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The therapeutic potential of pomegranate in the prevention and management of noncommunicable diseases

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Noncommunicable diseases (NCDs), including cardiovascular diseases, cancer, respiratory conditions, and metabolic and central nervous system disorders, are the leading causes of morbidity and mortality worldwide. These diseases are primarily driven by unhealthy diets and sedentary lifestyles. Pomegranate (*Punica granatum* L.), a fruit rich in diverse functional phytoconstituents, has emerged as a promising natural therapeutic agent for the prevention and management of NCDs. Every part of the fruit harbors distinct bioactive compounds that contribute to its health-promoting properties. The peels are particularly rich in punicalagins, the arils are abundant in anthocyanins and ellagic acid, and the seeds contain significant amounts of punicic acid, ellagic acid, and quercetin. Pomegranate peel extracts and juice demonstrate cardioprotective effects through inhibition of angiotensin-converting enzyme (ACE) activity, reduction of inflammatory cytokines, *e.g.*, interleukins and TNF-α, and improvements in lipid profiles. Additionally, their anticancer properties are associated with the upregulation of pro-apoptotic markers (Bax, cytochrome c, caspases 3 and 9, and p53) and the downregulation of tumor-promoting and inflammatory markers (Bcl-2, MMP-2, MMP-9, GOLPH-3, and N-cadherin), as well as the attenuation of reactive oxygen species (ROS) generation. Moreover, pomegranate extracts have exhibited hypoglycemic, nephroprotective, hepatoprotective, antidepressant, anti-Alzheimer's, and anti-Parkinson's properties, as demonstrated in *in vitro* and *in vivo* studies, and clinical trials. Recent investigations have identified key bioactive constituents, including punicalagin, ellagic acid, gallic acid, and urolithin A, as major contributors to these therapeutic effects. This review provides an overview of the metabolomic profile of pomegranate, its therapeutic potential, safety, and quality control assessments, and strategies to enhance the stability and bioavailability of its active constituents, thus underscoring its potential as a natural intervention for the prevention and treatment of NCDs.

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1. Introduction

Noncommunicable diseases (NCDs) are the leading cause of mortality worldwide. According to the World Health Organization (WHO), NCDs account for approximately 41 million deaths annually, representing 74% of all global fatalities. Alarmingly, 17 million of these deaths occur before the age of 70, with 86% taking place in low- and middle-income countries.[1] Among NCDs, cardiovascular diseases (CVDs) are the most significant contributors, responsible for 17.9 million deaths annually,[2] followed by cancer, chronic respiratory diseases (CRDs), and diabetes, which account for 9.3 million, 4.1 million, and 2 million deaths, respectively.[3,4] The major risk factors for NCDs fall into three groups: behavioral, metabolic, and environmental (Fig. 1). Behavioral factors include tobacco use and unhealthy dietary patterns, particularly excessive salt consumption, physical inactivity, and the harmful use of alcohol.[5] Metabolic risk factors encompass hypertension, obesity, hyperglycemia, and hyperlipidemia, which are often closely linked to poor nutritional practices.[6] Environmental factors, such as air pollution, significantly contribute to the development of chronic conditions like chronic obstructive pulmonary disease (COPD) and lung cancer.[7]

Proper nutrition plays a pivotal role in maintaining health and preventing disease. Recognizing the global burden of unhealthy diets, the WHO launched a global strategy on diet,

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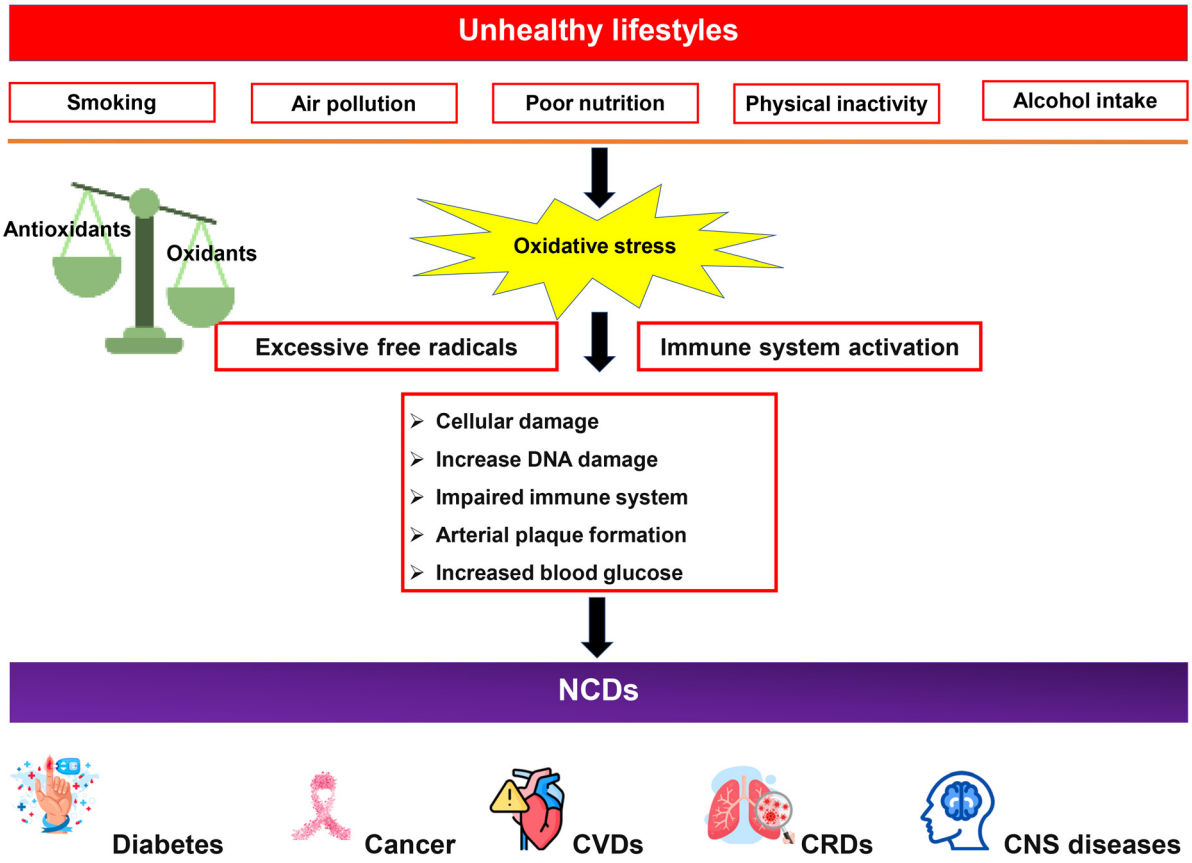

Fig. 1 Primary risk factors for NCDs.

physical activity, and health in 2004 to promote healthier lifestyles and improve public health outcomes.[8] Within the broad spectrum of dietary components, functional foods have garnered considerable attention for their potential health-promoting properties. These foods, often rich in bioactive compounds and essential oils and frequently classified as nutraceuticals, offer benefits that extend beyond basic nutrition, aiding in both the prevention and management of chronic diseases.[9]

Emerging evidence suggests that functional foods enriched with bioactive constituents can significantly reduce the risk of developing NCDs and support their management.[10] A range of fruits have been identified as functional fruits, including pomegranate,[11] apples,[12] blueberries,[13] acai berries,[14] cranberries,[15] avocado,[16] citrus fruits (orange[17] and lemon[18]), and grapes,[19] due to their rich composition of polyphenols, flavonoids, anthocyanin, proanthocyanidins, and vitamins.[20] Among these, pomegranate stands out as a particularly potent functional fruit, because it contains high concentrations of polyphenols,[21] anthocyanin,[22] and flavonoids,[23] all of which exhibit strong antioxidant, antidiabetic, anti-inflammatory, and anticancer properties.[24–26]

To date, numerous review articles have been published on *P. granatum* (pomegranate), including varietal differences, phytochemical, and general pharmacological properties.[27–30] As of June 2025, over 20 clinical trials reported promising benefits of pomegranate and its bioactive constituents in combating various NCDs. However, to the best of our knowledge, no comprehensive review has specifically focused on the therapeutic potential of pomegranate for the prevention and management of NCDs, based on evidence from both preclinical and clinical studies. Given the rising global burden of NCDs and increasing interest in functional foods, a systematic evaluation of pomegranate's role in this context is both timely and warranted. This review aims to fill that gap by providing an in-depth analysis of pomegranate's bioactive compounds, their mechanisms of action, therapeutic applications, safety profile, pharmacokinetics, pharmacodynamics, evidence from clinical trials, and recent advances in formulation technologies. By drawing on data from major scientific databases, including Google Scholar, ResearchGate, PubMed, Web of Science, and Scopus, this review provides comprehensive insights into the role of pomegranate as a functional fruit and its potential in developing effective, nature-based interventions for the prevention and management of NCDs.

2. Overview of NCDs

NCDs are primarily characterized by their prolonged duration and gradual progression, with minimal involvement of infec-

tious agents. Unlike infectious diseases, which can often be prevented or treated through vaccination and antimicrobial therapies, NCDs are largely driven by lifestyle-related risk factors and genetic predispositions.[31] In recent decades, there has been a significant rise in the global prevalence of NCDs, largely attributed to demographic shifts such as population aging, urbanization, and modifications in lifestyle behaviors.[32,33] As populations age and engage in increasingly sedentary lifestyles, the incidence of chronic conditions, including CVDs, cerebrovascular accidents, cancers, and diabetes mellitus, continue to rise.[34] The most abundant NCDs currently found are outlined in the following sections.

2.1 CVDs

CVDs represent a prominent category of NCDs characterized by dysfunctions of the heart and blood vessels. Lifestyle risk factors, particularly poor dietary choices, play a crucial role in their development.[35] The pathophysiology of CVDs reveals that diets high in saturated fats, trans fats, and cholesterol contribute to the progression of atherosclerosis by raising low-density lipoprotein (LDL), and cholesterol levels.[36] This increase leads to lipid accumulation within arterial walls and the formation of plaques, which narrow the arteries and impede blood flow, significantly elevating the risk of myocardial infarctions and strokes.[37] Furthermore, high-sodium diets contribute to hypertension, while excessive intake of sugars and processed foods promote obesity and insulin resistance, both of which are key components of metabolic syndrome and diabetes and are conditions that are closely linked to CVDs.[38] Conversely, insufficient consumption of fruits, vegetables, and wholegrains deprives the body of essential antioxidants and dietary fiber, which are vital for reducing inflammation, oxidative stress, and cholesterol levels.[39,40]

2.2 Cancer

Cancer is the second major NCD. The pathophysiology of cancer involves the unregulated proliferation of cells, primarily driven by mutations in oncogenes and tumor suppressor genes, leading to disruptions in the cell cycle, apoptosis, and DNA repair mechanisms.[41] Cancer cells gain the ability to invade surrounding tissues and metastasize to distant organs.[42] A significant contributing factor to cancer development is poor dietary habit, which is estimated to account for approximately 30–35% of all cancer cases.[43] Diets high in processed meat, red meat, and saturated fats have been linked to an increased risk of colorectal and other cancers,[44] as these foods can promote inflammation, oxidative stress, and DNA damage.[45] The body's antioxidant defense system weakens when there are low levels of antioxidants and other phytochemicals due to lower consumption of functional fruits that inhibit cancer proliferation and DNA support processes.[46] Additionally, obesity, often a result of high-calorie and nutrient-poor diets, increases the likelihood of developing malignancies, such as breast, colon, and pancreatic cancers, by contributing to chronic inflammation, insulin resistance, and hormonal imbalances.[47] Moreover, excessive alcohol consumption increases the risk of liver, oral, esophagus, and breast cancer by inducing oxidative stress and causing further DNA damage.[48]

2.3 CRDs

CRDs constitute a third major category of NCDs characterized by persistent respiratory dysfunction, leading to reduced airflow and impaired lung function.[49] The primary etiological factors for CRDs include tobacco smoke, which is the leading risk factor for COPD and contributes significantly to the incidence of asthma.[50] Additionally, exposure to air pollution, harmful dust and chemicals are the critical contributors to the development of CRDs.[51] Obesity can worsen respiratory issues by increasing inflammation and pressure on the lungs.[52] Furthermore, a diet lacking in fruits and vegetables may weaken the immune system and intensify inflammation.[53] Genetic factors and family history can predispose individuals to conditions such as asthma and alpha-1 antitrypsin deficiency, both of which are associated with COPD.[54] Previous respiratory infections, particularly during childhood, can result in lasting lung damage, further increasing the risk of CRDs later in life.[55]

2.4 Diabetes

Diabetes, a prominent and the fourth major NCD, is characterized by chronic hyperglycemia resulting from either inadequate insulin production or impaired utilization of insulin by the body. The two primary forms of diabetes are type 1 diabetes, which involves the autoimmune destruction of insulin-producing beta cells in the pancreas, and type 2 diabetes, which is characterized by insulin resistance.[56] Type 2 diabetes is the more prevalent type and significantly influenced by lifestyle factors, particularly poor diet, such as one high in processed foods, sugars, and unhealthy fats.[56] Obesity, especially the accumulation of visceral fat, increases the risk of developing insulin resistance.[57] Individuals with a family history of diabetes are also at a higher risk of developing the disease.[58] Other contributing factors include metabolic disorders, chronic stress, and a lack of physical activity, all of which can impair glucose regulation.[59,60] The global rise in diabetes presents a substantial public health challenge; however, it is preventable and manageable through improved nutrition, regular physical activity, and increased awareness.[61]

2.5 Inflammatory bowel disease

Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, is a chronic inflammatory condition of the gastrointestinal tract with a rising global incidence.[62] According to a public health report published by the US Centers for Disease Control and Prevention (CDC) on June 21, 2024, the prevalence of IBD in the United States was estimated to range between 2.4 and 3.1 million individuals, with a variable burden across demographic groups. The report also noted that the total annual healthcare cost of IBD in the US was approximately $8.5 billion. Although the precise etiology of IBD remains unclear, it is thought to arise from a complex interplay among genetic susceptibility, environmental

exposure, microbial dysbiosis, and immune system dysregulation. Genome-wide association studies and other genomic analyses have identified over 160 susceptibility loci, revealing shared pathways between childhood- and adult-onset IBD.[62,63] However, these genetic findings explain only a portion of the disease's heritability.

Environmental factors also play a critical role in modulating intestinal inflammation, primarily through their influence on microbiota composition. Persistent inflammation due to microbial dysbiosis is believed to occur only when both the innate immune system and the intestinal epithelial barrier are compromised.[62] Moreover, dysregulation of the balance between effector and regulatory immune cells in the intestinal mucosa is a key factor in triggering immune activation in IBD patients. In summary, IBD pathogenesis is driven by the interaction between genetic predisposition, environmental triggers, and microbiome alterations, which collectively disrupt mucosal homeostasis and promote chronic inflammation.[64]

2.6 Other NCDs

Chronic kidney disease, Alzheimer's disease and other forms of dementia, obesity, osteoporosis, cirrhosis and fatty liver disease, multiple sclerosis, epilepsy, anxiety disorders, and autoimmune conditions like rheumatoid arthritis and lupus are also prominent NCDs.[65,66] Common risk factors are unhealthy dietary habits, a lack of exercise, smoking and excessive alcohol consumption, chronic stress, aging, and genetic factors.[65] The presence of one chronic condition often leads to the development of others, highlighting the interconnection of various diseases.[67,68] Therefore, mitigating these shared risk factors through preventive measures and lifestyle modifications is crucial for alleviating the impact of NCDs.

