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Bioactive potential of punicalagin: A comprehensive review

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ABSTRACT

Pomegranates comprise bioactive components including polyphenols, tannins, and anthocyanins, which have demonstrated beneficial health effects. Pomegranates also act as a preventative measure for a variety of ailments, as per the promising results from human trials. Pomegranate juice consumption has shown promising outcomes in clinical trials against various diseases, including diabetes, prostate cancer, and cardiovascular disorders, and could be attributed to the punicalagin content of the juice. Punicalagin, a hydrolyzable tannin, is abundant in pomegranate juice and extracts. This review gives insight into the bioactive potential of punicalagin in the prevention of chronic ailments. The review includes the research conducted on punicalagin during 2010–2024. The origins of punicalagin, its method of action, and its therapeutic potential for diabetes, cardiovascular disease, cancer, neuroprotection, obesity, and respiratory illnesses are all discussed in this study. The antioxidant, anti-inflammatory, anti-cancer, and cardioprotective properties of punicalagin have been investigated. Punicalagin reduces inflammation by inhibiting multiple enzymes. Its potential to trigger cancer cell apoptosis may make it anti-cancer. Punicalagin reduces oxidative stress and improves endothelial function, enhancing cardiovascular health. Recent studies have shown that punicalagin has an excellent bioactive as well as therapeutic potential, and it has been suggested as a safe alternative for chemoprevention. As a natural substance, punicalagin shows potential for improving health in several ways. Its therapeutic potential and methods of action, however, need further investigation.

Abbreviations: AKI, endotoxemic acute kidney injury; ALT, alanine aminotransferase; AMPK, adenosine monophosphate-activated protein kinase; AST, aspartate aminotransferase; ATC, anaplastic thyroid carcinoma; ATPS, two-phase system; CAT, catalase; CHD, coronary heart disease; CVDs, cardiovascular diseases; DBP, diastolic blood pressure; DN, diabetic nephropathy; EA, ellagic acid; ER, endoplasmic reticulum; FBG, fasting blood glucose; FFA, free fatty acids; FINS, fasting serum insulin; FMD, flow-mediated dilatation; FTC, follicular thyroid carcinoma; GDM, gestational diabetes mellitus; GOLPH3, golgi phosphoprotein 3; GSH, glutathione; H_2O_2, hydrogen peroxide; HFD, high-fat diet; HOMA-IR, homeostasis model assessment for insulin resistance; HPLC, high performance liquid chromatography; HT, hydroxytyrosol; IAV, influenza A virus; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MIC, minimum inhibitory concentration; MTC, medullary thyroid carcinoma; NA, neuraminidase; oxLDL, oxidised low-density lipoproteins; PJ, pomegranate juice; PTC, papillary thyroid carcinoma; PUN, punicalagin; SBP, systolic blood pressure; SOD, superoxide dismutase; STZ, streptozotocin; TC, total cholesterol; TG, triglyceride; T-SOD, total superoxide dismutase.

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1. Introduction

Punicalagin (PUN) is an ellagitannin, a type of water-soluble, hydrolyzable tannin with high molecular weight (Ascacio et al., 2014), present in α and β isomeric forms in plants of the genera Myrtales like *Terminalia myriocarpa, Terminalia catappa,* or *Punica granatum* (Rongai et al., 2019). Its main source is aril, husk, fruit, juice, and peel of pomegranate (*Punica granatum)* (Valero-Mendoza et al., 2022). Pomegranate thinning fruits contain good amounts of potassium (10,171 mg kg^{-1} dw) as well as Zn (7.5 mg kg^{-1} dw). The high values of total phenolic content (TPC) are due to high levels of both isomers of PUN α & β and high values of antioxidant capability determined by FRAP, ABTS, or DPPH assays (Nuncio-Jáuregui et al., 2015; Valero-Mendoza et al., 2023). Chemically, it is 2,3-(*S*)-hexahydroxydiphenoyl-4,6-(S, S)-gallagyl-d-glucose, 2,3-(*S*)-hexahydroxydiphenoyl-4,6-(S, S)-gallagyl-4,6-(S, S)-gallagyl-4,6-(S, S). PUN has a molecular weight of 1084.7 g mol^{-1} and an atomic weight of 78. PUN has the chemical formula C_{48} H_{28} O_{30}. It is a polyphenol with significant anti-atherosclerotic, hepatoprotective, antioxidant, and chemo-preventive effects (Saparbekova et al., 2023). It also has anticancer, antiinflammation, anticoagulant, and antigenotoxic effects (Rozadi et al., 2022). PUN suppresses inflammatory pathways, and the activity of toxins has an antiproliferative effect against tumor cells and is highly resistant (Venusova et al., 2021; Sabzevari & Sabahi, 2023). Due to its great antioxidant capacity, and strong radical scavenging ability, it reduces the risk of diabetes, promotes wound healing, antibacterial and antifungal activity, bioavailability, and low toxicity, it is also considered to be an effective multifunctional component (Aloqbi *et al.*, 2016; Kiran *et al.*, 2024). In addition, the pretreatment of PUN can improve cell viability (Liu et al., 2020). PUN binds to bovine serum albumin & metal ions with greater affinity and non-specifically binding to DNA. Being a broad-spectrum antiviral drug, PUN could also be highly helpful in reducing recurrent disease-causing viruses (RSV, HCV, or HSV-1) that are known to exploit viral glycoprotein linkages with cell surface glycosaminoglycans to enter the host cell. Additionally, it also lessens the symptoms and signs of cardiovascular disease, bronchitis, cough, diabetes, asthma, diarrhoea, fever, atherosclerosis, bleeding disorders, inflammation, AIDS, mouth lesions, Alzheimer's disease, malaria, skin lesions, ulcers, child brain ischemia, male infertility, erectile dysfunction, vaginitis, and obesity. In the digestive system, ellagitannins are intricately metabolized. The ability of ellagitannins to be degraded into ellagic acid in the small intestine is the same for all ellagitannins, including PUN (Venusova et al., 2021). It also exhibited a strong anti-staphylococcal effect; due to its action method, it damages the morphology of cell membranes. PUN also effectively inhibits the growth of Staphylococcus aureus bacteria. The research shows that it has antibacterial and antibiotic properties against *S. aureus* (Rozadi et al., 2022). Due to the high antioxidant capability of pomegranate extracts, particularly peel, it could be utilized as a natural food preservative. Pomegranate peel's enhanced antioxidant properties make it suitable for use in nutritional supplements as well as health applications, such as adding fibre to food (Sabraoui et al., 2020; Siddiqui et al., 2024). It was observed that the utilization of water as an extraction solvent is quite successful, especially when mixed with ethanol (Cano-Lamadrid et al., 2017). Water is inexpensive and environmentally friendly; thus, it has essential application from the practical point of the extracts. Research revealed that the wild genotypes CREA-FRU6, CREA-FRU11, or CREAM-FRU76 of pomegranate showed a significant concentration of total phenol as well as punicalagin contents, as well as good antifungal activity. As a result, the fruits of such genotypes may be utilized to produce extracts that are highly concentrated in -punicalagin, the substance that gives pomegranate plants their bioactivity. These compounds could be utilized instead of synthetic substances to manage plant diseases and enhance the quality of vegetable products, mitigating the environmental effects of pesticides (Rongai et al., 2019). It easily undergoes hydrolysis in an aqueous environment, yielding d-glucose, ellagic acid, and gallic acid dilactone. It has been investigated that PUN and its derivative ellagic acid both protect DNA from mutations (Berdowska et al., 2021). In an investigation, PUN was employed as a wheat flour enhancer. It was found that at levels of 0.13 and 0.26 mg g^{-1}, it improved the dough's development time, tensile strength, stability, and extension as viscoelasticity. Incorporating 0.13 and 0.26 mg g^{-1} PUN, the dough's cross section showed a highly compact and organized network structure on scan electron microscopic scans (Peng et al., 2019). In addition to these characteristics, it has potent antifungal activity against *Candida parapsilosis* and *Candida albicans*, having MICs of 3.9 and 1.9 μg/mL, respectively (LI et al., 2020).

