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Research progress of natural antioxidants in foods for the treatment of diseases

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Abstract

A large amount of free radicals can be generated in human body during metabolic process. These free radicals can result in oxidative stress and homeostasis imbalance, even some chronic diseases and cancers if they are not promptly removed. Currently, many studies devote to exploring and utilizing natural antioxidants to remove excessive free radicals in human body, thus realizing the prevention and treatment of diseases. In the present study, the major species of natural antioxidants in foods that are benefit for the prevention and treatments of diseases have been summarized. Meanwhile, the research progress and future development have also been proposed. All of these studies, on the one hand, can provide a theoretical basis for the development of drugs and healthy foods; on the other hand, can offer novel development ideas for food industry, especially for food additive industry.

Keywords: Free radical; Oxidative stress; Functional food; Natural antioxidant

During metabolic process and contact process with external environment, a large amount of free radicals are produced in human body and attack biological macromolecules such as proteins, fatty acids and nucleic acids, correspondingly causing oxidative damage on cells or tissues or even resulting in gene mutation. Free radicals at high concentration level in human body can cause oxidative stress, thus destroying internal redox balance and causing a variety of chronic diseases, even premature senility [1]. Current researches have confirmed that many diseases including cancers, arteriosclerosis, diabetes, cataract, cardiovascular diseases, Parkinson's disease, Alzheimer's disease and arthritis, are highly correlated with free radicals and cellular redox imbalance [2]. Therefore, free radicals have become the culprit for influencing human health. In order to scavenge superfluous free radicals and maintain the balance of homeostasis in human body as well as accomplish the prevention and treatment of diseases, the consumption of antioxidants is necessary. However, synthetic antioxidants have toxic effects to some extents. Therefore, the uptake of natural antioxidants from foods is the first choice because natural antioxidants not only play an important role in the prevention and adjunctive treatment of diseases but also can avoid the adverse reactions to human health. In this article, common natural antioxidants such as vitamins (vitamin A, C and E), carotenoids (β-carotene, lycopene and astaxanthin), polyphenols (tea polyphenols and red wine polyphenols), and flavonoids (flavonoids, isoflavone, xanthones and anthocyanins) in foods are summarized. Meanwhile, the antioxidant mechanisms and research progress of these bioactive components from Chinese herbs in the prevention and treatment of diseases are reviewed, as shown in Table 1, which will provide a novel strategy for the development of pharmaceutical, healthcare and food industries.

1. Vitamins (vitamins C and E)

Vitamins are essential trace substances to maintain normal physiological function of human body. The majority of vitamins cannot be synthesized by human body and only can be uptaken from foods. Vitamin C and vitamin E are the most well known antioxidants and extensively studied. Vitamin C (ascorbic acid) is mainly found in fresh vegetables and fruits. The antioxidant effect of vitamin C is reflected by its reducing capacity, meaning that it can be directly and rapidly reacted with superoxide ion O_2^- and singlet oxygen such

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Table 1
Natural antioxidants in foods and their roles in prevention and treatment of diseases.

Natural antioxidants	Target diseases	Foods rich in natural antioxidants
Vitamin C	Cardiovascular disease, cancer, and cirrhosis [3–5]	Fresh fruits and vegetables
Vitamin E	Lung, skin and prostate cancers [6,7]	Nuts, green fruits and vegetables
Carotene	Eye diseases caused by diabetes [8]	Dark green or red and yellow fruits and vegetables
Lycopene	Parkinson's and Alzheimer's diseases [9,10]	Tomatoes
Astaxanthin	Aging, Alzheimer's disease and inflammation [11–13]	Shrimp shell, oysters and salmons
Cocoa polyphenol	Arteriosclerosis, coronary heart disease, and alcoholic liver [14,15]	Cocoa bean
Green tea polyphenols	Aging, Alzheimer's disease, diabetes, cardiovascular diseases, tumors and inflammation [16–20]	Green tea
Red wine polyphenols	Diabetes, cardiovascular diseases [21,22]	Red wine, grape seeds
Peach polyphenols	Breast cancer [23]	Peaches
Flavonoids	Cardiovascular disease, arthritis, Alzheimer's disease, stroke [24–27]	Plants, berries, honey
Isoflavonoids	Prostate, ovarian, cervical and breast cancers [28–31]	Soybean
Anthocyanins	Cardiovascular disease, neurodegenerative diseases, liver cancer [32–34]	Black rice, purple sweet potato, blueberry, mulberry and other dark foods
Xanthones	Inflammation, nerve injury [35,36]	Mangosteen
Components from Chinese herbs	Inflammation, cancer, Alzheimer's disease, diabetes, cardiovascular disease [25,37–40]	Chinese herbs

