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BRIEF REPORT

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The effect of a diet supplement containing S-acetyl-glutathione (SAG) and other antioxidant natural ingredients on glutathione peroxidase in healthy dogs: a pilot study

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ABSTRACT

Oxidative stress is common in several human and veterinary conditions and it is associated to alteration of the glutathione peroxidase (GPx) level. GPx is an enzyme present in erythrocytes, kidney, and liver and it has a role in protecting against oxidative damage. In this randomised double-blinded control trial on healthy dogs, we present findings indicating that the administration for a total of 35 days of a supplement containing S-acetyl-glutathione (SAG) alongside other antioxidant natural ingredients, leads to an increase in the GPx level. Furthermore, the supplement positively changes liver blood parameters, even in healthy dogs. These preliminary results hold promise for conducting new studies using the same supplement on dogs affected by liver conditions, thereby confirming its antioxidant effects and the potential improvement of altered blood parameters.

HIGHLIGHTS

- Oxidative stress characterises several conditions in dogs and the use of antioxidants can improve their health.
- The administration of a new supplement containing S-acetyl-glutathione (SAG) together with other antioxidant natural ingredients, increased the level of glutathione peroxidase (GPx).
- No adverse events were reported after the supplement administration.

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Diet; oral administration; oxidative stress; pet; GPx

Introduction

Glutathione is one of the most important agents of the cell antioxidant defense system and it plays a relevant role in the detoxification of various compounds including drugs, endogenous metabolic products, and toxic metals (Exner et al. 2000; Leonel et al. 2014). Oxidative stress occurs when there is an imbalance of systemic antioxidant and prooxidant factors and it plays a big role in the aetiology and pathogenesis of several diseases in humans and animals (Woolcock et al. 2020; Tomsič et al. 2016). Antioxidant enzymes, in particular glutathione peroxidase (GPx) is a commonly used marker of the antioxidant status in animals (Tomsič et al. 2016; Woolcock et al. 2020). GPx is involved in the glutathione metabolism and its reduction is necessary for GPx action (Stępniewska et al. 2014).

GPx plays an important role in protecting red blood cell enzyme activity and biological cell membranes against oxidative damage (Kendall et al. 2017) and it is predominantly present in erythrocytes, kidney, and liver (Zel et al. 2014). GPx was found to decrease in dogs and cats with different diseases (i.e. leishmaniasis, anaemia, cardiac, kidney, and liver diseases) (Spee et al. 2006; Britti et al. 2008; Zel et al. 2014; Kendall et al. 2017; Woolcock et al. 2020; Svete et al. 2021).

Indeed, increasing the levels of GPx can be beneficial and appropriate to reduce oxidative stress.

S-acetyl-glutathione (SAG), a glutathione precursor, it is very stable in plasma, being taken up directly by cells (Fanelli et al. 2018; Di Paola et al. 2022). SAG

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originates from the fermentation of *Saccharomyces cerevisiae* and it is based on GHS linked to a sulphur atom (Santos et al. 2007; Di Paola et al. 2022). In a recent *in vitro* study, GPx activity was impaired after CCl4 chronic exposure, as compared to the sham groups, whereas SAG administration significantly restored it (Di Paola et al. 2022). SAG administration, given its ability to maintain a cellular reductive state, significantly restores glutathione levels and GPx activity, while it strongly reduces Glutathione disulphide (GSSG) levels and lipid peroxidation in the liver (Di Paola et al. 2022). The contemporary administration of other natural ingredients with antioxidant function (i.e. vitamin E, vitamin B, bioflanoid) could help the SAG activity (Martello et al. 2023). It has been shown that these products can improve the GPx level (Roozbeh et al. 2011) and could also contribute to the improvement of liver and other organs function (Viviano and Vander Wielen 2013; Marchegiani 2020; Di Paola et al. 2022).

This randomised double-blinded control trial on healthy dogs has been performed for a total of 35 days to test a supplement containing SAG and other natural ingredients with antioxidant function to see any changes in the level of GPx and other liver parameters.

Materials and methods

This study was designed as a randomised double-blinded control trial. A total of 30 adult healthy dogs (American Staffordshire Terrier) were enrolled in this study. They all belonged to the same dog breeding centre (Meinstaffi, Cumiana (TO), Italy). Half of the dogs were randomly assigned to the control (CRT, $n = 7$ female, $n = 8$ male, mean age 3.8 yrs) and the other half to the treated group (TRT, $n = 7$ female, $n = 8$ male, mean age 3.3 yrs). Dogs in the TRT group received their regular diet (Monge Superpremium Bwild Grain Free, anchovies with potatoes and peas – all breeds adult) with the addition of the tested supplement (Table 1) at the dose of 1 tablet/15 kg BW, while in the CTR group with the addition of a placebo (Table 1). The duration of the study was set as 35 days equally divided in six experimental times (T0–T5). At each time point the following parameters were evaluated: Body weight (BW), complete blood analysis and GPx.