A critical analysis of publications in a review study on punicalagin's bioactive potential involves a thorough evaluation of the study design, data quality, result interpretation, and overall contribution to the field. Through the methodical use of these standards, the review provides a robust, reliable, and comprehensive overview of the present knowledge regarding punicalagin's bioactive effects. The study on the bioactive potential of punicalagin focuses on the bioactive characteristics, mechanisms of action, and possible health advantages of punicalagin. Research investigating related compounds in pomegranate with a focus on punicalagin was taken into consideration. To make sure the review contains the most cutting-edge findings, the study focuses on recent studies, usually those conducted in the last ten to fifteen years. Although important earlier research that offers fundamental understanding is also incorporated. This study includes research with a well-defined methodology, strong statistical analysis, and results that are supported by information. Studies concentrating on particular punicalagin bioactive effects, such as antibacterial, antioxidant, anti-inflammatory, anti-cancer, cardioprotective, and neuroprotective properties, are included in this specific study area. This review analyzes the studies investigating punicalagin's pharmacokinetics, bioavailability, and mechanisms of action. The review provides a distinctive assessment of the bioactive effects of punicalagin with other polyphenols and antioxidants, offering valuable insights into its relative effectiveness and potential synergistic effects. The study extensively analyzes the biochemical mechanisms that are responsible for the bioactivity of punicalagin and uncovers new molecular pathways and targets. The peels generated from the pomegranate are rich source of antioxidants, having various potential health benefits, and thus can be used for the development of new pharmaceuticals or nutraceuticals. In order to achieve both economic and environmental benefits, it is therefore worthwhile to investigate and use pomegranate peels. The study on the bioactive potential of punicalagin particularly included research that focused on punicalagin produced by pomegranate or comparable sources as its selection criterion. This analysis gave priority to recent studies in order to include the most current research findings and enhancements. This review contains studies on several bioactive effects, such as antioxidant, anti-inflammatory, anticancer, cardioprotective, antibacterial, and neuroprotective properties. Based on this, the review analyzes punicalagin sources, punicalagin mode of action, and punicalagin therapeutic possibilities for diabetes, cardiovascular disease, cancer, neuroprotection, obesity, and respiratory diseases.

2. Sources of punicalagin

PUN is a type of polyphenol prevalent in the husk, aril, fruit juice, peel of *Punica granatum, as well as Lafoensia pacari* leaves. It was revealed in α and β forms in Terminalia (T)genus, such as, *T. arborea* (fruit), *T. arjuna* (bark), *T. brachystemma* (leaves), *T. avicennioides* (bark), *T. calamansanai* (leaves), *T. laxifora* (root), *T. parvifora* (bark), *T. catappa* (bark), *T. chebula* (leaves, fruit), *T. brownie* (bark), *T. citrina* (fruit), T. ivorensis (bark), *T. myriocarpa* (leaves), *T. muelleri* (leaves), *T. macroptera* (bark), as well as *T. oblongata* (leaves) (Rozadi et al., 2022). It is present in pomegranate (*Punica granatum*), strawberries (*Fragaria sp.*), raspberries (*Rubus idaeus*), as well as walnuts (*Juglans regia*). Ellagitannins were hydrolyzed rather than absorbed directly into the bloodstream. PUN is hydrolyzed in the intestines or stomach to create ellagic acid (EA), wherein the intestinal bacteria then use to create urolithin A and B (Hering et al., 2021). The bioactive compound

PUN is the chief component of pomegranate husk. Due to PUN and ellagitannins, foods like pomegranate juice are consumed in many countries, and the production globally is approximately 1,500,000 tons. The significance of ellagitannins dwells in their biological characteristics, including anti-carcinogenic, anti-inflammatory, antimicrobial antioxidant, etc. (Zoofeen et al., 2024). Pomegranate husk, one of the main by-products of pomegranate juice, may include ellagitannins like ellagic acid, punicalin, hexosides, ellagic acid, and hexahydroxydiphenoyl (HHDP)-hexosides (Aguilar-Zárate et al., 2017). It was investigated that the main by-product of pomegranate is peel, but its flowers also contribute to the waste that can also be utilized as they contain a numerous number of polyphenols, including pedunculagin, punicalagin, PUN, and ellagic acids (Gigliobianco et al., 2022). From research, it was found that 87 % of the antioxidant capability in pomegranate juice is because of its hydrolyzable tannin content, like PUN. The core of it is made up of glucose. The two anomeric forms of glucose are ellagic acid (EA), gallic acid dimers, and esterified gallic acid and EA dimers. To validate PUN and associated compounds in pomegranate, analytical techniques like liquid chromatography (HPLC), gas chromatography, or mass spectrometry were frequently utilized (Venusova et al., 2021).

