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The Effects of Propolis in Animals Exposed Oxidative Stress

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1. Introduction

This chapter expresses the effects of propolis on oxidative stress in animals. The term "stress" was first coined by the endocrinologist Hans Selye (1936) more than 70 years ago to define the physiological adaptive responses of the organism to emotional or physical threats (stressors), whether real or perceived (Selye, 1936). Factors causing stress include physiological factors, such as climate, environment, nutrition, and diseases, and physical conditions, such as cage density and transport. Under stress, rapid and temporary changes occur in the body initially; with continuous stress, these are followed by permanent and irreversible changes (Tatli Seven, 2008). Stress responses are characterized as primary, secondary and tertiary. The primary stress response is a neuroendocrine response leading to corticosteroid and catecholamine release. The secondary stress response includes changes in plasma and tissue ion and metabolite levels induced by neuroendocrine hormones. The changes in disease resistance, growth, condition factor, and behaviors at a whole organism level are tertiary responses (Wedemeyer et al., 1990). Finally, a decline in yield and resistance to diseases may occur. Animals under stress become ill more easily, and excess medicine may be necessary to maintain health. As a result, drug residues increase in animal products and threaten public health directly. Stock health and welfare management are key factors in animal health and food safety. For this reason, stress conditions in animals need to be examined carefully (Tatli Seven, 2008). Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen. During times of environmental stress (e.g. ultraviolet or heat exposure, environmental pollutant), ROS levels can increase dramatically.This may result in significant damage to cell structures.This cumulates into a situation known as oxidative stress.

This chapter was written to demonstrate the importance of propolis that have effects antioxidant, antibacterial, antitumor, anti-inflammatory etc. in animals under oxidative stress.

2. Oxidative stress

Oxidative Stress is a general term used to describe the effect of oxidation in which an abnormal level of ROS, such as the free radicals (e.g. hydroxyl, nitric acid, superoxide) or the non-radicals (e.g. hydrogen peroxide (H_2O_2), lipid peroxide) lead of damage (called oxidative damage) to specific molecules with consequential injury to cells or tissue. Oxidative stress is caused by an imbalance between the production of reactive oxygen and a biological system's ability to readily detoxify the reactive intermediates or easily repair the resulting damage (Bulger & Helton, 1998). Oxidative stress occurs when the generation of ROS in a system exceeds the system's ability to neutralize and eliminate them. The imbalance can result from a lack of antioxidant capacity caused by disturbance in production, distribution, or by an over-abundance of ROS from an environmental or behavioral stressor. This damage can affect a specific molecule or the entire organism. If not regulated properly, the excess ROS can damage a cell's lipids, protein or DNA, inhibiting normal function. Because of this, oxidative stress has been implicated in a growing list of diseases as well as in the aging process (Sies, 1985).

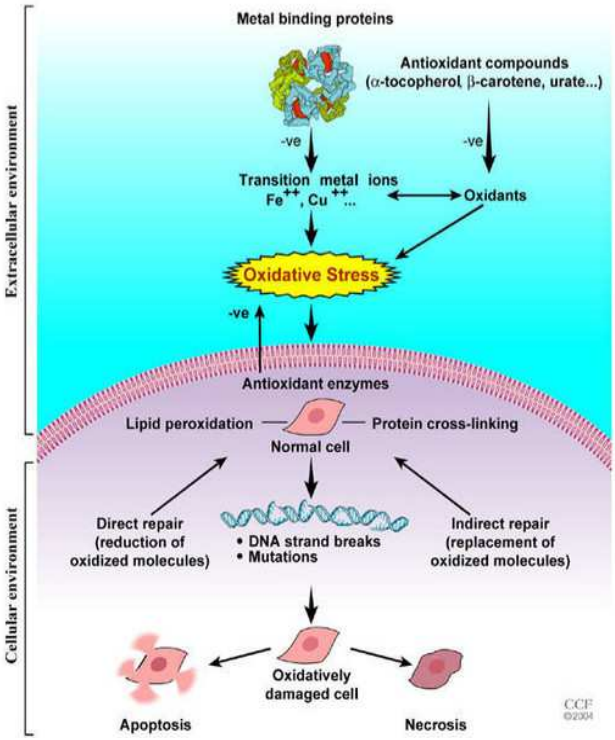

Fig. 1. Mechanisms of oxidative stress-induced cell damage (Agarwal et al., 2005).

ROS can impair lipids, proteins, carbohydrates and nucleotides, which are important parts of cellular constituents, including membranes, enzymes and DNA. Radical damage can be significant because it can generally proceed as a chain reaction (Chen and Pan, 1996; Wejil et al., 1997). These radicals can damage cell membranes inducing lipid peroxidation of polyunsaturated fatty acids in the cell membranes and other complexes (Fang et al., 2002; Stephan et al., 1995) Malondialdehyde (MDA) is one of the the final products of lipid peroxidation. The concentration of MDA is the direct evidence of toxic processes caused by free radicals (Talas & Gulhan, 2009; Tatli Seven et al., 2009). Damaged lipids lead to rigid cell membranes; oxidized cholesterol often leads to hardening of the arteries and poorly repaired DNA chains lead to cell mutation (future generation of cells) as implicated in cancer and aging. Scientific research has established that the root cause of more than seventy chronic degenerative diseases is due to oxidative stress development, i.e. cell damage caused by free radicals (Davies, 1995).

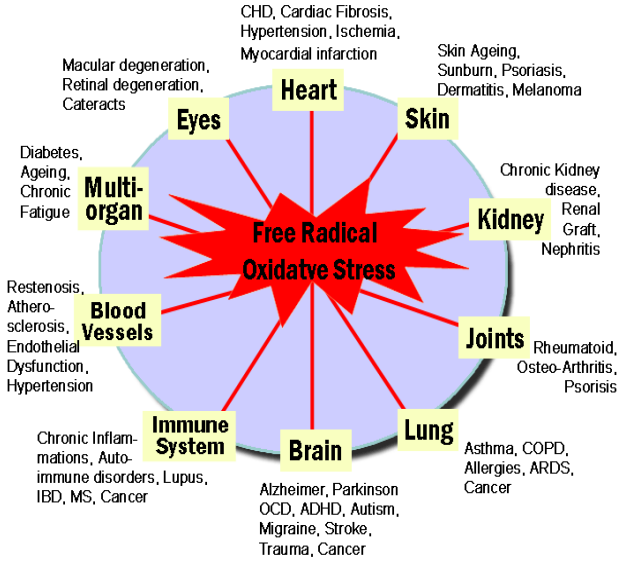

Fig. 2. Diseases related to oxidative stress (http://www.enzoprofessional.com/default).

