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The Neuroprotective Effect of a Waste Byproduct Obtained From Pomegranate (*Punica granatum*)

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ABSTRACT

Pomegranate is an exceptional fruit that can have several beneficial effects on human health. The peel of pomegranate, a waste product, should be recovered as it still contains valuable constituents, including phenolic compounds, minerals and fibre. The recovery of bioactive compounds occurs through eco-sustainable extraction techniques that reduce costs and promote environmental sustainability and public health. Neurodegeneration is a pathological process causing progressive neuronal damage, potentially leading to cell death. Currently, no drug is known to cure neurodegenerative diseases definitively. A balanced diet rich in fruits and vegetables is associated with a lower risk of certain neurodegenerative conditions. The phytochemicals of plants and their beneficial bioactive compounds demonstrate promising therapeutic potential for human neurological diseases, exhibiting antioxidant and anti-inflammatory properties in the brain. This review aims to highlight the currently existing knowledge on the effects of pomegranate peel against neurodegenerative diseases and their mechanisms of action. The manuscript is intended for those who explore strategies for recovering waste materials and for those who investigate the effects of natural products on neurodegeneration. Prospects could include clinical trials in which pomegranate peel is used in the management of human neurodegenerative diseases.

1 | Introduction

The pomegranate (*Punica granatum*, L.) is a member of the *Lythraceae* family (formerly *Punicaceae*) (Ge et al. 2021), belonging to the genus Punica. It originated in the Himalayas of Northern India; since then, it has been widely cultivated across Central Asian countries and throughout the Mediterranean region (Faria and Calhau 2011). In various cultures, the pomegranate symbolises themes like life, immortality, well-being, femininity and fertility (Karimi et al. 2017). Originally, pomegranate was used as an anti-parasitic, anti-helminthic and vermifuge (Eddebbagh et al. 2016), to treat ulcers, dysentery and diarrhoea (Abid et al. 2018). As knowledge about pomegranate spread, people began to use it for a range of health issues, including oral diseases, peptic ulcers, diabetes, hyperlipidemia, hypertension and certain types of cancer, thanks to its anti-inflammatory, antioxidant, antibacterial and antiviral properties (Moga et al. 2021).

The benefits of pomegranate stem from its diverse components, including polyphenols, amino acids, minerals, vitamins, fibre, flavonoids, unsaturated fatty acids, anthocyanins, alkaloids,

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steroids, phenylpropanoids, terpenes, organic acids, sterols and others (Sharma and Maity 2010). However, it should be emphasised that the exact composition of the pomegranate depends on several factors, including cultivar, ripening stage, climate, cultivation techniques, soil characteristics, processing and storage conditions (Kandylis and Kokkinomagoulos 2020). The rich composition of pomegranate is the basis of many beneficial activities that improve human health, including antioxidant, anti-inflammatory, anticancer, antiviral and antibacterial properties (Šavikin et al. 2018). Furthermore, more recently, the protective effects of pomegranate against metabolic diseases (diabetes, hypertension and hyperlipidemia), cardiovascular disorders and neurodegeneration have also been positively evaluated (Cordiano et al. 2024). Pomegranates are considered functional foods, with edible portions (50%) and juice yields between 36% and 63%, depending on location and season (Khwairakpam et al. 2018). The edible part of the pomegranate fruit is made up of 40% internal grains (aryllis) and 10% seeds. The other 50% of the total weight of the fruit corresponds to the inedible portion, including the peel, the hardest external part and the internal white part, which surrounds the grains (Melgarejo et al. 2021). The peel is rich in nutrients, including phenolic compounds (flavonoids, ellagitannins and proanthocyanidins), minerals (such as potassium, calcium, phosphorus, sodium and magnesium) and fibre (Man et al. 2022). The plant kingdom is the primary producer of waste, including parts of the plant that are not utilised, such as leaves, peels, deteriorated roots, membranes that separate portions of the fruit, processing residues and seeds (Tomar et al. 2023). In reality, what is commonly considered plant 'waste' could be recovered and would contribute to a more sustainable economy: plant waste is rich in substances and can be reused to produce compost, making the soil more fertile, biopesticides, biogas for thermal and electrical energy, biomethane for transport and packaging materials (Castro-Muñoz et al. 2022). Finally, waste can also provide agri-food by-products, responsible for the synthesis of nutraceuticals, supplements, functional foods and cosmetics (Fraga-Corral et al. 2021; Zhou et al. 2023). The recovery of bioactive compounds occurs through eco-sustainable extraction techniques that reduce costs and promote environmental sustainability and public health. These bioactive compound recovery mechanisms reflect the circular economy production model, which aims to extend the life cycle of products and resources while minimising waste generation through the reuse, reconditioning and recycling of existing materials (Tanveer et al. 2022).

Neurodegeneration is a pathological process causing progressive neuronal damage, potentially leading to cell death. Neurodegenerative diseases share a common feature: neurodegeneration, leading to functional, cognitive and motor impairments (Querfurth and Lee 2021). There are many causes responsible for neurodegeneration; among these, it is worth mentioning:

- Buildup of abnormal proteins: in some pathologies, such as Alzheimer's disease, the misfolded proteins accumulate and damage neurons (Hetz and Saxena 2017).
- Unstable molecules, called free radicals, have short lifespans and cause damage (MohanKumar et al. 2023).
- Neuroinflammation, a chronic brain inflammatory process involving the immune system, may cause neurodegeneration and poses a serious risk (Patani et al. 2023).
- Mitochondrial dysfunction, from morphological or functional damage, compromises their activity and can lead to neurodegeneration (Klemmensen et al. 2024).
- Acute and chronic brain injury resulting from a traumatic insult (Brett et al. 2022).
- Lysosomal system alteration (autophagy) (Somogyi et al. 2023).
- Gene mutations causing neuronal dysfunction underlie some neurodegenerative diseases (Verheijen et al. 2018).

Currently, no drug is known to cure neurodegenerative diseases definitively. Some lifestyles may help reduce your chances of developing these diseases (Breijyeh and Karaman 2020); for example, a balanced diet is associated with a lower risk of some neurodegenerative conditions. A diet focusing on fruits, vegetables, monounsaturated fats, fish, whole grains, legumes, nuts, moderate alcohol intake and limited red meat, dairy, saturated fats and refined cereals may help protect the brain (Gardener and Caunca 2018). These foods are characteristic of a Mediterranean diet and may help combat neurodegenerative diseases (Więckowska-Gacek et al. 2021). Phytochemicals, the bioactive compounds found in plants, exhibit promising therapeutic potential for various human diseases by potentially preventing or treating different pathological aspects (Fierascu et al. 2020). These substances often exhibit antioxidant and anti-inflammatory effects in the brain, activating protective mechanisms (Limanaqi et al. 2020; Abdolmaleky and Zhou 2023). Plants contain approximately 10,000 polyphenol structures, natural compounds characterised by at least one phenolic group (Silva and Pogačnik 2020; Dretcanu et al. 2021). Plants produce polyphenols as secondary metabolites featuring a single phenolic group (C_6H_5OH), where a hydroxyl replaces a hydrogen on a benzene ring (Mahajan et al. 2018). Polyphenols provide numerous health benefits, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic and anticancer effects (Tatipamula and Kukavica 2021; Fraga et al. 2018). Additionally, polyphenols can reduce cardiovascular risk and influence the regulation of lipids and glucose (Iqbal et al. 2023; Ma et al. 2023). However, the effectiveness of these benefits largely depends on what happens to the polyphenols after ingestion and how well the body can absorb them (Lippolis et al. 2023; Williamson 2025). A summarised diagram of the neurodegeneration process is shown in Figure 1.

This review aims to highlight the currently existing knowledge on the effects of pomegranate peel against neurodegenerative diseases. Can pomegranate peel considerably slow the progression of neurodegeneration? In this case, what are the mechanisms involved? In this review, we aim to address these questions. The manuscript is aimed not only at those who delve into strategies for recovering waste materials, but also at those who study the effects of natural products on neurodegeneration.

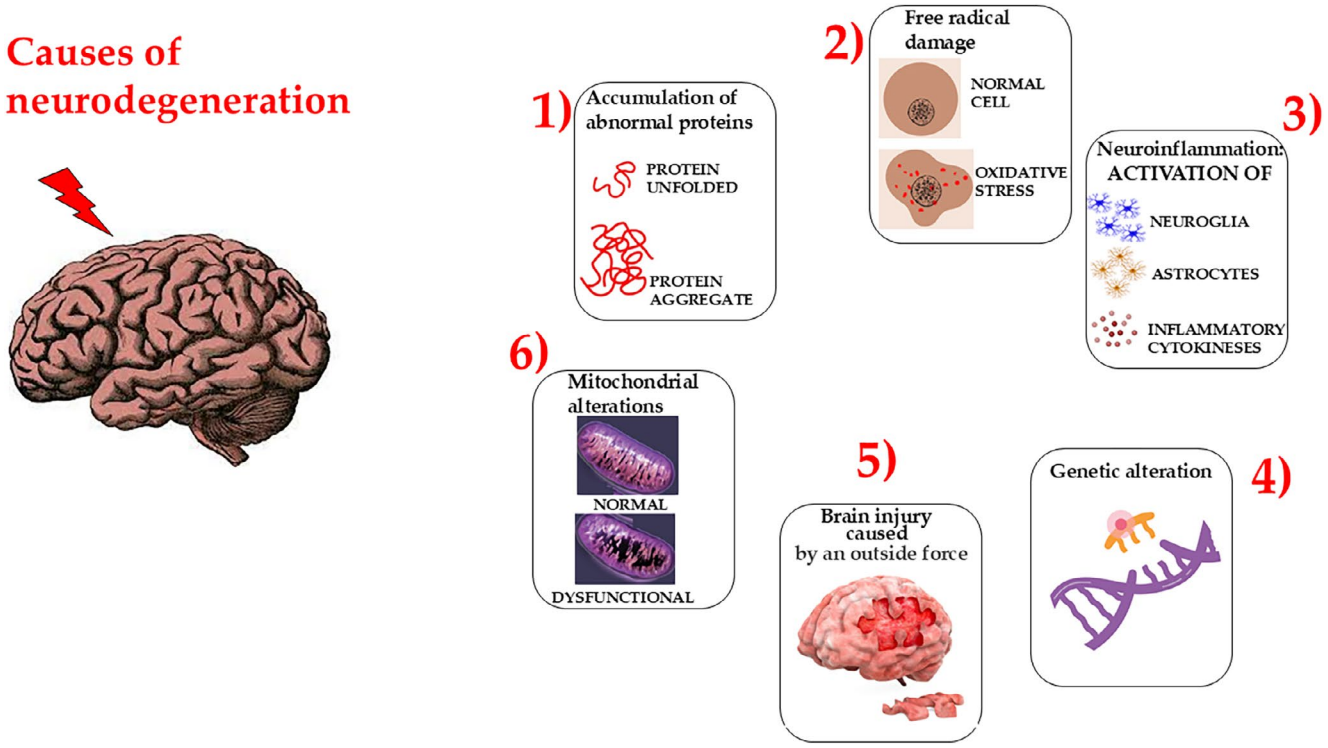


FIGURE 1 | Neurodegeneration. The illustration depicts the primary causes of neurodegeneration impacting the brain.

2 | General Characteristics of the Pomegranate

2.1 | Bioactive Compounds

Bioactive compounds in natural foods regulate cellular metabolic processes, bringing beneficial effects to human health. Pomegranate contains many phytochemicals, and this characteristic accentuates some protective effects; for this reason, the fruit is identified as a 'superfruit' (Wei et al. 2024). Globally, polyphenols can interact with each other or with other bioactive components, producing a combined interaction that yields a total synergistic effect greater than the sum of the effects of individual molecules (Song et al. 2022; Radwan et al. 2025). The numerous bioactive compounds of pomegranate can be categorised into two primary groups: phenolic compounds and fatty acids. Phenolic compounds are a large class of organic molecules of plant origin, structurally characterised by an aromatic ring with one or more hydroxyl groups. Polyphenols perform crucial functions for their well-being (acting on colour, defence, support) and offer important antioxidant benefits for human health. Two subgroups of phenolic compounds are hydrolyzable tannins and flavonoids. Hydrolyzable tannins are polyphenolic substances which are derived from gallic acid (3, 4, 5-trihydroxybenzoic acid) and, when subjected to hydrolysis, split into sugars and phenolic acids such as gallic acid or ellagic acid, included in gallotannins and ellagitannins, respectively; gallotannins can be hydrolysed into gallic acid, known for its powerful antioxidant, anti-inflammatory and antimicrobial properties (Piazza et al. 2022). Ellagitannins neutralise free radicals, possess protective properties for cellular mitochondria, are implicated in the resolution of certain metabolic diseases, and are associated with anti-inflammatory, cardioprotective and chemopreventive effects (Kiss and Piwowarski 2018). The most abundant type of ellagitannin is punicalagin, which can be hydrolysed into smaller phenolic compounds such as ellagic acid. Punicalagin is a natural bioactive of great interest for health and cosmetics, thanks to its high biological activity, which translates into antioxidant, anti-inflammatory, antitumor and antimicrobial effects (Xu et al. 2021; Alalawi et al. 2023). Punicalagin can be hydrolysed into smaller phenolic compounds, the most famous of which is ellagic acid. Ellagic acid is present in every portion of the pomegranate. It is responsible for the increased number of bioactivities, exhibiting positive effects against different types of cancer (Yin et al. 2024; Čižmáriková et al. 2023), possessing antiallergic, antidiabetic, anti-inflammatory, antimicrobial and anti-tyrosinase properties and has also been linked to protection against neurodegenerative diseases (Xue et al. 2022). Data on the absorption of ellagic acid are conflicting due to its almost zero solubility in the gastric environment and poor solubility in the intestinal environment. However, thanks to intestinal bacteria, ellagic acid is transformed into urolithins (A, B, C and D) (Tomás-Barberán et al. 2017), molecules with powerful beneficial effects, especially related to mitophagy and anti-ageing (Tow et al. 2022). Urolithins result from the transformation of ellagitannins through lactone-ring cleavage, decarboxylation and dehydroxylation reactions by intestinal microbiota (García-Villalba et al. 2023). Flavonoids are a large group of secondary plant metabolites, antioxidant and anti-inflammatory pigments belonging to the polyphenol family, responsible for bright colours (from yellow to purple) and offering benefits for cardiovascular, brain and cellular health. They protect against free radicals and reduce the risk of chronic diseases. The main flavonoids of pomegranate are anthocyanins (cyanidin and delphinidin), luteolin, quercetin, rutin, kaempferol, catechin and epicatechin (Shen et al. 2022).

Anthocyanins are water-soluble natural pigments belonging to the flavonoid family. Chemically, they are glycosides, sugars linked to a non-sugar portion called anthocyanidin, and change colour based on pH (Naróg and Sobkowiak 2023). They are responsible for the red colours of pomegranate fruit and its juice, although the intensity of the colour depends on the type of anthocyanin (e.g., Delphinidin derivatives are responsible for the blue and purple colour, while Pelargonidin is related to the red-orange colour), and its concentration (Wu et al. 2024). Anthocyanins act as powerful antioxidants, protecting cells from damage caused by free radicals. The antioxidant activity of these compounds is three times greater than that of red wine, and overall, together with the other phytochemicals contained in pomegranate, they guarantee an extremely high total antioxidant capacity (Wang, Wang, et al. 2024). Seeram et al., found that, considering some foods with antioxidant activity, it was possible to construct the following order with the greatest antioxidant effect towards the least: pomegranate > red wine > grape juice > blueberry juice > cranberry juice > orange juice > apple juice (Seeram et al. 2008). Luteolin is one of the most common flavonoids and is characterised by a double bond between C2 and C3. Luteolin of pomegranate has been shown to have antioxidant, antimicrobial, anti-inflammatory, anti-neurodegenerative and antitumor activities, suppressing uncontrolled cell growth, inhibiting cell migration and reducing metastasis formation (Jayawickreme et al. 2024; Wang, Li, et al. 2024). The absorption of luteolin is very rapid, while its elimination is slow, demonstrating a long-lasting permanence after ingestion (Zhu et al. 2024). Finally, it was shown that luteolin effects were higher when the entire pomegranate fruit was consumed, compared to taking the pure compound in an industrially produced supplement (Hayasaka et al. 2018).

The second main group of pomegranate bioactive compounds consists of fatty acids. Pomegranate fatty acids are predominantly polyunsaturated and play a crucial role in preventing various human diseases. The most important compound, contained in pomegranate, is punicic acid. Punicic acid is an isomer of alpha-linolenic acid, predominantly abundant (up to 80%) in pomegranate seed oil. Chemically, it consists of three double bonds (in the *cis*-9, *trans*-11 and *cis*-13 positions) and exhibits remarkable antioxidant, anti-inflammatory, antitumor, antidiabetic and skin revitalising properties (Holic et al. 2018). The absorption of this compound is quite slow, and its bioactivity appears to be correlated with its conversion to conjugated linoleic acid (Pereira de Melo et al. 2019).

2.2 | Beneficial Properties of Pomegranate

The bioactive compounds contained in pomegranate can exert numerous health benefits, as demonstrated by clinical and preclinical studies; the main ones are described below:

2.2.1 | The Antioxidant Activity

The antioxidant property of pomegranate is achieved thanks to its ability to reduce reactive oxygen species. This activity occurs following the involvement of numerous pathways, including the one that causes upregulation of the NAD-dependent deacetylase protein sirtuin-3, also known as SIRT3, a member of the sirtuin family (Velpuri et al. 2024). The human sirtuins have a range of molecular functions and have emerged as important proteins in ageing, stress resistance and metabolic regulation. SIRT3 is a soluble protein located in the mitochondrial matrix, and its overexpression increases respiration and also decreases the production of reactive oxygen species (Shen et al. 2020). SIRT3 is responsible for activating antioxidant enzymes such as superoxide dismutase 2 (SOD 2) (Zhao et al. 2016). When cellular production of ROS overwhelms the antioxidant capacity, this leads to a state of oxidative stress, and the cell activates some proteins, including the transcription factor nuclear factor-κB (NF-κB). Pomegranate intake, on the other hand, is responsible for the inhibition of NF-κB with a clear projection towards the antioxidant direction (Feng et al. 2020; Chen et al. 2024). Some clinical studies have highlighted that the consumption of pomegranate and its bioactive compounds has reduced lipid peroxidation metabolites (such as malondialdehyde, MDA), increased both the total antioxidant capacity (TAC, the overall effectiveness of a sample in neutralising free radicals) and the activity of the enzyme paraoxonase-1 (PON1, whose activity is the measurement of the function of this enzyme linked to HDL, crucial for antioxidant defense) (Sohrab et al. 2017). Another pathway that leads to the antioxidant effect of pomegranate is the activation of the Peroxisome Proliferator-Activated Receptor gamma (PPARγ) following the ingestion of this fruit or its juice. PPARγ is a nuclear receptor and key transcription factor that regulates overall cellular health, metabolism, cellular differentiation and inflammation, acting as a master switch for the expression of genes involved in maintaining cellular homeostasis (Li et al. 2020).

The antioxidant activity of pomegranate is also exploited in the food sector, and this fruit is used as an additive, exploiting it to increase the shelf life of some foods, such as meat, bread and ice cream (Kanatt et al. 2010; Sagdic et al. 2012).

