic and lipolytic bacterial counts of the (cream cheese containing 2% PPE) had the lowest total bacterial counts when compared to the control samples. These counts grew throughout the first 30 days of storage and subsequently declined at the finish of the 45 days. The lack of yeast and mold counts within the initial 15-day storage period could potentially be attributed to the fungicidal properties inherent in pomegranate peel extracts.

Meat products

Gutiérrez-Pacheco *et al.*[88] assessed the impact of incorporating pomegranate juice (PJ) and pomegranate peel (PP) powders on the physical, chemical, sensory, and antioxidant attributes of pork sausage was investigated. The study encompassed five treatment groups: control (without PJ or PP), PJ1 (1% PJ), PJ2 (2% PJ), PP1 (1% PP), and PP2 (2% PP). The addition of 1% and 2% PJ led to an increase in sausage hardness, while the addition of 2% PP resulted in reduced hardness. Notably, both PJ and PP additions elevated the total phenolic content (TPC) compared to the control.

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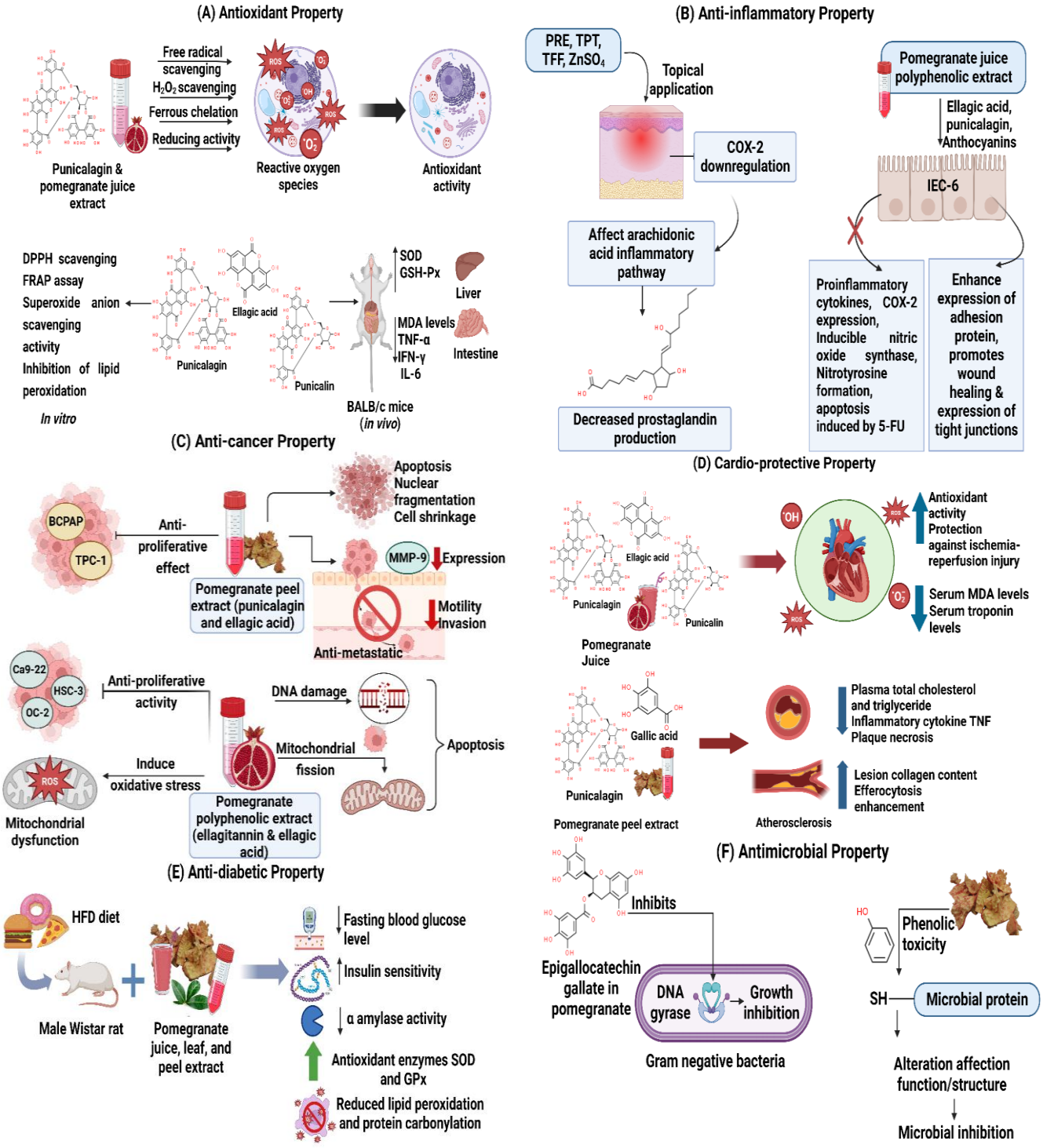

