



Antioxidant mechanisms and applications of apple polyphenols in food: A review

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Abstract Apple polyphenols are widely present in apple pulp, peel, kernel, and leaves. They are natural bioactive substances with a variety of health functions. This review describes the antioxidant functions of anthocyanins, quercetin, phlorizin, chlorogenic acid, and epicatechin in apple polyphenols through the regulation of signal pathways and transcription factors, and the inhibition or induction of enzymes. Massive food applications of apple polyphenols are summarized, including excellent color protection of fruits and vegetables, meat preservation, preparation of composite packaging films as active ingredients, enhancement of nutritional value as functional ingredients, and improvement of food taste and physical stability. This review would provide a reference for the exploration of apple polyphenol resources and its development in the food field.

Keywords: polyphenols; antioxidant; apple; functional food

1 Introduction

As people's understanding and demand for healthy and nutritious functional foods increase, apple polyphenols have attracted more and more attention as natural antioxidant active substances. Apple polyphenols (AP) are components produced by plant photosynthesis and with bitter, astringent and pigment character ^[1]. The composition and content of polyphenols in apples are different greatly due to the type of species, cultivation method, geographical environment, maturity and storage conditions ^[2]. They are mainly composed of flavonols, hydroxycinnamic acids, flavanols, anthocyanins, and dihydrochalcone ^[3]. An increasing number of studies have reported that

the hydroxyl and aromatic structures of polyphenols act as electron donors and mediators to generate stable non-radical products. The phenolic hydroxyl group, the reduced ketone structure, and the condensed structure of proanthocyanidins of apple polyphenols endow them with strong antioxidant power, which is the material and structural basis for the function and application of apple polyphenols. Representative compounds of apple polyphenols, as shown in Fig. 1, are cyanidin-3-*O*-glucoside in the anthocyanins, quercetin in the flavonols, phlorizin in the dihydrochalcone family, chlorogenic acid in the hydroxycinnamic acid family, and epicatechin in the flavanol family ^[4].

2 Antioxidant mechanisms of apple polyphenol compounds

Apple polyphenols is a natural free radical

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scavenger and has strong antioxidant properties. Apple polyphenols can scavenge free radicals by activating/inhibiting signal transduction pathways, regulating oxidative stress-related enzymes or antioxidant

substances, showing strong antioxidant capacity. The antioxidant mechanisms of anthocyanins, quercetin, phlorizin, chlorogenic acid and epicatechin are summarized in Table 1.