2.2.2 | The Anti-Inflammatory Activity

Numerous studies have shown that pomegranate extracts were able to prevent or reduce the deleterious effects of some types of inflammatory diseases. For example, in vitro studies have shown that inflammation triggered by lipopolysaccharide (LPS), an outer membrane molecule of Gram-negative bacteria and a potent stimulator of the immune system, was reduced by treatment with a pomegranate extract. The latter reduced inflammatory markers, such as nitric oxide (NO), Prostaglandin E2 (PGE2), Interleukin-1 beta (IL-1β), IL-6 and Tumour necrosis factor alpha (TNF-alpha) (Xu et al. 2017). These results were confirmed by in vivo studies performed on rats in which colitis was pharmacologically induced. After treatment with a pomegranate extract, animals showed preventive effects on disease development, reduction of biochemical markers, including NO levels, neutrophil infiltration, gene expression of IL-1β, IL-18, TNF-α and NF-κB (Marín et al. 2013). Interestingly, these effects were achieved both following the administration of pomegranate juice (400 mg/kg) and with purified punicalagin (4 mg/kg, the amount contained in pomegranate juice). However, the protective effect of pomegranate juice was greater than that

of punicalagin alone, demonstrating that several phytochemical components contributed synergistically to the desired effect (Shah et al. 2016). Ellagic acid (100 mg per day for 7 days) demonstrated similar protective effects on a mouse model of ulcerative colitis, significantly reducing intestinal inflammation markers, such as Cyclo-Oxygenase 2 (COX-2), inducible nitric oxide synthase (iNOS) and other pro-inflammatory markers expression (Jeong et al. 2023). In addition to ellagic acid, other secondary metabolites, such as urolithin A, punicalin, grantin B, strictinin and punicalagin, may contribute to the observed anti-inflammatory effect (Li, Ruan, et al. 2023). Clinical trials of ulcerative colitis patients also showed a symptomatic reduction (faecal incontinence, diarrhoea and rectal bleeding) after treatment with pomegranate extract (6 g/day for 4 weeks) (Larrosa et al. 2010).

2.2.3 | Neuroprotective Effects

Scientific literature has highlighted the role of pomegranate in neurodegenerative protection. Specifically, the bioactive components of this fruit, particularly ellagic acid, can regulate neurotransmitter metabolism. An in vitro analysis highlighted how ellagic acid, obtained from various pomegranate extracts, exhibits an inhibitory function against cholinesterase (Kamali et al. 2015). An interesting in vivo paper, conducted on obese rats due to a high-fat and high-fructose diet, confirmed the protective effects of pomegranate extracts, capable of inhibiting the brain cholinesterase enzyme and increasing antioxidant capacity (Konsoula 2018). Similarly, ellagic acid has demonstrated protective actions in both Alzheimer's disease and Parkinson's disease (Amri et al. 2017; Jha et al. 2018). Ellagic acid administration was also protective in experimental autoimmune encephalitis, the most common model for multiple sclerosis, delaying disease progression and reducing inflammatory cell infiltration into the central nervous system (Baluchnejadmojarad et al. 2017).

2.2.4 | Effects on the Cardiovascular System

The effects of pomegranate extracts or their bioactive compounds on the cardiovascular system have been extensively studied. Overall, pomegranate extracts containing at least 30% punicalagin were shown to significantly reduce endothelial dysfunction caused by a high-fat diet (Busto et al. 2018). In parallel, a pomegranate extract (500 mg/kg, administered for 6 weeks) to overweight and diabetic rats reduced triglycerides and fatty acids, thereby improving altered cardiac lipid metabolism (Vilahur et al. 2015). Treatment of rats with isoproterenol, a drug that enhances the action of the heart, increased heart rate and induced arrhythmias, when also supplemented with pomegranate juice (20 mL/day, for 1 month before receiving the drug), demonstrate less tissue necrosis, an increase in reduced glutathione, vitamin C, Superoxide Dismutase and catalase enzymes: all these results suggested a cardioprotective action of pomegranate juice (Huang et al. 2005). Pomegranate juice also protected rats exposed to cigarette smoke (for 1 month), showing less cardiac hypertrophy, aortic calcification than the control and overall an anti-atherosclerotic action (Jadeja et al. 2010). Clinical studies have confirmed the effects described in in vivo experiments. For example, a study was conducted in which 100 adults with myocardial infarction were supplemented for 5 days with 220 mL/day of pomegranate juice, containing 840 mg/g of dry weight of polyphenols and particularly rich in ellagic acid (about 88.8%). Pomegranate juice intake ensured an improvement in cardiac damage, a reduction in the incidence and severity of angina pectoris episodes, and a reduction in some blood markers (TNFα, IL-6, MDA, troponin) (Al Hariri et al. 2016).

Cardiometabolic risk factors include several conditions, such as dyslipidemia, obesity, hypertension, hyperglycemia and insulin resistance. These alterations increase the risk of developing numerous cardiovascular diseases, type 2 diabetes and metabolic syndrome (Razani et al. 2017; Virgen-Carrillo and Mojica 2025). Hyperglycemia is a metabolic condition highly related to diabetes mellitus in which glucose regulation is altered due to increased hepatic glucose production, impaired glucose uptake, reduced insulin secretion, or reduced glucose utilisation in peripheral tissues. Pomegranate intake has demonstrated hypoglycemic potential by improving insulin production, glucose absorption and utilisation (Hamo et al. 2024). In an in vivo model of rats with type 2 diabetes and fed a high-fat diet, administration of pomegranate, or its bioactive compounds punicalagin, ellagic acid and urolithin A, increased insulin secretion (Mouri and Badireddy 2024). Exposure to flavonoids, tannins and organic acids reduced glucose uptake and glucogenesis (Zhang, Hou, et al. 2021). Insulin sensitivity was also improved by arils juice (7.8 mg punicalagin/kg/day for 6 weeks (Bandawane et al. 2023), administered to diabetic rats). Furthermore, pomegranate reduced pancreatic β-cell apoptosis, improving insulin production. In diabetic mice, treatment with 50 mg/kg/day of urolithin A for 8 weeks reduced inflammation and β-cell death (El-Beih et al. 2019). Pomegranate affects glucose levels, increasing glycolysis and decreasing gluconeogenesis (Zhang et al. 2021). Finally, another interesting study (Zhang et al. 2020) involved the administration of pomegranate juice (0.15% in drinking water for 4 weeks) to obese rats, achieving a reduction in glucose transport and hepatic gluconeogenesis.

Hyperlipidemia is a metabolic disorder characterised by high levels of lipids in the blood, which increases the risk of cardiovascular disease.

Pomegranate has lipid-lowering potential, reducing cholesterol and triglyceride levels. Pomegranate seed oil is rich in punicic acid, and its administration to hyperlipidemic mice resulted in a reduction in the synthesis of triacylglycerol and cholesterol (Ahmed et al. 2015). In an in vitro study conducted on the human hepatocyte cell line, a strong lipid-lowering effect from ellagic acid through the increase in cholesterol metabolism (Franczyk-Żarów et al. 2023). Additionally, a pomegranate extract, enriched with 40% punicalagin and administered to male rats fed a fat diet, reduced the concentration of hepatic cholesterol and triglycerides (Lv et al. 2016). Endothelial dysfunction is a feature of early atherosclerosis and was prevented by a pomegranate extract (200 mg punicalagin/day), administered for 10 days to pigs fed a hypercholesterolemic diet (Zou et al. 2014). Another mechanism for reducing cholesterol accumulation is increased cholesterol efflux from cells. Zhao et al. demonstrated that punicalagin (20 and 40 μg/mL) was able to increase cholesterol efflux into steatotic liver cells (Zhao et al. 2014). The same result was obtained in in vivo experiments on hamsters

fed a hyperlipidemic diet; cholesterol efflux was induced after administration of ellagic acid (44, 88 and 177 mg/kg/pc) (Zhao et al. 2014).

Obesity is characterised by an abnormal accumulation of body fat or adipose tissue, which increases the risk of noncommunicable diseases, including cardiovascular pathologies (Liu et al. 2015). The pomegranate has anti-obesity potential, which is attributed to its ability to reduce lipid synthesis. Punicalagin (10, 20 μM and 4.2 IC50 μg/mL), ellagic acid (10, 50 μM and 1.31 IC50 μg/mL), and urolithin A (10, 50 μM) have reduced adipogenesis in a preadipocyte model in a dose-dependent manner and intracellular triglycerides (Chamarthi and Daley 2025). Punicalagin downregulated lipid synthesis and activated lipolysis, resulting in a decrease in hepatic lipid deposition in obese mice after 8 weeks of exposure (Li et al. 2020). A recent therapeutic approach to reduce obesity has considered increasing mitochondrial function in adipose tissue as a mechanism to increase energy expenditure; with this aim, obese mice were treated with urolithin 30 mg/kg/day for 10 weeks (Jiensi et al. 2023).

2.2.5 | Anticancer Effects

Pomegranate inhibits the growth of several types of tumour cells, including prostate, breast, pancreatic, lung, colon and hepatocellular cells, through several mechanisms (Echeverria et al. 2021; Teniente et al. 2023). For example, the antitumor properties of pomegranate against breast cancer have been attributed to anti-aromatase and antiestrogenic activity, since it is well known that high estrogen levels represent one of the main risk factors for the growth of this tumour (Pantiora et al. 2023).

In recent years, polyphenols of pomegranate have been tested for their antiproliferative effects and among the tannins, the most potent enzyme inhibitor was urolithin B, followed by gallagic acid (Adams et al. 2010). Jeune et al. studied the antitumour activity of pomegranate extract, in combination with the isoflavone genistein, in MCF-7 breast cancer cells (Jeune et al. 2005). After 24 h of treatment with pomegranate juice and genistein, in single and combined treatments, the cytotoxic effect and growth reduction were quantified: the results revealed that pomegranate extracts, plus Genistein was able to induce cell apoptosis (Eroglu Ozkan et al. 2021).

Punicalagin, ellagic acid and total pomegranate tannins also showed apoptosis and antiproliferative actions on human colon, oral and prostate cancer cells (Jeune et al. 2005). Dahlawi et al. demonstrated that pomegranate extract induced apoptosis in leukaemic cell lines (Dahlawi et al. 2012; Seeram et al. 2005), while Li et al. evaluated that pomegranate leaf extract induced apoptosis in lung cancer cells, together with cell cycle arrest in the G2/M phase (Li et al. 2016).

Antioxidant and anti-inflammatory effects have contributed to the antitumour effect. Several studies have found that COX2 overexpression, closely associated with cancer metastasis, could be significantly attenuated by treatment with pomegranate extract, rich in polyphenols (107.5 ± 3 mg/g tannic acid equivalents) and had antioxidant activity (Li et al. 2016; Shukla et al. 2008). Furthermore, the anti-inflammatory effect of pomegranate was able to counteract metastases of colon or prostate cancer (Hajleh and Al-Dujaili 2016). Ellagitannins were found in high amounts in prostate tissue, suggesting that pomegranate metabolites may play an antitumor role in this tissue. Following pomegranate juice ingestion, urolithins A and B were concentrated in the prostate, accentuating their beneficial role against prostate cancer (Thotambailu et al. 2019). The most common side effects of radiotherapy are mucositis and dermatitis. One study found that patients treated with 2 capsules/day of 300 mg pomegranate extract (containing 40% polyphenols and 27% punicalagin) for 6–7 weeks exhibited a protective effect in preventing radiation therapy-induced skin damage. In general, in the presence of neoplasms, consumption of pomegranate fruit determines an activation of the proinflammatory transcription factor NF-kB and an overexpression of caspase-3. It increases the blockade of the G0/G1 phase of the cell cycle (Pacheco-Palencia et al. 2008).

3 | Pomegranate Peel: A Precious Resource

A significant part of fruit and vegetables is discarded and considered as waste (Chen et al. 2022; Teplitski et al. 2023). Since these wastes can be recovered and reused for various purposes, a currently prevalent challenge is identifying potentially protective molecules present in by-products and wastes from the agri-food industry (Maiuolo et al. 2023). Therefore, pomegranate peels are considered agro-industrial waste, adding to environmental pollution from improper disposal. Nevertheless, the biological activity of pomegranate peel is even greater than that of pomegranate pulp, due to its chemical composition, which is particularly rich in secondary metabolites (Angeloni et al. 2022). For example, literature data have highlighted an antioxidant activity of pomegranate peel almost 10 times higher than that of the other parts of the pomegranate fruit and this property is closely linked to its chemical and polyphenolic structure (Azmat et al. 2024). The most common compound families found in pomegranate peel are: tannins, steroids, polyphenols, flavonoids, dietary fibre, anthocyanins, phenolic acids, alkaloids, terpenoids, catechins, vitamins, minerals and saponins (Hanafy et al. 2021), while the most represented individual phytochemicals are: ellagic acid, punicalins, punicalagins, gallic acid, p-coumaric acid, syringic acid, shikimic acid, chlorogenic acid, butyric acid, benzoic acid, caffeic acid, cinnamic acid, protocatechuic acid, ferulic acid, quinic acid, rutin, resorcinol, quercetin, vitamin A, vitamin B1, vitamin B2, vitamin C, vitamin E, calcium, potassium, sodium, phosphorus, iron (Mo et al. 2022; Singh et al. 2023; Senobari et al. 2022; Tomás-Barberán et al. 2017; Cortés-Martín et al. 2020; Palikaras et al. 2018; Magangana et al. 2020). The fibre, a significant component with established health benefits, is also found in various plant byproducts (Kujawska and Jodynis-Liebert 2020; Wang, Long, et al. 2024); its content in pomegranate peel varies from 33% to 62% (Caminiti et al. 2024), although its concentrations depend on the cultivar, ripening stage, climate, soil composition and nutrient analysis methods (Maiuolo, Liuzzi, et al. 2024; Xiong et al. 2023). Appropriate analyses have established that this fibre is composed primarily of lignin, cellulose, uronic acid and neutral sugars. It has been calculated that the ratio between the insoluble and soluble fibre is very close to 1 (Al-Rawahi et al. 2013). The role of fibre in pomegranate peel is

mainly to absorb cholesterol, actively participating in the protective role of the cardiovascular system (Maiuolo et al. 2024). The pomegranate peel, as already mentioned, has several protective effects, including antioxidant, anti-inflammatory, anti-diabetic, hypo-lipidic, neuroprotective, cardioprotective, anti-apoptotic, anti-mutagenic, anti-genotoxic, anti-cancer, anti-viral and anti-bacterial properties, potentially mitigating various chronic illnesses (Hasnaoui et al. 2014; Neyrinck et al. 2019). These countless beneficial properties, provided by the pomegranate peel, make this portion of the fruit a precious and irreplaceable part. The anti-oxidant and anti-inflammatory activities are particularly interesting since oxidative processes and the onset of inflammation are the common denominator of most pathologies. In particular, these two elements underlie the onset, development and progression of neurodegeneration (El-Hadary and Ramadan 2019). The results in the literature allow us to consider the bioactive compounds of pomegranate peel as components that oppose oxidative stress; in fact, the valuable constituents reduce/or eliminate free radicals, prevent the oxidation of biological macromolecules, transform toxic free radicals into less toxic compounds and increase the expression of antioxidant enzymes (Bido et al. 2021; Marogianni et al. 2020; Sun et al. 2017).

Ellagitannins are poorly bioavailable; they have a high molecular weight (300–3000 g/mol) and are poorly absorbed in the upper gastrointestinal tract. In the stomach and small intestine, they are partially hydrolysed into ellagic acid, the absorption of which is, however, limited. Most ellagitannins reach the colon intact, where the bacterial flora transforms them into urolithins. The latter are much more bioavailable and are primarily responsible for systemic beneficial effects (Elwej et al. 2016). Ellagitannin metabolites are eliminated mainly by the renal and faecal routes, but some compounds may persist in urine after ingestion; these metabolites show low toxicity and minimal side effects (Saparbekova et al. 2023). In contrast, anthocyanins have a low molecular weight (< 500 Da) and good potential inhibition of inflammatory and neurodegenerative pathways. They are absorbed in the intestine and are distributed in various tissues, showing beneficial effects on the heart, brain and eyes. They are rapidly metabolised in the liver and intestine into compounds such as phenolic acids, which retain some of their biological activity. They are excreted mainly through urine and bile and have low toxicity and mutagenicity (Aguilar-Zarate et al. 2018; Roberts et al. 2020). Finally, concerning fatty acids, it can be stated that the short and medium chain molecules are absorbed directly into the portal blood, while the long chain ones require the formation of micelles with bile salts to enter enterocytes. They can be stored as triglycerides in adipose tissue or incorporated into plasma membranes as phospholipids. Fatty acid metabolism preferably occurs through beta-oxidation in mitochondria, which converts fatty acids into acetyl-CoA for energy production. Small amounts of water-soluble metabolites can be excreted renally. High levels of free fatty acids can cause lipotoxicity, contributing to insulin resistance and metabolic diseases (Kumkum et al. 2024; Schönfeld and Wojtczak 2016).

Pomegranate peel has been used not only in the production of dietary products, supplements, edible coatings, flavours, colours and films for food packaging (Bremer and Norum 1982), but also as innovative products for making silver nanoparticles, for nanotechnology, bioengineering, catalysis and electrochemistry (Kharchoufi et al. 2018). Furthermore, numerous studies have demonstrated that pomegranate peel exhibits antibacterial and anti-inflammatory properties, prompting researchers to utilise this product in cosmetics (Thilagavathi et al. 2016). The food industry is also very interested in this product; some food products, including cereals, yoghurt and ice cream, contain added pomegranate peels. The antioxidant and antimicrobial properties of pomegranate peel extend the shelf life of some meat products by 2–3 weeks in the refrigerator, making it a useful natural additive (Liu et al. 2023). The antioxidant activity of pomegranate peel is based on the reduction of reactive species, chelation of metal ions, strengthening of antioxidant enzymatic activity, regulation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signalling pathway and reduction of lipid peroxidation (Zhuang et al. 2019). The properties and uses listed for pomegranate peel are valid as long as the chemical composition remains stable; alteration of individual compounds could affect the content of the molecules and, consequently, their functions (Diao et al. 2022).

3.1 | Extraction Techniques for Bioactive Compounds of Pomegranate Peel

The use of pomegranate peel in the food sector, as a natural antioxidant, involves the extraction of its bioactive components. An "extraction technique" is a method of separating a component from a mixture, exploiting property differences such as solubility, volatility or affinity for a component (Smaoui et al. 2019). The extraction techniques of the innumerable polyphenols contained in the pomegranate peel are divided into two broad categories: on the one hand, there are the traditional methods that use considerable volumes of extraction solvents and various manual processes, which make the results non-standardizable. On the other hand, green extraction methods have been developed to overcome the limitations set by traditional methods. The latter also provides for higher extractive yields, smaller equipment and fewer processing steps (El Maaiden et al. 2022). The traditional extraction method for recovering phenolic components involves immersing the pomegranate peel in solvents such as water, methanol, chloroform, acetone, ethanol and ethyl acetate (Alara et al. 2021; Rahnemoon et al. 2018). The results showed that water has a better capacity for the extraction of total phenolic content, which is higher than that obtained with other solvents (Pathak et al. 2017). In parallel, another study highlighted that the best solvent for separating components with antioxidant activity from pomegranate peel was ethanol 70% (Magangana et al. 2021). Extraction efficiency increases proportionally with temperature, probably because higher values increase solubility, reduce viscosity and facilitate the passage of solvents through the solid substrate. However, the temperature should not exceed 40°C, as many chemical structures could alter and reduce or lose functionality (Rafi et al. 2021). Another method of traditional extraction is Soxhlet extraction, in which the material is subjected to various solvents, including water, ether, hexane, chloroform, benzene, methanol, acetonitrile and ethanol, which capture the desired molecules. The Soxhlet machinery separates the various components according to their polarity and that of the solvent. The least polar compounds of the dry material are extracted using the less polar solvents,

like petroleum ether. Conversely, high polarity compounds are extracted with highly polar solvents (Sharmin et al. 2016). The limits of this type of extraction are the time required, the consumption of large amounts of solvent and the energy expenditure (Hasan et al. 2018). Among the green extraction techniques, there is one that uses pressurised liquid solvents (pressures > 4 MPa) and medium-high temperature (through HPLC). High pressure facilitates the ability of solvents to penetrate the pores of the matter and the dissolution and separation of the components (Pereira et al. 2021). Another type of Ultrasound Assisted Extraction is based on the phenomenon of acoustic cavitation, which involves the creation of bubbles and their subsequent breaking, causing the release of bioactive substances (Souza et al. 2021). Extraction can also be assisted by enzymes; the principle involves the hydrolysis of food materials with an enzyme that acts as a catalyst to release bioactive components such as polyphenols and other phytochemicals. The most commonly used enzymes are pectinases, proteases and cellulases (Cano-Lamadrid et al. 2022). When pomegranate peel is not subjected to extraction methods and is discarded or treated as waste, it would be advisable to recover it to exploit its countless benefits.

