Review

Oxidative Stress in Canine Diseases: A Comprehensive Review

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Review

Oxidative Stress in Canine Diseases: A Comprehensive Review

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Abstract: Oxidative stress (OS), defined as a disruption in redox balance favoring oxidants, has emerged as a major contributor to numerous diseases in human and veterinary medicine. While several reviews have explored the implication of OS in human pathology, an exhaustive review for the canine species is lacking. This comprehensive review aims to summarize the existing literature on the role of OS in canine diseases, highlighting its potentially detrimental effect on various organs and systems. Some inconsistencies among studies exist, likely due to varying biomarkers and sample types. However, there is substantial evidence supporting the involvement of OS in the development or progression of numerous canine disorders, such as cardiovascular, oncologic, endocrine, gastrointestinal, hematologic, renal, neurologic, infectious and parasitic diseases, among others. Additionally, this review discusses the efficacy of antioxidant and pro-oxidant therapeutic agents for these conditions. Dietary interventions to counteract OS in dogs have gained significant attention in recent years, although further research on the topic is needed. This review aims to serve a foundational resource for future investigations in this promising field.

Keywords: oxidation; antioxidants; redox; dog; disease; free radicals

1. Introduction

Reduction-oxidation (redox) reactions are central mechanisms of life in biological systems [1]. The concept of "oxidative stress" (OS) arose in 1985, describing a potentially harmful imbalance between the production of oxidants and the organism's antioxidant defenses, favouring the oxidants [2]. Since then, the knowledge on redox biology has undergone significant advancements and the concept has been redefined to account for the broad implications of redox homeostasis [1,3–5]. Prooxidant agents include a wide variety of molecules, some of which are free radicals and others non-radicals, collectively referred to as 'reactive species,' such as reactive oxygen species (ROS), reactive nitrogen species (RNS), and others [6]. These species originate from endogenous sources, such as normal cellular metabolism, inflammation, or immune cell activation, as well as from exogenous sources, including exposure to pollutants, chemicals, or radiations [4,7,8]. When maintained at controlled concentrations, reactive species play a crucial role in various physiological processes, including cellular signaling, phagocytosis, and regulation of vascular tone [8–10]. Nonetheless, elevated levels of reactive species and their by-products can cause severe damage to biomolecules, and contribute to the pathogenesis of numerous diseases [1,3,5].

Given the variety of compounds and pathways implicated in redox regulation, numerous methods have been developed to evaluate OS, leading to the identification of multiple measurable biomarkers. Direct measurement of reactive species (ROS, RNS) and reactive oxygen metabolites (d-ROMs) can be challenging due to their very short half-life and the requirement for expensive equipment. Therefore, a more practical approach involves measuring quantifiable products of oxidative damage to biomolecules, such as lipids, proteins and DNA [11–13]. The most frequently measured biomarkers of lipid peroxidation, such as the oxidation products of polyunsaturated fatty acids (PUFAs), are malondialdehyde (MDA), 4-hydroxy-2nonenal (4-HNE), F2-isoprostanes (IsoP)

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and acrolein [13,14]. Reactive species can also lead to DNA modifications in several ways, resulting in DNA-oxidation biomarkers such as 8-hydroxy-2'-deoxyguanosine (8-OHdG), one of the most extensively studied [7,15,16]. The oxidation of proteins can be measured as advanced oxidation protein products (AOPP) and protein carbonyls (PC) [17]. Another approach to evaluating OS is assessing antioxidant defenses, which include non-enzymatic agents [e.g. vitamins, thiol groups and reduced glutathione (GSH)], and numerous antioxidant enzymes, such as glutathione peroxidise (GPX), superoxide dismutase (SOD), or catalase (CAT) [7,13,17,18]. Additionally, several widely used indexes reflect the overall antioxidant capacity of a sample, such as the 2,2′-azinobis(3-ethylbenzthiazolin-6-sulfonic acid) (ABTS) test, also known as the Total Antioxidant Status (TAS) assay; the Cupric Reducing Antioxidant Power (CUPRAC) test; and the Ferric Reducing Antioxidant Power (FRAP) assay [17,19,20].

OS has been implicated in the development and progression of numerous diseases in humans. While the exact mechanisms in some cases remain unclear, a triad of OS, inflammation, and functional impairment appears to be involved in the pathogenesis of many clinical conditions [1,3,8,13,21]. In recent years, this field has gained growing interest in veterinary medicine, with mounting evidence suggesting a relevant role of OS in the pathogenesis of many canine diseases (Figure 1). While numerous reviews have been published in human medicine, to the author's knowledge, no exhaustive review exists for the canine species. Therefore, this review aims to summarize current evidence on the role of OS in canine pathology, offering a thorough overview of this expanding field.

