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Chapter

Stress, Natural Antioxidants and Future Perspectives

Nilay Seyidoglu and Cenk Aydin

Abstract

Stress can exist by a variety of daily challenges related to obesity, other eating disorders, long-term health issues and immune system suppression. Free radicals derived from oxygen, called reactive oxygen species, reactive nitrogen species and similarly antioxidants are part of the body's natural functioning. Oxidative stress occurs when free radicals and antioxidants are out of balance. The prooxidant-antioxidant balance is assessed by determination of both oxidant and antioxidant status, which can be measured simultaneously in blood and tissue. Dietary or natural antioxidants play an important role in helping the endogenous antioxidants in scavenging the excess of free radicals. Antioxidant supplements include several important substances such as beta carotene, lutein, phycocyanin and zeaxanthin, which are rich in vegetables, fruits and natural foods. All these contents have a key role in growth, immunity and lifetime quality. Still, high dose of the natural foods can cause the organism, not to assimilate the wastes by the mechanism. In this chapter, we'll inquire to explain the oxidative and antioxidative mechanisms and balance via importance of the natural antioxidants to life quality. For this purpose, oxidative stress, related diseases, antioxidants and their importance will be reviewed, and the correlation between natural antioxidants and health will be presented.

Keywords: stress, oxidant-antioxidant balance, diet, natural antioxidants, health problems

1. Introduction

Stress is a complex phenomenon that correlates with oxidative and antioxidative status in organism. The physiological stress responses include several biological mechanisms such as digestion, reproduction, hormone and immunity. In common, physical or psychological stresses cause stress and disrupt homeostasis. Likewise, environmental factors and diseases can be a threat of some impending conditions (malnutrition, weakness, cancer, etc.). Oxidative stress is defined as imbalance between oxidants and antioxidants, and with aging, endogenous antioxidant defenses decrease and production of reactive oxygen species increases [1]. Nevertheless, antioxidant defense system and protection mechanisms are important in maintaining the organism against the oxidative stress, and thereby homeostasis can be observed. Keeping a stable homeostasis requires, besides a better environment and gene structure, we should need to know what nutrients are needed to maintain hemostasis. Nutrition especially dietary antioxidants

decreases the adverse effects of reactive oxygen species and regulates the stress. Consequently, it is necessary to understand how antioxidants in nutrients exert its health protective effects.

Antioxidants, natural or synthetic, may protect cell damages during oxidative stress. New researches showed that natural antioxidants in foods are commonly belonged with a better health and life quality. At that place, there are several natural antioxidants, which can reduce oxidation in cell or lipid peroxidation. Several studies have been stated that natural antioxidants such as medicinal herbs, alga, ginger, curcuma, cloves and vitamins can be utilized for health maintenance. They have important biological activities which attributed to their compounds named carotenoids, polyphenols, phycocyanin and flavonoids. The biological actions of these antioxidants are anti-inflammatory, enzyme detoxification, cell damage prevention, gene regulation and antimicrobial, which have been conducted with human and animal studies [2, 3]. Besides, natural antioxidants are shown to possess the antioxidant activity in organism and maintain the normal physiological condition. Thereby, they can be applied for protective health as well as for therapeutic conditions.

Increasing world population impacts on the environmental stress like of biodiversity, air and water contamination. Physicochemical stress results from environmental agents and such effects result in chronic infections, autoimmune diseases and other physiological disorders. Because of this reason, regulation of homeostasis should be backed up by natural antioxidants. This chapter, we will attempt to explain the stress, oxidative-antioxidative balance and natural antioxidants with evaluating the association of natural antioxidants and health.

2. Stress mechanism and oxidative-antioxidative balance

Free radicals are called the reactive oxygen species (ROS), and they also include a subgroup of reactive nitrogen species (RNS) which are the products of normal cellular metabolism. Overwhelming production of these molecules leads to oxidative stress damage to lipids, proteins and DNA [4].

