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ORIGINAL ARTICLE

# Altered blood oxidative stress markers in association with antioxidant supplemented therapy for mange, tick, and flea allergic dermatitis of dogs

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**Abstract**
Skin diseases are among the most common health problems in dogs. The study aimed to evaluate the oxidative stress biomarker profile in mange-, tick-, and flea-infested dogs and to assess the value of antioxidant supplementation as complementary therapy to standard treatment. Thirty-seven dogs were enrolled in the study, and they were divided into three groups: apparently healthy group (11 dogs), mange group (8 dogs), and tick- and flea-infested group (18 dogs). Four dogs out of mange group and eleven dogs out of tick- and flea-infested group were treated with specific therapy supplemented with vitamin E and selenium (tocopherol 50 mg + Se 1.5 mg/ml) 0.5 ml/20 kg IM weekly in mange group and vitamin E capsule at dose of 40 IU/Ib in ticks and fleas group for 3 weeks as antioxidant therapy. Oxidative stress biomarkers were measured including SOD, GPX, catalase, and MDA. In mange group, there were significant increase in SOD, MDA, and significant decrease in GPX, catalase enzymes in diseased groups, while after treatment SOD was significantly decreased in antioxidant supplemented group only. Catalase was significantly increased, MDA was significantly decreased in specific and antioxidant supplemented groups but no significance differences between two types of treatment were noticed. In tick- and flea-infested group, there were significant decrease in GPX and increase in MDA in diseased groups; after treatment there were significant increase in GPX and catalase only in antioxidant supplemented group and significant variances between two protocols of therapy in catalase level only. Vitamin E and selenium can be used with standard therapy to accelerate the clinical recovery of external parasitism in dogs.

**Keywords** Sarcoptic · Demodicosis · Vitamin E and selenium · Oxidative stress markers

## Introduction

Sarcoptic manage, also known as canine scabies, is a highly contagious infestation caused by Sarcoptes scabiei canis, a burrowing mite. The canine sarcoptic mite can also infest cats, pigs, horses, sheep, and various other species. The burrowing mite digs into and through the skin, causing intense itching attributed to allergic reaction to the mite and crusting. Hair loss and crusting are commonly seen on elbows and ears. Skin injuries can occur due to intense scratching and biting (Diwakar and Diwakar 2017). There are two common clinical forms of mange in dogs: localized and generalized forms. The localized form occurs in dogs < 2 years, and the generalized occurs in older dogs (Niedringhaus et al. 2019). Demodicosis is also known as demodectic mange or red mange or follicular mange caused by Demodexcanis canis is a normal inhabitant of dog's skin. Demodicosis is divided into two types in dogs. Localized demodicos usually starts with one or two hairless spots especially on muzzle, face, leg, and around the eyes and needs no treatment. The generalized demodicos is characterized by the presence of five or more local lesions with patchy areas, erythematous lesions, scales, and papules. Affected skin becomes crusted, ulcerated due to secondary superficial and deep pyoderma. (Veena et al. 2017). Flea infestation is common in areas of the world where fleas are endemic; i.e., where fleas find the optimal environment in which to proliferate, clinical signs accompanying flea infestation are low to moderate pruritus (Laffort-Dassot 2009). Diseases secondary to