3. Prevention and management of NCDs

The effective management and prevention of NCDs necessitate lifestyle modifications, regular health evaluations, timely diagnosis, and appropriate medical interventions.[69] A well-balanced diet rich in fruits, vegetables, wholegrains, lean proteins, and healthy fats is crucial for mitigating risk factors associated with NCDs. Specific dietary guidelines recommend minimizing the intake of saturated fats, refined sugars, and processed foods.[70] Regular physical activity, with a recommendation of at least 150 minutes of moderate-intensity exercise per week, is vital for maintaining a healthy weight, enhancing cardiovascular health, and optimizing metabolic function.[71] Smoking cessation and moderation of alcohol consumption are vital strategies for reducing the risk of NCDs.[69] Routine health screenings play a crucial role in the early detection and management of NCDs. Regular assessments enable the monitoring of risk factors such as blood pressure, cholesterol levels, and blood glucose, facilitating timely interventions.[72] Regular consumption of fruits may lower blood pressure, improve lipid profiles, and enhance vascular function, thereby reducing the risk of CVDs.[73] Additionally, fruit's ability to alleviate oxidative stress and inflammation has implications for cancer prevention and neurological disorders, including Alzheimer's and Parkinson's diseases.[74] Incorporating functional fruits into a balanced diet not only adds flavor and variety but also provides a natural source of health-promoting phytoconstituents that may aid in the prevention and management of NCDs.[75,76]

4. Role of natural antioxidants in NCDs

It is well known that NCDs are caused by an imbalance between the body's oxidants and antioxidants leading to excess free radicals, which induce cellular damage and its pathophysiology.[77] Naturally occurring antioxidants are capable of reducing oxidative stress, assisting with the management and prevention of NCDs. To date, many natural antioxidants, such as flavonoids, polyphenols, carotenoids, and vitamins, have been found in fruits.[78] Their antioxidant properties are briefly described in the following sections.

4.1 Flavonoids

Flavonoids are an important group of plant bioactive compounds known for their preventive and therapeutic potential. Flavones, flavanones, flavonols, isoflavones, flavanols, xanthones, and anthocyanins are the common types of flavonoids. Various flavonoids have been identified and their antioxidant activities determined, for example, quercetin and its derivatives, such as quercetin-3-methoxy glucoside and quercetin-3′-*O*-β-glucopyranoside from *Punica granatum*[79] and myricetin from *Malus domestica*.[80] In addition, flavanols (quercetin),[81] flavanones (naringenin,[82] and hesperidin[83]), flavones (apigenin),[84] and flavan-3-ols (catechin)[85] found in various fruits have been shown to directly scavenge ROS and superoxide, and increased the levels of antioxidant enzymes. Furthermore, quercetin, mainly found in grapes and apples, enhances glucose metabolism and mitigates diabetes-related nephropathy resulting in morphological and neuroprotection.[86] Quercetin also alleviates doxorubicin-induced nephropathy in mice and prevents diabetic kidney injury.[87–89]

4.2 Polyphenols

Polyphenols are phytochemicals known for their therapeutic properties. A well-known polyphenol, namely resveratrol, which accumulates in grapes, strawberries, berries, breadfruit, apples, and tomatoes in high amounts, is reported to decrease uric acid levels and intracellular xanthine oxidase activity in HepG2 cells.[90] It also exhibits cardioprotective effects by regulating the metabolism of lipids and reducing inflammation. A clinical trial indicated that supplementation with resveratrol reduced metabolic parameters such as serum lipid profiles, uric acid, and xanthine oxidase levels in dyslipidemia patients. Furthermore, resveratrol significantly reduced oxidative and DNA damage following myocardial infarction and eliminated doxorubicin-induced cardiotoxicity.[91,92] In addition, a combi-

nation of resveratrol, syringic acid, and gallic acid significantly increased lipid metabolizing enzyme activities in isoproterenol-induced cardiac necrotic rats.[93]

4.3 Carotenoids

Carotenoids are the pigments and precursors of vitamin A found in fruits and vegetables. Epidemiological studies suggest that a high dietary intake of carotenoids is linked to a reduced risk of breast, cervical, ovarian, and colorectal cancers, as well as cardiovascular and eye diseases.[94] Common carotenoids, *i.e.*, beta-carotene, lycopene, lutein, and zeaxanthin, which are usually found in tomatoes, kiwis, guava, papayas, and oranges, show anti-hyperlipidemic and anti-atherogenic effects.[95] Lycopene reportedly decreases the risk of prostate and other cancers due to its capacity to neutralize free radicals that induce DNA damage.[96] Lycopene extracts also reduce the radiation-induced degradation of plasmid *pUC19* DNA in *Escherichia coli*.[97] Lutein is extensively reported for its antioxidant, anti-inflammatory, neuroprotective, hepatoprotective, cardioprotective and anticancer properties,[98] while zeaxanthin is capable of decreasing oxidative stress as well as exhibiting anti-inflammatory, anti-osteoporotic, and eye protective effects.[99]

4.4 Vitamins

Vitamins C and E are powerful antioxidants, predominantly found in citrus fruits. Based on preclinical studies, vitamin E induced apoptosis and exhibited anti-inflammatory, antiproliferative, and anti-angiogenesis properties through cellular signaling pathways.[100] A significant protective effect of vitamin E was reported in a cyclophosphamide-induced cardiotoxicity rat model.[101] Furthermore, clinical trials revealed that the intake of vitamin E reduced the risk of venous thromboembolism in women,[102] lowered the risk of Parkinson's disease,[103] and protected against congenital heart disease, particularly in female, obese, and smoking demographics.[104] Vitamin C leads to cardiac protection by reducing inflammation and oxidative stress caused by an organophosphate pesticide (quinalphos) in an animal model.[105] In addition, vitamin C supplements significantly improved the clinical signs and symptoms in a nonalcoholic fatty liver disease mice model (NAFLD C57BL/6) *via* decreasing the levels of ALT, AST, LDL, and TNF-α as well as exhibiting anti-inflammatory effects in an allergic asthma animal model.[106] Clinical trials indicated that vitamin C showed improved anti-asthmatic effects in patients. Furthermore, a combination of vitamin C and *N*-acetylcysteine administered once daily improved the antioxidant status of COPD patients.[107]

5. Functional ingredients of pomegranate and metabolomic analysis

Pomegranate fruits consist of three primary parts, namely the peels, arils, and seeds. Each part contains various bioactive compounds, which are beneficial for human health. The peels are enriched with polyphenolic compounds, including ellagitannins (such as punicalagins), flavonoids (such as catechin, epicatechin, hesperidin, neohesperidin, and rutin), phenolic acids (such as caffeic, chlorogenic, ellagic, and gallic acids) and dietary fibers. Additionally, the peels also contain bioactive anthocyanins, a group of phenolic pigments that are responsible for the red, purple, and blue coloration of the fruits. The major ones are delphinidin, cyanidin, and pelargonidin.[108–110] The arils are the juicy, edible portions of the fruits. They constitute approximately 50% of the total fruit weight, which consists of 80% juice and 20% seeds. Arils are rich in bioactive compounds, including flavonoids, such as quercetin, kaempferol, and luteolin; anthocyanins; ellagitannins; and phenolic acids, such as cyanidin, delphinidin, pelargonidin, ellagic acid, caffeic acid, and gallic acid. Moreover, they are a significant source of vitamins C and K, carbohydrates (glucose, fructose, and sucrose), organic acids (citric and malic acids), and essential trace minerals, including potassium, calcium, magnesium, and iron.[111,112] The seeds of the pomegranate fruit are enriched with various polyphenols, including punicalagins and flavonoids such as phloridzin, catechin, and quercetin. Additionally, they contain essential fatty acids (such as punicic acid and linoleic acid), beta-sitosterol, and vitamin E.[112–114]

A comparative metabolomic analysis of various fruit parts illustrates the composition and abundance of their active constituents. Analysis *via* a UHPLC-QqQ-MS/MS method revealed that the pulp (edible juicy part around the seed) was enriched with punicalagin and ellagic acid, the seeds were abundant in phlorizin, catechin, and quercetin, and the juice contained higher levels of naringenin and pelargonidin-3-pentoside. The peels were found to have higher concentrations of anthocyanins and flavonoids, such as cyanidin diglycoside, quercetin, and luteolin glycosides. Additionally, industrial by-products of pomegranate, such as the peel and pulp, are rich in various phenolic compounds, including cyanidin diglycoside, quercetin, phlorizin, 3-*O*-caffeoylquinic acid, naringenin, and liquiritin, as well as tannins such as granatin A, ellagic acid derivatives, and both α- and β-punicalagins.[115]

Another study utilized UHPLC-QTOF-MS and UPLC-QQQ-MS to profile the phytochemical composition of pomegranate peel from nine cultivars in China. In total, 64 phenolic compounds were identified, including 10 hydrolyzable tannins, 4 phenolic acids, and 50 flavonoids. The predominant compounds were punicalagin, ellagic acid, gallocatechin, punicalin, catechin, and corilagin.[116] Furthermore, the juice derived from organically grown plants exhibited higher concentrations of acetic acid, alanine, arginine, fumaric acid, galactose, glutamine, histidine, isoleucine, lactic acid, leucine, malic acid, mannose, methionine, phenylalanine, proline, sucrose, threonine, trigonelline, tyrosine, and valine compared to juice from conventionally grown fruits.[117]

Notably, the juice from plants subjected to stress conditions, where irrigation was reduced to 25% of the crops' water requirements during the ripening phase (three weeks before harvest), exhibited a significant increase in the querce-

tin, 6-hydroxydelphinidin 3-glucoside, 3′-methoxytricetin 7-glucuronide, and triferulic acid contents.[118] Another study integrated proton nuclear magnetic resonance (NMR) with principal component analysis (PCA) and orthogonal partial least squares discriminant analysis (OPLS-DA) to analyze the composition of pomegranate juice samples sourced from organic and conventional farms. The findings indicated that juice derived from organically cultivated plants produced high levels of amino acids, including alanine and arginine, as well as higher concentrations of organic acids such as lactic acid and malic acid. The flavonoid and total phenolic contents of organic juice (0.44 mg g^{-1} and 2.27% w/w, respectively) were also higher than those of conventionally grown pomegranate (0.33 mg g^{-1} and 1.65% w/w, respectively).[117]

6. Applications of pomegranate in NCDs

6.1 CVDs

Pomegranate has been extensively studied for its potential in the prevention and management of CVDs. In two separate studies, both the juice and hydroalcoholic extract derived from pomegranate peels were shown to significantly reduce systolic blood pressure, lower LDL and total cholesterol levels, improve cardiovascular markers, and enhance endothelium-dependent coronary relaxation in various animal models. Phytochemical screening of the peel extract revealed the presence of triterpenoids, glycosides, saponins, flavonoids, tannins, carbohydrates, and organic acids. In contrast, the juice contained total phenolic compounds ranging from 1.38 to 2.89 mg mL^{-1}, and anthocyanins ranging from 0.109 to 0.139 mg cyanidin-3-glucoside equivalents per milliliter (C3gE per mL). Among the diverse phenolic constituents identified in the juice, punicalagin, catechin, chlorogenic acid, and gallic acid were prominent.[119–121]

Notably, pomegranate juice fermented with *Lactobacillus plantarum* and seed oil exhibited the highest angiotensin-converting enzyme (ACE) inhibition at 60%, compared to non-fermented pomegranate juice (44%), and punicalagin (43%), underscoring their pronounced antihypertensive and anti-inflammatory properties.[122–125] Among its active constituents, pedunculagin, punicalin, and gallagic acid demonstrated ACE inhibitory activity with IC_{50} values of 0.91, 1.12, and 1.77 μM, respectively. Furthermore, pedunculagin reduced reactive oxygen species (ROS) levels and increased nitric oxide (NO) production, highlighting its antihypertensive potential.[126]

Pomegranate juice also exhibited cardioprotective and anti-arrhythmic effects by reducing the levels of cardiac injury markers such as creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), NO, prostaglandin E2 (PGE2), and interleukin (IL-6) in animal models.[127,128] Punicalagin was reported to mitigate myocardial oxidative damage, inflammation, and apoptosis in isoproterenol-induced myocardial infarction rats.[129] Additionally, pomegranate peel extract significantly attenuated cardiac damage and diabetic cardiomyopathy in rats by enhancing antioxidant enzymes (SOD, CAT, and GSH), and downregulating pyroptosis-related genes, including long non-coding RNA-MALAT1.[130,131] The proposed mechanisms underlying the cardioprotective effects of pomegranate against CVDs are illustrated in Fig. 2.

Based on current evidence, pomegranate and its bioactive constituents exhibit significant cardioprotective effects across various experimental models, primarily involving rodent species such as Wistar and Sprague–Dawley rats. Nevertheless, further investigations employing histopathological and immunohistochemical analyses are warranted to provide a clearer visualization of myocardial damage, fibrosis, and pyroptosis. While previous studies focused on biochemical markers such as CK-MB, LDH, IL-6, SOD, and CAT, future research would benefit from the application of gene expression profiling techniques, such as qPCR, western blotting, and RNA sequencing, to elucidate the molecular pathways involved in oxidative stress, inflammation, ACE inhibition, and programmed cell death.