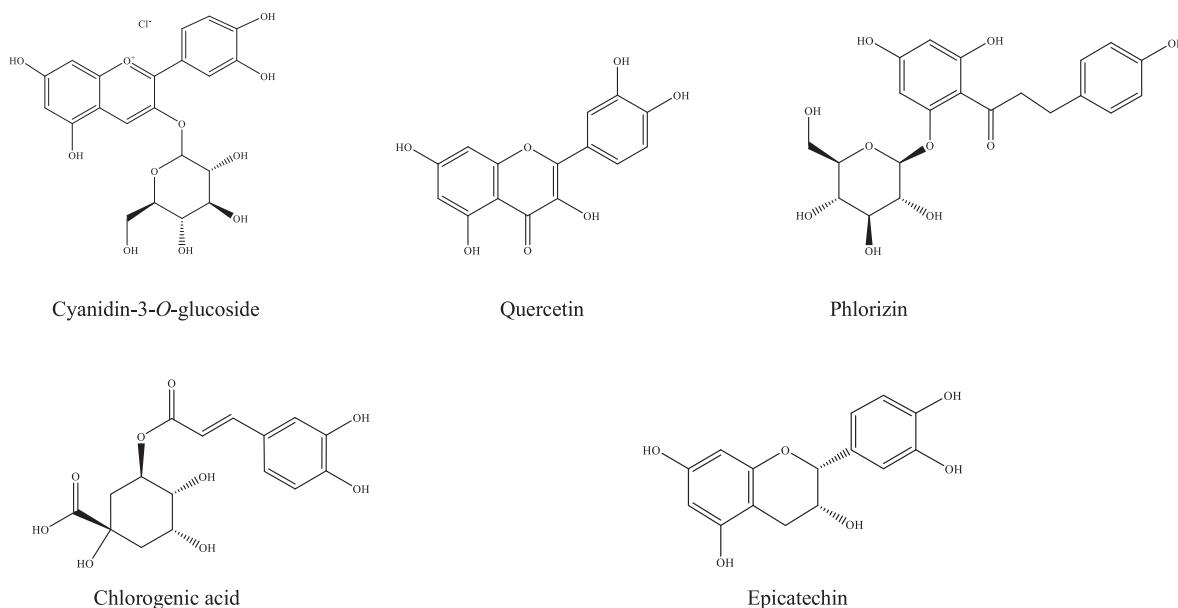


Fig. 1 Structure of compounds in apple polyphenols

Table 1 Antioxidant mechanisms of apple polyphenol compounds

Compounds	Pathways, transcription factors, enzymes	Reference
Cyanidin-3-O-glucoside	SET: $AH^+ \rightarrow e \rightarrow ROS/RNS$	[9]
	HAT: $AH^+ \rightarrow H^+ \rightarrow ROS/RNS$	[10]
	ROS ↓ GPX ↑ CAT ↑ SOD ↑	[13]
Quercetin	ROS ↓ ERK ↓ p38 ↓ JNK ↓	[15]
	Fe^{2+} ↓ Cu^{2+} ↓ ox-LDL ↓	[16–17]
	SOD ↑ CAT ↑ GSH-Px ↑	[19–20]
Phlorizin	SOD ↑ CAT ↑ GSH-Px ↑ GPX ↑ GR ↑	[22–23]
	HO-1 ↑ MDA ↓ d-Gal ↓	
	NF-κB ↓ PPAR γ ↓ NOX ↓	
Chlorogenic acid	Keap1-Nrf2-ARE ↑ ROS ↓ Nrf2 ↓	[37–41]
Epicatechin	GSH ↑ GPX ↑ GR ↑	[45–51]
	Nrf2 ↑ NOX ↑ NOS ↑	
	OS ↓ ROS ↓	

Note: →: Electron and hydrogen atom transfer; ↑: Irritation of signal pathways, transcription factors, enzyme activity; ↓: Inhibition of signal pathways, transcription factors, enzyme activity.

2.1 Anthocyanin

Anthocyanins are mostly present in apple peel and are water-soluble flavonoids [5]. The antioxidant

potential of anthocyanins depends on the chemical structure of the molecule, and the phenolic structure has antioxidant properties. Glycosylation of anthocyanins reduces free radical scavenger activity

compared to glycosidic ligands ^[6]. The antioxidant activity of anthocyanins can be enhanced by other phytochemicals or vitamins that are also abundant in fruits. They may interact in a synergistic or antagonistic manner ^[7].

Anthocyanins have the ability to scavenge free radicals, especially harmful oxidants, reactive oxygen species and reactive nitrogen species (ROS and RNS). Anthocyanin exhibit potent antioxidant activity by donating an electron or hydrogen atom to neutralize free radicals ^[8]. The unique structure of the flavin cation (AH⁺) confers unique antioxidant properties to anthocyanins. These compounds can neutralize reactive radical species through single electron transfer (SET) reactions or hydrogen atom transfer (HAT) mechanisms. In the SET, the antioxidant delivers an electron to the radical to neutralize it, while in the HAT, the antioxidant delivers a hydrogen atom to the radical and stabilizes it ^[9, 10]. The two mechanisms usually occur simultaneously and the reaction mechanism is determined by the structure, solubility, partition coefficient and solvent polarity of the antioxidant ^[11, 12]. In addition to the mode of action, they also inhibit enzymes involved in the production of ROS, upregulate or protect antioxidant defenses, and induce antioxidant enzymes, such as glutathione peroxidase (GPX), catalase (CAT), and superoxide dismutase (SOD), which decompose harmful compounds ^[13].