as HOO^- or OH^- through dehydrogenation, and generate dehydroascorbate. As hydrogen donor, it can also play an indirect antioxidant effect through the reduction of oxidized vitamin E and thiol. The chemical equation of reaction can be expressed as: $RO^\bullet + C_6H_7O_6^- \rightarrow RO^- + C_6H_7O_6^\bullet \rightarrow ROH + C_6H_6O_6$. As a water-soluble vitamin, vitamin C plays its antioxidant role through circulation flow in blood, body fluid and cells, thus protecting cells and tissues from free radicals [41]. In recent years, a large number of basic and clinical studies have discovered that vitamin C has the protective role in a series of diseases caused by oxidative stress, such as cardiovascular disease, cancer and cirrhosis. Vitamin C can act as the superoxide scavenger in primary hypertension to eliminate the symptoms of patients [3]. By providing continuous medication of vitamin C at the dosage of 500 mg to cardiovascular patients for 10 weeks, the content of low-density lipoprotein (LDL) in blood is obviously reduced. LDL is the major component causing oxidative damage to blood vessel, suggesting that vitamin C can execute a treatment effect on cardiovascular disease [4].

Vitamin E is a kind of fat-soluble vitamin, also known as tocopherol including α-tocopherol, β-tocopherol, γ-tocopherol and δ-tocopherol. Vitamin E has a very extensive function of protecting biological membrane in human body and nucleic acids in cells from the attacking of free radicals [41]. Vitamin E can directly remove O_2^-, quench singlet oxygen and superoxide dismutase (SOD) and establish an antioxidant system in human body together with glutathione peroxidase (GSH-Px). Through the reaction with lipid oxygen radicals and lipid peroxyl free radicals, vitamin E plays its antioxidant activity by providing the protons to interrupt lipid peroxidation chain reaction (as shown in Fig. 1). Vitamin E is rich in nuts such as almonds, walnuts, vegetable oil, kiwi fruits and green vegetables. Vitamin E is found to have suppressive function to tumors. Sundaram has conducted high performance liquid chromatographic analysis for the samples from 5,000 women and reported that the content of vitamin E in women with breast cancer is significantly lower than that in the normal group (4.7 mg/L *vs.* 6.0 mg/L), suggesting that vitamin E can reduce the risk of breast cancer [6]. In the experiments using mouse lung cancer model induced by human lung cancer cell A549, the intraperitoneally injected vitamin E derivative, vitamin E succinate (VES) (150 mg/kg) can significantly inhibit the tumor growth of the mice [7].

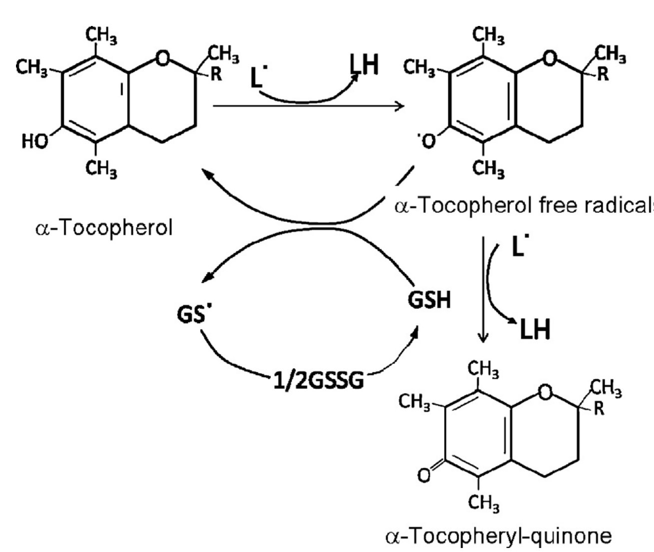

Fig. 1. Principle of scavenging lipid oxygen free radicals by α-tocopherol. L represents lipid oxygen free radicals.

