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Review Article

Protective benefits and mechanisms of *Phyllanthus emblica* Linn. on aging induced by oxidative stress: a system review

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Abstract: This review clarified the nutritional value of *Phyllanthus emblica* Linn. (PE) and summarized its application prospect as a health food which show anti-aging effects. This review highlighted the latest researches of PE to describe its anti-aging mechanism and related diseases induced by oxidative stress, as well as existing problems and future application directions. In general, PE is a fruit widely consumed in south of Asia, as well as one of the three medicinal plants been selected by the World Health Organization (WHO) for widespread cultivation. Polyphenols (including phenolics, flavonoid, tannins, etc.) are the main bioactive components in PE. Those bioactive compounds show anti-aging effects through scavenging free radicals, preventing mitochondrial damage, anti-triggering lipid peroxidation, and protecting protein structures. The development and research of nutritional foods derived from PE are limited, with most efforts focused on edible fruits and juice beverages. However, there is still significant potential for further high-value utilization of its nutritional properties focus on PE.

Keywords: *Phyllanthus emblica* Linn.; anti-aging; oxidative stress; polyphenols; health food

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1 Introduction

1.1 Aging and its prevention strategies

In a dynamic process of biological aging, cumulative damage cause cells to gradually deteriorate[1]. This leads to increased susceptibility and vulnerability of the organism to disease and death. Numerous age-related disorders, including diabetes, cancer, and cardiovascular diseases like atherosclerosis, as well as neurological ailments, are intimately correlated with aging in terms of their incidence and progression. The WHO[2] predicted that 1/6 of the population will be over 60 years by 2030. The growing older population and the prevalence of age-related ailments heavily burden families and the society.

As shown in Fig. 1, numerous methods have been employed to address the anti-aging needs, which can be roughly categorized as chemical drug therapy, biotherapy, lifestyle modification therapy (e.g. caloric restriction therapy, and natural product diets, regular routine, and exercise) based on their features. Chemical anti-aging medications such as metformin and aspirin lack extensive clinical data and may have several toxic side effects[3]. Biological therapies like stem cell transplantation[4] and fecal microbial transplantation[5] come with risks like a severe immunological rejection of allografts and lengthy cycle durations[3]. Intermittent fasting and time-restricted diets have potential adverse effects such as loss of bone density, reduced physical endurance, and decreased sexual drive[6,7]. The benefits of natural product diets, on the other hand, are gradually gaining popularity in the anti-aging field since they have a variety of approaches, multiple targets, and less toxic side effects[8]. Medicinal food homology (MFH) is recognized by traditional Chinese medicine (TCM) for a long time. This idea deems that foods in regular diets can be used as medicine because of their therapeutic benefits. Therefore, it is acceptable and practical for people to look for natural ingredients that help delay the aging process in their regular diets.

1.2 Food and medicine homology: an aging prevention measure

Phyllanthus emblica Linn. (PE) was categorized as a medicine and food homology-fruit by the previous Chinese Ministry of Health. Moreover, it is one of the three medicinal plants that have been selected by the WHO for widespread cultivation[9]. It is commonly utilized in the ancient Ayurvedic system (a kind of phgsiomedical from India) for achieving longevity in India and

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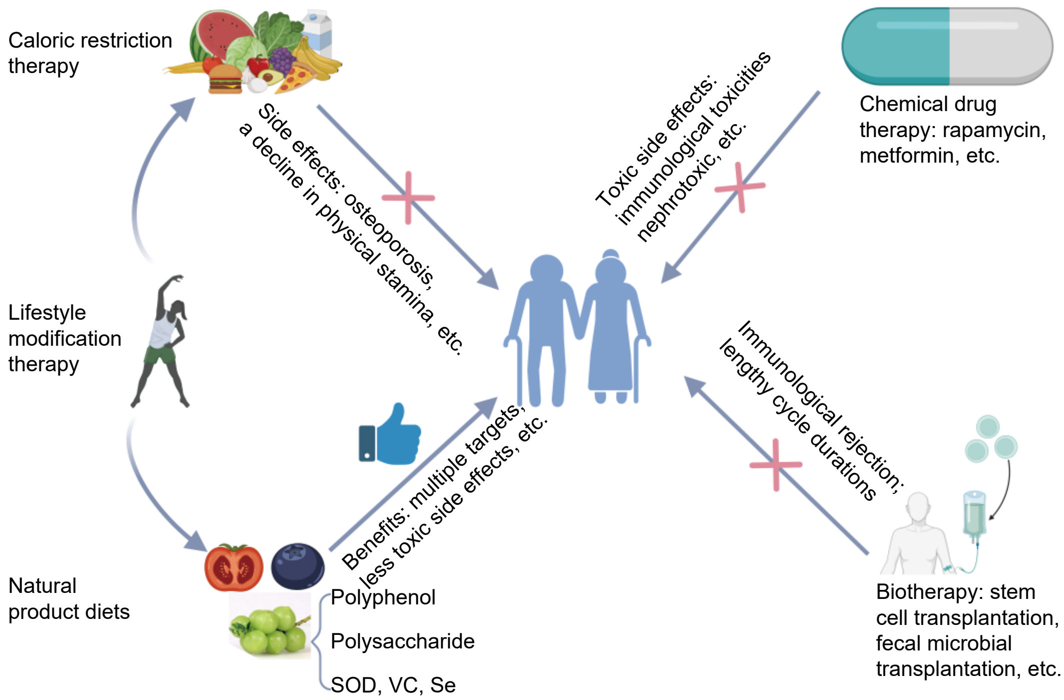

Figure 1 Current approaches to anti-aging: chemical pharmacotherapy, biological therapy, and lifestyle modifications are the primary methods available for combating the effects of aging. However, these methods each have their own limitations and drawbacks. As such, we recommend a natural product-based diet for anti-aging purposes, as it has fewer adverse side effects and is generally more conducive to overall health and wellness.

has been integrated into traditional medical practices of approximately 17 other countries or ethnic groups. According to the *Compendium of Materia Medica*, PE mainly plays Qi tonic (a concept in Chinese medicine), lightens the body when ingested frequently, and extends life. As illustrated in Fig. 1, modern studies have found that PE is rich in tannins, phenolic acids, flavonoids, polysaccharides, vitamin C (VC), superoxide dismutase (SOD) and other active ingredients[10]. Numerous studies have demonstrated that the active ingredients in PE exhibit anti-aging capabilities[11] as well as in anti-aging-related diseases such as tumor[12], cardiovascular[10], and type 2 diabetes[13]. In addition to being used as a traditional medicine, PE is widely used in food and health foods. However, there is still a large blank in the field of anti-aging-related health food and functional food research and development, and the biggest possible reason is that there is no systematic elaboration of the potential role of its active ingredients. Hence, it has a significant potential for research and development in the areas of specialized medical foods, anti-aging health foods, and other relevant subjects, as well as for being a guiding significance on the daily diets of the elderly.

To establish criteria for the delay of aging, reduction in aging-associated ailments, and enhancement of life quality via consumption of natural products, this article will present a review of the present research status of PE in anti-aging and anti-aging-linked disorders based on the free radical theory. The active constituents present and their anti-aging benefits will also be addressed. Additionally, this review will encompass the existing situation of food processing and usage, as well as the progress of anti-aging related food products.

2 Mechanisms of oxidative stress leading to aging

2.1 Free radicals

Free radicals are crucial in the aging process of mammals[14]. The main source of intracellular oxygen radicals is byproducts from mitochondrial molecular oxygen metabolism[15]. These highly reactive species are kept in check by the body's endogenous antioxidant system under normal circumstances[16]. However, in other conditions (e.g. illness, infection, stress, etc.), the balance in the oxidation-reduction of the body is lost. Due to the excess free radicals generated, the body has insufficient resources to scavenge reactive oxygen species (ROS). All sorts of biomolecules, including nucleic acids, lipids, and proteins, are damaged by excessive ROS, which eventually leads to aging and age-related diseases.

2.2 Mitochondrial damage

Mitochondrial DNA (mtDNA) plays a crucial role in aging[17]. Since mtDNA is constantly exposed to the ROS and free radicals produced by aerobic respiration[18]. These ROS and free radicals interact with mitochondrial polymerase, lowering its fidelity and preventing mtDNA replication, which causes deletions and mutations in mtDNA and eventually reach pathological levels[19]. Aging further reduces the ability of mitochondria to repair free radical damage by splitting or replacing their altered macromolecules[20]. The development and progression of aging and aging-related disorders may be accelerated or caused by the accumulation of harmful mtDNA mutations in human tissues, which may exacerbate the functional abnormalities. Thus, mitochondrial dysfunction as well as a decrease in mitochondrial stress response capacity can lead to biological aging[21].

2.3 Lipid peroxidation

Lipid chain autoxidation of polyunsaturated fatty acids (PUFA) leads to the formation of lipid hydroperoxides or interchain lipid peroxide dimers. At a crucial threshold level, these hydroperoxides may cause cell death (ferroptosis), resulting in membrane rupture and loss of cell contents or damage-associated molecular patterns (DAMPs). Lipid hydroperoxides and interchain lipid peroxide dimers also cause the release of new free radicals, which leads to additional oxidation and DAMPs. As a result, significant cellular oxidative damage occurs when reactive oxygen levels are raised to the point where lipid chain autoxidation events are triggered[22]. Meanwhile, in the cell membrane, protein adducts that are produced by the peroxidation of PUFA, such as 4-hydroxynonenal (HNE) and malondialdehyde (MDA), have been shown to trigger progressive cellular dysfunction and contributing to the aging process[23].