There are many isolation techniques for the extraction of PUN, including conventional solvent extraction and other modern techniques like microwave and ultrasound-assisted extraction, but these are energy-consuming, and due to overheating, product degradation can occur (Cano-Lamadrid et al., 2023; Mashile et al., 2024). The extraction of natural components from plant sources may benefit from the use of the aqueous two-phase system (ATPS) (Setlhodi et al., 2024; Cano-Lamadrid et al., 2022, 2020). Such systems are generated when two water-soluble polymers are combined in the aqueous solutions at a specific ratio above the critical level, such as polyethylene glycol as well as dextran, or when a polymer and salt are combined, such as sodium citrate, sodium sulphate, and potassium phosphate. This appeared to be the best alternative for extracting polyphenols at the top phase while partitioning polysaccharides and other pollutants at the bottom phase (Indurkar & Rathod, 2019). The extraction of PUN from the peel of pomegranate by supercritical fluid extraction was carried out at 400 bar at 43 °C and 20 % ethanol, and the PUN content at these conditions was found to be 0.4–9.5 %. While as in seed extracts, the punicic acid was found to be 65.1–78.4 % at 450 bar and 48 °C with 10 % ethanol employing the supercritical fluid extraction (Bustamante et al., 2017). It was found that peel extract is rich in these polyphenolic components compared to the Arils, especially in Punicalagin (Benchagra et al., 2021). In another study, PUN, ellagic acid, antioxidant activity, and TPC were discovered to be improved by using an artificial neural network coupled with a multiobjective genetic algorithm (ANN-MOGA) at optimal conditions of 35 ml of solvent, 23 min, 35 % amplitude, and 100 % duty cycle than Response surface methodology (RSM) predicted values, respectively. This investigation demonstrates that ANN-MOGA is efficient in calculating maximum PUN production from pome (Rakshit & Srivastav, 2021).

Apart from pomegranate, PUN is also found in the leaves of almonds (*Terminalia catappa)*, a tropical plant of the *Combretaceae* family. The trunk, leaves, bark, or fruit are generally utilized as folk medicine in Southeast Asia and are effective against bleomycin (Bleomycin)-induced genotoxicity (Kaneria et al., 2018). PUN contents, as determined by the UHPLC-MS/MS method in the fruits and leaves, were reported to be 74 and 49 mg/100 g dw. There have been findings of two ellagitannins; castalagin and punicalagin in the other native species of Terminalia in Australia (*T. oblongata)*. According to reports, the *T. oblongata* plant's punicalagin and castalagin induce liver and kidney toxicity in cattle and sheep (Akter et al., 2021). It was found that the ellagitannins from red raspberry fruit revealed in situ as well as in vitro antifungal capability against *Geotrichum candidum* (Klewicka et al.,2016). The ellagitannins from red raspberry are very effective as radical scavengers and, hence have a substantial antioxidant potential towards oxidation of both methyl linoleate and human lipo-density lipoprotein emulsions. Moreover, ellagitannins only showed a minimal to moderate amount of antioxidant potential when it came to bulk oil oxidation. Ellagitannins, which are more pertinent for food applications than lipoprotein environments, so considerably contribute to the antioxidant potential of cloudberries or red raspberries (Kahkonen et al.,2012).

3. Mechanism of action of punicalagin

Punicalagin, the most prevalent polyphenol in pomegranate juice (80% w/w), has considerable antioxidant properties in contrast to many other nutraceuticals (Cano-Lamadrid et al., 2016, 2019). The mechanism of PUN for treating various diseases is presented in Table 1. It also reduces cholesterol levels and oxidizes low-density lipoprotein (LDL). It standardizes various important procedures involved in atherosclerosis. It controls the IFN-γ-induced overexpression of monocyte chemoattractant protein-1 (MCP-1) as well as Intercellular adhesion molecule (ICAM-1) in macrophages by ten times and 3.49-fold, respectively, in comparison to the control and also decreased the MCP-1- mediated migration of monocytes by 28 %. PUN did not display any cytotoxicity and thus can be taken as safe for the prevention as well as treatment of atherosclerosis (Almowallad et al., 2020). Vargas-Torrico et al. (2024) developed and analyzed a film made of gelatin-carboxymethylcellulose that contains an extract from pomegranate (Punica granatum L.) peel. The purpose of this film is to preserve raspberry fruit. In another study, it

Table 1
Potential health benefits of Punicalagin in reducing the risk of various diseases.

Disease	Mechanism	Reference
Diabetes	PUN can ease diabetic nephropathy by downregulating the expression of NOX4, sinhibiting thioredoxin-interacting Protein / leucine-rich repeat and pyrin domain containing protein 3 (TXNIP/NLRP3) pathway-mediated pyroptosis, indicating its therapeutic implications for complications of diabetes	An et al.,2020
CVD	Adenosine monophosphate-activated protein kinase (AMPK), which could be responsible for mitochondrial loss intervention by promoting mitochondrial biosynthesis as well as oxidative stress reduction by upregulating phase II enzymes in HFD hearts, is activated by PUN to protect against HFD-induced cardiac disorders.	Wu & Zou, 2020.
Cancer	PUN has been demonstrated to have antiproliferative properties and the ability to make colon cancer cells poisonous. In the presence of PUN, superoxide radicals produced from mitochondria increased as a result of mitochondrial malfunction, but ROS generation decreased, defining antioxidant activity.	Omar et al., 2016.
Neurological	Punicalagin's neuroprotective effects are mediated at the cellular level by an up-regulation of intracellular antioxidants and a down-regulation of neurotoxic risk factors such hyperhomocysteinemia (HHcy), amyloid-β(Aβ), and TNF-α.	El-Missiry et al., 2018
Obesity	By its impact on the Nrf2/Keap1 signaling pathway (which controls inflammation, oxidative stress, and cell toxicity) and its anti-inflammatory activity connected with the modulation of the M_1 and M_2 ATM phenotypes, it reduced obesity-induced inflammatory responses.	Kang et al., 2019
Respiratory diseases	Pomegranate extracts appear to be capable of directly treating the respiratory inflammation seen in respiratory viral infections through the reduction of neutrophil ROS and methylperoxydase due to their propensity to neutralize ROS.	Aleksandrova et al., 2021.