3.2 | Recovery of Pomegranate Peel

This paragraph describes the main points to be made, should the pomegranate peel be recovered. According to the Food and Agriculture Organisation (FAO), the food processing and production stages are responsible for approximately 33% of the final product loss, and foods such as fruits, and vegetables can lose up to 50% (Priya et al. 2023). The pomegranate peel makes up, as previously mentioned, 50% of the total fruit weight, meaning there are roughly 3.6 million tons of peel generated annually worldwide. This huge amount of waste not only causes environmental pollution but also results in the loss of bioactive compounds that are beneficial for human health (Campos et al. 2022). It would be ideal to recover these beneficial compounds from the pomegranate peel, but it is also important to optimise the manufacturing process to preserve its phytochemical, biological and physical properties. First, the characteristics of the starting material can vary due to factors such as the growing region, fruit cultivar, climate and cultivation practices (Mirdehghan and Rahemi 2007). The pomegranate peel is characterised by a high degree of humidity, which is responsible for rapid alteration; therefore, it is necessary to treat it adequately to allow for its subsequent use. A dehydration process is advisable to reduce the moisture content of the pomegranate peel and prevent degradation, reduce enzymatic activity, limit fermentations and prolong its shelf life (Onwude et al. 2016; Sagar and Kumar 2010). The drying method is influenced by various factors such as the type of product, drying conditions, the availability of the drying equipment, the cost of operation and drying efficiency (Pateiro et al. 2022). The second step of processing the pomegranate peel is the extraction method and the solvent used (Benedetti et al. 2023). In compliance with this, three parameters are fundamental: the time necessary to carry out the drying technique, the temperature maintained and the solvent used for extraction (Kiran et al. 2024). The best conditions of these variables were those that determined a better yield of polyphenols, flavonoids, or vitamins content (Belwal et al. 2022). Numerous conventional methods of drying have been assessed in the literature, such as sun drying, hot air drying, freeze-drying, microwave drying and fluidised bed drying.

The longest times occur when the drying method involves direct exposure to the sun: from 3 to 5 days, depending on the thickness and consistency of the product to be dried. The leathery consistency of pomegranate peel requires 5 days of exposure to the sun (Akpinar 2010). The positive consideration is that this method is inexpensive, while the downside is that it requires a lot of space, time and offers few hygienic and microbiological controls. Hot air drying also takes a long time (3–4 days for pomegranate peel); this method is simple, effective and relatively inexpensive (Kumar et al. 2017). The limitation of this technique is that it can completely dehydrate the surface of the product, forming cracks or a heterogeneous result (Polat 2024).

The drying ovens require a use of approximately 48 h for pomegranate peel and are equipped with a ventilation system to eliminate humidity from the material in a controlled way. This process avoids the formation of pests and reduces costs (Tekgül and Erten 2022).

Cold drying or freeze drying takes advantage of low temperatures and a treatment time of approximately 16–24 h. It is a process of removing water to preserve perishable materials by freezing them, then sublimating the ice into steam under vacuum conditions. This technique removes water without altering the structure, extends shelf life and reduces the weight of the product. In addition, freeze drying preserves the nutritional and organoleptic qualities, maintaining the freshness and quality of the dehydrated products. The pomegranate peels require 20 h (El-Said et al. 2014).

Microwave drying is a very fast technique that takes up to 4–9 min. In fact, microwaves pass through and excite the water molecules present in the material, generating internal heat that makes it evaporate faster and more uniformly. Therefore, this technique reduces drying time, improving energy efficiency. These microwaves cause polar molecules, such as water, to rotate or vibrate, creating heat through friction between them. This heat causes the molecules of the substance to move more rapidly, uniformly and gradually absorb water (Kumar et al. 2017). Microwave drying of pomegranate peels has several positive points: speed, energy saving, cost reduction, uniformity of the result and maintenance of the high quality of the final product. A negative point of this method could be caused by an uneven distribution of power or airflow.

Often, some of these methods are used together to optimise moisture removal. The time required for methods of drying of pomegranate peel is associated with the temperature used: exposure to the sun requires a very high temperature (≅100°C); drying with hot air requires a temperature between 70°C and 200°C; drying in ovens requires a temperature between 50°C and 70°C; drying with microwaves requires temperatures of 35°C–50°C; freeze drying approximately −70°C (El-Said et al. 2014).

Finally, the last variable to consider is the choice of solvent for the extraction between water, methanol, ethanol, acetone and ethyl acetate (John et al. 2017; Kremer et al. 2023). In addition

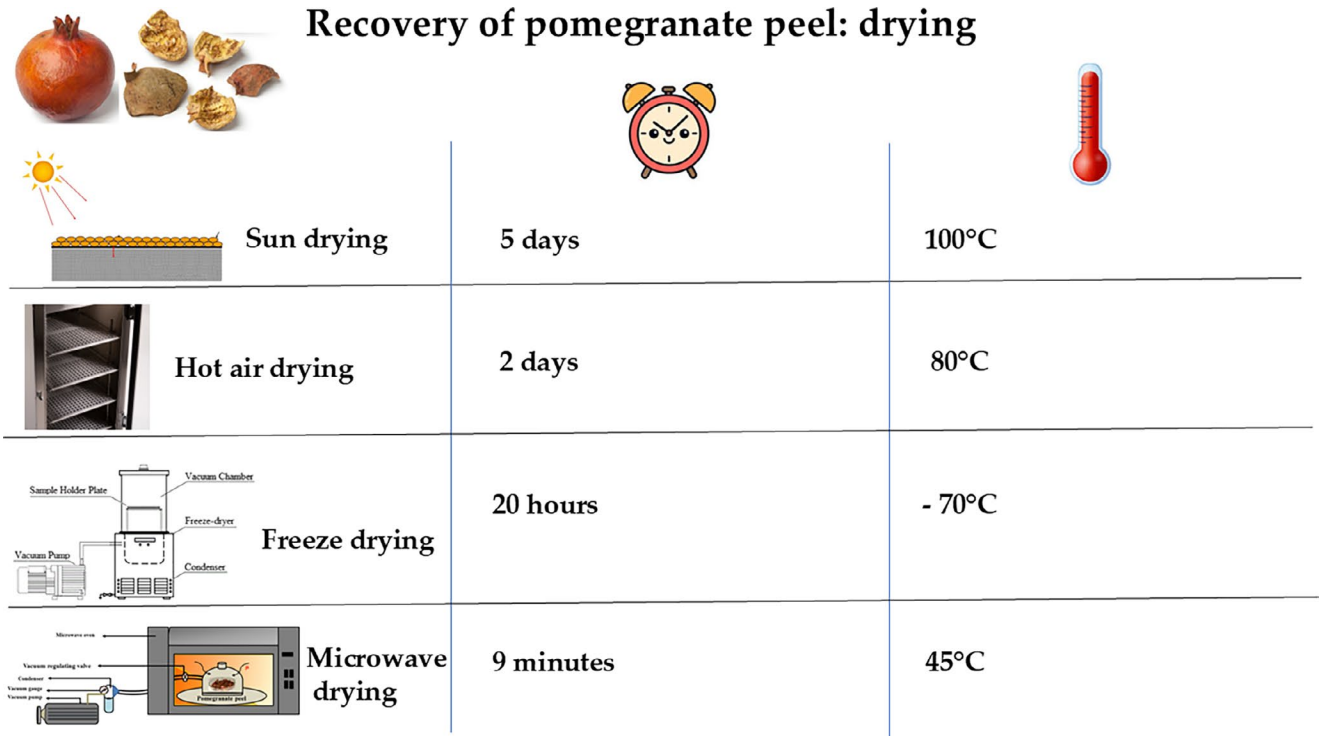


FIGURE 2 | The drying process during pomegranate peel recovery is illustrated.

to water extraction, as already mentioned, methanolic extracts from pomegranate peel have also been shown to provide very positive results on the yield of bioactive compounds (Feng et al. 2022; Singh et al. 2002). A summary map of the pomegranate peel recovery and drying process is represented in Figure 2.

4 | Peel of *P. granatum* and Neurodegeneration

Developed countries have seen significant increases in life expectancy in recent decades, as well as a rise in age-related neurodegenerative diseases. Sadly, effective therapies for most of these conditions are still lacking; we only have symptom relief. As noted, consuming fruits and vegetables provides numerous bioactive compounds essential for maintaining physical and mental well-being, thereby reducing the risk of neurodegeneration (Wang et al. 2011). Neuroinflammation, a nervous system inflammatory response primarily driven by microglia, is often linked to this phenomenon. Neurodegeneration and neuroinflammation are interrelated processes that play an important role in nervous system diseases, and neuroinflammation may be a contributing factor to the progression of neurodegeneration and neuronal deterioration (Mehdi et al. 2022). Brain inflammation disrupts neuronal communication and causes neuronal death (Maiuolo et al. 2018). Studies have shown that *P. granatum* has improved brain neurochemistry, inhibiting NF-kB—known for its importance in regulating the immune and inflammatory responses—decreasing COX2, involved in the management of pain and inflammation, enzymatic activity (Yu et al. 2020) and caspase enzyme catalytic activity (essential in implementing apoptotic cell death (Sun et al. 2013)). Pomegranate peel has been shown to improve neuronal development, synaptic plasticity, learning and cognition, while also reducing lipid peroxidation and the levels of inflammatory cytokines (Velagapudi et al. 2015). Furthermore, it has been found to inhibit acetylcholinesterase, a key enzyme involved in certain neurodegenerative diseases (Gates et al. 2022).

4.1 | Mechanisms Involved in Protection by Pomegranate Peel Against Neurodegeneration

The protection of pomegranate peel against neurodegeneration uses mechanisms of action that can be defined as 'direct' and 'indirect'. In the direct mechanism, an active component of the fruit portion in question acts on the brain through a direct connection. Conversely, the indirect mechanism involves the effect of pomegranate peel on another organ or apparatus, which subsequently acts on the brain. This concept is graphically represented in Figure 3.

4.1.1 | Direct Mechanisms

Many neurodegenerative pathologies are linked to a persistent inflammatory state (Kalkan et al. 2024; Tsuji and Molnár 2025; Irwin and Vitiello 2019). The anti-inflammatory effect, exerted by the pomegranate peel, has been found to produce beneficial effects on neurodegenerative diseases (Kwon and Koh 2020; Aleksandrova et al. 2023). Alzheimer's disease is characterised by the accumulation of unfolded proteins (beta-amyloid) and neurofibrillary tangles (tau proteins) in the brain, both of which are responsible for toxic deposits and the subsequent death of neurons (Venusova et al. 2021). Experimental data reported that treatment with pomegranate peel, rich in ellagic acid and punicalagin, in an animal model of mice affected by Alzheimer's disease, resulted in a significant reduction in beta-amyloid plaques and neurofibrillary tangles in the brain (Mphahlele et al. 2016).

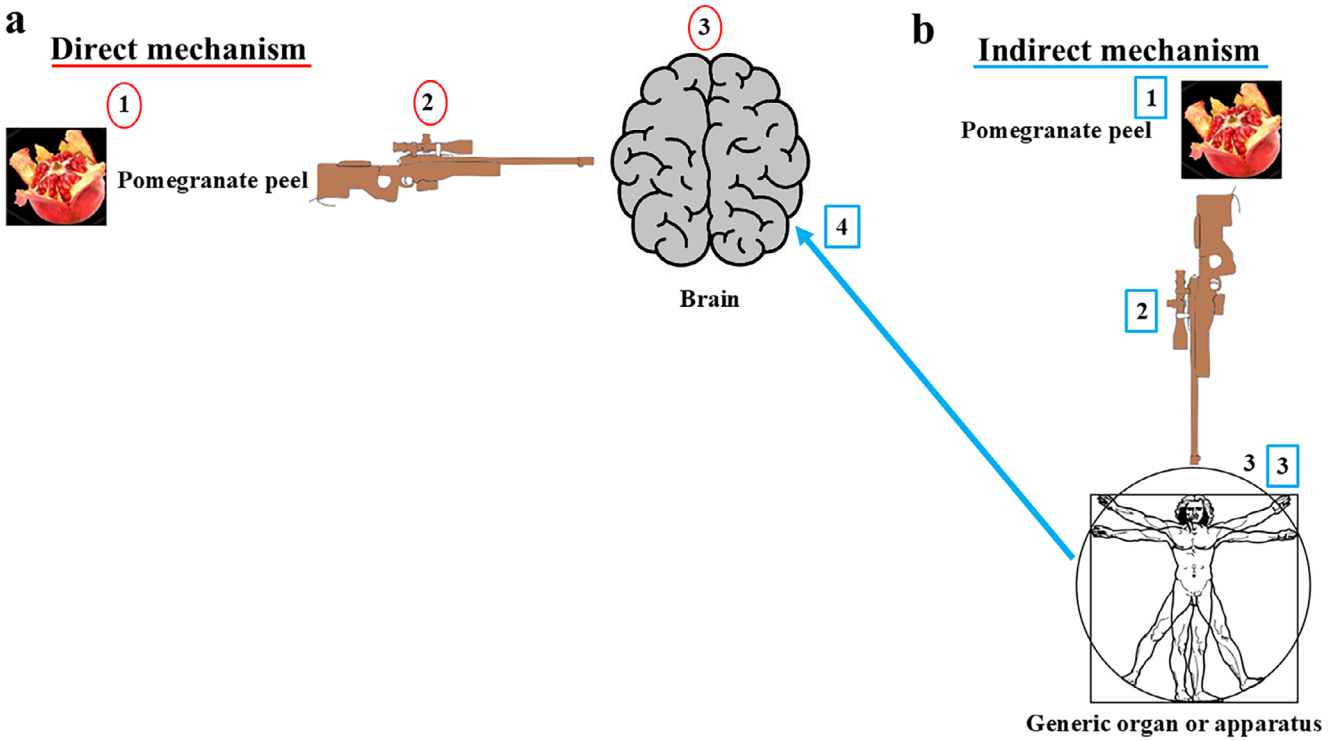


FIGURE 3 | Direct and indirect mechanisms. In panel (a), the direct mechanism is shown. The continuation of events is highlighted by the numerical sequence indicated in red. (1) Treatment with pomegranate peel is carried out, and (2) can reach directly to the brain (3), acting beneficially against neurodegeneration. Panel (b) shows the indirect mechanism. The continuation of events is highlighted by the numerical sequence indicated in blue. (1) Treatment with pomegranate peel is carried out, and (2) can reach any organ or apparatus (3). The effect of the latter causes benefits on the brain against neurodegeneration.

An in vivo study reported that mice in an Alzheimer's disease model, treated with pomegranate peel, showed positive results on the Barnes-Wallis labyrinth test, with improved spatial memory in the search for the escape pathway. Furthermore, these mice showed a notable reduction in the number of plaques compared to untreated mice. This interesting result can be attributed to ellagic acid and punicalagin, which inhibited beta-amyloid plaque formation (Urganci et al. 2025; Ciccone et al. 2023). In another study, conducted with the same animal models, it was highlighted that treatment with pomegranate peel reduced the levels of malonyldialdehyde and increased catalase and glutathione levels, compared to the counterpart with AD (Kwak et al. 2005). Finally, it was shown that the effects of pomegranate peel were more potent than the single molecules ellagic acid or punicalagin. The higher effect of peel extract compared to single components could be attributed to the copious amount of bioactive molecules contained in the peel, which probably act simultaneously through multiple pathways (Kwak et al. 2005). The observed protective effects could be explained by the anti-inflammatory property exerted by punicalagin. Indeed, data available in the literature suggest that this compound can reduce the levels of beta-amyloid$_{1-42}$, TNF-α, IL-6, IL-1β and the neuronal expression of the enzyme Beta-Secretase 1 (BACE1), a key aspartate protease in the brain, critical for the production of beta-amyloid peptide (Ahmed et al. 2014). The in vivo results were also confirmed in vitro; the treatment of human neuroblastoma cells with punicalagin highlighted the reduction in the expression of cyclooxygenase 2 (COX 2), responsible for the biosynthesis of molecules involved in inflammation (Kim et al. 2017). Furthermore, the treatment with punicalagin (10, 20 and 50 μM) in a co-culture model, composed of astrocytes and a liver cell line, highlighted the reduction of COX 2 and BACE1 gene expression (Ahmed et al. 2014). In addition to reducing inflammation, the antioxidant mechanism, with the elimination of free radicals, can also contribute to the observed neuroprotection (Kim et al. 2017).

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by loss of motor neurons, leading to progressive body weight loss, muscle weakness and paralysis (Harakeh et al. 2020). Congenital dysfunctions in ALS include mitochondrial alteration, redox imbalance, glutamate excitotoxicity, autophagic dysregulation, changes in RNA metabolism and astrocytic and microglial activation (Brown and Al-Chalabi 2017). The accumulation of damaged mitochondria, an increase in oxidative stress and a reduction in ATP levels are responsible for cellular damage and apoptosis (Al-Chalabi et al. 2014). In ALS, the functional alteration of the mitochondria contributes to the activation of astrocytes and microglia, which trigger a massive inflammatory response (Lou et al. 2020). To determine whether mitophagy played a central role in ALS, mice with the disease were treated with urolithin A (50 mg/kg/day), an activator of mitophagy. The results demonstrated that this compound improved motor function, mitigated neuroinflammation, alleviated muscle atrophy and fibrosis and reduced motor neuron loss. The strategy of urolithin A has been the activation of autophagy and mitophagy (Ziff et al. 2022).

Parkinson's disease (PD), a progressive neurodegenerative disease, is caused by degeneration of neurons that produce

dopamine, a neurotransmitter essential for movement control. PD pathogenesis is characterised by the accumulation of Lewy body deposits (mainly alpha-synuclein and ubiquitin) in the midbrain dopaminergic neurons (Zhang et al. 2025). It manifests with motor symptoms, such as tremor, slowness in movements, muscle stiffness and postural instability, but also with non-motor disorders, including anxiety, depression, alterations in mood, sleep problems and cognitive decline (Schneider and Alcalay 2017). The creation of an animal model that mimics PD is carried out with an acute and high-dose treatment of manganese chloride ($MnCl_2$) in the brain (Nair et al. 2018). $MnCl_2$-induced neurotoxicity in rats occurs through several mechanisms, including oxidative stress, perturbation of neurotransmitter production and metabolism, neuroinflammation, endoplasmic reticulum stress and apoptosis (Nadig et al. 2022). In particular, dysregulation of glutamate, norepinephrine, serotonin and dopamine occurs, resulting in motor dysfunction (Pajarillo et al. 2022). Treatment with the polyphenol punicalagin (30 mg/kg, orally using stomach gavage) showed a significant improvement in locomotion, recovery of norepinephrine, serotonin and dopamine neurotransmitters, a decrease in the process of degeneration of the cell nucleus, maintenance of the correct histological structure and preservation of brain tissue (Nyarko-Danquah et al. 2020). Furthermore, punicalagin has been shown to overcome the $MnCl_2$-induced damage, reducing both oxidative stress, inflammatory cascades and apoptosis (Kang et al. 2019; Yan et al. 2016). However, these effects could be explained predominantly by the antioxidant activity of the polyphenols contained in pomegranate peel. In fact, rats with PD, fed standardised pomegranate extract (40% ellagic acid) or exposed to punicalagin, showed attenuation of oxidative damage, reduction of malondialdehyde, reduction of inducible nitric oxide synthase (iNOS) activity, improved neuronal survival, locomotion and postural stability (Ali et al. 2022).