2.4 Structural damage of proteins

In the presence of an overwhelming flow of highly reactive oxidants, irreversible oxidation of amino acid residues on the protein backbone and side chains results in carbon- or oxygen-centered radicals[24], causing structural damage of proteins. Covalent cross-linking and zwitterionization, conformational alterations and protein misfolding, backbone breaking and spontaneous fracture, and other changes in protein structure can all result from irreversible oxidative protein modifications[25]. Moreover, protein hydrolase activity is inhibited by oxidative stress and oxidative protein adducts, such as hydrogen peroxide, and this encourages the intracellular buildup of damaged proteins[26]. Many age-related human diseases, including cancer, diabetes, cardiovascular disease, and neurological disorders, are linked to the accumulation of oxidatively damaged proteins[27-30].

2.5 DNA damage

The integrity of the genome is continuously challenged by ROS-induced damage. According to research[31], ROS-induced DNA damage (e.g. abasic sites, strand breaks, single-strand base oxidative modification, single-strand nicks, and downstream damage like chromosomal abnormalities) is associated with an increase in aging. DNA repair mechanisms can effectively remove genetic damage; however, ROS-induced DNA damage may cause suppression of DNA repair genes. Additionally, the age-related decline in DNA repair functionality results in extensive accumulation of DNA damage and subsequent cell senescence or apoptosis, consequently leading to compromised tissue homeostasis, stem cell depletion, disrupted tissue structure, and ultimately, aging[32]. Hence, ROS-induced DNA damage is an underlying cause of aging[33].

2.6 The role of endogenous and exogenous antioxidant in aging

Endogenous antioxidants include: 1) enzymatic scavengers; 2) hydrophilic radical scavengers; 3) lipophilic radical scavengers; 4) enzymes involved in the reduction of oxidized forms of small-molecule antioxidants (glutathione (GSH) reductase, dehydroascorbate reductase) or responsible for the maintenance of protein thiols (thioredoxin reductase); and 5) cellular mechanisms that maintain the redox environment (e.g., glucose-6-phosphate dehydrogenase, regenerable nicotinamide adenine dinucleotide phosphate (NADPH)). Secondary defense systems include lipolytic enzymes[34] and protein hydrolases[35]. In short, endogenous antioxidant systems can exert anti-aging effects by scavenging excess free radicals and oxidative damage products (lipid peroxidation products and oxidatively damaged proteins).

Several studies have demonstrated that exogenous antioxidants, both pharmaceutical and dietary, can scavenge excess free radicals and prevent oxidative damage, prolonging the lifespan of *Drosophila*, *Caenorhabditis elegans* and mice[36-39]. However, pharmacologic antioxidants have many toxic side effects[3]. In contrast, dietary antioxidants, which are mostly natural products, have fewer side effects and greater potential for human health. Hence, one of the healthiest and safest ways to anti-aging may be through the consumption of dietary antioxidants[8]. Figure. 2 summarized the mechanisms of oxidative stress-induced aging

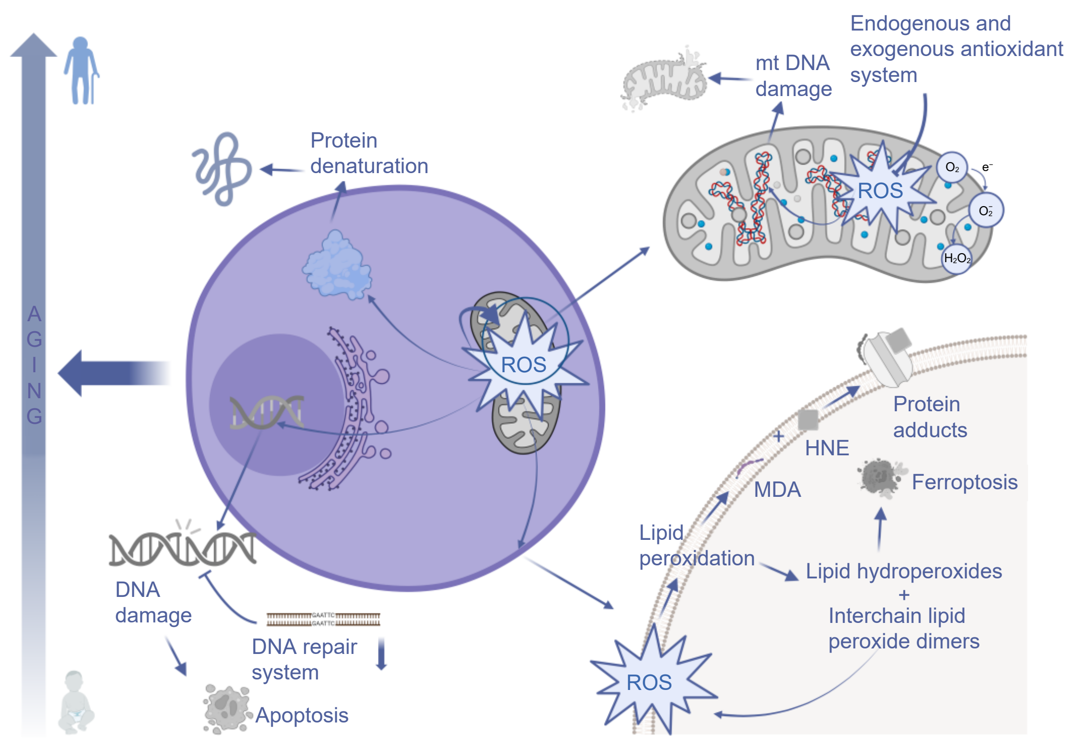

Figure 2 Mechanisms of oxidative stress-induced aging and the role of the antioxidant system in aging. Aerobic respiration carried out in mitochondria produces ROS. At the cellular level, ROS attack DNA, proteins, lipids, and mtDNA, leading to apoptosis which in turn leads to compromised tissue homeostasis through stem cell depletion and/or disrupted tissue structure, and ultimately lead to aging. Endogenous and exogenous antioxidant systems could scavenge free radicals.

and the role of endogenous antioxidant systems and exogenous antioxidants in aging.

3 Mechanisms of anti-aging benefits of PE induced by oxidative stress

3.1 The role of PE in anti-aging and anti-aging-related diseases

Many studies have been conducted on the anti-aging properties of PE (Table 1). According to the findings, PE could increase cell membrane mobility, resistance to thermal stimulation, and antioxidant damage of *C. elegans*[11, 40], and increase stress tolerance of *Drosophila*[41], weight-bearing swimming time in mice[42], SOD activity and decrease MDA levels in mouse serum, *C. elegans*, and *Drosophila* cells. It could also extend the lifespan of *Drosophila*[43] and *C. elegans*[44]. The research mentioned above support each other in that PE possesses anti-aging properties and can be utilized as a nutritional intervention to delay the onset of aging and aging-related disorders.

Moreover, PE has been shown in numerous research to have both therapeutic and preventative effects on aging-related disorders. The prevention and treatment of cancer, cardiovascular disease, neurological illnesses, and other aging-related diseases by PE were discussed in the following article (Table 2).

3.1.1 *Neurodegenerative diseases*

Brain is extremely sensitive to aging among all organs in the human body. Aging causes cognitive decline and memory loss in the brain, which dominates the aging of the body and influences the aging process of all other systems[46]. Delaying brain aging helps to maintain the physiological functions of all systems in the body and to somewhat reduce the occurrence of neurodegenerative diseases. Neurodegenerative diseases are incurable ailments caused by progressive degeneration of nerve cells and include mainly Alzheimer’s disease and epilepsy. PE has neuroprotective benefits and can help with age-related learning, memory, and cognitive deficiencies. In one study rats were gavaged with an ethanolic extract of PE, the results showed that the learning memory ability of rats in the PE treatment group was significantly better than that of the control group[47]. The concentrations of the antioxidant enzymes SOD, catalase (CAT), GSH, and glutathioneperoxidase (GSH-Px) were also significantly higher in the brain tissue homogenates of the experimental group, and concentration of thiobarbituric acid reactive substances (TBARS) and acetylcholinesterase activity were significantly reduced. Gan *et al.*[48] found that purified extracts of PE can significantly reduce paralysis in a transgenic *C. elegans* model of Alzheimer's disease. Thenmozhi *et al.*[49] used $AlCl_3$ to create a rat model of Alzheimer’s disease and discovered that oral administration of PE solution significantly reversed the changes in Al concentration, acetylcholinesterase activity, molecules linked to A-β synthesis in the rat brain domain, and impairment of spatial learning and memory caused by $AlCl_3$. The antioxidant properties of PE can reduce generalized tonic seizures and chronic epilepsy in epileptic mice[50]. Moreover, it has been demonstrated that PE helps mice with forgetfulness, delayed-onset dyskinesia, and depression[51, 52]. Thus, PE has excellent preventive and curative effects on neurodegenerative diseases.