6.2 Cancer

Pomegranate extracts and their phytoconstituents demonstrated significant cytotoxic effects against a variety of cancer cell lines. Notably, hydroalcoholic extracts derived from both seeds and peels exhibited potent cytotoxic effects against hepatocellular carcinoma (HepG2), with IC_{50} values of 7.8 and 1.95 μg mL^{-1}, respectively.[132] Additionally, methanolic peel extracts displayed cytotoxic activities against MCF-7 breast cancer, PC-3 prostate cancer, and A549 lung cancer cell lines, with an IC_{50} value of 5 μg mL^{-1}.[133] Juice extract also demonstrated cytotoxicity against MCF-7 cells, albeit at a higher IC_{50} value of 49.08 μg mL^{-1}.[134] Pomegranate seed oil exhibited remarkable cytotoxicity against MCF-7 and MDA-MB-231 breast cancer cell lines with IC_{50} values of 0.50 and 0.60 μL, respectively.[135] Moreover, polyphenolic compounds isolated from the peels were cytotoxic to PANC-1 (pancreatic cancer) cells, with an IC_{50} value of 50 μg mL^{-1},[136] while urolithin A exhibited cytotoxicity against HCT-116 colorectal cancer cells, with an IC_{50} value of 19 μM.[137,138]

Beyond cytotoxicity, pomegranate-derived products have demonstrated additional anticancer properties. Fruit juice was reported to reduce inflammatory markers and suppress pro-inflammatory gene expression,[139–141] while crude extracts modulated cancer-related microRNAs, particular colorectal cancer.[142] Peel extracts were shown to inhibit tumor growth[143] and induce apoptosis in MCF-7 cells.[144,145] Similarly, methanolic juice extract induced apoptosis in MCF-7 cells and normalized liver histology in hepatocellular carcinoma models.[134,140] Aril extract suppressed cancer cell proliferation and enhanced the expression of apoptotic markers,[146] whereas rind extracts decreased cancer cell viability and triggered caspase-dependent apoptosis.[147] Whole fruit extract was also shown to reduce tumor weight and angiogenesis in animal models.[143,148,149]

Among the bioactive constituents, punicalagin stands out for modulating DNA repair genes and apoptotic signaling

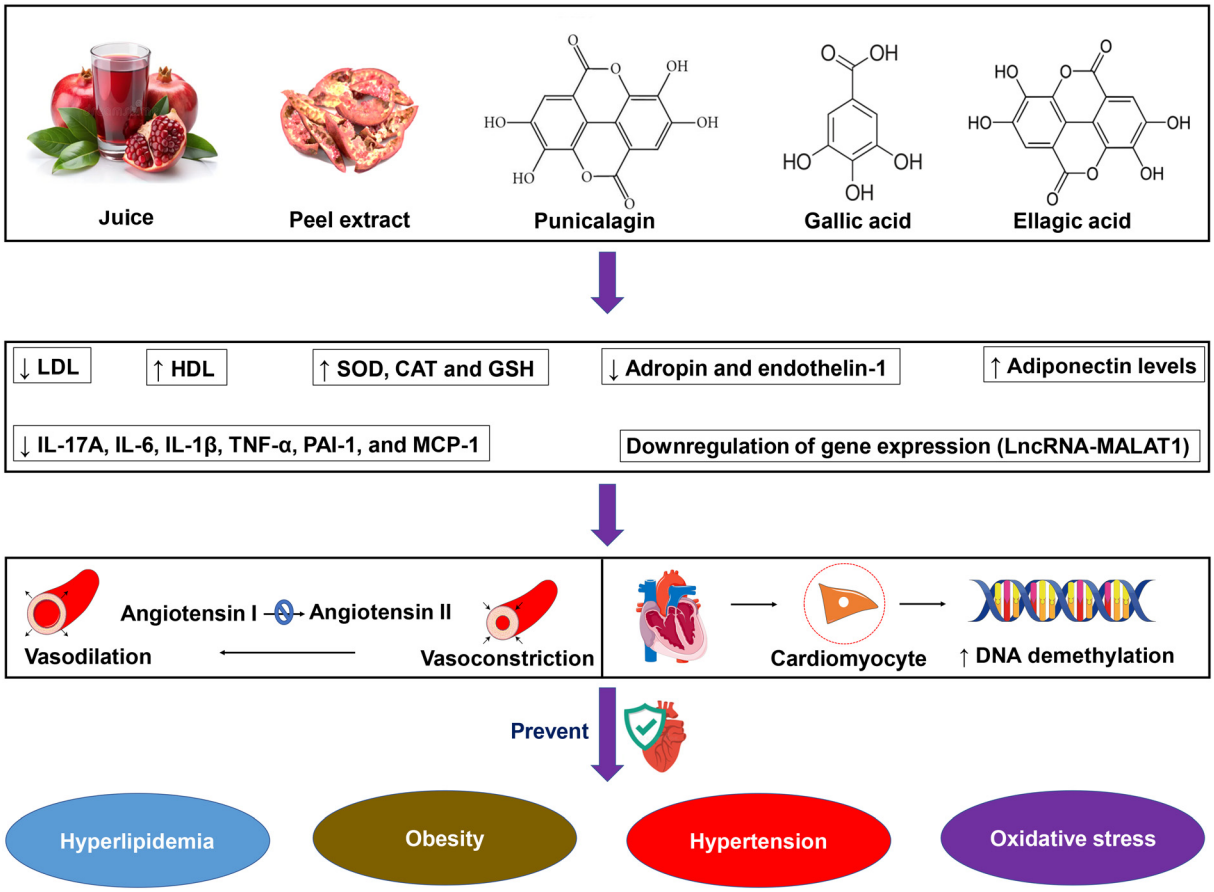

Fig. 2 Proposed mechanisms underlying the cardioprotective effects of pomegranate against CVDs.

pathways,[150] and for inhibiting critical transcription factors such as STAT-3 and NF-κB signaling.[151–153] Ellagic acid was also reported to inhibit cancer cell proliferation and migration, and induce apoptosis and cell cycle arrest.[154,155] The principal anticancer agents in pomegranate, namely punicalagin, ellagic acid, and gallic acid, consistently exhibit strong cytotoxic activity across various cancer cell lines, as summarized in Table 1. The underlying mechanisms of action are illustrated in Fig. 3.

Recent studies demonstrated that pomegranate and its bioactive constituents, including punicalagin, ellagic acid, and urolithins, exerted anticancer effects through multiple mechanisms. These include inhibition of cellular proliferation, induction of apoptosis, suppression of angiogenesis, and modulation of inflammatory pathways. However, the stage of cancer development at which these compounds exert their greatest effects remains a critical consideration for clinical application.

To address this, we categorize the reported anticancer activities into two stages: early-stage prevention and late-stage treatment. Early-stage prevention refers to interventions that target the initiation or promotion phases of carcinogenesis, such as blocking the transformation of chronic inflammation into malignancy or inhibiting the proliferation of precancerous cells. Several preclinical studies demonstrated that pomegranate extracts could effectively suppress biomarkers of inflammation and oxidative stress in various models of cancer, suggesting potential for chemoprevention.

In contrast, late-stage treatment refers to strategies aimed at suppressing tumor growth, metastasis, or recurrence after cancer has already developed. Some studies report that pomegranate bioactive compounds can enhance apoptosis in established tumor cells and sensitize them to conventional chemotherapeutic agents. However, evidence in this area remains limited compared to preventive studies.

Collectively, these findings suggest that pomegranate may be particularly effective as a preventive intervention, especially in individuals at high risk of cancer due to chronic inflammation or genetic predisposition. This perspective is consistent with the emerging view of dietary polyphenols as modulators of the tumor microenvironment during the early stages of cancer development.

To advance this field, comprehensive mechanistic investigations are required to elucidate the molecular targets underlying their cytotoxic, anti-inflammatory, and pro-apoptotic effects. Key signaling pathways, including STAT3, NF-κB, PI3K/Akt, and cancer-associated microRNAs, warrant particular attention. Concurrently, toxicological evaluations and pharma-

Table 1 Anticancer properties of pomegranate

Nature	Concentration/dose	Cancer type	Mechanisms of action	Ref.
Fruit juice	2.5 mL juice (equivalent to 20 mg gallic acid per kg body mass per day)	Sprague–Dawley rats	↓ IL-6, TNF-α, HIF-1, and TP53 gene expression	139
	10 mL per kg b.w.	DENA-induced hepato-carcinogenesis in Wistar albino rats	↓ GST, TNF-α, NF-κB-p65 levels	140
	5 and 10%	A2780 cells	↓ Cell proliferation and migration	141
	50 mg L^{-1}	HT-29	↓ TNFα-induced COX-2 protein production by 79% ↓ NFκB response element binding by 6.4-fold ↓ Suppressed p65 subunit phosphorylation Blocked TNFα-induced AKT activation	156
	50 mL per kg b.w.	C57BL/6 male and female mice	↓ Inhibition of tumor growth and proliferation	143
Crude extract of peel and whole fruit (standardized)	PE-1 (2 mg g^{-1} punicalin, 72 mg g^{-1} punicalagin, and 294 mg g^{-1} EA derivatives) PE-2 (5.4 mg g^{-1} punicalin, 155 mg g^{-1} punicalagin, and 28 mg g^{-1} EA derivatives)	Colorectal cancer patients	Altered the number of microRNAs responsible for colorectal cancer	142
Peel extract	10 and 50 mg per kg b.w.	C57BL/6 male and female mice	↓ Inhibition of tumor growth	143
	25–300 μg mL^{-1}	MCF-7	↑ Induction of apoptosis ↑ Bax/Bcl-2 expression	144
	20–320 μg mL^{-1}	MCF-7, MCF-10A, and MDA-MB-231	Blockage of [^{3}H] estradiol binding to the receptor, and reduced the transcription of estrogen-responsive genes	145
Methanol extract of juice	10–200 μg mL^{-1}	MCF-7	↑ Induction of apoptosis	134
	10 mL kg^{-1}	Hepatocellular carcinoma-induced rats	Normalization of liver histology Elevation of caspase-3 and Bax mRNA levels	140
Methanol, chloroform, & ethyl acetate extracts of arils	50–400 μg mL^{-1}	MCF-7	↓ Growth and proliferation ↑ Induction of apoptosis ↑ Bax, cytochrome-c, caspase-8 and 9 expression	146
Fruit extract	5, 10, and 20 μg per chick chorioallantoic membrane	Suit-2	↓ Tumor weight ↓ Average blood vessel branch count	148
	40 mg mL^{-1}	MCF-7	↑ Effects of tamoxifen by inducing apoptosis and reducing cell viability (50%)	149
	10 mg per kg b.w.	C57BL/6 male and female mice	↓ Inhibition of tumor growth	143
	50 and 100 μg mL^{-1}	T24	↓ Cell proliferation Cell cycle arrest in the S-phase; enhanced Bax/Bcl-2 ratio and induced activation of pro-caspase 3, 8, and 9 to promote apoptosis	157
	50–150 μg mL^{-1}	A549	↓ Cancer cell viability Arrest of cells in the G0-G1 phase ↓ Expression of CDK 2, CDK4, CDK6, and cyclins D1, D2, and E ↓ NF-κB DNA-binding activity and the phosphorylation of PCNA, PI3K, PKB, NF-κB, Ki-67, and MAPK proteins	158
Ellagitannin-rich extract	3.1–50 μg mL^{-1}	LNCaP, LNCaP-AR, and DU-145	↓ HSD3B2, AKR1C3, and SRD5A1 gene expression ↓ Regulation of androgen receptor expression	159
Hydromethanolic extract of seed oil	0.12–0.6 μL (0.4 mg L^{-1})	MCF-7 and MDA-MB-231	↑ Induction of apoptosis ↓ Cell proliferation ↑ Proportion of cells in the G0/G1 phase of the cell cycle ↓ VEGF ↓ Pro-inflammatory cytokines (IL-2, IL-6, IL-12, IL-17, IP-10, MIP-1α, MIP-1β, MCP-1 and TNF-α)	135
	—	MCF-7, and MDA-MB-231	↓ Lipoxygenase activity by 69–81% and COX-2 by 31–44% ↓ VEGF, IL-2, IL-6, IL-12, IL-17, MCP-1, MIP-1α/1β, and TNF-α	160

Table 1 *(Contd.)*

Nature	Concentration/dose	Cancer type	Mechanisms of action	Ref.
Polyphenols from peels	100, 200, and 300 μg mL^{-1}	HepG2	Cell cycle arrest at S-phase ↑ Levels of ROS Induction of apoptosis by means of Cyt-c propagation, caspase-3/9 activation, Bax/Bcl-2 ratio, and P53 expression	161
Polyphenols from seed oil, fermented juice, and pericarp extract	0.1–40 mg mL^{-1}	MCF-7 and MDA-MB-231	Inhibition of 17-β-hydroxysteroid dehydrogenase activity by 34–79% ↓ Cell proliferation ↓ Estrogenic activity of 17-β-estradiol by 55% ↓ Cell invasion ↑ Induction of apoptosis	162
Pomegranate emulsion	1 and 10 g per kg b.w.	DENA-induced hepato-carcinogenesis in rats	↓ Hepatic nodule incidence, number, multiplicity, size, and volume of hepatocarcinoma ↓ Hepatic foci positive for γ-glutamyl *trans* peptidase ↓ Lipid and protein oxidation ↑ Hepatic Nrf2's messenger RNA and protein expression	163
Punicalagin standardized extract	0–100 mg mL^{-1}	MCF-7	↑ 398 genes associated with apoptosis and cell proliferation ↓ BRCA1, BRCA2, BRCC3, RAD50, RAD51, and NBS1 Modulated miRNAs involved in DNA repair mechanisms	150
Punicalagin	10, 20, and 30 μM	A549 cells	Blocked STAT-3 translocation Induction of apoptosis ↓ Bcl-2 expression ↑ Bax, cytochrome-c, caspase-9, and caspase-3 IC_{50} = 20.5 μM (cytotoxicity)	151
	20 μg mL^{-1}	Hep-G2	↑ Induction of apoptosis ↓ Growth and proliferation ↑ Caspase-3 levels	152
	12.5–100 μM	MDA-MB-231, BT-20, and MCF-7	↑ Induction of autophagy ↑ Increased mitochondrial ROS in MDA-MB-231 ↑ Autophagic vacuole formation ↓ LC3-II/LC3-I ratio Activation of phosphorylated c-Jun N-terminal kinase (p-JNK) signaling ↓ PI3K/Akt pathway	153
	50 μM	MCF-7 and MDA-MB-231	↓ Cell viability, migration, and invasion; inhibited the expression of GOLPH3 ↓ Expression of EMT-related proteins (MMP-2, MMP-9, and N-cadherin) ↑ Expression of E-cadherin	164
	10–100 μM	ME-180	↓ Cell viability ↓ ROS generation ↓ Expression of NF-kB and upregulated the expression of caspase-3 and -9, Bax, and p53 mRNA	165
	12.5, 25, 50, 100, and 200 μM	HeLa	Induction of cell cycle arrest in the G1 phase ↓ β-catenin, cyclin D1 and c-myc ↓ Expression of anti-apoptotic Bcl-2 ↑ Expression of pro-apoptotic Bax ↓ Progression of cell migration ↑ Expression of MMP-9 and MMP-2 proteins	166
	10–210 μM	HeLa and SiHa	↓ Cell proliferation ↓ Expression levels of CASP3, CASP7, and CASP9 ↑ ROS, JNK, BCL2 phosphorylation, ↑ Autophagy Treatment with 140 μM punicalagin markedly inhibited the interaction between BCL2 and BECN1 in HeLa cells IC_{50} = 67 and 40 μM for HeLa and SiHa cells, respectively	167

Table 1 *(Contd.)*

Nature	Concentration/dose	Cancer type	Mechanisms of action	Ref.
	18.5 mg per kg b.w.	DENA-induced hepato-carcinogenesis in Wistar albino rats	Significant downregulation of Bcl-XL, Bcl-2 mRNA, and serum circulating miR-21 expression ↑ Bax/Bcl-2 ratio	140
	0–30 μg mL^{-1}	MCF-7 and Hs578T	↓ Cell growth and proliferation	168
Ellagic acid	1, 3, and 5 μg mL^{-1}	PANC-1	↓ Cell proliferation ↓ Migration of PANC-1 in dose dependent manner ↓ Tumor development and COX-2 and NF-κB expression Cell cycle arrest at G1 phase	154
	10–30 μM	HeLa, SiHa, and C33A	↓ Cell growth and proliferation (HeLa, SiHa and C33A) Inhibited JAK2 and STAT3 pathway (HeLa) Cell cycle arrest at G1 phase (HeLa)	155
	15, 30, and 45 μM	DU-145 and PC-3	↓ Cell growth and proliferation Induction of apoptosis ↓ Cyclin B1 and cyclin D1 S phase (DU-145), and G2/M phase (PC-3) cell cycle arrest	169
	10 and 100 μM	HOP62 and H1975	Reduced OCR ↓ Mitochondrial oxygen consumption, proton leak, and oxygen consumption-related oxygen granules	170
	40 and 80 mg per kg b.w.	C57 mice	↑ p-AMPK and p-ACC levels ↓ Tumor development, as evidenced by a reduction in tumor volume Significant drop in HIF-1α levels	170
	1, 5, 10, 50, and 100 μM	H358	↓ VEGF, MMP-9 and MMP-2 protein expression Cytotoxic effect (IC_{50} = 7.18 μM)	171
	20 μM	Hep3B and Huh7	↓ Colony formation ↓ DNA replication ↓ Decreased tumor size and weight Synergistic inhibition of the Akt/mTOR and MAPK signaling pathways in the xenograft tumor	172
	10^{-9} M and 10^{-5} M	MCF-7	↓ vhTERT α+β+ mRNA expression ↑ Production of hTERT α+β+ mRNA	173
	10 and 50 mg per kg b.w.	C57BL/6 male and female mice	↓ Inhibition of tumor growth	143
	0–30 μg mL^{-1}	MCF-7, and Hs578T	↓ Cell growth and proliferation	168
Ellagic acid and luteolin	5, 10, and 15 μg mL^{-1}	A2780	↓ Expression of MMP2 and MMP9	141
Gallic acid (juice)	2.5 mL	Sprague–Dawley rats	↓ IL-6, TNF-α, HIF-1, and TP53 gene expression	139
Cyanidin-3-glucoside	20 μM	MCF-7	↓ Angiogenesis by downregulating STAT3 expression through the induction of miR-124 ↓ VEGF	174
Urolithin-A	30, 60, and 90 μM	DU-145 and PC-3	Dose-dependent antiproliferative effects Cell cycle arrest at G2/M ↑ Phosphorylation of cyclin B1 and cdc2 at tyrosine-15	169

cokinetic profiling are crucial for determining the bioavailability, metabolism, and systemic safety of both crude extracts and purified constituents such as punicalagin, ellagic acid, and gallic acid.

