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THE USE OF A HOMEOPATHIC PRODUCT IN DOGS REDUCES THE NEGATIVE EFFECTS OF CANINE ATOPIC DERMATITIS

(Uso de um produto homeopático em cães reduz os efeitos negativos da dermatite atópica canina)

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ABSTRACT - This study aimed to determine whether a homeopathic product based on *Hepar sulfur*, *Rhus toxicodendron*, *Graphites*, and *Urtica urens* would prevent atopic dermatitis in dogs. Ten male beagle dogs were used, divided into two groups with five repetitions per group. The control (CO) animals received a diet with 0.5 mL/day of placebo for 30 consecutive days in a preventive manner, and we later added ethoxyquin at 0.4 mg/day. The treated group (TRA) received a ration with 0.5 mL/day of homeopathic for 30 consecutive days as a preventive, and we later added ethoxyquin at 0.4 mg/day. Blood samples were collected on days 1, 30, and 40 to analyze antioxidant and oxidant status. In an ethogram, the presence of a crusted lesion, alopecic lesion, or hair loss was evaluated at three timepoints: pre-challenge, 5, and 10 days post-challenge. No lesions were observed in the pre-challenge period. Dogs fed the homeopathic on day 5 after challenge presented 40% less crusted lesion and 60% less hair loss than the control. Nitric oxide (NOx) and reactive oxygen species (ROS) levels increased over time in both groups ($P < 0.001$). On day 40 of the experiment, lower levels of NOx ($P < 0.001$) and ROS ($P < 0.025$) were observed in the TRA group than in the CO group. In contrast, glutathione S-transferase activity increased over time in both groups ($P < 0.001$); however, this increase on day 40 was more significant in the dogs in the treated group than in the control ($P < 0.010$). We conclude that the preventive addition of homeopathic reduced the incidence of skin lesions and prevented oxidative stress caused by canine atopic dermatitis.

Key words: canines; dermatitis; homeopathy; oxidative stress.

RESUMO - O objetivo deste estudo foi avaliar se o produto homeopático formulado a base de *Hepar sulphur, Rhus toxicodendron, Graphites* e *Urtica urens* seria eficaz na prevenção de dermatite atópica em cães. Utilizaram-se dez cães machos beagles, divididos em dois grupos com cinco repetição por grupo, sendo identificados como controle (CO): animais que receberam ração com 0,5 mL/dia de placebo por 30 dias consecutivos de forma preventiva e posteriormente adicionou-se etoxiquim na dose de 0,4 mg/dia; enquanto, o grupo tratado (TRA): receberam ração com 0,5 mL/dia de homeopático por 30 dias consecutivos de forma preventiva e posteriormente adicionou-etoxiquim na dose de 0,4 mg/dia. Amostras de sangue foram coletadas nos dias 1, 30 e 40 para as análises de status antioxidante e oxidante. Já, no etograma a presença de lesão crostosa, lesão alopécica e perda de pelo foram avaliadas em três momentos: pré desafio, 5 e 10 dias pós desafio. Não observou se lesões no período de pré-desafio nos animais. Os cães alimentados com o homeopático no dia 5 após desafio apresentaram 40% a menos de lesão crostosa e 60% de perda de pelo em comparação ao controle. Os níveis de NOx e ROS aumentaram ao longo do tempo nos dois grupos ($P<0.001$). Enquanto, no dia 40 de experimento observou-se menor nível de NOx ($P<0.001$) e ROS

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(P<0.025) no grupo TRA em relação ao CO. Em contrapartida, a enzima GST também aumentou ao longo do tempo em ambos os grupos (P<0.001), porém, este aumento no dia 40 foi maior nos cães do grupo tratado em relação ao controle (P<0.010). Conclui-se que a adição preventiva do homeopático foi capaz de reduzir a incidência de lesões cutâneas e evitar o estresse oxidativo causada pela dermatite atópica canina.

Palavras-chave - caninos, dermatite, estresse oxidativo, homeopatia.

INTRODUCTION

Canine atopic dermatitis (CAD) affects 10–15% of dogs worldwide (Hillier and Griffin 2001). Owners/guardians often seek assistance from veterinarians (Prelaud and Laprais 2020). CAD is characterized by skin inflammation with typical characteristics and complex pathogenesis (Prelaud and Laprais 2020). These characteristics can be classified into three categories; in this study, we considered atopic dermatitis induced by food associated with sensitization by food allergens with the same signs of CAD (Ishimaru et al. 2020). Usually, dogs have alopecia, itching, and pustules, among other clinical signs, which can manifest themselves more intensely depending on the region of the animals' bodies (Hensel et al., 2015). Thus, it is necessary to seek alternatives to prevent and minimize these adverse effects that can affect pets at any time, mainly in animals with predispositions.

