Research Article

Investigation of Thiol Disulphide Balance in Dogs with Canine Leishmaniasis

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Abstract

Previous studies have demonstrated that oxidative stress plays a significant role in the etiopathogenesis of diseases. In this study, it was aimed to elucidate the etiopathogenesis of Canine Leishmaniasis by comparing the levels of thiol/disulfide, known as oxidative stress markers, in affected dogs and clinically healthy controls. Specifically, the objective was to determine the levels of dynamic Thiol-Disulfide Homeostasis in serum, including native thiol, total thiol, and disulfide, as well as to calculate the ratios of disulfide/total thiol and disulfide/native thiol.

A total of 30 dogs aged between 1 and 9 years were included in the study. These dogs were divided into two groups: positive and negative, to form the experimental and control groups. Blood samples were collected from dogs suspected of having leishmaniasis in veterinary clinics (Caniv-4 Leishmania, Vet Expert, Vet Planet Ltd., Poland). Using a diagnostic kit screening for four infectious diseases, dogs that tested positive only for leishmaniasis and negative for the remaining three were included in the infected group, while dogs that tested negative for all were included in the control group. Serum samples were stored at −20°C and analyzed in the laboratory for thiol, disulfide, and ischemia-modified albumin (IMA) levels.

Thiol-disulfide and IMA levels of dogs diagnosed with leishmaniasis (n=20) and healthy dogs (n=10) were compared. Native thiol and total thiol levels in leishmaniasis-positive dogs were found to be similar to those of healthy controls. The findings suggest that oxidative stress may occur in dogs with Canine Leishmaniasis when thiol-disulfide homeostasis is used as a reference marker.

Keywords: Canine leishmaniasis, Thiol-disulfide homeostasis, Oxidative stress, Ischemia-modified albumin

Introduction

Canine leishmaniasis (CanL), caused by Leishmania spp. parasites, is a significant zoonotic disease that can lead to severe systemic infections in dogs. This disease is endemic in regions such as the Mediterranean basin, South America, and certain parts of Asia, and it is transmitted through the bite of infected female sandflies belonging to the Phlebotomus genus (Ready, 2014). CanL may manifest within a broad clinical spectrum ranging from cutaneous lesions to systemic organ involvement, and if left untreated, it can result in fatal outcomes.

Leishmaniasis presents in three main clinical forms: visceral (VL), cutaneous (CL), and mucocutaneous (MCanL). Approximately 1.3 million new cases are reported annually, with around 300,000 of these being VL cases, while the remaining cases consist of CanL and MCanL (WHO, 2013).

In the pathogenesis of the disease, the host's immune response plays a crucial role. In host cells, the production of reactive oxygen species (ROS) increases in response to infection, which facilitates the elimination of parasites. However, excessive ROS production can also lead to oxidative stress and tissue damage (Persson et al., 2014). Oxidative stress is defined as an imbalance between the rate of production of reactive oxygen and nitrogen species (ROS/RNS) and the antioxidant defense capacity (Yi & Khosla, 2016).

The thiol-disulfide balance is an important biochemical parameter in the evaluation of oxidative stress. Thiols maintain cellular redox homeostasis by neutralizing free radicals. Oxidation of thiol groups results in the formation of disulfide bonds, reflecting the organism's oxidative stress burden (Erel & Erdoğan, 2020). In this process, antioxidants prevent the formation of ROS or repair the damage caused, thereby playing a critical role in the organism's defense mechanisms (Valko et al., 2007).

Alterations in thiol-disulfide homeostasis have been closely linked to disease severity and prognosis in various infectious conditions, including Canine Leishmaniasis (CanL). Oxidative stress, resulting from excessive production of reactive oxygen species (ROS), can contribute to cellular dysfunction and suppression of the immune system. Emerging evidence suggests that the thiol-disulfide balance may serve as a critical biomarker for monitoring the clinical course of infectious diseases (Halliwell & Gutteridge, 1984).

The present study aims to investigate the role of thiol-disulfide homeostasis in dogs diagnosed with CanL, evaluating its association with oxidative stress and clinical outcomes. Furthermore, serum levels of ischemia-modified albumin (IMA) were measured to explore their potential impact on disease progression. The overall objective was to enhance understanding of the pathophysiological mechanisms involved and to support the development of more effective diagnostic and therapeutic strategies in the management of Canine Leishmaniasis.