3.1.2 *Cardiovascular disease*

Heart and vascular problems known as cardiovascular diseases include deep vein thrombosis, pulmonary embolism, rheumatic heart disease, coronary heart disease, and cerebrovascular disease. Aging is a significant risk factor for cardiovascular diseases, and cellular senescence is a fundamental mechanism of various cardiovascular diseases[53]. Cardiovascular diseases are the main cause of mortality worldwide. Several pharmacological investigations have demonstrated the cardiovascular preventive benefits of PE, including its ability to prevent thrombosis[54], and protect endothelial cells[55]. In rabbits with cholesterol-induced hypercholesterolemia, studies have demonstrated that PE can lower serum and liver total and low-density cholesterol levels while raising high-density cholesterol levels[56]. The antioxidant properties of PE can shield the rat heart from oxidative stress brought on by ischemia-reperfusion injury (IRI) in ischemia-reperfusion-induced rats[57]. Through modifying eNOS and

Table 1 Role of PE in varied anti-aging models

Form of PE	Models	Effects of anti-aging	Mechanism	Reference
Juice, powder	Drosophila	Lifespan of *Drosophila*↑	-	[43]
Extracts, powder	*α*-Galactose-induced Kunming mice	SOD, GSH-Px in serum↑ MDA, LPF↓	Antioxidant	[45]
Fruit juice	*α*-Galactose-induced Kunming mice	Weight-bearing swimming time of mice↑ SOD, GSH-Px in serum↑ MDA, LPF↓	Antioxidant	[42]
Extracts	*C. elegans*	Lifespan of *C. elegans*↑ Mobility↑ SOD↑	Antioxidant	[40]
Extracts	*C. elegans*	Lifespan of *C. elegans*↑ Mobility↑ SOD↑ Oxidant damage↓ Heat tolerance of *C. elegans*↑	Antioxidant	[11]
Extracts	*C. elegans*	Lifespan of *C. elegans*↑ Cholinesterase activity↓ Antioxidant enzyme↓ MDA↓	Antioxidant	[44]
Amalaki Rasayana (AR)	*Drosophila* melanogaster	Stress tolerance↑ ROS↓ Lipid peroxidation↓ SOD↑	Antioxidant	[41]

Note: “-” indicates that the mechanism is not mentioned in the article.

Table 2 Role of PE in varied range of aging-related diseases

Diseases	No.	Form of PE	Models	Results	Mechanism	Reference
				Alzheimer's		
Neurodegenerative diseases	1	Ethanol extract	*In vivo* (Rats)	Increases the concentration of antioxidant enzymes SOD, CAT, etc. in rat brain tissue homogenates, reduces AChE levels and improves learning memory in rats	PE regulates antioxidant capacity in rats	[47]
	2	Purified extract of fruit pomace	*In vivo* (Alzheimer's disease transgenic *C. elegans*)	Reduces paralysis rates in a transgenic *C. elegans* model of Alzheimer's disease	Polyphenols in PE maintain redox homeostasis in *C. elegans*	[48]
	3	Aqueous solution	*In vivo* ($AlCl_3$-induced Alzheimer's disease in rats)	Significantly restores $AlCl_3$-induced changes in Al concentration, AChE activity, amyloid precursor protein (APP) and A-β synthesis-related molecule levels in rat brain, significantly restores spatial learning, memory and motor abilities	PE is rich in tannins and has powerful antioxidant properties	[49]
	4	Methanol extract	*In vitro*	Inhibits acetylcholinesterase activity	PE is rich in polyphenols and has powerful antioxidant properties	[75]
				Epilepsy		
	5	Ethanol extract	*In vivo* (pentylenetetrazole (PTZ)-induced epilepsy in rats)	Reliefs tonic seizures and status epilepticus	Antioxidant effect of PE	[50, 75]
	6	Ethanol extract	*In vivo* (kainic acid (KA)-induced epilepsy in rats)	Restores KA-induced increase in TNF-α and TBARS levels and decrease in GSH levels; improves KA-induced cognitive deficits	Antioxidant and anti-inflammatory effect of PE	[76]
				Depression		
	7	Aqueous extract	*In vivo*	Reduces levels of monoamine oxidase A (MAO-A) in brain	Antioxidant activity of PE may show antidepressant activity through inhibition of MAO-A and GABA	[51]
				Tardivedyskinesia (TD)		
	8	Extracts	*In vivo* (haloperidol-induced TD in rats)	Reduces TD parameters in rats	Antioxidant effect of PE	[52]
				Amnesia		
	9	Anwala churna	*In vivo* (scopolamine and diazepam-induced amnesia in rats)	Dose-dependent improves memory scores in rats; reverses of scopolamine and diazepam-induced amnesia	-	[77]
				Others		
	10	-	*In vivo*	Compared with control group, memory retention are enhanced and protein content and cholinesterase activity in the brain are elevated in the treatment group	-	[78]
	11	Extracts	*In vivo* (acute paradoxical sleep deprivation (SD)-induced cognitive impairment)	PE fruit polyphenols (PEFPs) effectively alleviated behavioral abnormalities induced by acute paradoxical SD, and prevented histopathological and morphological damage to hippocampal neurons	PEFPs markedly counteracted oxidative stress damage and neuroinflammation by activating the nuclear factor-erythroid 2-related factor 2 (Nrf2) pathway	[79]
				Hypercholesterolemia		
Cardiovascular disease	12	Extracts	*In vivo* (cholesterol-induced hypercholesterolemia in rabbits)	Reduces total cholesterol, triglycerides and LDL cholesterol in rabbits serum; elevates high-density lipoprotein cholesterol; reduces aortic plaque	Antioxidant effect of PE	[56]
				IRI		
	13	Aqueous extract	*In vivo* (IRI-induced rats models)	Compared with the control group, the echocardiography of the treatment group showed an increase in ejection fraction and shortening fraction and a decrease in left ventricular internal diameter	PE upregulates PI3K/Akt/GSK3β/β-linked protein signaling pathway to protect heart	[57]
				Hypertension		
	14	Extracts	*In vivo* (deoxycorticosterone acetate-salt (DOCA)-induced hypertension in rats)	Reduces systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate were reduced in the treatment rats, increases serum NO levels, reduces serum sodium and potassium levels	PE regulates eNOS and endogenous antioxidant activity	[58]

(Continued)

Diseases	No.	Form of PE	Models	Results	Mechanism	Reference
				Cardiotoxicity		
	15	-	*In vivo* (isoprenaline-induced cardiotoxicity in rats)	Restores hemodynamics and left ventricular function, decreases cardiomyocyte injury-specific marker enzymes, inhibits lipid peroxidation	Antioxidant effect and free radical scavenging activity of PE	[80]
				Endothelial dysfunction		
	16	-	*In vitro* (human umbilical vein endothelial cells, HUVECs)	Promotes production of NO, closure of endothelial wound, and germination of endothelial	Antioxidant effect of PE	[55]
				Platelet aggregation		
	17	Extracts	*In vivo* (grade 1 obese/overweight adults)	Significantly reduces LDL cholesterol and total cholesterol/HDL, circulating hs-CRP levels, significantly downregulates ADP and collagen-induced platelet aggregation	PE is rich in polyphenols and has powerful antioxidant properties	[54]
				Others		
	18	Extracts	*In vitro* (HUVECs) *In vivo* (lipopolysaccharide-induced endotoxemia in rats)	Reduces the release of LPS-induced tissue factor from HUVECs, reduce the expression of endothelial leukocyte adhesion factor-1 in HUVEC. Reduces the concentration of serum pro-inflammatory factors, TNF-α and IL-6 in rats	Anti-inflammatory effect of PE	[81]
	19	Aqueous extract	*In vivo* (healthy adults)	Compered with control group, mean percentage change in AIx (radial and aortic blood pressure) is significantly lower in the treatment group	-	[59]
	20	Extracts	*In vivo* (healthy adults)	Reduces total cholesterol and low-density lipoprotein cholesterol, elevates HDL cholesterol levels, reduces CRP level	PE is rich in tannins and has powerful antioxidant properties	[12]
				Breast cancer		
Cancer	21	Fruit Juice	*In vivo* (7, 12-dimethylbenzanthracene (DMBA)-induced breast cancer in female rats)	Significantly ($P < 0.05$) reduces TBARS, lipids, estrogen/progesterone levels in tumor-bearing rats	PE is rich in polyphenols and has powerful antioxidant properties	[61]
	22	-	*In vitro* (SKOV3)	Inhibits the proliferation, migration and invasiveness of ovarian cancer cells, increases the expression of miR-37, reduces the expression of insulin-like growth factor 1 receptor (IGF1R) and snail family transcriptional repressor 1 (SNAIL1) proteins during SKOV3 transplant tumor growth	-	[82]
	23	Extracts	*In vitro* (SKOV3) *in vivo* (transplanted tumor-bearing mice)	Significantly increases the expression of autophagy proteins beclin 1 and microtubule-associated protein 1 light chain 3B-I, significantly reduces the expression of several angiogenic factors, including hypoxia-inducible factor-1α (HIF-1α)	-	[83]
	24	Extracts	*In vitro* (HGSOC) *In vivo* (ovarian cancer in mice)	Significantly reduces the migratory and invasive capacity of all HGSOC cell phenotypes, significantly reduces the expression of HIF-1α, IGF1R and SNAIL1, increases the expression of E-cadherin in tumor tissues	-	[84]
	25	Shemamruthaa (SM, mixture of *Hibiscus rosasinensis*, *Phyllanthus emblica* and honey)	*In vivo* (DMBA-induced breast cancer in female rats)	Significantly reduced lipid peroxidation (LPO) levels and reversed the antioxidant status of cancer animals to near normal levels	Antioxidant effect of SM	[85]
				Cervical cancer		
	26	Extracts	*In vitro* (HeLa)	Inhibits activator protein-1 (AP-1) activity and human papilloma virus (HPV) transcription	-	[63]
				Colon cancer		
	27	Extracts	*In vitro* (Caco-2)	Inhibits the growth of Caco-2 colorectal cancer cells in a dose-dependent manner	Antioxidant effect of PE	[65]