A balance between free radicals and antioxidants is necessary for proper function. If free radicals overwhelm the organism's ability to regulate the stress, a circumstance is known as stress. The mechanisms of stress could be explained with two parts as acute and chronic. Acute stress is termed as an emergency response of organism, which affects by short term stressors. In response to acute stress, sympathetic nervous system is triggered due to release of hormones and the response prepares the body to either fight or flight response. The sympathetic nervous system has signaled to adrenal glands for releasing epinephrine and cortisol hormones, which act on endocrine, cardiovascular, respiratory, musculoskeletal and gastrointestinal systems. All the same, the parasympathetic nervous system regulates rest and digests functions. It works without conscious control of cardiac muscle, smooth muscle and exocrine and endocrine glands, which regulate the blood pressure, glucose and thermoregulation, etc. On the other hand, chronic stress is induced by stress over a prolonged time and conducts the stress hormones to release in a long period. Also, hypothalamic-pituitary-adrenal axis is kept active by chronic stress. This can have several symptoms either physical or psychological. Chronic stress is linked the risk of certain illnesses and lower life expectancy, such as obesity, cholesterol, anxiety and depression, and so on.

Oxygen is one of the most abundant and essential elements for all the life forms on the earth. It is critical for the energy production in both prokaryotes and eukaryotes via electron transport chain [4]. As a result of stress in cellular metabolism, reactive oxygen species are produced and these molecules can damage the proteins, carbohydrates, nucleic acids and lipids, which are the important cell structures. This situation is termed oxidative stress. Oxidative stress causes to increase of free radicals production and reduction of antioxidant defense system. According to this issue, within the consumption of antioxidant, either increase or decrease of oxidant and antioxidant amounts should be assessed for determining the oxidative status [5]. The free radical effect of fatty acids is to stimulate the lipid peroxidation and thereby several damages occur. The most important molecule of lipid peroxidation is malondialdehyde (MDA), which takes in an ability to inactive the cellular proteins by forming protein linkages [6]. In additionally, MDA level increases during oxidative stress and so, in clinical studies, the measurement of the MDA on biological fluids such as plasma or tissue should be taken out for reflection oxidative stress status in vivo.

Antioxidant molecules are classified as enzymatic and nonenzymatic by structures, endogen or exogen by sources, water-soluble and lipid-soluble by resolution, and intracellular and extracellular antioxidants by placement in organism. The enzymatic antioxidants called as glutathione (GSH, GST), glutathione peroxidase (GPx), catalase (CAT) and super oxide dismutase (SOD) have a big role in eliminating free radicals. They can restrain the negative effects of free radicals on DNA, proteins and lipids [7]. The nonenzymatic antioxidants, Vitamin C and E, beta carotene and polyphenol have an efficiency of free radical chain reactions by catching the oxygen molecules [8]. Measurement antioxidant response in biological fluids should be necessary for evaluating the oxidative stress. However, besides individual oxidant and antioxidant molecules, total oxidant and antioxidant status has been important to reflect the cumulative effect of oxidative stress in the organism [9]. Endogenous and exogenous antioxidants act synergistically to maintain or reestablish the redox homeostasis, such as during regeneration of vitamin E by glutathione or vitamin C to prevent the lipid peroxidation process [10].

The oxidant-antioxidant balance is associated with increasing free radicals, inactivation or insufficiency of antioxidants and accumulation of oxidant molecules. Also, maintaining the balance between beneficial and harmful effects of reactive oxygen species is very important. Antioxidants encounter low concentrations of oxidant substances or inhibit the oxidation of target molecules [11]. They reduce the activation of oxidants or convert these molecules to weaker new molecule. Likewise, they can bind the oxidants and act on a reaction chain as in break/repair balance. Thereby, cellular prevention occurs and immunity is balanced [12]. There are both endogenous and exogenous defense against oxidative stress but endogenous defense mechanism is insufficient to completely protect against reactive oxygen species. Exogenous defense comes from the diet in the form of antioxidants, especially from fruits and vegetables [13].

3. Antioxidants in health and disease

The relationship between free radicals and antioxidants shows the unbalance of oxidant-antioxidant status. If antioxidant levels decrease, oxidant levels increase in

an organism during oxidative stress. The initial defense response can be explained with SOD, which modifies the superoxide radicals to less harmful molecular oxygen [14]. Nevertheless, GSH, GPx, and CAT have a protective role on lipid peroxidation. Although GSH and GPx can reduce the hydrogen peroxide and lipid hydrogen peroxide, CAT, which has iron, brings down the hydrogen peroxide on liver and erythrocytes [15, 16].