Robust *in vivo* validation using physiologically relevant animal models of cancer is also essential to corroborate *in vitro* findings and explore potential synergistic effects with conventional chemotherapeutics. Moreover, the development of advanced drug delivery platforms, such as nanoparticles, liposomes, or microemulsions, may significantly enhance the bioefficacy, stability, and tissue-specific delivery of these bioactive agents.

Finally, to facilitate clinical translation, well-designed early-phase clinical trials should be initiated to evaluate therapeutic efficacy, tolerability, and optimal dosing regimens in cancer patients. Such integrated research efforts are imperative to transform the anticancer potential of pomegranate into evidence-based functional products or adjunct therapies in oncology.

6.3 Respiratory diseases

Pomegranate has demonstrated therapeutic potential in the management of NCRDs, including asthma and idiopathic pulmonary

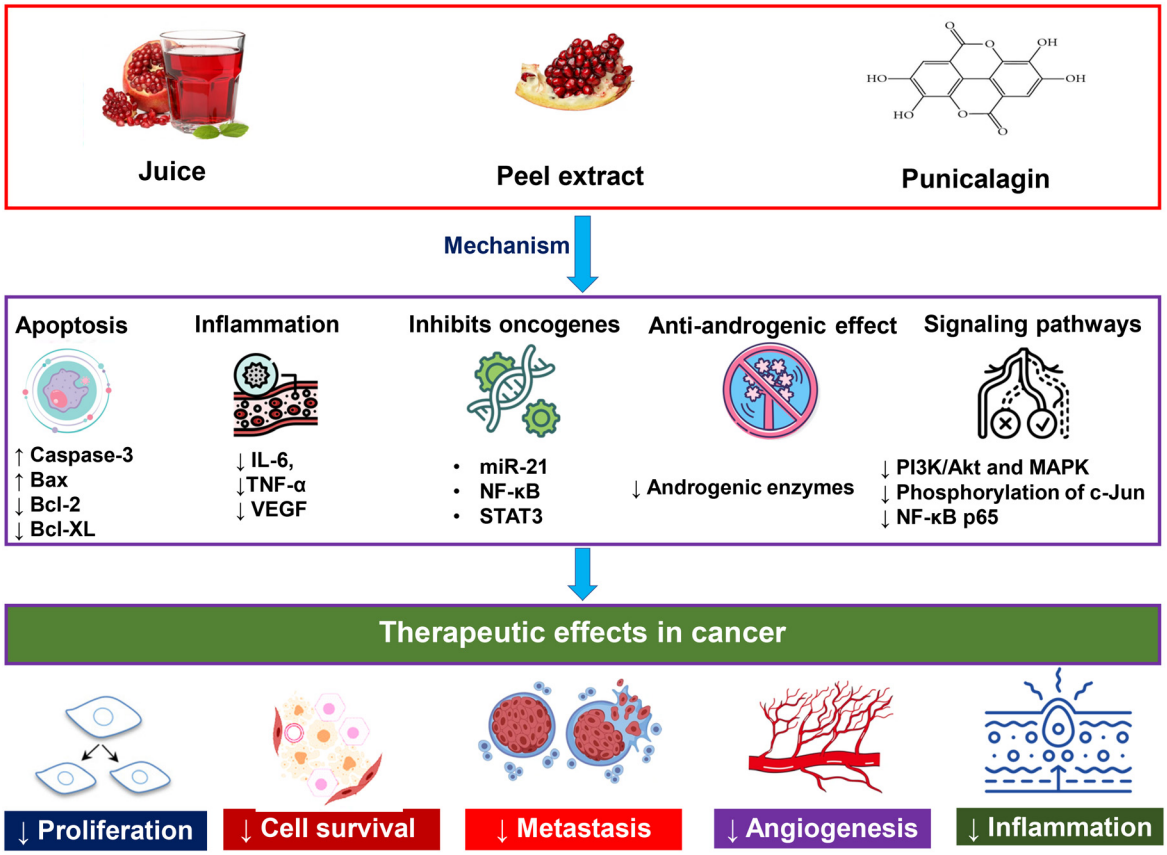

Fig. 3 Anticancer mechanism of pomegranate.

fibrosis (IPF). Asthma, characterized by airway inflammation and hyperresponsiveness, may benefit from the antioxidant-rich properties of lactic acid-fermented pomegranate juice. Several studies suggest that pomegranate, particularly in combination with licorice, may alleviate coughing and improve asthma-related symptoms.[175,176] In a bleomycin-induced lung fibrosis model using male Sprague–Dawley rats, pomegranate seed extract exhibited significant antioxidant and protective effects against lung damage.[177] Furthermore, when combined with carvacrol, the extract reduced methotrexate-induced pulmonary fibrosis in mice.[178] Pomegranate peel powder also shows promising anti-inflammatory and anti-fibrotic properties, suggesting a potential role in the prevention of lung injury. Additionally, gallic acid, a bioactive compound found in pomegranate, was reported to attenuate oxidative stress and suppress pro-inflammatory cytokines, thereby mitigating both lung injury and fibrosis. A comprehensive review article detailing the role of pomegranate in the treatment of CRDs was published previously.[175]

While current findings highlight the therapeutic potential of pomegranate and its phytoconstituents in the management of NCRDs, such as asthma and IPF, further investigations are essential to fully elucidate their clinical applicability. Future studies should aim to dissect the specific molecular mechanisms by which pomegranate-derived compounds, including gallic acid, exert their antioxidant, anti-inflammatory, and anti-fibrotic effects in pulmonary tissues. Rigorous *s* studies using well-established disease models are warranted to assess long-term efficacy, optimal dosing, and toxicity profiles of both individual phytochemicals and whole extracts. In addition, given the promising results observed in combination therapies, such as pomegranate with carvacrol or licorice, there is a need to systematically evaluate synergistic interactions and their pharmacodynamic implications. Moreover, the role of fermentation in enhancing bioactivity, particularly in lactic acid-fermented pomegranate juice, remains an underexplored area deserving of greater scientific attention. Finally, to bridge preclinical and clinical research, controlled clinical trials should be initiated to assess the therapeutic potential of pomegranate-based interventions in patients with chronic respiratory diseases, focusing on parameters such as lung function, inflammatory markers, symptom relief, and quality of life. Such studies will be critical for validating pomegranate as a complementary or integrative therapeutic strategy in respiratory health management.

6.4 Antidiabetic

Emerging evidence from multiple studies underscores the antidiabetic potential of pomegranate and its bioactive constituents. Compounds such as punicalin, punicalagin, and ellagic acid demonstrated promising antidiabetic effects in *in-silico*

studies by interacting with key protein targets, including glutamine-fructose-6-phosphate aminotransferase (GFAT), protein tyrosine phosphatase 1β (PTP1β), peroxisome proliferator-activated receptor gamma (PPAR-γ), tyrosine kinase insulin receptor (TKIR), retinol-binding protein 4 (RBP4), α-amylase, α-glucosidase, glucokinase (GCK), and aquaporin-2 (AQP-2). These molecular interactions support their therapeutic role in diabetes management.[179] Peel extracts from three pomegranate cultivars, namely Hicaz, Devedişi, and Zivzik, exhibited significant inhibitory activity against α-amylase with IC_{50} values of 0.14, 0.02, and 0.06 mg mL^{-1}, respectively, and against α-glucosidase with IC_{50} values of 3.50, 3.01, and 3.64 mg mL^{-1}.[180] Furthermore, both fruits and peel extracts inhibited α-amylase activity by 30% and 50%, respectively, in high-fat and high-fructose-fed rats.[24]

In vivo studies using streptozotocin and alloxan-induced diabetic mice revealed that pomegranate fruit and peel extracts possessed notable antidiabetic and antioxidant properties.[181,182] Polyphenol-rich extracts were reported to reduce blood lipid levels and enhance the expression of insulin receptor (InsR) and phosphorylated insulin receptor substrate-1 (IRS-1) in skeletal muscle tissue.[183] Additionally, mesocarp extract was found to reduce inflammation and oxidative stress while improving insulin sensitivity.[184]

Clinical trials further support the antidiabetic efficacy of pomegranate. In one study, 52 obese diabetic patients who consumed 1 g of pomegranate seed extract three times daily for eight weeks exhibited significantly reduced fasting blood glucose levels.[185] Another trial involving 85 diabetic patients demonstrated that oral administration of fresh juice at a dosage of 1.5 mL kg^{-1} improved insulin resistance and β-cell function.[186] Similarly, a separate study with 50 diabetic individuals showed that daily consumption of 200 mL day^{-1} of pomegranate juice for six weeks significantly decreased fasting blood sugar levels.[187] The proposed antidiabetic mechanisms of pomegranate are illustrated in Fig. 4.

Despite the promising antidiabetic potential of pomegranate and its bioactive constituents demonstrated in *in silico*, *in vitro*, *in vivo*, and clinical studies, several areas warrant further investigation to advance the development of pomegranate-based preventive or therapeutic products for diabetes management. Firstly, comprehensive pharmacokinetic and pharmacodynamic studies are essential to elucidate the bioavailability, metabolic pathways, and tissue distribution of key compounds such as punicalagin, ellagic acid, and punicalin. Secondly, mechanistic studies using advanced omics technologies, *e.g.*, transcriptomics, proteomics, and metabolomics, could provide deeper insights into the molecular pathways

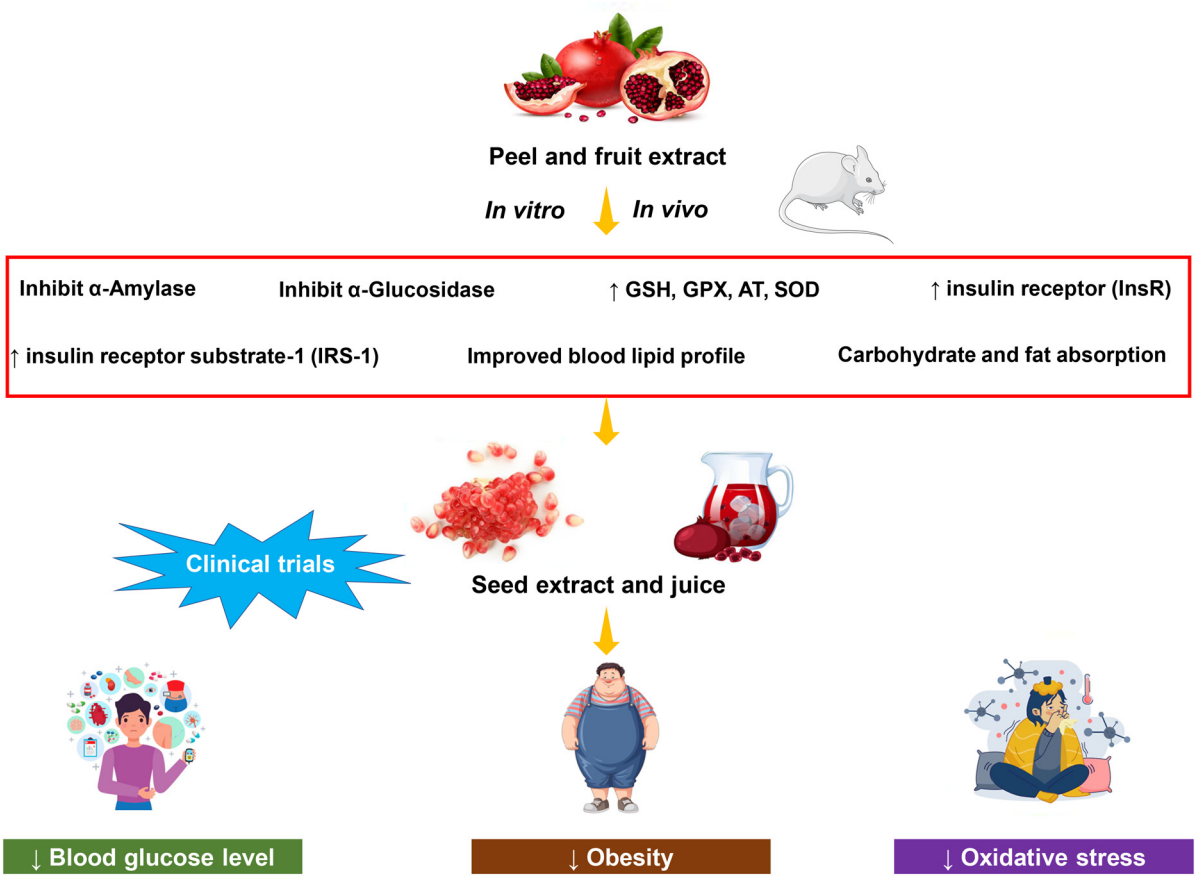

Fig. 4 Proposed antidiabetic mechanisms of pomegranate.

modulated by pomegranate constituents, particularly in insulin signaling and glucose metabolism. Thirdly, well-designed, large-scale randomized controlled trials with standardized pomegranate extracts are needed to validate clinical efficacy and safety across diverse diabetic populations and to determine optimal dosages and treatment durations. Moreover, investigations into the synergistic interactions between different phytochemicals within the whole fruit matrix may reveal enhanced bioactivities compared to isolated compounds. Lastly, formulation development studies, including nanoencapsulation or targeted delivery systems, could improve the stability and therapeutic efficacy of pomegranate-derived compounds. Addressing these research gaps will facilitate the translation of current findings into evidence-based nutraceutical or pharmaceutical interventions for diabetes prevention and treatment.