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tick bites can be occurring to tick-borne infectious agents or as a result of inflammatory or neurotoxic salivary components injected by the tick. Clinical signs are an acute onset of lethargy, anorexia, pain, pyrexia, and swelling at the site of tick attachment and signs during tick feeding. Signs resolve within 72 h of tick removal, often but not always in conjunction with medical treatments (Strong-Klefenz and Gaskill 2008). Skin is a main goal of oxidative stress due to reactive oxygen species (ROS) that originate in the environment and in the skin itself. ROS are oxygen-containing reactive molecules that can be naturally generated from biological systems. When produced at low levels, ROS act as important signaling molecules involved in a variety of physiological activities such as immune response, muscle contraction, and exercise adaptation. Endogenous antioxidants including catalase, SOD, and GPx are important ROS scavengers that are responsible for maintaining ROS at normal levels. However, under specific pathological conditions, antioxidant defenses can be overwhelmed, resulting in cellular oxidative stress (Zhou et al. 2018). In skin diseases, animal's body protects itself against injurious effects of free radicals via antioxidants, involving antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and glutathione reductase and dietary antioxidants such as vitamins C and E, zinc, folate, selenium, and carotenoids. Increase in level of endogenous oxidants occurs in numerous disorders including inflammation, sarcoptic mange, and canine demodicosis (Bhattacharya 2015). Selenium (Se) plays an essential role in antioxidant defense systems, thyroid hormone metabolism, and cell growth. It participates in seleno protein compounds formation as glutathione peroxidase (GPx) and provides protection against oxidative damage (Neamat-Allah et al. 2019). Addition of vitamin E and selenium in conjugation to standard therapy can relieve these modifications, accelerating the clinical improvement of diseased dogs and can be used as a complementary therapy with miticides for canine sarcoptic mange (Behera et al. 2011). On the other hand, malondialdehyde (MDA) is widely used as oxidative stress biomarker in biomedical fields. Monitoring of MDA levels in different biological systems can be used as an important indicator of lipid peroxidation that results in formation of various active compounds resulting in cellular damage (Singh et al. 2014). The current investigation was accomplished to evaluate the oxidative stress biomarker profile in mange as well as tick and flea infestation and to assess the value of antioxidant supplementation as complementary therapy to standard treatment to accelerate clinical improvement of external parasitism in dogs.

## Materials and methods

**Animals** Thirty-seven (37) dogs including eleven apparently healthy dogs used as control group, eight dogs affected by mange (sarcoptic and demodectic), and eighteen affected with external parasites (ticks and fleas) of different breeds (German Shepherd, Golden Retriever, Griffon, Great Dane, Dogo Argentino, PitBull, Rottweiler, Boxer, Siberian Husky, Labrador Retriever, and mixed breeds mongrel) presented to private clinics in Giza and Cairo governorate. Their age ranged from few months to 6 years. Definitive diagnosis included detailed history, physical examination, close inspection of entire skin; skin scraping, and appropriate diagnostic tests were performed at time of admission.

**Dermatological examination** Superficial and deep skin scrapings, and hair plucks were collected from dermatologically affected dogs for laboratory examination using scalpel blades till oozing of blood to ensure that epidermis was removed, and the materials obtained were used for detection of sarcoptic or demodexmites (Sharma and Wadhwa 2018).

**Blood sample collection and erythrocytelysate preparation** Blood samples were collected from animals before and after treatment on heparin anticoagulant for preparation of plasma and erythrocyte lysates. For preparation of erythrocyte lysate, red cells were obtained via centrifugation at 4000 rpm for 10 min at 4 °C and the plasma was collected. The obtained cells were washed for three times with four volume colds a line. The red cell pellets were lysed by adding 4 volumes of cold deionized water to the estimated pellet volume. The red cell stroma was removed by centrifugation at 4000 rpm for 10 min at4°c.

**Blood sample analysis** The resulting clarified supernatant was used in the assay of SOD and GPX using colorimetric test kits (Bio-Diagnostic Company Egypt) according to manufacturer's instructions (Nishikimi et al. 1972; Paglia and Valentine 1967), respectively. Samples were frozen at − 70 °C before use if they would not be assayed at the same day. Heparinized plasma samples were used for estimation of catalase and MDA levels using respective test kits (Bio Diagnostic Company, Egypt) made according to manufacturer's directions (Aebi 1984; Begenik et al. 2013), respectively.

**Medicinal protocols** In mange group, four dogs were treated with specific therapy included Deltametherindip and S/C ivermectin injection for sarcoptic mange, amitrazrinse, S/C ivermectin injection, and systemic antibiotics for secondary bacterial infestation for 10 days (Diwakar and Diwakar 2017). The other four dogs were treated with standard therapy with supplementations of vitamin E and selenium (tocopherol 50 mg + Se 1.5 mg/ml) at 0.5 ml/20 kg IM at weekly intervals for three times. Two consecutive negative skin scrapings after treatment were considered as recovery (Behera et al. 2011; Mueller 2004). In tick- and flea-affected group, seven dogs were treated specifically with insecticide preparations and antihistamines to control pruritis and eleven dogs treated with vitamin E capsules at dose of 40 IU/Ib along with the specific treatment. Blood samples were collected from all groups before and after treatment (Majagi et al. 2011).

## Ethical approval

The research procedures were approved by the Institutional Animal Care and Use Committee with document serial number (Vet CU20022020136), Faculty of Veterinary Medicine, Cairo University, Egypt.