The intensity of oxidative stress is determined by the balance between the rate at which oxidative damage is induced (input) and the rate at which it is efficiently repaired and removed (output). The balance provides certain steady-state ROS level (Lushchak, 2011). The rate at which damage caused is determined by how fast ROS are generated and then eliminated by endogenous defense agents called antioxidants. The rate at which damage is removed depends on the efficiency of repair enzymes (Sies, 1985). Detoxification of ROS is one of the prerequisites of aerobic life, and hence an elaborate antioxidant system has evolved (Sies, 1991). Antioxidants are agents that scavenge ROS, prevent their formation, or repair the damage they cause (Halliwell, 1991). Antioxidants are effective because they are capable to donate their own electrons to free radicals. When a free radical gains the electron from an antioxidant, it no longer attack the cell and the chain reaction of oxidation is broken. After donating an electron, an antioxidant becomes a free radical by definition. Antioxidants

in this state are not harmful because they have the ability to accommodate the change in electrons without becoming reactive. The body has an elaborate antioxidant defense system. Antioxidants are produced within the body and can also be received from food such as fruits, vegetables, seeds, nuts, meats, and oil. There are two lines of antioxidant defense within the cell. The first line, found in the fat-soluble cellular membrane consists of vitamin E, beta-carotene, and coenzyme Q. Of these, vitamin E is considered the most potent chain breaking antioxidant within the membrane of the cell (Yilmaz et al., 2006). Inside the cell, water soluble antioxidant scavengers are present. These include vitamin C, glutathione (GSH), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) (Atessahin et al., 2005).

This complex system consists of GSH, ancillary enzymes (such as glutathione reductase (GR), glutathione S-transferase (GST), glucose-6-phosphate dehydrogenase (G6PD)), metal-binding proteins (transferrin, ceruloplasmin, and albumin), flavonoids, and urate (Sies, 1991; Halliwell, 1994). In addition to those antioxidants herbs, such as bilberry, blueberry, turmeric (curcumin), grape seed or pine bark extracts, licopen, propolis and ginkgo can also provide powerful antioxidant protection for the body. Thus, there is a delicate balance between the generation and elimination of oxidant agents, which may be beneficial or deleterious to the organism. Consuming a wide variety of antioxidant enzymes, vitamins and minerals may be the best way to provide the body with the most complete protection against free radical damage (Sies & Masumoto, 1997; Yaralioglu Gurgoze et al., 2005; Yilmaz et al., 2006).

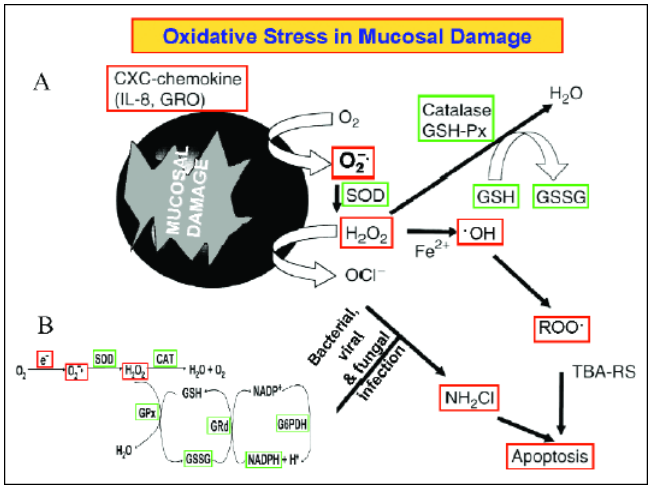

Fig. 3. The formation of various types of reactive radicals in response to enhanced steady-state ROS levels related to mucosal damage and antioxidative enzymes involved in neutralization of free radicals (Czesnikiewicz-Guzik et al., 2007).

In order to protect against lipid peroxidation and oxidative damage, all living organisms have evolved an interdependent antioxidant system that includes enzymatic and non-enzymatic components in the liver and erythrocytes. The major antioxidant enzymes are SOD, CAT, and GPx. GSH, melatonin, ceruloplasmin (Cp), and albumin are non-enzymatic

antioxidants. Antioxidant enzymes play a vital role in protecting cellular damage from the harmful effects of ROS. In addition, the stimulation in lipid peroxidation decreases with the addition of some antioxidant matters (Seven et al., 2010).

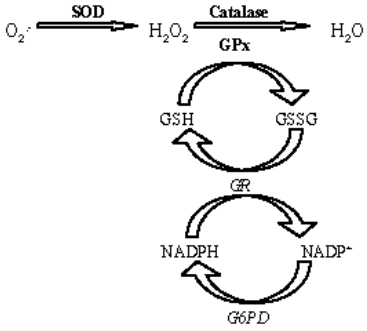

Fig. 4. Detoxification of ROS by the primary antioxidant enzymes (bold) (Kahlos, 1999). GR and G6PD are ancillary enzymes of the antioxidant system.

3. Antioxidant supplements in animal diets

Antioxidant dietary supplement greatly helps in boosting the immune system and thus aids in preventing the onset of degenerative diseases. Vitamin C antioxidant dietary supplement is perhaps the most famous form of antioxidant available. Also known as ascorbic acid, bottles or pills with this antioxidant dietary supplement can be found in any pharmacy or health food store. Another popular form of antioxidant dietary supplement is vitamin E. This antioxidant dietary supplement works best when taken with vitamin C as it seems that both vitamins have synergistic effect when taken in combination. Besides vitamins, antioxidant dietary supplements may be in the form of botanicals. Antioxidant sources are rich of the flavonoid derivatives (polyphenols). Antioxidant polyphenols are chemical compounds that are naturally found in plants. Their function is to hunt down free radicals and neutralize them. In so doing, they not only prevent free radicals from causing damage but repair any damages (www.webcontent.com/articles/52/1/Antioxidant-Dietary-Supplement/Page1.html). Propolis is recently a most important dietary supplement as antioxidant compound (Tatli Seven, 2008; Tatli Seven et al., 2008; Tatli Seven et al., 2009; Seven et al., 2011).