Materials and methods

Ethical Approval

This study was conducted with the approval of the Kırıkkale University Local Animal Experiments Ethics Committee (approval number: 2025-01/06).

Animal Material

The animal material used in this study consisted of dogs presented to veterinary clinics located in Bodrum, Muğla province in the Aegean region of Turkey. Informed consent was obtained from all owners of the animals included in the study. A total of 30 dogs were used: 20 dogs diagnosed with CanL and 10 clinically healthy dogs, varying in breed, sex, and age (between 1 and 9 years).

Blood Sample Collection

Blood samples were collected from the cephalic vein of the participating dogs into anticoagulant-free tubes and allowed to clot for 20 minutes at room temperature. Following this, the samples were centrifuged at 3000 rpm for 10 minutes, and sera were separated. The obtained sera were tested using a rapid diagnostic kit (Caniv-4 Leishmania, Vet Expert, Vet Planet Ltd., Poland) for Leishmania, Ehrlichia, Anaplasma, and Dirofilaria infections. Dogs that tested positive only for Leishmania and negative for the other three pathogens were included in the CanL group, while those testing negative for all four were assigned to the control group. Sera designated for analysis were stored at −20 °C until testing.

Laboratory Analyses

Once sampling was completed, the thawed sera were analyzed in the laboratory. Native thiol (NT),

total thiol (TT), and disulfide (D) levels were measured using the method described by Erel and Neşelioğlu (2014). Ischemia-modified albumin (IMA) levels were determined using the method proposed by Bar-Or et al. (2000).

Statistical Analysis

The variables were examined with the Shapiro-Wilk test and Levene test as parametric test assumptions. The differences in NT, TT, Disulfide, Disulfide/NT, Disulfide/TT, NT/TT and IMA among the groups were analyzed using Student t test. Receiver operating characteristic (ROC) analysis was used to determine a predicted threshold for identification of canine Leishmaniasis. ROC curves for the detection of canine Leishmaniasis was obtained for the parameters that were found to be statistically significant. Sensitivity, specificity, 95 % confidence interval, and area under the curve (AUC) were calculated for the parameters. Differences with $p < 0.05$ were considered statistically significant. All statistical analyses were performed using IBM SPSS 23.0 and MedCalc Version 9.2. The comparison of serum native thiol, total thiol, disulfide, disulfide/native thiol, disulfide/total thiol, native thiol/total thiol ratios, and ischemia-modified albumin (IMA) levels between dogs diagnosed with Leishmaniasis and clinically healthy (control group) dogs is presented in Table 1. The results indicated that native thiol and total thiol levels were significantly lower in dogs with Leishmaniasis ($p<0.05$), while changes in the other parameters were not statistically significant ($p>0.05$).

Results

Among the control group dogs, 4 (40%) were female and 6 (60%) were male. In the Leishmania group, 11 (55%) were female and 9 (45%) were male. The youngest dog in the control group was 2 years old, and the oldest was 8 years old, with a mean age of 4.7 years. In the Leishmania group, the youngest was 2 and the oldest 12 years old, with a mean age of 5.6 years. The control group consisted of 10 dogs, 5 of which were mixed-breed, while the others were terrier (1), pointer (1), cavalier king charles (1), doberman (1), and dogo argentino (1). The positive group (CanL) included 7 mixed-breed dogs and 13 purebred dogs, including beagle (1), husky (1), pointer (2), rottweiler (1), golden retriever (2), terrier (1), labrador retriever (2), chihuahua (1), schnauzer (1), and yorkshire terrier (1).