6.5 Hepatoprotective effects

Pomegranate was identified as a hepatoprotective fruit, as demonstrated by a growing body of preclinical and clinical evidence. Notably, pomegranate peel exhibits potent hepatoprotective and anti-inflammatory properties, significantly reducing liver damage and agrin expression in animal models.[188–191] In one comparative study, the effects of a single oral dose of *N*-acetylcysteine (150 mg kg^{-1}) and aqueous peel extract (430 mg kg^{-1}) were evaluated for paracetamol-induced hepatotoxicity. The peel extract alone significantly reduced levels of matrix metalloproteinase-1 (MMP-1), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), and total bilirubin levels by 18.5%, 38%, 16.6%, and 75.3%, respectively. When used in combination, these reductions were further enhanced to 50.2%, 53.1%, 34.5%, and 84.4%, respectively, compared to the paracetamol control group.[192]

Clinical evidence also supports the hepatoprotective effects of pomegranate. In a trial involving patients with non-alcoholic fatty liver disease (NAFLD), administration of hydroalcoholic eel extract (1500 mg orally, twice daily for 8 weeks) resulted in significant reductions in fasting blood glucose, mean body weight (MBW), body mass index (BMI), body fat index (BFI), and total body composition (TBC). When combined with a weight-loss regimen, the extract also contributed to hepatic steatosis and improved markers of metabolic syndrome.[193] Additionally, a 12 week randomized, double-blind clinical trial involving 44 NAFLD patients demonstrated that supplementation with 225 mg of pomegranate extract combined with 90 mg of ellagic acid significantly reduced hepatic transaminases and hepatokines, including fibroblast growth factor 21 and fetuin-A. The intervention also led to decreased interleukin-6 (IL-6) levels and enhanced overall antioxidant capacity.[194] The proposed hepatoprotective mechanisms of pomegranate are illustrated in Fig. 5.

While current preclinical and clinical evidence underscores the hepatoprotective potential of pomegranate, particularly its peel extract, further investigations are warranted to support the development of standardized therapeutic or preventive liver health products. Future studies should prioritize large-scale, multicenter clinical trials with diverse patient populations to validate the efficacy and safety profiles of various pomegranate-derived formulations. Standardization of bioactive constituents, such as punicalagins and ellagic acid, is critical for ensuring reproducibility and dose consistency across studies. Additionally, mechanistic studies at the molecular and cellular levels are needed to elucidate the pathways involved in hepatoprotection, including the modulation of oxidative stress, inflammatory cytokines, and fibrogenic signaling cascades. Exploring the synergistic effects of pomegranate with conventional hepatoprotective agents, such as *N*-acetylcysteine, may provide insights into combinatorial therapies. Moreover, pharmacokinetic and pharmacodynamic evaluations will be essential to determine optimal dosing strategies and formulation bioavailability. Lastly, long-term safety assessments and investigations into potential herb–drug interactions are crucial to guide clinical application and product development for liver disease prevention and management.

6.6 Nephroprotective effects

The nephroprotective effect of pomegranate was demonstrated in numerous studies. Its juice, peel extracts, and key phytochemicals, such as gallic acid, exhibit potent antioxidant, anti-inflammatory, and nephroprotective effects in animal models of cisplatin- and fluoride-induced oxidative kidney injury.[21,195–197] Oral administration of pomegranate juice (2.5 mL day^{-1} for 21 days) significantly attenuated cyclosporine-induced nephrotoxicity (25 mg kg^{-1} day^{-1}) in rats, as evidenced by reductions in plasma creatinine, blood urea nitrogen, and urinary levels of kidney injury markers KIM-1 and NGAL, along with improved creatinine clearance. Histopathological analysis confirmed the preservation of renal structure, while biochemical assays revealed decreased MDA levels and the restoration of antioxidant enzyme activities, indicating a nephroprotective mechanism involving oxidative stress attenuation and inflammation reduction.[198]

In another model, gentamicin (100 mg kg^{-1}, i.p., for 10 days) induced marked nephrotoxicity in rats, characterized by elevated serum markers, total protein, and albumin, alongside reductions in sodium and potassium levels. Histopathological findings showed severe interstitial nephritis, cystic tubular dilatation, and enlargement of Bowman's space. Oral pre- and post-treatment with extracts of pomegranate, blueberry, or their combination (500 mg kg^{-1}) ameliorated these changes. The combination therapy was most effective, showing superior improvement in both biochemical and histological parameters compared to monotherapy.[199]

Vancomycin (443.6 mg kg^{-1}, i.p., every other day for 2 weeks) administration resulted in pronounced hepato- and nephrotoxicity, as indicated by increased MDA and C-reactive protein (CRP) levels, reduced antioxidant enzyme activity, and decreased total protein. Histological evaluations revealed cytotoxic, vascular, and inflammatory damage in both liver and kidney tissues. Immunohistochemical staining showed upregulation of pro-apoptotic caspase-3 and downregulation of anti-apoptotic BCL-2. Co-treatment with pomegranate peel

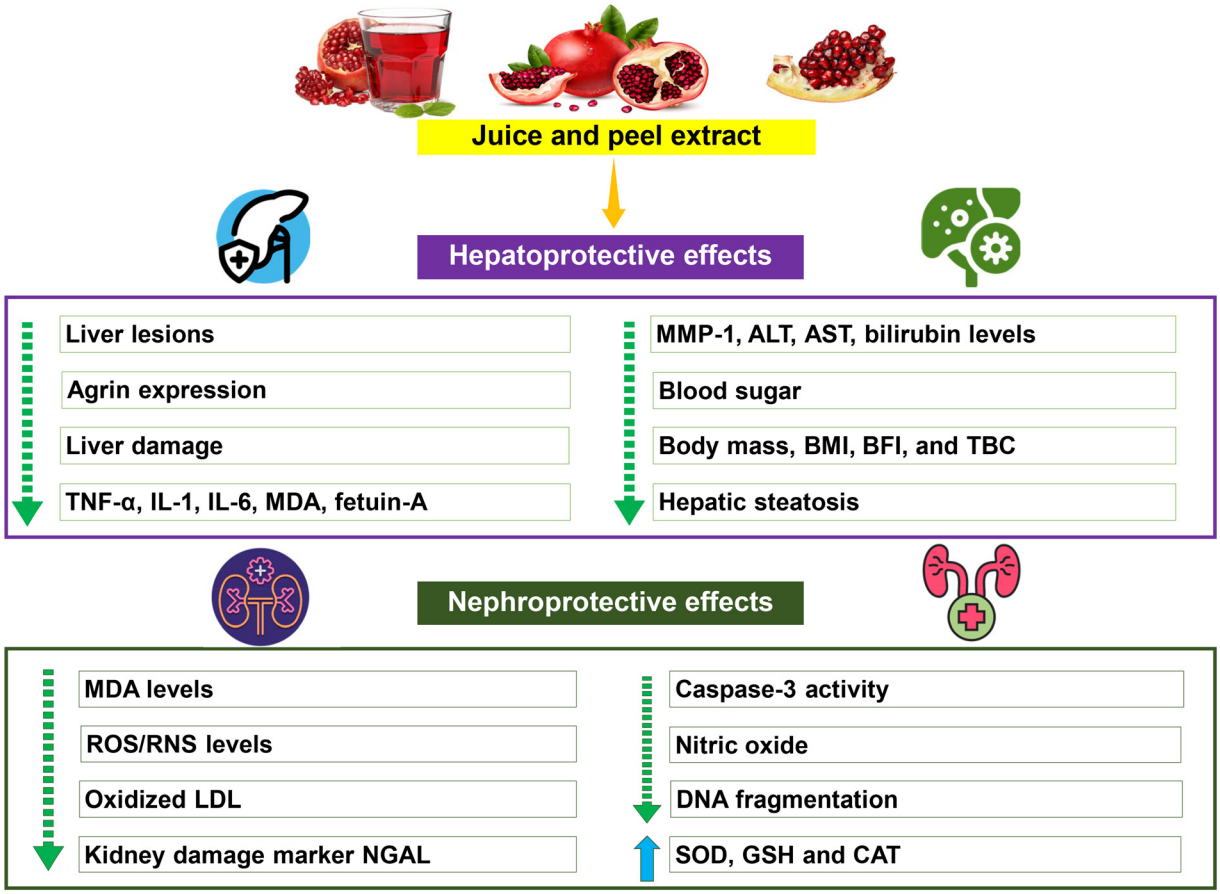

Fig. 5 Proposed hepatoprotective and nephroprotective mechanisms of pomegranate.

ethanol extract (100 mg kg^{-1} day^{-1}) mitigated these effects, restoring oxidative balance, reducing inflammation, and modulating apoptotic pathways. Notably, both pre-treatment and concurrent administration preserved renal histoarchitecture and improved biochemical profiles compared to vancomycin-only treatment.[200]

Furthermore, peel extract (100 and 300 mg mL^{-1}, oral), containing punicalagin, epigallocatechin gallate, chlorogenic acid, and ellagic acid, exerted protective effects in a lipopolysaccharide (LPS, 10 mg kg^{-1}, i.p.)-induced acute kidney injury model in Sprague–Dawley rats. Treatment resulted in GSH depletion and a dose-dependent inhibition of NF-κB activation. Histopathological and immunohistochemical analyses indicated that TLR4 and NF-κB expression levels were significantly elevated in the LPS group compared to controls, and were attenuated by the extract.[201]

In a double-blind randomized clinical trial involving 50 patients with diabetic nephropathy, supplementation with freeze-dried pomegranate juice powder resulted in significant reductions in urinary microalbumin and 24 h urine protein levels after 4 and 8 weeks, compared to baseline and placebo groups. No significant changes were observed in fasting blood glucose, serum creatinine, liver enzymes, or lipid profiles. Importantly, no adverse effects were reported during the study period.[202] The mechanisms underlying the nephroprotective actions of pomegranate are illustrated in Fig. 5.

While current evidence from animal and preliminary clinical studies supports the nephroprotective potential of pomegranate and its bioactive constituents, future research should employ advanced experimental platforms such as kidney organoids, 3D bioprinted renal tissues, and genetically modified animal models (*e.g.*, $Nrf2^{-/-}$) to further elucidate the precise molecular mechanisms involved. Additionally, integration of multi-omics approaches, exploration of the gut–kidney axis, and validation using renal-specific biomarkers will be critical for optimizing its therapeutic application.

6.7 Effect on the CNS

Both whole fruit and peel extracts demonstrate significant antidepressant properties, as evidenced by reduced immobility and increased swimming behavior in animal models, effects likely mediated through activation of the serotonergic system and estrogen receptor-β. Furthermore, peel extract was found to attenuate lipid peroxidation in the brain and mitigate stress associated with elevated monoamine oxidase-B (MAO-B) activity.[203,204] In the forced swim test (FST), administration of aqueous extract (0.125, 0.50, and 2.0 mg kg^{-1}) in combination with subtherapeutic doses of citalopram (0.77, 3.06, and

12.24 mg kg^{-1}) produced a synergistic antidepressant effect, resulting in 40% reduction in immobility, along with enhanced dendritic complexity and increased spine density in the granular cell layer of the hippocampal dentate gyrus.[205] Furthermore, both punicalagin and ellagic acid were found to suppress ROS production, lipid peroxidation, and MDA levels in rat brain tissue, as confirmed by *ex vivo* assays, with ellagic acid exhibiting superior efficacy compared to punicalagin.[206]

Pomegranate peel, juice, and seed extracts showed anxiolytic and antidepressant effects in both mice and ischemic rat models, primarily attributed to the antioxidant properties of their bioactive compounds, including phenols, flavonoids, and tannins.[207–210] An ellagitannin-rich pomegranate extract (15.77 ± 0.15 mg g^{-1} of dry extract) reduced phosphorylated extracellular signal-regulated kinase 1/2 (pERK1/2) levels in the amygdala by 31%, alleviating anxiety-like behavior *via* activation of peroxisome proliferator-activated receptor gamma (PPAR1) through the ERK1/2 signaling pathway.[211] Moreover, peel, juice, combined ellagic acid and gallic acid, urolithin A, and punicalagin exhibited neuroprotective, anti-Parkinson's, and anti-Alzheimer's effects. These effects were mediated through restoration of H_2O_2-induced imbalance in the Bax/Bcl-2 ratio, inhibition of the β-secretase (BACE) pathway, modulation of MAPK signaling, and a reduction in oxidative stress, as demonstrated in various *in vitro* and *in vivo* studies.[212–214]

The mechanisms by which pomegranate exerts its effects on central nervous system disorders are illustrated in Fig. 6.

Despite key evidence discussed above, there remains room for advanced experimental models, including human brain organoids and induced pluripotent stem cell (iPSC)-derived neuronal cultures, to better mimic human neurobiology and disease processes. Additionally, transgenic animal models of neurodegenerative disorders such as Alzheimer's (*e.g.*, APP/PS1 mice) and Parkinson's disease (*e.g.*, 6-OHDA lesion models) can help clarify its neuroprotective and antidepressant mechanisms.