(Continued)

Diseases	No.	Form of PE	Models	Results	Mechanism	Reference
	28	-	*In vitro* (HCCSCs)	Inhibits proliferation and induces apoptosis in HCCSCs	-	[86]
	29	Ether extract	*In vitro* (HCT-16 colon cancer cells)	Both the ether extract and the isolated compounds show significant cytotoxicity against HCT-16 cell line	-	[87]
	30	Aqueous extract	*In vitro* (colon cancer cells)	Aqueous extracts induce cell necrosis and reduce nuclear division index (NDI) in a dose and time-dependent manne. Dose and time-dependent increases the frequency of chromosomal instability (CIN). Significantly induces apoptosi	-	[88]
				Liver cancer		
	31	Aqueous extract	*In vitro* (HepG2)	Incubation with PE for 24 h resulted in significant diminution in the levels of lipid hydroperoxide (18%−42%) and ROS (11%−29%). PE increased the levels of GSH (18%−32%); antioxidant capacity (19%−31%); and activities of antioxidant enzymes	PE enhances antioxidant defenses of the cells	[66]
				Lung cancer		
	32	Ethanol extract	*In vitro* (Lewis lung cancer (LLC) cells) *In vivo* (C57BL/6J mice)	Tannins in PE inhibited lung cancer cells growth and tumorigenesis in vivo/vitro and promoted anti-tumor immune responses	Tannins in PE induced the formation of intracellular protein aggregates and following activation of PERK/ATF4/CHOP-dependent endoplasmic reticulum stress-related immunogenic cell death	[89]
				Gastric cancer		
	33	Gold nanoparticles from *Phyllanthus emblica* fruit extract (PEFE-AuNPs)	*In vitro* (AGS)	Inhibits AGS cell autophagy, down-regulates LC3-II/LC3-I and Beclin-1 expression, and up-regulates p62 expression	-	[64]
				Skin cancer		
	34	Extracts	*In vivo* (albino Swiss mice)	Compared with the control group, the tumor incidence and tumor yield of mice in the treatment group were significantly lower	PE is rich in tannins and has powerful antioxidant properties	[90]
				Common diabetes		
	35	Aqueous extract	*In vivo* (streptozotocin (STZ)-induced type 2 diabetic rats)	Compared with the control group, the treatment group has lower fasting plasma glucose	Antioxidant effect of PE	[67]
	36	Methanol extract	*In vivo* (STZ-induced type 2 diabetic rats)	Compares with diabetic rats, fasting plasma glucose is significantly lower and insulin levels is significantly higher in the experimental group. The liver and kidney tissues of diabetic rats show significant increases in GSH, GSH-Px, SOD and CAT, and decreases LPO level	Free radical scavenging ability of PE	[91]
Diabetes	37	Powder	*In vivo* (normal people and diabetic patients)	Fasting plasma glucose and 2 h postprandial plasma glucose levels are both significantly lower than baseline values in treatment group, reduction in both total cholesterol and triglycerides	-	[69]
				Complications of diabetes		
	38	-	*In vivo* (STZ-induced type 2 diabetic rats)	Inhibits phosphorylation of Akt (Thr308) in the aorta	PE ellagitannin metabolite urolithin A regulates Akt/β-linked protein signaling	[13]

Note: "-" indicated that the mechanism was not mentioned in the article.

endogenous antioxidant activity, PE can also influence how deoxycorticosterone acetate-induced hypertension in rats develops[58]. When compared to mean baseline levels, subjects supplemented with a standard extract of PE for 12 weeks showed a significant reduction in body low-density lipoproteins (LDL) cholesterol, total cholesterol/high-density lipoproteins (HDL) was significantly lower, high-sensitivity C-reactive protein (hs-CRP) levels were significantly lower, and collagen-induced platelet aggrega showed a significant reduction. A study found that PE can considerably boost NO generation, endothelial wound repair, and germination in terms of protecting the vascular endothelium, which in turn lowers the risk of cardiovascular disease[55]. The impact of PE extract on modifications in cardiovascular parameters and aortic wave reflection brought on by cold pressor tests (CPT) in healthy adults was assessed by Fatima *et al.*[59]. The findings showed that PE extracts enhanced subendocardial viability ratio (SEVR), an index of myocardial perfusion with CPT, while significantly reduced the mean percentage change in arterial stiffness index (AIx, radial, and aortic blood pressure). In a 6-months study including human volunteers, Antony *et al.*[12] examined the effects of two dosages of PE extract (500 and 1,000 mg/day) on markers of systemic inflammation and dyslipidemia. HDL cholesterol increased whereas total and LDL cholesterol decreased in blood samples taken at 3 and 6 months. Blood CRP levels, a measure of inflammation, were also markedly decreased. This demonstrates the beneficial cardioprotective properties of PE and how it lowers the risk of cardiovascular disease.

3.1.3 *Cancer*

The incidence of cancer increases dramatically with age while the effectiveness of cellular repair mechanisms tends to decline, thus threatening the health of the elderly. Much research has been done to demonstrate the anticancer effects of PE on a range of human cancers, including those of the colon, ovarian, breast, lung, liver, and stomach. Ngamkitidechakul *et al.*[60] found that 50–100 μg/mL of PE extract significantly inhibited cell growth in six human cancer cell lines, namely A549 (lung), HepG2 (liver), HeLa (cervical), MDA-MB-231 (breast), SK-OV3 (ovary), and SW620 (colorectal); reduced the number and volume of tumors in mice. Furthermore, 25 and 50 μg/mL of PE extract inhibited the invasiveness of MDA-MB-231 cells in a stromal gel invasion assay *in vitro*. In an earlier study[61], 7, 12-dimethylbenz(a)anthracene was used to create a female rat breast cancer model after gavage of PE juice, it was discovered that tumor-bearing animals had significantly ($P < 0.05$) lower levels of oxidation (TBARS), lipids, estrogen receptor (ER) and progesterone receptor (PR). Histopathological and immunohistochemical analyses also supported the antiproliferative effects of the juice. According to Zhu *et al.*[62,63] and Mahata *et al.*[62,63], PE has an anti-cervical cancer impact by preventing the growth of cervical cancer cells and trigger their apoptosis. Gold nanoparticles of PE was synthesized by Wang *et al.*[64], who discovered that it had good therapeutic and preventative effects on liver and gastric malignancies, respectively. Additionally, *in vitro* research revealed that PE's antioxidant properties prevented the growth, migration, and invasiveness of colon[65] and liver[66] cancer cells and promoted apoptosis. Thus, research on PE's antitumor effects on a range of human tumors offers a theoretical foundation for its use as a nutritional intervention and the creation of PE anticancer products, which have promising practical potential.

3.1.4 *Other diseases*

PE has been shown to reduce blood glucose levels in hyperglycemic model rats[67]. In hyperglycemic rats, Zhou *et al.*[13] showed that PE can enhance vascular function by controlling the Akt/catenin signaling pathway, which is mediated by the ellagitannin metabolite urolithin A. PE can ameliorate three metabolic disorders (i.e., type 2 diabetes mellitus (T2DM), obesity, and nonalcoholic fatty liver disease (NAFLD))[68,69]. PE was found to have a reducing effect on the severity of clinical symptoms and CRP levels in patients of COVID-19 in a randomized, double-blind, controlled experiment[70]. From an immunological perspective, Huabprasert *et al.*[71] discovered that PE can boost NK cell function as well as splenocyte proliferative activity in mice in a dose-dependent manner. Moreover, studies have demonstrated that PE has protective effects against acute renal injury[72], cough and phlegm alleviation effects[73], and plays a preventive role against hair loss[74]. Figure. 3 summarizes the known research targets and pathways controlled by PE.

3.2 Bioactive compounds and its mechanism of PE for aging prevention

Since the health effects of PE are inextricably linked to its active ingredients, we have sorted out the active substances in PE. Rencently, many studies have focused on the extraction, separation, and purification of PE, both domestically and internationally. These studies primarily used solvent extraction, column chromatography for separation and purification, physicochemical properties and spectroscopic techniques to identify the chemical structures of the bioactive compounds. In addition to polyphenols and flavonoids, organic acids, polysaccharides, triterpenoids, sterols, fatty acids, amino acids, vitamins, and minerals were also discovered. Several portions of the PE contain distinct chemical components. The chemical components found in the roots, bark, branches, leaves, seeds, and fruits of PE are listed in subsections below, along with their anti-aging properties.

