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Review

The Role of Oxidant and Antioxidant Parameters in the Infectious Diseases: A Systematic Literature Review

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Abstract

The formation of reactive oxygen species is a physiological event in aerobic life. In case of infection, if the increased oxidant substances cannot be cleaned sufficiently by antioxidants, oxidative stress occurs. As a result, a number of pathological problems occur by damaging DNA, protein, carbohydrate and lipids. In biological systems, the balance between oxidants and antioxidants is important. In oxidative stress situations where the balance cannot be achieved sufficiently, support can be provided with the use of exogenous antioxidants. However, the molecular structure, route of administration and concentrations of these exogenous antioxidants are important. Otherwise, they may show a pro-oxidative effect. The present rewiev study makes a general overview of oxidative-nitrosative stress markers commonly used in infective clinical studies, antioxidant enzymes and parameters and antioxidant supplements.

Keywords: *Infectious diseases, Oxidant, Antioxidant, Oxidative stress*

Enfektif Hastalıklarda Oksidan ve Antioksidan Parametrelerin Rolü: Sistematik Bir Literatür Değerlendirmesi

Öz

Reaktif oksijen türlerinin oluşumu arerobik yaşamda fizyolojik bir olaydır. Bu serbest radikal türlerinin daha fazla üretilmesine neden olan paraziter, bakteriyel ve viral enfeksiyonlarda antioksidan sistemin kapasitesi bu reaktifleri yeterince temizleyemez ise oksidatif stres gelişir. Sonuçta DNA, protein, karbonhidrat ve lipidlerde hasar oluşarak bir takım patolojik problemler meydana gelir. Biyolojik sistemlerde oksidan ve antioksidanlar arasındaki denge önemlidir. Dengenin yeterince sağlanamadığı oksidatif stres durumlarında bazan eksojen antioksidan kullanımı ile destek sağlanabilir. Ancak bu eksojen antioksidanların molekül yapısı, veriliş yolu ve konsantrasyonları önemlidir. Aksi takdirde pro-oksidatif etki gösterebilirler. Bu çalışma ile yaygın olarak görülen enfektif klinik çalışmalarda kullanılan oksidatif-nitrozatif stres belirteçlerinin, antioksidan enzim ve parametreleri ile ileriye yönelik olarak yapılacak bazı antioksidan supplementlerinin genel bir durumu değerlendirilmiştir.

Anahtar sözcükler: *Enfeksiyöz hastalıklar, Oksidanlar, Antioksidanlar, Oksidatif stres*

INTRODUCTION

Free radicals are high energy atoms or molecules that contain one or more unpaired electrons in their outer orbitals. Nitric oxide (·NO), nitrogen dioxide (NO_2·), superoxide (O_2·$^-$), hydroxyl (·OH), lipid peroxy (LOO·), peroxyl (ROO·) and alkoxyl (RO·) radicals can be given as examples [1,2]. Of these free radicals, those originating from oxygen area called reactive oxygen species (ROS) and those originating from nitrogen are called reactive nitrogen species (RNS) [2]. Under physiological conditions, the most important source of intracellular reactive products is mitochondria. These reactive products are produced in large quantities in neutrophils, macrophages and monocytes. In addition to being produced with mitochondrial electron transfer system (ETS) chain and phagocyte activation, endogenously produced free radicals are also released as a result of the activity of many enzymes such as xanthine oxidase (XOD), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, neutrophil myeloperoxidase (MPO), cyclooxygenase, lipoxygenase [3-6]. Sources of exogenous free radicals (ROS) are UV, X-ray, gamma and microwave rays, air pollutants such as asbestos, benzene, carbon monoxide, formaldehyde, ozone and toluene, chemicals such as cleaning products, glue, paint, thinner, perfumes and pesticides, sudden and excessive oxygen entry, medical hyperbaric oxygen exposure, increase in catecholamines, increased lactic acid in muscles and blood, elevation in lytic enzyme activities such as lactate

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dehydrogenase, creatine phosphokinase, different and difficult physiological conditions such as exercise, pregnancy and old age, intense stress, cigarette and alcohol use, large amounts of and long-term consumption of diets containing polyunsaturated and easily peroxidable fats. Antioxidant system deficiencies or exceeding the defensive wall disrupts the oxidant-antioxidant balance in favour of oxidants and oxidative stress occurs [7-10]. Because reactive species have very short shelf life and difficult measurement, NO, lipid peroxidation marker malondialdehyde (MDA), total oxidant capacity (TOC), which is easy to measure with kits and 8-hydroxydeoxyguanosine as the marker of ROS in DNA oxidation are the most used parameters [11-14].