6.8 Anti-inflammatory effect

Inflammation, mediated by a wide array of biological markers, plays a central role in the pathogenesis of various NCDs. Bioactive compounds derived from pomegranate, such as its juice, peel, catechin, punicalagin, and ellagitannin, demonstrated potent antioxidant, anti-inflammatory, and anti-arthritis properties, as well as efficacy for ameliorating inflammatory bowel disease (IBD) and colitis. These effects are primarily mediated through the inhibition of key molecular pathways and biomarkers, including glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT), lipase activity, cupric ion-induced LDL–cholesterol oxidation, tumor necrosis factor-alpha (TNF-α), interleukins (IL-18 and IL-1β), cyclooxy-

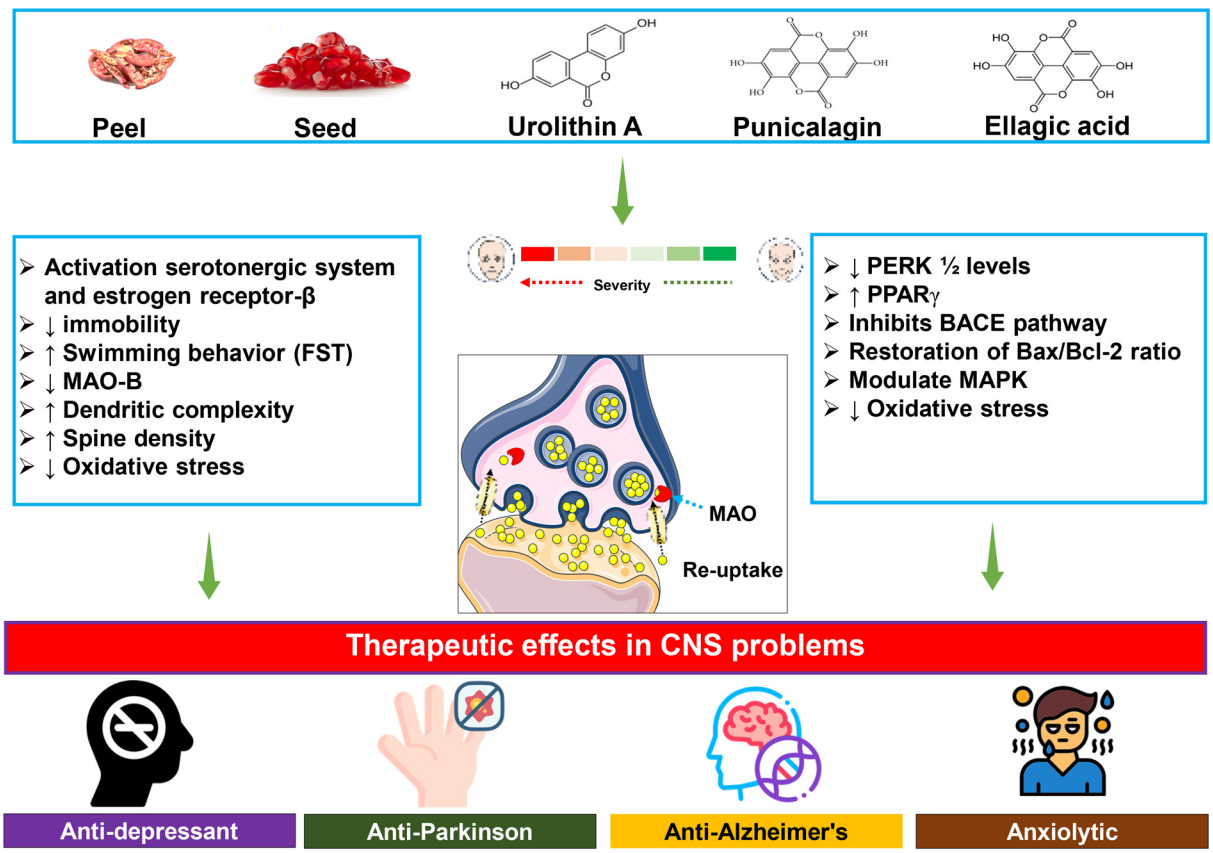

Fig. 6 Effects of pomegranate on CNS disorders.

genase-2 (COX-2), transforming growth factor-beta 1 (TGF-β1), and caspase-3 in various animal models.[215–219]

Several preclinical studies elucidated the mechanisms by which pomegranate and its constituents exerted anti-inflammatory effects, particularly in the context of IBD. For instance, in a dinitrobenzene sulfonic acid (DNBS)-induced colitis model in rats, both pomegranate juice (400 mg kg^{-1}) and purified punicalagin (4 mg kg^{-1}) significantly attenuated inflammation *via* inhibition of the NF-κB signaling pathway. Treated groups exhibited marked improvements in colon mucosal damage index (CMDI) and disease activity index (DAI) scores compared to controls. Notably, pomegranate juice reduced NF-κB mRNA expression by 84%, while punicalagin achieved 64% reduction, alongside decreases in TNF-α, IL-1β, and IL-18 levels.[216] In a dextran sulfate sodium (DSS)-induced colitis model, pomegranate juice significantly protected against colon inflammation and ulceration, reducing their severity by 50% and 66.7%, respectively. Treatment also suppressed the Ki-67 proliferative index and downregulated TNF-α, IL-1β, COX-2, and iNOS at both mRNA and protein levels. Additionally, expression of p70S6 kinase 1 and hypoxia-inducible factor 1-alpha (HIF-1α) was reduced, while tumor suppressor microRNA miR-145 was upregulated in both *in vivo* and *in vitro* models.[220]

Another study using a DSS-induced acute colitis mouse model found that oral administration of pomegranate extract (200 mg kg^{-1}) restored intestinal barrier integrity, regenerated the mucus layer, and prevented bacterial translocation into the mucosa.[221] Similarly, rats treated with pomegranate extract (250 or 500 mg kg^{-1} day^{-1}), ellagic acid (10 mg kg^{-1} day^{-1}), or ellagic acid-enriched extract (250 mg kg^{-1} day^{-1}) showed significant reductions in myeloperoxidase (MPO) activity and TNF-α levels compared to the trinitrobenzene sulfonic acid group. These treatments markedly downregulated COX-2 and iNOS, inhibited phosphorylation of MAPKs (p38, JNK, ERK1/2), and prevented NF-κB nuclear translocation.[222]

Furthermore, in a rat model of diarrhea-predominant irritable bowel syndrome (IBS-D), peel extract (200 and 400 mg kg^{-1} for 1 week) significantly alleviated intestinal inflammation and improved barrier function. These effects were mediated *via* modulation of MAPK and NF-κB pathways. Molecular docking and western blot analyses confirmed strong binding affinities and downregulation of p-IκB, p-p65, p-JNK, p-p38, and p-ERK1/2 expression.[223] Pomegranate seed oil also showed protective effects in an acetic acid-induced colitis model by reducing neutrophil activation, lipid peroxidation, NF-κB expression, proinflammatory cytokines, and MPO activity.[224]

In human studies, a randomized, placebo-controlled clinical trial evaluated the effect of pomegranate peel extract (6 g day^{-1} for 4 weeks) in patients with ulcerative colitis. While both groups exhibited reductions in Lichtiger Colitis Activity Index (LCAI) scores, the clinical response rate (≥3-point LCAI decrease) was notably higher in the peel extract group compared to placebo (41.4% *vs.* 18.2%). The extract was well tolerated, with additional benefits including reduced incontinence and decreased need for anti-diarrheal medications.[225] Another randomized, double-blind, placebo-controlled trial assessed the effects of ellagic acid (180 mg day^{-1} for 8 weeks) in 44 patients with IBS. Supplementation significantly reduced markers of oxidative stress and inflammation, including malondialdehyde (MDA), C-reactive protein (CRP), and IL-6, while increasing total antioxidant capacity (TAC). Quality of life, measured by the IBS-QOL questionnaire, improved significantly in the intervention group, with no corresponding improvement in the placebo group.[226] While current preclinical evidence predominantly relies on DNBS- and DSS-induced colitis models, future research should prioritize the use of more clinically relevant systems, including humanized and organoid models, to better capture the complexity of IBD pathophysiology and further validate the therapeutic potential of pomegranate-derived interventions.

6.9 Other NCDs

In addition to the major NCDs, emerging evidence indicates that pomegranate and its bioactive constituents offer therapeutic potential across a diverse array of other chronic conditions, including neurological, musculoskeletal, hepatic, metabolic, and autoimmune disorders.

In the context of neurological diseases, pomegranate demonstrated promising neuroprotective and anticonvulsant effects. Methanolic leaf extract (50–400 mg per kg body weight) showed significant, dose-dependent anticonvulsant activity in multiple experimental seizure models, including 6 Hz, maximal electroshock (MES), and pentylenetetrazole (PTZ)-induced seizures in Swiss albino mice. These effects were associated with a marked increase in GABA levels in the brain, highlighting the extract's modulatory influence on inhibitory neurotransmission.[227]

Complementing this, long-term dietary supplementation with 4% pomegranate fruit extract in APPsw/Tg2576 transgenic mice, a model of Alzheimer's disease, ameliorated cognitive deficits, preserved synaptic plasticity, and suppressed neuroinflammation. Restoration of synaptic protein levels (PSD-95, Munc18-1, SNAP25, synaptophysin) and increased phosphorylation of CaMKIIα and CREB provided molecular evidence of its cognitive-enhancing properties.[228]

Pomegranate has also been studied for its role in preserving bone health. In murine models of osteoporosis, supplementation with pomegranate seed oil (5% of the diet) prevented bone loss by stimulating osteoblast activity, suppressing osteoclastogenesis, and reducing systemic inflammation.[229] Similarly, pomegranate peel extract supported osteoblastic differentiation and bone preservation in preclinical studies,[230] suggesting multifaceted skeletal benefits.

In autoimmune and inflammatory diseases, a double-blind randomized clinical trial in patients with rheumatoid arthritis evaluated the effects of standardized pomegranate extract (250 mg twice daily, containing 40% ellagic acid). Treatment led to significant reductions in the Disease Activity Score-28 (DAS28), swollen and tender joint counts, pain intensity, and erythrocyte sedimentation rate (ESR). Additionally, improvements in patient-reported outcomes such as Health

Assessment Questionnaire (HAQ) scores and morning stiffness were observed, alongside increased levels of the antioxidant enzyme glutathione peroxidase.[231]

In the hepatic domain, pomegranate juice (60 mL day^{-1}) administered to male Sprague–Dawley rats significantly attenuated the pathological features of non-alcoholic fatty liver disease, including steatosis, lobular and portal inflammation, and hepatocellular ballooning. This hepatoprotective effect was accompanied by reduced hepatic expression of pro-inflammatory and pro-fibrotic genes and decreased plasma levels of ALT, AST, and insulin.[232]

Immunomodulatory effects of pomegranate were also demonstrated in models of autoimmune diseases. A hydroethanolic peel extract enriched with punicalin, punicalagin, and ellagic acid suppressed IL-17 production in activated T cells and alleviated disease severity in experimental autoimmune encephalomyelitis (EAE) in Dark Agouti rats. In a type I diabetes model (streptozotocin-induced) using C57BL/6 mice, the same extract inhibited immune cell infiltration into pancreatic islets and modulated cytokine expression (IL-17 and IFN-γ) in gut-associated lymphoid tissue (GALT), suggesting a regulatory role in the gut–immune–pancreas axis.[233]

Finally, cardiovascular benefits beyond traditional endpoints were observed. Administration of standardized hydroethanolic pomegranate peel extract (200 mg kg^{-1} for 12 weeks) in mice improved plaque stability by reducing necrotic core formation and increasing collagen content in atherosclerotic lesions. Mechanistic studies linked these effects to enhanced macrophage efferocytosis mediated by upregulation of Mer tyrosine kinase (MerTK) expression. *In vitro* data further confirmed that the extract inhibited MerTK shedding, thereby preserving phagocytic function and contributing to atheroprotection.[234]

Taken together, these findings underscore the broad therapeutic potential of pomegranate across a spectrum of non-communicable diseases, mediated by its anti-inflammatory, antioxidant, immunomodulatory, neuroprotective, and tissue-regenerative properties.

6.10 Clinical trials and applicability

As discussed throughout this review, pomegranate and its bioactive constituents, particularly ellagitannins, ellagic acid, punicalagin, and urolithins, exhibit diverse pharmacological effects against various NCDs. To assess their translational potential and clinical relevance, several human trials have been conducted in recent years. These studies evaluated the efficacy, safety, and practical applicability of pomegranate-derived interventions in both preventive and therapeutic settings, as summarized in Table 2; data retrieved on June 16, 2025 (*ClinicalTrials.gov*).

For cancer prevention and management, several clinical trials investigated the anticancer potential of pomegranate, particularly in colorectal and prostate cancers. In colorectal cancer, a phase 1–2 clinical trial (NCT01916239) assessed the pharmacokinetics and molecular effects of pomegranate-derived phenolics, namely ellagitannins, ellagic acid, and their gut-derived metabolite urolithin A. Patients received 900 mg day^{-1} of ellagitannin-rich extract for up to 35 days prior to surgery. The intervention significantly modulated the expression of colorectal cancer-related genes (*e.g.*, CD44, CTNNB1, CDKN1A, EGFR, TYMS) in both tumor and adjacent normal tissues, though with notable interindividual variability. These findings highlight the potential of ellagitannin-rich pomegranate extract as a complementary therapeutic strategy for colorectal cancer. In prostate cancer, a phase 2 randomized, double-blind, placebo-controlled trial (NCT02095145) evaluated the long-term preventive effects of 1000 mg day^{-1} pomegranate extract in individuals at high risk. Conducted over one year, the study suggested a potential protective role for pomegranate supplementation. Additionally, another phase 2 trial (NCT01220817) examined the effects of two different doses (1 g and 3 g daily) of POMx on the prostate-specific antigen doubling time (PSADT) in men with recurrent prostate cancer. Both doses significantly prolonged PSADT compared to the baseline, indicating biological activity, though the clinical significance requires further investigation.

For cognitive function and neurological recovery, emerging clinical evidence supports pomegranate's neuroprotective potential. A randomized trial (NCT02093130) reported that 12 months of daily pomegranate juice consumption helped preserve visual memory in older adults. Similarly, a placebo-controlled study (NCT01950221) found that 1000 mg day^{-1} pomegranate polyphenol extract improved memory, attention, and executive function over one year. Additionally, in a randomized, placebo-controlled study of acute stroke patients (NCT02442804), short-term POMx supplementation (equivalent to ~8 oz pomegranate juice daily for 1 week) improved cognitive recovery in areas such as memory and attention, suggesting a role in post-stroke rehabilitation.

In cardiovascular and renal applications, a recent randomized placebo-controlled trial (NCT07017296) evaluated both fresh pomegranate juice (150 mL) and microencapsulated juice (20 g) in mildly hypertensive patients. Both forms, rich in phenolics and anthocyanins, significantly reduced postprandial blood pressure, with the microencapsulated form showing effects comparable to those of standard antihypertensives. In contrast, a randomized, crossover pilot study in hemodialysis patients (NCT01562340) assessed the short-term safety and antioxidant effects of pomegranate juice and extract. While both interventions were safe and well tolerated, neither significantly impacted oxidative stress, lipid profiles, or inflammation markers, suggesting limited short-term benefits in this population. In patients with cardiomyopathy and heart failure, a phase 2 trial (NCT01102140) tested supplementation with POMx for 12 weeks but found no significant improvements in oxidative stress or fibrosis biomarkers. The study was ultimately terminated early due to a lack of efficacy, highlighting the complexity of translating preclinical findings into advanced cardiac conditions.