Multiple sclerosis (MS) is a chronic autoimmune disease affecting the brain and spinal cord, caused by a progressive demyelination responsible for interruptions in the transmission of nerve signals, axonal damage and neurodegeneration. MS is characterised by visual, sensory and motor disorders along with fatigue, muscle spasms, bladder and bowel dysfunction, paralysis and cognitive impairment (Subkorn et al. 2021). The animal model of Experimental Autoimmune Encephalomyelitis (EAE) is widely used to study multiple sclerosis. Under these experimental conditions, mice showed development of neuroinflammation, demyelination and axonal loss (Dendrou et al. 2015). The administration of ellagic acid (50 mg/kg) significantly alleviated the symptoms observed in the animal model, protecting the brain from damage, reducing pro-oxidant and inflammatory effects, reducing demyelination, axonal loss and neuroinflammation, attenuating microgliosis and preventing apoptosis of oligodendrocytes (Robinson et al. 2014). Ellagic acid has protective effects on multiple sclerosis models, but it is not decisive. Ellagic acid could act both by exploiting its anti-inflammatory potential, reducing IL-17 (a pro-inflammatory protein crucial for the immune system that, if in excess, is involved in autoimmune diseases) and antioxidant activity, attenuating cerebral lipid peroxidation and inhibiting demyelination (Depaz et al. 2011; Binyamin et al. 2015). However, it is desirable that its long-term use may be associated with neuronal protection and fewer adverse effects compared to the synthetic drugs currently used for this disease (Kiasalari et al. 2021).

Huntington's disease (HD) is an inherited and progressive neurodegenerative disease that affects the central nervous system. It is characterised by the repetition of trinucleotide (cytosine-adenine-guanine) in the huntingtin gene (Htt), leading to the production of an abnormal protein, called huntingtin, which damages neurons in specific areas of the brain (Volpi et al. 2019). Characteristic clinical features are not only involuntary movement, cognitive and mental disorders, but also skeletal muscle atrophy, unintended weight loss and gastrointestinal dysfunction (Cepeda and Tong 2018). Since mitochondrial abnormalities and redox imbalance are major pathogenic factors in Huntington's disease, using antioxidants could attenuate disease progression. Ellagic acid (50 and 100 mg/kg) showed improvements in the cognitive abilities of rats affected by the disease (Wasser et al. 2020). Another compound that demonstrated excellent potential in the treatment of HD was urolithin A, which, by improving mitochondrial function, could slow the progression of the disease (Sharma et al. 2021).

4.1.2 | Indirect Mechanisms

The compounds contained in the pomegranate peel also act on the brain through the intestine. The intestine is responsible for much more than digesting the food ingested: it contains millions of cells and neuronal fibres which constitute a real nervous system operating in complete autonomy and which, independently of the central nervous system, can give rise to specific actions, such as intestinal contractions or release of digestive enzymes (Darwish et al. 2023). The intestine can also integrate and process the stimuli that the body receives, both internal and external and interact with the central nervous system. The intestine affects the brain and its development, while mental stress and emotions can irritate the intestine, causing inflammation and gastrointestinal disorders (Barbero Mazzucca et al. 2024). Intestinal inflammation can lead to neurological problems such as anxiety, depression and cognitive difficulties, emphasising the importance of a healthy gut for overall well-being (Barrio et al. 2022). Changing one district causes the other to malfunction (Liu et al. 2022). Conditions of strong emotional stress can activate the circuits of anxiety and fear. The latter causes an increase in intestinal motility, resulting in the release of cytokines. In this way, the intestinal mucosa becomes irritated and inflamed and, in the most serious cases, can give rise to pathologies or even serious conditions such as irritable bowel syndrome or inflammatory bowel disease (Ferreiro et al. 2023). The intestine and the brain influence each other and it is precisely in this way that they influence, positively or negatively, the individual's state of physical and emotional well-being. The gastrointestinal tract and the central nervous system can interact via the gut-brain axis, which ensures two-way communication through (1) the modulation of the immune system, (2) the involvement of the vagus nerve, (3) the enteric nervous system (SNE), (4) the neuroendocrine system and (5) the circulatory system (with production of neuroactive substances, such as metabolites and hormones) (Wang and Wang 2016). Figure 4 summarises the mechanisms that ensure gut-brain interaction.

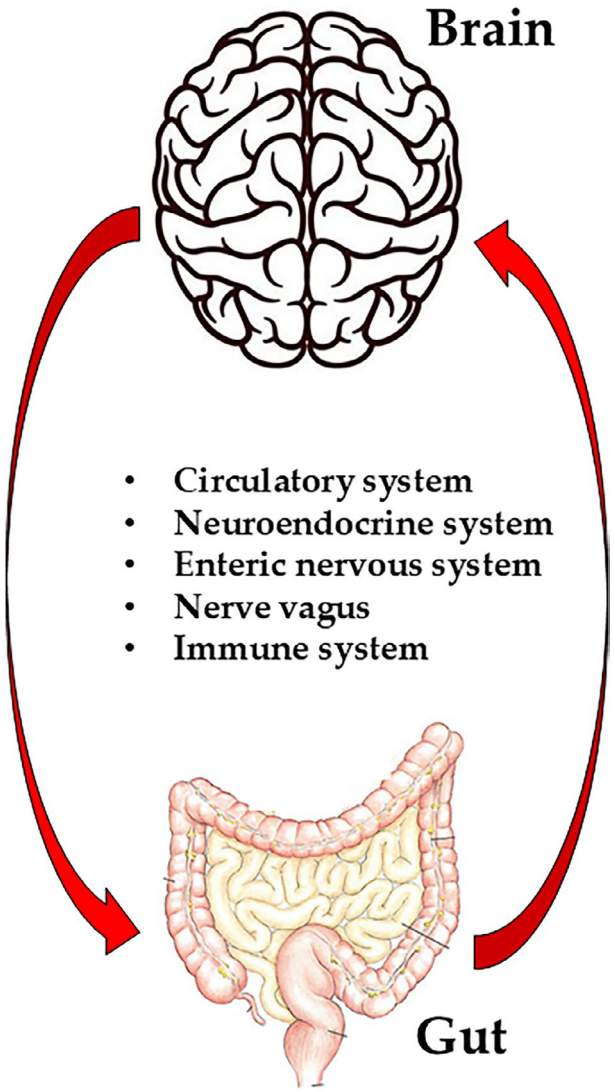


FIGURE 4 | A close connection between the brain and the intestine. The systems that ensure the bi-univocal connection between the brain and the intestine are shown.

Another mechanism that correlates the intestine with the brain is the gut microbiota. The body's microbiota comprises all microorganisms (bacteria, fungi, viruses and protozoa) inhabiting areas in contact with the external environment—skin, mouth, nose, ears, eyes, lungs, gut and vagina—without causing harm (Chitnis and Weiner 2017). The intestinal microbiota is the most extensive, accounting for about 70% of the total (Di Vincenzo et al. 2023). In the human gut, only a few bacterial divisions have been identified: *Bacteroidetes*, *Proteobacteria*, *Firmicutes*, *Actinobacteria*, *Verrucomicrobia* and *Fusobacteria* (Adak and Khan 2019). Each individual is composed of different bacterial species, so the composition of the intestinal microbiota can be considered unique, much like a fingerprint (Pant et al. 2023). A healthy gut microbiota is characterised by adequate biodiversity and a good balance between beneficial and disadvantageous microorganisms (a condition known as eubiosis) (Álvarez-Mercado and Plaza-Diaz 2022). When the balance is altered (dysbiosis), a pathological condition is established that affects not only the digestive system but also the whole organism, generating neurological, cardiovascular, oncological and psychiatric dysfunctions (Sánchez et al. 2017).

Preclinical and clinical studies confirmed that microbial intestinal dysbiosis is responsible for the pathogenesis of central nervous system disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, prion disease and frontotemporal lobar degeneration (Manos 2022), but also neuropsychiatric disorders such as autism spectrum, epilepsy and major depressive disorder (Kowalski and Mulak 2019). In particular, gastrointestinal symptoms often precede neurological symptoms several years before the development of neurodegenerative diseases (Block and Hong 2005). Changes in gut bacteria increase gut permeability and immune activation, causing widespread inflammation (Spielman et al. 2018).

The intestine and the entire bacterial population, gut microbiota, are considered key players in the health-disease binomial and are often referred to as the 'second brain' (Seo et al. 2023). The main neurodegenerative diseases that affect the brain and that show, at the same time, an alteration of the intestinal microbiota are Alzheimer's disease, Parkinson's disease, multiple sclerosis, autism spectrum disorder, epilepsy and major depressive disorder (Ghasemi et al. 2021).

Recent studies have suggested that intestinal dysbiosis and *Staphylococcus*, *Streptococcus*, *Citrobacter*, *Salmonella*, *Klebsiella*, *Mycobacteria* and *Bacillus* genera can trigger protein misfolding, accumulate Aβ structures in the brain, and exacerbate neuroinflammation (Ray et al. 2025). Another study was conducted in vivo on mice in which Alzheimer's disease was transgenically induced; these animals had Aβ plaques, neurofibrillary tangles, reactive gliosis in the brain, memory defects, loss of integrity of the intestinal barrier, intestinal inflammation and alteration of the microbiota. These dysfunctions have been improved following the transplantation of microbiota from healthy wild-type mice. Mice showed decreased levels of Aβ and tau proteins, improved synaptic plasticity, and a composition of intestinal microbiota similar to wild-type mice (Catanzaro et al. 2015).

Several studies have shown a strong interconnection between intestinal dysbiosis and ALS; in fact, ALS is linked not only to alterations in the composition of the intestinal microbiota but also to the production of intestinal neurotoxins (tetanus and botulinum toxins) (Jyothi et al. 2015). These toxins could cross the intestinal lumen and reach the systemic circulation due to increased endothelial permeability (Wilson et al. 2010). Recent studies have reported that patients with ALS have low levels of anti-inflammatory bacteria (*bacteroidetes*) compared to pro-inflammatory bacteria (*Cyanobacteria*) (Uesaka et al. 2016).

PD patients reported prodromal nonmotor symptoms 20 years before the onset of the disease, including dysphagia, constipation, nausea, hypersalivation and altered bowel habit (Stenson et al. 2024). Studies conducted on animal models have shown that PD occurs in the enteric nervous system and spreads from the intestine to the brain via the vagus nerve (Gotkine et al. 2020). Some experimental data support a close connection

between PD and gut microbiota: when mice affected by PD were treated with antibiotics and deprived of the intestinal microbiota, the symptoms of the pathology improved significantly; moreover, when germ-free mice received a faecal microbial transplantation from PD patient donors, the animals showed an increased neuroinflammatory state and motor dysfunction (Wu et al. 2015).

Intestinal dysbiosis is one of the main factors responsible for MS (Li, Meng, et al. 2023), and patients reported this disorder. MS patients exhibited a reduction in anti-inflammatory bacteria and an increase in pro-inflammatory bacteria, resulting in a microbial intestinal profile that differed significantly from that of healthy individuals. Additionally, germ-free mice exhibited higher myelin expression than sick mice (Pellegrini et al. 2020).

A correlation between intestinal dysbiosis and HD is usually observed before the onset of disease, when altered circulating intestinal metabolites (secreted by the enteric nervous system) are measurable (Dugger et al. 2017). In addition, there is evidence of an increase in the level of *Bacteroidetes* and a decrease in the level of *Firmicutes*. The *Firmicutes*/*Bacteroidetes* (F/B) ratio is a biomarker of the intestinal microbiota and can provide information on the body's ability to metabolise nutrients. A high ratio, with more *Firmicutes*, has been associated with obesity, while a lower ratio, with more *Bacteroidetes*, has been linked to a lean constitution. This specific intestinal dysbiosis may indicate a reduction in body weight (typical of the disease) despite increased dietary intake (Zhou et al. 2022).

Recent studies have shown that the consumption of pomegranate peel can enrich the intestinal microbiota: in particular, the polyphenols contained in the peel increase the abundance of specific bacterial metabolites (Mowry and Glenn 2018). Research on human gut microbiota revealed that pomegranate peel treatment boosts gamma-aminobutyric acid (GABA), a fundamental inhibitory neurotransmitter in the human central nervous system. Its main function is to reduce neuronal arousal, helping to regulate anxiety, stress and sleep. GABA neurotransmitter production may potentially ease Parkinson's motor symptoms (Gubert et al. 2022). Moreover, studies indicate that pomegranate peel stimulates the production of short-chain fatty acids (SCFAs) (van der Burg et al. 2011); intestinal bacteria ferment dietary fibre and resistant starch, generating SCFAs such as butyrate, acetate and propionate. SCAFAs protect intestinal health by fortifying the intestinal barrier, influencing motility and promoting epithelial cell growth. In addition, SCFAs may also affect the brain via the gut-brain axis (Sorrenti et al. 2019). Pomegranate peel polyphenols boost beneficial gut bacteria like *Bacteroides*, *Lactobacilli*, *Christensenellaceae* and *Ruminococcaceae* (Mosele et al. 2015). Figure 5 summarises how the functioning of the brain is linked to the intestine.

5 | Discussion

Neurodegeneration involves the deterioration and loss of neurons, which is responsible for the onset of neurodegenerative diseases and alterations in cognitive and/or motor functions.

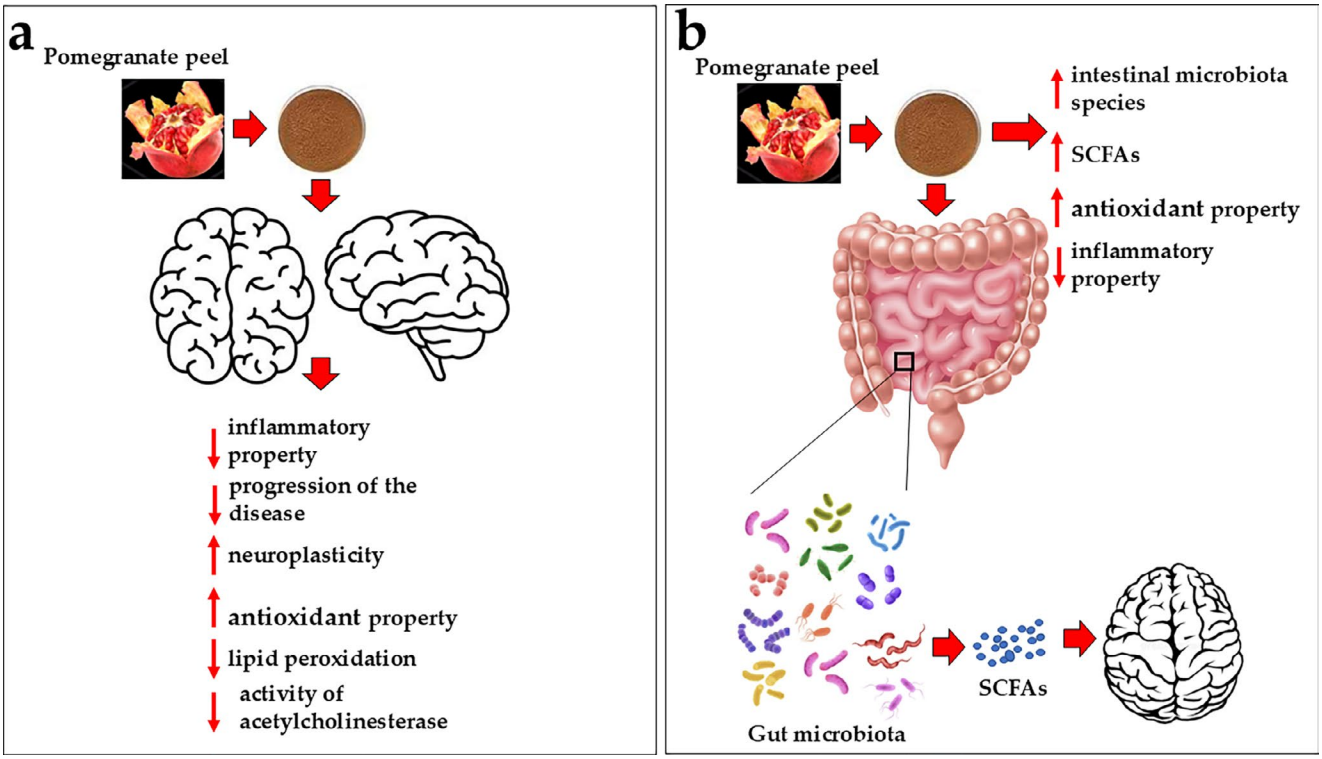


FIGURE 5 | Protective effects of pomegranate peel on neurodegeneration. In panel (a), it is shown that the pomegranate peel can act directly on the brain, decreasing inflammatory properties, disease progression, lipid peroxidation and acetylcholinesterase activity; in addition, it can increase neuroplasticity, antioxidant properties and protective activities. In panel (b), the intestine takes on the pomegranate peel and, as a result, increases the variability of the species that make up the intestinal microbiota and their products, short-chain fatty acids (SCFAs). Microbiota bacteria and SCAFs act beneficially on the brain.

These events result from various neuroinflammatory processes involving alterations in proper glia–neuron communication. Although the causes that determine the onset of a neurodegenerative disease may be different, there is always a common biochemical pathway that characterises them and explains the loss of neuronal cells (George et al. 2023). In a non-pathological context, astrocytes are multifunctional cells that ensure brain homeostasis, regulating blood flow (Fiacco and McCarthy 2006) and extracellular pH (Boyarsky et al. 1993), maintaining synaptic transmission (Ventura and Harris 1999) and carrying out the removal of free radical species of the brain (Drukarch et al. 1998). Microglial cells are dynamic immunocompetent cells, termed 'brain-resident macrophages'. Their role is to phagocytose neuronal debris, maintain brain homeostasis and ensure central nervous system activities, including neuronal survival (Yang et al. 2004), brain development (Bilimoria and Stevens 2015), synaptic remodelling and neurogenesis (Shin et al. 2020). Conversely, under adverse conditions, microglial cells become chronically activated and adopt the pro-inflammatory M1 phenotype. The latter involves the expression of numerous inflammatory cytokines such as IL-1β, IL-6, interferon alpha (INF-α), tumour necrosis factor alpha (TNF-α) and chemokines. When the M1 phenotype persists, it leads to chronic neuroinflammation (Ismail et al. 2020), oxidative stress (Cheignon et al. 2018), blood–brain barrier disruption (Galea 2021; Huang et al. 2021), reduced neuronal viability, neuronal apoptosis (Hu et al. 1998), brain atrophy and astrocyte hyper-reactivity (Danesi and Ferguson 2017). Pomegranate peel phytochemicals and polyphenols may play an important role, reducing the risk of developing both chronic inflammation and oxidative stress-related diseases (Alami et al. 2024). Ellagic acid, ellagitannins, punicalagin and urolithins are just some of the beneficial components found in pomegranate and particularly in the fruit peel. Yet their role in protecting against neurodegeneration has become evident, as they are capable of extinguishing the oxidative potential and inflammatory processes involved in neurodegenerative diseases (Chang et al. 2019). It has been shown that the effects of pomegranate extracts or fruit peel are greater than those of the individual components. When natural products simultaneously contain many phytochemicals (flavonoids, anthocyanidins, anthocyanins, phenolic acids, hydrolyzable tannins, carotenoids) and this characteristic accentuates some protective effects, we can identify them as "superfoods" (Zhu et al. 2015). These phenomena also include the pomegranate fruit, which, by containing excellent categories of polyphenols, presumably amplifies their effects. Globally, polyphenols can interact with each other or with other plant components; this combined interaction produces a total synergistic effect, which is greater than the sum of the effects of individual molecules (Gigliobianco et al. 2020).