A large number of studies have been published on oxidative stress markers in the field of veterinary science. This review makes a general overview of oxidative-nitrosative stress markers commonly used in infective clinical studies, antioxidant enzymes and parameters and antioxidant supplements to be made prospectively.

PHYSIOLOGICAL STATES OF RADICALS

In addition to being harmful, free radicals also fulfil some physiological functions depending on their concentrations. For example, ·NO is an important mediator in the relaxation of smooth muscles and regulation of microcirculation as an intracellular messenger; additionally in addition, free radicals are used in vascular tone and signal transmission, protein phosphorylation, transcription factor activation, cell differentiation, apoptosis, oocyte maturation, embryonic development, steroidogenesis, spermatogenesis, pregnancy and immune defence system [15-20]. NO leukocyte adhesion, which is used by endothelial cells, is necessary for leukocyte adhesion, platelet aggregation, angiogenesis, thrombosis and for vascular smooth muscles to regulate blood pressure. In addition to these, NO produced by neurons is an important transmitter substance and has a key in role for neural plasticity. On the other hand, NO produced by macrophages is an important mediator to create an immune response. Superoxide and H_2O_2 can act like second messengers. NO is a molecule that has significant cytotoxic effect in defence against tumour cells, parasite, fungi, protozoa, helminths and mycobacteria, but it is not effective against extracellular pathogens. $O_2^{\cdot-}$ can stimulate collagen synthesis through fibroblast proliferation, H_2O_2 has a role in NFkB activation. They can be said to have important roles on cellular signals such as killing cancer cells with cytotoxic lymphocytes and macrophages during phagocytosis in viral, parasitic and microbial infections; detoxification of xenobiotics with p450; activation of ROS and RNS nuclear transcription factors, Ca release from intracellular stores, tyrosine phosphorylation amino acid; activation of non-receptor tyrosine kinase and activation of some cytokines and growth factor signals. In addition to being produced with phagocyte activation, mitochondrial ETS chain also occurs as a result of the activation of many enzymes such as XOD, NADPH oxidase, MPO, cyclooxygenase, lipoxygenase. Apart from these, ROS participates in the biosynthesis of molecules such as prostaglandin and thyroxin and stimulates the development of these processes. In luteal phase in the oestrus cycle and in follicular (oestrus) period, oxidation level is high. Reactive oxygen species are dissolved in cell and are used in the regulation of guanylate cyclase activity and in vital activities such as gene transcription [2,21-30].

DISEASES AND SYNDROMES REPORTED TO BE CAUSED BY OXIDATIVE DAMAGE

There are a large number of studies reporting that oxidative stress markers are the basis of many diseases. MDA, hydroxy-2-nonenal (HNE), 2-propenal (acrolein), isoprostanes, oxide glutathione (GSSG), NO, total oxidant capacity (TOC), 8-hydroxy-2-deoxyguanosine (8-OHdG) are among the most studied oxidative markers clinically for this purpose. Although oxidative stress has been studied with too many diseases and syndromes, it has been reported to be effective in the development of cancer, cardiovascular disease, neural disorders, Alzheimer's disease, mild cognitive disorder, Parkinson's disease, alcohol-related liver disease, ulcerative colitis, aging and atherosclerosis, lead poisoning, liver damage due to carbon tetrachloride, aminoglycoside, reactions from drugs and toxins, such as heavy metal toxicity, chronic and degenerative diseases such as glomerulo-nephritis, emphysema, porphyria, bronchopulmonary dysplasia, atherosclerosis, pancreatitis, rheumatoid arthritis, aging, neurodegenerative disorders, hemolytic anemia, cardiovascular diseases, pneumonia, sepsis, mastitis, metritis, retentio secundinarum, genital tract inflammation, acidosis, tongue-playing, sepsis, mastitis, ketosis, enteritis, respiratory, joint diseases and autoimmune disorders [14,26,28,31-43].