The latest studies have found that vitamin C and vitamin E have synergistic antioxidant effect. Betancor et al. [42] have reported that the combinatorial application of vitamin C and vitamin E can synergistically increase mRNA expression level of catalase (CAT), SOD and GSH-Px in Largemouth Bass juvenile; in contrast, can reduce oxidative stress indicators such as TBARS. During the administration of vitamin C, or vitamin E or combinatorial administration of vitamin C and vitamin E for the mice with liver fibrosis, the mitigation of liver fibrosis in mice was only observed in the combinatorial administration group with vitamin C and vitamin E, which indicates that vitamin C and vitamin E has the synergistic antioxidant effect for the treatment of diseases [43]. The redox status in human body is a dynamic balance and excessive antioxidants are not necessary. The daily administration of 1,400 mg of vitamin C and 800 mg of vitamin E for 180 consecutive days was used for the treatment of sickle cell anemia patients. The combinatorial application of both vitamins did not result in the symptom removal of sickle cell anemia patients; on the other hand, an obvious increase of hemolysis index was observed. However, the corresponding mechanisms are still not clear [44].

2. Carotenoids (β-carotene, lycopene and astaxanthin)

Carotenoid is a fat-soluble natural pigment in dark green or red and yellow fruits and vegetables, and is a general definition of polyunsaturated hydrocarbons containing 40 carbon atoms. Carotenoids contain many double bonds. They can quench singlet oxygen in a physical way and can also react with oxygen free radicals in three ways such as electron transfer, hydrogen atom transfer and radical coupling. The reaction equations are $ROO^{\bullet} + Car \rightarrow ROO^{-} + Car^{\bullet +}$; $ROO^{\bullet} + Car \rightarrow ROOH + Car^{\bullet}$; and $ROO^{\bullet} + Car \rightarrow (ROO)Car^{\bullet}$, respectively. The most common carotenoids are β-carotene, γ-carotene and lycopene in plants, and astaxanthin in animals.

Previous studies have confirmed that carotenoid antioxidants have protective functions for diabetes, and neurodegenerative, cardiovascular and inflammatory diseases. Oxidative stress and inflammation caused by free radicals are important factors for diabetes with the complication of eye problems. Kowluru et al. [8] have discovered that the combinatorial application of carotenoid antioxidants can reduce the apoptosis of capillary cells, decrease the damage of retinal mitochondria, down-regulate the expression of VEGF and inflammatory factors in patients with diabetes, thus slowing down the process of eye diseases in patients with diabetes. Studies show that lycopene can effectively protect the damage of neurons; administration of lycopene for rotenone-induced mouse model with Parkinson's disease could result in the significant increase in the number of dopaminergic neurons and reduced activity of oxidative stress indicators such as MDA, SOD, GSH-Px and CAT, indicating that the damage level of oxidative stress is mitigated due to the application of lycopene [9]. Alzheimer's disease is another neurodegenerative disease that is closely correlated with oxidative stress and can seriously affect the health and the life quality of patients. A research based on the nutrition and health survey and corresponding analysis of 6,958 elderly people with the age over 50 years old showed that there is a significantly negative correlation between the levels of lycopene and lutein in serum and the risk of Alzheimer's disease, which indicates that the increased dietary intake of foods rich in lycopene and lutein can reduce the risk of Alzheimer's disease [10].

Astaxanthin is reported to have anti-aging and anti-inflammatory activities by many studies. In the aging model mice induced by D-galactose, astaxanthin treatment can recover the activities of GSH-Px and SOD, enhance GSH content and reduce oxidative stress, improve pathological injury of hippocampus, and increase the expression level of BNDF, thus achieving the anti-aging role finally [11] *in vitro* studies have found that astaxanthin treatment can also reduce the activity of ROS and the expression of SP1 in PC12 cells induced by $NR1MPP^{+}$ toxin. Similarly, the expression of SP1 and NR1 under oxidative stress conditions can lead to the death of neuronal cells. Both results suggest that astaxanthin may have protective roles in patients with Parkinson's disease and delay the progress of Parkinson's disease [12]. Previous studies have also demonstrated that astaxanthin not only has the function of oxidation resistance, but also plays an important role in anti-inflammation. Santos et al. [13] have treated rat macrophages with synthetic astaxanthin and shrimp extract and found that astaxanthin can significantly inhibit the generation of superoxide anion free radicals such as O_2^{-} and NO, and also can inhibit the secretion of pro-inflammatory cytokines such as TNF-α. All of these studies prove the antioxidant and anti-inflammatory activity of astaxanthin.