2.2 Quercetin

Quercetin is one of the flavonols in apple polyphenols which can be used as a potent antioxidant. Quercetin has been reported to scavenge intracellular accumulation of hydroxyl radicals, hydrogen peroxide, and superoxide anions both *in vitro* and *in vivo* ^[14]. Zhang showed that ROS could activate the MAPK pathway, resulting in phosphorylation of ERK, p38, and JNK and leading to myocardial fibrosis in myocardial fibroblasts ^[15]. Quercetin significantly reduces the phosphorylation levels of ERK, p38 and JNK by scavenging ROS, inhibits the activation of MAPK pathway, and inhibits the proliferation of

cardiomyoblasts induced by ROS.

Quercetin can chelate metal ions to exert antioxidant effects. When the homeostasis of iron and copper in the body is disrupted, excess Fe²⁺ and Cu²⁺ accumulate in the cell to cause lipid peroxidation. Fe²⁺ also catalyzes hydroxyl radicals ^[16], which induce oxidative stress. Quercetin can exert antioxidant effects through catechol chelating Cu²⁺ and Fe²⁺ in its structure. Cherrak studied the activity of flavonoid compounds *in vitro* for antioxidant and metal ion chelating properties, and found that Fe²⁺ addition to four methoxylated derivatives of quercetin, rutin and catechin changed in absorption spectra ^[17]. The results showed that the absorption spectrum of quercetin with the largest variation and the strongest ability to chelate metal ions. The antioxidant activity was evaluated by 1,1-diphenyl-1-picrylhydrazyl (DPPH) free radical, and quercetin had the highest free radical scavenging ability and strong antioxidant activity.

Quercetin can inhibit ox-LDL-induced oxidative damage ^[18]. Quercetin may increase antioxidant enzyme activity. Quercetin can modulate the enzyme-mediated antioxidant and the non-enzyme-dependent antioxidant defense system to exert its antioxidant. Altered levels of oxidative free radicals have been reported in patients with diabetes, with a significant decrease in total anti-oxidant status (TAS) and a decrease in levels of antioxidant enzymes (SOD, CAT and GSH) and non-enzymatic components (vitamins C and E) ^[19]. Quercetin also has strong antioxidant capacity *in vivo*. Oyedemi fed diabetic rats at 50 mg/kg quercetin for 28 days, which showed significantly increased pancreatic SOD, CAT and GSH-Px activity and nearly normal pancreatic function ^[20].

2.3 Phlorizin

Phlorizin, a dihydrochalcone found in apple plants, is classified as a flavonoid, and was first isolated from the bark of apple trees ^[21]. Studies have shown that phlorizin increase the activity of antioxidant enzymes *in vivo*, such as SOD, CAT, GSH-Px, GPx and GR. This leads to a reduction in malondialdehyde (MDA) and d-galactose(d-Gal)-induced oxidative stress

in PC12 cells, thereby slowing down aging [22]. By activating these enzymes, the accumulation of harmful free radicals in the body can be effectively scavenged, maintaining intracellular redox balance and reducing oxidative stress-induced cellular damage.

In addition, phlorizin has been found to inhibit a variety of oxidative stress-related signal pathways, including NF- κ B, peroxisome proliferator-activated receptor γ (PPAR γ) and NADPH oxidase (NOX). Through these mechanisms, phlorizin can inhibit inflammatory responses and apoptosis, thereby protecting cells from oxidative stress damage. Molecular docking studies have also shown that root pepsin binds to the Keap1 protein, which interacts with Nrf2. Activation of Nrf2 leads to its translocation to the nucleus and binding to the ARE region of the target gene. This activation is mediated in part by JNK phosphorylation. The expression of SOD, GPx, HO-1 and GCLC proteins is regulated by Nrf2 [23]. Phlorizin has strong antioxidant and anti-aging activities and can ameliorate the conditions of several age-related diseases [24].