3.2.1 *Phenolic compounds*

Phenolic compounds, mainly flavonoids, phenolic acids, and tannins, are among the secondary plant metabolites. Phenolic compounds have significant effects as antioxidant, anti-aging, and anti-cancer properties. Zhao *et al.*[92] assessed the activities of polyphenols from PE, using tea polyphenols, VC, vitamin E, and butylated hydroxytoluene (BHT) as controls, based on 1, 1-diphenyl-2-picrylhydrazyl (DPPH), superoxide anion, hydroxyl radical, and anti-lipid peroxidation models. They demonstrated that the polyphenols of PE are very promising antioxidants with excellent activities.

3.2.1.1 *Tannins*

Plant polyphenols with relative molecular weights of 500–3,000 are often known as tannins, a family of multi-phenolic compounds with complex structures and a wide range of biological functions in plants.

Fresh PE fruit had the highest tannin concentration (about 45% of tannin), followed by unripe fruit (about 30%–35% of tannin), and dried fruit (about 14% of tannin)[93]. However, dried fruit had higher content of rutin, total flavonoids, and gallic acid[94].

Total tannin concentration in PE fruit varies greatly depending on where it was grown. Indian and Nepalese origins of the fruit having the highest levels[95]. In addition to the fruits, the roots and branches of PE are also abundant in tannins. Tannins can be divided into three groups including condensed tannins, complex tannins, and hydrolyzable tannins based on their chemical structures. The majority of the tannins in PE are hydrolyzable tannins, as indicated in Table 3.

Polyphenolic hydroxyl structure of tannins has potent hydrogen-donating and reducing properties that can interact directly with free radicals. These structures could scavenge excess levels of free radicals in the body to render antioxidant and anti-aging effects. *In vitro* studies have found that tannins have a powerful scavenging effect on hydroxyl radicals, superoxide

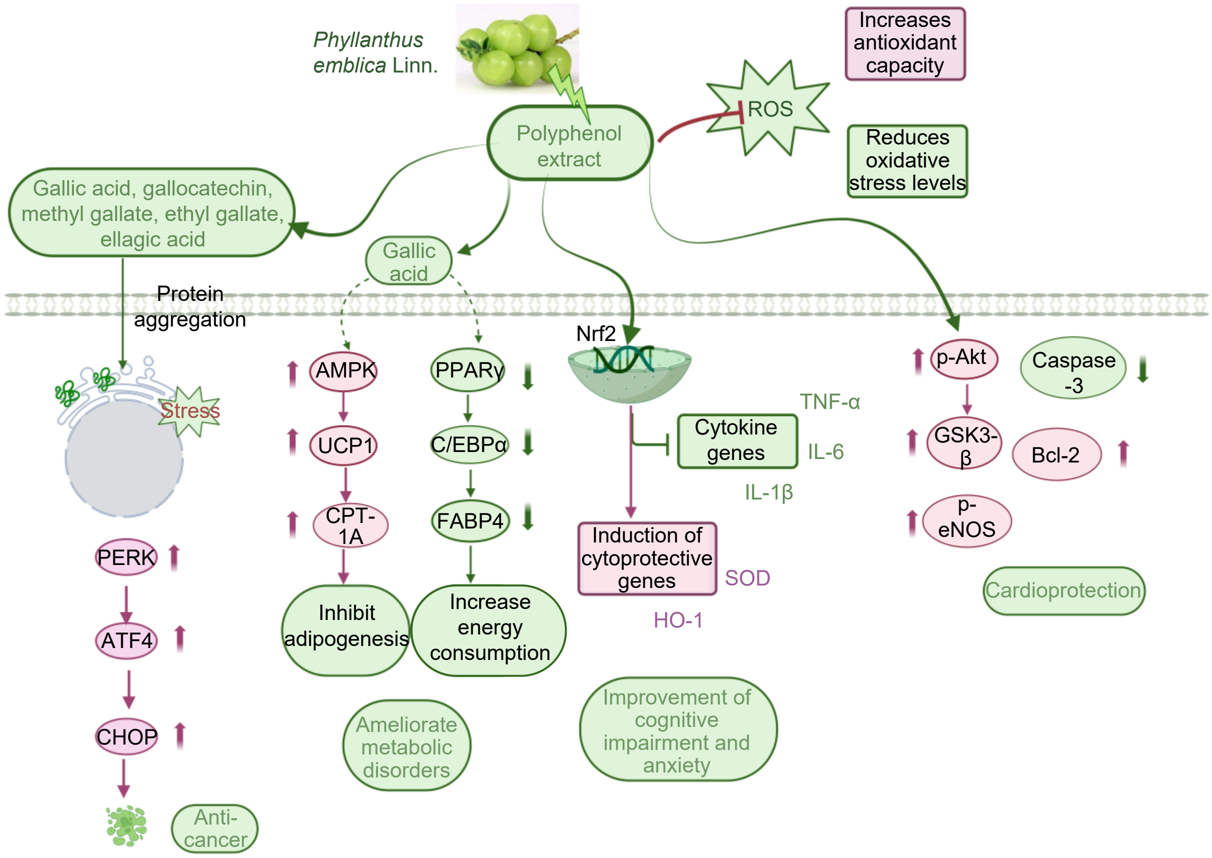

Figure 3 Known research targets and pathways controlled by PE. PERK (Protein kinase R-like endoplasmic reticulum kinase), ATF4 (Activating transcription factor 4), CHOP (C/EBP-homologous protein), AMPK (Adenosine 5'-monophosphate (AMP)-activated protein kinase), UCP1 (Uncoupling protein 1), CPT-1A (Carnitine Palmitoyltransferase 1A), PPARγ (Peroxisome proliferator-activated receptor γ), C/EBPα (CCAAT/enhancer binding proteins α), FABP4 (Fatty acid-binding protein 4), TNF-α (Tumor necrosis factor-α), IL-6 (Interleukin-6), IL-1β (Interleukin-1β), HO-1 (Heme oxygenase 1), p-Akt (phosphorylated protein kinase B), GSK3-β (Glycogen synthase kinase 3β), p-eNOS (phosphorylated Endothelial NOS), Bcl-2 (B-cell lymphoma-2).

radical anion, and DPPH radicals; their antioxidant capacity is more robust than that of commonly used antioxidants (e.g. VC, vitamin E), and low molecular weight polyphenols (e.g. gallic acid). The ability of tannins containing gallic acyl group is quite high in blocking mitochondrial and microsomal induced lipid peroxidation in the murine liver and considerably increase the mean lifespan of *Drosophila*[96], which further demonstrates the antioxidant and anti-aging actions of tannins. The monomeric tannins mallotusinin, cotinine, carbolic acid, iso corilagin, and quercetin, isolated from dried fruits of PE showed antioxidant ability in *in vitro* experiments[97] .These results revealed that all of these tannins have potent free radical scavenging activity.

3.2.1.2 *Phenolic acids and other phenolic compounds*

Polyphenolic substances are excellent donors of electrons or hydrogen atoms. Due to low reactivity of the produced phenolic free radical intermediates and lack of molecular oxygen attack sites, they serve as effective antioxidants and may quickly be oxidized as a result of chain reactions.

PE contains gallic acid and its derivatives (mainly contains muconic or malic acid combined with gallic acid compounds). In addition, as shown in Table 3, it also contains certain additional phenolic compounds.

The monomeric phenolic acid compounds, such as muconic acid-1, 4-lactone-3-*O*-gallate, gallic acid, and pyrogallic gallic acid isolated from the dried fruits of PE were subjected to antioxidant experiments *in vitro*[97]. The results revealed that all of the phenolic acids tested showed strong free radical scavenging activities. Among them, gallic acid, the structurally simplest natural polyphenolic compound, had the ability to scavenge DPPH radicals more effectively than VC in inhibiting lipid peroxidation. They also increased the ratio of cellular reduced GSH to oxidized GSH[98], and inhibited high glucose-mediated ROS production[99]. The gallic acid in PE can also maintain glucose homeostasis by regulating the PI3K/p-Akt pathway and lessen insulin resistance by regulating the PPARγ/AMPK/NF-κB pathway. They inhibit adipogenesis by down-regulating PPARγ, C/EBPα, and FABP4 protein expression and increase energy consumption by up-regulating UCP1 and CPT-1A protein expression[100]. Hu *et al.*[89] supposed that five compounds in PE, including gallic acid, gallocatechin, methyl gallate, ethyl gallate and ellagic acid, which could induce immunogenic cell death *in vitro* and might be considered as the potential antitumor pharmacodynamic substances.

3.2.1.3 *Flavonoids*

Phenolic substances with the greatest diversity are flavonoids. Several types of flavonoids are present in PE, including anthocyanidins (e.g. delphinidin), flavones (e.g. apigenin), flavonols (e.g. kaempferol and quercetin), flavanonols (e.g. dihydro kaempferol), and flavanols (e.g. catechins and epicatechins).