ROS FORMATION IN INFECTIOUS CONDITIONS

In many animal studies, the common picture in the clinical biochemistry of parasitic, microbial or viral diseases is the increase in oxidant parameters such as ROS and NO in the cell in order to fight the infectious agent. An increase in MDA level has been reported as a result of lipid peroxidation with the increase in cell damage. Although ROS production is useful in removing invasive pathogens, its excessive and prolonged production can cause permanent damage to host and non-infected cells. ROS production can affect the pro-inflammatory response of inflammatory cell significantly. Intracellular ROS formation by NADPH oxidase triggers pro-inflammatory cytokine production in macrophages, neutrophils and microglia. Free radicals are particularly known to be effective in the last step of phagocytosis, that is, in the step of killing microorganisms. The rapid production of free radicals by a mechanism induced by

inflammation and known as Respiratory Burst causes oxidative stress and cell damage. During this event, O_2 consumption in phagocytic cells increases 4 to 100 times. Activated phagocytic cells (neutrophil, eosinophil and all types of macrophages) produce $O_2^{\cdot-}$ with NADPH oxidase. This function is important in cleaning phagocytosed bacteria. There are five mechanisms under the control of the oxidative explosion;

Endogenous GTPase limits NADPH oxidase activation,

Lactoferrin in phagocyte granules binds free iron,

Phagocytes have self-protective antioxidant systems such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase; dense taurine substance is thought to neutralize hypochlorous acid (HOCl),

Some cells sacrifice themselves apoptosis,

Liquids and cells surrounding the target have protective systems [30,44].

When cells are activated, as a result of the activation of macrophages against the agent, chemotactic chemokine such as tumour necrosis factor- alpha (TNF-α), interleukin-6 (IL-6), interferon gamma (IFN-γ), interleukin-8 (IL-8), monocyte chemo attractant protein-1 (MCP-1), macrophage inflammatory protein 2 (MIP-2) are released. As an early response to inflammation, they can cause an abnormal persistent cascade known as cytokine storm as a result of excessive release of inflammatory cytokines. $O_2^{-}\bullet$ is released as a result of the reaction of NADPH oxidase enzyme with respiratory burst in order to eliminate the pathogen in the pathogenesis of the infection. $O_2^{-}\bullet$ radical formed as a result of reaction is converted into H_2O_2, a cytotoxic molecule catalysed by SOD. The most toxic radical, hydroxyl radical ($HO^{\cdot}$) is produced as a result of H_2O_2 and O_2^{-} reaction (Heber-Weiss reaction) or H_2O_2 and Fe^{2+} reaction (Fenton reaction), while hypochlorous acid is produced as a result of the reaction of H_2O_2 and chlorine (Cl^{-}) catalysed by the enzyme myeloperoxidase. This acid produced forms a part of the antimicrobial defence by destroying bacterial DNA and causing DNA replication to stop. The events that characterize leukocyte activation are rapid increase in oxygen use, increase in glycogenolysis and glucose oxidation and rapid formation of ROS. Especially neutrophils and monocytes form highly reactive oxidants by using the H_2O_2-MPO-Halid system. Chloride, bromide, iodide and thiocyanate can be used as substrate in this system; however, due to its *in vivo* concentrations, chloride (Cl^{-}) appears to be the most preferred halide. Highly reactive hypochlorous porphyrins react rapidly with a large number of molecules such as proteins and amines and kill microorganisms with halogenation, protein, lipid peroxidation reactions [30,45-51].

Oxidative Stress in Parasitic Infestations

Parasites cause tissue and cell damage in the host as they increase the amount of free radical and lipid peroxidation in the tissues, organs and cells they settle. It has been reported that following *Nippostrontrongylus brasilliensis*, *Trichinella spiralis* and *Dictyocaulus viviparus* infestation, MDA level increases significantly in the lung tissue of the host and that this increase may have been caused by the damage of free radicals to various cell components during infection. Increased lipid peroxidation has been associated with lung lesions due to parasite and oxidative stress caused by respiratory distress that occurs as a result of these lesions [52-54].