2.4 Chlorogenic acid

Chlorogenic acid (CA) belongs to the group of hydroxycinnamic acids and has many biological functions, including anti-inflammatory [25], antioxidant [26], and anticancer [27], as well as hypoglycaemia and hypolipidaemia effects [28, 29], anti-apoptotic effects [30, 31]. In addition, chlorogenic acid has been reported to be an activator of the Nrf2-ARE signaling pathway, providing cytoprotection in different cell types [32-34].

Chlorogenic acid acts as a direct and effective ROS neutraliser by scavenging free radicals *in vitro*. More importantly, chlorogenic acid also activates the Nrf2-ARE pathway to enhance the endogenous antioxidant system in PC12 cells. These processes contribute to the cytoprotective effect of chlorogenic acid against oxidative stress-induced damage in PC12 cells, but the latter is likely to be more important because endogenous antioxidants are sustainably available to neutralize ROS through enzymatic processes [35]. The Keap1-Nrf2-ARE pathway is a major regulatory system that protects the cells from

oxidative/electrophilic damage [36]. One of the most general mechanisms for activation of this pathway involves modification of the Cys residue of the inhibitory protein Keap1, which leads to stabilize and subsequent nuclear accumulation of Nrf2.

In addition, protein kinases (GSK-3 β , PI3K, JNK, and p38) [37], epigenetic factors (micro-RNA 144, 28, 200, and 34) [38], and other protein chaperones (p21, caveolin-1) have all been shown to have the potential to stabilize Nrf2 [39]. Small molecules with one of two common motifs, ortho or para-dihydroquinone and Michael receptor, are potent Nrf2 activators. CA contains an O-dihydroquinone portion and a Michael receptor unit. The O-dihydroquinone portion is considered to be an electrophilic reagent that is readily oxidised by ROS to form the corresponding O-quinone, ready to modify the Cys residue in Keap1 [40]. The cinnamic acid unit is a Michael receptor and is reactive to thiols. Modification of the Cys residue in Keap1 by the O-dihydroquinone portion of chlorogenic acid and the cinnamic acid unit may be the molecular basis for activation of Nrf2 [41].

2.5 Epicatechin

Epicatechin (EC), the flavanol present in apple polyphenols, is known for its excellent antioxidant activity. The metabolites of epicatechin in the human body are present in the plasma and accumulate in organs such as the brain, liver, heart, intestines and kidneys. Therefore, epicatechin may play a beneficial role in various tissues and organs of the human body [42, 43]. EC is structurally composed of two aromatic rings and an oxygenated heterocycle. The presence of multiple phenolic hydroxyl groups contributes to the potent antioxidant properties of epicatechin, which can directly or indirectly scavenge ROS by chemical reactions between hydroxyl groups and ROS or by modulating ROS pathway scavenging compounds and enzymes [44].

Changes in GSH within the body are closely related to OS [45]. Under heat stress, EC can enhance the production of GSH and reduce ROS levels, while methylated EC derivatives can prolong the average lifespan of nematodes [46, 47]. GPx and GR

are critical factors in building the body's anti-oxidant defense system. EC prevents oxidative damage in cells, enhances GPx and GR activities, reduces ROS production, and restores GSH production^[48]. Nrf2 is a key factor in the cellular OS response. It is regulated by Keap1 and interacts with anti-oxidant response elements to regulate the expression of antioxidant proteins and phase II detoxifying enzymes^[49]. EC is a natural activator of Nrf2, which can regulate the OS response related to this pathway by activating the Nrf2 pathway^[50].

EC has the ability to regulate NOX and NOS, thereby mediating the bioavailability of NO and resisting OS in the body^[51]. EC can also regulate OS pathways by affecting the redox sensitive pro-inflammatory pathways^[52]. Dietary supplementation with EC can regulate the production of oxidants

in mice, increase the bioavailability of NO, down-regulate redox-sensitive pro-inflammatory pathways (mainly inducible nitric oxide synthase (iNOS)-related OS pathways), and prevent OS-induced chronic inflammation^[53].