It is important not to forget that pomegranate peel is considered a waste product, even if its components can have a protective activity against neurodegenerative diseases, acting directly on the brain or, indirectly, on the same organ, but starting from the intestine (Hrelia et al. 2023). Therefore, it would be optimal to recover these valuable, sustainable and easily accessible resources from waste, thanks to a circular economy process (Hrelia et al. 2025; Jalila et al. 2016). The circular economy is an economic model that minimises the extraction of new resources, keeps materials and products in use for as long as possible and promotes reuse and recycling (Ojha et al. 2020). This approach not only reduces environmental impact but can also lead to new economic and trade opportunities (Osorio et al. 2021). Pomegranate peel can be considered a highly sustainable portion of the fruit and a confirmation of the success of the circular economy in the efficient recovery of agri-food waste (Ballistreri et al. 2024). Another key point to discuss is that pomegranate peel improves the gut microbiota, regulating gut bacteria, increasing positive bacteria and decreasing harmful ones (Chen et al. 2025; Jose et al. 2017). Prebiotics are non-digestible substances that promote the growth of beneficial bacteria in the intestine, contributing to the balance of bacterial flora and well-being. These compounds are fermented by intestinal bacteria, producing short-chain fatty acids (SCFAs) that have positive effects on the intestine and general health (Noor et al. 2022). Pomegranate peel fully complies with this definition and, for this reason, we can state that this waste product is a prebiotic.

6 | Conclusions and Perspectives

Although this review has highlighted some interesting potential for using pomegranate peel, some limitations have emerged that could be addressed in future perspectives: first of all, data from human clinical trials involving neurodegenerative diseases are lacking, and the available data are few and do not include significant numbers. Second, the available results do not address the actual ability of pomegranate peel components to reach the neuronal compartment, the interaction of polyphenols with the blood–brain barrier and their penetrability.

Author Contributions

Conceptualization: J.M., V.M. (Vincenzo Mollace), C.M. Writing: J.M., V.M. (Valeria Mazza), R.C. Original draft preparation: F.O., S.N., S.R. Editing: S.I., L.C.P., L.T., G.T. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

References

Abdolmaleky, H. M., and J.-R. Zhou. 2023. "Underlying Mechanisms of Brain Aging and Neurodegenerative Diseases as Potential Targets for Preventive or Therapeutic Strategies Using Phytochemicals." *Nutrients* 15, no. 15: 3456.

Abid, M., H. Yaich, H. Hidouri, H. Attia, and M. A. Ayadi. 2018. "Effect of Substituted Gelling Agents From Pomegranate Peel on Colour, Textural and Sensory Properties of Pomegranate Jam." *Food Chemistry* 239: 1047–1054.

Adak, A., and M. R. Khan. 2019. "An Insight Into Gut Microbiota and Its Functionalities." *Cellular and Molecular Life Sciences* 76, no. 3: 473–493.

Adams, L. S., Y. Zhang, N. P. Seeram, D. Heber, and S. Chen. 2010. "Pomegranate Ellagitannin–Derived Compounds Exhibit Antiproliferative and Antiaromatase Activity in Breast Cancer Cells In Vitro." *Cancer Prevention Research* 3: 108–113.

Aguilar-Zarate, P., J. E. Wong-Paz, J. J. Buenrostro-Figueroa, J. A. Ascacio, J. C. Contreras-Esquivel, and C. N. Aguilar. 2018. "Ellagitannins: Bioavailability, Purification and Biotechnological Degradation." *Mini Reviews in Medicinal Chemistry* 18, no. 15: 1244–1252.

Ahmed, A. H., G. M. Subaiea, A. Eid, L. Li, N. P. Seeram, and N. H. Zawia. 2014. "Pomegranate Extract Modulates Processing of Amyloid-β Precursor Protein in an Aged Alzheimer's Disease Animal Model." *Current Alzheimer Research* 11, no. 9: 834–843.

Ahmed, M. M., E.-S. A. A. Samir, M. El-Shehawi, and M. E. Alkafafy. 2015. "Anti-Obesity Effects of Taif and Egyptian Pomegranates: Molecular Study." *Bioscience, Biotechnology, and Biochemistry* 79, no. 4: 598–609.

Akpinar, E. K. 2010. "Drying of Mint Leaves in a Solar Dryer and Under Open Sun: Modelling, Performance Analyses." *Energy Conversion and Management* 51: 2407–2418.

Al Hariri, M., K. Zibara, W. Farhat, et al. 2016. "Cigarette Smoking-Induced Cardiac Hypertrophy, Vascular Inflammation and Injury Are Attenuated by Antioxidant Supplementation in an Animal Model." *Frontiers in Pharmacology* 7: 397.

Alalawi, S., F. Albalawi, and D. P. Ramji. 2023. "The Role of Punicalagin and Its Metabolites in Atherosclerosis and Risk Factors Associated With the Disease." *International Journal of Molecular Sciences* 24, no. 10: 8476.

Alami, M., K. Boumezough, E. Zerif, et al. 2024. "In Vitro Assessment of the Neuroprotective Effects of Pomegranate (*Punica granatum* L.) Polyphenols Against Tau Phosphorylation, Neuroinflammation, and Oxidative Stress." *Nutrients* 16, no. 21: 3667.

Alara, O. R., N. H. Abdurahman, and C. I. Ukaegbu. 2021. "Extraction of Phenolic Compounds: A Review." *Current Research in Food Science* 4: 200–214.

Al-Chalabi, A., A. Calvo, A. Chio, et al. 2014. "Analysis of Amyotrophic Lateral Sclerosis as a Multistep Process: A Population-Based Modelling Study." *Lancet Neurology* 13: 1108–1113.

Aleksandrova, S., R. Alexova, S. Dragomanova, et al. 2023. "Preventive and Therapeutic Effects of *Punica granatum* L. Polyphenols in Neurological Conditions." *International Journal of Molecular Sciences* 24, no. 3: 1856.

Ali, A. A., M. M. Kamal, M. G. Khalil, et al. 2022. "Behavioral, Biochemical and Histopathological Effects of Standardised Pomegranate Extract With Vinpocetine, Propolis or Cocoa in a Rat Model of Parkinson's Disease." *Experimental Aging Research* 48, no. 2: 191–210.

Al-Rawahi, A. S., M. S. Rahman, N. Guizani, and M. M. Essa. 2013. "Chemical Composition, Water Sorption Isotherm, and Phenolic Contents in Fresh and Dried Pomegranate Peels." *Drying Technology* 31: 257–263.

Álvarez-Mercado, A. I., and J. Plaza-Diaz. 2022. "Dietary Polysaccharides as Modulators of the Gut Microbiota Ecosystem: An Update on Their Impact on Health." *Nutrients* 14, no. 19: 4116.

Amri, Z., A. Ghorbel, M. Turki, et al. 2017. "Effect of Pomegranate Extracts on Brain Antioxidant Markers and Cholinesterase Activity in High Fat-High Fructose Diet Induced Obesity in Rat Model." *BMC Complementary and Alternative Medicine* 17: 339.

Angeloni, C., M. Malaguti, C. Prata, M. Freschi, M. C. Barbalace, and S. Hrelia. 2022. "Mechanisms Underlying Neurodegenerative Disorders and Potential Neuroprotective Activity of Agrifood By-Products." *Antioxidants (Basel)* 12, no. 1: 94.

Azmat, F., M. Safdar, H. Ahmad, et al. 2024. "Phytochemical Profile, Nutritional Composition of Pomegranate Peel and Peel Extract as a Potential Source of Nutraceutical: A Comprehensive Review." *Food Science & Nutrition* 12: 661–674.

Ballistreri, G., M. Amenta, S. Fabroni, N. Timpanaro, and G. M. Platania. 2024. "Sustainable Extraction Protocols for the Recovery of Bioactive Compounds From By-Products of Pomegranate Fruit Processing." *Food* 13, no. 12: 1793.

Baluchnejadmojarad, T., N. Rabiee, S. Zabihnejad, and M. Roghani. 2017. "Ellagic Acid Exerts Protective Effect in Intrastriatal 6 Hydroxydopamine Rat Model of Parkinson's Disease: Possible Involvement of ERβ/Nrf2/HO-1 Signaling." *Brain Research* 1662: 23–30.

Bandawane, D., A. Kotkar, and P. Ingole. 2023. "Protective Effect of Hydroalcoholic Extract of *Punica granatum* Leaves on High Fructose Induced Insulin Resistance in Experimental Animals." *Cardiovascular & Hematological Disorders Drug Targets* 23, no. 4: 263–276.

Barbero Mazzucca, C., G. Cappellano, and A. Chiocchetti. 2024. "Nutrition, Immunity and Aging: Current Scenario and Future Perspectives in Neurodegenerative Diseases." *CNS & Neurological Disorders Drug Targets* 23, no. 5: 573–587.

Barrio, C., S. Arias-Sánchez, and I. Martín-Monzón. 2022. "The Gut Microbiota-Brain Axis, Psychobiotics and Its Influence on Brain and Behaviour: A Systematic Review." *Psychoneuroendocrinology* 137: 105640.

Belwal, T., C. Cravotto, M. A. Prieto, et al. 2022. "Effects of Different Drying Techniques on the Quality and Bioactive Compounds of Plant-Based Products: A Critical Review on Current Trends." *Drying Technology* 40, no. 8: 1539–1561. https://doi.org/10.1080/07373937.2022.2068028.

Benedetti, G., F. Zabini, L. Tagliavento, F. Meneguzzo, V. Calderone, and L. Testai. 2023. "An Overview of the Health Benefits, Extraction Methods and Improving the Properties of Pomegranate." *Antioxidants (Basel)* 12, no. 7: 1351.

Bido, S., S. Muggeo, L. Massimino, et al. 2021. "Microglia-Specific Overexpression of Alpha-Synuclein Leads to Severe Dopaminergic Neurodegeneration by Phagocytic Exhaustion and Oxidative Toxicity." *Nature Communications* 12, no. 1: 6237.

Bilimoria, P. M., and B. Stevens. 2015. "Microglia Function During Brain Development: New Insights From Animal Models." *Brain Research* 1617: 7–17.

Binyamin, O., L. Larush, K. Frid, et al. 2015. "Treatment of a Multiple Sclerosis Animal Model by a Novel Nanodrop Formulation of a Natural Antioxidant." *International Journal of Nanomedicine* 10: 7165–7174.

Block, M. L., and J.-S. Hong. 2005. "Microglia and Inflammation-Mediated Neurodegeneration: Multiple Triggers With a Common Mechanism." *Progress in Neurobiology* 76: 77–89.

Boyarsky, G., B. Ransom, W.-R. Schlue, M. B. E. Davis, and W. F. Boron. 1993. "Intracellular PH Regulation in Single Cultured Astrocytes From Rat Forebrain." *Glia* 8: 241–248.

Breijyeh, Z., and R. Karaman. 2020. "Comprehensive Review on Alzheimer's Disease: Causes and Treatment." *Molecules* 5, no. 24: 5789.

Bremer, J., and K. R. Norum. 1982. "Metabolism of Very Long-Chain Monounsaturated Fatty Acids (22:1) and the Adaptation to Their Presence in the Diet." *Journal of Lipid Research* 23, no. 2: 243–256.

Brett, B. L., R. C. Gardner, J. Godbout, K. Dams-O'Connor, and C. D. Keene. 2022. "Traumatic Brain Injury and Risk of Neurodegenerative Disorder." *Biological Psychiatry* 91, no. 5: 498–507.

Brown, R. H., and A. Al-Chalabi. 2017. "Amyotrophic Lateral Sclerosis." *New England Journal of Medicine* 377: 162–172.

Busto, R., J. Serna, A. Perianes-Cachero, et al. 2018. "Ellagic Acid Protects From Myelin-Associated Sphingolipid Loss in Experimental Autoimmune Encephalomyelitis." *Biochimica et Biophysica Acta (BBA)* 1863: 958–967.

Caminiti, R., M. Serra, S. Nucera, et al. 2024. "Antioxidant Activity and Seasonal Variations in the Composition of Insoluble Fiber From the Cladodes of *Opuntia ficus-indica* (L.) Miller: Development of New Extraction Procedures to Improve Fiber Yield." *Plants (Basel, Switzerland)* 13, no. 4: 544.

Campos, L., L. Seixas, M. H. F. Henriques, A. M. Peres, and A. C. A. Veloso. 2022. "Pomegranate Peels and Seeds as a Source of Phenolic Compounds: Effect of Cultivar, By-Product, and Extraction Solvent." *International Journal of Food Sciences and Nutrition* 2022: 9189575.

Cano-Lamadrid, M., L. Martínez-Zamora, N. Castillejo, and F. Artés-Hernández. 2022. "From Pomegranate Byproducts Waste to Worth: A Review of Extraction Techniques and Potential Applications for Their Revalorization." *Food* 11: 2596.

Castro-Muñoz, R., E. Díaz-Montes, E. Gontarek-Castro, G. Boczkaj, and C. M. Galanakis. 2022. "A Comprehensive Review on Current and Emerging Technologies Toward the Valorization of Bio-Based Wastes and by Products From Foods." *Comprehensive Reviews in Food Science and Food Safety* 21, no. 1: 46–105.

Catanzaro, R., M. G. Anzalone, F. Calabrese, et al. 2015. "The Gut Microbiota and Its Correlations With the Central Nervous System Disorders." *Panminerva Medica* 57: 127–143.

Cepeda, C., and X. P. Tong. 2018. "Huntington's Disease: From Basic Science to Therapeutics." *CNS Neuroscience & Therapeutics* 24, no. 4: 247–249.

Chamarthi, V. S., and S. F. Daley. 2025. "Comprehensive Assessment and Diagnosis of Metabolic and Biomechanical Complications in Obesity." In *StatPearls [Internet]*. StatPearls Publishing.

Chang, S. K., C. Alasalvar, and F. Shahidi. 2019. "Superfruits: Phytochemicals, Antioxidant Efficacies, and Health Effects—A Comprehensive Review." *Critical Reviews in Food Science and Nutrition* 59, no. 10: 1580–1604.

Cheignon, C., M. Tomas, D. Bonnefont-Rousselot, P. Faller, C. Hureau, and F. Collin. 2018. "Oxidative Stress and the Amyloid Beta Peptide in Alzheimer's Disease." *Redox Biology* 14: 450–464.

Chen, P., Z. Guo, J. Lei, and Y. Wang. 2024. "Pomegranate Polyphenol Punicalin Ameliorates Lipopolysaccharide-Induced Memory Impairment, Behavioral Disorders, Oxidative Stress, and Neuroinflammation via Inhibition of TLR4-NF-B Pathway." *Phytotherapy Research* 38, no. 7: 3489–3508.

Chen, W., Y. Huang, W. Li, et al. 2025. "The Potential of Pomegranate Peel Supplementation in Yellow-Feathered Broilers: Effects on Growth Performance, Serum Biochemistry, Antioxidant Capacity, Intestinal Health, Intestinal Microbiota, and Duodenal Mucosal Metabolites." *Poultry Science* 104, no. 4: 104983.

Chen, X. X., S. Khyeam, Z. J. Zhang, and K. Y. Zhang. 2022. "Granatin B and Punicalagin From Chinese Herbal Medicine Pomegranate Peels Elicit Reactive Oxygen Species-Mediated Apoptosis and Cell Cycle Arrest in Colorectal Cancer Cells." *Phytomedicine* 97: 153923.

Chitnis, T., and H. L. Weiner. 2017. "CNS Inflammation and Neurodegeneration." *Journal of Clinical Investigation* 127: 3577–3587.

Ciccone, L., S. Nencetti, A. Rossello, and E. Orlandini. 2023. "Pomegranate: A Source of Multifunctional Bioactive Compounds Potentially Beneficial in Alzheimer's Disease." *Pharmaceuticals* 16: 1036.

Čižmáriková, M., R. Michalková, L. Mirossay, et al. 2023. "Ellagic Acid and Cancer Hallmarks: Insights From Experimental Evidence." *Biomolecules* 13, no. 11: 1653.

Cordiano, R., L. Gammeri, D. Salvo, S. Gangemi, and P. L. Minciullo. 2024. "Pomegranate (*Punica granatum* L.) Extract Effects on Inflammaging." *Molecules* 29, no. 17: 4174.

Cortés-Martín, A., M. V. Selma, F. A. Tomás-Barberán, A. González-Sarrías, and J. C. Espín. 2020. "Where to Look Into the Puzzle of Polyphenols and Health? The Postbiotics and Gut Microbiota as Sociated With Human Metabotypes." *Molecular Nutrition & Food Research* 64: 1900952.

Dahlawi, H., N. Jordan-Mahy, M. R. Clench, and C. L. Le Maitre. 2012. "Bioactive Actions of Pomegranate Fruit Extracts on Leukemia Cell Lines In Vitro Hold Promise for New Therapeutic Agents for Leukemia." *Nutrition and Cancer* 64: 100–110.

Danesi, F., and L. R. Ferguson. 2017. "Could Pomegranate Juice Help in the Control of Inflammatory Diseases?" *Nutrients* 9: 958.

Darwish, S. F., A. M. M. Elbadry, A. S. Elbokhomy, G. A. Salama, and R. M. Salama. 2023. "The Dual Face of Microglia (M1/M2) as a Potential Target in the Protective Effect of Nutraceuticals Against Neurodegenerative Diseases." *Frontiers in Aging* 4: 1231706.

Dendrou, C. A., L. Fugger, and M. A. Friese. 2015. "Immunopathology of Multiple Sclerosis." *Nature Reviews Immunology* 15: 545–558.

Depaz, R., B. Granger, I. Cournu-Rebeix, A. Bouafia, and B. Fontaine. 2011. "Genetics for Understanding and Predicting Clinical Progression in Multiple Sclerosis." *Revue Neurologique (Paris)* 167, no. 11: 791–801.

Di Vincenzo, F., A. Del Gaudio, V. Petito, L. R. Lopetuso, and F. Scaldaferri. 2023. "Gut Microbiota, Intestinal Permeability, and Systemic Inflammation: A Narrative Review." *Internal and Emergency Medicine* 19, no. 2: 275–293.

Diao, M., Y. Liang, J. Zhao, J. Zhang, and T. Zhang. 2022. "Complexation of Ellagic Acid With Alpha-Lactalbumin and Its Antioxidant Property." *Food Chemistry* 372: 131307.

Dretcanu, G., C. I. Iuhas, and Z. Diaconeasa. 2021. "The Involvement of Natural Polyphenols in the Chemoprevention of Cervical Cancer." *International Journal of Molecular Sciences* 22: 8812.

Drukarch, B., E. Schepens, J. C. Stoof, C. H. Langeveld, and F. L. Van Muiswinkel. 1998. "Astrocyte-Enhanced Neuronal Survival Is Mediated by Scavenging of Extracellular Reactive Oxygen Species." *Free Radical Biology & Medicine* 25: 217–220.

Dugger, B. N., D. P. Perl, and G. A. Carlson. 2017. "Neurodegenerative Disease Transmission and Transgenesis in Mice." *Cold Spring Harbor Perspectives in Biology* 9, no. 11: a023549.

Echeverria, F., P. A. J. Patino, M. Castro-Sepulveda, et al. 2021. "Microencapsulated Pomegranate Peel Extract Induces Mitochondrial Complex IV Activity and Prevents Mitochondrial Cristae Alteration in Brown Adipose Tissue in Mice Fed on a High-Fat Diet." *British Journal of Nutrition* 126, no. 6: 825–836.

Eddebbagh, M., M. Massoudi, A. Abourriche, et al. 2016. "Correlation of the Cytotoxic and Antioxidant Activities of Moroccan Pomegranate (*Punica granatum*) With Phenolic and Flavonoid Contents." *Journal of Pharmacy and Pharmacology* 4, no. 9: 511–519.

El Maaiden, E., S. Bouzroud, B. Nasser, et al. 2022. "A Comparative Study Between Conventional and Advanced Extraction Techniques:

Pharmaceutical and Cosmetic Properties of Plant Extracts." *Molecules* 27, no. 7: 2074.

El-Beih, N. M., G. Ramadan, E. A. El-Husseiny, and A. M. Hussein. 2019. "Effects of Pomegranate Aril Juice and Its Punicalagin on Some Key Regulators of Insulin Resistance and Oxidative Liver Injury in Streptozotocin-Nicotinamide Type 2 Diabetic Rats." *Molecular Biology Reports* 46, no. 4: 3701–3711.