It is known that cellular and humoral immune response occurs against cystic echinococcosis, T-lymphocytes play an important role in the immunological control of parasite and macrophage and neutrophils fight metasestodes [55]. NO produced by macrophages is an important mediator to create immune response. In addition, superoxide and hydrogen peroxide increase in macrophage and neutrophils due to XO, MPO and NADPH oxidase activity, which causes an increase in oxidant production [56]. Lipid peroxidation caused by ROS causes cell membrane disruption and ultimately necrotic deaths [57]. In studies conducted on patients infected with liver cystic echinococcosis, an increase was found in MDA levels, while a decrease was found in antioxidant levels; thus, oxidative stress was reported [55-61]. In addition, in the study conducted by Heidarpour et al.[59], the decrease in albumin level was associated with its being used as free radical scavenger in oxidative process. In lung infections, an increase occurs in TOC level, while a decrease occurs in TAC level and has in OSI index [60,62].

Similarly, oxidative stress increase was found in *Toxocara vitulorum*, *Eimeria spp and* coccidiosis, *Nematodiasis*, *Leishmaniasis, Hypoderma spp*., *Toxoplasma gondii, Eimeria*, *Anaplasmosis, Theileriosis, Babesiosis, Cryptosporidium parvum* infections in other parasitic diseases involving intestines, kidneys and blood, etc. [12,13,63-72]. In Helminth infestations, these are fought thanks to oxidizing enzymes of increased eosinophil [73]. When studies conducted were examined, the common point found was increased oxidation in parasitic infestations, and increased oxidative stress as a result of decreased antioxidative defence. Specifically, the use of oxidant-antioxidant parameters in differential diagnosis is difficult because oxidative stress is similarly increased in the pathogenesis of many parasitic infestations. On the contrary, these parameters can be used to get information about the healing success or clinical course of the disease.

Oxidative Stress in Bacterial Infections

Although there are different types of microorganisms causing respiratory diseases, studies conducted on beef cattle with microorganisms such as *Actinomyces spp., Staph. epidermidis, Corynebacterium spp., Pasteurella multocida, Manheimia haemolytica, S. aureus and Escherichia coli* have reported increased oxidative stress [74]. In studies conducted with different types and biological materials, similar to

bacterial pneumonia, increase was fond in serum, broncho-alveolar fluid, while decrease was found in antioxidant system. M. bovis increases neutrophil apoptosis and ROS production, while it decreases NO production [30,75-77]. High oxidative stress index in brucella can be used in showing the severity of inflammation [67,78]. Paratuberculosis, one of the inflammatory bowel diseases of the digestive system, *Mycobacterium avium* subtype paratuberculosis (MAP) infections in the aetiology of Johne and Crohn disease are frequently encountered [79]. In the pathophysiology of such inflammatory bowel diseases, high production of ROS and RNS species is closely associated with decreased antioxidant activity and oxidative stress shaped with increased glutathione peroxidase (GPx) activity. In addition, in nonsteroidal anti-inflammatory drugs, it signals apoptosis with oxidative stress through mitochondrial pathway. As a result of increased oxidative stress, the functions of fatty acids and proteins in cell membrane deteriorate, even causing DNA damage and mutations. Another factor contributing to these inflammatory diseases is T-helper cells releasing high amount of interferon (Th-1, Th-2). With the deterioration of epithelial barrier, intestinal permeability increases and inflammation becomes un-controlled [1,80-82]. While an increased picture is seen in studies conducted in general on infective diseases due to an increase in oxidative parameters and a decrease in antioxidant activity, Johne and Crohn reported increased oxidation and increased GPx activity unlike other studies [83,84]. In Crohn's aetiology, there is no change in GPx activity in case of absence of MAP, while typical finding in those with MAP is on increase in GPx activity. It has been reported that the consistent correlation between MAP infection and GPx activity can potentially be used to find out the MAP infection status.