The flavonoid extract of PE has been demonstrated to considerably lengthen the lifespan of *C. elegans*, and significantly raise the peroxidase activity, thus resulting in antioxidant protection[11, 40].

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Table 3 Bioactive compounds in PE

No.	Parts of PE	Compounds	Molecular formula	Reference
		Tannins		
1	Fruit juice, roots, branches and leaves	1(*β*), 4-di-*O*-Galloyglucose	$C_{20}H_{20}O_{14}$	[136]
2	Fruit juice, roots, branches and leaves	1, 2, 3, 6-tetra-*O*-Galloy-*β*-*D*-glucose	$C_{34}H_{28}O_{22}$	[136]
3	Fruit juice, roots, branches and leaves	1, 2, 3, 4, 6-penta-*O*-Galloy-*β*-*D*-glucose	$C_{41}H_{32}O_{26}$	[136]
4	Fruit juice, roots, branches and leaves and dried fruits	1-*O*-Galloy-*β*-*D*-glucose	$C_{13}H_{15}O_{10}$	[136, 137]
5	Fruit juice, roots, branches and leaves and dried fruits	1-*O*-Digalloy-*β*-*D*-glucose	$C_{14}H_{18}O_{10}$	[136, 137]
6	Fruit juice, roots, branches and leaves and dried fruits	1, 6-di-*O*-Galloy-*β*-*D*-glucose	$C_{20}H_{20}O_{14}$	[136]
7	Dried fruits	3, 6-di-*O*-Galloy-*β*-*D*-glucose	$C_{20}H_{20}O_{14}$	[137]
8	Dried fruits	Chebulinic cacid	$C_{41}H_{32}O_{27}$	[137]
9	Fruits	Chebulic acid	$C_{14}H_{12}O_{11}$	[137]
10	Fruit juice, roots, branches and leaves and dried fruits	Chebulagic acid	$C_{41}H_{30}O_{27}$	[136, 137]
11	Fruits	Terchebin	$C_{41}H_{30}O_{27}$	[137]
12	Dried fruits	Chebulanin	$C_{27}H_{24}O_{19}$	[138]
13	Fruits	Methyl chebulagate	$C_{42}H_{34}O_{28}$	[133]
14	Fruits	Dimethyl neochebulagate	$C_{42}H_{34}O_{28}$	[133]
15	Dried fruits	Neochebulagic acid	$C_{41}H_{32}O_{28}$	[137]
16	Fruits	Chebulic acid trimethyl ester	$C_{17}H_{20}BO_{14}$	[133]
17	Fruit juice, roots, branches and leaves and fruits	Corilagin	$C_{27}H_{22}O_{18}$	[133, 136]
18	Dried fruits	Ellagic acid	$C_{14}H_{6}O_{8}$	[137]
19	Branches	3, 4, 3'-tri-*O*-Methylellagic acid	$C_{17}H_{12}O_{8}$	[134]
20	Fruits	Elaeocarpusin	$C_{47}H_{34}O_{32}$	[139]
21	Fruits	Geraniin	$C_{41}H_{28}O_{27}$	[93]
22	Fruits	Furosin	$C_{27}H_{22}O_{19}$	[140]
23	Fruits	Carpinusnin	$C_{41}H_{34}O_{29}$	[141]
24	Fruit juice, roots, branches and leaves and fruits	Tercatain	$C_{34}H_{26}O_{22}$	[133, 136]
25	Fruits	Isocorilagin	$C_{27}H_{22}O_{18}$	[93]
26	Roots and fruits	Phyllaemblicin A	$C_{27}H_{34}O_{14}$	[93]
27	Roots and fruits	Phyllaemblicin B	$C_{33}H_{44}O_{19}$	[93]
28	Roots and fruits	Phyllaemblicin C	$C_{38}H_{52}O_{23}$	[93]
29	Fruits	Phyllaemblicin D	$C_{21}H_{34}O_{13}$	[93]
30	Fruits	Phyllaemblicin E	$C_{38}H_{54}O_{23}$	[93]
31	Fruits	Phyllaemblicin F	$C_{54}H_{66}O_{27}$	[93]
32	Fruits	Phyllanthunin	$C_{32}H_{30}$	[142]
33	Fruit juice, roots, branches and leaves and fruits	Putranjivain A	$C_{46}H_{36}O_{31}$	[93, 136]
34	Fruits	Putranjivain B	$C_{53}H_{44}O_{36}$	[93]
35	Fruit juice, roots, branches and leaves	Prodelphinidin B-1	$C_{30}H_{26}O_{14}$	[136]
36	Fruit juice, roots, branches and leaves	Prodelphinidin B-2	$C_{30}H_{26}O_{14}$	[136]
37	Fruits	2, 3-(*S*)-Hexahydroxydiphenoyl-*D*-glucose	$C_{20}H_{33}O_{22}$	[93]
38	Fruits	2-(2-Methylbutyryl)phloroglucinol-1-*O*-(6''-*O*-*β*-*D*-apiofuranosyl)-*β*-*D*-glucopyranoside	$C_{20}H_{27}O_{13}$	[93]
39	Branches	3, 4, 8, 9, 10-Pentahydroxydibenzo[b, d] pyran-6-one	$C_{13}H_{8}O_{7}$	[134]
40	Fruits	Epigallocatechin-(2→7, 4*β*→8)-gallocatechin	$C_{30}H_{22}O_{14}$	[93]
41	Fruits	Epicatechin-(4*β*→8)-epigallocatechin3-*O*-gallate	$C_{37}H_{30}O_{17}$	[93]
42	Fruits	Epicatechin-(4*β*→8)-epigallocatechin	$C_{30}H_{26}O_{13}$	[93]
43	Fruits	3-*O*-Methylellagic acid-4-*O*-*α*-*L*-rhamnopyanoside	$C_{22}H_{20}O_{12}$	[93]
44	Fruits	2, 3-(*S*)- Hexahydroxydiphenoyl-*D*-glucose	$C_{20}H_{33}O_{22}$	[93]
45	Fruits	Punicafolin	$C_{41}H_{30}O_{26}$	[137]
46	Fruits	Mallotusinin	$C_{41}H_{26}O_{25}$	[143]
47	Roots	Prodelphindin A-1	$C_{30}H_{24}O_{14}$	[93]

(Continued)