Figure 3 : Pharmacological properties of different parts of Punica granatum L.

Among the treatments, PP2 exhibited the highest TPC and antioxidant levels. The chromatograms identified gallic acid, punicalagins (α and β isomers), and ellagic acid as the phenolic compounds present in pork sausage with 1% and 2% PP. PP exhibited greater antioxidant activity than PJ across all evaluated procedures. Its increased phenolic content is thought to be the cause of this discrepancy.

Jahan *et al.*[89] conducted a study where pomegranate extract was added and its effects on sensory, proximate, physicochemical, biochemical, and microbiological analysis were examined. The study's outcomes were employed to suggest the incorporation of pomegranate extract to enhance beef meatballs and to evaluate its natural antioxidant effectiveness alongside a synthetic antioxidant (BHA) in preventing lipid oxidation during refrigeration. Control, BHA, 0.1, 0.2, and 0.3% pomegranate extract treated samples were the five treatment groups. 0.3% of the pomegranate extracts group outperformed the control and synthetic antioxidant groups in terms of color, taste, tenderness, juiciness, and overall acceptability. Each of the treatments considerably enhanced the crude protein content of the meat. Both in beef meatballs treated with BHA and pomegranate extract, the pH of the beef meatballs dramatically rose when they were raw and cooked. Among these concentrations, the utilization of 0.3% pomegranate extract exhibited optimal pH levels for both raw and cooked samples throughout the 60-day storage period. Notably, in the group treated with beta hydroxyl anisole as well as in the pomegranate extract

group, all biochemical parameters including free fatty acids (FFA), peroxide value (PV), and thiobarbituric acid reactive substances (TBARS) experienced significant reductions. Beef meatballs in the BHA and pomegranate extracts group had considerably lower total counts of viable, coliforms, and yeast mold. Considering the analytical techniques (sensory assessment, nutritional value assessment, physical and chemical characteristics, analysis of biological molecules and microorganisms) used, 0.3% pomegranate extract is suggested for a formulation of beef meatballs with added value that was infused with natural antioxidants.

Shahamirian *et al.*[90] investigated how adding pomegranate juice (PJ) and pomegranate rind powder extract (PRPE) to beef burgers affected their physicochemical and sensory qualities, oxidation stability, and bacterial growth over the course of 90 days in storage. Three sets of samples were developed, each of which included 100 ppm of either PJ, PRPE, or BHT. Up to the 45th day, the pH values of the control and BHT-containing burgers remained consistent. Whereas the pH dropped in the burgers containing PJ and PRPE after 60 days. The production of peroxide was decreased as a result of the addition of PJ, PRPE, and the synthetic antioxidant BHT. Due to their antioxidant properties, the integration of PJ and PRPE into the formulation of the burger reduced lipid oxidation in comparison to the control. The number of aerobic bacteria increased during storage. The highest microbiological count corresponded with control burgers, followed by BHT-containing burgers. At the completion of the storage period, burgers made with pomegranate rind powder extract had the fewest aerobic microorganisms. On the first day of storage, all burgers received close scores, but the color of burgers with PJ received the highest scores. Burgers with PRPE had the greatest ratings for color, flavor, odor, texture, and overall acceptability after 90 days.