was found that PUN displayed respectable antibacterial and antibiofilm effects against *Staphylococcus aureus*. It induced morphological damage to the cell membrane, which was determined by the leakage of potassium along with microstructural changes. The agar diffusion method was employed to observe the growth inhibition activity, as well as minimum inhibitory concentration (MIC) was inspected by the agar dilution method. These observations and conclusions suggest that PUN may be used to prevent S. aureus infection in the food business sector (Xu et al., 2017). PUN's potential to change the cell cycle of fungi as well as interfere with the formation of ergosterol in the yeast plasma membrane might be because of its antifungal activities. Compared to untreated cells, it resulted in ultrastructural alterations in *C. albicans* and *C. gattii*, like, decreased cytoplasmic content or thicker cell walls. Moreover, it led to a concentration-dependent decline in the amount of ergosterol in yeast plasma membranes (Silva et al., 2020). Ellagitannins (punicalagins) function with the gut flora to encourage the development of *B. infantis* and *B. breve* along with the production of short chain fatty acids. These fatty acids have a number of beneficial effects because PPARs, which are the receptors for endogenous lipid molecules like prostaglandins or hydroxy-containing PUFA like 12/15-hydroxyeicosatetraenoic (Viladomiu et al., 2013). Every year globally influenza A virus (IAV) causes illness and death. However these are ineffective due to the limited availability of drugs and the appearance of drug-resistant strains. This raises the need for the development of anti-influenza agents. Punicalagin, chebulagic acid, and chebulinic acid are novel neuraminidase (NA) inhibitors that can be employed in the production of antivirals to combat influenza viruses. By blocking neuraminidase activity, it prevents the spread of many influenza A and B virus strains and reduces the discharge of the virus from infected cells.

Moreover, it inhibits the growth of both oseltamivir-sensitive and -resistant IAVs (Li et al., 2021). Initiating apoptosis in various cancer cell types, like, breast, cervical, bone, glia, and liver, could counteract the cytotoxic effects of PUN. One intriguing target for the treatment of cancer is the specific activation of apoptosis in cancer cells by chemicals derived from plants. The mechanism by which pathway apoptosis operates is the overexpression of pro-apoptotic protein (Bax) as well as tumor suppressor p53, concurrent with a declined appearance of anti-apoptotic protein (Bcl-2). The activation of the poly (ADP-ribose) polymerase (PARP) and caspase pathway, as well as inhibition of nuclear factor κb (NFκB) nuclear translocation, are additional mechanisms for inducing apoptosis (Ramlagam et al., 2022). The toxic effects of myocardial ischemia/reperfusion (MI/R) injury, which can result in myocardial shock, arrhythmia, microvascular blockage, or even cardiac mortality, are lessened by punicalagin therapy when taken orally. Its potent inhibitory impact against nitrosative/ oxidative stress as well as inflammatory response damage, may be because of this; myocardial SIRT1-NRF-2-HO-1 signaling is also activated during this phase. Therefore, PUN can be beneficial for people with myocardial ischemia (Yu et al., 2019). The antimicrobial, anticancer, antiviral, and antioxidant effects of punicalagin are presented in Table 2.

It was demonstrated via fluorescence spectroscopy that PUN interacts with pepsin in a spontaneous manner and loses the power of the inherent fluorescence. Static quenching was discovered to be PUN and pepsin's quenching mechanism per steady-state fluorescence and fluorescence persistence. According to synchronized fluorescence spectroscopy, 3-D fluorescence, CD, FT-IR, and UV–Vis results, PUN induced structural changes in pepsin. Complementary molecular docking and dynamics simulations made it clear that establishing hydrogen bonds and Van der Waals interactions allowed pepsin and PUN to bind to one another (Yue et al., 2022). Fluorescence quenching spectra of pepsin (3 μM) at the wavelength (λex) = 290 nm in the presence of rising punicalagin concentrations at 0 μM to 5 μM.

4. Therapeutic prospects of punicalagin

The PUN has been discovered to be mainly responsible for the pomegranate's antioxidant properties. It has a very strong antioxidant potential of about 50 %, whereas ellagic acid has a 3 % antioxidant potential per molecule. It may prevent the growth of human tumor cells and the death of prostate, breast, colon, lung, and skin cancer cells by apoptosis (Packova et al., 2014). The various effect of punicalagin on human health is presented in Table 3.

Table 2
Biologic effect of punicalagin.

Activity of Punicalagin	Model	Experimental Outcome	Reference
Antimicrobial	*Aspergillus parasiticus* CECT 2947, *Aspergillus flavus* CECT2686 etc.	Pomegranate peel methanolic extracts inhibited the growth of *Aspergillus flavus, Alternaria alternata Fusarium verticillioides* or *Botrytis cinerea*.	Rosas-Burgos et al., 2017
	Staphylococcus aureus	Punicalagin enhanced potassium efflux and inhibited Staphylococcus aureus from forming biofilms.	Valdés et al., 2019
Anticancer	Colorectal cancer cell HCT116	Punicalagin has a selective cytotoxic impact on HCT116 as opposed to CCD841 and inhibits Anx-A1 protein to have an anticancer effect.	Ganesan et al., 2020
Antiviral	Epithelial Vero host cell	Punicalagin reduces the virucidal plaque of HSV-1	Houston et al., 2017
Antioxidant	L-NAME induced hypertension pregnant rats	Supplemental punicalagin reduced oxidative stress levels.	Wang et al., 2018
	CCl_4-induced mice liver injury	Punicalagin boosted SOD, GPX activity, and Nrf2 expression while lowering MDA levels.	Luo et al., 2019

CCl-4: Carbon tetrachloride; NG-nitro-l-arginine methyl ester; HSV: Herpes simplex virus.

Table 3
Effect of punicalagin on human health.

Component	Effect	Reference
Punicalagin	Decreased production of ROS, adipocyte differentiation, and the proinflammatory cytokines IL-6, MCP-1, and TNF-α.	Annie-Mathew et al., 2021.
	Inhibits the production of triglyceride accumulation, α-glucosidase, lipase, dipeptidyl peptidase-4, and adipogenesis in 3T3-L1 cells.	Annie-Mathew et al., 2021.
	Increase in total bile acid content	Hou et al., 2019.
	LXR and ABCA1′s mRNA expression is elevated whilst TG and TC are reduced.	Hou et al., 2019.
	Mitochondrial biogenesis, Oxidative stress	Wu & Zou, 2020.
	Cardiac dysfunction	Wu & Zou, 2020.
	Enhanced potassium efflux and an inhibitory action on Staphylococcus aureus biofilm formation	Xu et al., 2021.
	Reducing the virucidal plaque of HSV-1	Xu et al., 2021.
	Inhibiting chicken RBC agglutination and reducing IFV-A proliferative development in conditions of single as well as multiple cycle growth infected MDCK cells.	Santhi et al., 2021.
	Reduction of viral infectivity and reduction of replication to 8-fold with no toxicity	Santhi et al., 2021.
	Decreased hyperplasia and inflammatory cell infiltration	Aleksandrova et al., 2021.
	Having antiviral effect against influenza virus A; H3N2; H1N1 and influenza B	Jalal et al., 2021.