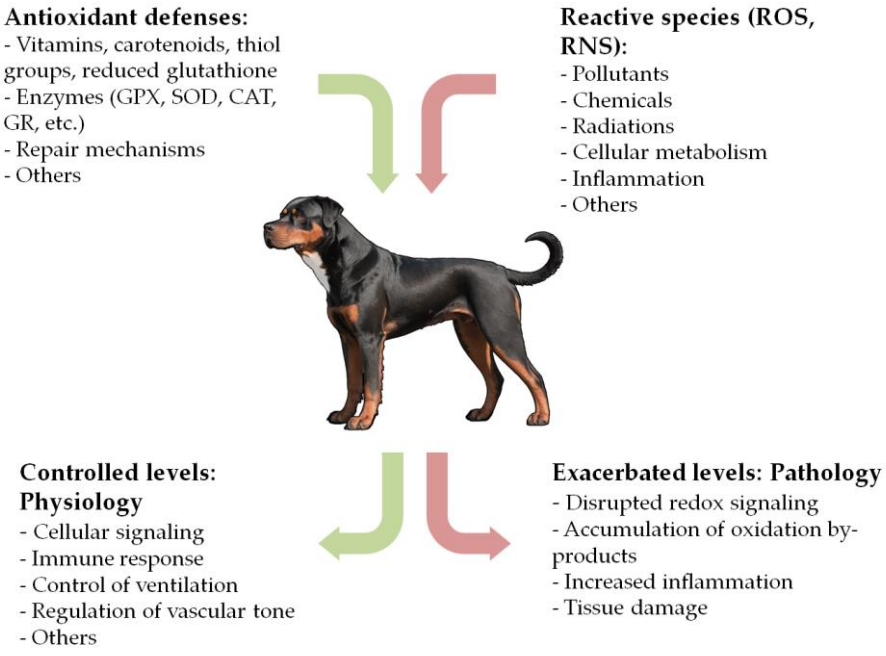

Figure 1. Simplified mechanisms of oxidative stress.

2. OS in Canine Diseases

2.1. Cardiovascular, Respiratory and Related Diseases

Cardiovascular diseases are likely among the most extensively studied OS-related pathologies in both human and canine medicine. Cardiac tissue has several sources of reactive species, primarily the mitochondrial electron transport chain, followed by various enzymatic sources such as xanthine oxidase, NADPH oxidase (NOX), and nitric oxide (NO) synthase, among others [10,22,23]. At moderate levels, reactive species play physiological roles, such as regulating vascular tone and signaling cascades in cardiac myocytes. However, increased ROS formation damages subcellular organelles, leading to myocyte contractile dysfunction, loss of functional myocardium, and a decrease in cardiac output. As a result, OS has been linked to various pathological conditions in humans,

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including hypertension, atherosclerosis, myocardial infarction, ischemia/reperfusion and heart failure [8–10,22,24].

Consistent evidence supports that OS is also present in canine cardiovascular pathology. Several circulating biomarkers of oxidation, mainly lipid peroxidation markers such as MDA and IsoP, as well as antioxidant defense markers, including vitamins, enzymes, and total antioxidant capacity indexes, have been studied in dogs with myxomatous mitral valve disease (MMVD) and dilated cardiomyopathy (DCM) [25–35]. While some studies show discrepancies in results, most report significant differences in OS biomarkers between dogs with MMVD or DCM and healthy controls, suggesting increased oxidative assault and a decline in the efficacy of the antioxidant forces [25–31,33,34]. Additionally, some studies have shown significant correlations between OS parameters and cytokines, natriuretic peptides, other inflammatory markers, or echocardiographic measurements in dogs with heart failure. This suggests a combined effect of oxidative and inflammatory processes in these patients [31,33,35]. A few studies have failed to show such OS changes in dogs with cardiac conditions, possibly due to the specific biomarkers studied, non-linear changes in oxidation across stages of MMVD or DCM, or potential antioxidant effects of some therapeutic agents such as benazepril or sildenafil, which have yet to be conclusively studied [25,32,35].

To address potential complications arising from OS in dogs with heart disease, several studies have evaluated the efficacy of nutrients and antioxidant administration, especially in dogs with MMVD. Supplementation with specific lipids (omega-3 PUFAs or medium-chain triglycerides) and other compounds (e.g. magnesium, methionine or lysine) seems to provide benefits by reducing mitochondrial ROS production and supporting other metabolic functions [36]. Boosting the antioxidant defenses through the administration of vitamins, taurine, melatonin and atorvastatin, has also shown cardioprotective effects by attenuating OS in dogs with heart disease [36–38]. In contrast, Coenzyme Q10 has not demonstrated similar benefits [39].

Additionally, canine models have been extensively used to study induced atrial fibrillation [40–45], cardiac arrest [46,47] and heart failure [48,49]. Recent studies have demonstrated increased levels of oxidation markers (ROS, 8-OHdG) and decreased antioxidant enzymes (GPX, SOD) in blood and cardiac tissue of dogs with induced atrial fibrillation, suggesting an important role of OS in promoting atrial tissue fibrosis, conduction disturbances and therefore atrial arrhythmias [40–45]. These negative effects have been shown to be attenuated by antihypertensive [45] and antidiabetic [40,42] drugs, among others [41,43,44].