El-Hadary, A. E., and M. F. Ramadan. 2019. "Phenolic Profiles, Antihyperglycemic, Antihyperlipidemic, and Antioxidant Properties of Pomegranate (*Punica granatum*) Peel Extract." *Journal of Food Biochemistry* 43: 1–9.

El-Said, M. M., H. F. Haggag, H. M. F. El-Din, A. S. Gad, and A. M. Farahat. 2014. "Antioxidant Activities and Physical Properties of Stirred Yoghurt Fortified With Pomegranate Peel Extracts." *Annals of Agricultural Science* 59: 207–212.

Elwej, A., G. Salah, K. C. Ben, F. Fakhfakh, N. Zeghal, and A. I. Ben. 2016. "Protective Effects of Pomegranate Peel Against Hematotoxicity, Chromosomal Aberrations, and Genotoxicity Induced by Barium Chloride in Adult Rats." *Pharmaceutical Biology* 54, no. 6: 964–974.

Eroglu Ozkan, E., M. F. Seyhan, O. Kurt Sirin, et al. 2021. "Antiproliferative Effects of Turkish Pomegranate (*Punica granatum* L.) Extracts on MCF-7 Human Breast Cancer Cell Lines With Focus on Antioxidant Potential and Bioactive Compounds Analyzed by LC-MS/MS." *Journal of Food Biochemistry* 45: e13904.

Faria, A., and C. Calhau. 2011. "The Bioactivity of Pomegranate: Impact on Health and Disease." *Critical Reviews in Food Science and Nutrition* 51, no. 7: 626–634.

Feng, X., Q. Yang, C. Wang, W. Tong, and W. Xu. 2020. "Punicalagin Exerts Protective Effects Against Ankylosing Spondylitis by Regulating NF-kappaB-TH17/JAK2/STAT3 Signaling and Oxidative Stress." *BioMed Research International* 2020: 4918239.

Feng, Y., J. Lin, G. He, et al. 2022. "Compositions and Biological Activities of Pomegranate Peel Polyphenols Extracted by Different Solvents." *Molecules* 27, no. 15: 4796.

Ferreiro, A. L., H.-H. Choi, J. Ryou, et al. 2023. "Gut Microbiome Composition May Be an Indicator of Preclinical Alzheimer's Disease." *Science Translational Medicine* 15, no. 700: eabo2984.

Fiacco, T. A., and K. D. McCarthy. 2006. "Astrocyte Calcium Elevations: Properties, Propagation, and Effects on Brain Signalling." *Glia* 54: 676–690.

Fierascu, R. C., E. Sieniawska, A. Ortan, I. Fierascu, and J. Xiao. 2020. "Fruits By-Products—A Source of Valuable Active Principles. A Short Review." *Frontiers in Bioengineering and Biotechnology* 8: 319.

Fraga, C. G., P. I. Oteiza, and M. Galleano. 2018. "Plant Bioactives and Redox Signaling: (−)-Epicatechin as a Paradigm." *Molecular Aspects of Medicine* 61: 31–40.

Fraga-Corral, M., P. Otero, J. Echave, et al. 2021. "By-Products of Agri-Food Industry as Tannin-Rich Sources: A Review of Tannins' Biological Activities and Their Potential for Valorization." *Food* 10, no. 1: 137.

Franczyk-Żarów, M., T. Tarko, A. Drahun-Misztal, I. Czyzynska-Cichon, E. Kus, and R. B. Kostogrys. 2023. "Pomegranate Seed Oil as a Source of Conjugated Linolenic Acid (CLnA) Has no Effect on Atherosclerosis Development but Improves Lipid Profile and Affects the Expression of Lipid Metabolism Genes in ApoE/LDLR−/−Mice." *International Journal of Molecular Sciences* 24, no. 2: 1737.

Galea, I. 2021. "The Blood—Brain Barrier in Systemic Infection and in Fl Ammation." *Cellular & Molecular Immunology* 8: 2489–2501.

García-Villalba, R., F. A. Tomás-Barberán, C. E. Iglesias-Aguirre, et al. 2023. "Ellagitannins, Urolithins, and Neuroprotection: Human Evidence and the Possible Link to the Gut Microbiota." *Molecular Aspects of Medicine* 89: 101109.

Gardener, H., and M. R. Caunca. 2018. "Mediterranean Diet in Preventing Neurodegenerative Diseases." *Current Nutrition Reports* 7, no. 1: 10–20.

Gates, E. J., A. K. Bernath, and A. Klegeris. 2022. "Modifying the Diet and Gut Microbiota to Prevent and Manage Neurodegenerative Diseases." *Reviews in the Neurosciences* 33, no. 7: 767–787.

Ge, S., L. Duo, J. Wang, J. Z. Yang GegenZhula, and Y. T. Li. 2021. "A Unique Understanding of Traditional Medicine of Pomegranate, *Punica granatum* L. and Its Current Research Status." *Journal of Ethnopharmacology* 271, no. 27: 13877.

George, N., M. AbuKhader, K. Al Balushi, B. Al Sabahi, and S. A. Khan. 2023. "An Insight Into the Neuroprotective Effects and Molecular Targets of Pomegranate (*Punica granatum*) Against Alzheimer's Disease." *Nutritional Neuroscience* 26, no. 10: 975–996.

Ghasemi, M., K. Keyhanian, and C. Douthwright. 2021. "Glial Cell Dysfunction in *C9orf72*-Related Amyotrophic Lateral Sclerosis and Frontotemporal Dementia." *Cells* 10, no. 2: 249.

Gigliobianco, M. R., B. Campisi, D. V. Peregrina, et al. 2020. "Optimization of the Extraction From Spent Coffee Grounds Using the Desirability Approach." *Antioxidants* 9: 370.

Gotkine, M., D. Kviatcovsky, and E. Elinav. 2020. "Amyotrophic Lateral Sclerosis and Intestinal Microbiota-Toward Establishing Cause and Effect." *Gut Microbes* 11: 1833–1841.

Gubert, C., J. M. Choo, C. J. Love, et al. 2022. "Faecal Microbiota Transplant Ameliorates Gut Dysbiosis and Cognitive Deficits in Huntington's Disease Mice." *Brain Communications* 4, no. 4: fcac205.

Hajleh, M. A., and A. Al-Dujaili. 2016. "Anti-Cancer Activity of Pomegranate and Its Biophenols; General Review." *EC Nutrition* 6: 28–52.

Hamo, C., F. Schlamp, K. Drenkova, et al. 2024. "Burden of Cardiometabolic Risk Factors and Vascular Health." *American Heart Journal* 269: 201–204.

Hanafy, S. M., Y. M. Abd El-Shafea, W. D. Saleh, and H. M. Fathy. 2021. "Chemical Profiling, In Vitro Antimicrobial and Antioxidant Activities of Pomegranate, Orange and Banana Peel-Extracts Against Pathogenic Microorganisms." *Journal of Genetic Engineering and Biotechnology* 19, no. 1: 80.

Harakeh, S., W. S. Ramadan, M. S. A. Muhayawi, S. A. Jaouni, S. Mousa, and K. R. Hakeem. 2020. "Pomegranate Peel Extract Lessens Histopathologic Changes and Restores Antioxidant Homeostasis in the Hippocampus of Rats With Aluminium Chloride-Induced Alzheimer's Disease." *Asian Pacific Journal of Tropical Medicine* 13: 456.

Hasan, A. M., A. A. Redha, and Q. Mandeel. 2018. "Phytochemical Determinations of Pomegranate (*Punica granatum*) Rind and Aril Extracts and Their Antioxidant, Antidiabetic and Antibacterial Activity." *Natural Product Chemistry & Research* 6: 1000332.

Hasnaoui, H., B. Wathelet, and A. Jiménez-Araujo. 2014. "Valorization of Pomegranate Peel From 12 Cultivars: Dietary Fibre Composition, Antioxidant Capacity and Functional Properties." *Food Chemistry* 160: 196–203.

Hayasaka, N., N. Shimizu, T. Komoda, et al. 2018. "Absorption and Metabolism of Luteolin in Rats and Humans in Relation to In Vitro Anti-Inflammatory Effects." *Journal of Agricultural and Food Chemistry* 66, no. 43: 11320–11329.

Hetz, C., and S. Saxena. 2017. "ER Stress and the Unfolded Protein Response in Neurodegeneration." *Nature Reviews. Neurology* 13, no. 8: 477–491.

Holic, R., Y. Xu, K. M. P. Caldo, et al. 2018. "Bioactivity and Biotechnological Production of Punicic Acid." *Applied Microbiology and Biotechnology* 102, no. 8: 3537–3549.

Hrelia, S., C. Angeloni, and M. C. Barbalace. 2023. "Agri-Food Wastes as Natural Source of Bioactive Antioxidants." *Antioxidants* 12: 351.

Hrelia, S., M. C. Barbalace, and C. Angeloni. 2025. "Agri-Food Wastes as Natural Source of Bioactive Antioxidants-Third Edition." *Antioxidants* 14, no. 2: 198.

Hu, J., K. T. Akama, G. A. Krafft, B. A. Chromy, and L. J. Van Eldik. 1998. "Amyloid-β Peptide Activates Cultured Astrocytes: Morphological Alterations, Cytokine Induction and Nitric Oxide Release." *Brain Research* 785: 195–206.

Huang, T. H. W., G. Peng, B. P. Kota, et al. 2005. "Pomegranate Flower Improves Cardiac Lipid Metabolism in a Diabetic Rat Model: Role of Lowering Circulating Lipids." *British Journal of Pharmacology* 145: 767–774.

Huang, X., B. Hussain, and J. Chang. 2021. "Peripheral Inflammation and Blood–Brain Barrier Disruption: Effects and Mechanisms." *CNS Neuroscience & Therapeutics* 27: 36–47.

Iqbal, I., P. Wilairatana, F. Saqib, et al. 2023. "Plant Polyphenols and Their Potential Benefits on Cardiovascular Health: A Review." *Molecules* 28, no. 17: 6403.

Irwin, M. R., and M. V. Vitiello. 2019. "Implications of Sleep Disturbance and Inflammation for Alzheimer's Disease Dementia." *Lancet Neurology* 18: 296–306.

Ismail, R., P. Parbo, L. S. Madsen, et al. 2020. "The Relationships Between Neuroinflammation, Beta-Amyloid and Tau Deposition in Alzheimer's Disease: ALongitudinal PET Study." *Journal of Neuroinflammation* 17: 151.

Jadeja, R. N., M. C. Thounaojam, D. K. Patel, R. V. Devkar, and A. Ramachandran. 2010. "Pomegranate (*Punica granatum* L.) Juice Supplementation Attenuates Isoproterenol-Induced Cardiac Necrosis in Rats." *Cardiovascular Toxicology* 10: 174–180.

Jalila, B., S. Cazaux, M. Mars, and J. Bouajila. 2016. "In Vitro Anti-Cholinesterase and Anti-Hyperglycemic Activities of Flowers Extracts From Seven Pomegranate Varieties." *Industrial Crops and Products* 81: 176–179.

Jayawickreme, D. K., C. Ekwosi, A. Anand, M. Andres-Mach, P. Wlaź, and K. Socała. 2024. "Luteolin for Neurodegenerative Diseases: A Review." *Pharmacological Reports* 76, no. 4: 644–664.

Jeong, S., S. Bae, E. C. Shin, J. H. Lee, and J. H. Ha. 2023. "Ellagic Acid Prevents Particulate Matter-Induced Pulmonary Inflammation and Hyperactivity in Mice: A Pilot Study." *International Journal of Environmental Research and Public Health* 20, no. 5: 4523.

Jeune, M. L., J. Kumi-Diaka, and J. Brown. 2005. "Anticancer Activities of Pomegranate Extracts and Genistein in Human Breast Cancer Cells." *Journal of Medicinal Food* 8: 469–475.

Jha, A. B., S. S. Panchal, and A. Shah. 2018. "Ellagic Acid: Insights Into Its Neuroprotective and Cognitive Enhancement Effects in Sporadic Alzheimer's Disease." *Pharmacology, Biochemistry, and Behavior* 175: 33–46.

Jiensi, R.-N., Z.-Y. Chang, R.-H. Niu, and X.-L. Gao. 2023. "Punicalagin Inhibits Hepatic Lipid Deposition in Obese Mice via AMPK/ACC Pathway." *China Journal of Chinese Materia Medica* 48, no. 7: 1751–1759.

John, K. M. M., A. A. Bhagwat, and D. L. Luthria. 2017. "Swarm Mortility Inhibitory and Antioxidant Activities of Pomegranate Peel Processed Under Three Drying Conditions." *Food Chemistry* 235: 145–153.

Jose, T., A. K. Pattanaik, S. E. Jadhav, N. Dutta, and S. Sharma. 2017. "Nutrient Digestibility, Hindgut Metabolites and Antioxidant Status of Dogs Supplemented With Pomegranate Peel Extract." *Journal of Nutritional Science* 6: e36.

Jyothi, H. J., D. J. Vidyadhara, A. Mahadevan, et al. 2015. "Aging Causes Morphological Alterations in Astrocytes and Microglia in Human Substantia Nigra Pars Compacta." *Neurobiology of Aging* 36: 3321–3333.

Kalkan, Ö. F., A. Türk, C. Çitil, et al. 2024. "Pomegranate Juice Treatment Reverses Carbon Tetrachloride (CCl4)-Induced Increased Acetylcholinesterase Activity and Cell Death via Suppression of Oxidative Stress in Rats." *Roczniki Państwowego Zakładu Higieny* 75, no. 3: 293–302.

Kamali, M., H. Tavakoli, M. Khodadoost, et al. 2015. "Efficacy of the *Punica granatum* Peels Aqueous Extract for Symptom Management in Ulcerative Colitis Patients. A Randomized, Placebo Controlled, Clinical Trial." *Complementary Therapies in Clinical Practice* 21: 141–146.

Kanatt, S. R., R. Chander, and A. Sharma. 2010. "Antioxidant and Antimicrobial Activity of Pomegranate Peel Extract Improves the Shelf Life of Chicken Products." *International Journal of Food Science and Technology* 45: 216–222.

Kandylis, P., and E. Kokkinomagoulos. 2020. "Food Applications and Potential Health Benefits of Pomegranate and Its Derivatives." *Food* 9, no. 2: 122.

Kang, B., C. Y. Kim, J. Hwang, et al. 2019. "Punicalagin, a Pomegranate-Derived Ellagitannin, Suppresses Obesity and Obesity-Induced Inflammatory Responses via the Nrf2/Keap1 Signaling Pathway." *Molecular Nutrition & Food Research* 63: 1900574.

Karimi, M., R. Sadeghi, and J. Kokini. 2017. "Pomegranate as a Promising Opportunity in Medicine and Nanotechnology." *Trends in Food Science and Technology* 69: 59–73.

Kharchoufi, S., L. Parafati, F. Licciardello, et al. 2018. "Edible Coatings Incorporating Pomegranate Peel Extract and Biocontrol Yeast to Reduce Penicillium Digitatum Postharvest Decay of Oranges." *Food Microbiology* 74: 107–112.

Khwairakpam, A. D., D. Bordoloi, K. K. Thakur, et al. 2018. "Possible Use of *Punica granatum* (Pomegranate) in Cancer Therapy." *Pharmacological Research* 133: 53–64.

Kiasalari, Z., S. Afshin-Majd, F. Fereidouni, et al. 2021. "Ellagic Acid Ameliorates Neuroinflammation and Demyelination in Experimental Autoimmune Encephalomyelitis: Involvement of NLRP3 and Pyroptosis." *Journal of Chemical Neuroanatomy* 111: 101891.

Kim, Y. E., C. J. Hwang, H. P. Lee, et al. 2017. "Inhibitory Effect of Punicalagin on Lipopolysaccharide-Induced Neuroinflammation, Oxidative Stress and Memory Impairment via Inhibition of Nuclear Factor-kappaB." *Neuropharmacology* 117: 21–32.

Kiran, S., A. Tariq, S. Iqbal, et al. 2024. "Punicalagin, a Pomegranate Polyphenol Sensitizes the Activity of Antibiotics Against Three MDR Pathogens of the Enterobacteriaceae." *BMC Complementary Medicine and Therapies* 24, no. 1: 93.

Kiss, A. K., and J. P. Piwowarski. 2018. "Ellagitannins, Gallotannins and Their Metabolites—The Contribution to the Anti-Inflammatory Effect of Food Products and Medicinal Plants." *Current Medicinal Chemistry* 25, no. 37: 4946–4967.

Klemmensen, M. M., S. H. Borrowman, C. Pearce, B. Pyles, and B. Chandra. 2024. "Mitochondrial Dysfunction in Neurodegenerative Disorders." *Neurotherapeutics* 21, no. 1: e00292.

Konsoula, Z. 2018. "A Preliminary In Vitro Investigation of Anticholinesterase Activity of Pomegranate Peel Extracts." *Journal of Biotechnology* 280: S88.

Kowalski, K., and A. Mulak. 2019. "Brain-Gut-Microbiota Axis in Alzheimer's Disease." *Journal of Neurogastroenterology and Motility* 25: 48–60.

Kremer, T. A., C. Carfaro, and S. Klacik. 2023. "Effects of Time, Temperature, and Humidity on Soil Drying on Medical Devices." *Biomedical Instrumentation & Technology* 57, no. 2: 58–66.

Kujawska, M., and J. Jodynis-Liebert. 2020. "Potential of the Ellagic Acid-Derived Gut Microbiota Metabolite—Urolithin A in Gastrointestinal Protection." *World Journal of Gastroenterology* 26: 3170–3181.

Kumar, G. S., R. Nagaraju, K. Swarajyalakshmi, P. Latha, and M. Balakrishna. 2017. "Standardization of Drying Techniques for di Erent Fruit Peel for Making Potpourris." *Plant Archives* 17: 1587–1593.

Kumkum, R., K. Aston-Mourney, B. A. McNeill, D. Hernández, and L. R. Rivera. 2024. "Bioavailability of Anthocyanins: Whole Foods Versus Extracts." *Nutrients* 16, no. 10: 1403.

Kwak, H.-M., S.-Y. Jeon, B.-H. Sohng, et al. 2005. "K.-S.-Secretase(BACE1) Inhibitors From Pomegranate (*Punica granatum*) Husk." *Archives of Pharmacal Research* 28: 1328–1332.

Kwon, H. S., and S. H. Koh. 2020. "Neuroinflammation in Neurodegenerative Disorders: The Roles of Microglia and Astrocytes." *Translational Neurodegeneration* 9, no. 1: 42.

Larrosa, M., A. González-Sarrías, M. J. Yáñez-Gascón, et al. 2010. "Anti-Inflammatory Properties of a Pomegranate Extract and Its Metabolite Urolithin-A in a Colitis Rat Model and the Effect of Colon Inflammation on Phenolic Metabolism." *Journal of Nutritional Biochemistry* 21: 717–725.

Li, H., J. Ruan, J. Huang, et al. 2023. "Pomegranate (*Punica granatum* L.) and Its Rich Ellagitannins as Potential Inhibitors in Ulcerative Colitis." *International Journal of Molecular Sciences* 24, no. 24: 17538.

Li, Q., L. B. Meng, L. J. Chen, et al. 2023. "The Role of the Microbiota-Gut-Brain Axis and Intestinal Microbiome Dysregulation in Parkinson's Disease." *Frontiers in Neurology* 14: 1185375.

Li, T., L. Zhang, C. Jin, Y. Xiong, Y.-Y. Cheng, and K. Chen. 2020. "Pomegranate Flower Extract Bidirectionally Regulates the Prolifera Tion, Differentiation and Apoptosis of 3T3-L1 Cells Through Regulation of PPARγ Expression Mediated by PI3K-AKT Signaling Pathway." *Biomedicine & Pharmacotherapy* 131: 110769.