3.1 Propolis and its properties

Propolis (bee glue) is an adhesive, dark yellow to brown colored balsam that smells like resin. It is collected from the buds, leaves and similar parts of trees and other plants like pine, oak, eucalyptus, poplar, chestnut, and so on by bees and mixed with their wax (Seven et al., 2010). Propolis is not a new discovery. It has been used for folk medicine and foods since ancient times in many parts of the world. The use of propolis goes back to ancient times, at least to 300 BC, and it has been used as a medicine in local and popular medicine in many parts of the world, both internally and externally. Egyptians, Greeks and Romans reported the use of propolis for its general healing qualities and for the cure of some lesions of the skin. Propolis has always been reputed as an anti-inflammatory agent and to heal

sores and ulcers. Ancient Egyptians used it to embalm their dead, and more recently it was used during the Boer War for healing wounds and tissue regeneration (Ghisalberti, 1979). However, its use continues today in remedies and personal products, and the list of preparations and uses is endless. It is still one of the most frequently used remedies in the Balkan States (Bankova, 2005), and it has only been in the last decades that scientists have investigated its constituents and biological properties. Propolis is a complex resinous material that honey bees (*Apis mellifera*) produce from the exudates of various plants. Beeswax is derived from the buds and bark of certain trees and other plants. The substance populus, a favour ingredient, has been confused with propolis. Etymologically, the Greek word propolis means *pro*, for or in defense, and *polis*, the city, that is "defense of the hive". Bees use it to seal holes in their honeycombs, smooth out internal walls as well as to cover carcasses of intruders who died inside the hive in order to avoid their decomposition (Sforcin, 2007).

Fig. 5. Collecting propolis from plant of honeybee

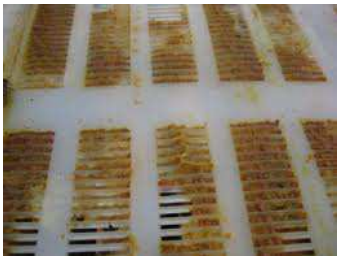

Fig. 6. The propolis collecting trap

Fig. 7. Raw propolis

Compounds	TB	TBA	TA	TT
Aromatic alcohols				
Benzyl alcohol	0.38	0.57	0.19	0.89
Phenyl ethanol	0.66	0.59	0.88	0.83
2-methoxy-4-vinylphenol	–	1.74	–	0.24
2-napthalenemethanol	2.18	1.45	0.87	0.30
5-azulenementhanol	0.80	0.04	–	–
1-naphtlenemethanol	1.20	0.50	–	1.09
Bisabolol-alpha	–	0.20	0.53	0.33
2-phenanthrenol	–	0.41	–	–
Aromatic acids				
Benzoic acid	0.96	1.20	0.53	4.30
Benzenepropanoic acid	–	–	0.04	–
4-pentenoic acid, 5-phenyl	2.40	–	–	0.03
Ferulic acid	–	0.60	–	0.12
Caffeic acid	1.20	0.44	0.05	0.61
2-propenoic Acid,3-phenyl	2.23	0.81	1.06	1.53
2-propenoic acid, 3-(4-methoxyphenyl)	1.21	0.39	0.32	0.16
1-phenanthrenecarboxylic acid	0.30	0.21	0.18	0.41
Aromatic aldehydes				
Benzaldehyde	–	–	0.04	–
Cinnamic acid and its esters				
Cinnamyl cinnamate	5.28	1.32	0.23	0.86
Benzyl cinamate	0.14	0.45	0.12	0.37
Benzyl benzoate	0.32	0.13	0.05	0.02
Cinnamic acids	–	–	–	–
1-3-hydroxy-4-methoxycinnamic acid	0.80	0.80	0.08	0.85
Fatty acids				
Lauric acid	–	0.07	–	–
Myristic acid	–	0.04	–	0.03
Palmitic acid	0.22	0.42	0.20	0.21
Oleic acid	–	1.10	–	0.47
Stearic acid	–	1.26	1.78	0.16
Linoleic acid	0.26	0.37	0.67	0.35
Linear hydrocarbons and their acids				
Cyclohexadecane	0.18	0.75	0.10	2.10
Hexadecane	–	–	–	–
Nonadecane	0.40	0.18	–	–
Octadecane	–	–	0.11	0.20
Octadecanoic acid	0.41	0.41	–	–
Flavanone				
Isalpinin	6.17	5.76	4.97	5.04
Pinocembrin	13.61	14.76	7.01	16.26
Pinostropin	13.06	11.45	4.46	2.26
Naringenin	6.20	1.40	0.90	6.20
40,5-dihydroxy-7-methoxyflavanone	1.79	–	0.84	0.69
Chrysin	1.45	2.29	3.11	9.86
3,40,7-trimethoxy flavanone	–	0.31	0.12	0.51
Hexadecanol	–	0.11	–	–
Flavonones				
Pinobanksin and its derivatives	4.3	11.5	8.3	7.6
Quercetin and its derivatives	5.1	6.2	9.1	1.1
Galangine and its derivatives	0.9	3.1	3.4	1.6
Apigenin and its derivatives	0.2	3.2	3.8	2.6

The yields of dry propolis extracts were; 44.80% (w/v) for Bartın (TBA), 36.63% (w/v) for Trabzon (TT), 31.58% (w/v) for Bursa (TB) and 20.51% (w/v) for Ankara (TA) using 96% ethanol as solvent.

Table 1. Chemical compositions of ethanol extract of Turkish propolis samples (% of total ion current) (Uzel et al., 2005)

Propolis has antioxidative, cytostatic, antimutagenic and immunomodulatory properties. These properties of propolis are based on its rich, flavonoid, phenolic acid and terpenoid contents (Seven et al., 2010). Propolis antioxidant, antibacterial and antifungal properties, combined with the fact that several of its constituents are present in food and/or food additives, and are recognized as Generally recognized as Safe (Burdock, 1998), make it an attractive candidate as a natural preservative in new food applications. This meets the demand for natural antioxidants and antimicrobials, fuelled by the increasing consumer awareness for natural, minimally processed foods with traditional preservatives absent or at very low concentrations (Han & Park, 1995; Tosi et al., 2007). Most recent studies have shown that natural preventive compounds have gained popularity day by day as some of the widely used synthetic pharmaceuticals and therapeutics might have some undesirable effects. One can think that certain natural food ingredients would be better and safer than synthetic ones. Many of these compounds, such as plant phenolics, often exhibit antioxidant activities; therefore the addition of these compounds into food products may be helpful to the health of consumers and also to the stabilization of food products.