3 Food application of apple polyphenols

Apple polyphenols have many applications in the food industry because of their antioxidant and antibacterial activities. As shown in Fig. 2, it can be used to preserve fruits and vegetables, extend the storage time of meat products, and improve the color. It can also be prepared as composite film with chitosan and other ingredients to improve the preservation effect of food. Apple polyphenols can also be added to food as effective ingredients.

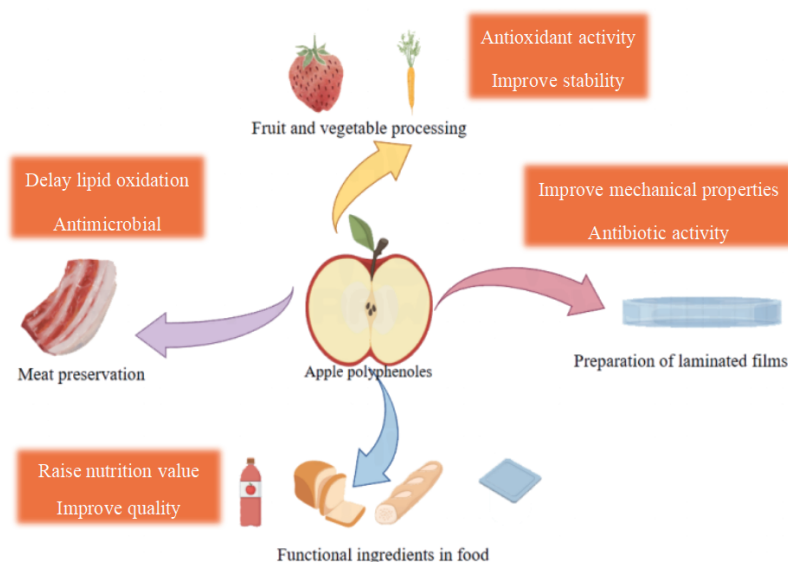


Fig. 2 Application of apple polyphenols in food

3.1 Preservation of fruits and vegetables

Apple polyphenols can exert strong antioxidant and antibacterial ability, which is of great significance and help for the preservation and storage of fruits and vegetables. Apple polyphenols participate as active antioxidants in the melanoidin reaction and other chemical reactions of food systems^[54, 55]. Dong systematically investigated the mechanism and products of enzymatically induced non-enzymatic reactions of

apple polyphenols on the formation of browning in apple juice processing^[56]. It was found that the p-/o-quinone compounds formed by the oxidation of chlorogenic acid could induce the non-enzymatic browning of catechins and epicatechins at a rate lower than that of polyphenols themselves. Moreover, the chemical properties of phlorizin are stable and have no polymerization effect. At the same time, chlorogenic acid o-quinone has no inducing effect on it, and browning can only occur under polyphenols

oxidase induced browning. In addition, the quinone formed by the oxidation reaction of chlorogenic acid accelerates the decomposition of flavanol monomers through coupled oxidation to form new products with enhanced coloration^[57]. The coupled oxidation reaction of phlorizin with chlorogenic acid and catechins may have a synergistic effect in color presentation^[58].

As endogenous antioxidants in apples, apple polyphenols have applications in other fruit and vegetable juice processing. Zhang found that phlorizin was added to low ester pectin, and the antioxidant property of pectin was positively proportional to the amount of phlorizin added, indicating that phlorizin has the ability to improve the antioxidant property of fruit juice^[59]. Sun investigated the color protection effect of apple polyphenols on carrot juice and found that apple polyphenols at a concentration of 0.10 g/100 mL could protect β -carotene well, and the juice had the best color protection effect. But the added apple polyphenols exceeded a certain critical amount, leading to an increase in the acidity of the solution and a decrease in the antioxidant effect, which led to the browning of carrot juice^[60].