The word homeopathy comes from the Greek *hómoios* + *pathos,* meaning similar + disease. Homeopathy is based that during the preparation of an "active" component, this confers a curative or preventive property due to the transfer of this property from the active component to the diluent or even by transforming the diluent, i.e. the greater the dilution and succussion, the more potent the effect of the homeopathic components (Lees et al. 2017). Most studies with homeopathic are carried out to treat a clinical sign or a disease already diagnosed (Lees et al., 2017; Teixeira, 2007), however, few studies explore homeopathy as a preventive way as in this study.

The use of homeopathic products can improve immunity and reduce the symptoms generated by some diseases that affect production and companion animals. The use of homeopathic has reduced the incidence of diarrhea in pigs (Ellinger, 2019), lambs (Fortuoso et al. 2019), and dogs, in addition to stimulating the production of neutrophils and eosinophils and increasing globulin levels (Jaguezeski et al. 2021), immune system cells that act against pathogens, mainly due to the components present in homeopathic, that are based on plant extracts that have anti-inflammatory, antimicrobial, antioxidizing, among others. Homeopathic products can be produced from vegetables, minerals, and animals (Cermin et al. 2019). Homeopathy appears as a

preventive and curative alternative for treating various diseases in dogs, among them DAC.

In this context, the scientific literature has carried out several types of research using homeopathic in animals; however, there are few high-quality randomized clinical trials with veterinary homeopathy (Mathie and Clausen 2014). Ranjan et al. (2014) observed that graphite effectively treated canine demodicosis caused by *Demodex canis*. Raj *et al*. (2020) found that a combination of homeopathic (*Sulfur* + *Thuja* + *Graphites* + *Psorinum*) reduced canine papillomatosis. Queiroz et al. (2015) report the efficacy of a homeopathic product based on *Thuya occidentalis* to control canine papillomatosis, demonstrating antiviral activity and stimulating the immune response. Hill et al. (2009) observed that the effectiveness of homeopathy in atopic dermatitis in dogs depended on the animal and the dosage used of the product, as each animal reacts differently. Nevertheless, the effectiveness of homeopathic products is highly contested (Ranjan et al. 2013); however, there is still much controversy about the beneficial effects of homeopathy among researchers due to the lack of control groups known as placebos (Mathie and Clausen 2014), but a great acceptance among producers and tutors. Therefore, to resolve these disputes, it is necessary to invest in scientific research, including randomized experimental designs and controlled conditions. To that end, the objective of the present study was to determine whether a homeopathic product based on *Hepar sulfur*, *Rhus toxicodendron*, *Graphites*, and *Urtica urens* would prevent atopic dermatitis in dogs, according to the principle of similar.

MATERIAL AND METHODS

Homeopathic product

The Orgaderm® product assists with skin problems such as dermatitis of allergic, atopic, and fungal origin. The mode of action is inhibiting inflammatory reactions and purulent disorders, consequently improving the appearance of the coat. The preparation consists of *Hepar sulfur* 30CH, *Rhus toxicodendron* 30 CH, *Graphites* 30CH, *Urtica urens* 30CH, and *vehicle* (water or H_2O) 30CH.