Li, Y., F. Yang, W. Zheng, et al. 2016. "*Punica granatum* (Pomegranate) Leaves Extract Induces Apoptosis Through Mitochondrial Intrinsic Pathway and Inhibits Migration and Invasion in Non-Small Cell Lung Cancer In Vitro." *Biomedicine & Pharmacotherapy* 80: 227–235.

Limanaqi, F., F. Biagioni, F. Mastroiacovo, M. Polzella, G. Lazzeri, and F. Fornai. 2020. "Merging the Multi-Target Effects of Phytochemicals in Neurodegeneration: From Oxidative Stress to Protein Aggregation and Inflammation." *Antioxidants* 9: 22.

Lippolis, T., M. Cofano, G. R. Caponio, V. De Nunzio, and M. Notarnicola. 2023. "Bioaccessibility and Bioavailability of Diet Polyphenols and Their Modulation of Gut Microbiota." *International Journal of Molecular Sciences* 24, no. 4: 3813.

Liu, L., J. R. Huh, and K. Shah. 2022. "Microbiota and the Gut-Brain-Axis: Implications for New Therapeutic Design in the CNS." *eBioMedicine* 77: 103908.

Liu, R., J. Li, Y. Cheng, et al. 2015. "Effects of Ellagic Acid-Rich Extract of Pomegranates Peel on Regulation of Cholesterol Metabolism and Its Molecular Mechanism in Hamsters." *Food & Function* 6, no. 3: 780–787.

Liu, Z., Y. Tang, Z. Zhang, et al. 2023. "Engineering Neurovascular Unit and Blood-Brain Barrier for Ischemic Stroke Modeling." *Advanced Healthcare Materials* 12, no. 19: e2202638.

Lou, G., K. Palikaras, S. Lautrup, M. Scheibye-Knudsen, N. Tavernarakis, and E. F. Fang. 2020. "Mitophagy and Neuroprotection." *Trends in Molecular Medicine* 26: 8–20.

Lv, O., L. Wang, J. Li, Q. Ma, and W. Zhao. 2016. "2016 Effects of Pomegranate Peel Polyphenols on Lipid Accumulation and Cholesterol Metabolic Transformation in L-02 Human Hepatic Cells via the PPARγ ABCA1/CYP7A1 Pathway." *Food & Function* 7, no. 12: 4976–4983.

Ma, Z., S. Wang, W. Miao, et al. 2023. "The Roles of Natural Alkaloid and Polyphenols in Lipid Metabolism: Therapeutic Implications and Potential Targets in Metabolic Diseases." *Current Medicinal Chemistry* 30, no. 32: 3649–3667.

Magangana, T. P., N. P. Makunga, O. A. Fawole, and U. L. Opara. 2020. "Processing Factors Affecting the Phytochemical and Nutritional Properties of Pomegranate (*Punica granatum* L.) Peel Waste: A Review." *Molecules (Basel, Switzerland)* 25: 4690.

Magangana, T. P., N. P. Makunga, C. la Grange, M. A. Stander, O. A. Fawole, and U. L. Opara. 2021. "Blanching Pre-Treatment Promotes High Yields, Bioactive Compounds, Antioxidants, Enzyme Inactivation and Antibacterial Activity of 'Wonderful' Pomegranate Peel Extracts at Three Different Harvest Maturities." *Antioxidants (Basel)* 10, no. 7: 1119.

Mahajan, R., S. Attri, V. Mehta, M. Udayabanu, and G. Goel. 2018. "Microbe-Bio-Chemical Insight: Reviewing Interactions Between Dietary Polyphenols and Gut Microbiota." *Mini-Reviews in Medicinal Chemistry* 18: 1253–1264.

Maiuolo, J., F. Bosco, L. Guarnieri, et al. 2023. "Protective Role of an Extract Waste Product From *Citrus bergamia* in an In Vitro Model of Neurodegeneration." *Plants (Basel)* 12, no. 11: 2126.

Maiuolo, J., M. Gliozzi, V. Musolino, et al. 2018. "The "Frail" Brain Blood Barrier in Neurodegenerative Diseases: Role of Early Disruption of Endothelial Cell-To-Cell Connections." *International Journal of Molecular Sciences* 19, no. 9: 2693.

Maiuolo, J., F. Liuzzi, A. Spagnoletta, et al. 2024. "Studies on the Comparative Response of Fibers Obtained From the Pastazzo of *Citrus bergamia* and Cladodes of *Opuntia ficus-indica* on In Vitro Model of Neuroinflammation." *Plants (Basel, Switzerland)* 13, no. 15: 2123.

Maiuolo, J., S. Nucera, M. Serra, et al. 2024. "Cladodes of *Opuntia ficus-indica* (L.) Mill. Possess Important Beneficial Properties Dependent on Their Different Stages of Maturity." *Plants (Basel, Switzerland)* 13, no. 10: 1365.

Man, G., L. Xu, Y. Wang, X. Liao, and Z. Xu. 2022. "Profiling Phenolic Composition in Pomegranate Peel From Nine Selected Cultivars Using UHPLC-QTOF-MS and UPLC-QQQ-MS." *Frontiers in Nutrition* 8: 807447.

Manos, J. 2022. "The Human Microbiome in Disease and Pathology." *APMIS* 130, no. 12: 690–705.

Marín, M., R. M. Giner, J.-L. Ríos, and M. C. Recio. 2013. "Intestinal Anti-Inflammatory Activity of Ellagic Acid in the Acute and Chronic Dextrane Sulfate Sodium Models of Mice Colitis." *Journal of Ethnopharmacology* 150: 925–934.

Marogianni, C., M. Sokratous, E. Dardiotis, G. M. Hadjigeorgiou, D. Bogdanos, and G. Xiromerisiou. 2020. "Neurodegeneration and Inflammation-An Interesting Interplay in Parkinson's Disease." *International Journal of Molecular Sciences* 21, no. 22: 8421.

Mehdi, A., B. Lamiae, B. Samira, et al. 2022. "Pomegranate (*Punica granatum* L.) Attenuates Neuroinflammation Involved in Neurodegenerative Diseases." *Food* 11, no. 17: 2570.

Melgarejo, P., D. Núñez-Gómez, J. J. Martínez-Nicolás, E. Giordani, F. Tozzi, and P. Legua. 2021. "Fatty Acids Compositional Variations Between the Edible and Non-Edible Fruit Part of Seven Pomegranate Varieties." *Food Chemistry: Molecular Sciences* 3: 100046.

Mirdehghan, S. H., and M. Rahemi. 2007. "Seasonal Changes of Mineral Nutrients and Phenolics in Pomegranate (*Punica granatum* L.) Fruit." *Scientia Horticulturae* 111: 120–127.

Mo, Y., J. Ma, W. Gao, et al. 2022. "Pomegranate Peel as a Source of Bioactive Compounds: A Mini Review on Their Physiological Functions." *Frontiers in Nutrition* 9: 887113.

Moga, M. A., O. G. Dimienescu, A. Bălan, et al. 2021. "Pharmacological and Therapeutic Properties of *Punica granatum* Phytochemicals: Possible Roles in Breast Cancer." *Molecules* 26, no. 4: 1054.

MohanKumar, S. M. J., A. Murugan, A. Palaniyappan, and P. S. MohanKumar. 2023. "Role of Cytokines and Reactive Oxygen Species in Brain Aging." *Mechanisms of Ageing and Development* 214: 111855.

Mosele, J. I., M. J. Gosalbes, A. Macià, et al. 2015. "Effect of Daily Intake of Pomegranate Juice on Fecal Microbiota and Feces Metabolites From Healthy Volunteers." *Molecular Nutrition & Food Research* 59: 1942–1953.

Mouri, M. I., and M. Badireddy. 2024. "Hyperglycemia." In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK430900/.

Mowry, E. M., and J. D. Glenn. 2018. "The Dynamics of the Gut Microbiome in Multiple Sclerosis in Relation to Disease." *Neurologic Clinics* 36: 185–196.

Mphahlele, R. R., O. A. Fawole, N. P. Makunga, and U. L. Opara. 2016. "Effect of Drying on the Bioactive Compounds, Antioxidant, Antibacterial and Antityrosinase Activities of Pomegranate Peel." *BMC Complementary and Alternative Medicine* 16: 143.

Nadig, A. P. R., B. Huwaimel, A. Alobaida, et al. 2022. "Manganese Chloride ($MnCl_2$) Induced Novel Model of Parkinson's Disease in Adult Zebrafish; Involvement of Oxidative Stress, Neuroinflammation and Apoptosis Pathway." *Biomedicine & Pharmacotherapy* 155: 113697.

Nair, A. T., V. Ramachandran, N. M. Joghee, S. Antony, and G. Ramalingam. 2018. "Gut Microbiota Dysfunction as Reliable Non-Invasive Early Diagnostic Biomarkers in the Pathophysiology of Parkinson's Disease: A Critical Review." *Journal of Neurogastroenterology and Motility* 24: 30–42.

Naróg, D., and A. Sobkowiak. 2023. "Electrochemistry of Flavonoids." *Molecules* 28, no. 22: 7618.

Neyrinck, A. M., E. Catry, B. Taminiau, et al. 2019. "Chitin-Glucan and Pomegranate Polyphenols Improve Endothelial Dysfunction." *Scientific Reports* 9, no. 1: 14150.

Noor, U., S. Soni, and E. Gupta. 2022. "*Punica granatum* Peel Waste—An Underutilized Substrate of Therapeutic Potential: An Overview." *Recent Advances in Food, Nutrition & Agriculture* 13, no. 2: 103–119.

Nyarko-Danquah, I., E. Pajarillo, A. Digman, K. F. A. Soliman, M. Aschner, and E. Lee. 2020. "Manganese Accumulation in the Brain via Various Transporters and Its Neurotoxicity Mechanisms." *Molecules* 25: 5880.

Ojha, S., S. Bußler, and O. K. Schlüter. 2020. "Food Waste Valorisation and Circular Economy Concepts in Insect Production and Processing." *Waste Management* 118: 600–609.

Onwude, D. I., N. Hashin, R. B. Janius, N. M. Nawi, and K. Abdan. 2016. "Modeling the Thin-Layer Drying of Fruits and Vegetables: A Review." *Innovative Food Science & Emerging Technologies* 15: 559–618.

Osorio, L. L. D. R., E. Flórez-López, and C. D. Grande-Tovar. 2021. "The Potential of Selected Agri-Food Loss and Waste to Contribute to a Circular Economy: Applications in the Food, Cosmetic and Pharmaceutical Industries." *Molecules* 26, no. 2: 515.

Pacheco-Palencia, L. A., G. Noratto, L. Hingorani, S. T. Talcott, and S. U. Mertens-Talcott. 2008. "Protective Effects of Standardized Pomegranate (*Punica granatum* L.) Polyphenolic Extract in Ultraviolet-Irradiated Human Skin Fibroblasts." *Journal of Agricultural and Food Chemistry* 56: 8434–8441.

Pajarillo, E., I. Nyarko-Danquah, A. Digman, et al. 2022. "Mechanisms of Manganese-Induced Neurotoxicity and the Pursuit of Neurotherapeutic Strategies." *Frontiers in Pharmacology* 13: 1011947.

Palikaras, K., E. Lionaki, and N. Tavernarakis. 2018. "Mechanisms of Mitophagy in Cellular Homeostasis, Physiology and Pathology." *Nature Cell Biology* 20: 1013–1022.

Pant, A., T. K. Maiti, D. Mahajan, and B. Das. 2023. "Human Gut Microbiota and Drug Metabolism." *Microbial Ecology* 86, no. 1: 97–111.

Pantiora, P. D., A. I. Balaouras, I. K. Mina, et al. 2023. "The Therapeutic Alliance Between Pomegranate and Health Emphasizing on Anticancer Properties." *Antioxidants* 12: 187.

Patani, R., G. E. Hardingham, and S. A. Liddelow. 2023. "Functional Roles of Reactive Astrocytes in Neuroinflammation and Neurodegeneration." *Nature Reviews. Neurology* 19, no. 7: 395–409.

Pateiro, M., M. Vargas-Ramella, D. Franco, et al. 2022. "The Role of Emerging Technologies in the Dehydration of Berries: Quality, Bioactive Compounds, and Shelf Life." *Food Chem X* 16: 100465.

Pathak, P. D., S. A. Mandavgane, and B. D. Kulkarni. 2017. "Valorisation of Pomegranate Peels: A Biorefinery Approach." *Waste and Biomass Valorization* 8: 1127–1137.

Pellegrini, C., L. Antonioli, V. Calderone, R. Colucci, M. Fornai, and C. Blandizzi. 2020. "Microbiota-Gut-Brain Axis in Health and Disease: Is NLRP3 Inflammasome at the Crossroads of Microbiota-Gut-Brain Communications?" *Progress in Neurobiology* 2020, no. 91: 101806.

Pereira, D. T. V., G. L. Zabot, F. G. R. Reyes, A. H. Iglesias, and J. Martínez. 2021. "Integration of Pressurized Liquids and Ultrasound in the Extraction of Bioactive Compounds From Passion Fruit Rinds: Impact on Phenolic Yield, Extraction Kinetics and Technical-Economic Evaluation." *Innovative Food Science and Emerging Technologies* 67: 102549.

Pereira de Melo, I. L., L. Tedesco Yoshime, J. A. Gasparotto Sattler, E. B. Teixeira de Carvalho, and J. Mancini-Filho. 2019. "Punicic Acid Was Metabolised and Incorporated in the Form of Conjugated Linoleic Acid in Different Rat Tissues." *International Journal of Food Sciences and Nutrition* 70, no. 4: 421–431.

Piazza, S., M. Fumagalli, G. Martinelli, et al. 2022. "Hydrolyzable Tannins in the Management of Th1, Th2 and Th17 Inflammatory-Related Diseases." *Molecules* 27, no. 21: 7593.

Polat, A. 2024. "Drying Strawberry Slices: A Comparative Study of Electrohydrodynamic, Hot Air, and Electrohydrodynamic-Hot Air Techniques." *Food Science & Nutrition* 12, no. 11: 9621–9631.

Priya, S. S., S. K. Dixit, S. Kabiraj, and M. S. Priya. 2023. "Food Waste in Indian Households: Status and Potential Solutions." *Environmental Science and Pollution Research International* 30, no. 59: 124401–124406.

Querfurth, H., and H. K. Lee. 2021. "Mammalian/Mechanistic Target of Rapamycin (mTOR) Complexes in Neurodegeneration." *Molecular Neurodegeneration* 16, no. 1: 44.

Radwan, M., A. E. Mekky, M. A. Moussa, M. Fares, and W. M. Al-Otaibi. 2025. "Potential Effects of Dietary Fermented *Sargassum muticum* on Growth Performance, Intestinal Health, Immune-Antioxidant Related Gene Responses, and Resistance to Bacterial Infection in Nile Tilapia." *Fish & Shellfish Immunology* 167: 110695.

Rafi, M., L. Wulansari, D. A. Septaningsih, et al. 2021. "Antioxidant Capacity, Phytochemical Profile, and Clustering of Pomegranate (*Punica granatum* L.) Peel Extracts Using Different Solvent Extraction." *Journal of Tropical Life Science* 11: 375–382.

Rahnemoon, P., M. Sarabi Jamab, M. Javanmard Dakheli, A. Bostan, and O. Safari. 2018. "Comparison of Two Methods of Solvent Extraction of Phenolic Compounds From Pomegranate (*Punica granatum* L.) Peels." *Journal of Agricultural Science and Technology* 20: 939–952.

Ray, H., J. Khatum, S. Haldar, and P. Bhowmik. 2025. "Second Brain: Reviewing the Gut Microbiome's Role in Lifestyle Diseases." *Biotechnologia* 106, no. 1: 103–122.

Razani, Z., M. Dastani, and H. R. Kazerani. 2017. "Cardioprotective Effects of Pomegranate (*Punica granatum*) Juice in Patients With Ischemic Heart Disease." *Phytotherapy Research* 31: 1731–1738.

Roberts, K. M., E. M. Grainger, J. M. Thomas-Ahner, et al. 2020. "Dose-Dependent Increases in Ellagitannin Metabolites as Biomarkers of Intake in Humans Consuming Standardized Black Raspberry Food Products Designed for Clinical Trials." *Molecular Nutrition & Food Research* 64, no. 10: e1900800.

Robinson, A. P., C. T. Harp, A. Noronha, and S. D. Miller. 2014. "The Experimental Autoimmune Encephalomyelitis (EAE) Model of MS: Utility for Understanding Disease Pathophysiology and Treatment." *Handbook of Clinical Neurology* 122: 173–189.

Sagar, V. R., and S. P. Kumar. 2010. "Recent Advances in Drying and Dehydration of Fruits and Vegetables: A Review." *Journal of Food Science and Technology* 47: 15–26.

Sagdic, O., I. Ozturk, H. Cankurt, and F. Tornuk. 2012. "Interaction Between Some Phenolic Compounds and Probiotic Bacterium in Functional Ice Cream Production." *Food and Bioprocess Technology* 5: 2964–2971.

Sánchez, B., S. Delgado, A. Blanco-Míguez, A. Lourenço, M. Gueimonde, and A. Margolles. 2017. "Probiotics, Gut Microbiota, and Their Influence on Host Health and Disease." *Molecular Nutrition & Food Research* 61, no. 1: 1–15. https://10.1002/mnfr.201600240.

Saparbekova, A. A., G. O. Kantureyeva, D. E. Kudasova, Z. K. Konarbayeva, and A. S. Latif. 2023. "Potential of Phenolic Compounds From Pomegranate (*Punica granatum* L.) By-Product With Significant Antioxidant and Therapeutic Effects: A Narrative Review. *Saudi*." *Journal of Biological Sciences* 30, no. 2: 103553.

Šavikin, K., J. Živkovi'c, A. Alimpi'c, et al. 2018. "Activity Guided Fractionation of Pomegranate Extract and Its Antioxidant, Antidiabetic and Antineurodegenerative Properties." *Industrial Crops and Products* 113: 142–149.

Schneider, S. A., and R. N. Alcalay. 2017. "Neuropathology of Genetic Synucleinopathies With Parkinsonism: Review of the Literature. Journal of Movement Disorders." *Movement Disorders* 32: 1504–1523.

Schönfeld, P., and L. J. Wojtczak. 2016. "Short- and Medium-Chain Fatty Acids in Energy Metabolism: The Cellular Perspective." *Journal of Lipid Research* 57, no. 6: 943–954.

Seeram, N. P., L. S. Adams, S. M. Henning, et al. 2005. "In Vitro Antiproliferative, Apoptotic and Antioxidant Activities of Punicalagin, Ellagic Acid and a Total Pomegranate Tannin Extract Are Enhanced in Combination With Other Polyphenols as Found in Pomegranate Juice." *Journal of Nutritional Biochemistry* 16: 360–367.

Seeram, N. P., Y. Zhang, R. McKeever, et al. 2008. "Pomegranate Juice and Extracts Provide Similar Levels of Plasma and Urinary Ellagitannin Metabolites in Human Subjects." *Journal of Medicinal Food* 11, no. 2: 390–394.

Senobari, Z., G. Karimi, and K. Jamialahmadi. 2022. "Ellagitannins, Promising Pharmacological Agents for the Treatment of Cancer Stem Cells." *Phytotherapy Research* 36: 231–242.

Seo, D.-O., D. O'Donnell, N. Jain, et al. 2023. "ApoE Isoform- and Microbiota-Dependent Progression of Neurodegeneration in a Mouse Model of Tauopathy." *Science* 379, no. 6628: eadd1236.

Shah, T. A., M. Parikh, K. V. Patel, K. G. Patel, C. G. Joshi, and T. R. Gandhi. 2016. "Evaluation of the Effect of *Punica granatum* Juice and Punicalagin on NFκB Modulation in Inflammatory Bowel Disease." *Molecular and Cellular Biochemistry* 419: 65–74.

Sharma, J., and A. Maity. 2010. "Pomegranate Phytochemicals: Nutraceutical and Therapeutic Values." *Pomegranate Phytochemicals: Nutraceutical and Therapeutic Values* 4, no. 2: 56–76.