Taken together, these studies illustrate that carotenoid antioxidants play important roles in delaying the pathological process and mitigating the symptoms of many diseases by fighting against free radicals and oxidative stress.

3. Polyphenols (tea polyphenols, red wine polyphenols and chocolate polyphenols)

Polyphenols are natural organic compounds rich in fruits and vegetables, tea, red wine, honey and cocoa beans. Polyphenols with multiple hydroxyl groups can effectively remove free radicals including O_2^{-} and singlet oxygen to execute healthcare functions. Similarly, according to the previous studies, cocoa polyphenols can significantly decrease the level of oxidative stress in alcoholic fatty liver. The model mice with alcoholic fatty liver subjected to the treatment of cocoa polyphenols can reveal a significantly decreased level of PLOOH as the oxidative stress indicator of phospholipid hydroperoxide in animal liver, suggesting that cocoa polyphenols have obvious protective effect on liver [14]. In addition, cocoa polyphenols also have an inhibitory effect on the oxidation of low-density lipoprotein, thus preventing arteriosclerosis, coronary heart disease and myocardial infarction. After the administration of model rabbits with high cholesterol with cocoa polyphenols for a month, the content of LDL in blood was significantly reduced. The damaged area of arteriosclerosis in mice subjected to the treatment of cocoa polyphenols was significantly smaller than that in the control group. The contents of cholesterol and TBARS, and the oxidative stress in tissues were significantly lower than those in the control group [15].

Moreover, green tea polyphenols have obvious protective effect on neurodegenerative diseases such as Alzheimer's disease. In the pathogenesis of AD, Aβ aggregation can lead to the generation of a large amount of free radicals such as active oxygen species and active nitrogen species, correspondingly resulting in oxidative stress and accelerating neuronal death. (−)-Epigallocatechin-3-gallate (EGCG) as the effective component in green tea polyphenols was reported to significantly reduce the Aβ deposition in transgenic mice with the over-expression of Aβ and increase the activity of α-secretase, suggesting that green tea polyphenols have an important role in decreasing oxidative stress in the brain of AD patients [16]. Another study on model mice with high-fat and high-sugar diet for 4 weeks and green tea polyphenol solution instead of drinking water revealed that green tea polyphenols can result in the significant reduction in the permeability of large artery and ROS levels as well as protein expression level of NAD(P)H oxidase subunit $p22^{phox}$ and $p67^{phox}$ in high-fat and high-sugar diet-induced model mice. As NAD(P)H oxidase is an important source of ROS *in vivo*, the antioxidant effect of green tea polyphenols *in vivo* may implement through inhibiting the expression of NAD(P)H oxidase [19]. Baba et al. [18] have also found that the contents of derivatives from ROS metabolites in patients with hepatocellular carcinoma reveal a significant decrease when provided with green tea tablets during the chemotherapy treatment. In addition, the free radical analysis system 4 (FRAS4) has shown that the potential of biological antioxidant is greatly improved. Moreover, green tea polyphenols also have an important function in inhibiting tumor and inflammation [17,20,45].

Grape seeds and red wine also contain a large amount of polyphenols. French scientists have confirmed that grape polyphenols can inhibit the oxidative stress and insulin resistance induced by fructose in type II diabetic patients at the first phase. In their experiments, 18 male and 20 female patients were randomly divided into two groups and treated with grape polyphenols and placebo. The results showed that the reduced negative effects such as insulin resistance and oxidative stress induced by fructose were observed due to the treatment of grape polyphenols [21]. Grape seed polyphenol can also inhibit the apoptosis of vascular cells through inhibiting ROS produced by xanthine oxidase [22]. Polyphenols in peach fruits was found to have an obvious inhibitory effect on the cell growth and metastasis of breast cancer. In addition, human breast cancer cells were transplanted into the model mice, and the model mice were subjected to the treatment of 0.8-1.6 mg peach polyphenol each day. The results showed that the expression of metalloproteinases (MMPs) such as MMP1, MMP2 and MMP13 associated with the cell growth and metastasis of tumors was significantly inhibited, and the tumor volume of the model mice in the treatment group was significantly reduced, suggesting that peach polyphenols can be used as a combinatorial treatment method of chemotherapy to inhibit tumor development at the early stage of tumor [23]. British scientists have found that polyphenols can reduce oxidative stress for maintaining the health status of cardiovascular system recently. In their experiment, 66 health adults with the consumption of fruits and vegetables less than 2 portions a day were divided into 3 groups and were provided with placebo (water), low concentration of black currant juice (rich in polyphenols and vitamin C), and high concentration of black currant juice for 6 successive weeks, respectively. The results demonstrated that the content of oxidative stress indicator F2-isoprostane in black currant juice group was lower than that in the placebo group, and that the health index of cardiovascular system for the regulation and relaxation capacity of blood flow was significantly higher than that in the placebo group [24].