In a study conducted on calves with septicaemia caused by *E. coli*, while no change was reported in MDA and albumin levels, increase was reported in SOD and GPx activity. The absence of increase in MDA was attributed to the important increase in bilirubin level [85]. Negative correlation was reported between MDA and hyperbilirubinemia [86].

Oxidative Stress in Viral Infections

Parvovirus infection in dogs has been stated to be significantly associated with oxidative stress and reactive oxygen/nitrogen species, lipid peroxidation and poor antioxidant reserve. In a study conducted by Aydoğdu et al.[87] TOS was increased, while no change was seen in TAS and naturally OSI index was high. There are also situations in which increase was detected in SOD and GPx activity with oxidants such as MDA, H_2O_2 and decrease in CAT activity [88]. In sheep infected with sheeppox virus, an increase was found in MDA, while a decrease was found in GSH and albumin [89]. This decrease in albumin results from suppression of the antioxidative system and negative acute phase reactant due to infection.

In studies conducted on bulls, cattle and sheep with Foot-and-mouth disease (FMD), the common point is the increase in MDA, NO, TOC level and decrease in GSH and TAC level [90-94]. Researchers have reported that oxidant stress is strong in such a viral disease. In viral infectious diseas, even if the disease changes, results are similar in oxidative stress markers. In malignant catarrhal fever (MCF) disease seen in cattle, while MDA and NO levels were increased GSH was decreased [95,96]. In the pneumonia table in goats, MDA was increased, while SOD, GPx, GSH were decreased [97]. Low level of GSH causes higher ROS production, resulting in unbalanced immune response, inflammation and susceptibility to infection.

Increased RNS production in viral infections is increased through induction of inducible NO synthase enzyme. Cytokines related to Th1 trigger ROS/ RNS production in tissues in infected host tissues. Imbalance in ROS/RNS production and its removal results in oxidative/nitrosative stress that can increase virus replication and the mutation rate of viral RNA, resulting in increased damage to host tissues [98-101]. In viral hepatitis, the main mechanism that triggers cell death is reactive oxygen species formed against pathogen in neutrophil and kupffer cells. ROS increase causes an increase in collagen production by stimulating profibrinogenic cytokines such as TGF-β, PDGF and the regulation of collagen gene transcription in fibroblasts, which is involved in the pathogenesis of the formation of fibrosis. Increased 8-OHdG with infection can be used as a marker in hepatocarcinogenesis [102-104]. While a decrease has been reported in GPx and SOD activity in Herpes virus infections, increase in GPx activity and suppression of SOD activity has been reported in BHV-1 infections [96,102-106]. Since an increase in MDA and NO and decrease is seen in GSH in zoonotic viral diseases such as ecthyma contagiosum, oxidative stress can be mentioned in the pathogenesis [107].

We have stated that the weapon used by the body to phagocytize the pathogen as a defence system to prevent parasitic, bacterial and viral infections from entering the cell and infecting the host is free radicals. The common point in various diseases mentioned above was the increase of oxidants in biological fluids such as serum, tissue, etc. and increase in oxidative stress as a result of the deficiency or suppression in the antioxidative defence system. Oxidative stress (OS) occurs when the antioxidant defence system is insufficient against free radical products. If this stress continues excessively and for a long time, lipid, protein and DNA modifications are seen. Oxidative damage to DNA can form base or sugar lesions of DNA, single and double-strand breaks, abasic regions, DNA-protein or cross-linking between strains. Damaged nucleosides accumulate in both nuclear and mitochondrial DNA. Disruption of this redox balance triggers cell signal change, causing loss of basic cellular functions, tissue inflammation, ageing, apoptosis and ultimately tissue damage [2,6,108-113].