Bakery products

Bourekoua *et al.*[91] examined the impact of pomegranate seed powder (PSP) inclusion on gluten-free bread's physical, sensory, and antioxidant qualities. The ratios of rice/field bean semolina and pomegranate seed powder used to make the slices of bread were 100/0, 97.5/2.5, 95/5, 92.5/7.5, and 90/10 w/w. Following the inclusion of PSP, the specific volume of gluten-free loaves increased dramatically from 0% to 10%. When PSP was added to bread, it became less hard and chewy than control bread. PSP substantially improved the springiness of the crumb. PSP raised TPC in obtained bread by 2.8 times by adding 10% PSP in comparison to control bread. In comparison to the control bread, gluten-free loaves containing PSP had greater DPPH and ABTS activity levels. The maximal activity for DPPH was discovered in bread containing 10% PSP, whereas the maximum activity for ABTS was discovered in bread with 7.5% PSP addition. The range from 5% to 10% of PSP addition yielded the greatest texture assessment results, while control bread had the lowest values. The inclusion of 5% PSP led to a higher overall evaluation.

Gül and Şen,[92] studied pomegranate seed flour (PSF) for its potential use as a functional ingredient in wheat bread. The research focused on pomegranate seed flour's effects on the physical, textural, and sensory qualities of bread than on their nutritional value. PSF mixes at levels of 0%, 5%, 7.5%, and 10% were created by substituting wheat flour. When PSF was added, stability was increased, especially when PSF was added at a 10% level. As the PSF substitution rose the resistance to extension increased while the extensibility of the dough dropped. It was determined how the addition of PSF affected the dough's ability to resist stretching (pressure, P), extensibility, and deformation energy, W). PSF substitution raised P in comparison to controls, but there was no discernible difference in PSF-added dough pressures. Bread's volume, width, height, and brightness all decreased with the addition of PSF substitution, while the nutritional fiber content, a and b values, and textural qualities like hardness and chewiness increased.

Ayoubi *et al.*[93] examined the usage of various pomegranate seed powder (PSP) concentrations as a functional component in cupcake recipes and found out how they affect the product's physicochemical, microbiological, and sensory qualities. Various concentrations (2.5%, 5%, 7.5%, and 10%) of pomegranate seed powder (PSP) were incorporated into the cupcake recipe. The incremental addition of PSP led to significant increases in fiber, protein, and fat content within the cake. Elevated PSP quantities correlated with higher moisture content in the cake samples, likely due to water absorption facilitated by fiber-rich components. Remarkable rises in total phenolic content were observed with increasing PSP levels in the cake batter. While higher PSP content resulted in reduced specific cake volumes, these alterations weren't statistically significant. The incorporation of PSP substantially increased cake hardness. Throughout the storage duration, no viable counts were detected in the cake samples. Up to 7.5% PSP enrichment of cupcakes did not significantly alter the cakes' overall acceptability in terms of crust color, crumb color, texture, or mouthfeel.

Other products (edible films/coatings)

Kumar *et al.*[94] investigated how the incorporation of pomegranate peel extract, serving as a natural antibacterial and antioxidant agent, affected the chemical, thermal, mechanical, physical, and biological characteristics of chitosan-based edible films. Pomegranate peel powder was employed to produce chitosan-based edible films enriched with varying concentrations of pomegranate peel extract (0.2 g/mL, 0.4 g/mL, 0.6 g/mL, 0.8 g/mL, and 1.0 g/mL). The introduction of pomegranate peel extract led to an increase in the thickness of the edible films (0.142-0.159 mm) due to intermolecular interactions among functional groups. As the concentration of pomegranate peel extract within the matrix increased, the moisture content of the chitosan-based films also elevated; notably, the F5 film samples exhibited the highest moisture content (15.28±0.45%). Concurrently, the addition of pomegranate peel extract led to enhanced opacity in the film samples (0.039-0.061%). The water vapor permeability of the edible films supplemented with pomegranate peel extract ranged from 1.38±0.47 to 1.60±0.51 g.mm/m². The inclusion of pomegranate peel extract, which encompasses phenolic constituents, led to a slight enhancement in the water vapor permeability of chitosan-based films when compared to the control film. The tensile strength of chitosan films enriched with pomegranate peel extract exhibited a range of 32.45±0.98 to 35.23±0.61 MPa. The incremental rise in pomegranate peel concentration corresponded to a modest increase in mechanical strength. This phenomenon is likely attributed to the expansion of free volume, flexibility, and molecular mobility within the chitosan matrix chains. The phenolic potential of the chitosan-based edible film exhibited a significant elevation with the augmentation of pomegranate peel extract content, ranging from 5.75 to 32.41 mg/g. The antioxidant efficacy of chitosan films displayed a positive correlation with the increment of pomegranate peel extract. Notably, the chitosan film enriched with a concentrated pomegranate peel extract of 1.0 g/mL showcased optimal antioxidant capability (76.54%±0.34%). Conversely, heightened incorporation of pomegranate peel extracts led to marked reductions in film transparency, solubility, swelling, and color intensity.