The above studies fully illustrate the roles of polyphenol antioxidants in the protection and adjuvant therapy of common diseases. However, as the research development, more polyphenols and their functions have been discovered, which will provide a new choice for the treatment of the diseases and the development of healthcare foods.

4. Flavonoids (flavonoids, isoflavones, xanthones and anthocyanins)

It is well known that plants have many kinds of flavonoids, and flavonoids play important roles in the growth and disease prevention of plants. Common flavonoids compounds include flavones, isoflavones, anthocyanins and xanthonoids. Flavonoids execute the clearance of free radicals by transforming them into phenolic radicals (inert) after supplying the hydrogen to lipid compounds radicals. Prostate cancer is the first malignant disease with serious influence on the health of men in Europe. Many investigations have demonstrated that soybean has high content of isoflavones and the Asians have higher consumption of soybean from diets than the Europeans and Americans. Moreover, the content of isoflavones in serum of Japanese was detected to be 10–100 times higher than that in Europeans. Therefore, the incidence of prostate cancer in Asia is much lower than that in Europe and USA, suggesting that isoflavone has a preventive effect on prostate cancer [28].

The flavonoids extracted from some plants have an excellent antioxidant function for the protection of vascular system and the treatment of arthritis and Alzheimer's disease. For example, quercetin can significantly reduce the level of oxidative stress index F2-isoprostane in athletes. In arthritis model mice treated through oral administration of *Daphne genkwa* flavonoids extract at the dose of 50 mg/kg for 15 consecutive days, the arthritis score (ACS) was decreased while the expression of SOD and GSH-Px enzymes was increased when compared with the control group [26,27,46]. Studies have found that catechin procyanidin in *Ginkgo biloba* extract can inhibit the aggregation of Aβ and disaggregate the formed fiber, suggesting their roles in the treatment of Alzheimer's diseases and other neurodegenerative diseases [47]. A study on 32 elderly people treated with fresh *G. biloba* extract revealed the improved microcirculation of skin and liver, accelerated scavenging of free radicals and the improvement of arteriosclerosis. 30 days after 270 mg *G. biloba* extract or placebo treatment, the red cell perfusion nodes and blood flow of small veins, and red blood cell volume revealed an obvious higher in the *G. biloba* extract treatment group when compared with the control group. Moreover, a significantly higher level of GSH as a radical scavenger in the *G. biloba* extract treatment group than that of the control group was also observed. Therefore, *G. biloba* has a beneficial effect on the health of the elderly population [29].

Isoflavones are flavonoids in soybean with anti-cancer function. Isoflavones can prevent ovarian, cervical and breast cancers. A previous pathological study revealed that the intake of soybean foods at the amount of 75.3 ± 53.6 g/d in patients with ovarian cancer was significantly lower than that from the control group (110.7 + 88.8 g/d). Logistic regression analysis indicated that the consumption of soybean diets can significantly reduce the incidence of ovarian cancer [30,31].

Anthocyanins are natural water-soluble pigments widely existing in plants, and with strong antioxidant activity. Foods with dark color such as purple sweet potato, black rice, blueberry, grape, mulberry and so on have plentiful anthocyanins. Based on the current studies, anthocyanins have an important function in the prevention and treatment of cardiovascular diseases, neurodegenerative diseases and cancer [32,48]. The rats subjected to the long-term (7 weeks) or short-term (2 weeks) administration of the diet rich in blueberry fruits revealed the significantly reduced damage from light-induced retinal injury, indicating the protective role of anthocyanins in neural cells [33]. Blackcurrant richs in anthocyanins is a common drug for the treatment of Asian and European diseases. A new finding has demonstrated that cyanidin-3-*O*-rutinoside as one of the bioactive components in blackcurrant extract can significantly inhibit the growth of liver cancer HepG2 cells [34].