In oral health, a triple-blind randomized controlled trial (NCT93747064) conducted in Iran evaluated the efficacy of a traditional pomegranate-based mouth rinse ("Golnaar") in

Table 2 List of clinical trials for supporting the clinical translational feasibility of pomegranate therapeutic potential in the prevention and management of various NCDs. Data retrieved on June 16, 2025 (ClinicalTrials.gov)

Clinical trial number	Trial	Intervention details	Purpose	Clinical use	Participants	Phase
NCT00060086	Single group assignment	Pomegranate juice once daily for 18 months	Treatment	Prostate cancer	47	NA
NCT00336934	Randomized, parallel assignment	Pomegranate fruit juice	Treatment	Prostate Cancer	183	NA
NCT00668954	Randomized, placebo controlled parallel assignment	Pomegranate juice (8 oz or 236.5 mL day^{-1} for 12 weeks)	Basic science	Type 2 diabetes mellitus	26	NA
NCT00719030	Randomized, parallel assignment	POMx capsule, once daily for up to 4 weeks	Prevention	Prostate cancer	25	NA
NCT01033435	Prospective, case-control	1 cup pomegranate juice 3× per week for 1 year	Observation	Inflammation, oxidative stress	49	—
NCT01102140	Randomized, parallel assignment	POMx capsule for 12 weeks	Treatment	Cardiomyopathy and heart failure	20	Phase 2
NCT01220817	Randomized, double-blind, dose-finding study	POMx (1 or 3 capsules per day)	Treatment	Recurrent prostate cancer	104	Phase 2
NCT01562340	Randomized cross-over	Pomegranate juice (100 mL) 3× per week before hemodialysis	Prevention	ESRD, CVD	24	NA
NCT01916239	Randomized, parallel assignment	Standardized pomegranate extract with 20% punicalagin	Treatment	Colorectal cancer	60	Phase 1, phase 2
NCT01950221	Double-blind placebo controlled	Pomegranate polyphenol extract (1000 mg day^{-1} for 12 months)	Treatment	Alzheimer's disease	212	Phase 2
NCT02005939	Randomized, parallel assignment	Pomegranate extract capsule 650 mg for 4 weeks	Prevention	Cardiovascular risk factors	29	NA
NCT02061098	Placebo-controlled, dose–response, randomized	Pomegranate extract capsule, once daily for 3 weeks	Treatment	CV risk and overweight	50	Phase 1, phase 2
NCT02093130	Randomized double-blind placebo controlled	Pomegranate juice (8 oz or 236.5 mL daily for 12 months)	Treatment	Alzheimer's disease	212	Phase 2
NCT02095145	Randomized, placebo-controlled	Pomegranate fruit extract 1000 mg day^{-1} for 1 year	Prevention	Prostate cancer	38	Phase 2
NCT02107053	Non-randomized parallel assignment	Pomegranate juice ($\frac{1}{2}$ cup, 3× per week for 1 year)	Basic science	Cardiovascular disease	25	NA
NCT02227485	Triple-blind randomized	Pomegranate mouth rinse (Golnaar®, 10 mL every night for 2 weeks)	Treatment	Diabetic gingivitis	80	NA
NCT02298621	Randomized placebo cross-over trial	Pomegranate juice (500 mL)	Supportive care	Cardiometabolic disorder	30	NA
NCT02442804	Randomized placebo controlled	Pomegranate supplement (1 g) twice per day for 1 week	Treatment	Ischemic stroke	16	Phase 2
NCT02935777	Double-blind, randomized, crossover placebo-controlled	POMANOX® (2 capsules)	Health services research	Cognition	20	Phase 1
NCT03000101	Randomized, parallel assignment	125 mL pomegranate juice twice per day for 12 weeks	Basic science	Inflammatory bowel disease	18	NA
NCT03902288	Single group assignment	Fresh pomegranate juice (1.5 mL kg^{-1})	Treatment	Type 2 diabetes	85	NA
NCT06034106	Randomized controlled	Pomegranate peel compress (3 days per week for 3 weeks)	Supportive care	Osteoarthritis	67	NA
NCT06659523	Double-blind, placebo-controlled	Ellagitannin pomegranate supplement (1.5 g daily for 12 weeks)	Prevention	Prediabetes	60	NA
NCT07017296	Randomized placebo controlled	Microencapsulated pomegranate juice (20 g in 150 mL water)	Treatment	Hypertension	20	NA

NA; not applicable, POMx; pomegranate polyphenol supplement capsule.

treating diabetic gingivitis, using chlorhexidine (0.2%) as a comparator. After two weeks of use, followed by dental bleaching, participants in the Golnaar group demonstrated complete resolution of gingival inflammation, with high levels of patient satisfaction and no adverse events reported.

Collectively, these clinical trials highlight both the therapeutic promise and limitations of pomegranate-based interventions. While compelling evidence supports benefits for cancer prevention, cognitive enhancement, blood pressure regulation, and oral health, findings for advanced cardio-

vascular and renal conditions are less conclusive. Nonetheless, the overall safety profile of pomegranate-derived products remains favorable. Future large-scale, placebo-controlled trials with standardized formulations, extended durations, and rigorous outcome measures are essential to establish clear clinical guidelines for the use of pomegranate in NCD management.

7. Quality control of pomegranate fruit extracts

The maintenance of juice and fruit quality is crucial to prevent adulteration, as such compromises affect both the nutritional value and overall quality of pomegranate products, especially with long-term consumption.[235,236] Metabolomics has emerged as a powerful analytical approach for comprehensive food profiling. High-performance liquid chromatography (HPLC) and gas chromatography (GC), typically coupled with mass spectrometry (MS), are widely used to accurately quantify metabolites present in significant concentrations.[237] For instance, one study investigated multiple pomegranate juice samples to detect signs of adulteration. A recent analysis utilizing solid-phase microextraction coupled with comprehensive two-dimensional gas chromatography–mass spectrometry (GC × GC-MS) identified 123 volatile compounds linked to pomegranate juice adulteration. The results accounted for 87.4% of the total variation, effectively distinguishing authentic pomegranate juice from adulterated products.[238]

The presence of pesticides on fruit surfaces poses serious health risks to consumers. One study using liquid chromatography–mass spectrometry (LC-MS) reported imidacloprid residue levels of 56 and 39 μg kg^{-1} in two fresh fruit samples obtained from retail outlets. Another investigation documented the accumulation of fluopyram and tebuconazole residues across various anatomical parts of the pomegranate, including the whole fruit, arils, outer peel, mesocarp, and leaves. Notably, substantial concentrations of these fungicides remained on the fruit surface, with minimal translocation into the mesocarp.[239] Additionally, GC-MS, operated in selective ion monitoring mode, was employed for the quantitative and qualitative analysis of tebuconazole and fluopyram. The findings revealed that tebuconazole accounted for 7.5–24.4% of the residues found in the pericarp, while fluopyram constituted 5.7–9.2% of the residues detected in the mesocarp. The terminal residue concentrations of fluopyram and tebuconazole in the entire pomegranate fruit ranged from 0.037 to 0.094 mg kg^{-1} and 0.036 to 0.096 mg kg^{-1}, respectively. The estimated half-lives of fluopyram and tebuconazole in pomegranate fruit and leaves were approximately 7.3–9.1 and 15 days, respectively.[240] Furthermore, trace concentrations of fluopyram with suspension concentrations (active ingredient value 200 g L^{-1}) of 0.45 and 0.60 mg kg^{-1}, as well as tebuconazole (active ingredient value 200–400 g L^{-1}) at concentrations of 0.74 and 1.47 mg kg^{-1}, were detected in pomegranate fruit through LC-MS/MS analysis.[241]

8. Safety assessment

8.1 Polyphenol-rich extract

The safety evaluation of crude extract and pure bioactive compounds is essential for their clinical application. Patel *et al.* conducted a sub-chronic toxicity study (OECD-408) on a standardized pomegranate extract containing 70% polyphenols, including 30% punicalagin, 5% ellagic acid, and 0.3% gallic acid, as quantified using a HPLC method. The oral LD_{50} in both rats and mice exceeded 5 g per kg b.w., while the intraperitoneal (i.p.) LD_{50} was determined to be 217 mg per kg b.w. in rats and 187 mg per kg b.w. in mice. No abnormalities were observed in biochemical, hematological, and histopathological parameters. The no-observed-adverse-effect level (NOAEL) was established at 600 mg per kg b.w. per day, which was the highest dose tested.[242] Additionally, a polyphenol-rich hydroethanolic extract derived from pomegranate peel, quantified *via* UPLC-PDA, was administered to Zucker diabetic fatty rats at doses of 100 and 200 mg per kg b.w. for 8 weeks. The treatment did not cause any adverse effects on the tissue structure or cellular integrity in the heart and aortic segments.[243] In another study, oral administration of microencapsulated hydroethanolic extract of pomegranate peel (1 : 1 v/v) at high doses of 1600, 2900, and 5000 mg per kg b.w., according to OECD-425 guidelines, revealed no toxicological effects. Furthermore, a sub-chronic toxicity study (OECD-408) in CD-1 mice receiving 3000 mg per kg b.w. daily for 90 days showed no biochemical and histopathological signs of toxicity.[244] Clinical evaluation also supported the safety of pomegranate extracts: daily administration of 100 mL of pomegranate juice or 1050 mg of extract in tablet form to dialysis patients did not significantly affect predialysis blood pressure or oxidative stress markers.[245]

8.2 Urolithin A

Urolithin A demonstrated no genotoxic or mutagenic effects in rats. Both 28 day (OECD-407) and 90 day (OECD-408) dietary studies on administering concentrations of 0, 0.175, 1.75, and 5.0% urolithin A showed no significant alterations in biochemical, hematological or histological parameters. The NOAEL was determined to be the highest tested concentration of 5%, corresponding to 3451 mg per kg b.w. per day in males and 3826 mg per kg b.w. per day in females in the 90 day study.[246]

8.3 Lectin

A study evaluating the acute toxicity of lectin, a protein isolated from pomegranate juice, was conducted in female mice using OECD-423 guidelines at a dosage of 100 mg per kg b.w. Lectin exhibited no signs of toxicity at the biochemical, hematological, or histological levels. Furthermore, a micronucleus assay, a well-established biomarker for mutagenicity, revealed no increase in micronuclei formation in polychromatic erythrocytes, supporting its genetic safety at the administered dose.[247]

9. Pharmacokinetics and pharmacodynamics

9.1 *In silico* study

Punicalagin, epicatechin, catechin, gallic acid, punicalin, ellagic acid, quercetin, punicic acid, naringin, and kaempferol were reported to exhibit inhibitory effects on ACE, α-amylase, α-glucosidase, and anti-inflammatory enzymes (interleukins). Detailed pharmacokinetic and dynamic studies were reported previously in the literature.[126,179,195] In a molecular docking study against the C-terminal domain of ACE (PDB: 2XY9), several active compounds from pomegranate exhibited strong binding affinities. Gallagic acid demonstrated the highest binding energy of −12.4 kcal mol^{-1}, followed closely by punicalin (−12.2 kcal mol^{-1}), pedunculagin (−11.9 kcal mol^{-1}), and punigluconin (−11.7 kcal mol^{-1}). Castalagin and corilagin also showed significant binding energies of −11.6 kcal mol^{-1} and −10.3 kcal mol^{-1}, respectively. Against the N-terminal domain of ACE (PDB: 2XYD), castalagin showed the strongest interaction with a binding energy of −12.8 kcal mol^{-1}, while gallagic acid also showed a comparable strong binding of −12.3 kcal mol^{-1}. Other compounds including punicalin (−11.8 kcal mol^{-1}), corilagin (−11.4 kcal mol^{-1}), punigluconin (−10.5 kcal mol^{-1}), and pedunculagin (−10.6 kcal mol^{-1}) also exhibited strong affinities in comparison with the standard drug captopril (−8.9 kcal mol^{-1}).[126] Punicalin, punicalagin, and ellagic acid, were investigated for their antidiabetic activity against nine key protein targets involved in glucose metabolism namely GFAT, PTP1β, PPAR-γ, TKIR, RBP4, α-amylase, α-glucosidase, GCK, and AQP-2. Results show that all three compounds exhibit strong and significant interactions with these targets. Specifically, punicalin demonstrated binding scores ranging from −8.1 to −11.3 kcal mol^{-1}, punicalagin showed binding affinities between −8.5 and −10.4 kcal mol^{-1}, and ellagic acid exhibited binding scores from −6.8 to −8.7 kcal mol^{-1}. Punicalin showed the highest binding affinity with α-amylase (−11.3 kcal mol^{-1}), punicalagin with RBP4 (−10.4 kcal mol^{-1}), and ellagic acid with RBP4 (−8.7 kcal mol^{-1}).[179] Against key inflammatory and apoptotic protein targets, punicalgin exhibited the strongest binding affinity for IL1 (−11.6 kcal mol^{-1}), IL-6 (−10.6 kcal mol^{-1}), IL-10 (−11.7 kcal mol^{-1}), TNF-α (−12.1 kcal mol^{-1}), caspase-3 (−10.1 kcal mol^{-1}), Bcl-2 (−10.8 kcal mol^{-1}) and Bax (−10.4 kcal mol^{-1}). Naringin showed high affinity, particularly for IL-1 (−9.0 kcal mol^{-1}), IL-10 (−9.0 kcal mol^{-1}), and Bax (−8.7 kcal mol^{-1}), while kaempferol and quercetin demonstrated moderate binding energies, with kaempferol binding strongly to IL-1 (−7.7 kcal mol^{-1}) and Bax (−8.4 kcal mol^{-1}).[194]

9.2 *In vivo* study

The human digestive system plays a critical role in the bioavailability of ellagic and ellagitannins. These compounds are typically metabolized by the gut microbiota into ellagic acid and minor metabolites, such as urolithins, as demonstrated in several studies.[248,249] Ellagic acid was rapidly detected in systemic circulation following the oral administration of pomegranate peel extract, as analyzed by UHPLC-HRMS. The peak plasma concentration (53 ± 14 ng mL^{-1}) was observed at 1 h post-administration, consistent with previous findings using a higher dose of ellagic acid (50 mg kg^{-1}).[123] Upon ingestion of ellagitannin-rich pomegranate extracts, ellagic acid undergoes further transformation into urolithins A, B, and C, which are subsequently absorbed by colonic cells. In a clinical study, the consumption of 180 mL of juice containing 318 mg punicalagins and 12 mg free ellagic acid resulted in the detection of urolithin A derivatives as the predominant plasma and urinary metabolites, as determined by HPLC and LC-MS/MS.[250] Preclinical evidence supports the neuroprotective role of these urolithins, particularly in models of Alzheimer's disease, with their effects attributed to the microbial metabolism of ellagitannins. However, interindividual variability in urolithin production, driven by differences in the gut microbiota composition, has significant implications for clinical outcomes. Individuals can be categorized into three distinct urolithin metabotypes (UM-A, UM-B, and UM-0), which reflect their capacity to produce specific urolithins.[251] Supporting this, a recent clinical study demonstrated that the health effects of ellagitannin-rich pomegranate polyphenols were contingent upon their microbial conversion into urolithins. Individuals with the UM-B phenotype exhibited higher baseline fecal levels of bile acids and coprostanol, biomarkers linked to enhanced lipid absorption and gut cytotoxicity, but also showed the most pronounced response to supplementation with pomegranate extract.[252] This finding underscores the importance of metabolic phenotyping for optimizing personalized nutrition interventions. Urolithins are not only absorbed systemically but also accumulate in colonic tissues. In a study of colorectal cancer patients, participants consumed pomegranate extract formulations with either a low (PE-1) or high (PE-2) punicalagin-to-ellagic acid ratio for 15 days prior to surgery. Analysis by UPLC-ESI-QTOF-MS/MS identified 23 metabolites in plasma, urine, and both normal and malignant colon tissues, with no intact ellagitannins detected. Urolithin A and isourolithin A were the dominant metabolites, with total concentrations higher in normal tissue than in tumor tissue. Notably, the PE-1 formulation resulted in greater tissue accumulation of urolithins, whereas the higher punicalagin content in PE-2 was associated with reduced urolithin production. These findings suggest that extract composition may significantly influence microbial conversion efficiency and, consequently, the bioavailability of active metabolites.[253]