BW was evaluated by the same experienced veterinarian, the complete blood analysis was performed with an automated analyser (RX Daytona^{TM}; Randox Laboratories Ltd., Crumlin, UK). For determining the concentration of the erythrocyte GPx, heparinised whole blood aliquots were frozen at −80 °C immediately after collection and then analysed with using a commercial assay kit (Randox Ransel assay, Randox Laboratories Ltd., Crumlin, UK) on an automated analyser (RX Daytona^{TM}; Randox Laboratories Ltd., Crumlin, UK).

Table 1. Ingredients of the tested supplement and placebo.

Ingredients	g/100 g	mg/tablet
Supplement		
Excipients	39.5	790
Orange bioflavonoid	8.0250	160.50
Vitamin B12	3.0000	60.00
Vitamin E	15.9750	319.50
S-acetyl-L-glutathione	1.4250	28.50
Vitamin B1 hydrochloride	0.6375	12.75
Vitamin B2	2.0025	40.05
Vitamin B6 hydrochloride	0.4350	8.70
Silybin	2.0000	40.00
Total	100.0000	2000.00
Placebo		
Eccipients	34.5	690
Maltodextrin	60.5	1200
Appetite stimulants	5	100
Total	100.0000	2000.00

The statistical analysis was performed using the R language. The effect of the supplement on GPx and on other blood parameters (Total Proteins (TP), Albumins (ALB), Alanine Transaminases (ALT), Alanine Aminotransferases (AST), Alkaline Phosphatases (ALP), Gamma-Glutamyl Transferase (GGT), Bilirubin (BIL) and triglycerides (TRI)) was investigated using a regression model. The model was built as a generalised linear mixed model (GLMM) with Gaussian likelihood. The model included a non-linear variable describing the link between each time point within and between the CTR and TRT group, sex, BW and age. The identification of the subject was included in the model as a random effect to account for repeated measurements and the heterogeneity of individuals.

Results and discussion

This study confirms the safety of the product as no dogs were excluded during the trial and no side effects (vomiting, diarrhea) were recorded. A good palatability of the product was reported by the breeder as none of the dogs refused to take the supplement at any time and no change in the intake was observed. Dogs weight ranged between 15.4 and 24.7 kg at the beginning of the study. We did not expect any effect of the supplement on BW but it was included in the statistical model for the correct interpretation of the results on GPx and n the other blood parameters. The complete blood analysis performed demonstrated that the product does not have any

influence as the values were always within normal range (Table 2), also confirming no ongoing pathologies at T0. This was expected by the research team as the animals were healthy and not affected by any known disease. However, the statistical model also included parameters clinically relevant for the monitoring of liver function as these preliminary results will be used to set a new trial on ill dogs (TP, ALB, ALT, AST, ALP, GGT, BIL and TRI) (Table 2). In the TRT group AST, ALP and GGT statistically decreased at T4 and T5, while ALT decreased at T5 (Table 2, $p < 0.05$). The GGT levels were also significantly different between the two groups at T2 ($p < 0.05$). Interestingly, as these biochemical markers of hepatic injury showed a signicant decrease following the administration of the supplement, it would be of great interest to test the potential benefits on animals affected by liver disease. Our raw data clearly shown an increase in the GPx levels over time in the TRT group with no records of values out of normal ranges (300–700 U/gHb) then confirming the safety of the supplement in our dogs. A human study showed that a single oral dose administration of SAG, is able to signicantly increase the rate and the extent of glutathione absorption with very high tolerability and safety (Fanelli et al. 2018). On the other hand, at our knowledge, no studies on dogs has used SAG as part of a dietary supplement. Furthermore, the model results which takes into account sex, BW and age and the non-independence of the observations, highlighted a significant increase in the GPx level in the TRT group compared to the CTR group from T2, as reported in Table 3. A recent study reported the evaluation of antioxidant parameters such as GPx in healthy dogs (Tomsič et al. 2016).

The increase in GPx could be the result of the synergic effect of all the antioxidant ingredients present in the supplement (Table 1). In fact, having the SAG, originated from the fermentation of *Saccharomyces cerevisiae* in the formulation is probably an advantage as it is more stable in plasma (Fanelli et al. 2018; Di Paola et al. 2022). SAG administration, thanks to its ability to maintain a cellular reductive state, enhances antioxidants, causes scavenging of reactive oxidants, replenishes endogenous antioxidants, in particular GPx, and restores glutathione levels (Di Paola et al. 2022; Palvannana et al. 2018). SAG also reduces GSSG

Table 3. Glutathione peroxidase (GPx) mean and 95% Confident Interval (95% CI) resulted from the GLMM in the control (CTR) and treated (TRT) group in the study period. Time: T0 (day 0), T1 (day 7), T2 (day 14), T3 (day 21), T4 (day 28), T5 (day 35).