There are numerous studies that observe the consumption of antioxidants in tissues or blood samples, and also reviewed the correlation between balance and important diseases both for humans and animals. Uzar et al. [17] observed the lower antioxidants in tissues in brain ischemia-reperfusion damage due to the higher oxidant value. Yigiter et al. [18] determined the increase of MDA and decrease of GSH in kidney tissue damage due to increase of DNA oxidation in the kidney. Tok et al. [19] found the higher MDA and MPO and lower GSH and GST levels in oxidative situations [20, 21]. As well, some researchers reported that free radicals were the most important components for ischemia damages in several organs such as brain, heart, liver and lung [22, 23]. Atherosclerosis, hypercholesterolemia and cancer are universally accepted as important diseases due to either antioxidant depletion or unbalance of oxidant and antioxidant status [24, 25]. Generation of antioxidants in oxidative status and correlation with pulmonary, cardiovascular or nutritional diseases were reviewed [26].

The role of oxidative stress in health and disease of animals has been critiqued by some researchers [27, 28]. Metabolic diseases, heat stress and nutrition have been documented as well as performance parameters, immune defense, milk production and energy balance [29, 30]. In addition, some important biological molecules damage by oxidative stress, such as DNA, RNA, cholesterol and proteins. It was reported that high starch nutrition was resulted in an increase of oxidative stress in dairy cows [14]. In horses, it was observed that overload feeding of grains, sugar or fructans was resulted with laminitis which is associated with oxidative stress [31].

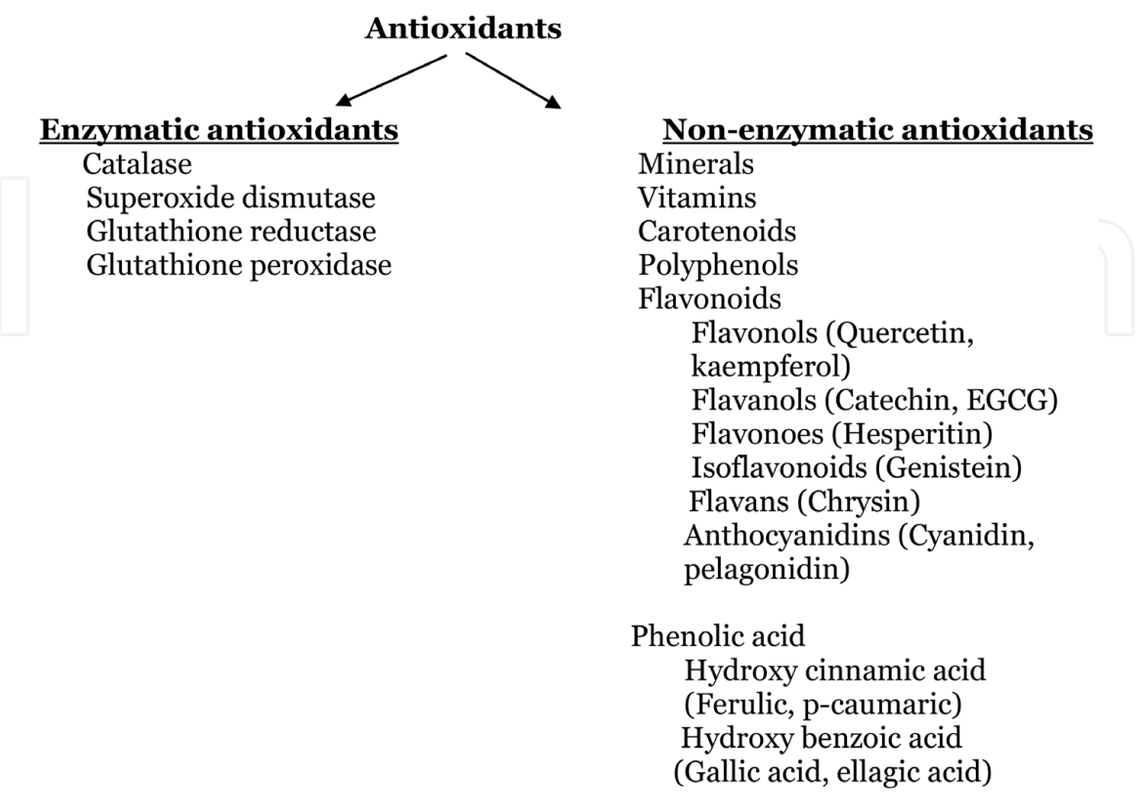


Figure 1.
Classification of antioxidants.

Besides, protein oxidation was reported important for meat quality of both ruminant and poultry [32].