Apple polyphenols can resist oxidation, but the presence of polyphenol oxidase poses a threat to the preservation and storage of food. Li found that Gallarhois water extract inhibited enzymatic browning in apple juice by binding to polyphenol oxidase and inactivating it^[61]. Recently, it has been found that aluminum-based metal-organic frameworks can be used to inactivate polyphenol oxidase in apple juice to inhibit browning in fruits and vegetables^[62].

3.2 Meat preservation

Adding apple polyphenols to meat products can improve the organoleptic properties of meat products. As a natural antioxidant, it is more natural, safe and non-toxic than chemically synthesized antioxidants. The effect of apple polyphenols on the color stability and fat oxidation of fresh meat showed that apple polyphenols in combination with ascorbic acid/nicotinamide could significantly improve the color

stability of fresh pork packed in oxygen permeable cling film, achieving higher and prolonged color protection^[63]. The application in bacon treatment showed that apple polyphenols made the sensory evaluation and color of bacon better than the untreated sample group^[64]. It was found that microencapsulated apple polyphenols could significantly improve the oxidative stability and texture properties of protein in frozen meat^[65]. The relative content of volatile flavor substances in apple polyphenol-treated bacon samples was high and varied, and the bacon samples had good flavor, which was analyzed by gas chromatography-mass spectrometry (GC-MS) and showed a high relative content of esters and ketones with characteristic flavor^[66]. Lan found that chitosan and apple polyphenol coating treatment can inhibit the increase of total volatile basic nitrogen and biogenic amines, slow down the increase of *K* value, delay the growth of microorganisms, and extend the shelf life of large yellow croaker for another 8 days^[67]. Cao found that 0.20% AP had the best inhibitory effect on PAH in grilled meat, and the elasticity, cohesion, adhesion, chewiness and recovery rate of grilled meat were significantly improved^[68].

3.3 Preparation of composite packaging films

In recent years, many scientists use apple polyphenols as active substances to prepare food composite membranes to achieve different effects. Tang developed collagen-hydroxypropyl methyl cellulose blend films with apple polyphenols as crosslinking agent and antioxidant compounds to produce biodegradable active packaging films. The results showed that the active film had obvious antibacterial effect on *Escherichia coli* and *Staphylococcus aureus*, which could effectively prevent the oxidation of vitamin C and reduce the accumulation of malondialdehyde in green pepper during storage^[69]. Xu prepared a biodegradable film of pea starch and pulp cellulose nanofiber hybrid matrix^[70]. It was found that the antioxidant properties of the film were significantly positively correlated with the content of apple polyphenols. When the content of

apple polyphenols was 4.5%, the DPPH free radical scavenging rate of the film reached 73.77%. Liu added apple polyphenols as an antioxidant to give the film antioxidant function. It is proved that the prepared polysaccharide-based edible packaging film has good comprehensive packaging performance and outstanding oxidation resistance ^[71]. Shen prepared a novel composite membrane made of sodium alginate/chitosan/apple polyphenol. After adding 1% AP, the average DPPH free radical scavenging activity of the membrane was significantly increased to 98% ± 0.88%. Compared with sodium alginate membrane, all the composite membranes have good antibacterial properties ^[72].

The composite film after adding apple polyphenols not only has better antioxidant and antibacterial properties, but also has better physical and mechanical properties. Shi used chitosan and gelatin as the matrix, and the introduction of appropriate proportion of apple polyphenols can effectively improve the mechanical properties of the composite film ^[73]. The team of Li prepared pea starch and pulp cellulose nanofiber hybrid matrix biodegradable films using apple polyphenols as active substances. The antioxidant properties of the films showed a significant positive correlation with the content of AP, and the biodegradability also showed an upward trend ^[74]. The scientists used cassava starch and sodium carboxymethyl cellulose as basic raw materials, and apple polyphenols as bioactive components to prepare edible films. The addition of AP increased and then decreased the flexibility of the films, while the tensile strength was slightly decreased and the barrier capacity was significantly improved ^[75].