It was observed that 60% of the control dogs had a regular vaccination schedule. Among the

Table 1 : Comparison of native thiol, total thiol, disulfide levels, their ratios, and IMA levels between dogs with Leishmaniasis and healthy (control) dogs

Parameter	Group	Mean	Std Error	Std Dev.	Median	Minimum	Maximum	p
NT	Control	250,53	16,55	52,35	255,50	168,90	317,00	0,014*
	Leish	205,97	8,84	39,54	210,00	132,10	256,40	
TT	Control	318,07	19,87	62,83	337,45	220,50	396,60	0,019*
	Leish	265,20	11,36	50,82	274,20	168,20	327,80	
Disulfide	Control	33,77	2,18	6,89	33,05	24,80	42,55	0,115
	Leish	29,62	1,44	6,44	30,45	18,05	41,05	
Disulfide/NT	Control	13,64	0,62	1,97	13,55	10,79	16,20	0,290
	Leish	14,40	0,39	1,74	14,08	11,77	18,20	
Disulfide/TT	Control	10,68	0,39	1,22	10,66	8,88	12,23	0,278
	Leish	11,15	0,23	1,04	10,99	9,53	13,34	
NT/TT	Control	78,64	0,77	2,45	78,68	75,53	82,25	0,278
	Leish	77,69	0,47	2,08	78,03	73,32	80,95	
IMA	Control	0,77	0,02	0,06	0,76	0,68	0,86	0,873
	Leish	0,77	0,02	0,07	0,76	0,66	0,92	

Control: Control group; Leish: Leishmaniasis group; NT: Native thiol; TT: Total thiol; IMA: Ischemia-Modified Albumin.

*: Significant difference between groups ($p < 0.05$).

In the assessment conducted in terms of oxidative stress, a significant difference was observed between the groups for total thiol and native thiol levels. Based on these differing values, ROC curve analysis was performed (Table 2). When comparing total and native thiol levels, total thiol was found to be more specific in evaluating leishmaniasis in infected dogs (Figure 1, Figure 2).

Table 2: Comparison of total thiol and native thiol levels using ROC curve analysis

Parameter	Threshold	Se	%95 CanL for Se	Sp	%95 CanL for Sp	AUC	p
NT	≤ 246,8	85,00	62,1 - 96,6	70,00	38,4 - 93,0	0,765	0,008
TT	≤ 327,8	100,00	83,0 - 100,0	60,00	26,4 - 87,6	0,765	0,008

NT: Native thiol, TT: Total thiol

Figure 1: ROC curve comparison of native thiol and total thiol measurements in dogs with Leishmaniasis.

Leishmania-positive dogs, 13 (65%) had mixed breeding and 6 (30%) were selected from shelters, while 10% were identified as street-origin dogs. In contrast, all dogs in the control group (30%) were reported to be raised in home. In the Leishmania group, 10 dogs (50%) were also reported to be raised and were living in gardens.

Dogs in the control group weighed between 4 and 45 kg, with an average body weight of 23.3 kg. Dogs in the Leishmania group weighed between 3–40 kg, with an average weight of 22.3 kg. In the control group all except for one dog(%10) received regular external anti-parasitic treatment. Whereas only 9 dogs(%45) in the Leishmania group were reported to undergo regular external parasitic treatment. 13(%65) of the dogs in the Leishmania group were reported of not having regular anti-parasitic drug treatment.

As shown in Table 1, when comparing serum levels of native thiol, total thiol, disulfide, disulfide/native thiol, disulfide/total thiol, native thiol/total thiol, and ischemia-modified albumin between dogs with leishmaniasis and healthy controls, it was found that native and total thiol levels were significantly lower in dogs with Leishmaniasis ($p<0.05$). No statistically significant differences were found in the other measured parameters ($p>0.05$).

Discussion

Canine leishmaniasis (CanL) is recognized as one of the most significant vector-borne zoonotic diseases affecting dogs worldwide (Dantas-Torres et al., 2012). Its chronic and multisystemic course, characterized by a broad spectrum of clinical manifestations, complicates both diagnosis and management (Mann et al., 2021; Baneth et al., 2021). The most frequently reported clinical findings include dermatological lesions and localized or generalized lymphadenomegaly (Cardoso et al., 2021). The clinical diagnosis of Canine Leishmaniasis (CanL) remains particularly intricate, given that approximately half of the infected canine population exhibit no overt clinical symptoms (Mancianti et al., 1988). Moreover, the clinical presentation is marked by considerable heterogeneity and lacks specificity. Typically, the disease manifests as a chronic, multisystemic condition with potential involvement of multiple organ systems throughout the body (Solano-Gallego et al., 2011).