4.1. Therapeutic prospects of punicalagin for diabetes

Dietary polyphenols have several benefits for type 2 diabetes, including protection of pancreatic beta-cells from anti-inflammatory, glucose toxicity, and antioxidant effects. These inhibitions of amylases or glucosidases reduce the digestion of starch and prevent the synthesis of advanced glycation end products. A supplementation with pomegranate peel raises insulin levels and lowers serum glucose levels, as per various investigations (Atrahimovich et al., 2018). Diabetic liver injury is recognized as a dangerous problem of type 2 diabetes. Punicalagin lowered fasting blood glucose (FBG), fasting serum insulin (FINS), and the homeostasis model assessment for insulin resistance (HOMA-IR) in diabetic liver injury mice as a result of its beneficial effects on a high-fat diet (HFD) as well as streptozotocin (STZ)-induced diabetic liver injury. Additionally, there was a substantial decline in the serum as well as liver levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), free fatty acids (FFA), total superoxide dismutase (T-SOD) and malondialdehyde (MDA), along with a decrease in inflammatory cells and (CAT) (Zhang et al., 2022). Diabetes also causes diabetic nephropathy (DN), which affects 30 % to 50 % of people with end-stage renal disease and is characterized by hypertension, proteinuria, and a progressive decline in renal function. PUN has therapeutic prospects for diabetes-related issues because it can reduce the expression of NOX4, which in turn inhibits pyroptosis caused by the thioredoxin-interacting Protein/leucine-rich repeat and pyrin domain-containing protein 3 (TXNIP/NLRP3) pathway (An et al.,2020). Maternal hyperglycemia, which has major health consequences for both the mother and the child, is the main cause of neural tube abnormalities (NTDs), also called diabetic embryopathy. It is not to achieve and maintain euglycemia, also a brief exposure to elevated glucose levels can result in aberrant embryonic development. The incidence of NTDs is decreased by strict glycemic control, which uses dietary adjustments, insulin, and other antidiabetic medications, but it is challenging to attain and maintain. It has been discovered that PUN could remove the detrimental consequences of high glucose, preventing the expression of oxidation-sensitive genes and therefore removing endoplasmic reticulum (ER) stress (Zhong et al., 2015). Gestational diabetes mellitus (GDM) is demarcated as "a carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy" and occurs in up to 20 % of pregnancies worldwide. Obesity is described with a body mass index (BMI) of over 30 kg/m^2 and is predominant in up to 50 % of pregnancies, with regional variations. These scenarios may provide challenges for both mother and child in the form of obesity, cardiovascular disease, metabolic syndrome, type 2 diabetes, and numerous cancers. PUN has been demonstrated to protect against stress brought on by high glucose levels and to raise serum glucose levels in HFD mice in vivo mouse models. In many forms of inflammation, the phenolic acids are hypothesized to act on mitogen-activated protein kinase (MAPK) pathways. There is evidence that phenolic acids also function through other mechanisms, such as the NF-kB or Akt pathways, which are known to activate activated B cells (Nguyen-Ngo et al.,2020). It was studied that pomegranate punicalagin blocks α-amylase, in turn releasing sugars more slowly, therefore checking spikes in sugar levels (Olvera-Sandoval et al., 2022). Thus, it can be concluded that PUN shows promising renoprotective effects in diabetes, endotoxemic acute kidney injury (AKI), and lupus nephritis in mice (Aladaileh et al., 2021).

4.2. Therapeutic prospects of punicalagin for cardiovascular diseases (CVDs)

CVDs are disorders associated with the heart as well as vessels and are comprised of coronary heart disease (CHD) as well as stroke. According to the WHO, they were responsible for 17.5 million deaths in 2012, or 31 % of all fatalities worldwide, making them the main causes of mortality worldwide. Vegan eating habits are associated with a lower incidence of CVDs. PUN is recognized to have cardiovascular preventive properties due to its antioxidant capacity as a hydrogen peroxide scavenger and ferrous chelator (Zhao et al., 2017). According to research, pomegranate juice enhances lipid profiles in diabetic individuals with hyperlipidemia, but pomegranate flower extract lowers cardiac fibrosis or boosts lipid metabolism in diabetic rat models. In obese rats, PUN increases cardiac mitochondrial dysfunction while reducing HFD-induced cardiac metabolic abnormalities (Giamogante et al., 2018). Adenosine monophosphate-activated protein kinase (AMPK), which could be responsible for mitochondrial loss intervention by promoting mitochondrial biosynthesis as well as oxidative stress reduction by upregulating phase II enzymes in HFD hearts, is activated by PUN to protect against HFD-induced cardiac disorders (Wu & Zou, 2020). PUN pretreatment enhanced cardiac function, decreased serum creatine kinase-MB (CK-MB), reduced infarct size and lactate dehydrogenase (LDH) activity, and suppressed cardiomyocyte apoptosis to provide cardioprotective benefits against myocardial ischemia/reperfusion (MI/R) injury. Besides that, PUN pretreatment prevented I/R-induced cardiac oxidative stress, as shown by the declined production of superoxide content, enhanced antioxidant capacity, and a decrease in malonaldialdehyde accumulation.

Moreover, PUN pretreatment enhanced the phosphorylation of ACC and adenosine monophosphate-activated protein kinase (AMPK) in I/R hearts. AMPK inhibitor drug that reduced PUN-mediated cardioprotective and antioxidative benefits by inhibiting AMPK phosphorylation (Ding et al., 2017). It also helps in preventing the increase in the concentration of malondialdehyde (MDA), hydrogen peroxide (H_2O_2), controls the concentration of glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) in the heart; and elevated serum markers of heart function such as levels of troponin T level. This bioactive component of pomegranate shields the heart from apoptosis, inflammation, necrosis, or DNA damage by enhancing the redox state, suppressing caspases as well as P53, and enhancing BCL-2 (El-Missiry et al., 2015). The intake of supplements containing Hydroxytyrosol (HT) and PUN for eight weeks aids in the reduction of c-LDL oxidation as well as improves Diastolic Blood Pressure (DBP), Systolic Blood Pressure (SBP), and Flow-Mediated Dilatation (FMD) in middle-aged persons. Such enhancement in blood pressure, FMD, and circulating oxidized low-density lipoproteins (ox-LDL) levels were most marked in subjects with variations in atherosclerotic markers. Therefore, the systematic consumption of supplements containing HT and PC is beneficial for decreasing the chances of CV in such subjects (Quirós-Fernández et al., 2019). PUN works through an endothelial-mediated mechanism in order to treat conditions including rheumatoid arthritis, cancer, and cardiovascular disease (Liu et al., 2021).