Some cardiorespiratory diseases in dogs, such as tracheal collapse, Brachycephalic Obstructive Airway Syndrome and exposure to pollutants, have also been linked to OS, possibly associated with inflammatory stages or recurrent hypoxia/reoxygenation events [50–54]. Oxidation markers (MDA) have been reported to decrease in dogs with tracheal collapse receiving acupuncture and fatty acid supplementation [50,54], and increased antioxidant enzymes (SOD) have been found in dogs with Brachycephalic Obstructive Airway Syndrome after corrective surgery [51]. Conversely, one study did not detect significant differences in lipid (MDA) and protein oxidation (PC) markers in a canine model of hypoxia-induced neurogenic pulmonary edema [55]. Exposure to chromium and petrol generator exhaust fumes, simulating highly polluted environments, has also been linked to increased oxidation (MDA, ROS) and inflammatory biomarkers, along with a decrease in certain antioxidant enzymes (SOD, CAT) [52,53].

2.2. Oncologic Diseases

As demonstrated in various types of human cancers, reactive species are involved in multiple stages of carcinogenesis, including preneoplastic events driven by chronic inflammation, oxidative DNA mutations, proto-oncogene activation, neoplastic cell proliferation, invasion, angiogenesis, and metastasis [3,10,16,56–58]. The relationship between OS and cancer is complex, as ROS can both contribute to and result from tumorigenesis. Additionally, ROS can trigger cell death pathways, such as apoptosis and ferroptosis, which may prevent neoplastic events [3,16,59]. In light of these intricate phenomena, the therapeutic approach can be challenging. While enhancing antioxidant defenses might seem appropriate, many chemotherapeutic drugs and radiation therapies actually work by increasing OS in neoplastic cells to induce apoptosis [3,16,60]. However, this strategy also carries the risk of inducing toxic effects in normal tissues [16].

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The role of OS in canine oncology has been studied in dogs with various types of cancer, particularly mammary gland tumours [57–59,61–66], lymphoma [67–71], and mast cell tumour [56,64], among others [64,72–74].

OS has been evidenced in dogs with mammary gland tumours, although its manifestation in OS biomarkers appears to depend on the type of sample analyzed. Consistently elevated markers of lipid (i.e. MDA, LOOH) and DNA (i.e. 8-OHdG) oxidation, along with significant alterations in various enzymatic and non-enzymatic antioxidants, have been detected in neoplastic mammary tissue compared to normal mammary gland tissue [57,59,61,62]. Conversely, some studies have reported significant variations in serum or plasma biomarkers in these dogs [63,64], while others have not observed such changes in circulating markers [59,65,66]. Therefore, some researchers recommend direct measurement in target tissues or the collection of multiple blood samples at different time points to account for the detoxification effect on circulating levels [59]. Additionally, a recent study found that female dogs with mammary cancer who received ozone therapy alongside chemotherapy (carboplatin) had a better oxidative profile compared to those receiving standard chemotherapy alone [58].

The literature on OS in canine lymphoma is limited but has produced interesting findings. Studies have reported an altered antioxidant balance in dogs with multicentric lymphoma, as indicated by changes in circulating markers of oxidation (ROS, MDA, AOPP) and antioxidant defense (antioxidant capacity indexes, vitamins, and enzymes) [64,67,69–71]. Notably, two studies observed a correlation between higher OS levels and more aggressive lymphoma characteristics, such as advanced stages (IV and V) and T immunophenotype [67,71]. The impact of treatment on OS remains unclear, potentially due to variations in chemotherapy protocols or the specific biomarkers studied. While some studies have reported a significant correlation between the improvement in OS markers and better clinical response [70,71], others have not found such a correlation [69]. Interestingly, Bottari and colleagues reported even higher circulating markers of oxidation (MDA and AOPP) after CHOP chemotherapy (cyclophosphamide, vincristine, doxorubicin, and prednisone) in dogs with multicentric lymphoma, suggesting that the treatment might exacerbate OS levels [67]. A transient increase in ROS concentrations has also been observed in canine lymphoma and leukemia cell cultures after treatment with benzyl isothiocyanate, suggesting a therapeutic approach targeting OS in these cancers [68].

Lastly, one study revealed increased circulating MDA concentrations in a heterogeneous group of cancer-bearing dogs compared to control, and another study showed elevated d-ROMs levels and decreased antioxidant capacity in dogs with mast cell tumour [56]. Conversely, another study dismissed the diagnostic value of IsoP for detecting canine urothelial carcinoma [74]. Recent research has also explored the potential of compounds like tepoxalin and myricetin to induce ROS generation and subsequent apoptosis in canine osteosarcoma cell lines [72,73].