Due to its unique geographical and climatic

characteristics, Turkey is considered an endemic region for CanL, where the disease has evolved into a notable public health concern (Toz et al., 2013). Reported prevalence rates across different regions of Turkey vary significantly, ranging from 0% to 37.4% (Aslan Çelik et al., 2019). Epidemiological data have demonstrated regional disparities in CanL prevalence across Turkey: a seroprevalence of 0% has been reported in Southeastern Anatolia, approximately 2% in Central Anatolia, and the highest burden in the Aegean region, with a documented prevalence of 37.4% (Aydenizöz et al., 2010; Aslan Çelik et al., 2019; Bakırcı and Topçuoğlu, 2021). The present investigation was accordingly conducted in the Aegean region, recognized as the most endemic area for CanL within the country.

This study aimed to evaluate alterations in thiol-disulfide homeostasis (TDH) in dogs diagnosed with CanL, with a specific focus on the role of oxidative stress in disease pathogenesis. The findings demonstrated a statistically significant decrease in native thiol (NT) and total thiol (TT) levels in infected dogs, whereas the increase in disulfide levels was not statistically significant. This observation may be interpreted as indicative of thiol reservoir exhaustion, potentially attributable to the heightened oxidative stress burden experienced by the affected organisms.

The pathogenesis of CanL involves an immune response triggered by the intracellular replication of Leishmania spp. within macrophages, which in turn leads to increased production of reactive oxygen species (ROS). However, excessive ROS production can induce oxidative damage to host cells and impair immune function (Persson et al., 2014; Yi & Khosla, 2016). During this process, thiol groups are oxidized into disulfide bonds, thereby disturbing the physiological thiol-disulfide equilibrium (Erel & Erdogan, 2020).

Numerous veterinary studies have investigated the oxidative stress induced by various infectious diseases through the evaluation of TDH parameters. Çamkerten et al. (2019) reported significantly reduced NT, TT, and disulfide levels in sheep with sarcoptic mange, although disulfide/NT, disulfide/TT, and NT/TT ratios showed no significant difference between the infected and control groups. These results suggest that oxidative stress in sarcoptic mange is accompanied by a decrease in antioxidant capacity. In alignment with these findings, Değirmençay et al. (2021) reported a significant perturbation in the thiol–disulfide homeostasis among distemper virus-infected canines. Similarly, Terzi et al. (2021) documented decreased concentrations of total thiol (TT) and native thiol (NT) in diarrheic calves. Collectively, the converging evidence from these three clinical investigations underscores a consistent biochemical trajectory associated with systemic inflammatory conditions. In another investigation, Kurtdede et al. (2022) demonstrated that asymptomatic dogs infected with canine parvovirus (CPV) exhibited increased levels of malondialdehyde (MDA), paraoxonase-1 (PON-1), and disulfide, accompanied by reduced NT and TT levels. In contrast, Şenel et al. (2024) reported that NT and TT levels were higher in symptomatic CPV-infected dogs compared to controls. These data suggest that in acute pathologies such as canine parvoviral enteritis (CPV), particularly those progressing with sepsis, endogenous antioxidant defense mechanisms may be mobilized at earlier stages of disease progression. Furthermore, the elevated levels of antioxidant markers such as TT and NT during convalescence—when compared to control subjects—could imply an active role of redox homeostasis in the recovery cascade. Contrastingly, in the current study, dogs afflicted with CanL exhibited significantly diminished TT and NT levels, reflective of a pronounced oxidative stress status. In the present study, the significant decrease in NT and TT levels among dogs with CanL indicates a state of oxidative stress. While these results diverge from those of Şenel et al. (2024), they are in agreement with findings from other chronic disease models. It is therefore plausible to suggest that the oxidative stress profile in CanL resembles that observed in chronic infections such as sarcoptic mange rather than in acute, rapidly progressing diseases like CPV.