4.3. Therapeutic prospects of punicalagin for cancer

In modern society, after heart disease, cancer is the second main cause of death. Despite substantial progress in cancer therapy over the past few years, dietary and naturally occurring substances are gaining popularity as an alternative cancer prevention and management strategy. Because pomegranates contain polyphenols, including flavonoids and ellagitannins, they have a significant potential for preventing and treating cancer (Wong et al., 2021). In the US, colorectal cancer is the third most frequently detected cancer and the main cause of cancer deaths in both men and women. Pomegranate juice (PJ) treatment of HT-29 cancer cells prevented TNF α -induced COX-2 protein production as well as nuclear factor κ B (NF κ B) DNA binding and AKT activity. In colon cancer cells, PJ is essential for decreasing inflammatory signaling pathways (Sharma et al., 2017). PUN showed antiproliferative properties and the ability to turn colon cancer cells toxic. The formation of cytoplasmic reactive oxygen species (ROS), which determines antioxidant activity, decreased in the presence of PUN, although the amount of superoxide radicals released from the mitochondria increased as a result

of mitochondrial malfunction (Omar et al., 2016). PUN has a specific cytotoxic impact on HCT116 as opposed to CCD841 and inhibits the Anx-A1 protein from treating cancer (Xu et al., 2021). Particularly for women, cervical malignancies are regarded as global health problems. It is most commonly seen in third cancer and the fourth cause of death from cancer in women globally. By inhibiting NF-κB activity, PUN prevents cervical cancer cell proliferation and promotes cell death. Promoting mitochondrial-mediated apoptosis and inhibiting activities on NF-B signaling networks to stop cancer cell growth decreases the survival of cervical cancer cells in a dose-dependent manner. Hence, acting as a traditional candidate for developing anticancer drugs (Zhang et al., 2020). PUN prevents cell proliferation and migration in HeLa human cervical cancer cells, downregulates metalloproteinases-2 (MMP 2) and metalloproteinase-9 (MMP 9), upregulates TIMP 2 and TIMP 3, causes cell cycle arrest in the G1 phase, induces apoptosis via modifications of B cell lymphoma (Bcl 2) and X protein (Bax), and decreased expression catenin and its downstream proteins, These data suggest that PUN may block the catenin signalling pathway to have chemotherapeutic and chemopreventive influence against cervical cancer in people (TANG et al., 2017). Breast cancer (BC) is the most prevalent malignancy around the globe and has become more prevalent since the late 1970s, necessitating significant scientific research. These cells' migration, viability, and invasion were found to be suggestively prevented by high doses of PUN treatment (50 M or higher), whereas overexpressed Golgi phosphoprotein 3 (GOLPH3) promoted cell migration, viability, and invasion and partially reversed the impact of PUN treatment on BC cells. This substance increased the expression of E-Cadherin, which is the primary landmark change throughout epithelial-mesenchymal transformation (EMT) while inhibiting the expression of GOLPH3, MMP-9, MMP-2, and N—Cadherin, which encourages tumor cell adhesion to the extracellular matrix as well as the endothelium. Overexpression of GOLPH3 partially reversed the effects attributable to PUN. Consequently, altering GOLPH3 prevents cell viability and metastasis in BC, offering a potential therapeutic route for the treatment of BC (Pan et al., 2020). According to morphological studies and cell viability tests, PUN has a harmful effect at concentrations of 50 and 75 μM on lung cancer cells but not on healthy lung cells. PUN stopped the cell cycle in the G1/S phase at the tested doses. The apoptosis process is induced by changes in cell shape, phosphatidylserine exposure, activation of caspases, and PARP breakage (Berköz & Krośniak, 2020). Papillary thyroid carcinoma (PTC), anaplastic thyroid carcinoma (ATC), follicular thyroid carcinoma (FTC), and medullary thyroid carcinoma (MTC) are the four subtypes of thyroid cancer that fall under the category of endocrine malignancies. PTC is the most prevalent clinical type of thyroid cancer. PUN promotes cell death by activating the many physiological and pathologically relevant Ataxia-telangiectasia mutant gene encoded protein (ATM)--mediated DNA damage response (DDR) in human papillary thyroid cancer BCPAP cells, which is independent of ROS and DNA conformational change (Yao et al., 2017). Senescence-associated -galactosidase (SAβGal) staining, altered shape, and increased cell granularity are all signs of senescence in BCPAP cells after PUN treatment. Activating NF-κB caused senescent growth arrest and the senescence-associated secretory phenotype (SASP) (Cheng et al., 2018). In prostate cancer (PCa) cells, PUN has antiproliferative as well as apoptosis-inducing properties. PCa cells' cellular viability is often diminished as a result of the impacts, but noncancerous prostate cells are the least damaged (Adaramoye et al., 2017).