Animals, accommodation, and feed

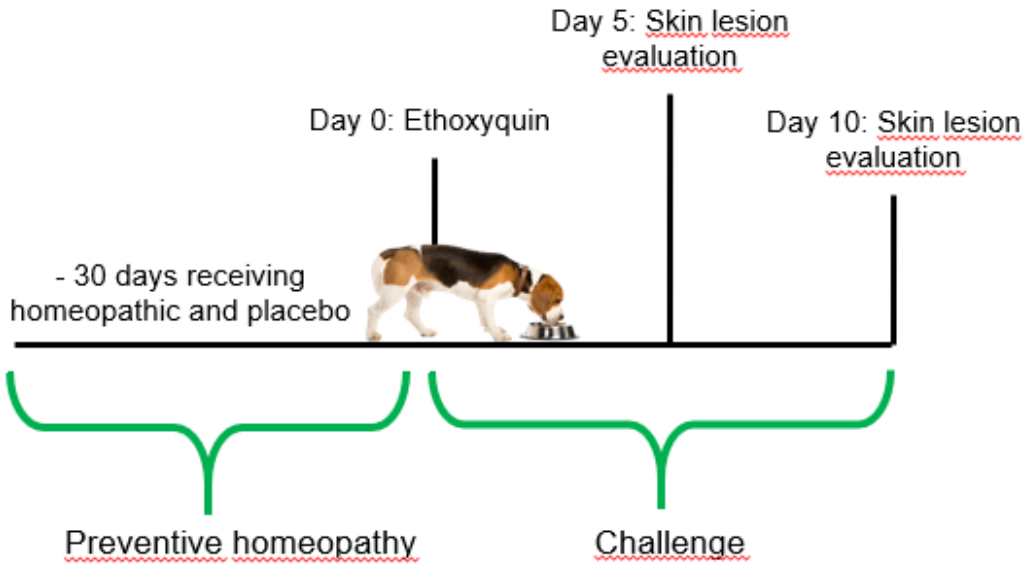
Ten male beagles with a mean weight of 10.21 ± 0.64 kg were used, randomly distributed in a completely randomized experimental design with two groups. The dogs were kept in an experimental kennel located at the Experimental Farm at the State University of Santa Catarina, divided into two large collective kennels in which they

stayed during the day and night. We used ten small kennels for individual feeding in the morning and afternoon. Externally connected to the collective kennels, there was a shaded and gravelly space to which the animals had access during the day.

The dogs received water *ad libitum* and 300 grams of commercial dog food two times during the day. The homeopathic was sprayed on the feed at 0.5 mL/day for one group of dogs (TRA, n = 5), divided into two doses to allow the animals to consume the homeopathic product twice a day. The control group of dogs (CO, n = 5) received the same dose as the placebo: the vehicle used to produce the homeopathic. Healthy dogs consumed both the placebo and the homeopathic without any skin lesions for 30 consecutive days. After this period, the use of homeopathic was maintained, but the animals were challenged with synthetic antioxidants (Etoxiquim®) known to cause dermatitis in dogs. We mixed 2 g of ethoxyquin in 1 kg of commercial wet food and fed this to dogs for five days. Each dog consumed 200 g of wet food per day, reflecting a dose of 0.4 mg/day of ethoxyquin.

Changes in the dogs' skin were evaluated three times: 30 days after consuming the product and 5 and 10 days after being challenged with wet food containing ethoxyquin (Fig 1). On day 4, after the challenge, it was possible to see lesions on the dogs' skin, and it was based on the appearance of these lesions that the ethogram was adjusted to analyze the dogs' skin problems (Table 1).

Figure 1 - Ethogram of the experiment:



Sample collection

Blood was collected from the dogs on days 1, 30, and 40 of the experiment. The dogs were restrained manually; using a 3-ml syringe, blood was collected from the jugular vein. Subsequently, blood was transferred to tubes without anticoagulants to obtain serum. This material was centrifuged at 3500 rpm for 10 minutes, and the serum was separated, collected, and frozen (–20 °C) to determine antioxidant and oxidant status.

Serum oxidant/antioxidant status

The oxidative profile is an essential tool to measure cause and effect in experiments with a low degree of invasiveness and skin lesions because biomarkers are sensitive to small changes in the animals.

Reactive oxygen species

Levels of free radicals (ROS) in the plasma were determined according to the technique described by Halliwell and Gutteridge (2007). The samples were diluted at 1:10 with 10 mM Tris (pH 7.4) and 5 µL of dichlorofluorescein diacetate (DCFH-DA). The results were expressed as U DCF/mg of protein.

Lipid peroxidation

The levels of non-homogeneous serum lipid peroxidation were determined by levels of antibodies reactive to thiobarbituric acid (TBARS), ten percent (serum homogenate was mixed with sodium dodecyl sulfate, acetate buffer [pH 3.5]), and aqueous thiobarbituric acid solution. After heating at 95 °C for 60 min, the red pigment produced was extracted with mixing of n-butanol-pyridine and estimated by absorbance at 532 nm, according to the method described by Ohkawa et al. (1978) and expressed as nmol MDA/mg of protein.

Levels of nitric oxide

Nitric oxide (NOx) levels were measured according to the Griess method that indirectly quantifies the levels of nitrite/nitrate as previously described in detail by Tatsch et al. (2011), and the results were expressed as µmol/L.