No.	Parts of PE	Compounds	Molecular formula	Reference
48	Fruits	Prodelphinidin B-2-3'-*O*-gallate	$C_{37}H_{30}O_{18}$	[93]
49	Fruits	Punigluconin	$C_{34}H_{26}O_{23}$	[93]
50	Fruits	Pedunclagin	$C_{34}H_{24}O_{22}$	[93]
51	Fruits	Mallonin	$C_{33}H_{28}O_{24}$	[137]
52	Dried fruits	Mallotusinin	$C_{41}H_{26}O_{25}$	[97]
		Phenolic acids and other phenolic compounds		
53	Fruits, roots, peel and branches	Gallic acid	$C_7H_6O_5$	[134, 144, 145]
54	Dried fruits	Pyrogallol	$C_6H_6O_3$	[97]
55	Branches, peel	Methyl gallate	$C_8H_8O_5$	[134, 146]
56	Fruits	Ethyl gallate	$C_9H_{10}O_5$	[141]
57	Fruits	Mucic acid 3-*O* gallate	$C_{13}H_{14}O_{13}$	[147]
58	Fruits	Mucic acid 2-*O* gallate	$C_{13}H_{14}O_{13}$	[147]
59	Fruits	Mucic acid 2, 5-di-*O*-gallate	$C_{20}H_{25}O_{16}$	[138]
60	Fruits	Mucic acid	$C_6H_{10}O_8$	[138]
61	Fruits	Mucic acid 1-methylester 2-*O*-gallate	$C_{14}H_{20}O_{12}$	[93]
62	Fruits	Mucic acid dimethyl ester 2-*O*-gallate	$C_{16}H_{22}O_{15}$	[93]
63	Fruit juice	Mucic acid 6-methylester 2-*O*-gallate	$C_{14}H_{20}O_{12}$	[137]
64	Fruits	Mucic acid 1, 4-lactone 3-*O*-gallate	$C_{14}H_{12}O_{11}$	[147]
65	Fruit juice	Mucic acid 1, 4-lactone-6-methylester 2-*O*-gallate	$C_{15}H_{14}O_{11}$	[137]
66	Fruit juice	Mucic acid 1, 4-lactone-6-methylester 5-*O*-gallate	$C_{15}H_{14}O_{11}$	[137]
67	Fruits	Mucic acid 1, 4-lactone 5-*O*-gallate	$C_{14}H_{12}O_{11}$	[147]
68	Fruits	Mucic acid 1, 4-lactone 2-*O*-gallate	$C_{14}H_{12}O_{11}$	[138]
69	Fruits	Mucic acid 1, 4-lactone 2, 5-di-*O*-gallate	$C_{21}H_{16}O_{15}$	[138]
70	Fruits	Mucic acid 1, 4-lactone 3, 5-di-*O*-gallate	$C_{21}H_{16}O_{15}$	[93]
71	Fruits	3-Ethoxy-4, 5-dihydroxy-benzoic acid	$C_{14}H_{10}O_6$	[137]
72	Fruits	*L*-Malic acid 2-*O*-gallate	$C_{13}H_{14}O_{13}$	[93]
73	Fruits	Mucic acid 1-methyl ester 6-ethyl ester	$C_9H_{15}O_8$	[144]
74	Fruits	*trans*-Cinnamic acid	$C_9H_8O_2$	[148]
75	Fruits	Cinnamic acid	$C_9H_8O_2$	[141]
76	Fruits	Protocatechuic acid	$C_7H_6O_4$	[145]
77	Fruits	Isovanillic acid	$C_8H_8O_4$	[145]
78	Fruits	Vanillic acid	$C_8H_8O_4$	[141]
79	Fruits	Methyl caffeate	$C_{10}H_{10}O_4$	[141]
80	Fruits	Vanillin	$C_8H_8O_3$	[141]
81	Fruits	Isostrictiniin	$C_{27}H_{22}O_{18}$	[147]
82	Fruits	1, 3, 5-trihy-Droxybenzenel-*O*-galloyl-*β*-*D*-glucoseide	$C_{12}H_{16}O_9$	[93]
83	Fruits	2, 6-Dimethoxy-4-(2-hydroxyethyl)phenol-*O*-β-*D*-glucopyranoside	$C_{16}H_{24}O_9$	[93]
84	Fruits	2-Carboxylmethylphenol1-*O*-3-*D*-glucopyranoside	$C_{14}H_{18}O_8$	[93]
85	Fruits	Tuberonic acid glucoside	$C_{18}H_{28}O_9$	[141]
86	Fruits	3, 3'-Dihydroxy-4, 4'-biphenyl-2, 2'-propenyldicarboxylic acid	$C_{20}H_{18}O_6$	[137]
		Flavonoids		
87	Branches, leaves and dried fruits	Quercetin	$C_{15}H_{10}O_7$	[137]
88	Fruits	Quercetin-3-*β*-*D*-glucoside	$C_{21}H_{20}O_{12}$	[93]
89	Fruits	Quercetin-3-*O*-glucoside	$C_{21}H_{20}O_{12}$	[93]
90	Branches and pulverized pulp	Quercetin 3-*O*-rhamnoside	$C_{33}H_{40}O_{19}$	[93, 134]
91	Fruits	Quercetin 7-*O*-glucoside	$C_{21}H_{20}O_{12}$	[93]
92	Branches and leaves	Kaempferol	$C_{15}H_{10}O_6$	[137]
93	Branches and leaves	Dihydrokaempferol	$C_{15}H_{12}O_6$	[137]
94	Fruits	Kaempferol-3-*O*-rhamnoside	$C_{33}H_{40}O_{19}$	[148]
95	Fruits	Kaempferol-3-*O*-*β*-*D*-glucoside	$C_{21}H_{19}O_{11}$	[93]

(Continued)

No.	Parts of PE	Compounds	Molecular formula	Reference
96	Branches and leaves	Myricetin3-*O*-rhamnoside	$C_{21}H_{20}O_{12}$	[93]
97	Roots	4-*O*-Methylellagic acid 3"-*α*-rhamnoside	$C_{21}H_{18}O_{12}$	[135]
98	Fruits	3-*O*-Methylellagic acid-4'-*O*-*L*-rhamnppyanside	$C_{21}H_{18}O_{12}$	[141]
99	Branches and leaves	Eriodictyol	$C_{15}H_{12}O_6$	[137]
100	Branches and leaves	Eriodictyol-7-*O*-glucoside	$C_{21}H_{22}O_{11}$	[137]
101	Fruits	Delphinidin	$C_{15}H_{11}ClO_7$	[121]
102	Fruits	Wogonin	$C_{16}H_{12}O_5$	[121]
103	Fruits	Rutin	$C_{27}H_{30}O_{16}$	[149]
104	Fruits	Myricetin	$C_{15}H_{10}O_8$	[145]
105	Fruits	Naringenin	$C_{15}H_{12}O_5$	[148]
106	Branches and leaves	Naringenin-7-*O*-glucoside	$C_{21}H_{22}O_{10}$	[137]
107	Fruits	Apigenin-7-*O*-(6"-butyryl-*β*-glucopyranoside)	-	[150]
108	Fruits	5, 7-Dihydroxy-2-(4-hydroxyphenyl)-4*H*-chromen-4-one	$C_{15}H_{10}O_5$	[121]
109	Fruits and roots	Luteolin-4'-*O*-neohesperiodoside	$C_{27}H_{30}O_{15}$	[150]
110	Fruits, branches and leaves	2-(2-Methylbutyryl) phloroglucinol-1-*O*-(6″-*O*-*β*-*D*-apiofuranosyl)-*β*-*D*-glucopyranosidea	$C_{22}H_{32}O_{13}$	[93, 137]
111	Fruits	2-(2-Methylbutyryl) phloroglucinol (multifidol)glucosidea	$C_{16}H_{25}O_{10}$	[137]
112	Fruits	Tuberonic acid glucoside	$C_{18}H_{28}O_9$	[141]
113	Branches and leaves	(*S*)-Eriodictyol-7-*O*-(6"-*O*-trans-*p*-coumaroyl)-*β*-*D*-glucopyranoside	$C_{29}H_{29}O_{13}$	[137]
114	Branches and leaves	(*S*)-Eriodictyol-7-*O*-(6"-*O*-galloyl)-*β*-*D*-glucopyranoside	$C_{22}H_{17}O_{10}$	[137]
115	Branches and leaves	Naringenin-7-*O*-(6"-*O*-trans-*p*-coumaroyl)-glucoside	$C_{30}H_{28}O_{12}$	[137]
116	Branches and leaves	Naringenin-7-*O*-(6"-*O*-galloyl)-glucoside	$C_{28}H_{26}O_{14}$	[137]
		Flavanols and their derivative compounds		
117	Fruits	(−)-Epigallocatechin-3-*O*-gallate	$C_{22}H_{18}O_{11}$	[137]
118	Fruits	(−)-Epicatechin-3-*O*-gallate	$C_{22}H_{18}O_{10}$	[137]
119	Fruits	(−)-Epiafzelechin	$C_{15}H_{14}O_5$	[137]
120	Fruits	(−)-Epigallocatechin	$C_{15}H_{14}O_7$	[137]
121	Fruits	(−)-Epicatechin	$C_{15}H_{14}O_6$	[137]
122	Fruits	(+)-Gallocatechin	$C_{15}H_{14}O_7$	[137]
123	Fruits	(+)-Catechin	$C_{15}H_{14}O_6$	[137]
124	Fruits	(−)-Gallocatechin	$C_{15}H_{14}O_7$	[137]

Many monomeric flavonoids in PE have been found to possess anti-aging and anti-aging-related properties. For example, quercetin, kaempferol, and myricetin are the most common flavonoids found in food and are also present in PE[101]. Quercetin has powerful antioxidant qualities that shields our bodies from free radicals. It is the most effective antioxidant flavonoid found in nature. Furthermore, quercetin and its glycoside derivatives[102] have potent *in vitro* anti-inflammatory and antioxidant properties. According to Belinha *et al.*[103], quercetin can lengthen the lifespan of yeast cells by lowering the level of ROS and oxidizing GSH in Saccharomyces cerevisiae cells. This prevents H_2O_2-induced lipid peroxidation and protein carbonylation. In addition, quercetin is beneficial for certain health conditions, including cancer[104], neurological illnesses[105], and other diseases linked to aging. Kaempferol and its glycosides were suggested to enhance the expression of cellular antioxidant genes, particularly *HO-1* gene expression, SOD activity, and GSH levels[106]. In addition to increasing SOD, CAT, and GSH-Px activities, myricetin dramatically decreased intracellular ROS and MDA generation as well as GSH depletion induced by aluminum phosphide[107]. Other flavonoids contained in PE, besides these three, have also been demonstrated to have anti-aging properties. According to Jin *et al.*[108], rutin has a powerful capacity to scavenge free radicals, and in it had a stronger antioxidant effect than quercetin in scavenging hydroxyl radical and superoxide radical anion. Li *et al.*[109, 110] and Peng *et al.*[109, 110] have shown that delphinidin has strong anti-radical properties and enhances SOD, GSH-Px, and glutathione-*S*-transferase (GST) activities in rat retinal tissues while decreasing the level of TBARS. With its potent antioxidant properties, (−)-epigallocatechin-3-gallate (EGCG) may efficiently scavenge singlet oxygen, hydroxyl radicals, superoxide anions, and hydrogen peroxide radicals[111, 112]. The average lifetime of *C. elegans* has favorably been linked with EGCG in the concentration range of 0–300 mol/L[113]. Epicatechin (EC) significantly reduced human lipid peroxidation, and its antioxidant effect was superior to that of pure resveratrol or quercetin[114]. EC also enhanced GSH-Px and glutathione reductase (GR) activity, restored GSH and reduced ROS levels, thus preventing cellular damage caused by oxidative stress[115]. Furthermore, EC is a natural activator of Nrf2 and regulates oxygen species (OS) responses associated with this pathway by activating the Nrf2 pathway[116]. Methylated EC derivatives increased the mean lifespan of *C. elegans* as well[117].