Ehrlichia, Anaplasma, and Dirofilaria infections have also been shown to trigger oxidative stress responses in dogs. In a recent study by Dokuzeylül et al. (2024), it was reported that dogs infected with Anaplasma and Ehrlichia had significantly increased total oxidant capacity (TOC) and nitric oxide (NO) levels, along with reduced total

antioxidant capacity (TAC), indicating oxidative stress. Elevated oxidative stress index (OSI) levels in these vector-borne diseases support the concept of disrupted redox homeostasis. These findings are in agreement with the current study, which also suggests an imbalance in oxidative status related to Leishmania infection.

In another study by Gültekin et al. (2017), oxidative stress markers were evaluated in CanL-positive dogs, and a significant reduction in the enzymatic antioxidant PON-1 activity was observed compared to healthy dogs ($p<0.001$), although no significant difference in total antioxidant capacity (TAC) levels was found. The results of the current study are consistent with those of Gültekin et al., confirming the presence of oxidative stress in dogs with CanL. This study also demonstrated through ROC analysis that NT and especially TT levels could serve as potential biomarkers in the diagnosis of CanL. The high sensitivity and specificity of TT levels support their use as potential diagnostic indicators. In line with previous literature, decreased thiol levels and increased oxidative stress load were observed in CanL-positive dogs (Halliwell & Gutteridge, 1984; Valko et al., 2007). However, ischemia-modified albumin (IMA) levels showed no statistically significant difference between groups, suggesting that IMA may not be a specific marker for CanL.
Total oxidant and antioxidant capacity, ceruloplasmin and ischemia-modified albumin (IMA) are some of the important biomarkers of oxidative stress (Ateş et al., 2016; Elmas et al., 2017; Hanikoğlu et al., 2016; Erel and Neşelioğlu 2014). Ischemia-modified albumin is an oxidant marker which is a derivative of albumin (Lippi and Montagnana, 2009). In human medicine, many studies are available on the relationship between IMA and increased oxidative stress (Özcan et al. (2018).

They indicated that the levels of IMA were positively correlated with other oxidant parameters (Ds, Ds/NT, and Ds/TT) and negatively correlated with antioxidant parameters (NT, TT, and NT/TT). (Değirmencay et al. (2021). In a 2021 publication on oxidative stress in dogs with distemper, they found that IMA was higher in dogs with distemper compared to the control group (Değirmencay et al., 2021). In the study conducted by Terzi et al. in 2023 with calves, a total of 50 calves were included in the study. There were 25 calves in both the diarrheal and healthy groups. In neonatal diarrheal calves, natural thiol ($P=0.025$) and total thiol ($P=0.041$) values were significantly decreased compared to the healthy control group. Disulfide ($P=0.133$), disulfide/natural thiol ratio ($P=0.001$) and IMA ($P=0.0018$) parameters were lower in the healthy group and the difference between the two groups was significant for parameters other than disulfide. This study shows that TDH is impaired in neonatal calf diarrhea and IMA levels increase due to oxidative stress (Terzi et al., 2023). A negative correlation was observed between thiol and IMA in these two studies. In this study, no significant difference was detected in IMA levels between the infection and control groups.

Based on the findings, it has been proposed that preserving thiol-disulfide balance and reducing oxidative stress may be beneficial for clinical management of CanL. Antioxidant therapies containing thiol-based agents such as N-acetylcysteine (NAC) and alpha-lipoic acid (ALA) could provide therapeutic benefits in this context (Güler et al., 2021; Tunalı et al., 2022).
Nevertheless, the study has certain limitations. The relatively small sample size and lack of inclusion of various disease stages may limit the generalizability of the results. Future studies involving a larger and more homogeneous population, including longitudinal designs, would allow for a more comprehensive evaluation of thiol-disulfide balance and other oxidative stress markers.

Conclusion

In conclusion, this study demonstrated that thiol-disulfide homeostasis is disrupted in dogs with CanL, and oxidative stress plays a central role in the pathogenesis of the disease. The observed reductions in NT and TT levels indicate that these parameters may serve as reliable diagnostic and prognostic biomarkers. Targeting oxidative stress and using appropriate antioxidant support may provide a promising therapeutic approach for CanL management. However, this approach needs to be validated through larger, randomized controlled trials.

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This manuscript reports the results of the same-name graduate study and has never been published in another place.

Conflict of Interest

The authors declare that there is no conflict of interest for this study.

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