Enzymatic antioxidant

The activity of glutathione S-transferase (GST) was determined in serum according to Habig and Jakoby (1981), with modifications. The formation rate of dinitrophenyl-S-

glutathione determined GST activity at 340 nm in a medium containing 50 mM potassium phosphate, pH 6.5, 1 mM GSH, 1 mM 1-chloro-2,4-dinitrobenzene (CDNB) as substrate and tissue supernatants (approximately 0.045 mg protein). The results were calculated and expressed as U GST/mg protein.

Statistical analysis

Skin lesion data were assessed descriptively. The Shapiro-Wilk test was used to analyze data normality; that presented normal distribution. Data on oxidative stress were subjected to the mean comparison test (Student's T-test). Differences were considered significant when $P < 0.05$.

RESULTS

Descriptive analysis of skin lesions

The descriptive analysis of the cutaneous lesions of the dogs is shown in Table 1. No lesions were observed in the pre-challenge period in the animals. On day 5, after the challenge, the control dogs showed crusted lesions (80%), alopecia lesions, and hair loss (100%), with an average of eight lesions per dog. In the treatment group in dogs in the same period, a crusted lesion was observed in 40% of the animals, alopecia lesions (100%), and hair loss (40%), with an average of two lesions per dog (Fig 2).

Table 1 - Descriptive analysis of the cutaneous lesions (skin) of beagles dogs challenged with ethoxyquin and treated with a homeopathic product.

Identification Number of animals per treatment	Pre-challenge	Five days after the challenge	Ten days after the challenge
Control			
1	No change	There were five dry crusted lesions and two alopecic lesions on the head and limbs (Total = seven), with great hair loss.	There were four dry crusted lesions and two alopecic lesions on the head and limbs (Total = six), with great hair loss.
2	No change	With substantial hair loss, there were six crusty lesions (four dry and two with pus) and seven alopecia on the head, body, and limbs (Total = 13).	Six dry crusted lesions and five alopecic lesions on the head, body, and limbs (Total = 11), with great hair loss.
3	No change	One dry crusted lesion and three alopecic lesions on the head (Total = four) moderate hair loss.	Three dry crusted and four alopecic lesions on the head, body, and limbs (Total = seven) moderate hair loss.
4	No change	Six areas of alopecia on the head (Total = six), with slight loss of hair.	Five areas of alopecia on the head (Total = five), with moderate hair loss.
5	No change	There were five crusted lesions (four dry and one with pus) and five alopecic lesions on the head, body, and limbs (Total = ten), with slight hair loss.	There were five dry crusted lesions and 13 alopecic lesions on the head, body, and limbs (Total = 18), with high hair loss.
General description of the control group	***No change***	***Crusted lesion - 4/5 dogs Alopecia lesion - 5/5 dogs The average number of injuries/dog - 8 Hair loss - 5/5 dogs***	***Crusted lesion - 4/5 dogs Alopecia lesion - 5/5 dogs The average number of injuries/dog - 9 Hair loss - 5/5 dogs***
Treated			
1	No change	One dry crusted lesion and three alopecic lesions on the head (Total = four), with slight hair loss.	A crusty head injury (Total = one), with slight loss of hair.
2	No change	With no hair loss, one dry crusted lesion and two alopecic lesions on the head (Total = three).	With no hair loss, one dry crusted lesion, and four alopecia on the head (Total = five).
3	No change	Alopecic on the head (Total = one), with slight loss of hair.	Two areas of alopecia on the head (Total = two), with slight hair loss.
4	No change	Alopecia on the head (Total = one), with no hair loss.	Alopecia on the head (Total = one), with no hair loss.
5	No change	Alopecia on the head (Total = one), with no hair loss.	Alopecia on the head (Total = one), with no hair loss.
General description of the treated group	***No change***	***Crusted injury - 2/5 dogs Alopecia lesion - 5/5 dogs The average number of injuries/dog - 2 Hair loss - 2/5 dogs***	***Crusted injury - 2/5 dogs Alopecia lesion - 5/5 The average number of injuries/dog - 2 Hair loss - 2/5 dogs***

