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Research progress on antioxidant activity of natural products

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Abstract: Natural or synthesized antioxidants are compounds that can inhibit or delay the onset oxidation. Due to the wide availability of natural antioxidants and the increasing concerns on the safety of synthetic antioxidants, the beneficial effects of natural antioxidants on the maintenance of human health have become an important topic among scientific researches worldwide. Research showed that multiple natural products including polyphenols, flavonoids, vitamins, carotenoids, polysaccharides, alkaloids and saponins could scavenge excessive free radicals in cells effectively. Searching for new antioxidants from natural products has be-come an inevitable trend for the modern food and medicine industries. In this paper, we chose seven natural products and discussed their properties and functions. The aim of this review is to conclude the progress of natural antioxidants research and provide a theoretical basis for the development of healthy food and drugs.

Key words: Antioxidants; free radicals; natural products.

Introduction

Antioxidants are important in terms of their ability to protect cells against oxidative damage that can lead to me-dical conditions such as Alzheimer's disease, cancer, heart disease and chronic inflammation (1). A large amount of oxygen free radicals can be generated in human body through metabolic process, such as DPPH•, O2−•, •OH, 1O2 and so on. Few oxygen free radicals have no bad effect on human health. Moreover, moderate amounts of oxygen free radicals play an indispensable role in strengthening the immune system, eliminating inflammation and inhibi-ting tumor growth. However, excessive free radicals will attack biological macromolecules, such as proteins, fatty acids and DNA, in human body, damage cell structure, in-terfere with normal metabolism in human body, hastening the aging process and even cause disease (2). Antioxidants (e.g., flavonoids, phenolic acids, tannins, vitamin C, vita-min E) have diverse biological properties such as anti-in-flammatory, anti-carcinogenic and anti-atherosclerotic activities (3). The effects of antioxidants also include re-ducing the incidence rate of coronary diseases and contri-buting to the maintenance of gut health by the modulation of the gut microbial balance.

In the last few years, antioxidants have become the indispensable supplements in the nutritional world. It is defined as the substances which at low concentration can significantly inhibit or delay the oxidative process (4,5). In addition, synthetic antioxidants always have the un-derlying defects. For example, animal experiments have shown that butylated hydroxyl anisole (BHA) is car-cinogenic (6). In order to scavenge superfluous free ra-dicals, to maintain the balance of homeostasis in human body, and to accomplish the prevention and treatment of diseases, constant intake of antioxidants is necessary. The following sections will summarize the main natural antioxidants such as polyphenols, flavonoids, vitamins, ca-rotenoids, polysaccharides, alkaloids, and saponins.

Polyphenols

In recent years, lots of attentions were paid to the stu-dy of polyphenols and their derivatives, mainly because of their availability and strong antioxidant activity. Plant polyphenols are a series of complicated secondary meta-bolites abundantly existing in the skin, roots, leaves and fruits of plants as well as vegetables, tea, red wine, honey and cocoa beans.

Polyphenols with multiple hydroxyl groups has been found with functions of removing free radicals effectively including O2− and reactive oxygen. Previous studies in-dicated that many natural phenolic compounds have an-tioxidant activity. The embryos of the grains have higher anti-oxidative activity than tocopherol. Tocopherol have eight different structural configurations including α-to-copherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-To-cotrienol, β-Tocotrienol , γ-Tocotrienol and δ-Tocotrienol. Among these substances, α-tocopherol has the strongest activity while other tocopherols only have 50% activity of α-tocopherol. Grape polyphenols (OPC) extracted from red grape seed has antioxidant activity 20 times higher than vitamin C and 50 times higher than Vitamin E (7). Previous study have also shown that labiatae plants rose-mary and sage have stronger anti-oxidation ability than 2,6-Di-tert-butyl-4-methylphenol(BHT) and BHA (8). Moreover, polyphenols in fenugreek seed (FPET) can sca-venge O2- and H2O2, increase antioxidant activity of liver cells, and protecting liver cells from oxidant damage (9).