**Statistical analysis** Values were expressed as mean SD. Statistical comparisons among the means of different experimental groups were achieved with completely randomized one-way ANOVA by Spss program version 16.00.The measured parameters were expressed as mean value ± SE. A probability "$P$" value of $\geq 0.05$ was assumed as statistically significant.

## Results

The clinical signs of demodicosis, sarcoptic mange, and tick and flea infestations were recorded before and after treatment (Fig. 1).The diagnosis was confirmed using microscopic examination of deep skin scrapings (Fig. 1b). Results of oxidative stress markers before and after treatment in mange, tick- and flea-infested dogs are represented respectively in Tables 1 and 2.Regarding mange-infested dogs, SOD was significantly increased in mange-affected dogs when compared with control dogs ($P \leq 0.05$). In antioxidant supplemented group, SOD level was significantly decreased when compared with diseased and specifically treated group ($P \leq 0.05$). GPX activity was significantly decreased in diseased and treated groups when compared with the control one ($P \leq 0.05$). In treated groups, no significant changes were observed when compared with diseased group and there were no significant differences between the two types of treatment. Catalase level was significantly reduced in mange group when compared with the control group ($P \leq 0.05$). It significantly increased after both protocols of therapy ($P \leq 0.05$) when compared with diseased group, but no significant changes were noticed between the two types of treatment. MDA activity was significantly increased in diseased dogs when compared with the control dogs ($P \leq 0.05$). MDA was significantly decreased after both specific and antioxidant therapy ($P \leq 0.05$) when compared with diseased group, but it remained significantly higher than control group ($P \leq 0.05$) and no significance variations between two types of treatment were observed. Regarding tick- and flea-infested group no significant changes in SOD level in diseased dogs and treated dogs when compared with control group and there were no significant variations between the two types of treatment. GPX activity was significantly lower in tick and flea allergic dermatitis affected dogs and both treated groups when compared with the control one ($P \leq 0.05$), and its level was significantly higher ($P \leq 0.05$) in antioxidant-treated group when compared with diseased group, but no significant variations were detected between the two types of therapy. Catalase activity was significantly higher ($P \leq 0.05$) in antioxidant-treated group when compared with control, diseased, and specifically treated groups. MDA was significantly increased in diseased when compared with the control dogs ($P \leq 0.05$), maintained significantly higher than control group even after treatment, and there were no significant changes between the two kinds of treatment that were identified.

## Discussion

Dermatologic ailments considered one of the most frequent of small animal cases are important for their consequence on the animal as distress, pruritis, irritation, offensive odor, and transmission of various zoonotic diseases (Kehrer and Klotz 2015).

**Table 1** Oxidative stress biomarkers of dogs infested with mange before and after treatment

| Parameters | Control ($n = 11$) Mean ± SE | Mange-affected group ($n = 8$) Mean ± SE | Mange group after specific therapy (no = 4) Mean ± SE | Mange group after specific therapy with antioxidant (no = 4) Mean ± SE |
|---|---|---|---|---|
| SOD (U/ml) | 195.25 ± 8.64 | 234.40 ± 2.95[a] | 217.30 ± 4.76 | 162.27 ± 19.71[b,c] |
| GPX (mU/ml) | 270.97 ± 13.72 | 142.91 ± 1.37[a] | 145.26 ± 1.96[a] | 157.08 ± 13.03[a] |
| Catalase (U/l) | 237.48 ± 11.38 | 86.30 ± 1.64[a] | 277.08 ± 56.09[b] | 333.41 ± 84.53[b] |
| MDA (μm/l) | 19.72 ± 1.13 | 148.99 ± 5.19[a] | 74.75 ± 9.87[a,b] | 82.24 ± 5.74[a,b] |

Data are presented as mean ± SE

[a] Significant difference in comparison to normal control group ($P \leq 0.05$)

[b] Significant difference in comparison to diseased group ($P \leq 0.05$)

[c] Significant difference in comparison to treated specifically group ($P \leq 0.05$)