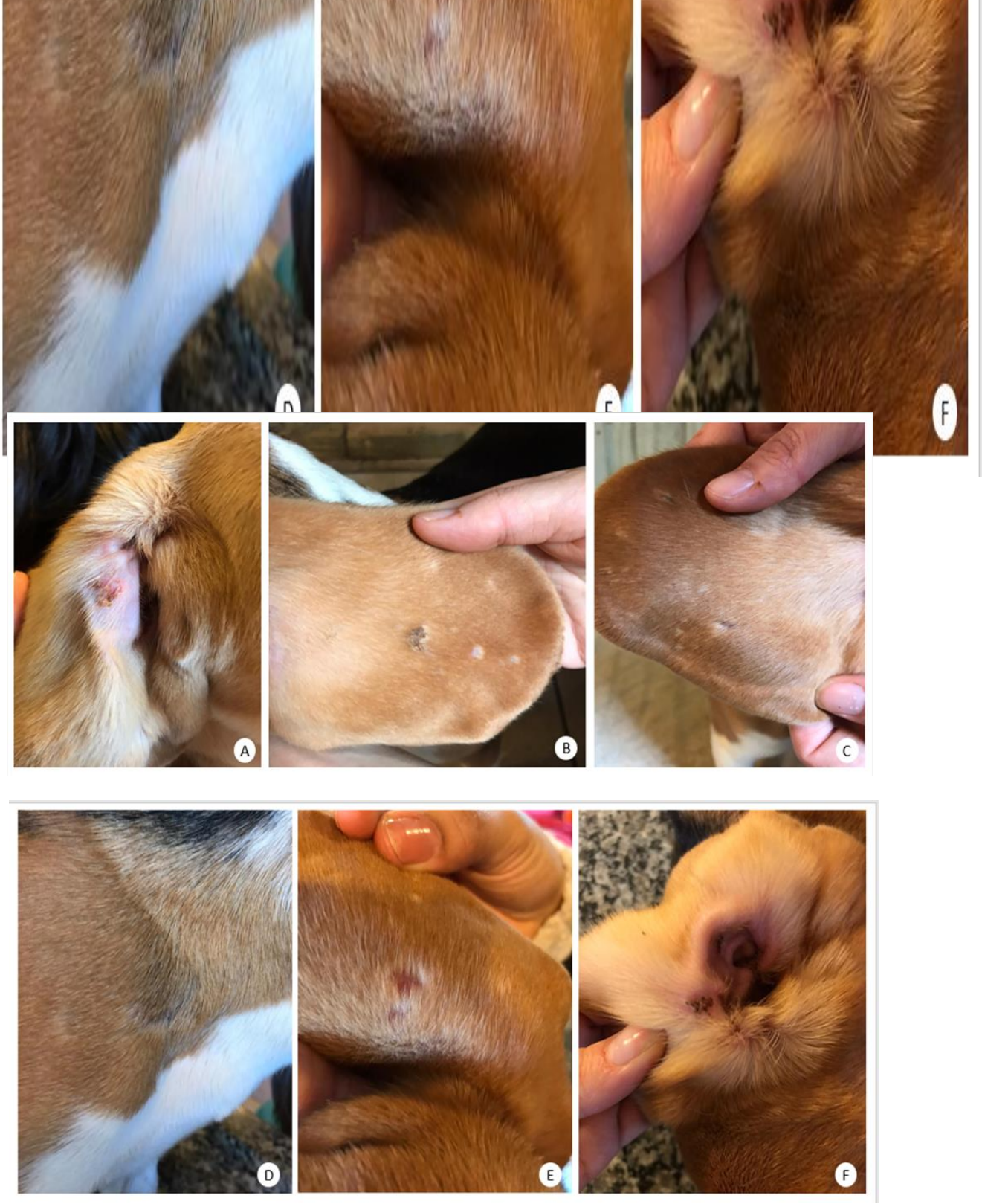


Figure 2- Illustration of the cutaneous lesions found in animals challenged with ethoxyquin. Dogs with crusty lesions: A, B, and F; alopecic lesions: B, C, and E; Hair loss: D.

Serum oxidant/antioxidant status

NOx levels increased over time in both groups ($P < 0.001$), and at 40 days of the experiment, values in the treated group were lower than the control ($P < 0.001$). There was an increase in ROS over time ($P < 0.001$), as well as between groups; that is, in the dogs of the treated group, ROS levels were lower than the control on day 40 ($P < 0.025$).

GST activity also increased over time in both groups (P < 0.001); however, this increase on day 40 was greater in the dogs in the treated group than in the control (P < 0.010). For TBARS, there was no difference over time and between groups (P > 0.05). No difference was observed between groups on days 1 or 30 of the experiment (P > 0.05; Tab 2).