2.3. Gastrointestinal and Exocrine Pancreatic Diseases

Remarkable evidence suggests that OS plays a significant part in both acute and chronic canine enteropathies, particularly in Inflammatory Bowel Disease (IBD). This is due to the release of reactive species by leukocytes in the inflamed intestinal mucosa and impaired tissue perfusion. Such OS can lead to further cellular damage, perpetuation of inflammation and delayed recovery time [75–80]. Consequently, OS-derived molecules have been proposed as promising biomarkers for canine enteropathies. Studies have consistently reported elevated levels of various oxidation biomarkers in serum or plasma of dogs with IBD and acute enteropathies, including ROS, d-ROMs, MDA and IsoP, with some also correlating with the severity of clinical presentation [75,78]. Notably, dogs with IBD often exhibit lower levels of several antioxidant biomarkers, such as TAS, CUPRAC, FRAP, and thiol groups [78–80]. Interestingly, Minamoto et al. [77] employed a comprehensive untargeted metabolomic approach and identified a significant impact of OS in canine IBD, which persisted even in dogs with apparent clinical improvement. A recent study investigating the response to treatment with allogeneic mesenchymal stem cells in these dogs did not observe changes in MDA levels but proposed albumin as an alternative antioxidant marker in IBD [76]. These observations highlight the potential therapeutic value of antioxidant supplementation as a supportive or alternative approach to antimicrobial treatment in canine enteropathies, although further clinical trials are warranted [75,76].

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OS has also been proposed to participate in the pathogenesis of canine pancreatitis, although research in this area has been more limited [81,82]. A recent study found elevated levels of reactive metabolites in dogs with acute pancreatitis, and identified a significant correlation between urinary IsoP, C-reactive protein and canine specific pancreatic lipase [82]. These findings suggest a potential link between OS, pathological calcium signaling, mitochondrial dysfunction, and the amplification of inflammation in canine pancreatitis through ROS. However, the exact mechanisms underlying this relationship require further investigation [81,82].

2.4. Hepatobiliary Diseases

The liver plays a central role in redox regulation, making it both a major producer of reactive species and a target for their damaging effects. This vulnerability arises from the liver's crucial functions in metabolism and toxin biotransformation, which contribute significantly to reactive species production [83,84]. Notably, copper metabolism is a significant source of ROS in the liver, and its dysregulation can contribute to the development of hepatitis and cirrhosis [85]. Additionally, the liver is the primary site for synthesizing GSH, considered the major intracellular antioxidant [83,86].

The implications of OS in hepatic diseases in dogs have been studied through the quantification of oxidants and antioxidants in various samples, such as blood, urine, and liver tissue, using a range of methods [83–97]. Elevated urinary IsoP levels have been found in dogs with liver disease of various origins, with a particularly pronounced increase in those with congenital portosystemic shunts [87,93]. Increased levels of plasmatic reactive metabolites and higher immunohistochemical expression of MDA in liver tissue have been reported in dogs with chronic hepatitis and copper-associated hepatitis. These markers have also shown a significant correlation with copper accumulation, necroinflammatory activity, and fibrosis scores [95,96]. The literature on impaired antioxidant defence due to hepatic depletion of GSH dogs is extensive. Low reduced and oxidized glutathione ratios (GSH/GSSG) are often found in dogs with various hepatopathies (i.e. necroinflammatory liver disorders, extrahepatic bile duct obstruction, copper toxicosis, chronic extrahepatic cholestasis, and chronic hepatitis), along with decreased values of antioxidant enzymes and total antioxidant capacity indexes [83–85,95,97]. Further support for these findings comes from transcriptome and gene array analyses of liver tissue from dogs with hepatitis and age-related hepatic changes, which suggest enhanced expression of genes related to OS and inflammation in hepatic dysfunction [88,92]. Overall, OS biomarkers appear to be promising for assessing canine liver disease of various origins, with only few studies reporting differently [87,90,95].

Consequently, several authors advocate for antioxidant therapeutic interventions in canine hepatopathies, and various supplements have traditionally been included in their medical management [84,86,87,89,91]. However, the efficacy of antioxidant administration in these patients remains a topic of debate [84,87,93]. Given the complexity of redox homeostasis, supplementing with a single antioxidant may not sufficiently alter OS biomarkers to be detectable by statistical analysis [84]. Traditionally, therapeutic approaches have focused on replenishing depleted GSH [86,87] by administering glutathione precursors like S-adenosylmethionine (SAMe), which is more readily available for clinical practice. Other antioxidant products with evidence of efficacy in canine hepatopathies include vitamin E, ursodeoxycholic acid and extracts of the milk thistle plant (Silymarin, Silybin, Silybinin), among others [84,86,89,91]. Webb and Twedt's review provides recommended dosages for these products in dogs and suggests the potential benefits of combination therapy [84].

2.5. Endocrine Diseases and Obesity

The contribution of OS to canine endocrinopathies has been studied mainly in dogs with hypothyroidism [98–100], Cushing syndrome [101–103], diabetes [104–107], obesity [108–112] and hyperlipidemia [113].