**Table 2** Oxidative stress biomarkers of dogs infested with tick and flea allergic dermatitis before and after treatment

| Parameters | Control ($n = 11$) Mean ± SE | Tick and flea allergic dermatitis ($n = 18$)Mean ± SE | Tick and flea dermatitis group after specific therapy (no = 7) Mean ± SE | Tick and flea dermatitis group after specific therapy with antioxidant(no = 11)Mean ± SE |
|---|---|---|---|---|
| SOD (U/ml) | 195.25 ± 8.64 | 204.02 ± 6.97 | 175.66 ± 14.63 | 167.14 ± 19.33 |
| GPX (mU/ml) | 270.97 ± 13.72 | 115.91 ± 5.15[a] | 123.78 ± 14.88[a] | 153.02 ± 4.55[a,b] |
| Catalase (U/l) | 237.48 ± 11.38 | 321.77 ± 22.7 | 360.90 ± 109.3 | 586.88 ± 24.61[a,b,c] |
| MDA (μm/l) | 19.72 ± 1.13 | 153.23 ± 3.03[a] | 154.47 ± 58.42[a] | 155.39 ± 6.41[a] |

Data are presented as mean ± SE

[a] Significant difference in comparison to normal control group ($P \leq 0.05$)

[b] Significant difference in comparison to diseased group ($P \leq 0.05$)

[c] Significant difference in comparison to treated specifically group ($P \leq 0.05$)

In our study, sarcoptic mange–affected dogs showed partial and complete alopeciaon medial aspects of the hind limbs, axillae, brisket, and abdomen. Skin thickening and wrinkles, with cracks and fissures with dandruff, may occur on the neck and abdominal region; the obtained clinical findings came in agreement with Oluchi (2015).The most common lesions in case of dogs affected with localized demodicosis were partial alopecia on the face or legs, milderythema, and/or comedones. In cases with generalized demodicosis, the lesions were multi focalalopecia, erythema, comedones, follicular casts, and hyperpigmentation that affected two or more feet or large regions of skin. Additionally, some animals had secondary bacterial infections and folliculitis (Mueller et al. 2011). Diagnosis of mange was confirmed with deep skin scrapings at the periphery of lesions that were taken for microscopic examination for confirmation. Results of the examination confirmed a diagnosis of Sarcoptes scabies varcanis infestation (Martinez-Subiela et al. 2014). In dogs suffered from tick and flea infestation, close examination of skin and haircoat using flea comb revealed the presence of flea dirt and adult fleas and some dogs showed clinical anemia because of severe flea infestation (Lam and Yu 2009). Dogs with ticks had the clinical signs of alopecia, pruritis, inappetence, restlessness, and itching and were rubbing their bodies against the walls in the houses continuously. Lesions were distributed all over the body, but particularly confined to shoulders, neck, back, ears, and over the tail head; similar findings were documented by Ayodhya (2014). Oxidative stress is the state of imbalance between the reactive oxygen species (ROS) and the ability of a biological system to detoxify readily the reactive intermediates. Development of oxidative stress because of free oxygen radical generation has been implicated in the pathogenesis of various infectious, inflammatory, and degenerative diseases (Ewans and Halliwell 2001; Singh et al. 2014; Reimann et al. 2017). Oxidative stress may lead to increase in the free calcium ions and iron within the cells, and this rise in intracellular free $Ca^{2+}$ result in gin DNA damage by endonuclease activation. Severe oxidative stress can result in cell damage and even cell death (Singh et al. 2014). Antioxidants diminish the destructive influences of ROS. Though, increased or continued free radical action can overcome ROS protection mechanisms, participating in the development of cutaneous ailments (Wang et al. 2016). In the current study, SOD was significantly increased in mange-affected dogs when compared with control dogs. These changes agreed with previous reports (Dimri et al. 2008; Salem et al. 2020). The reason of observed elevation in SOD level in mange affected dogs may be attributed to its role as the first-line defense antioxidant as it help the body to remove the superoxide radicals by converting it to hydrogen peroxide ($H_2O_2$) (Singh et al. 2014; Abdulaziz et al. 2019). Additionally, some authors suggest that the increase in the antioxidant enzymes is not necessarily desirable, as the antioxidant enzymes are not always decreased in disease conditions (Russo and Bracarense 2016). After antioxidant supplement, SOD was significantly lower than group treated with specific treatment and these alterations may suggest that antioxidant therapy was helpful for relief of oxidative stress, and therefore, it can be used as an aid to accelerate clinical recovery, but no significant changes occur in tick- and flea-infested group. Glutathione peroxidase is a selenium containing enzyme, which lessens hydrogen peroxide and thus serve for detoxification of activate oxygen (Sharma et al. 2017). GPX activity was significantly decreased in mange as well as in tick and flea allergic dermatitis affected dogs when compared with the control one. In a previous study, analysis of oxidative stress markers showed a significant decrease of GPX and catalase enzyme in demodicosis-infected dogs, while showing a significant increase of the mean value of SOD enzymes (Kubesy et al. 2017). Intensified revocation of the result ant free radicals produced in response to infection may be causes decline in GPx levels in the patients (Dimri et al. 2008). GPX increased in tick- and flea-affected group after treatment with antioxidants plus specific therapy when compared with diseased group, which may be occurred due to reduction of oxidative stress implications after antioxidant supplementations as GPX is known to