Previous studies have shown that cocoa polyphenols can significantly decrease the oxidative stress in alcoholic fatty liver disease (AFLD). The mouse model with AFLD showed a significantly decrease of phospholipid hydrope-

roxide (PLOOH) after being treated with cocoa polyphe-nols, which indicate that the phospholipid hydroperoxide oxidative stress is largely resolved in animal liver. Ob-viously, cocoa polyphenols have protective effect on liver (10). Moreover, green tea polyphenols have an inhibitory effect on a vast array of diseases, including neurological disease (Alzheimer's, Parkinson's), viral and bacterial in-fections (hepatitis and herpes virus) and skin disorders. It can control sugar levels in diabetic patients and depres-sion as well. Green tea polyphenols also have an impor-tant function in inhibiting tumor and inflammation. Tang et al (11) found the high affinity of tea catechins for the li-pid bilayers of muscle and the radical scavenging abilities of tea catechins may be possible mechanisms to explain the oxidative stability in cooked muscle foods. Grape seeds and red wine contain a large amount of polyphenols (12). French scientists have confirmed that grape polyphe-nols can reduce the oxidative stress and insulin resistance induced by fructose at the first phase of diabetics. Grape seed polyphenol can also inhibit the apoptosis of vascular cells through inhibiting ROS produced by xanthine oxi-dase (13).

Plant polyphenol compounds have strong antioxi-dant activity because they can scavenge oxygen free ra-dicals. Most of polyphenols play a role by capturing free radicals or chelating metal ions. The above studies illus-trate the roles of polyphenol antioxidants in prevention of common diseases. As research developed, majority of polyphenols and their functions have been discovered, which will provide a new option for the development of healthcare food and medicines.

Flavonoids

Many types of flavonoids have high antioxidant acti-vity, such as quercetin, silymarin and baicalin. Common flavonoids compounds include flavones, isoflavones, an-thocyanins and xanthonoids. Flavonoid can clear free ra-dicals by transforming them into phenolic radicals after supplying the hydrogen to lipid compounds radicals (14).

The flavonoids extracted from purple grape skins, hawthorn, spinach, sweet potato leaf, eggplant skin and black buckwheat bran have strong ability to eliminate free radicals (15). Xu et al. detected the activity of isoflavones by Pyrogallol method and Fenton method (16). The results have shown that isoflavones have strong antioxidant ac-tivity. Tea polyphenol extracted from tea, pycnogenol in pinus pinaste, anthocyanin in grape seeds and apple as well as genistein and daidzein in soybean all belong to flavonoids. Flavonoids show high synergistic effects when exist with vitamin C or vitamin E (17). Isoflavones with significant anti-cancer function mainly were found in soy-bean. Isoflavones can also prevent ovarian, cervical and breast cancers (18,19). The natural water-soluble pigment anthocyanins, found widely in plants, showed strong an-tioxidant activity (20). Food with dark color such as purple sweet potato, black rice, blue-berry, grape, and mulberry contain plenty anthocyanins. Based on the current studies, anthocyanins play an important role in prevention and treatment of cardiovascular diseases, neurodegenerative diseases and cancer (21,22). Researches also show that the total flavones in cirsium japonicum DC and loquat leaf flavonoids have antioxidant activity.

The antioxidant activity of Flavonoid compounds mainly which depends on the relative position of hydroxyl group. Chromone structure enhances the anti-oxidative activity of flavonoids through unsaturated double bonds (2,3-flavonoid). Electron-withdrawing property of carbon ring decreases the antioxidant activity of natural flavo-noids. Being complexed with metal ions is another way to prevent free radical oxidation (23,24). At present, various flavonoids extracts from plants have been applied for the development of drugs and healthcare products.

Vitamins

Vitamins are not only indispensable food nutrients but also the most important antioxidants for humans. Vitamin C and vitamin E are two well known and deeply studied antioxidants.

Vitamin E

Vitamin E refers to a group of chemical compounds (tocopherols and tocotrienols) that mainly exist in cells mitochondrial membrane and endoplasmic reticulum. Vi-tamin E is rich in nuts, vegetable oil, kiwi fruits and green vegetables. Vitamin E is formed by four tocopherols and four tocotrienols, which exhibit chain-breaking antioxi-dant activity. Vitamin E has extensive capability to protect biological membrane and nucleic acids in cells from being attacked by free radicals. α-tocopherol has maximum bio-logical activity. Based on α-tocopherol, the biological ac-tivity of β-tocopherol, γ-tocopherol, δ-tocopherol are 40%, 8%, 20% (25).

Vitamin E is generally accepted as the primary lipid-so-luble antioxidant and acts as an antioxidant via two prima-ry mechanisms. The first is a chain-breaking electron do-nor (CBD) mechanism and the second is a chain-breaking acceptor (CB-A) mechanism. Vitamin E directly acts on the human cell membrane and has super strong antioxi-dant activity. It can capture oxygen-free radicals exclu-sively, protect the lipid on cell membrane from being oxi-dized, keep bad cholesterol from sticking on blood vessels and keep the blood clear (26).