Insight of this information, if the antioxidant mechanisms in organism are insufficient against oxidative stress, exogenous antioxidant supplements should be added to feed both human and animals for a better health. Antioxidants can be divided into two groups generally as natural and synthetic sources (**Figure 1**). Although synthetic antioxidant is produced from chemical processes, the important one natural antioxidant is more useful for health due to its natural contents.

4. Natural antioxidants

The relationship between food and health has addressed for many years. Diet has an essential part in maintaining our health. Natural antioxidants play decisive roles in risk reduction of so many diseases. Dietary or natural antioxidants play a persuasive role in serving the endogenous antioxidants in scavenging the excess of free radicals. Nonetheless, the dietary antioxidants can only have helpful effects in the radical scavenging if they are present in tissues or body fluids at adequate concentrations. For many dietary components, absorption is limited or metabolism into derivatives that can be easily incorporated reduces the antioxidant capacity. As well, it is important to know that some specific antioxidants have limited function because of their inability to penetrate the blood-brain barrier, poor absorption and conversion to the pro-oxidants under certain physiological conditions [33].

Natural antioxidants are widely spread in food and medicinal plants and exhibit a wide range of anti-inflammatory, anti-aging and anticancer effects. These natural antioxidants from plant materials are mainly polyphenols, carotenoids and vitamins. The most important are those coming from routinely consuming vegetables and fruits, flowers as well as traditional medicinal plant [34–37] (**Table 1**). It has been reported that medicinal plants have been used 70–80% of the world population [38]. Bioactive compounds, which mean phytonutrients as well as named natural antioxidants, are health promoting compounds that can bring down the risk of diseases.

Antioxidants contents	**Natural sources**
Polyphenols	Green tea, strawberries, apples, broccoli, onion, chocolate, coffee, red wine, blackberries
Flavonoids	Oranges, lemons, green tea, berries, grapes, spinach
Vitamin C	Vegetables, citrus fruits, strawberries, potatoes, green vegetables
Vitamin E	Whole grains, fish liver oil, nuts, seeds, green vegetables
Phycocyanin	Seaweed (algae)
Zeaxanthin	Egg yolks, peas, broccoli, carrots, pumpkin
Beta carotene	Tomatoes, potatoes, carrots, broccoli, peaches
Lutein	Green leafy vegetables, cooked spinach, cooked kale, egg yolks
Glutathione	Avocado, fish, meat, grapefruit, peach, broccoli, strawberries, squash
Selenium	Fish, shellfish, red meat, grains, chicken, eggs and garlic.
Cysteine	Animal protein
Peroxidase	Mango, fruit

Table 1.
Some interesting antioxidants sources.

Natural antioxidants have been valued for their contents, antioxidant activities and usage for both humans and animals feeding. Its biochemical compositions and functional attributes of these antioxidants have been important for selection criteria. It is well known that the mainly contents of the natural antioxidants are polyphenols, flavonoids, carotenoids, glutathione and some vitamins (E and C). Carotenoids and polyphenols have greater biological effects on organism such as antibacterial, anti-inflammatory, anticancer, etc. The important compounds of polyphenols are phenolic acids, lignans and flavonoids. It was proven that these contents can serve as metabolites by blocking the oxidation and clean the free radicals in the organism [39, 40]. As well, plants and spices which used for antioxidant properties have a strong hydrogen activity against oxidative stress [41, 42]. It was also reported that absorption of polyphenols in gut barrier can be linked up with increasing antioxidant efficiency [43]. In addition, although phenolic acids can be derived from apples, kiwis or cherries, flavonoids are in several common fruits and vegetables including onion, tea, citrus fruits, grapes, red pepper and broccoli [44, 45]. Carotenoids, which are also nominated as natural pigment, include beta carotene, lutein and zeaxanthin [46]. Among the carotenoids, beta carotene can be found in mango, carrot and nuts. Carotenoids can protect the protein and DNA structure of the organism against oxidative stress [47]. It was reported that carotenoids may inhibit fat oxidation [48]. Also, carotenoids have been reviewed as a health promoter from cancer due to their deactivation effect on ROS, but are not sure. It was seen that the contradictory findings have been related to the variety of carotenoids [47].