ANTIOXIDANTS

High doses of oxidants used clinically to clarify the pathogenesis of the disease cause pathophysiological changes, especially in parasitic, bacterial and viral infective conditions. The defence system developed by the organism to decrease oxidative stress in the face of this increased oxidation is antioxidants. While endogenous antioxidant enzymes form the superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase (GR) enzymatic defence line; endogenous protective antioxidants are non-enzymatic antioxidant defence systems such as glutathione (GSH), uric acid, melatonin, bilirubin, coenzyme Q10, albumin, α-lipoic acid, lactoferrin, ferritin, haptoglobulin, ceruloplasmin, transferrin. Cleansing or chain breaking antioxidants taken exogenously are lipid or water soluble materials such as tocopherol, carotenoids, ascorbate, urate. Besides, zinc, selenium, lycopene, lutein, zeaxanthin, chlorogenic acids, gallic acid, caffeic acid, quercetin, kaempferol, myricetin, naringenin, eriodictyol, hesperetin, luteolin and apigenin are also antioxidants that can be taken in the organism exogenously. These react with free radicals before living structures, take this burden on them and form a product that cannot sustain the harmful reaction. These antioxidant defence systems are parameters used in determining oxidative stress index in serum, plasma, tissue and urine. CAT, GSH, GPx, GR activities and total antioxidant capacity (TAC), ceruloplasmin, albumin, bilirubin parameters are frequently measured in clinical studies as antioxidant markers. Exogenous antioxidants and endogenous antioxidants work together to maintain redox balance [2,6,114,115]. Deficiencies in advanced age caused by insufficient intake or excessive consumption of antioxidant vitamins disrupt immune regulation [116]. As with inhibition by Vit-C or regeneration of Vit-E by GSH, endogenous and exogenous antioxidants work together to maintain redox balance. XO activity, which is accepted as the primary source of ROS, is inhibited by some flavonoids such as quercetin, silibin and luteolin. The most studied polyphenols in clinical infective animal studies due to both their anti-inflammatory and antioxidant effects are resveratrol, quercetin, rutin, tangeretin, homoplantaginin, ellagic acid, catechin, apigenin [117-119]. While flavonoids decrease peroxidase activity, they inhibit the release of free radicals by neutrophils and the activation of these cells by *α* 1-antitrypsin [120]. Anti-inflammatory activities of polyphenols such as quercetin, rutin, morin, hesperetin and hesperidin have been reported in acute and chronic inflammation of animal models. For example, rutin is only effective in chronic inflammatory processes, especially in arthritis, while flavones are effective in the neurogenic inflammation caused by xylene. It has been reported that inflammatory reaction induced by LPS injection can be modulated with daidzin, glycidyl, genistein and their glycosides. Also, exogenous antioxidants such as polyphenols can affect enzymatic activity such as protein kinase and signalling systems during inflammation process, and these enzymes play a role in cell activation processes such as cell proliferation, B lymphocyte activation or cytokine production by stimulated monocytes. They also significantly inhibit the release of arachidonic acid from the cell membrane [117,121,122]. *In vivo* and *in vitro* studies conducted show that plant derived polyphenol molecules have anti-genotoxic and anti-cytotoxic effect on cells exposed to oxidative stress [123]. Again, the ability of quercetin and naringenin to inhibit cytochrome P450 enzymes which include bioactivation of chemical carcinogens constitutes the other chemopreventive mechanism of polyphenols against cancer development, including lung cancer [124]. Exogenous antioxidants also show pro-oxidant activity in high concentrations and especially in the presence of metal ions such as iron and copper. Pro-oxidative effects of polyphenol compounds such as quercetin, catechin and gallic acids, the antioxidant properties of which are known and emphasized in previous studies, have also come to the fore in recent studies. It has been shown that prooxidant activity in flavonoids is associated with the number of hydroxyls in the molecule and flavonoids containing more than three OH in B group increase the production of hydroxyl radicals [2,119,125-128]. For this reason, molecular structures and concentrations of antioxidant substances to be used in studies should be well determined.

ANTIOXIDANTS IN INFECTIOUS ANIMAL DISEASES

If considered in a broad sense, it can be thought that antioxidant stress resulting from the excessive or inappropriate inflammatory response in severe-fulminant infections and complications of chronic infections may be at the centre of events that harm the patient or even lead to death to overcome the disease. In which infections, duration and doses can supplemental antioxidant treatment be used for the benefit of the host? There are many unclear issues about how these treatments will affect the immune response. Therefore, it may be recommended to study the effects of antioxidant supplements first *in vitro* and then start *in vivo* studies to clarify the situation in the whole system.