Due to the presence of some of these effective compounds such as flavonoids (flavones and flavanones), phenolic acids and their esters in propolis and propolis extract, if the positive physiological properties and the non-toxicity of the propolis sample are proven it could be used as a mild antioxidant and preservative (Talas & Gulhan, 2009).

Characteristics	Mean value
Balsam, %	57
Phenolics, %	28
Flavones and flavonols, %	8
Flavanones and dihydroflavonols, %	6
MIC, µg.mL−1 [1]	210

[1] MIC (Minimum Inhibitory Concentration)

Table 2. Characteristics of poplar propolis samples, based on 114 samples (Popova et al., 2007)

After administration to mice or to humans, propolis does not appear to have side effects (Sforcin, 2007). Although few in number, some events of propolis allergy and contact dermatitis have been informed (Callejo et al., 2001), differently from the common allergy to honey, which contains allergens obtained flowers. Ethanol and water extracts of propolis possess antiallergic action, restraining histamine release in rat peritoneal mast cells (Miyataka et al., 1998). However, in higher concentrations (300 µg/ml), propolis directly activated mast cells, promoting inflammatory mediator release, what could be linked to allergic processes in propolis-sensitive individuals (Orsi et al., 2005). In a study (Kashkooli et al., 2011), to determine the possible toxicity and side effects of propolis, fishes (Rainbow Trout) were fed on diets containing 0, 0.5, 1.5, 4.5 and 9 g propolis/kg diet for 8 weeks. Their results showed that all dosages induced no significant alterations in growth parameters and the levels of total protein, albumin, globulin, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and activities of glutamic pyruvic transaminase (ALT), glutamic oxaloacetic transaminase (AST), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH), when compared to the control group. On the basis of their findings, propolis is a non-toxic substance for Rainbow Trout and its long-term administration might

not have any side effects. Recently, the presence of radioactive particles in propolis samples was investigated, since these particles may be concentrated in the soil, contaminating the plants, insects and its products, and, consequently, humans as well. Cesium (Cs_{137}) was not found in the samples, and only natural radioactive particles such as potassium (K_{40}) and beryllium (Be_7) were found. These data suggested that propolis may be studied as an environmental pollution indicator in order to understand the soil–plant–bee–propolis chain (Orsi et al., 2006).

Antioxidative effect of propolis extracts has been reported in different methods including iodometric method, thiobarbituric acid (TBA) method and free radical scavenging ability with reduction of radical diphenylpicrylhydrazyl (DPPH) (Mohammadzadeh et al., 2007), but Mohammadzadeh et al. (2007) reported that the ferric reducing ability of plasma (FRAP) assay the reagents are inexpensive and simple to prepare, results are fast and reproducible and the equipment required is of a type commonly found in biochemical laboratories. FRAP assay is based on ferric to ferrous ion reduction at low pH. In this method the ferric reducing ability of antioxidant compound is measured. At low pH, ferric-tripyridyltriazine (Fe^{+3}-TPTZ) complex is reduced to the ferrous (Fe^{+2}) blue colour complex with an absorption maximum at 593 nm. Test conditions favour reduction of the complex and, thereby, colour development, provided that an antioxidant is present (Mohammadzadeh et al., 2007).

3.2 The effects of propolis supplementation in animals

3.2.1 Antioxidant effects of propolis

Propolis contains about 300 constituents (Türkez et al., 2010). Latterly, propolis has gained popularity in connection with oxidative stress (Tatli Seven, 2008; Tatli Seven & Seven, 2008; Tatli Seven et al., 2008; Tatli Seven et al., 2009) and used widely in healthy drinks and foods to recuperate health and prevent diseases such as inflammation, heart disease, diabetes and even cancer (Burdock, 1998; Banskota et al., 2000). Because of such broad spectrum of biological properties and their different uses, there is a renewed interest in its biological activities. Several investigations on propolis in Eastern Europe and South America have showed that flavonoids concentrated in propolis are powerful antioxidants which are capable to scavenge free radicals (Basnet et al., 1997; Banskota et al., 2000).

Flavonoids of propolis are one of the most important compounds. Flavonoids are thought to be responsible for many of its biological and pharmacological activities including anticancer, anti-inflammatory, antimicrobial and antioxidant effects. Active free radicals, together with other factors are responsible for cellular aging and many conditions such as cardiovascular diseases, cancer, diabetes, arthritis, heat stress, environmental pollution (Tatli Seven et al., 2008; Seven et al., 2010; Sforcin & Bankova, 2011). The antioxidant serves as a defensive factor against free radicals in the body. Enzymes such as SOD, CAT and GPx are the main system that opposes oxidation. If production free radicals overwhelm the capacity of enzymatic system, the second line of defense (vitamins) may come to action (Tatli Seven, 2008; Tatli Seven et al., 2009). Such as antioxidants vitamins C and E extinguish free radicals and become oxidized and non-active (Halliwell, 1994). Flavonoids and various phenolics in propolis have been appeared to be capable of scavenging free radicals and thereby defending lipids and other compounds such as vitamin C from being oxidized or destroyed during oxidative damage (Tatli Seven et al., 2009). Besides, flavonoids inhibit lipid

peroxidation, platelet aggregation, capillary permeability and fragility, and the activity of enzyme systems including cyclooxygenase (COX) and lipoxygenase (Havsteen, 2002). Cardio protective effects have also been reported for flavonoids (Celle et al., 2004). Chopra et al. (1995) reported that doxorubicin-induced cardiomyopathy in rats followed by treatment with propolis induced a significant reduction of creatine phosphokinase, aspartate aminotransferase, blood and tissue GSH levels and TBA-reactive substances. It was also observed a decreased degeneration of cardiac fibers in propolis-treated rats, suggesting that this effect could be due to flavonoids present in propolis composition (Pinchuk & Lichtenberg, 2002).