In addition, phycocyanin and zeaxanthin can be found in several plants such as microalga, broccoli and peas [46, 49]. Phycocyanin, which is an important extract of microalgae named *Spirulina platensis*, can inhibit the microsomal lipid peroxidation and hydroxyl and peroxyl radicals [47]. It was also observed that phycocyanin can improve the antioxidant activity and support the immunity and wellbeing [50, 51]. Moreover, it was reviewed that ascorbic acid (Vitamin C) and alpha-tocopherol (Vitamin E), which require for nutrition, could change the enzyme system for free radicals and protect the cellular membranes from oxidation [52–54]. Both of these vitamins can diminish the side effects of oxidative molecules with a huge amount. Vitamin E is known as a chain-breaking antioxidant, and it can protect the cell from lipid peroxidation. Also, ascorbic acid can restore the vitamin E. It was known that vitamin C is mainly rich in the peel of fruits such as orange and vitamin E is in candied orange and lemon [55]. Glutathione, which is an another antioxidant, is also produced in the body; several food resources have this important antioxidant naturally, such as melons, avocado, grapefruit, spinach, fishes and so on [56]. Especially, fish and sulfur containing amino acids are evaluated for maintaining and also increase the glutathione levels in organism.

Natural antioxidants have been extracted by several technological methods, including hot water bath and Soxhlet extraction, and different solvents have been used for the extraction of antioxidants from food and medical plants [57, 58]. Numerous works have been based on medicinal plant extraction and special antioxidant compounds. The extraction techniques, industrial applications, costs and procedures have been considered for getting more and useful extracts. The better the extraction efficiency of antioxidant components from plant materials, different methods have been developed such as ultrasound-assisted extraction, microwave-assisted extraction, enzyme-assisted extraction and electric field extraction. Still, necessity of standardization of sample collection and the analysis method has been reported [59].

5. Importance of natural antioxidants for health

The importance of natural antioxidants has been increasingly investigated for oxidative-antioxidative balance and wellness because of the consumer concern regarding the safety of using synthetic antioxidant and its low cost and strong H donating capacities. Natural antioxidants and their derivatives could be obtained from vegetables, fruits and medicinal plants. So, there have been several researches about these compounds for evaluating the effects on both humans and animals. It is known that natural antioxidants have several physiological roles on organism and actually they can act as a radical scavenger [60].

Oxidative stress can be linked to cancer, cardiovascular or respiratory diseases, immune deficiency and inflammatory conditions. Studies have shown that more antioxidant in diets being important and gets more health to the organism (**Table 2**). Nevertheless, there have been contradictory results about the effects of natural antioxidants on health. It was also reported that flavonoids, which can be metabolized by microbiota in the intestine, can be effected in the nervous system, can take down the blood pressure and reduce serum triglyceride [61]. On the other hand, antioxidant effects of polyphenols have not been awarded thus far due to its limited bioavailability in systemic circulations. It has been suggested that polyphenols may not protect oxidative damage directly, but it can be a versatile proactive rather than antioxidants [62, 63]. It was reported that polyphenols in green tea can protect the cardiovascular diseases [64–66], reduce cholesterol [67] and glucose [68], and as well it can be a cardiovascular and an anticancer medicine [69–71] in humans. Phenols have been read widely for human health as well as animals especially flavonoid compound. Researchers reported the increase in villus height [72] and improvement of duodenum health [73] in broiler belong to polyphenol rich feeding. Polyphenols and flavonoids can affect positively on intestinal health due to inhibition of pathogenic bacteria, and thereby can stimulate the animal performance such as monogastric animals, chicken and pigs [73–76]. It was observed that flavonoids (*Ginkgo biloba*) could improve the immune system parameters via expression of the constituents of interleukins and cytokines [77–79].

It was proven that the beta carotene in food could reduce the risk of cardiovascular diseases, although vitamin C could avoid the cardiovascular mortality [80, 81]. It was conducted that beta carotene, vitamin E and vitamin C may improve the mortality ratio [82]. Even so, it was reported by the National Institutes of Health (NIH) that Vitamin C, vitamin E or beta carotene has no effect on cancer and some cardiovascular diseases as heart attack or stroke. This place has been associated with several reasons such as insufficient antioxidants consumed in foods, not given long enough time, lower doses, individual differences and differences in the chemical compounds of antioxidants [83]. Even so, it was determined that vitamin C additive had a great role on germs and bugs in resting mice due to the reduced effect of vitamin C on stress hormones' amounts [84]. Additionally, vitamin E additive in sows showed the similar results in fertility and mating success compared to animals in feeding with polyphenols [85]. Another work, the SOD, GPx and total antioxidant capacity parameters were found higher in chickens fed by either polyphonic or vitamin E [86]. It was indicated that vitamin C additive in animals is related to improvement of osteoclast formation and bone health [87]. Also, in fishes vitamin C helps with proper health was reported by researchers [88, 89].