	GPx (300–700 U/g Hb)	
Time	CTR	TRT
T0	403 (371.8; 427.3)	372.7 (349.2; 399.8)
T1	392.8 (362.2; 416.7)	391.2 (366.6; 417.6)
T2	391.1 (359.4; 415.4)	426.8 (402.4; 455.8)*
T3	402 (371.3; 426.2)	443.5 (420.7; 472.1)*
T4	397.3 (365; 422.4)	448 (423.6; 479.3)*
T5	398.3 (366.3; 422.2)	453.6 (429.6; 483.2)*

*Significant difference from T0 within group ($p < 0.05$).

Table 2. Mean and 95% Confident Interval (95% CI) resulted from the biochemical analyses (total proteins (TP), albumins (ALB), glucose (GLU), alanine transaminases (ALT) alanine aminotransferases (AST), alkaline phosphatases (ALP), Gamma-glutamyl transferase (GGT), bilirubin (BIL) and triglycerides (TRI)) in the control (CTR) and treated (TRT) group in the study period.

Time	CTR	TRT	CTR	TRT	CTR	TRT
	TP (5.4–7.5 g/dL)		ALB (2.3–3.9 g/dL)		GLU (67–132 mg/dL)	
T0	6.2 (6.2; 6.2)	6.2 (6.2; 6.2)	2.9 (2.9; 3.0)	3.0 (2.9; 3.0)	99.3 (98.9; 99.7)	99.4 (99.0; 99.8)
T1	6.2 (6.2; 6.2)	6.2 (6.2; 6.2)	3.0 (2.9; 3.0)	3.0 (2.9; 3.0)	99.4 (99.0; 99.8)	99.4 (98.9; 99.8)
T2	6.2 (6.2; 6.2)	6.2 (6.2; 6.2)	3.0 (2.9; 3.0)	2.9 (2.9; 3.0)	99.4 (99.0; 99.8)	99.3 (98.8; 99.7)
T3	6.2 (6.2; 6.2)	6.2 (6.2; 6.2)	2.9 (2.9; 3.0)	2.9 (2.9; 3.0)	99.3 (98.9; 99.7)	99.3 (98.9; 99.7)
T4	6.2 (6.2; 6.2)	6.2 (6.2; 6.2)	2.9 (2.9; 3.0)	3.0 (2.9; 3.0)	99.3 (98.9; 99.7)	99.3 (98.9; 99.8)
T5	6.2 (6.2; 6.2)	6.2 (6.2; 6.2)	2.9 (2.9; 3.0)	2.9 (2.9; 3.0)	99.3 (98.9; 99.8)	99.3 (98.9; 99.7)
	ALT (0–40 UI/L)		AST (0–40 UI/L)		ALP (20–150 UI/L)	
T0	18.3 (16.5; 20.2)	21.7 (19.9; 23.5)	18.2 (15.8; 20.6)	21.4 (19.0; 23.8)	90.4 (87.9; 92.8)	94.2 (91.7; 96.7)
T1	18.5 (16.7; 20.3)	21.6 (19.8; 23.4)	19.7 (17.3; 22.1)	21.1 (18.7; 23.5)	91.4 (88.9; 93.9)	94.1 (91.6; 96.6)
T2	19.9 (18.1; 21.7)	21.1 (19.3; 22.9)	19.1 (16.7; 21.5)	19.8 (17.4; 22.2)	92.2 (89.8; 94.7)	92.5 (90.0; 95.0)
T3	20.6 (18.8; 22.4)	20.2 (18.4; 22.0)	18.9 (16.5; 21.3)	17.3 (14.9; 19.7)	91.7 (89.2; 94.2)	90.6 (88.1; 93.0)
T4	21.1 (19.3; 22.9)	18.5 (16.7; 20.3)	18.0 (15.6; 20.4)	14.4 (12.0; 16.8)*	90.8 (88.3; 93.3)	88.8 (86.3; 91.3)*
T5	21.3 (19.5; 23.1)	17.3 (15.5; 19.1)*	18.1 (15.7; 20.5)	13.4 (11.0; 15.8)*	90.7 (88.2; 93.2)	85.1 (82.6; 87.6)*
	GGT (2–8 UI/L)		BIL Tot (0–0.7 mg/dL)		TRI (23–110 mg/dL)	
T0	3.8 (3.6; 4.1)	4.4 (4.1; 4.7)	0.4 (0.4; 0.4)	0.4 (0.4; 0.4)	65.3 (64.9; 65.7)	65.3 (64.9; 65.8)
T1	3.9 (3.7; 4.2)	4.3 (4.1; 4.6)	0.4 (0.4; 0.4)	0.4 (0.4; 0.4)	65.3 (64.8; 65.7)	65.3 (64.9; 65.7)
T2	4.0 (3.7; 4.3)	4.3 (4.0; 4.5)§	0.4 (0.4; 0.4)	0.4 (0.4; 0.4)	65.2 (64.7; 65.6)	65.3 (64.9; 65.7)
T3	4.1 (3.8; 4.4)	4.0 (3.8; 4.3)	0.4 (0.4; 0.4)	0.4 (0.4; 0.4)	65.2 (64.8; 65.7)	65.2 (64.8; 65.7)
T4	4.1 (3.9; 4.4)	3.7 (3.5; 4.0)*	0.4 (0.4; 0.4)	0.4 (0.4; 0.4)	65.3 (64.9; 65.7)	65.2 (64.8; 65.6)
T5	4.1 (3.8; 4.3)	3.5 (3.2; 3.7)*	0.4 (0.4; 0.4)	0.4 (0.4; 0.4)	65.3 (64.9; 65.8)	65.2 (64.8; 65.7)