Vitamin C

Vitamin C is a type of acidic polyol including six car-bon atoms and α-keto mycolactone. Vitamin C (ascorbic acid) is mainly found in fresh vegetables and fruits. The antioxidant capability of vitamin C is reflected by its re-ducing capacity, which means it can directly and rapidly react with superoxide ion $O2^-$ and singlet oxygen through dehydrogenation and generate dehydroascorbate (27). Vi-tamin C is mainly absorbed in jejunum. Its concentration in healthy human's blood is 48.3-79.5 μmol/L (28). The function of Vitamin C will be largely improved when com-bined with some specific compounds. Liu et al (29) pre-pare a complex by chitosan and Vitamin C and found that the stability of this complex is higher than Vitamin C. Its ability to eliminate hydroxyl radical is stronger than chi-tosan. In recent years, a large number of basic and clinical studies have discovered that vitamin C play an important role in a series of diseases caused by oxidative stress, such as cardiovascular disease and cancer.

Carotenoid

Carotenoid is widespread in natural world, with ele-ven double bonds of isoprenoid structure. β-carotene is

a typical example of carotenoid. Carotenoid is a general definition of polyunsaturated hydrocarbons containing 40 carbon atoms. Carotenoid is a fat-soluble natural pig-ment in dark green, red and yellow fruits and vegetable. Studies have confirmed that lycopene, astaxanthin, lutein and zeaxanthin also have significant antioxidant activi-ties. They can quench singlet oxygen in a physical way and react with oxygen free radicals in three ways inclu-ding electron transfer, hydrogen atom transfer and radical coupling. The most common carotenoids are α-carotene, β-carotene and lycopene in plants and astaxanthin in ani-mals.

β-carotene is a precursor of vitamin A, which is made up of four isoprene double bonds end to end. There is a β-isomethyl ionone rings on both sides of the molecule, mainly four types including all-trans, 9-cis, 13-cis and 15-cis and all of them have great antioxidant activity. Re-search show that lycopene can effectively protect neurons from damage. Administration of lycopene for rotenone-in-duced mouse model with Parkinson's disease could result in the significant increase in the amount of dopaminergic neurons and reduced activity of oxidative stress indicators such as MDA, SOD, GSH-Px and CAT. This indicates that the damage level of oxidative stress is mitigated due to the application of lycopene (30,31). Previous studies have also demonstrated that astaxanthin not only has the func-tion of oxidation resistance but also plays an important role in anti-inflammation.

These studies illustrated that carotenoid antioxidants have a good influence on many diseases by fighting against free radicals and oxidative stress.

Polysaccharides

Polysaccharides are made up of more than 10 glycosyls linked by glucosidic bond, including homopolysaccharide and heteropolysaccharide. As the most abundant prima-ry metabolites, polysaccharides have special biological activity in many aspects such as heart vascular disease, anti-tumor, anti-oxidation, anti-aging, treatment hepatitis and relatively low cytotoxicity.

Polysaccharides can not only enhance immune func-tion but also increase antioxidant capacity and free radical scavenging activities. Studies have found that the poly-saccharides extracted from traditional Chinese medicine ginseng, astragalus membranaceus, twotooth achyranthes root, dwarf lilyturf, and rhubarb show good antioxidant activity. The active polysaccharides extracted from tea, ginkgo leaf, bamboo leaf have certain anti-tumor activity and the polysaccharides extracted from mushrooms, gano-derma lucidum, grifola, black fungus and fungus fruiting body have anti-cancer effects (32,33). The Sulfated fucan extracted from kelp can regulate immune system and has anti-oxidation effect. When hyperlipidemia concentra-tion increased in rats, the level of lactate dehydrogenase in serum increased significantly and the activity of SOD in serum and tissue decreased. LMSF can inhibit these changes and make the index return back to nearly nor-mal level (4). Liang et al (34) have studied that water-so-luble polysaccharides in atractylodes, which can be divi-ded into two groups: F1(Galactose, rhamnose, arabinose, mannose), F2 (xylose, galactose and arabinose). The results showed that both of the two groups have strong antioxidant activity. Moreover, F2 has stronger antioxi-dant activity. Previous studies have confirmed that balsam pear polysaccharide, the kiwi polysaccharide, ganoderma lucidum Polysaccharide, Chinese wolfberry polysaccha-rides, ginseng stem leaf polysaccharide, fucoidin, seabuc-kthorn tea water-soluble polysaccharide, polysaccharide from Sargassum thunbergii Kuntze, Ginkgo biloba exo-carp polysaccharide and etc have antioxidant effect to some extent (6,35).