Data on hypothyroidism and OS, both in humans and dogs, are particularly conflicting. Thyroid hormones significantly influence redox homeostasis, yet their specific effects in hyper- and hypothyroidism remain intriguing, as discussed in a previous review [114]. Various studies have examined comprehensive panels of biomarkers in hypothyroid dogs, suggesting that increased OS is present, although results vary widely depending on the biomarker studied and the sample type. Some studies have reported elevated d-ROMs and MDA levels in the blood and saliva of hypothyroid

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dogs [98–100], while others have found lower AOPP levels [98,99]. Similarly, literature shows both increased [98,100] and decreased [99] levels of several antioxidant indexes. In this context, sample type seems to be relevant, with whole-blood samples potentially providing a better reflection of the altered redox homeostasis in these patients [99].

Unlike the well-established link between increased OS and diabetes in humans, which is associated with dysfunctional mitochondria and glucose auto-oxidation [3,104], studies in dogs have produced variable results. Some studies have reported increased markers of lipid and DNA oxidation, particularly in poorly-controlled diabetic dogs, suggesting an association with disease severity [104,106]. Additionally, significant improvements in OS biomarkers have been observed following antioxidant supplementation with N-acetylcysteine [106] and Fibroblast growth factor-21 [105]. Conversely, a recent study found no differences in MDA or SOD levels between diabetic and control dogs, and did not observe a significant benefit of another antioxidant, Andrographis paniculata [107].

Regarding Cushing's syndrome, research in canine species has been limited but consistent. Two studies reported increased markers of lipid and protein oxidation in dogs with hypercortisolism, particularly in poorly controlled patients. These studies also noted a significant reduction in oxidation markers following treatment, highlighting both the presence of increased OS and the significant benefits of medical control in these patients [101,102].

A reasonable question arises when evaluating OS, particularly lipid peroxidation, in dogs with endocrinopathies (e.g. Cushing syndrome and hypothyroidism): the potential influence of the patient's body condition score in the results [100,102]. Since obesity in humans has been associated with chronic inflammation and increased OS, several studies have studied this relationship in dogs [108–112]. Although this aspect is remains unclear [111,112], significant variations in OS biomarkers have been detected in the blood, saliva and adipose tissue of obese dogs [108–110,112]. Additionally, the impact of hyperlipidemia [113] and the significant interference of lipemia with OS biomarkers such as MDA and TAS has been reported [115]. This interference should be considered when interpreting results from dogs with endocrine diseases.

2.6. Hematologic Diseases

Red blood cells (RBCs) are particularly vulnerable to ROS attacks due to their ubiquity, proximity to oxygen molecules and elevated iron concentrations. In humans, OS has been proposed as both a cause and consequence of anemia, through mechanisms such as reducing the mean lifespan of RBCs or increasing tissue oxygen demand and ROS production [116–118]. While literature on this topic in dogs is scarce, it has provided some interesting data on anemia of various causes: haemolytic, non-hemolytic, secondary to kidney, infectious and oncologic diseases, among others [117–121]. Studies have shown variable changes in oxidation markers (ROS, IsoP, and MDA) [117–119], but substantial evidence suggests that OS and antioxidant depletion are involved in the development of anemia in dogs. This link is likely due to decreased antioxidant defenses, both enzymatic and non-enzymatic (GPX, Vitamin E, GSH) [118–121]. Further investigation is needed to determine whether OS is a primary cause or a secondary effect of anemia and to explore if antioxidant therapy could improve survival and overall outcomes in dogs with anemia from various causes [118–120]. It is also important to consider that hemolysis and icterus can be potential sources of interference, frequently affecting plasma or serum samples from these patients [115].

Additionally, two studies have highlighted that OS could be a significant concern in canine hemotherapy. Accumulation of oxidation products (MDA, PC) and depletion of natural cellular antioxidants (TAS, SOD, GPX, CAT) have been detected in stored canine whole blood, along with increased hemolysis. These findings suggest that prolonged storage periods (>28 days) might discourage the use of stored blood in certain cases [122]. Furthermore, the therapeutic efficacy of canine bone marrow mesenchymal stem cell transplantation may be compromised by OS-mediated senescence, as indicated by increased levels of ROS and decreased antioxidant enzymes. This effect has been mitigated by adding antioxidants, such as mitoquinone, to cell cultures [123].

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2.7. Infectious and Parasitic Diseases

2.7.1. Vector-Borne Diseases

- Leishmaniosis

The role of OS in the pathogenesis of canine leishmaniosis (CanL) has been extensively studied, and substantial evidence has been gathered on the relevance of OS and its association with the clinical stages of CanL [124–135]. The interplay between the host's immune response, the parasites, and OS creates a complex pathogenic landscape.