Xanthone compounds are natural antioxidants rich in mangosteen. Xanthones have effects on neuroprotection, anti-inflammation, anti-oxidative stress and anti-DNA damage. It was reported that the mangosteen extract can execute the protective function on DNA damage through scavenging $^{\bullet}$OH and DPPH$^{\bullet}$ free radicals [35,36]. At present, a variety of flavonoids extracts from plants have been applied for the development of drug and healthcare products.

5. Bioactive components in Chinese herbs

Chinese herbs are the plentiful heritages from our ancients. Recent studies have also found that many bioactive components in Chinese herbs can execute strong antioxidant effects. Scholars from Taiwan have screened and identified 195 kinds of Chinese herbs with excellent antioxidant activities, which accounts for half of the currently used Chinese herbs. Flavonoids from *Panax notoginseng* have strong antioxidant and antibacterial activity [49]. *Salvia miltiorrhiza* also contains a lot of bioactive components with antioxidant and anti-inflammatory functions. Guo et al. [37] reported that tanshinol plays a protective role in apoptosis induced by γ-ray through reducing the generation of ROS, inhibiting the release of cytochrome C and blocking the activation of apoptotic factors. The pretreatment of tanshinol on L-02 cells can significantly reduce the level of ROS caused by γ-ray and the activity of Caspase 3 as well as the expression of Bax. Tanshinone IIA can weaken neuronal damage induced by hydrogen peroxide [38]. Flavonoids in *Glycyrrhiza* such as licorice chalcone and licorice isoflavones also have strong antioxidant activity, which plays an important role in the clearance of free radicals and prevention of diseases [25,50]. The traditional prescription "Siwu Decoction" can prevent oxidative damage, and execute anti-cancer function through NRF2 signal pathway [51]. Kozics et al. [39] found that the extracts of sage and thyme can significantly reduce DNA damage caused by oxidative stress form H_2O_2 and 2,3-bimethoxyl-1,4-naphthoquinone in hepatoma cells and the levels of oxidative stress markers such as DPPH, FRAP and ABTS. Another prescription "Suhexiang pill" can reduce Aβ deposition in model mice with Alzheimer's disease, enhance memory and inhibit the apoptosis caused by Aβ and decrease oxidative stress in brain, suggesting its effect on the treatment of Alzheimer's disease [40].

In recent years, the treatment efficacy of natural herbs has gained increasing attention, and therefore they have been applied for the prevention and treatment of cancers, diabetes, cardiovascular diseases and other diseases. Meanwhile, more and more studies on their bioactive components have been conducted. Thus, it will have great and practical significance for the exploitation and utilization of natural antioxidant components in Chinese herbs.

6. Conclusion

Antioxidants play an important role in scavenging free radicals and maintaining body balance. Here, we discussed the contribution of natural antioxidants in diseases prevention and treatment. In modern life in which nature is advocated, the application of synthetic drugs for the healthcare and prevention of diseases apparently is not an optimum choice. Searching natural antioxidants to replace synthetic antioxidants is not only the trend of pharmaceutical and healthcare industries, but also the demand of Food Nutriology, even the new development direction of food industry. Traditional Chinese herbs have attracted more and more attention from scholars at home and abroad, especially, the treatment efficacy of diseases and healthcare functions as well as the bioactive components of these natural herbs. More and more bioactive components have been isolated and identified, which enables traditional Chinese medicine to be an important development direction of modern medicine and healthcare products. In addition, some scholars have isolated bioactive substances with strong antioxidant function from fungi, yeast and algae. Natural antioxidants can be used as natural food additives with the new concept of natural healthcare concepts in food processing and preservation, which will better meet with the demands of modern society. The extraction and preservation process of natural antioxidants is the development target for the future food and medical healthcare industries. The innovation and improvement in analysis and extraction technology of natural antioxidants in foods is also an urgent matter during the development of related industries.

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