Chyrisin is one of the propolis compounds which is has hepatoprotective and antioxidant activities in rats (Sathiavelu et al., 2009). Benzoic acid derivate exhibits antioxidant effects using inhibition assays of luminol luminescence, 2,2-diphenyl-1-picrylhydrazyl, and lipoperoxidation. Particularly caffeic acid, caffeoylquinic acid and cinnamic acid are effective O_{2^-} scavenging activity (Christov et al., 2006; Nakajima et al., 2007).

Propolis is effective in neurotoxicity. Kwon et al. (2004) examined the effects of the antioxidant propolis on seizures induced by kainic acid (KA) in rats. They found that KA induced increases in the levels of MDA and protein carbonyl, and decreases in the ratio of GSH/GSSG. In addition, the researchers determined that these changes in oxidative stresses markers at neuronal degenerations were significantly attenuated by pretreatment with propolis, and that the neuroprotective effects of propolis appeared to be counteracted by adenosine receptor antagonists. Their results suggest that the protective effect of propolis against KA-induced neurotoxic oxidative damage is, at least in part, via adenosine A_1 receptor modulation. Thus, they postulate that propolis significantly blocks seizure-induced neuronal loss by attenuating the impairment of GSH metabolism via, in part, adenosine A_1 receptor modulation. The novel antioxidant/anticonvulsant effect could be an important contribution to extending the neuroprotective potential of propolis.

A recent study (Mannaa et al., 2011), it was found that oral administration of propolis in epileptic animals which received the anticonvulsant drug valproate, resulted in significant improvements in the neurotransmitter levels in both hippocampus and in serum. The results obtained in the mentioned study, regarding the lipid peroxide (LPO) level and total antioxidant capacity (TAC) in the hippocampus homogenate of epileptic rats showed a significant increase and a significant decrease in both parameters. This may be explained by the fact that generalized epilepsy is a chronic disorder characterized by recurrent seizures which can increase the content of ROS and superoxide generation in the brain. Free radical generation can induce seizure activity by direct inactivation of glutamine synthase thereby permitting an abnormal construct of excitatory neurotransmitter glutamic acid (Oliver et al., 1990). The onset of oxygen-induced convulsions in animals correlated with a decrease in the cerebral content of neurotransmitter gamma-aminobutyric acid (the main inhibitory neurotransmitter) because of the inhibition of enzyme glutamate decarboxylase by oxygen free radicals. Thus, it appears that free radicals may be responsible for the development of convulsions. The mentioned study showed that propolis improved the effect of valproate on LPO level towards the normal values (Mannaa et al., 2011).

Brain oxidative injury, resulting from excessive generation of free radicals, likely contribute to the initiation and progression of epilepsy after brain injury. Therefore, antioxidant

therapies aimed attenuation of oxidative stress have received considerable attention in the treatment of epilepsy. The researchers demonstrated that propolis possessed neuroprotective effects both against neurotoxicity in cell cultures and against ischemic neuronal damage (Shimazawa et al., 2005). The neuroprotective effects of propolis may be related to its constituents, such as 3,4-di-*O*-caffeoylqunic acid, 3,5-di-*O*-caffeoylqunicacid and/or *p*-coumaric acid (Inokuchi et al., 2006).

Propolis effects were analyzed on macrophages of BALB/c mice submitted to immobilization stress as well as on the histopathological analysis of the thymus, bone marrow, spleen and adrenal glands. Stressed mice showed higher H_2O_2 generation by peritoneal macrophages, and propolis treatment (200 mg/kg) potentiated H_2O_2 generation and inhibited nitric oxide production by these cells. Histopathological analysis of stressed mice showed no alterations in the thymus, bone marrow and adrenal glands, but an increase in germinal centers in the spleen was seen. Propolis treatment counteracted the alterations found in the spleen of stressed mice (Missima & Sforcin, 2008).

The chemical content of Turkish propolis was investigated with the focus on protective effect against alcohol-induced oxidative stress (Kolankaya et al., 2002). The authors declared that the ethanolic propolis extract of propolis, at dose of 200 mg/kg body weight/day, was given, by gavage, to male rats for 15 days. It was found that HDL level decreased and LDL level increased in the alcohol group, while HDL level increased and LDL level decreased in the alcohol+propolis group. There were decreases in cholesterol and triglyceride levels in the alcohol+propolis group. Also, there were decreases in activities of serum ALP and AST, but increases in LDH activity in the propolis treated group compared to the alcohol group. No toxic effects of Turkish propolis were found, while it caused an increase in HDL level and a decrease in LDL level. They suggest that these effects are protective against degenerative diseases and against alcohol-induced oxidative stress via free radicals (Kolankaya et al., 2002).

Heat stress is an important stressor resulting in the reduced welfare of birds. Heat stress increased lipid peroxidation as a consequence of increased free radical generation. The rise of lipid peroxidation increases the MDA level in blood and tissues (Tatli Seven et al., 2009). Tatli Seven et al. (2009) were found that heat stress-induced oxidative stress was indicated by increased plasma, liver and muscle MDA levels. Dietary propolis and vitamin C supplementation significantly decreased plasma, liver and muscle MDA levels. It may be considered that dietary vitamin C and high dose of propolis attenuated lipid peroxidation. Besides, 3 g/kg dietary propolis was found to be more effective than dietary vitamin C, on especially liver and muscle MDA levels. Likewise, Okonenko et al. (1988) reported that propolis had more pronounced antioxidant action compared to that of vitamin E that has a similar activity to vitamin C. Living organisms are able to adapt to oxidative stress by inducing the synthesis of antioxidant enzymes and damage removal/repair enzymes (Tatli Seven et al., 2009).

Antioxidant enzyme activities such as SOD and CAT under stimulation of lipid peroxidation may sometimes decrease (Wohaieb & Godin, 1987; Ozkaya et al., 2002) or increase (Huang et al., 1999; Aliciguzel et al., 2003). The increase of antioxidant enzyme activities such as SOD, CAT and GSH may be considered as a protective mechanism against heat-induced free radical production and lipid peroxidation (Tatli Seven et al., 2009).