Kumar *et al.*[95] conducted study aimed at assessing the influence of a chitosan-pullulan (50:50) composite edible coating enriched with pomegranate peel extract on the postharvest physicochemical attributes of Safeda mangoes throughout an 18-day storage period at both room temperature (23 °C, RH-45%) and cold storage (4 °C, RH-95%). The composite coating, created using pomegranate peel extract (0.02 g/mL), was designed as an active antioxidant. Notably, the incorporation of the chitosan-pullulan composite edible coating with pomegranate peel extract led to a significant reduction in mango fruit mass loss at both room temperature and cold storage conditions (4 ℃) when compared to the control group Mangoes subjected to the control condition could be stored at room temperature for 9 days, albeit with unsatisfactory Total Soluble Solids (TSS) content (11.52±0.08 ºBx). However, the application of the composite coating led to improved fruit condition and reduced TSS levels (10.24±0.15 ºBx). During 18 days of cold storage, mangoes treated with the edible coating exhibited a TSS value of 10.93±0.08 degrees Brix, significantly lower than the control (11.54±0.04 ºBx). The chitosan-pullulan composite edible coating enriched with pomegranate peel extract led to notably lower titratable acidity at both room and cold temperatures (4℃) compared to the control. This composite coating effectively mitigated firmness loss in mangoes during storage at room temperature and 4℃, possibly due to reduced water and gas transpiration. Additionally, coated

mangoes demonstrated significantly reduced phenolic content loss during both room temperature and cold storage conditions. The mangoes kept in regulated storage at room temperature saw the greatest and most noticeable decrease in phenolic content. In comparison to other fruits, the coated mango fruit demonstrated a statistically significant and minimal loss of flavonoid components during cold storage. When compared to a control, the edible coating applied prevented the antioxidant content from degrading during storage at ambient temperature and cold storage temperatures.