**Fig. 1** Mange-, tick-, and flea-infested dogs before and after treatment: **a** Generalized demodicosis with intense erythema and alopecia in male 6-month mixed breed dog. **b** Demodex canis adults, eggs, and larvae under microscope. **c** Two-month-old male mongrel dog affected with sarcoptic mange showed generalized alopecia, scaling, and skin thickening. **d** Two-month old mongrel dog affected with sarcoptic mange after 2 months and half of specific treatment of sarcoptic mange together with oral vitamin E supplements. **e** Ten-year-old male Griffon with alopecia heavily infested with fleas showed lichenification and hyperpigmentation over the dorsal lumbosacrallesion. **f** Ten-year-old male Griffon after 2 weeks of specific treatment along with supplementation with vitamin A and E

counteract ROS effects on body (Yoda et al. 1986). Catalase was significantly reduced in mange group when compared to the control group. The decrease in levels of catalase might be due to their exhaustion in neutralizing free radicals during the oxidative process (Saleh et al. 2011). Catalase catalyzes the breakdown of $H_2O_2$ to water and oxygen. It is a very important enzyme in protecting the cell from oxidative damage by reactive oxygen species (ROS) (Fang et al. 2002). So, the potential cause of decreased catalase activity is the increase in its consumption for converting $H_2O_2$ into H2O during oxidative stress process (Hanzneci et al. 2005). In mange group, it significantly increased after both specific treatment and antioxidant supplemented therapy, while in tick and flea group, catalase was significantly increased in antioxidant supplemented group only. These findings may be attributed to decreased consumption of catalase after treatment and can support our hypothesis of addition of antioxidants in protocol of treatment of such cases. Infestation cause disturbance of the oxidant–antioxidant balance. In a study, the treatment of infested rabbits with vitamin A, D3, and E exhibited prophylactic effect against oxidative stress caused by infestation (Kanbur et al. 2008). MDA was significantly increased in diseased dogs when compared with the control dogs in both diseased groups, and it remained unchanged after treatment. These findings may be due to that MDA is a highly toxic and mutagenic molecule produced from polyunsaturated fatty acid peroxidation (Del Rio et al. 2005; Tsikas 2017). The oxidative stress could be interceded by primarily by pro-inflammatory cytokine liberation of cytokines during external parasitic infestation, and this could be properly the cause of lipid peroxides and therefore MDA increase (Beigh et al. 2016). The endogenous formation of MDA during intracellular oxidative stress and its reaction with DNA forms MDA DNA adducts, which makes it an important biomarker of endogenous DNA damage. Determination of MDA in blood plasma or tissue homogenates is one of the useful methods to predict the oxidative stress levels (Saleh et al. 2011; Singh et al. 2014). The obtained findings in the present investigation substantiate the existence of oxidative stress in external parasitic infestation in dogs and the diminution of oxidative stress consequences following anti-oxidant supplementation.

## Conclusion

Oxidant/antioxidant imbalance occurs during external parasitism and may participate in the pathogenesis and clinical manifestations of such disorders. Administration of vitamin E and selenium in conjunction with standard therapy can hasten the clinical recovery of diseased dogs and can be recommended as an adjunct therapy with miticides for mange as well as tick- and flea-infested dogs.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** The authors declare that the present study was carried out under the compliance of ethical standards and the protocol has approved by the Institutional Animal Care and Use Committee (VET. CU. IACUC) according to reference Animal Use Protocol (AUP). Vet CU20022020136.

**Informed consent** The research plan has been approved by the board of department of Medicine and Infectious Diseases and the Council of Faculty of Veterinary Medicine, Cairo University.

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