Antioxidant Use in Parasitic Infestations

Studies on the use of antioxidant supplements in parasitic infestations are more limited compared to viral and bacterial infections. The nephrotoxic effect occurs as a side effect during the application of first generation platinum containing cisplatin, which is mostly used as an antineoplastic for the treatment of Leishmaniasis. The application of antioxidant complex (Vit-C, Vit-E, silibinin) to reduce nephrotoxicity has been described as a promising study because of the decrease in the parasite load and toxic effect [129]. Ram et al. recommend the use of copper, manganese, selenium and zinc injections in new born calves with theileriosis since they help improve immunological

imbalance [130]. Similarly, it is stated that N-acetyl-L-cystein, which is known to have antioxidant activity, can be used as a drug in the treatment of babesiosis [131]. Vit-E and selenium application can be used as an adjunct therapeutic agent to regulate intravascular hemolysis caused by oxidative stress in babesiosis in cattle [132].

Antioxidant Use in Bacterial Infections

In the samples of the infectious studies that we found in our review, oxidative stress has been reported in the pathogenesis of patients with sepsis and it has been suggested mitochondrial dysfunction may be a causal factor in the development of multiple organ failure. This is because ROS, which increases as a result of oxidative stress in the cell, simultaneously causes the collapse of mitochondrial membrane potential and pathological ROS burst due to ETZ. These may cause ROS release in neighbouring mitochondria by being released into the cytosol; that is, ROS-induced ROS release occurs [133-137]. It has been shown that mitochondrial functions are significantly impaired in the created liver sepsis model and the impairment is strongly associated with the extent of mitochondrial ultra-structural abnormalities [138]. Oxidative stress is one of the main pathogenic factors causing mitochondrial dysfunction in acute kidney injury. Since the kidney suffers from oxidative stress during sepsis, one of the most promising approaches to mitigate such damaging results has been proposed as the use of antioxidants. For this purpose, the results of the study in which the mitochondria targeted antioxidant, plastoquinol decylrhodamine 19 (SkQR1) is applied, showed that antioxidant use is beneficial against renal tissue damage. In order not to disturb the redox balance, it has been deemed appropriate to use mitochondria-specific oxidative explosion-extinguishing supplements instead of high-dose traditional antioxidant application [139]. Mitochondria are one of the key organelles involved in the development of pathogenic cascades under septic conditions, acting both as a source and as a target for ROS. For this reason, antioxidant use has been recommended to prevent the development of oxidative stress by stopping or decreasing pathological ROS production in mitochondria. Besides, antioxidants such as multi-antioxidant Ceria-Zirconia nanoparticles developed to remove ROS for sepsis treatment have been studied and recommended for the treatment of inflammatory diseases [140]. It has been stated that selenium, which is used for antioxidant purposes in animal models of bacterial infections such as *Escherichia coli, Listeria monocytogenes, Dichelobacter nodosus, Staphylococcus aureus, has positive effects and can be used in healing* [141-144]. In the experimental study of *Microcystis aeruginosa* against Microcystin LR toxin, melatonin, Vit-E and Vit-C, which are used as a supplement to reduce the cell damage and increased 8-OH-dG, have a very high protective effect. Among these antioxidants, the effect of melatonin was 60 times higher against Vit-C and 70 times higher against Vit E [11]. Melatonin protects the DNA against oxidative damage by activating antioxidant enzymes and inhibiting prooxidative enzymes. Additionally, it is unique as an antioxidant in its ability to cross biological barriers and multiple action pathways. It is also known to have minimum toxicity even in high doses and thus to be within a wide range of dosage [145-147].