As a type of important biological active substance, polysaccharides can remove physical chemical and bio-logical sources of ROS, reduce the production of lipid pe-roxide MDA and increase the activity of SOD and GS-HPx. polysaccharides show a tempting prospect in an-tioxidant effect (36).

Alkaloids

Most alkaloids have complicated nitrogen ring struc-ture. Majority of alkaloids exist in higher plants, especially in dicotyledon, such as ranunculaceae, poppy, solanaceae, rutaceae, leguminous. Alkaloids exist in all parts of plant. A plant can have several kinds of alkaloids. Alkaloids can be used as reactive oxygen quencher transforming the 1O2 into 3O2 by colliding with reactive oxygen. Li Yang et al (37) found that alkaloids in lotus seed skin clearly have antioxidant activity *in vitro* and can well eliminate DPPH·, ·OH. Total alkaloids of Clivia Miniata (TACM) can in-crease the antioxidant activity of liver and kidney tissues and reduce their oxidative damage (38,39). Zheng et al (40) proved that rubus alkaloid parviaraliifolius (RAP) can prevent non-alcoholic fatty liver disease (NAFLD) of rat. Scavenging oxygen free radicals, reducing lipid peroxidation products, inhibiting the release of inflam-matory cytokines and reducing the inflammation might be its mechanism. In addition, ligustrazine, berberine, jateorhizine, magnoline, glaucine and anonaine also have antioxidant activities (40,41). Main structure factors to influence the antioxidant activity of alkaloids are stereo-chemical structure and electrical factors. Electron-dona-ting group or structural factors which can add electrons to nitrogen atoms can also enhance the antioxidant activities of alkaloids (42).

Saponins

Saponins are a series of active substance in herbs. Base on the chemical structural differences, saponins can be differentiated into steroid saponins and triterpenoid sapo-nins. Steroid saponins mainly exist in liliaceae and dios-coreaceae plants while triterpenoid saponins mainly exist in araliaceae and umbelliferae plants. Previous studies have shown that saponins in ginseng, American ginseng and panax notoginseng have significant antioxidant acti-vities (43).

Li et al (44) extracted and purified saponins from pha-seolus vulgaris by ethanol - ultrasonic method. They ex-plored the ability of phaseolus vulgaris saponins to elimi-nate DPPH free radical, hydroxyl radical and alkyl radi-cal. Results have shown that both of phaseolus vulgaris saponins and vitamin C have the ability to scavenge free radicals.

Conclusions

In recent years, with the development of advanced

chromatography and spectrum technology, people have gained a better understanding of the natural antioxidants (45,46). Antioxidants play an important role in scaven-ging free radicals and maintaining normal body metabo-lism. Searching natural antioxidants to replace synthetic antioxidants is not only the trend of pharmaceutical and healthcare applications, but also directs the development of food industry.

Previous studies have fully confirmed that natural an-tioxidants have the biological activities in protecting car-dio-cerebral-vascular system, scavenging free radicals and treating tumor diseases. With the summary of current studies, we have confirmed that antioxidants, with its re-ducing capacity, can exert antioxidant effect through in-hibiting the activity of enzymes related to the oxidation, reducing lipid oxidation and degradation, scavenging free radicals and chelating transition metals (47,48). However, antioxidant activities of natural antioxidants are relatively weak compared to synthetic ones. For example, flavo-noids have special chemical structure which affect their absorption *in vivo* and weaken its antioxidant activities. Further studies could be done by modifying structure at suitable position to increase its solubility, absorption and anti-oxidative activities *in vivo*. In another word, base on different antioxidant mechanism, targeted modifying or transforming the structures of anti-oxidant will be an important breakthrough in improving activities of natural antioxidants.

As a type of important active substances, natural pro-ducts can scavenge free radicals with high efficiency and low toxicity, prevent aging and treat medical conditions. With the further development of food industry, phamarco-logy and molecular biology studies (24), more biomedical applications of natural antioxidants, including polyphe-nols, flavonoids, vitamins, carotenoid, polysaccharides, alkaloids and saponins are expected.

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