While *Leishmania spp.* can initially evade the immune system by suppressing ROS production by phagocytes, the subsequent development of inflammation in CanL is characterized by an increased influx of activated neutrophils and macrophages that generate high levels of oxidants. This contributes to the progression of the disease and a concomitant weakening of antioxidant defenses [125,126,131–133]. These aspects are supported by several studies that have found increased circulating oxidation markers (e.g. ROS, MDA, total oxidant status) [124–127,129,130] and variable changes in antioxidant markers (e.g. TAS, CUPRAC, FRAP, GSH, and thiol groups) depending on the clinical stage [125,126,129,133–135]. Almeida and colleagues also found that OS in CanL causes neutrophil dysfunction, leading to their apoptosis, particularly in severe stages and in association with uremia [124,125]. More recent findings suggest that increased OS impairs lymphoproliferative response and therefore cellular immunity in dogs with CanL [126]. Additionally, correlations between OS biomarkers and parasite load have been observed [135], as well as improvements in antioxidant defense following successful therapy, indicating that OS may be a useful tool for monitoring the treatment and clinical follow-up of sick dogs [133].

Despite the established link between OS and disease progression in CanL, therapeutic strategies targeting the redox state have not been extensively explored. While some authors advocate for tailoring CanL treatment plans based on the patient's redox status [132], research on the efficacy of enhancing the antioxidant defense system in this disease remains limited. A recent study reported a decrease in circulating MDA and PC, along with an increase in GSH, after the addition of nutritional adjuvants (omega-3 PUFAs and B vitamins) to standard anti-Leishmania treatment [128]. However, further research on this topic is needed.

- Ehrlichiosis

Significant alterations of redox status have been documented in canine ehrlichiosis [136–144]. Increased levels of ROS, MDA and AOPP, have been observed in both naturally and experimentally infected dogs [136–139,141,143], while a decrease in nitric oxide (NO) and MDA was noted following doxycycline treatment [141]. Antioxidant markers (e.g. TAS, CUPRAC, FRAP, GPX, thiol groups and others) have shown either increases or decreases depending on the disease stage (acute versus subclinical). These fluctuations likely reflect the complex interplay between OS and infectious agents [136,138,139,142,143].

- Babesiosis

Studies on OS canine babesiosis have consistently found elevated levels of reactive species (NO), lipid (MDA) and DNA oxidation markers (8-OHdG), along with variable alterations in antioxidant enzymes and indexes (e.g. TAS, SOD, CAT and GPX) in infected dogs [137,140,145–150]. Various authors have proposed that OS could be one of the mechanisms leading to anemia in dogs with babesiosis, as result of oxidative damage to erythrocytes, favouring their destruction [147,148,150]. Additionally, infected dogs with secondary multiple organ dysfunction have shown more pronounced redox alterations, suggesting OS biomarkers could serve as indicators of disease severity and outcomes in canine babesiosis [147].

- Other vector-borne diseases

Similar trends of increased DNA and lipid oxidation have been observed in dogs with heartworm disease, alongside variable findings in antioxidant markers [151–153]. Additionally, OS has been proposed to play a role in the pathogenesis of canine hepatozoonosis and trypanosomosis and may be related to the development of anemia due to increased lipid peroxidation in erythrocytes [154,155].

2.7.2. Infectious and Parasitic Gastrointestinal Diseases

Canine parvoviral enteritis is associated with OS, as evidenced by increased circulating MDA and NO levels, along with alterations in enzymatic and non-enzymatic antioxidant markers, likely

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due to virus-induced release of pro-inflammatory cytokines [156–159]. The addition of antioxidants such as N-acetylcysteine, resveratrol, and vitamin C to standard therapy can reduce the concentrations of MDA and NO and enhance the activity of certain antioxidant enzymes. However, a clear improvement of clinical scores or survival rates following antioxidant therapy has not been consistently demonstrated, and further research is necessary to determine the optimal selection and dosage of antioxidants for this purpose [156,157].

Regarding gastrointestinal parasites, the role of OS in their pathogenesis remains unclear. A study found significant changes in ROS metabolites and thiol levels in dogs with gastrointestinal nematodosis [160], while another study failed to demonstrate alterations in antioxidant markers in parasitized dogs [161].

2.7.3. Ectoparasites and Dermal Fungal Diseases

Canine demodicosis [162–166] and sarcoptic mange [167–170] are associated with increased OS. This is believed to result from the presence of parasites in the skin, which release antigenic material and trigger the production of pro-inflammatory cytokines. These factors may contribute to the pathological changes in the tissue, such as erythema, edema, hypersensitivity, pruritus and hyperkeratosis [165–168]. Elevated levels of peripheral oxidation biomarkers (MDA and other lipid hydroperoxides) have been consistently observed in dogs with both localized and generalized demodicosis, as well as in those with sarcoptic mange [162,163,165,167–170]. Markers of antioxidant defense have shown variable changes: while most of the studies have reported significant depletions in antioxidans like SOD, CAT, GPX and vitamins [162,167,168,170], others have found no change or even increased levels in infested dogs compared to control [163–165,169]. This variability might be explained by an initial upregulation of antioxidant defenses, followed by their overutilization or sequestration in the skin as the disease progresses [162]. Interestingly, some authors have identified a relationship between OS, the severity of infestation, and the rate of apoptosis in peripheral leukocytes in dogs with sarcoptic mange [168,170]. Moreover, treatment with ivermectin appears to normalize OS markers in both demodicosis and sarcoptic mange, especially when antioxidants such as vitamin E and selenium are added to standard therapy [164,167]. Additionally, a study reported increased OS in canine dermatophytosis, specifically noting a rise in circulating MDA and a decrease in both enzymatic and non-enzymatic antioxidants [171].