Table 2 - Biomarkers of serum oxidative stress in dogs challenged with ethoxyquin and treated with a homeopathic product.

Variables	Day	Control	Treated	P-value*
NOx	1	10.6 (1.89)^{B}	9.74 (2.06)^{B}	**0.912**
µmol/L	30	9.76 (2.2)^{B}	7.56 (3.62)^{B}	**0.569**
	40	17.5 (2.96)^{Aa}	13.4 (1.82)^{Ab}	**0.001**
Valor de P£		**0.001**	**0.001**	
ROS (x 10^7)	1	11.7 (2.85)^{B}	9.85 (4.10)^{B}	**0.759**
U DCF/mg protein	30	8.87 (3.58)^{B}	7.55 (2.36)^{B}	**0.847**
	40	75.3 (8.96)^{Aa}	56.3 (10.8)^{Ab}	**0.025**
Valor de P£		**0.001**	**0.001**	
TBARS	1	29.7 (4.6)	30.7 (5.4)	**0.950**
Mmol MDA/Ml	30	32.4 (5.8)	32.8 (6.3)	**0.903**
	40	37.4 (6.0)	35.2 (5.7)	**0.924**
P-value£		**0.145**	**0.201**	
GST	1	120 (24.9)^{B}	118 (10.9)^{B}	**0.803**
µmol/CDNB/min	30	106 (15.3)^{B}	113 (13)^{B}	**0.847**
	40	705 (85.2)^{Ab}	978 (88.0)^{Aa}	**0.010**
P-value£		**0.001**	**0.001**	

Note: *P < 0.05 shows the difference between treatments (groups), illustrated by different lower case letters on the same line. £ P < 0.05 shows the difference over time (day 1 to 30; day 1 to 40; and day 30 to 40), illustrated by capital letters in the same column in each group.

DISCUSSION

Skin lesions influenced dogs' oxidative/antioxidant status, with minor disturbances in the animals that consumed the homeopathic product and fewer injuries per dog. Oxidative stress is generated when there is an imbalance between the generation and neutralization of free radicals (Zhang et al. 2019), commonly occurring in pathologies. The body's non-enzymatic and enzymatic antioxidant defenses act to decrease free radicals. However, when production is exacerbated, antioxidant defenses become inefficient (Cioffi et al., 2019). Oxidative stress damages DNA, RNA, lipids, and proteins (Pacheco et al., 2018). In humans, oxidative stress is related to atopic dermatitis. It was observed that

there were increased levels of oxidative stress during disease and decreased antioxidant capacity (Ji and Li 2016).

Almela et al. (2018) observed that CAD decreased the antioxidant capacity and oxidative stress involved in the pathogenesis of this disorder. Kapun et al. (2012) found that the inflammation caused by CAD increases ROS production and causes tissue damage. Ji and Li (2016) reported that oxidative stress caused by atopic dermatitis causes epithelial barrier dysfunction. These findings explain the result found in the present study. Fewer injuries were observed in the group of dogs that preemptively consumed the homeopathic product; this may have occurred due to the effects of Orgaderm®, reducing ROS production and increasing GST activity.

Glutathione-S-transferase is an antioxidant enzyme that counteracts oxidative stress (Park et al. 2020). It detoxifies agents by conjugating them with glutathione. This way, GST protects the organism from elevated ROS levels (Wen et al. 2019). Chang et al. (2016) observed that atopic dermatitis in humans caused lower conversion from glutathione to glutathione disulfide, suggesting greater production of free radicals. This exact mechanism may have occurred in the present study, explaining the lower GST activity in dogs in the control group.

Meza et al. (2019) reported that NOx is an enzyme with the primary function of generating ROS in the ordinary, healthy state. By contrast, excess ROS is produced in cases of pathological conditions that contribute to tissue and cellular damage. This might occur during the inflammatory process of CAD, which would explain the increase in NOx in the control group; this group had a larger number of injuries and noticeably larger and deeper injuries.

The smaller number of skin lesions observed in dogs in the treated group may be due to the properties found in the homeopathic product's components. *Rhus toxicodendron* has anti-inflammatory activity (Huh et al., 2013). Carvalho et al. (2017) observed that *Urtica urens* have anti-inflammatory and antioxidant activity. Mourão et al. (2014) supplied a homeopathic product based on *Merc sol* + *Bell* + *Hepar sulph* to patients with periodontitis and found that it reduced oxidative stress, due to the lower production of TNFa, in addition to stimulating the immune system. The homeopathic component *Hepar sulph* is used to treat pruritus associated with dermatitis in dogs (Hill et al., 2009); however, the exact mechanism remains unknown. Graphite has anti-psoriatic activity; therefore, it treats rashes on the skin and mucosal surfaces (Ranjan et al., 2014). These components together have shown preventive effects against CAD.