Times: T0 (day 0), T1 (day 7), T2 (day 14), T3 (day 21), T4 (day 28), T5 (day 35).
*Significant difference from T0 within group ($p < 0.05$), §Significant difference between the two groups ($p < 0.05$).

levels, lipid peroxidation and H_2O_2 liver levels by restoring the oxidative balance reducing liver inflammation (Di Paola et al. 2022).

Vitamin E which is also present in this formulation, has a critical role in protecting cell membranes from oxidative damage. It has been shown that vitamin E is able to enhance GPx activity in dogs. In a study conducted by Thammacharoen et al. (2015), dogs supplemented with vitamin E for eight weeks showed a significant increase in GPx activity compared to dogs in the control group. Similarly, a study by Takada et al. (2010) found that vitamin E significantly increased GPx activity in dogs with chronic hepatitis.

In a human study it has also been demostred that oral supplementation with *Silymarin* and vitamin E increase GPx in patients with end stage renal disease (Roozbeh et al. 2011). Similarly, in a study on mice it has been demostred the success of *Sylibum marinum* administration in preventing oxidative stress following damaging effects of CCl4-induced injury in hepatocytes (Hermenean et al. 2015).

The concentration of antioxidants in commercial food is variable depending on the length of food storage or the type of food (pellets or canned diet) (Zentrichová et al. 2021). In fact, the use of supplements rich in antioxidants, especially in ill patients, could be necessary. Furthermore, the route of administration plays a crucial role in animal treatment. Utilising the oral route for this tested supplement offers distinct advantages over other commonly used drugs or supplements. For instance, in the case of a decreased endogenous antioxidant like N-acetyl cysteine (NAC), which typically necessitates intravenous administration and continuous veterinary supervision, oral administration of the supplement proves to be advantageous. These products are commonly used in hospitalised dogs with critical illnesses (McMichael 2007; Viviano and Vander Wielen 2013; Verrilli et al. 2021). The product tested in this study based on SAG and other antioxidant ingredients (i.e. Vitamin E, vitamin B, bioflanoid), has the advantage of being not specific for a single disease, as it can be used for different conditions involving multiple organs and mainly fighting against oxidative stress (Di Paola et al. 2022).

Conclusion

The results of our pilot study on healthy dogs are very promising for planning future studies in particular on dogs affected by liver disease. In addition, different pathological conditions which involve oxidative stress (i.e. endocrinopathy, kidney disease, liver disease, acute pancreatitis) could be considered. New studies will help confirming that the administration of this supplement can counteract oxidative stress increasing the GPx concentration and improving other clinically relevant blood parameters. It would also be interesting to see the effect of the supplement on a longer administration time period and on other additional antioxidant biomarkers such as superoxide dismutases, haemoxygenases, and catalases.

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Ethical approval

The dogs' owners were informed and signed an informed consent. The study was performed in compliance with the guidelines of the Italian Minister of Health for the care and use of animals (D.L. n 26 2014) and the use of supplements was regulated by the Regulation (EC) No 767/2009. The experimental protocol was approved by the Ethical Committee of the Department of Veterinary Science (DVS) of the University of Turin (Italy, 19/07/2022, prot. n. 2740).

Disclosure statement

One of the authors is employee of the Candioli Pharma S.r.l. Two of the authors are scientific consultants for the Candioli Pharma S.r.l. Candioli Pharma S.r.l is a company that may be affected by the research reported.

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Data availability statement

Data is available upon request to the first author.

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