Exposure of broilers to heat stress resulted in a significant increase in SOD and CAT (Altan et al., 2003). Moreover, significant differences between enzymes were obtained in antioxidant enzyme responses to heat treatment. A similar response has been reported in many human diseases, in which MDA concentrations increased concomitantly with an increase in antioxidant enzyme activities. McArdle and Jackson (2000) have also demonstrated a significant increase in free radical production together with an increase in the expression of antioxidant enzymes during a period of non-damaging exercise in muscle. These increases in antioxidant enzyme activities have been considered as a protective response against oxidative stress (Altan et al., 2003). A previous study (Okutan et al., 2005), investigated the effects of caffeic acid phenethyl ester (CAPE) which is a component of propolis on lipid peroxidation and antioxidant enzymes in diabetic rat heart. They found that in untreated diabetic group, the SOD activities and CAT levels have significantly decreased, while GSH-Px activity was increased in the CAPE-treated diabetic rats compared to those observed in untreated diabetic rats. The GSH-Px activities in blood, liver and kidneys of heat stressed birds were significantly reduced, while SOD, CAT and GSH activities were increased in blood and some tissues. This may be explained by GSH-Px inhibition at increased free radical levels in tissues (Nakazawa et al., 1996). It can be concluded that in broilers heat stress induced oxidative stress in blood and tissues. Dietary propolis decreased lipid peroxidation and regulated antioxidant enzymes activities in the broilers exposed to heat stress. The protective role of propolis might be related to its antioxidant effect. Researchers suggest that propolis and especially propolis in dose supplemented 3 mg/kg diet might be considered to prevent oxidative stress in the broilers exposed to heat stress (Tatli Seven et al., 2009).

Heavy metal pollution is provoked cardio toxicity, nephrotoxicity and neurotoxicity and they are show pro-oxidative effects. They demonstrate adverse effects, such as the production of ROS, disruption of tissue oxidant/antioxidant balance, and alteration of lipid metabolism (Seven et al., 2010; Türkez et al., 2010). For example, aluminum induced changes in biochemical parameters, stimulated lipid peroxidation and decreased the activities of the antioxidant enzymes in plasma and different tissues of male rabbits and rats. Also, aluminum chloride caused deterioration in sperm quality, enhancement of free radical levels and alterations in antioxidant enzymes in both *in vivo* and *in vitro*. The mechanisms of Al-induced toxicity may be attributed to the potentiation of Fe^{+2} oxidationto Fe^{+3} to cause oxidative damage (Xie & Yokel, 1996). Türkez et al. (2010) found effectiveness of propolis (50 mg propolis/kg of body weight (BW)) in modulating the $AlCl_3$ (34 mg $AlCl_3$/kg BW) was genotoxic and hepatotoxic in liver of rats. $AlCl_3$ significantly increased the amount of micronucleated hepatocytes ALP, activities of transaminases (AST and ALT) and LDH. Furthermore, severe pathological damages such as sinusoidal dilatation, congestion of central vein, lipid accumulation and lymphocyte infiltration were found in liver. On the contrary, the researchers mentioned that treatment with propolis alone did not cause any adverse effect on above parameters. The physiological effects of propolis in hepatocytes are not clear; a hypothesis is that Al-induced genetic damage can be prevented by inductive effects of propolis on antioxidant capacity. Because the toxic effects of Al appear to be intervened, at least in part, by free radicals (Abubakar et al., 2003). As known, genetic damages mainly develops related with oxidative stress. Propolis can be proposed to prevent Al toxicity as a nutritional supplement or a functional food component (Türkez et al., 2010).

Seven et al. (2010) investigated the effects of propolis in broilers exposed to lead-induced oxidative stress. The authors found that the addition of lead increased the plasma MDA level. The authors found that the addition of propolis significantly decreased blood SOD activity and the CAT activity of heart tissue. The researchers suggested that propolis (1 g/kg) supplementation in broiler diets might overcome the adverse effects of oxidative stress induced dietary lead. Antioxidant effects of propolis are based on flavonoids and CAPE. It was reported that CAPE decreased MDA levels by blocking ROS production as an antioxidant (Seven et al., 2010).

Propolis supports liver metabolism under oxidative stress. Seven et al. (2010) observed that dietary propolis significantly decreased the blood triglyceride levels in the lead supplemented group. According to this finding, the decrease in triglyceride level of propolis might indicate that the addition of propolis relieved the adverse effects on triglyceride level of oxidative stress. Seven et al. (2010) suggested that using 1 g/kg of propolis supplementation in maize soybean meal type broiler diets may attenuate the adverse effects of oxidative stress on the antioxidant defense system.

Heat stress stimulates lipid peroxidation as a consequence of increased free radical generation. The increase in lipid peroxidation decreases antioxidant levels such as vitamin C and vitamin E in tissues (Tatli Seven et al., 2008). Performance of animals in heat stress is decreased (Tatli Seven, 2008; Tatli Seven et al., 2008; Seven et al., 2011). Antioxidants such as vitamin C, vitamin E and propolis are used poultry diet because of their anti-stress effects and because their levels is reduced during heat stress (Tatli Seven, 2008; Tatli Seven et al., 2008). Propolis prevented negative effects caused by heat stress on performance, digestibility and egg qualities (Tatli Seven, 2008). The authors reported that supplementation with propolis (5 g/kg diet) was the most efficient treatment, and increased feed intake and improved hen day egg, egg weight and digestibility (of dry matter, organic matter, crude protein (CP) and ether extract) in laying hens. Tatli Seven (2008) explained that the positive results appeared due to palatable and antioxidant properties of propolis. Especially, effects on performance and digestibility of propolis dietary supplementation may appear more powerful under stress. Moreover, it was declared that propolis supplementation increased egg shell thickness and egg shell weight in heat stressed laying hens. It was due to improved calcium digestibility and absorption resulting from the acid derivates such as benzoik, 4-hydroxy-benzoic, etc., which are found in propolis (Haro et al., 2000; Tatli Seven, 2008).

3.2.2 Antimicrobial, anti-inflammatory and antitumor effects of propolis

In addition to antioxidant properties, propolis demonstrate other beneficial effects. Especially its antibacterial, anti-inflammatory and antitumor effects are very important for human and animal health, and animal production.

Itavo et al. (2011) indicated that propolis is an alternative to the use of dietary antibiotics. Propolis has bacteriostatic activity against gram-positive and some gram-negative bacteria. The action of propolis is likely related to changes in the bioenergetic status, which inhibits bacterial motility. This is similar to the action of ionophores. The chemical composition of propolis is complex and variable because it is intrinsically related to the floristic and ecological composition of the environment visited by the bees. The combination of these factors affects the pharmacological properties of propolis, which is in fact classified into different types such as brown, green and red propolis.