Numerous studies have evaluated the drug interaction potential of pomegranate. In healthy subjects, consumption of 8 oz (236.5 mL) of juice did not alter the pharmacokinetics of midazolam (administered IV at 2 mg and orally at 6 mg). Specifically, the juice had no effect on midazolam's clearance, volume of distribution, elimination half-life, maximum concentration (C_{max}), or area under the curve (AUC), as assessed using HPLC/MS and LC/MS techniques.[254] Similarly, a 5 day pomegranate juice regimen in healthy volunteers did not sig-

nificantly affect the pharmacokinetics of dapoxetine (60 mg) or midazolam (7.5 mg). A slight, statistically non-significant increase in AUC_0-∞ and C_{max} for dapoxetine was observed, with geometric mean ratios remaining within the acceptable range of 80–125%. Additionally, the absorption rate of midazolam, as indicated by T_{max}, remained unchanged, with geometric mean ratios of 98% and 103%.[255] In animal models, juice administration (10 mL kg^{-1} for one week) in White New Zealand rabbits enhanced the bioavailability of buspirone (2.5 mg mL^{-1}) presumably through inhibition of CYP3A4 enzymes.[256] Furthermore, juice administration (10 mL kg^{-1}) resulted in a 1.88-fold increase in the AUC for the antidepressant rexpiprazole (30 mg kg^{-1}), as analyzed *via* UHPLC-QTOF-MS, suggesting enhanced systemic exposure due to intestinal CYP3A4 inhibition.[257] Similar findings were reported with sildenafil.[258]

In a study involving Wistar rats, co-administration of pomegranate juice with saquinavir (100 mg kg^{-1}) for 15 days led to significant increases in pharmacokinetic parameters. Single and repeated doses of juice (0.5, 1, and 2 mL per 200 g) elevated C_{max} from 5.85 ± 1.28 μg mL^{-1} to 10.20 ± 1.64 μg mL^{-1} and 8.47 ± 1.57 μg mL^{-1}, respectively. The half-life decreased from 4.30 ± 1.21 h to 2.91 ± 0.65 h, while the AUC was significantly altered ($p < 0.001$) for both the 0.5 and 1 mL doses.[259] No significant pharmacokinetic changes were observed following a single dose of peel extract (100 mg kg^{-1}) in rats over a five-day period, except for an increase in prothrombin time when co-administered with warfarin (0.5 mg kg^{-1}).[260] In another rat model, co-administration of tacrolimus (3 mg kg^{-1}) with pomegranate peel extract (200 mg kg^{-1}) significantly increased pharmacokinetic parameters, with C_{max} rising to 22.48 ± 3.07 ng mL^{-1} and AUC_0-∞ increasing to 153.08 ± 13.24 ng mL^{-1}. While this interaction may raise concerns, it also presents potential therapeutic benefits, such as allowing for dose reduction of tacrolimus or necessitating caution when being co-administered with pomegranate products.[261]

10. Smart delivery of pomegranate bioactive compounds

The primary phytoconstituents of pomegranate, including anthocyanins and ellagitannins, are inherently unstable and prone to degradation processes such as oxidation, polymerization, and condensation.[262] Polyphenols, in general, are highly sensitive to external stressors, including elevated temperatures, oxygen, and light, leading to their rapid degradation during food processing and storage.[263] Moreover, exposure to gastrointestinal conditions significantly limits the biological activity and health benefits of polyphenol.[264,265] Additionally, peel-derived phenolics may impart an undesirable astringent flavor when incorporated into food products.[266]

To address these challenges, encapsulation of polyphenols is widely recommended in industrial applications. This strategy not only enhances the physicochemical stability and bioavailability of polyphenols but also mitigates bitterness and astringency, allowing for the controlled release of bioactive compounds.[267] High concentrations of anthocyanins, such as cyanidin, delphinidin, and pelargonidin, 3-glucoside, and their 3,5-diglucoside derivatives, in pomegranate juice are particularly vulnerable to color changes due to various factors during processing and storage. Encapsulation offers a viable solution to preserve color stability under such conditions.[268] Thermal processing technologies can enhance the visual appeal of polyphenols by promoting the hydrolysis of anthocyanins into aglycones and sugars, thereby intensifying juice coloration. To maintain this coloration, it is critical to store freshly squeezed juice at low temperatures (~5 °C), and to select pomegranate cultivars with naturally low pH levels (~2), which contribute to anthocyanin stabilization.[269]

Recent innovations in encapsulation techniques markedly improved the stability of polyphenols. For example, epigallocatechin gallate (EGCG) was effectively stabilized using a double-emulsification method with carboxymethyl cellulose, achieving an encapsulation efficiency exceeding 95% and maintaining structural integrity for over 30 days.[270] Similarly, a nanoemulsion derived from pomegranate seed oil enriched in punicic acid, an unstable bioactive unsaturated fatty acid, demonstrated 100% physical stability after 50 days, with 9.5% encapsulation efficiency and 2.6% loading capacity. This nanoemulsion also exhibited anti-tumor efficacy by reducing the Ehrlich tumor size in a dose-dependent manner in C57BL/6 mice.[271,272] Nanoemulsions show promise in food preservation by shielding phenolic compounds from environmental degradation, thereby delaying fruit spoilage. For instance, seed oil-based nanoemulsion coatings significantly prolonged the shelf life of strawberries, while nanochitosan emulsion containing pomegranate peel extract extended the freshness of apricots.[273,274]

Further advancements focused on enhancing the therapeutic potential of nanoparticle-based pomegranate extracts. One study demonstrated that low-dose oral administration (3 mg kg^{-1} day^{-1}) of pomegranate extract nanoparticles exerted nephroprotective and hepatoprotective effects against cisplatin-induced toxicity in an Ehrlich solid tumor mouse model. This formulation improved renal and hepatic function and attenuated histopathological damage.[275] Additionally, a nanoemulsion of omega-5, derived from pomegranate extract, exhibited hepatoprotective effects by reducing hepatic fat accumulation and promoting fatty acid oxidation in mice fed a high-fat diet.[276]

Pomegranate seed oil formulated in a self-nanoemulsifying delivery system showed superior antioxidant activity compared to Trolox. It also inhibited α-amylase with potent (IC_{50}: 43.6 ± 1.9 μg mL^{-1}) and moderate (IC_{50}: 354.8 ± 2.3 μg mL^{-1}) activity levels, surpassing orlistat in some comparisons.[277] Given the neuroprotective potential of phenolic-rich seed oil in Alzheimer's disease, a novel microemulsion system incorporating seed oil and galantamine hydrobromide was developed. This formulation significantly enhanced antioxidant capacity, protected against Aβ-induced cytotoxicity, and demonstrated

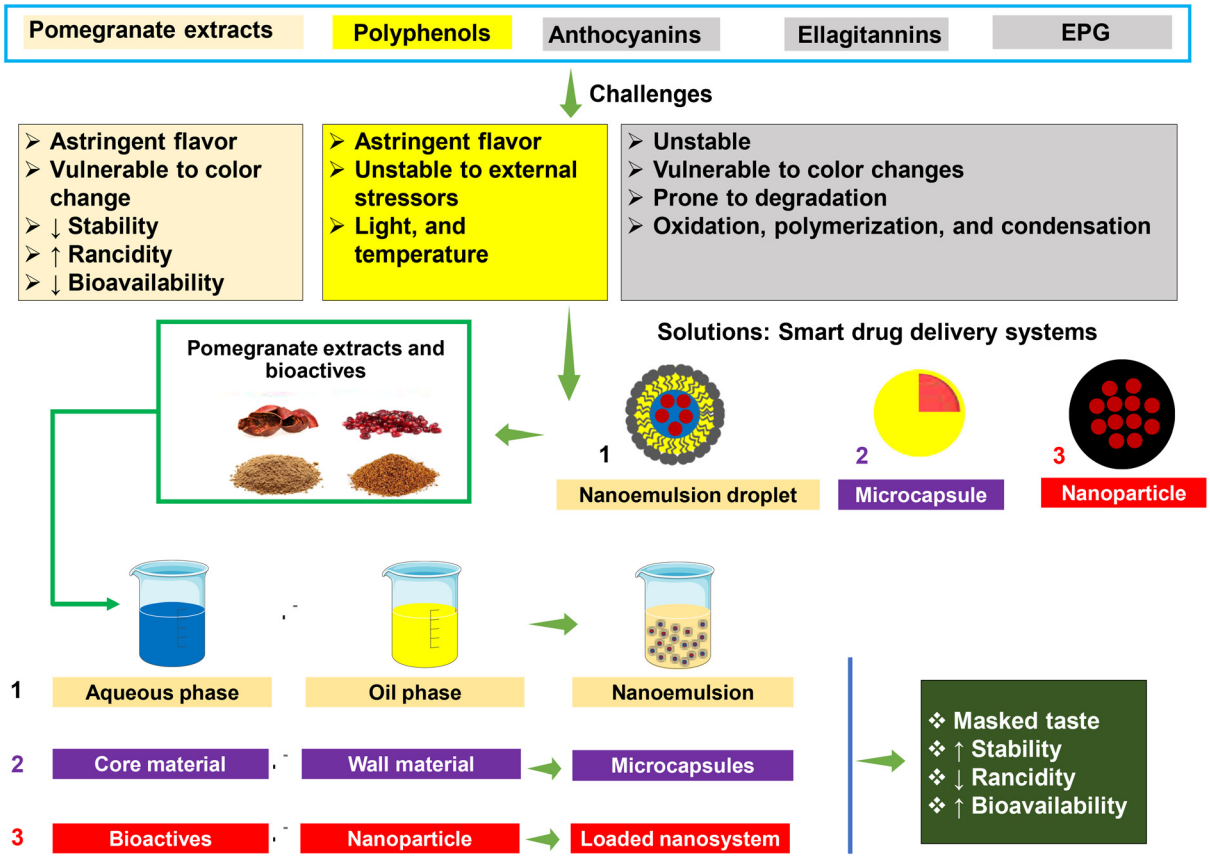

Fig. 7 Proposed mechanism for the smart delivery of pomegranate bioactive compounds.

low cellular toxicity, highlighting its potential for the targeted delivery of phenolics to the brain.[278]

Furthermore, pomegranate peel extract-loaded alginate nanospheres and nanocapsules exhibited antibacterial activity against *Salmonella enterica*, *Escherichia coli*, *Staphylococcus aureus*, and *Listeria monocytogenes*, maintaining a high encapsulation efficiency (79.30 ± 0.42%) and physical stability during a 3 week storage period at 4 °C on coated chicken meat samples.[279] Nanoencapsulation of pomegranate peel hydroethanolic extract using maltodextrin and whey protein isolate enabled a controlled release of bioactive compounds, such as resveratrol and quercetin, primarily in the intestine rather than the stomach. This method improved anticancer efficacy against HT-29, MCF-7, and HeLa cell lines compared to the unencapsulated extract, indicating its promise in cancer therapy.[280]

A novel preservation method involving the electrospinning of pomegranate seed oil into polyvinyl alcohol-based mats was proposed to extend the shelf life of perishable food items such as cheese and fish. After nine days of storage, these mats reduced the bacterial load by 1.22 log CFU and enhanced oxidative stability, thereby maintaining food freshness.[281] Additionally, a nanoemulsion formulation of punicalagin designed for oral delivery improved its release profile (22.14% in 2 h, 86.72% after 48 h), enhanced absorption, and demonstrated reduced cytotoxicity (88.62% cell viability) compared to its unencapsulated counterpart (69.76% cell viability) in MARC-450 fibroblast cells.[282] Fig. 7 presents the proposed mechanism for the smart delivery of pomegranate bioactive compounds.

11. Conclusions

Pomegranate demonstrates substantial therapeutic promise in the prevention and management of NCDs, owing to its rich profile of bioactive compounds, particularly punicalagin, ellagic acid, and gallic acid, which exhibit a broad spectrum of pharmacological activities, including antioxidant, anti-inflammatory, anticancer, antidiabetic, cardioprotective, nephroprotective, hepatoprotective, and neuroprotective effects. Preclinical evidence consistently supports its ability to modulate key molecular and cellular pathways, positioning pomegranate as a valuable functional food and adjunctive therapeutic agent. Advanced analytical and toxicological assessments confirm the safety, authenticity, and clinical viability of pomegranate-derived extracts, reinforcing their suitability for food and pharmaceutical applications. Furthermore, the biotransformation of ellagitannins into urolithins by the gut microbiota contributes to their systemic bioactivity, with a generally

favorable pharmacokinetic and safety profile. However, potential interactions *via* CYP3A4 modulation highlight the need for further clinical evaluation. Lastly, encapsulation technologies markedly enhance the physicochemical stability, bioavailability, and targeted delivery of pomegranate polyphenols, offering innovative solutions for overcoming formulation challenges and maximizing therapeutic outcomes.

Author contributions

Asad Ur Rahman and Muhammad Esa developed the methodology, conducted the database search, extracted the data, interpreted the results, and wrote the original draft of the manuscript. Pharkphoom Panichayupakaranant generated the idea, supervised, and reviewed and revised the manuscript. All the authors approved the final version of the manuscript.

Conflicts of interest

There is no conflict of interest among the authors.

Abbreviations

ACE	Angiotensin-converting enzyme
ALT	Alanine aminotransferase
AMPK	AMP-activated protein kinase
AQP-2	Aquaporin-2
AST	Aspartate aminotransferase
BMI	Body mass index
BFI	Body fat index
BP	Blood pressure
CVDs	Cardiovascular diseases
CAT	Catalase
CK-MB	Creatine kinase-mb
CRDs	Chronic respiratory diseases
eNOS	Endothelial nitric oxide synthase
GCK	Glucokinase
GFAT	Glutamine fructose-6-phosphate aminotransferase
GPX	Glutathione peroxidase
GSH	Reduced glutathione
GST	Glutathione *S*-transferase
HDL	High-density lipoprotein
HIF-1	Hypoxia inducible factor-1
IL-1β	Interleukin-1 beta
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-17A	Interleukin-17A
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LncRNA-MALAT1	Long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1
MAPK	Mitogen-activated protein kinase
MBW	Mean body weight
MCP-1	Monocyte chemoattractant protein-1
MMP-1	Matrix metalloproteinase-1
NAFLD	Nonalcoholic fatty liver disease
NCDs	Non-communicable diseases
NCRDs	Noncommunicable respiratory diseases
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
Nrf2/HO-1	Nuclear factor erythroid 2-related factor 2/heme oxygenase-1
OPLS-DA	Orthogonal partial least squares discriminant analysis
PAI-1	Plasminogen activator inhibitor-1
PCA	Principal component analysis
PG E2	Prostaglandin E2
PI3K/AKT	Phosphatidylinositol-3-kinase/protein kinase B
PPAR-γ	Peroxisome proliferator-activated receptor gamma
PTP1β	Protein tyrosine phosphatase 1 beta
Raf/MEK/ERK	Raf kinase/mitogen-activated protein kinase/extracellular signal-regulated kinase
RBP4	Retinol binding protein 4
ROS	Reactive oxygen species
SOD	Superoxide dismutase
TBC	Total blood cholesterol
TGF-β1	Transforming growth factor beta 1
TKIR	Tyrosine kinase insulin receptor
TNF-α	Tumor necrosis factor-alpha
TP53	Tumor protein p53
UHPLC-QqQ-MS/MS	Ultrahigh-performance liquid chromatography coupled with a triple quadrupole tandem mass spectrometer
UHPLC-QTOF-MS	Ultrahigh performance liquid chromatography quadrupole time-of-flight mass spectrometer
UPLC-QQQ-MS	Ultra-performance liquid chromatography coupled with a triple quadrupole mass spectrometer

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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