4.4. Applications of punicalagin for neuroprotection

The ability of functional foods or supplements to treat neurodegenerative conditions like Huntington's, Parkinson's, or Alzheimer's is very promising. Particular protein growths are present in these disorders, like prion proteins in Creutzfeldt-Jakob disease. Especially PUN from pomegranates exhibits strong neuroprotective properties against Alzheimer's disease (Chen et al., 2023). In a transgenic mouse model of Alzheimer's disease, drawing nanodroplets in pomegranate seed oil could minimize lipid oxidation and prevent neuronal death. Pomegranate juice is said to provide neuroprotective properties for the developing new-born brain (Cano-Lamadrid et al., 2016). Due to the reduced activity of caspase-3, its inclusion in pregnant mothers' diets can considerably reduce brain tissue loss and prevent neonates from hypoxic-ischemic encephalopathy (Das et al., 2021). Due to the elevated amounts of polyunsaturated fatty acids and lesser levels of brain-resident antioxidants, in addition to high oxygen consumption, central neurons are especially vulnerable to damage triggered by oxidative stress. While under oxidative stress, damaged mitochondria could release ROS, harming nucleic acids, proteins, and polyunsaturated fatty acids in membranes. Lipid peroxidation results in membrane integrity loss and increases Ca^{2+} permeability in the plasma membrane. PUN regulates neuroprotective effects on human neuroblastoma cells injured by beta-amyloid peptides by stimulating the activation of methionine-sulfoxide reductase (MsrA), which plays a crucial role in the catalytic antioxidant system that protects against oxidative stress-induced cell injury (Clementi et al., 2014). This could reduce neuro-inflammation in the brain's non-neuronal microglia cells, which is one of the hypothesized causes of dementia and Alzheimer's disease. PUN may be a potential treatment for neuroinflammatory disorders like Parkinson's disease and Alzheimer's disease because researchers discovered that it suppressed TRAF-6-mediated neuroinflammation (Coyle et al., 2016). It is hypothesized that urolithins, a metabolite generated from ellagitannins (ETs), mediates the neuroprotective properties of pomegranate. The transformation of Punicalagins to urolithins is presented in Fig. 1. Treatment with its juice provides neuroprotection, as shown by the enhancement in mitochondrial aldehyde dehydrogenase activity, enhancement in neuronal survival, improvements in postural stability, and maintenance of anti-apoptotic B-cell lymphoma-extra-large (Bcl-xL) protein at the control level (Kujawska *et al.*, 2019). Many neurodegenerative conditions include neuronal cell loss as a symptom of oxidative stress. PUN protects the cells from oxidative stress-induced damage resulting from hydrogen peroxide (H_2O_2), which is typically utilized as an experimental model to examine cellular damage and ascertain the antioxidant benefits of novel medicinal compounds.

The protective effect is thought to be connected to the control of both the production of radical oxygen species and mitochondrial activities. Although the pretreatment with PUN preserved both the cellular availability and the mitochondrial membrane identical to the control, the cells treated with H_2O_2 showed altered mitochondrial membrane integrity (Clementi et al., 2018). PUN can inhibit the enhanced level of homocysteine, Plasma tumor necrosis factor alpha (TNF-α), and amyloid-β, a cell signaling protein that takes part in systemic inflammation and apoptotic cell death. PUN is one of the important nutritional, and pharmacological agents for ameliorating potential neuropathy associated with neurodegenerative disorders (El-Missiry et al., 2018). PUN also shows positive effects against glutamate-mediated neuronal cell death by scavenging free radicals and restoring mitochondrial membrane integrity (Pathakoti et al., 2017). This compound also prevents diabetes-related neuronal apoptosis by upregulating 5-hydroxymethylcytosine (5hmC) in the diabetic mouse brain via activating AMPK and maintaining Krebs cycle homeostasis. Thus, inhibiting neuronal apoptosis in the diabetic mouse brain (He et al., 2022).

4.5. Applications of punicalagin against obesity

Obesity is a state identified by the formation of abnormal or unwanted body fat that might harm human health. Also, it is among the top preventable causes of death around the globe and raises the prevalence of certain metabolic diseases like metabolic syndrome, type 2 diabetes, and cardiac conditions. The pathogenesis of obesity may be influenced by a number of factors, including genetic, social, and environmental factors, like, polymorphism of some genes, physical activity, nutrition,

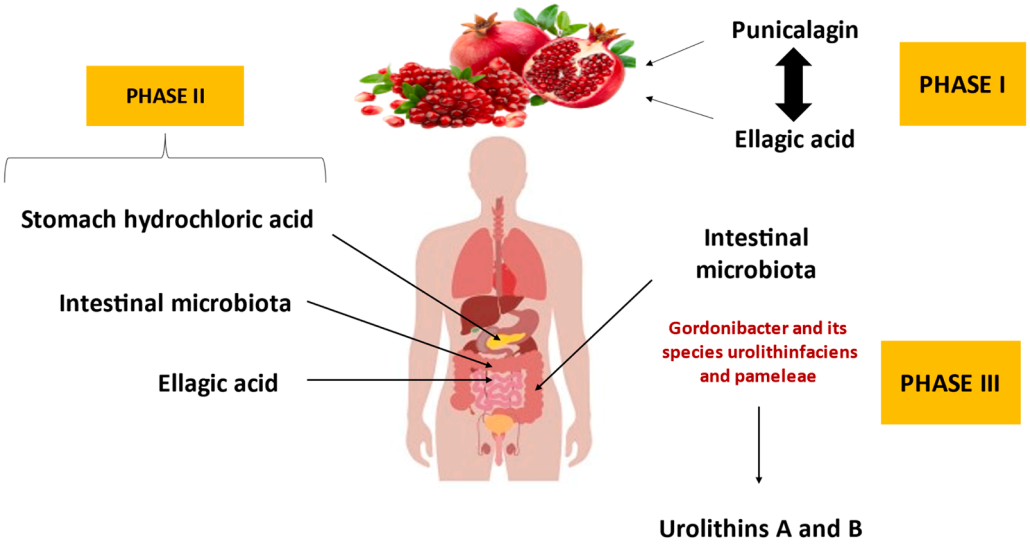

Fig. 1. Transformation of Punicalagins to Urolithins.

intestinal microbiota, body metabolism, as well as some social status. Due to the availability of secondary metabolites derived from plants that include significant amounts of naturally occurring active ingredients such as flavonoids, polyphenols, and anthocyanins, plants have been employed in the treatment of a wide range of metabolic dysfunctions, including obesity (Mir et al., 2019). Because of the hydrolyzable tannins found in pomegranate peel, PUN has significant anti-radical and anti-lipid peroxidation properties. As a result, giving cattle feed containing pomegranate peel containing large amounts of tannins (particularly punicalagin) could benefit cattle in numerous ways (Stover & Watson, 2014). PUN inhibits oxidative and inflammatory reactions brought on by obesity as well as those caused by it. By its impact on the Nrf2/Keap1 signaling pathway (which controls inflammation, oxidative stress, or cell toxicity) and its anti-inflammatory activity connected with the modulation of the M1 and M2 ATM phenotypes, it reduced obesity-induced inflammatory responses. PUN is, therefore, a possible oral medication for the management of metabolic illnesses linked to obesity (Kang et al., 2019). Chronic oxidative stress in obesity is thought to play a significant role in developing diseases like insulin resistance, lipid disorders, and diabetes. By regulating the expression of enzymes that detoxify and neutralize excess RO`S, Nrf2 is an essential regulator of cellular response against oxidative stress. Thus, it is thought that Nrf2 is a crucial target for treating metabolic diseases linked to obesity (Xia et al., 2022). The observation that PUN and ellagic acid only inhibited lipolysis in a dose-dependent pattern suggests that pomegranate extracts may regulate lipid metabolism in adipose tissue. Supplementation of pomegranate extracts with 40 % PUN restricts obesity-related non-alcoholic fatty liver disease (NAFLD-represented by the hepatic disorder of lipid homeostasis with an improvement in synthetic fatty acids, the decline in the lipid catabolism, as well as deficiency of liver lipoprotein output) by enhancing mitochondrial activity, demonstrating that treatment with pomegranate extract increases the mitochondria's capacity to metabolize fatty acids (Hou et al., 2019). Hydroxytyrosol and PUN are proven to have beneficial effects on the circulation of oxidized LDL when added to the diet (Annie-Mathew et al., 2021). It may be useful to prevent obesity if triglyceride accumulation is reduced in adipocyte-like cells as well as lipase is inhibited by PJ, and polyphenols, particularly by urolithin A (Les et al., 2018).