3.2.2 *Flavones*

Cai *et al.*[118] analyzed and compared total flavonoid content of

PE in organs, species, and wild resources. Their findings demonstrated that flavonoids were generally present in all of PE's organs, predominately in the leaves and fruits and less in the branches and roots. The total flavonoid content of natural resources varied greatly and depended on different varieties. The wild fruits of PE had a higher total flavonoid content than farmed types did. Using high-performance liquid chromatography. Liang *et al.*[119] examined the levels of quercetin and kaempferol in the leaves of PE and discovered that the leaves from Gongcheng had the highest levels (0.68% of quercetin and 0.12% of kaempferol).

High-performance liquid chromatography was used by Wei *et al.*[120] to measure the quercetin content of PE. They discovered that the quercetin content of Sichuan PE purchased from Chengdu Hehua Chi herb market was 0.086 mg/g and that from Xinping County, Yunnan Province, China was 0.056 mg/g.

3.2.2.1 Flavanols and their derivative compounds

Flavanols are tannin precursors and can form tannins by condensation. A total of nine flavanols were present in PE, as shown in Table 3.

3.2.3 SOD

As the body's natural free radical scavenger, SOD can convert superoxide anion radicals into molecular oxygen and hydrogen peroxide, rendering them harmless and producing antioxidant and anti-aging effects.

SOD activity in PE can reach 14,000 U/g or higher[121]. Cai *et al.*[122] examined the SOD activity of PE. All organs contained SOD activity, but the fresh fruit flesh had the most (above 200.00 U/g), and the seeds had the lowest level (below 20.00 U/g). It was discovered that PE juice contains SOD, with the enzyme activity per milliliter of fresh juice being 964.28 international units. After the older adults consumed PE juice for 2 months, the SOD activity of red blood cells increased by 1.5 times and reduced the content of lipid peroxide in plasma, showing that PE juice has anti-aging health effects on the human body.

3.2.4 Vitamin

PE fruits were rich in VC with a content of 0.60%–0.92%. Vitamins B_1, B_2, E, PP, and carotenoids were also present in PE[121], but there were no studies to quantify these substances.

VC is a powerful antioxidant with demonstrated ability to react rapidly with superoxide radical anion, hydroperoxyl radical and hydroxyl radical to generate semi-dehydroascorbic acid, scavenging singlet oxygen and reducing sulfur radicals, which has antioxidant and anti-aging effects. The content of VC of PE is higher than those of citrus fruits, lychee, banana, apple and hawthorn by 6.4, 60, 41, 160 and 1.8 times, respectively[123]. Many kinds and origins of PE as well as the harvest time affect the VC contents. Generally, fruits picked in October have the highest VC concentration[124]. It was shown that PE fruit juice could block the synthesis of carcinogenic solid *N*-nitroso compounds in animals by > 90% which is higher than the same concentration of VC, through *in vitro* simulations, animal tests, human tests, and clinical trials[125].

3.2.5 Polysaccharides

According to Li *et al*,[126], polysaccharides contained in PE include galacturonic acid (GalA), galactose (Gal), rhamnose (Rha), and arabinose (Ara) with a mole ratio of 3.21:6.59:1:0.23. In addition, it contains xylose, mannose, and Ara[127]. When Wang *et al.*[128] isolated and purified polysaccharides from driaed PE and the yield was 16.4%.

By using the ultrasound-water extracting-alcohol precipitating method, soluble polysaccharides were extracted from PE[129]; it was demonstrated that PE polysaccharides have a good antioxidant effect *in vitro*, comparable to that of tea polyphenols. The antioxidant activities were related to its high uronic acid content[126].

3.2.6 Inorganic elements

Yuan *et al.*[130] found a total of 19 inorganic elements in the various organs (roots, stems, leaves, fruits, and seeds) of PE; these were boron (B), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), nickel (Ni), zinc (Zn), calcium (Ca), potassium (K), sodium (Na), phosphorus (P), sulfur (S), selenium (Se), silicon (Si), cobalt (Co), chromium (Cr), lead (Pb), cadmium (Cd), and molybdenum (Mo). Of these, Se has been proven to be an excellent antioxidant with a critical role in anti-aging[131]; 100 g of PE fresh fruit contains 0.24 mg of Se, which is the highest of all known foods[132]. Thus, PE serves as a potential Se food source with anti-aging activity.

3.2.7 Other compounds

Other classes of compounds have also been isolated and identified, such as lignans[133], terpenoids[134], sterols[135], fatty acids[93], and amino acids in PE. However, there is no report as of yet to demonstrate that these components of PE have antioxidant and anti-aging properties because the existing research on these components has only been limited to their isolation and identification; their physiological activities remain to be investigated.

Overall, numerous constituents in PE, including polyphenols, polysaccharides, VC, SOD, and Se, have proven to have anti-aging effects; all of which hint to a strong connection to the free radical theory.

4 Application of healthy foods

As a widely cultivated and easily accessible crop, PE has been transformed into several products because of its positive health effects. In the area of general foods, in addition to its direct consumption, PE has frequently been processed into juice[9], fruit powder, fruit wine, jam, canned food, and preserved fruit[151]. Food processing can successfully improve its sour and astringent taste to expand its full application in other food products. As a MFH-fruit, PE and its related products can be categorized as both food and medicine, which is a great opportunity for the development of related health foods.

PE has also also used to make a variety of health foods and was chosen by the WHO as one of three medicinal plants for global cultivation. For instance, Scholars' brand Yuganzi triple-layer tablet Yingneng-99[152], oral health liquid, and health fruit wine[137]. Among these, clinical trials based on human beings have demonstrated[152] that Yingneng-99 has the effects of enhancing immune function, promoting DNA synthesis, enhancing physical strength, intelligence, and memory, as well as inhibiting lipid peroxidation, and lowering blood lipids. PE health juice has a potent free radical scavenging ability and it was demonstrated that oral gavage of PE juice may enhance serum SOD and GSH-Px levels, decrease serum MDA and cerebral lipofuscin (LPF) levels, and extend the weight-bearing swimming time in Kunming mice[42]. Therefore, PE has great potential for development as a health products.

The use of PE as a part of traditional medical therapies by some

17 nations or ethnic groups has been reported. It has 35 kinds of medicinal effects, such as liver protection, anticancer, stomachic and cardiovascular protection, as well as treatment of respiratory disorders. The treatment of obesity, hyperlipidemia[153], and cardiovascular disorders (e.g. hypertension, stroke, myocardial ischemia) are the main emphasis of the therapeutic use of PE for anti-aging-related diseases. Several other diseases remain curable only through laboratory research using cell or animal models, with little clinical relevance. According to studies in the field of anti-aging[154], PE capsules are effective against stress-induced premature aging.

As a MFH-fruit, PE has been developed and utilized in food. Nonetheless, clinical applications and health products of PE used for the anti-inflammatory, anti-tumor, antioxidant, and anti-aging pharmacological effects are still in their infancy. Few related products are available and it is mainly limited to fruit juice or extracts and lacks multi-level product development. Thus, PE-related research and products still have room for further development.

5 Conclusions and perspectives

The aging has become a major global public health problem that places an enormous burden on families and societies. Nevertheless, a lot of anti-aging treatments have harmful side effects. Natural product diets, in contrast, have fewer risks and provide more health benefits. PE has proven to have anti-aging ability and can potentially treat conditions linked to aging, including cancer, cardiovascular disease, and neurological disorders. PE has anti-tumor action on numerous types of cancer and cardiovascular protective properties that can reduce the incidence of such illnesses. Moreover, it helps improve cognitive function, memory, and learning. Hence, PE holds considerable promise for advancement in anti-aging and anti-aging-related diseases.

PE, including its tannin fractions, extracted into water, methanol, ethanol, ether, lyophilized powder, and juice, are potent antioxidants and anti-aging compounds. Since there are very few medications available for anti-aging, and that clinical trials are scarce, there is great potential for creating specialty medicine food homology products or taking a fresh direction to creating special medical foods. It may also provide some opportunity for its use in the daily meals of the elderly.

A wealth of evidence to support that aging and its associated illnesses correlate well with the high level of free radicals. Thus the rich polyphenolic and flavonoid PE may have an anti-aging effect by scavenging excessive free radicals in aging organisms, reducing oxidative stress, influencing the production of inflammatory factors, and controlling the expression of proteins involved in related pathways. Research on the specific plant components with pharmacological activity and the molecular pathways behind the observed action is scarce. In addition, there are many studies on the anti-aging targets of polyphenols, but no one has yet analyzed the anti-aging targets of PE. Consequently, clarifying the key targets in PE that play an anti-aging role, as well as the molecular mechanisms by which specific active ingredients exert anti-aging effects should be the focus of future research.

Due to its affordable cost, safe ingestion, and plentiful resources, PE has had a long history of the planting and practical value for scientific usage, both in the pharmaceutical and food areas. A thorough investigation into anti-aging mechanism-related products of PE would lead to developing anti-aging daily health products or clinical therapies. Further research on the action mechanism and functional products of PE remains to be a big challenge.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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