3.4 Functional ingredients in food

Severe lipid-protein co-oxidation ultimately causes a decline in food quality, reduced shelf life, a considerable loss of nutrients and economic value, and even the formation of toxic substances. Studies have shown that apple polyphenols can enhance the physical stability of protein while protecting against hydrophobic nutrients, unsaturated fatty acids and

protein oxidation ^[76]. Apple polyphenols mainly bind to protein through hydrogen bonding and hydrophobic interaction, which improves the antioxidant and emulsifying properties of protein. Song developed a new plant-based antioxidant emulsifier using soy protein isolate and apple polyphenols, and discovered its potential interaction mechanism using multi-spectral technology and molecular docking, which was used to transport functional oil and nutrients to the nanometer, thus broadening the application of soy protein isolate and apple polyphenols in the food industry ^[77].

Apple polyphenols added to food can improve the flavor and quality of food. Apple polyphenols can be successfully used as prebiotics in yoghurt to increase the number of live probiotics ^[78]. Five concentrations of apple polyphenols were added to probiotic yoghurt, stored at 4 °C for 21 days and analyzed for physicochemical and microbiological properties. Acidity, water holding capacity and viscosity increased with the addition of apple polyphenols. The results showed that the addition of apple polyphenols improved the probiotic survival and antioxidant activity of yoghurt with better taste, flavor and color, and better texture. Apple polyphenols can maintain the original flavor and taste of pickles, and greatly reduce the nitrite content in pickles ^[79]. Adding apple pomace rich in natural apple polyphenols to gluten-free bread could improve the nutritional value of bread and is friendly to patients with celiac disease ^[80]. In gluten-free bread containing 5% apple pomace, it performed well in labeling phenolic compounds and antioxidant potential. Compared to the control, this level of apple pomace bread had 2.5 times more polyphenols, 8 times more flavonoids, 4 times more chlorogenic acids, 21 times more phlorizin and 6.5 times more antioxidant potential. Marek used apple pomace to enrich gluten-free biscuits, and found that apple pomace in gluten-free biscuits led to an increase in the content of phenolic acids, quercetin derivatives, flavan-3-ols and dihydrochalcones. Increases in protein, fat and minerals were also observed. The increase in the share of apple pomace led to a significant increase in the content of total fiber, soluble

and insoluble fractions, but led to an increase in the hardness and brown of biscuits, while reducing their volume^[81]. Apple polyphenols also influenced on the process and quality of three-dimensional (3D) printed foods^[82]. Comparative analyses of the moulding effect and dimensional characteristics of the final prints showed that apple polyphenols can be used as antioxidant additives, and the addition of them can effectively improve the antioxidant and structural stability of 3D printed processed cheese.

Weight loss and antibacterial hygiene are potential research and promotion directions for apple polyphenols in food. Studies have found that diluted apple polyphenols inhibit bad breath-related bacteria by damaging cell membranes^[83], and apple polyphenol extracts improve weight gain caused by high-carbohydrate diets by regulating gut microbiota and appetite^[84]. Apple polyphenols in cloudy apple juice prevent obesity by regulating gut microbiota and protecting gut health^[85]. Li found that apple polyphenol extracts alleviated lipid accumulation in HepG2 cells exposed to free fatty acids by activating SIRT1 / AMPK signaling-mediated autophagy^[86]. As people's diet management becomes more and more refined, apple polyphenols will have more and more room for development in functional foods.

4 Conclusion

Apple polyphenols, as important constituents in apples, because of their unique structural features and mechanism of action, they exhibit powerful antioxidant activity. In the field of food storage and preservation, the antioxidant and antibacterial properties of apple polyphenols play a great role. The higher the concentration in a certain range, the better the protective effect. Adding apple polyphenols to functional foods can improve the physical stability of foods, increase nutritional value, and regulate and improve taste and flavor. With the continuous improvement of apple polyphenol extraction technology and the in-depth study of antioxidant mechanism, apple polyphenol has gradually entered people's daily life, which has played a huge role in

promoting the research and innovative development of natural functional foods. Apple polyphenols will better contribute to people's health and quality of life.

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