CONCLUSION

The homeopathic product produced based on *Hepar sulfur*, *Rhus toxicodendron*, *Graphites,* and *Urtica urens* reduced the occurrence of cutaneous lesions characteristic of CAD. This finding might be related to the lower degree of oxidative stress in dogs that consumed the homeopathic preventively. In this manner, the commercial product minimized skin problems in the face of a challenge with ethoxyquin.

Ethics committee

The animal use research committee approved the State University of Santa Catarina's project, protocol number 6524030419, and the rules issued by the National Council for Control of Animal Experimentation (CONCEA).

REFERENCES

ALMELA, R.M.; RUBIO, C.P.; CERÓN, J.J. et al. Selected serum oxidative stress biomarkers in dogs with non-food-induced and food-induced atopic dermatitis. **Veterinary Dermatology**, v.29, n.3, p.229–e82, 2018.

CARVALHO, A.R.; COSTA, G.; FIGUEIRINHA, A. et al. *Urtica spp.*: Phenolic composition, safety, antioxidant and anti-inflammatory activities. **Food Research International**, v.99, p.485–494, 2017.

CERMIN, A.; BERRY, C.; BURTON S. et al. The effects of the FTC-mandated disclosure on homeopathic product purchase intentions and efficacy perceptions. **Journal of Business Research**, v.101, p.47-58, 2019.

CIOFFI, F.; **ADAM**, R.H.I. **BROERSEN**, K. Molecular Mechanisms and Genetics of Oxidative Stress in Alzheimer's Disease. **Journal of Alzheimers Disease**, v. 72, n.4, p.981–1017, 2017.

CHANG, H.Y.; SUH, D.I.; YANG, S.I. et al. Prenatal maternal distress affects atopic dermatitis in offspring mediated by oxidative stress. **Journal of Allergy and Clinical Immunology**, v.138, n. 2, p.468–75 e5, 2016.

FORTUOSO, B.F.; GEBERT, R.R.; GRISS, L.G.; et al. Reduction of stool bacterial counts and prevention of diarrhea using an oral homeopathic product in newborn lambs. **Microbiol Pathogenis,** v.127, p.347–351, 2019.

HABIG, W.H.; JAKOBY, W.B. Assays for differentiation of glutathione S-transferases. **Methods in Enzymology**, v.77, p.398-405, 1981.

HALLIWELL, B.; GUTTERIDGE, J.M.C. Free radicals in biology and medicine, 4th edn. Oxford University Press, New York, 2007.

HENSEL, P.; SANTORO, D.; FAVROT, C. et al. Canine atopic dermatitis: detailed guidelines for the diagnosis and allergen identification. **BMC Veterinary Research**, v.11, n.1, 2015.

HILL, P.B.; HOARE, J.; LAU-GILLARD, P. et al. Pilot study of the effect of individualized homeopathy on the pruritus associated with atopic dermatitis in dogs. **Veterinary Record**, v.164, n.12, p. 364-370, 2009.

HILLIER, A., GRIFFIN, C. E. The ACVD task force on canine atopic dermatitis (I): incidence and prevalence. **Veterinary Immunology Immunopathology**, v.81, p.147–151, 2001.

HUH, Y. H.; KIM, M.J.; YEO, M.G. Homeopathic *Rhus toxicodendron* treatment increased the expression of cyclooxygenase-2 in primary cultured mouse chondrocytes. **Homeopathy**, v.102, n.4, p.248–253, 2013.

ISHIMARU, H.; OKAMOTO, N.; FUJIMURA, M. et al. (2020). IgE sensitivity to Malassezia pachydermatis and mite allergens in dogs with atopic dermatitis. **Veterinary Immunology and Immunopathology**, v. 226, p.110070, 2020.

JAGUEZESKI, A. M.; GLOMBOWSKY, P.; DA ROSA, G. et al. Daily intake of a homeopathic agent by dogs modulates white cell defenses and reduces bacterial counts in feces. **Microbial Pathogenesis**, v.156, p.104936, 2021.