Tatli Seven & Seven (2008) reported that propolis stimulated immune system and decreased mortality rate by improving immunity in broilers. They remarked that propolis supplementation in poultry diets as alternative to antibiotics may be recommended in broilers in heat stress conditions.

Epidemiological studies provide evidences that propolis protect humans against cancer, and also results from animal experiments and *in vitro* microorganism manipulations showed its efficiency to reduce pathogenic bacteria. Moreover, propolis showed substantial protection against cariogenic bacteria and oral pathogens suggesting its valuable clinical use. Kouidhi et al. (2010) declared that Tunisian propolis presented potential activity against oral *Streptococci* causing dental diseases as well as different kind of cancer cell proliferations. Those excellent activities could be due to specific bioactive compounds of the Tunisian propolis.

Also, propolis is effective on the rumen environment in ruminants. Brodiscou et al. (2000) determined that propolis affected fermentation and methanogenesis of continuous microbial culture in ruminants; it decreased protozoa population and raised propionate levels by 10.3%. However, some negative propolis effects could be related to high flavonoid levels (14.9 g/kg propolis) reported (Itavo et al., 2011). Lambs fed by the diet supplemented with propolis spent more time resting and less time ruminating. Researchers (Itavo et al., 2011) explained that this may have had a negative on digestibility because this diet provided the highest food intake with the worst feed conversion. The higher flavonoid and phenol content of their diet was probably toxic to the ruminal environment of lambs, which accelerated food passage through the gastrointestinal tract, causing lower nutrient absorption and increased dry matter intake, corroborating Van Soest (1994). Rumination rate was therefore higher in lambs fed propolis because of their increased neutral detergent fiber intake and reduced rumination time. However, improvement in rumination rate itself was not enough to raise the productivity of these lambs, which had the lowest weight gain. Rumination quality is essential to optimize food use, but this was apparently compromised by the high flavonoid and total phenolic content of propolis, resulting in reduced lamb performance (Van Soest, 1994).

Propolis also affects bone metabolism (Amany et al., 2008). In the study, it was used orally fish liver oil and propolis as protective natural products against the effect of the antiepileptic drug valproate on immunological markers of bone formation in rats. Propolis increased the bone formation markers and decreases the bone resorption ones. it also increased the osteoprotegrin and decreased tumor necrosis factor-alpha-α (TNF-α), and NF kappa-B ligand which inhibited the osteoclastogenesis. The researchers recommended the use of propolis as a prophylactic treatment for epileptic patients using valproate against the side effect of valproate on bone.

Propolis is effective in inflammation-related diseases such as rheumatoid arthritis (RA). The main characteristic of RA is the ongoing damage in arthrosis of cartilage and bone, and at the same time with a disturbance of immune function. In the context of RA, there exist neutrophils, activation macrophages, lymphocytes and other elements associated with the abduction, activation and releasing of cytokine, which is perhaps one of the mechanisms of RA development (Hu et al., 2005). In the case of RA, the concentration of cytokine derived from T cells was generally low, whereas that of mononuclear macrophage levels were significantly higher (Shuyun, 1996). Propolis inhibited the increase of inflammatory medium and decreased the activation and inducing effects of cytokines, which indicated that both extracts exhibited the same anti-inflammatory effects (Hu et al., 2005).

Propolis was used in a tumor event (Nada & Ivan, 2003). The tumor was a transplantable mammary carcinoma of mouse. Metastases in the lung were induced by injection of $2x10^5$ viable tumor cells i.v. and propolis was given intraperitoneally at doses of 50 or 150 mg/kg before or after tumor cell inoculation. Researchers (Nada & Ivan, 2003) demonstrated that therapies reduced the number of metastases in the lung and tumor growth was suppressed significantly by propolis. They commented that it is likely antimetastatic activity of the propolis is mainly mediated by immunomodulatory activity. Flavonoids in propolis stimulated macrophages to produce lymphocyte activating factor, a factor relevant for control of immune cell cooperation.

The observed anti-inflammatory effects of propolis have been attributed to its flavonoid, phenolic acid and caffeic acid contents. Flavonoids were reported to inhibit the activity of enzymes involved in the conversion of membrane polyunsaturated fatty acids such as phospholipase A_2, COX and lipoxygenase, to inhibit the release of lysosomal enzymes from rabbit polymorphonuclear leucocytes and scavenge free radicals. Aqueous extracts of propolis were formed to have inhibitory effects on dihydrofolate reductase similar to the well-known non-steroidal anti-inflammatory drugs. CAPE, which is an active component of propolis extract, was found to inhibit 5-lipoxygenase in micro molar concentrations, and to block the production of ROS in neutrophils and xanthine/xanthine oxidase system. It was also believed to contribute to the anti-inflammatory activity of propolis by being both a lipoxygenase–cyclooxygenase inhibitor and an antioxidant (Onlen et al., 2007).

Sy et al. (2006) investigated the activities of propolis using an OVA-induced asthma animal model. Mice were immunized and sensitized by exposure to ovalbumin (OVA) antigen and administered with low (65 mg/kg body weight) and high-dose (325 mg/kg body weight) propolis water extracts by tube feeding. The serum OVA-specific IgE titer and cytokine profiles in cultured splenocytes and bronchoalveolar lavage fluids (BALF) were analyzed. The number of eosinophils in BALF was counted. Here we demonstrate that propolis extracts can suppress the serum levels of OVA-specific IgE and IgG1, and airway hyper responsiveness in OVA-sensitized mice. Results suggest that propolis extracts may be a potential novel therapeutic agent for asthma. CAPE, an anti-inflammatory component of propolis, is known to be an inhibitor of nuclear factor-kappa B and significantly reduces the levels of pro-inflammation cytokines (TNF-α and Interleukin 1, beta) in rats (Fitzpatrick et al., 2001).

CAPE is essential for the anti-inflammatory activity of propolis. Because CAPE derivatives are more lipophilic, thus easily facilitate their entry into cells (Michaluart et al., 1999). It has been reported that (Michaluart et al., 1999) CAPE, possesses anti-inflammatory activity by inhibiting the release of arachidonic acid from cell membrane, suppressing the enzyme activities of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), and inhibiting the activation of COX-2 gene expression. Propolis with CAPE and CAPE produce a significant inhibition of both exudate volume and leukocytes migration induced by carrageenin injection into the pleural cavity (Borrelli et al., 2002). Furthermore, the observed anti-inflammatory activity of propolis appears to be due to the presence of flavonoids, especially galangin. Indeed, this flavonoid has shown to inhibit COX and lipooxygenase activity, decrease prostaglandin E-2 release and the expression of the inducible isoform of COX- 2 (Gabor & Razga, 1991; Raso et al., 2001).