2.8. Neurologic Diseases

The nervous system, particularly the brain, is highly vulnerable to oxidative damage due to its high energy and oxygen consumption, the large concentration of PUFAs in myelin membranes, and its relatively low antioxidant defences [172,173]. While OS has been linked to the etiopathology of several neurologic diseases in humans [173], research in dogs remains limited. A recent study in dogs with idiopathic epilepsy, experiencing either focal or generalized seizures, revealed significant alterations in circulating OS biomarkers, including higher levels of AOPP and lower levels of GSH, thiol groups and other antioxidants [174]. These findings may be attributed to neuroinflammation and accelerated ROS-mediated neuronal deterioration, which could induce subsequent seizures [174,175]. Furthermore, Marquis et al. [172] evaluated IsoP, acrolein and GSH levels in urine, cerebrospinal fluid and spinal cord tissue of dogs with ascending–descending myelomalacia following spinal cord injury, finding exacerbated OS and a potential association with neurodegeneration and necrosis. In contrast, while the role of OS in canine motor neuron disease and degenerative myelopathy in Pembroke Welsh Corgi dogs has been studied, it has not been fully clarified [176–178].

2.9. Renal Diseases

Renal cells, particularly tubular epithelial cells, are significant sources of endogenous ROS due to their high mitochondrial activity, arterial blood flow, and the activity of ROS-producing NOX family enzymes [179,180]. Increases in renal ROS production can lead to the release of pro-inflammatory cytokines, and, if persistent, to inflammation and renal fibrosis, making OS a proven contributing factor to Chronic Kidney Disease (CKD) in both humans and animal models [179–182]. This issue becomes even more concerning when the few remaining nephrons become hyperfunctional, further increasing mitochondrial oxidative phosphorylation and ROS production

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[179,181,182]. Additionally, several factors commonly present in humans and animals with CKD can exacerbate OS, including activation of the renin-angiotensin system, systemic hypertension, chronic inflammation, proteinuria, anemia, and advanced age [179,182].

Various authors have studied the implication of OS in dogs with renal disease [117,179,181–187]. With very few exceptions in some circulating antioxidant indexes [181], most studies on canine CKD have evidenced significant alterations in OS biomarkers, especially in MDA, ROS, TAS, and antioxidant enzymes [117,183,187]. Some studies have also found significant correlations between MDA, creatinine concentration [117], and the degree of renal dysfunction [184]. The role of OS has also been observed in nephrotoxicity caused by hemoglobinuria [185], chemotherapeutic drugs (cisplatin) [186] and uremic toxins (methylguanidine) in dogs [183]. Additionally, it has been shown that OS accelerates neutrophil apoptosis in canine CKD, potentially affecting their innate immune response [183,187]. Protecting the kidney from OS through antioxidant supplementation and other therapeutic actions has been suggested in dogs, as summarized in Brown's review [179]. However, further clinical investigations are warranted due to the limited research in this area [179,182].

2.10. Dermatologic Diseases

The skin is continuously exposed to reactive species from both endogenous and environmental sources, necessitating robust enzymatic and non-enzymatic antioxidants, such as vitamins and carotenes [188,189]. Similar to humans, altered dermal redox homeostasis in dogs has been linked to certain skin diseases, particularly atopic dermatitis [189–193]. Despite some discrepancies exist depending on the specific biomarkers used, several studies have demonstrated a correlation between clinical scores (i.e. Canine Atopic Dermatitis Extent and Severity Index, CADESI) and OS biomarkers like MDA, antioxidant enzymes and vitamin E [189–191]. The contribution of OS to atopic dermatitis is likely related to the infiltration of the skin with inflammatory cells and cytokines, which promote ROS formation and disrupt skin's antioxidant barrier [188,190,191]. Consequently, OS biomarkers have been proposed as useful tools for precision medicine in dogs with atopic dermatitis [190]. Furthermore, various researchers advocate for a multimodal therapeutic approach that includes nutritional interventions and antioxidant supplementation (e.g., vitamins and carotenes) alongside standard therapies [189,190,193]. Limited data suggests that OS might also play a role in canine zinc-responsive dermatosis, although further investigation is warranted [194].

2.11. Ophthalmologic Diseases

OS is considered a risk factor for eye diseases [195], and has been studied primarily in two ophthalmologic disorders in dogs: cataracts [196–202] and glaucoma [203–206].