JI, H.; LI, X.K. Oxidative Stress in Atopic Dermatitis. **Oxidative Medicine and Cellular Longevity**, p.1–8, 2016.

KAPUN, A.P.; SALOBIR, J.; LEVART, A. et al. Oxidative stress markers in canine atopic dermatitis. **Research in Veterinary Science**, v.92, n.3, p.469–470, 2012.

LEES, P.; PELLIGAND, L.; WHITING, M. et al. Comparison of veterinary drugs and veterinary homeopathy: part 2. **Veterinary Record**, v.181, n.8, p.198–207, 2017.

ELLINGER, L.; Antimicrobial resistance in production animals. Can homeopathy offer solutions? – Homeopathy as a replacement to antibiotics in the case of neonatal diarrhea in piglets. **Revue d'Homeopathie**, v.10, p.e41–e45, 2019.

MATHIE, R.T.; CLAUSEN, J. Veterinary homeopathy: a systematic review of medical conditions studied by randomized placebo-controlled trials. **Veterinary *Record***, v.175, n.15, P.373–381, 2014.

MEZA, C.A.; LA FAVOR, J.D.; KIM, D.H. et al. Endothelial Dysfunction: Is There a Hyperglycemia-Induced Imbalance of NOX and NOS? **International Journal of Molecular Sciences**, v.20, n.15, p.3775, 2019.

MOURÃO, L.C.; CATALDO, D.M.; MOUTINHO, H. et al. Additional effects of homeopathy on chronic periodontitis: a 1-year follow-up randomized clinical trial. **Complementary Therapies in Clinical Practice**, v.20, p.141-146, 2014.

OHKAWA, H.; OHISHI, N.; YAGI, K. Assay for lipid peroxides in animal tissues by the thiobarbituric acid reaction. **Analytical Biochemistry**, v.95, p.351–358, 1978.

PACHECO, G.F.E.; BORTOLIN, R.C.; CHAVES, P.R. et al. Effects of the consumption of polyunsaturated fatty acids on the oxidative status of adult dogs. **Journal of Animal Science**, v. 96, n.11, p. 4590–4598, 2018.

PARK, J.C.; HAGIWARA, A.; PARK, H.G. et al. The glutathione *S*-transferase genes in marine rotifers and copepods: Identification of GSTs and applications for ecotoxicological studies. **Marine Pollution Bulletin**, **v.156**, p.111080, 2020.

PRELAUD, P.; LAPRAIS, A. What Can We Learn from Canine Atopic Dermatitis History? **Current Dermatology Reports**, v.9, p.52–57, 2020.

QUEIROZ, F.F.; RODRIGUES, A.B.F.; DI FILIPPO, P.A. et al. *Thuya occidentalis* CH12 as an alternative treatment to dog papilomatosis. **Revista brasileira de plantas medicionais**, v.17, n. 4, 2015.

RAJ, P.A.A.; PAVULRAJ, S.; KUMAR, M.A. et al. Therapeutic evaluation of homeopathic treatment for canine oral papillomatosis. **Veterinary World**, v.13, n.1, p.206-213, 2020.

RANJAN, R.; DUA, K.; TURKAR, S. ET AL. Successful management of refractory cases of canine demodicosis with homeopathy medicine *Graphitis*. **Journal of Parasitic Diseases**, v.38, n.4, p.417–419, 2014.

ŞENEL, E. Evolution of homeopathy: A scientometric analysis of global homeopathy literature between 1975 and 2017. **Complementary Therapies in Clinical Practice**, v.34, p.165-173, 2019.

TATSCH, E.; BOCHI, G.V.; PEREIRA, R.S. A simple and inexpensive automated technique for measurement of serum nitrite/nitrate. **Clinical Biochemistry**, v.44, p. 348-350, 2011.

TEIXEIRA, M.Z. Homeopathy: coadjutant medical practice. **Revista da Associação Médica Brasileira**, v.53, n,4, 2007.

WEN, H.J.; WANG, S.L.; CHEN, P.C. et al. Prenatal perfluorooctanoic acid exposure and glutathione s-transferase T1/M1 genotypes and their association with atopic dermatitis at 2 years of age. **Plos One**, v.14, n.1, p.e0210708, 2019.

ZHANG, Z.; RONG, L.; LI, Y.P. *Flaviviridae* Viruses and Oxidative Stress: Implications for Viral Pathogenesis. **Oxidative Medicine and Cellular Longevity**, p.1409582, 2019.