Sharma, P., M. Kumar, and N. Bansal. 2021. "Ellagic Acid Prevents 3-Nitropropionic Acid Induced Symptoms of Huntington's Disease." *Naunyn-Schmiedeberg's Archives of Pharmacology* 394, no. 9: 1917–1928.

Sharmin, T., N. Ahmed, A. Hossain, et al. 2016. "Extraction of Bioactive Compound From Some Fruits and Vegetables (Pomegranate Peel, Carrot and Tomato)." *American Journal of Food and Nutrition* 4: 8–19.

Shen, N., T. Wang, Q. Gan, S. Liu, L. Wang, and B. Jin. 2022. "Plant Flavonoids: Classification, Distribution, Biosynthesis, and Antioxidant Activity." *Food Chemistry* 383: 132531.

Shen, Y., Q. Wu, J. Shi, and S. Zhou. 2020. "Regulation of SIRT3 on Mitochondrial Functions and Oxidative Stress in Parkinson's Disease." *Biomedicine & Pharmacotherapy* 132: 110928.

Shin, W. H., D. Y. Lee, K. W. Park, et al. 2020. "Microglia Actively Remodel Adult Hippocampal Neurogenesis Through the Phagocytosis Secretome." *Journal of Neuroscience* 40: 1453–1482.

Shukla, M., K. Gupta, Z. Rasheed, K. A. Khan, and T. M. Haqqi. 2008. "Bioavailable Constituents/Metabolites of Pomegranate (*Punica granatum* L.) Preferentially Inhibit COX2 Activity Ex Vivo and IL-1beta-Induced PGE2 Production in Human Chondrocytes In Vitro." *Journal of Inflammation* 5: 9.

Silva, R. F. M., and L. Pogaˇcnik. 2020. "Polyphenols From Food and Natural Products: Neuroprotection and Safety." *Antioxidants* 9: 61.

Singh, J., H. P. Kaur, A. Verma, et al. 2023. "Pomegranate Peel Phytochemistry, Pharmacological Properties, Methods of Extraction, and Its Application: A Comprehensive Review." *ACS Omega* 8: 35452–35469.

Singh, R. P., K. N. C. Murthy, and G. K. Jayaprakasha. 2002. "Studies on the Antioxidant Activity of Pomegranate (*Punica granatum*) Peel and Seed Extracts Using In Vitro Models." *Journal of Agricultural and Food Chemistry* 50: 81–86.

Smaoui, S., H. B. Hlima, A. C. Mtibaa, et al. 2019. "Pomegranate Peel as Phenolic Compounds Source: Advanced Analytical Strategies and Practical Use in Meat Products." *Meat Science* 158: 107914.

Sohrab, G., S. Ebrahimof, G. Sotoudeh, et al. 2017. "Effects of Pomegranate Juice Consumption on Oxidative Stress in Patients With Type 2 Diabetes: A Single-Blind, Randomised Clinical Trial." *International Journal of Food Sciences and Nutrition* 68: 249–255.

Somogyi, A., E. D. Kirkham, E. Lloyd-Evans, et al. 2023. "The Synthetic TRPML1 Agonist ML-SA1 Rescues Alzheimer-Related Alterations of the Endosomal-Autophagic-Lysosomal System." *Journal of Cell Science* 136, no. 6: jcs259875.

Song, L., K. Leng, K. Xiao, and S. Zhang. 2022. "Administration of Krill Oil Extends Lifespan of Fish *Nothobranchius guentheri* via Enhancement of Antioxidant System and Suppression of NF-κB Pathway." *Fish Physiology and Biochemistry* 48, no. 4: 1057–1073.

Sorrenti, V., C. L. Randazzo, C. Caggia, et al. 2019. "Beneficial Effects of Pomegranate Peel Extract and Probiotics on Pre-Adipocyte Differentiation." *Frontiers in Microbiology* 10: 660.

Souza, M. C., L. C. Silva, J. O. Chaves, et al. 2021. "Simultaneous Extraction and Separation of Compounds From Mate (*Ilex paraguariensis*) Leaves by Pressurized Liquid Extraction Coupled With Solid-Phase Extraction and In-Line UV Detection." *Food Chemistry: Molecular Sciences* 2: 100008.

Spielman, L. J., D. L. Gibson, and A. Klegeris. 2018. "Unhealthy Gut, Unhealthy Brain: The Role of the Intestinal Microbiota in Neurodegenerative Diseases." *Neurochemistry International* 120: 149–163.

Stenson, K., T. E. Fecteau, L. O'Callaghan, et al. 2024. "Health-Related Quality of Life Across Disease Stages in Patients With Amyotrophic Lateral Sclerosis: Results From a Real-World Survey." *Journal of Neurology* 271, no. 5: 2390–2404.

Subkorn, P., C. Norkaew, K. Deesrisak, and D. Tanyong. 2021. "Punicalagin, a Pomegranate Compound, Induces Apoptosis and Autophagy in Acute Leukemia." *PeerJ* 9: e12303.

Sun, S. C., J. H. Chang, and J. Jin. 2013. "Regulation of Nuclear Factor-kB in Autoimmunity." *Trends in Immunology* 34: 282–289.

Sun, Y. u., X. Tao, X. Z. Men Xia, and T. Wang. 2017. "In Vitro and In Vivo Antioxidant Activities of Three Major Polyphenolic Compounds in Pomegranate Peel: Ellagic Acid, Punicalin, and Punicalagin." *Journal of Integrative Agriculture* 16, no. 8: 1808–1818.

Tanveer, M., S. A. R. Khan, M. Umar, Z. Yu, M. J. Sajid, and I. U. Haq. 2022. "Waste Management and Green Technology: Future Trends in Circular Economy Leading Towards Environmental Sustainability." *Environmental Science and Pollution Research International* 29, no. 53: 80161–80178.

Tatipamula, V. B., and B. Kukavica. 2021. "Phenolic Compounds as Antidiabetic, Anti-Inflammatory, and Anticancer Agents and Improvement of Their Bioavailability by Liposomes." *Cell Biochemistry and Function* 39: 926–944.

Tekgül, Y., and E. S. Erten. 2022. "Quality Properties and Headspace Volatiles of Hot Air-Dried Strawberries." *Anais da Academia Brasileira de Ciências* 94, no. 2: e20201277.

Teniente, S. L., A. C. Flores-Gallegos, S. C. Esparza-González, L. G. Campos-Múzquiz, S. D. Nery-Flores, and R. Rodríguez-Herrera. 2023. "Anticancer Effect of Pomegranate Peel Polyphenols Against Cervical Cancer." *Antioxidants* 12: 127.

Teplitski, M., J. W. Touchman, E. Almenar, et al. 2023. "Bio-Based Solutions for Reducing Loss and Waste of Fresh Fruits and Vegetables: an Industry Perspective." *Current Opinion in Biotechnology* 83: 102971.

Thilagavathi, T., R. Renuka, and R. S. Priya. 2016. "Bio-Synthesis of Silver Nanoparticles Using *Punica granatum* (Pomegranate) Peel Extract: A Novel Approach Toward Waste Utilization." *International Journal of Advanced Science and Engineering* 3: 234–236.

Thotambailu, A. M., B. S. K. Bhandary, and K. Sharmila. 2019. "Protective Effect of *punica granatum* Extract in Head and Neck Cancer Patients Undergoing Radiotherapy." *Indian Journal of Otolaryngology and Head & Neck Surgery* 71: 318–320.

Tomar, G. S., R. Gundogan, A. Can Karaca, and M. Nickerson. 2023. "Valorization of Wastes and By-Products of Nuts, Seeds, Cereals and Legumes Processing." *Advances in Food and Nutrition Research* 107: 131–174.

Tomás-Barberán, F. A., A. González-Sarrías, R. García-Villalba, M. A. Núñez-Sánchez, M. T. García-Conesa, and J. C. Espín. 2017. "Urolithins, the Rescue of "Old" Metabolites to Understand a "New" Concept: Metabotypes as a Nexus Among Phenolic Metabolism, Microbiota Dysbiosis, and Host Health Status." *Molecular Nutrition & Food Research;* 61, no. 1. https://10.1002/mnfr.201500901.

Tow, W. K., P. Y. Chee, U. Sundralingam, and U. D. Palanisamy. 2022. "The Therapeutic Relevance of Urolithins, Intestinal Metabolites of Ellagitannin-Rich Food: A Systematic Review of In Vivo Studies." *Nutrients* 14, no. 17: 3494.

Tsuji, M., and Z. Molnár. 2025. "Costs of Underfunding Brain Development." *Developmental Neuroscience* 48, no. 2: 130–142.

Uesaka, T., H. M. Young, V. Pachnis, and H. Enomoto. 2016. "Development of the Intrinsic and Extrinsic Innervation of the Gut." *Developmental Biology* 417: 158–167.

Urganci, Ü., F. Isik, and S. Arslan. 2025. "An Investigation on Amyloid Beta Plaque Dissociation in U87MG Cells of In-Vitro Digested Pomegranate Peel." *Scientific Reports* 15, no. 1: 36242.

van der Burg, J. M. M., A. Winqvist, N. A. Aziz, M. L. C. Maat-Schieman, and N. Wierup. 2011. "Gastrointestinal Dysfunction Contributes to Weight Loss in Huntington's Disease Mice." *Neurobiology of Disease* 44: 1–8.

Velagapudi, R., G. Baco, S. Khela, U. Okorji, and O. Olajide. 2015. "Pomegranate Inhibits Neuroinflammation and Amyloidogenesis in IL-1β-Stimulated SK-N-SH Cells." *European Journal of Nutrition* 55: 1653–1660.

Velpuri, P., P. Patel, A. Yazdani, A. Abdi, V. Rai, and D. K. Agrawal. 2024. "Increased Oxidative Stress and Decreased Sirtuin-3 and FOXO3 Expression Following Carotid Artery Intimal Injury in Hyperlipidemic Yucatan Microswine." *Cardiology and Cardiovascular Medicine* 8, no. 1: 33–42.

Ventura, R., and K. M. Harris. 1999. "Three-Dimensional Relationships Between Hippocampal Synapses and Astrocytes." *Journal of Neuroscience* 19: 6897–6906.

Venusova, E., A. Kolesarova, P. Horky, and P. Slama. 2021. "Physiological and Immune Functions of Punicalagin." *Nutrients* 13, no. 7: 2150.

Verheijen, B. M., M. Vermulst, and F. W. van Leeuwen. 2018. "Somatic Mutations in Neurons During Aging and Neurodegeneration." *Acta Neuropathologica* 135, no. 6: 811–826.

Vilahur, G., T. Padró, L. Casaní, et al. 2015. "Polyphenol-Enriched Diet Prevents Coronary Endothelial Dysfunction by Activating the Akt/eNOS Pathway." *Revista Española de Cardiología* 68: 216–225.

Virgen-Carrillo, C. A., and L. Mojica. 2025. "Bioactive Compounds From Pomegranate: A Systematic Review of Mechanistic Insights for the Management of Cardiometabolic Risk Factors." *Journal of Food Science* 90, no. 6: e70358.

Volpi, C., C. Orabona, A. Macchiarulo, R. Bianchi, P. Puccetti, and U. Grohmann. 2019. "Preclinical Discovery and Development of Fingolimod for the Treatment of Multiple Sclerosis." *Expert Opinion on Drug Discovery* 14, no. 11: 1199–1212.

Wang, H. X., and Y. P. Wang. 2016. "Gut Microbiota-Brain Axis." *Chinese Medical Journal* 129, no. 19: 2373–2380.

Wang, J., H. Li, Z. Wang, and S. Ruan. 2024. "Luteolin: A Comprehensive and Visualized Analysis of Research Hotspots and Its Antitumor Mechanisms." *American Journal of Chinese Medicine* 52, no. 8: 2377–2401.

Wang, J., J. Wang, J. Hao, M. Jiang, C. Zhao, and Z. Fan. 2024. "Antioxidant Activity and Structural Characterization of Anthocyanin-Polysaccharide Complexes From *Aronia melanocarpa*." *International Journal of Molecular Sciences* 25, no. 24: 13347.

Wang, W., P. Long, M. He, et al. 2024. "Pomegranate Polyphenol Punicalagin as a Nutraceutical for Mitigating Mild Cognitive Impairment: An Overview of Beneficial Properties." *European Journal of Pharmacology* 977: 176750.

Wang, Z., Z. Pan, H. Ma, and G. G. Atungulu. 2011. "Extract of Phenolics From Pomegranate Peels." *Open Food Science Journal* 5: 17–25.

Wasser, C. I., E. C. Mercieca, G. Kong, et al. 2020. "Gut Dysbiosis in Huntington's Disease: Associations Among Gut Microbiota, Cognitive Performance and Clinical Outcomes." *Brain Communications* 2, no. 2: fcaa110.

Wei, X., J. Wang, Y. Wang, et al. 2024. "Dietary Fiber and Polyphenols From Whole Grains: Effects on the Gut and Health Improvements." *Food & Function* 15, no. 9: 4682–4702.

Więckowska-Gacek, A., A. Mietelska-Porowska, M. Wydrych, and U. Wojda. 2021. "Western Diet as a Trigger of Alzheimer's Disease: From Metabolic Syndrome and Systemic Inflammation to Neuroinflammation and Neurodegeneration." *Ageing Research Reviews* 70: 10139.

Williamson, G. 2025. "Bioavailability of Food Polyphenols: Current State of Knowledge." *Annual Review of Food Science and Technology* 16, no. 1: 315–332.

Wilson, R. S., S. E. Leurgans, P. A. Boyle, J. A. Schneider, and D. A. Bennett. 2010. "Neuro Degenerative Basis of Age-Related Cognitive Decline." *Neurology* 75: 1070–1078.

Wu, G., Z. Zhao, J. Hu, Y. Li, J. Sun, and W. J. Bai. 2024. "Optimized Synthesis and Antioxidant Activity of Anthocyanins Delphinidin-3-O-Glucoside and Petunidin-3-O-Glucoside." *Agric Food Chemistry* 72, no. 26. https://doi.org/10.1021/acs.jafc.4c03237.

Wu, S., J. Yi, Y. G. Zhang, J. Zhou, and J. Sun. 2015. "Leaky Intestine and Impaired Microbiome in an Amyotrophic Lateral Sclerosis Mouse Model." *Physiological Reports* 3, no. 4: e12356.

Xiong, M., M. Feng, Y. Chen, et al. 2023. "Comparison on Structure, Properties and Functions of Pomegranate Peel Soluble Dietary Fiber Extracted by Different Methods." *Food Chem X* 19: 100827.

Xu, J., K. Cao, X. Liu, L. Zhao, Z. Feng, and J. Liu. 2021. "Punicalagin Regulates Signaling Pathways in Inflammation-Associated Chronic Diseases." *Antioxidants (Basel)* 11, no. 1: 29.

Xu, J., Y. Zhao, and H. A. Aisa. 2017. "Anti-Inflammatory Effect of Pomegranate Flower in Lipopolysaccharide (LPS)-Stimulated RAW264. 7 Macrophages." *Pharmaceutical Biology* 55: 2095–2101.

Xue, P., G. Zhang, J. Zhang, and L. f. Ren. 2022. "Synergism of Ellagic Acid in Combination With Radiotherapy and Chemotherapy for Cancer Treatment." *Phytomedicine* 99: 153998.

Yan, C., W. Sun, X. Wang, et al. 2016. "Punicalagin Attenuates Palmitate-Induced Lipotoxicity in HepG2 Cells by Activating the Keap1-Nrf2 Antioxidant Defense System." *Molecular Nutrition & Food Research* 60: 1139–1149.

Yang, M. S., E. H. Joe, and B. K. Jin. 2004. "Microglia Expressing Interleukin-13 Undergo Cell Death and Contribute to Neuronal Survival In Vivo." *Glia* 46: 142–152.

Yin, S., W. Dai, T. Kuang, et al. 2024. "Punicalagin Promotes Mincle-Mediated Phagocytosis of Macrophages via the NF-kappaB and MAPK Signaling Pathways." *European Journal of Pharmacology* 970: 176435.

Yu, X., C. Ji, and A. Shao. 2020. "Neurovascular Unit Dysfunction and Neurodegenerative Disorders." *Frontiers in Neuroscience* 14: 334.

Zhang, B., Q. Li, J. Tu, and B. Zhou. 2020. "Effect of Punicalagin on Multiple Targets in Streptozotocin/High-Fat Diet-Induced Diabetic Mice." *Food & Function* 11, no. 12: 10617–10634.

Zhang, H., o., C. Ga, D. Yang, et al. 2025. "Urolithin a Improves Motor Dysfunction Induced by Copper Exposure in SOD1(G93A) Transgenic Mice via Activation of Mitophagy." *Molecular Neurobiology* 62, no. 6: 6922–6937.

Zhang, W., C. Hou, L. Du, X. Zhang, M. Yang, and J. Li. 2021. "Protective Action of Pomegranate Peel Polyphenols in Type 2 Diabetic Rats *via* the Translocation of Nrf2 and FoxO1 Regulated by the PI3K/Akt Pathway." *Food & Function* 12, no. 22: 11408–11419.

Zhang, Y. Z., G. Aisker, H. Dong, G. Halemahebai, Y. Zhang, and L. Tian. 2021. "Urolithin A Suppresses Glucolipotoxicity-Induced ER Stress and TXNIP/NLRP3/IL-1β Inflammation Signal in Pancreatic β Cells by Regulating AMPKandAutophagy." *Phytomedicine* 93: 153741.

Zhao, C., T. Sakaguchi, k. Fujita, et al. 2016. "Pomegranate-Derived Polyphenols Reduce Reactive Oxygen Species Production via SIRT3-Mediated SOD2 Activation." *Oxidative Medicine and Cellular Longevity* 2927131: 1–9.

Zhao, W., J. Li, X. He, O. Lv, Y. Cheng, and R. Liu. 2014. "In Vitro Steatosis Hepatic Cell Model to Compare the Lipid-Lowering Effects of Pomegranate Peel Polyphenols With Several Other Plant Polyphenols as Well as Its Related Cholesterol Efflux Mechanisms." *Toxicology Reports* 1: 945–954.

Zhou, M., O. A. Fakayode, and H. Li. 2023. "Green Extraction of Polyphenols via Deep Eutectic Solvents and Assisted Technologies From Agri-Food By-Products." *Molecules* 28, no. 19: 6852.

Zhou, Q., R. Jia, and J. Dang. 2022. "Correlation Between the Neutrophil-to-Lymphocyte Ratio and Multiple Sclerosis: Recent Understanding and Potential Application Perspectives." *Neurology Research International* 2022: 3265029.

Zhu, F., B. Du, L. Zheng, and J. Li. 2015. "Advance on the Bioactivity and Potential Applications of Dietary Fibre From Grape Pomace." *Food Chemistry* 186: 207–212.

Zhu, M., Y. Sun, Y. Su, et al. 2024. "Luteolin: A Promising Multifunctional Natural Flavonoid for Human Diseases." *Phytotherapy Research* 38, no. 7: 3417–3443.

Zhuang, S., Y. Li, S. Jia, H. Hong, Y. Liu, and Y. Luo. 2019. "E_ects of Pomegranate Peel Extract on Quality and Microbiota Composition of Bighead Carp (Aristichthys Nobilis) Fillets During Chilled Storage." *Food Microbiology* 82: 445–454.

Ziff, O. J., B. E. Clarke, D. M. Taha, H. Crerar, N. M. Luscombe, and R. Patani. 2022. "Meta-Analysis of Human and Mouse ALS Astrocytes Reveals Multi-Omic Signatures of Infammatory Reactive States." *Genome Research* 32, no. 71–84: 48–84.

Zou, X., C. Yan, Y. Shi, et al. 2014. "Mitochondrial Dysfunction in Obesity Associated Nonalcoholic Fatty Liver Disease: The Protective Effects of Pomegranate With Its Active Component Punicalagin." *Antioxidants & Redox Signaling* 21, no. 11: 1557–1570.