Antioxidant Use in Viral Diseases

It has been reported that the application of Vit-E, Vit-C and Zn as antioxidants provides antioxidant protection during the treatment process against oxidative damage caused by both viral infection and antiviral therapy in common viral hepatitis [148]. In studies conducted with selenium, it has been reported that selenium not only enhances Th1 type host immunity against viral infections, but also inhibits the evolution of more virulent strains of viral pathogens in RNA viruses [149-151]. Resveratrol has been reported to be effective as an inhibitor against viral replication and viral-induced inflammation in diseases caused by various pathogenic viruses, including respiratory viruses such as RSV, HCoV and HRV, influenza virus [152]. Anti-inflammatory and antioxidant activities of resveratrol may contribute to alleviating the symptoms of the virus associated with pathological signs [153]. Although it has been reported that the application of N-acetylcysteine (NAC) in infection with influenza virus clinically decreases the incidence of the disease, there are also some researchers who think that it is not healthy to recommend NAC without conducting further studies since it may decrease GSH while increasing the amount of GSSG as a result of showing prooxidant effect when the dose gets higher [154-156]. It has been reported that high doses of ascorbic acid in viral infections clears superoxide anion, inhibits virus proliferation and decreases expression of viral antigens and cellular viral load. It has also been reported to have immunomodulatory characteristics, concentrate in leukocytes, lymphocytes and macrophages, heal chemotaxis, increase neutrophil phagocytic capacity and oxidative killing, support lymphocyte proliferation and function, significantly restore decreased mitochondrial membrane potential and decrease gene expression of pro-inflammatory cytokines [157,158]. It has been reported that ROS production increases for viral replication in BHV-1 infection and causes mitochondrial dysfunction in the cell [159]. SOD activation decreases in cells infected with this virus, quercetin application increases SOD activation and ceruloplasmin level and number of apoptotic cells [105]. In a study conducted on poultry, it was suggested that oxidative stress with duodenal and jejunal mucosa in Newcastle disease virus infection causes pathological damage, while this damage can be eliminated with Vit-E given as supplement and can be used in the treatment of Newcastle disease [160]. It has also been reported that resveratrol application in poultry is useful both as antiviral and as an antioxidant [161]. It has been reported that the application of antioxidant preparates (zinc, methionine,

Vit-E, selenium) to sheep with foot-and-mouth disease improves the general health conditions and performance of animals since it increases TAC and GPx activity and decreases DNA damage [94]. It has been stated that in viral hepatitis, antioxidants can be used against viruses because they reduce virus replication and oxidant damage due to virus and increase in response to oxidative damage. Antioxidants may be effective in weakening replication and making antiviral interferon therapy more effective [162].

CONCLUSION

There is a great deal of research in animal studies on the mechanism of oxidative stress in the pathogenesis of the disease. Basically, the common point in infectious diseases is the increase in oxidative stress. When the organism encounters an infective pathogen, it increases the amount of ROS in neutrophils to protect the immune defence system. With the high and prolonged continuation of ROS which increases initially to remove the pathogen agent, oxidation and DNA modifications start in lipids and proteins. Disruption of this redox balance triggers cell signal change, causing loss of basic cellular functions, change in tissue structure, apoptosis and eventually tissue damage. It is difficult to use increased oxidative parameters in the differential diagnosis of diseases; however, it will be useful to determine oxidative stress index in determining the pathogenesis and severity of the infection and following the treatment process. On the other hand, antioxidant parameters vary in infective disease studies conducted. While GPx activity and ceruloplasmin increased in some of the studies conducted, there are also studies reporting a decrease. Since SOD activity and TAC are generally suppressed, redox balance cannot be maintained and oxidative stress occurs in the organism. Studies to supplement with antioxidants exogenously are carried out so as not to cause to give more damage with the increasing OSI. In some of these studies, prooxidative effects are seen in the presence of especially metal ions such as iron and copper depending on the molecular structure and concentrations of antioxidants, contrary to what is expected. Studies investigating the preventive effects of rations or supplements rich in antioxidants on the development, progression and treatment in studies on infectiously ill patients or in experimental studies are limited or in dose-determination stages. As the pro-oxidative effects of polyphenol compounds such as quercetin, catechin and gallic acid have come to the fore in recently conducted studies, the need for *in vitro* and *in vivo* studies on the dose, solubility, reliability and administration route of antioxidative substances has been increasing. Therefore, epidemiological studies on the effects of antioxidant molecules in healthy and sick animals will play a key role in research.

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