Natural antioxidants and their products have a vast potential for both human and animal feeding and health [90–94]. Understanding of natural antioxidants

Natural antioxidants	Functional properties	Reference
Polyphenols	Antioxidant parameters↑ MDA↑ Minimize the adverse effects of lipid peroxidation	Lipinski et al. [86]
Flavonoids	Anticancer Triglyceride↓	Gengatharan et al. [2], Lipinski et al. [86]
Vitamins (C-E)	Total antioxidant↑ GSH↑	Lipinski et al. [86]
Phycocyanin	Anticancer Regression of leukoplakia Antioxidant parameters↑ Induces apoptosis	Pinero et al. [50], Karkos et al. [51]
Zeaxanthin	Protect DNA structure	Mezzomo and Ferrira [46], Seyidoglu et al. [49]
Beta carotene	Protect DNA structure Anticancer Anti-inflammatory	Mezzomo and Ferrira [46], Pinero et al. [50]
Lutein	Antioxidant Reduction of cataract and macular degeneration related to age	Mezzomo and Ferrira [46]
Glutathione	Antioxidant Protects cells from free radicals	Ashadevi and Gotmare [56]
Selenium	Anticancer Antioxidant Reduce cancer incidence and mortality	Ashadevi and Gotmare [56], Helzlsouer et al. [90]
Cysteine	Antioxidant Blocks oxidants of the free radical	Ashadevi and Gotmare [56]
Garlic	Antioxidant Prophylactic and therapeutic medicinal agent	Elosta et al. [91]
Ginger	Antioxidant Reduce or delay the progression of diseases Extracts of ginger have different antioxidant capacities	Tohma et al. [92]
Curcumin	Antioxidant, Anti-inflammatory ROS scavenger Exert chemopreventive effects on carcinogenesis	Menon and Sudheer [93]
Saffron	Antioxidant Antimicrobial agent	Kakouri et al. [94]

Table 2.
Functional properties of some natural antioxidants.

in the context of coordinated oxidative stress and antioxidants and translation of this knowledge to improve animal and human health is a large challenge. In order to attain the health benefits, molecular mechanism of protective effects of fruits and vegetable has been enlightened. Future efforts should be addressed to explain in detail the mechanism of the natural antioxidants health promoting effects, increase in public attention and their utilization in animal and human foods and their recommended dosages, thereby achieving their health advantage and reducing health care expense.

6. Conclusions

Stress has been the most important problem in life for years. Nutrition, unhealthy environmental conditions, genetic factors and physiological insufficiency may create the stress. Although oxidative stress is related to diseases, antioxidant strategies or use has been still questionable.

Today, there is an increasing intake of the antioxidants, especially natural ones, to maintain the antioxidative status in both humans and animals. Natural antioxidants have several beneficial effects, which are considered to protect the homeostasis of the organism. Assessment of natural antioxidants, extracts and functional properties are summed in this chapter. At that place, several studies include oxidative stress mechanism and natural antioxidant consumption in both humans and animals. These findings enrich our knowledge of natural antioxidants in both humans and animals, and the scientific evidence suggests that a well-balanced homeostasis should be associated with a good balanced diet that is rich in antioxidants. Besides, future direction studies in oxidative stress and natural antioxidants should be correlated with intake of antioxidants and impression of oxidative stress markers.

Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

ROS	reactive oxygen species
RNS	reactive nitrogen species
MDA	malondialdehyde
GPx	glutathione peroxidase
CAT	catalase
SOD	super oxide dismutase
Vitamin C	ascorbic acid
Vitamin E	alpha-tocopherol
DNA	deoxyribonucleic acid
Spirulina	algae
Ginger	*Zingiber officinale*
Curcuma	*Curcuma longa*
Cloves	*Syzygium aromaticum*
Carotenoids	tetraterpenoids
Vitamins	organic compounds
Polyphenols	micronutrients
Phycocyanin	pigment of plants
Flavonoids	a class of plant and fungus secondary metabolites

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