4. Conclusion

As a result, propolis began to attract the attention of scientists extremely (Table 3). It is used in researches related to important diseases such as cancer and diabetes. Besides, propolis is used as diet supplement in poultry researches. Many animal researches's results showed that propolis might be relieve the negative effects of oxidative stress. But, new researches should be made related to propolis.

Table 3. The Effects of Propolis in Animals

Form used of Propolis	Animal	Oxidative Stress	Given shape	Dose of propolis	Activity	Significantly		Authors
Commercial preparation	Mice	Induced in Ehrlich ascitis carcinoma cell line	Orally	160 mg/kg BW	Antitumoral and antioxidant characteristics of propolis the reduction of viability and the number of tumor cells. Induction of apoptosis.	MDA (-), GST (+), GSH (+), Total protein (-), DNA (-) and RNA (-) concentrations, Tumor volume (-), Viability of tumor cells (-)	P<0.05	El-khawaga et al., 2003.
Commercial preparation	Rat	Pilocarpin Epileptic rats	Orally	50mg/kg BW + volproate (400 mg/ kg BW)	Neuroprotective, antioxidant characteristics of propolis	Hippocampus serotonin (-), Serum dopamin (-) and serotonin (-)	P<0.05	Manna et al., 2011.
						Hippocampus MDA (-) and TAC (+)	P<0.05	
EEP	Fish (Rainbo wtrout)	No stress	Dietary	0.5, 1.5, 4.5, 9.0 g/kg diet	Non toxic effect of propolis	BWG, SGR, ALT, AST, ALP, albumin, globulin, HDL, LDL	P>0.05	Kashkooli et al., 2011.
Alchol extraction	Lambs	No stress	Dietary	199 g/kg	Bacteriostatic effects on Rumen medium	DMI (-), DWG (-), NDFI (-), FCR (+)	P<0.01	Itavo et al., 2011.
						Ruminating, Resting	P>0.05	
EEP	Laying Hens	Heat stress	Dietary	3g/kg	antibacterial antioxidant, antiseptic, palatable characteristics of propolis	EW (+), FCR (+), digesibility of CP (+), EST (+) and ESW (+)	P<0.05	Seven et al., 2011.
					Rises values of EST and ESW increasing digestibilty of Ca and P due to acid derivates such as benzoik, 4-hydroxy-benzoik which are found in propolis			
EEP	Laying Hens	Heat stress	Dietary	5 g/kg	antioxidant, immuno stimulatory, palatable characteristics of propolis	FI (+), BW (+), FCR (+), HEP (+), EW (+), Digestibility (+), EST and ESW (+)	P<0.05	Tatli Seven, 2008.
					antioxidant, immuno stimulatory			
					Rises values of EST and ESW increasing digestibilty of Ca and P due to acid derivates such as benzoik, 4-hydroxy-benzoik which are found in propolis			
EEP	Broiler	Heat stress	Dietary	0,5 g/kg 1 g/kg 3 g/kg	Antioxidant effects on lipit peroxidation of flavonoids and CAPE in propolis	Plasma MDA (-) and SOD (-); serum AST (-); kidneys (-) and heart (-) CAT; kidneys (-) and heart (-) GSH; blood (+), liver (+) and kidneys (+) GSHPx	P<0.05	Tatli Seven et al., 2009.
						Serum ALT; liver (-), muscle (-) MDA; blood (-) and liver (-) CAT; muscle (-) GSH	P<0.01	
EEP	Broiler	Heat stress	Dietary	3 g/kg	antioxidant and palatable characteristics of propolis	BWG (+) and FI (+), BWG (+), Digesibility of CP (+), EE (+), Tryglyceride (-)	P<0.05	Tatli Seven et al., 2008.
EEP	Broiler	Heat stress	Dietary	5 g/kg	antibacterial, antioxidant, palatable, growth promoter characteristics of propolis			Tatli Seven and Seven, 2008.
EEP	Broiler	Lead-Induced	Dietary	1 g/kg	Antioxidant effects of flavonoids and CAPE in propolis	Plasma MDA (-), SOD (-) and heart CAT (-)	P<0.01	Seven et al., 2010.

BWG: Body Weight Gain; **DMI:** Dry Matter Intake; **DWG:** Daily Weight Gain; **EEP:** Ether Extract of Propolis; **EST:** Egg Shell Thickness; **ESW:** Egg Shell Weight; **FCR:** Feed Convertion Ratio; **FI:** Feed Intake; **HEP:** Hen-day Egg Production; **NDFI:** Neutral Detergent Fiber Intake; **SGR:** Specific Growth Rate; **GST:** Glutathione S-Transferase; **TAC:** Total Antioxidant Capacity; **BW:** Body Weight; **CP:** Crude Protein; **CAPE:** CAT; **(+):** Significatly Increased; **(-):** Significatly Decreased.

Table 3. The Effects of Propolis in Animals

5. References

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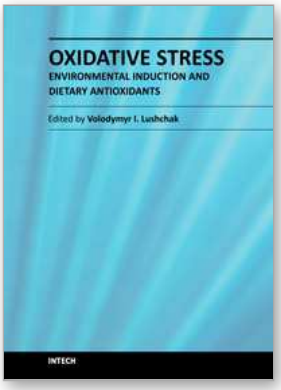

Oxidative Stress - Environmental Induction and Dietary Antioxidants

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This book focuses on the numerous applications of oxidative stress theory in effects of environmental factors on biological systems. The topics reviewed cover induction of oxidative stress by physical, chemical, and biological factors in humans, animals, plants and fungi. The physical factors include temperature, light and exercise. Chemical induction is related to metal ions and pesticides, whereas the biological one highlights host-pathogen interaction and stress effects on secretory systems. Antioxidants, represented by a large range of individual compounds and their mixtures of natural origin and those chemically synthesized to prevent or fix negative effects of reactive species are also described in the book. This volume will be a useful source of information on induction and effects of oxidative stress on living organisms for graduate and postgraduate students, researchers, physicians, and environmentalists.

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