Lenses are chronically exposed to photo-oxidation of their proteins and lipids due to UV radiation, leading to protein aggregation and ultimately lens opacification. Despite the presence of antioxidant agents within the lens (such as vitamins and antioxidant enzymes), OS is widely recognized as a major contributor to cataract development, alongside other environmental and endogenous factors [196,197,201,202]. Significant alterations in oxidative biomarkers (MDA) and antioxidant biomarkers (TAS, SOD, CAT, GPX) have been detected in the blood and aqueous humor of cataractous dogs [198,200]. Additionally, decreased antioxidant capacity and vitamin C levels have been observed in the aqueous humor of dogs following extracapsular lens extraction and experimental phacoemulsification, suggesting that these surgical procedures initially induce an OS condition in the eye [197,199]. Attempting to prevent or delay cataract formation, both oral antioxidant supplements and topical antioxidant eye drops have been used in humans and dogs [201,202]. Examples of antioxidant agents demonstrating protective effects in dogs, particularly in incipient cataracts, include grape seed extracts, vitamins C and E, curcuminoids, and others [196,201].

Similarly, OS appears to be a major contributor to retinal ganglion cell degeneration and glaucoma development [203,205,206]. Increased immunolabeling for OS biomarkers has been observed in retinal tissue of dogs with acute glaucoma [204], and lower antioxidant enzymes (GPX) have been related to increased risk of inherited glaucoma in Euraiser dogs [203]. Although antioxidants have been proposed to protect canine retinal membranes under experimental conditions [195], the literature on this topic remains limited.

2.12. Orthopaedic Diseases

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Reactive species are considered important mediators in the pathophysiology of osteoarthritis. Chondrocytes and activated inflammatory cells in this condition release increased amounts of ROS, which further damage collagen, proteoglycans and hyaluronic acid, and enhance chondrocyte senescence and cartilage degradation [207–211]. This redox imbalance has been documented in dogs with both naturally occurring and experimentally induced osteoarthritis, as evidenced by OS biomarkers in blood and canine chondrocyte cell cultures [208–212]. Enhanced oxidative processes have also been observed in circulating OS biomarkers in dogs suffering from hip dysplasia, likely due to similar mechanisms of cartilage inflammation and degradation [207,213].

Dietary composition, particularly the lipid profile with a focus on omega-3 PUFAs and eicosapentaenoic acid (EPA), appears to play a critical role in mitigating these processes. Both pharmaceutical interventions (e.g., N-acetylcysteine) [209] and nutraceutical products (e.g., fish oil, corn oil, and other plant-derived compounds) [208,211,212] have demonstrated protective effects against OS in canine osteoarthritis.

2.13. Reproductive System Diseases

Recent studies have shown consistent alterations in OS biomarkers measured in blood, urine and uterine tissue, in bitches with cystic endometrial hyperplasia and pyometra. These findings suggest that excessive ROS production may be a significant factor contributing to uterine damage by weakening local antioxidant defenses and exacerbating these disorders [214–216]. Additionally, as summarized in Domosławska-Wyderska and colleagues' recent review [217], various studies indicate that OS may play a relevant role in the pathogenesis of canine benign prostatic hyperplasia. This association could be linked to age-related hormonal changes and chronic inflammation of the prostate. However, further research is needed to evaluate the potential benefits of antioxidants in this condition [217].

2.14. Dental Diseases

Studies investigating OS markers in canine periodontal disease have yielded mixed results [218,219]. While one recent study found no changes in salivary MDA concentrations [219], a previous study detected significant accumulation of MDA and 8-OHdG in the saliva of dogs with periodontal disease, along with an increase in salivary SOD activity [218]. This earlier study also found correlations between OS biomarkers and the severity of gum and teeth clinical signs, which were attributed to the inflammatory processes in the oral cavity [218].

2.15. Others

Additionally, other studies have demonstrated OS is present in dogs with ischemia-reperfusion injury [220], as well as in systemically ill dogs undergoing hospitalization due to various underlying disorders (e.g. infectious, inflammatory, immune-mediated, metabolic, neoplastic) [221,222]. It has been observed that hospitalized dogs exhibit increased lipid peroxidation (elevated urinary IsoP levels) and antioxidant depletion, particularly in GSH and vitamin E. While N-acetylcysteine supplementation did not appear to improve overall redox state in these dogs, further research is needed to explore other antioxidant therapeutic options and their impact on longer-term outcomes [221,222].

3. Conclusions

Solid evidence demonstrates the role of OS in a multitude of canine diseases, impacting diverse organs and systems. In some conditions, it remains unclear whether reactive species are significant causative agents or merely byproducts of the inflammatory processes involved. Inconsistencies across studies may arise from differences in sample selection, the specific OS biomarkers used, and variations in analytical methods. Moreover, interpreting increased antioxidant defenses as a response to OS or antioxidant depletion as a sign of imbalance can be challenging.

Therapeutic approaches to managing OS vary widely among canine diseases. Certain antioxidants are commonly used in some diseases (e.g., hepatopathies), while pro-oxidant drugs are employed in others (e.g., oncology). In some areas this issue remains underexplored.

To our knowledge, this is the first comprehensive review summarizing current understanding of OS in canine pathology, with the aim of paving the way for further research in such a broad and evolving field.

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