4.6. *Applications of punicalagin against respiratory diseases*

These are the leading causes of disability and death worldwide. Various lung diseases are treatment-resistant. Thus, research on novel drugs/components with fewer side effects for treating lung diseases is critical. Pomegranate is currently utilized in the prevention and treatment of a variety of respiratory disorders. The control of respiratory diseases by natural dietary components is presently a promising platform of pulmonology that attracts significant attention from researchers from both the clinical and basic sciences due to the capacity of natural substances to prevent or suppress chronic diseases (Shaikh & Bhandary, 2021). PUN is an active pomegranate compound with virucidal properties against influenza viruses (influenza viruses A, H1N1, H3N2, and B). It prevents viral RNA duplication. It has been discovered that combining polyphenolic pomegranate extract and oseltamivir improves the anti-influenza effect of oseltamivir (Jalal et al., 2021). PUN has been shown to reduce the proinflammatory cytokines TNF, IL-6, and IL-1, which are abundantly secreted during influenza virus infection and may be related to intracellular ROS production. It may influence the production of proinflammatory cytokines and reduce their inter-gene and protein levels by influencing the level of ROS production, which has been identified as one of the punicalagin's targets in the anti-inflammatory process (Aghaei et al., 2021). Pomegranate extracts, which can neutralize ROS, appear capable of directly addressing the respiratory inflammation seen in respiratory viral infections by inhibiting neutrophil ROS and methylperoxydase. Incorporating these bioactive compounds may thus benefit individuals, particularly those with high risk factors for severe COVID-19 progression, such as aging, type 2 diabetes, cardiovascular pathology, atherosclerosis, neurodegenerative diseases, and so on (Aleksandrova et al., 2021). As a component of a natural product used as food, these components have a proven safety profile, which is an important advantage in disease treatment because it can also be used in anti-SARS-Cov-2 in vitro studies (Suručić et al., 2021). PUN has been identified as an allosteric inhibitor of the SARS-CoV-2 3CLpro main protease, which cleaves polyproteins to produce non-structural proteins. It also disrupts the association between the virus spike glycoprotein and the cellular receptor ACE2, potentially inhibiting virus entry into host cells. PUN-targeting proteins play various roles in the virus life cycle; thus, the potent anti-SARS-CoV-2 efficacy of PUN in cells could be ascribed to the multi-targeting effect (Lu et al., 2022).

The need for antioxidants from natural sources in the food sector has developed steadily over the past few years, particularly as a result of the rising number of adverse toxicological findings on numerous synthetic chemicals. Pomegranate, therefore, has a lot of potential for use in food items due to its extraordinarily strong antioxidant and antibacterial characteristics. Until now, several in vitro, as well as in vivo research on

pomegranate juice and the numerous compounds obtained from it, have demonstrated their advantageous physiological activity, particularly their antioxidative, antibacterial, and anti-inflammatory characteristics. Punicalagin's pharmacological effects include antioxidant, anticancer, antibacterial, neuroprotective, antiinflammation, antidiabetic, and antihyperlipidemic properties. Punicalagin's anticancer properties are achieved by preventing autophagy, lowering apoptosis, stifling proliferation, and preventing cell viability, migration, and invasion. Punicalagin reportedly exhibits significant antioxidant activity. Punicalagin's antioxidant activity enables it to counteract oxidative stress, reduce inflammation, and have anticancer potential. Several reports showed that pomegranate-derived products act efficiently for one's health and may even prevent or slow the progression of numerous serious diseases.

5. Conclusions

Pomegranates and pomegranate by-products like juice and extract are the primary sources of punicalagin. The fruit's skin and arils (juicy seed sacs) have the greatest quantities of punicalagin. Punicalagin showed substantial antioxidant activity, assisting in the neutralization of free radicals and the reduction of oxidative stress. Punicalagin shows anti-inflammatory properties, which help in the management and prevention of chronic inflammatory illnesses such as arthritis, and cardiovascular diseases. Punicalagin enhances cardiovascular health by optimizing lipid profiles, lowering blood pressure, and inhibiting the development of atherosclerosis. The effects are mostly attributed to its antioxidant and anti-inflammatory characteristics. Punicalagin's complexity makes it the most important ellagitannin because of its high molecular weight. By enhancing insulin sensitivity and cellular glucose absorption, punicalagin assists in the control of blood sugar levels. Diabetes is exacerbated by oxidative stress and inflammation, all of which have been proven to be mitigated by this treatment. Inducing apoptosis (programmed cell death) in cancer cells, blocking tumor development and spreading, and lowering inflammation and oxidative stress are all mechanisms proposed by research to explain punicalagin's potential anti-cancer benefits. In addition, punicalagin has been shown to lessen inflammation and oxidative stress, two factors that are linked to the growth and spread of cancer. Therefore, pomegranate juice consumption has shown promising outcomes in clinical trials against various diseases, including diabetes, prostate cancer, and cardiovascular disorders. Further research is required to understand the exact mechanisms of action, long-term consequences, and possible interactions with other bioactive substances and drugs of Punicalagin.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declarations

Human and Animal rights and Informed consent: This article does not include any experiments with human or animal subjects done by the authors.

Ethical Statement - Studies in humans and animals

This study does not involve any animals or human subjects.

Data availability

Data will be made available on request.

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