Table 4: Utilization and application of pomegranate and its derivatives

Product	Derivative	Outcomes/Results	Reference
Dairy Products			
Low-fat probiotic yogurt	Pomegranate pomace powder	↑total solids, ↑ash, ↑proteins, ↑phenolic, ↑dietary fiber, ↑pH, ↑viscosity, ↑the viability of probiotic culture, ↑organoleptic properties	[85]
Yogurt drinks	Raw pomegranate juice	↑ash, ↑fat, ↑protein, ↑total carbohydrates, ↓viscosity, ↓pH, ↓total bacterial counts	[86]
Goat's cream cheese	Pomegranate peel extract (PPE)	↑moisture, ↑protein, ↑acidity, ↓fat, ↓salt, ↓pH, 2% PPE cream cheese (↑DPPH, ↑TPC, ↑TFC), ↓yeast/mold counts, ↓lipolytic bacteria, ↓proteolytic bacteria, ↓total bacterial count.	[87]
Meat products			
Pork sausage	Pomegranate juice (PJ) and pomegranate peel (PP) powder	↓hardness (PP 2%), ↑hardness (PJ 1% & 2%), ↑TPC (PJ & PP), ↑antioxidant activity (PP)	[88]
Beef meatballs	Pomegranate extract	↑crude protein, ↑raw and cooked pH, ↓free fatty acids, ↓peroxide value, ↓TBARS, ↓total viable count, ↓total coliform count, ↓total yeast/mold count	[89]
Beef burgers	Pomegranate juice (PJ) and pomegranate rind powder extract (PRPE)	↓pH (PJ & PRPE incorporated burgers after 60 days), ↓peroxide production, ↓lipid oxidation	[90]
Bakery products			
Gluten-free bread	Pomegranate seed powder	↑specific volume, ↑springiness, ↓hardness, ↓chewiness, ↑Total phenolic content, ↑DPPH, ↑ABTS	[91]
Wheat bread	Pomegranate seed flour	↑stability, ↑resistance to extension, ↑ability to resist stretching, ↑nutritional fiber, ↑hardness, ↑ chewiness, ↓extensibility, ↓volume, ↓width, ↓height, ↓brightness	[92]
Cupcake	Pomegranate seed powder	↑protein, ↑fat, ↑fiber, ↑moisture, ↑total phenolic content, ↓ ↓lightness & yellowness of crust and crumb, specific volume.	[93]
Other products (Edible films/coatings)			
Chitosan-based edible films	Pomegranate peel extract	↑thickness, ↑moisture, ↑opacity, ↑water vapor permeability, ↑tensile strength, ↑phenolic content, ↑antioxidant activity, ↓solubility, ↓swelling, ↓color, ↓transparency	[94]
Chitosan-pullulan composite edible coating (effect on postharvest physicochemical properties of Safeda mango)	Pomegranate peel extract	↓physiological loss in weight. Maintained the TSS value and acidity, ↓loss in firmness, ↓phenolic content loss, ↓flavonoid content loss, ↓antioxidant degradation	[95]

Note: DPPH: 2,2 diphenyl-1-picrylhydrazyl; ABTS: 2,2-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid; TPC: total phenolic compounds; TFC: total flavonoid content; TBARS: thiobarbituric acid reactive substances; TSS: total soluble solids.

Conclusion and Future Perspectives

The prevalence of lifestyle-related diseases has increased the consumer's acceptance of nutrient-rich and therapeutic food as a preventive measure against these ailments. Pomegranate has been classified as a 'super fruit' due to its numerous health-promoting benefits. Pomegranate use in traditional medicine is a testament to its pharmacological attributes. Pharmacological studies have revealed pomegranate's significant effects as an antioxidant, anti-diabetic, anti-microbial, anticancer, anti-inflammatory, and cardio-protective agent. Bioactive compounds present in both edible as well as non-edible parts of pomegranate are accountable for its health benefits. Each bioactive component possesses its distinct mechanism of action. The occurrence of these bioactive compounds in pomegranate has encouraged its utilization and application in the formulation of various value-added products.

Looking ahead, there is a promising outlook for harnessing the potential of pomegranates and their bioactive constituents across diverse sectors. Pomegranate extracts have the potential to be integrated into functional foods, beverages, and supplements, tailored to cater to specific health needs as the focus on health and wellness gains momentum among consumers. This trend is projected to drive further exploration into the intricate mechanisms underpinning the health-promoting properties of various pomegranate elements, potentially leading to the development of targeted interventions for a spectrum of health conditions. Pomegranate's antimicrobial attributes, attributed to compounds like punicalagins and ellagic acid, extend beyond nutritional value, offering avenues for natural food preservation solutions. As the demand for transparent labeling and sustainable ingredients gains traction, pomegranate extracts may emerge as viable replacements for synthetic preservatives, extending shelf life while adhering to eco-conscious practices. The versatility of pomegranate's bioactive compounds can extend into pioneering domains, with nanoencapsulation and nano delivery systems holding potential for enhancing compound availability and controlled release, spanning both food and pharmaceutical arenas. Moreover, synergistic interactions between pomegranate and other natural constituents or pharmaceutical agents could foster innovative combination therapies, introducing novel approaches to address diverse ailments. Positioned at the nexus of health, food innovation, and sustainability, pomegranate is poised to play a pivotal role, offering a canvas of possibilities spanning from personalized nutrition to environmentally conscious food production. As research progresses and collaborations flourish, the comprehensive spectrum of pomegranate's potential is poised to be unlocked, enriching human well-being, and advancing the broader food industry.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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