HUSBANDRY AND NUTRITION

Meta-analysis of Selenium Supplementation and the Activity of Enzyme Glutathione Peroxidase in Blood Serum of Pigs

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ABSTRACT

Background: The evaluation of the enzymatic activity of glutathione peroxidase (GPH-Px), as an indicator of selenium (Se) levels has been studied thoroughly, with variable results. Accordingly, the aim of this study was to determine the effect of Selenium supplementation on GPH-Px activity in blood serum, and the possible impact of other dietary nutrients, as well as elements of experimental design on the response variable.

Methods: Meta-analysis followed the model of random effects, which included extent of the effect, heterogeneity, meta-regression, and publication bias.

Results: Dietary supplementation of Selenium increases ($P < 0.00001$) the enzymatic activity of the general analysis (0.326 units.mL^{-1}), similar to supplementation of inorganic (0.327 units.mL^{-1}), organic (0.325 units.mL^{-1}), in suckling pigs (0.261 units.mL^{-1}), and growing-finishing pigs (0.328.mL^{-1}). The effect of supplementation on enzymatic activity was not consistent among the studies, as shown by the values of the inconsistency test (> 95 %). The activity of GPH-Px during the meta-regressions was affected ($P < 0.001$) by the number of repetitions per treatment, number of individuals per experimental farm, levels of selenium, copper, and zinc, and vitamins A and E in the food.

Conclusions: Selenium supplementation favors GPH-Px activity in serum; various other factors linked to the experimental design and other nutrients with antioxidant function were observed to affect the variable studied.

Key words: *nutrition, feeding, swine, antioxidants, minerals*

INTRODUCTION

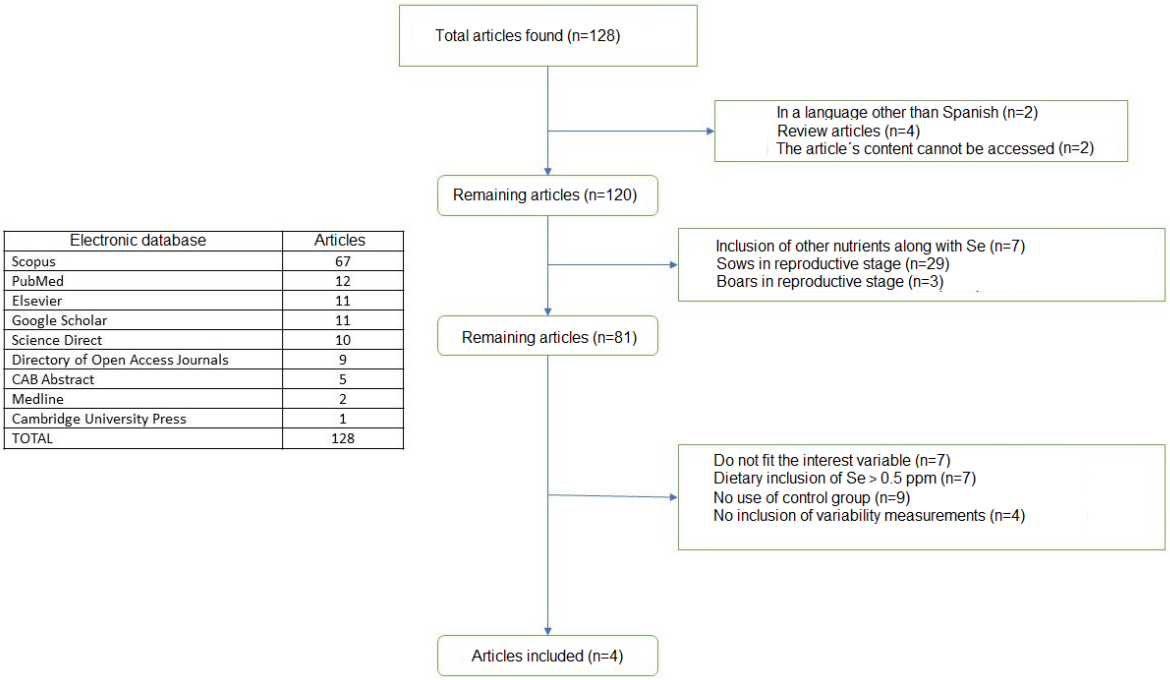
Selenium is a trace element (Duntas and Benvenga, 2015), which is demanded in very low concentrations, and it is critical for antioxidant defense (Cao *et al.*, 2015), the immune system (Huang, Rose, and Hoffmann, 2012; Markley *et al.*, 2017; Dalgaard, Briens, Engberg, and Lauridsen, 2018; Falk *et al.*, 2018), and breeding (Ahsan *et al.*, 2014; Martins *et al.*, 2014; and Surai and Fisinin, 2015). Many of the selenium containing proteins (selenoproteins) are part of the antioxidant system in which several enzymes containing or requiring micro minerals (Chiba, 2013; Labunskyy, Hatfield, and Gladyshev, 2014; Roman, Jitaru, and Barbante, 2014), take part. Selenium is a component of enzyme glutathione peroxidase, which detoxifies lipid peroxides, and provides protection to the cell and sub-cell membranes against oxidative stress (Lubos, Loscalzo, and Handy, 2011). The antioxidant function of Se has been proved to persist in muscle tissues, even after death, favoring the preservation of carcass (Lisiak *et al.*, 2014; Mahan *et al.*, 2014; Calvo, Toldrá, Rodríguez, López-Bote, and Rey, 2017; Jiang, Tang, Xue, Lin, and Xiong, 2017). The main biochemical change caused by Se deficiency is a decrease in the synthesis of selenoproteins (Seyedali and Berry, 2014), and a reduction of enzymatic activity of GPH-Px (Oropeza-Moe, Wisløff, and Bernhoft, 2015). Therefore, serum GPH-Px is a reliable index of Se in pigs (Adkins and Ewan, 1984). Selenium is known as an essential nutrient, at 0.15 mg/kg of food for growing-finishing pigs, and 0.3 mg/kg for suckling pigs (National Research Council, 2012). This problem has been previously studied (Adkins and Ewan, 1984; Zhan, Wang, Zhao, Li, and Xu, 2007). The demand of selenium is based on the concentration it reaches in tissues, not yet established upon the enzymatic activity of GPH-Px (Jenkins and Winter, 1973; Young, Castell, and Edmeades, 1977). The sources of inorganic (ISe) or organic (OSe) selenium added to the diet of pigs influence the amounts of retained and excreted selenium. The retention of seleni-

um is high, and excretion is low when the source is OSe (Ma, Lindemann, Pierce, Unrine, and Cromwell, 2014; Surai and Fisinin, 2014, 2016). None of the sources favors the productive performance of growing-finishing pigs significantly (Mahan and Parrett, 1996). Serum GPH-Px activity reaches a plateau when 0.05 ppm (Mahan, Cline and Richert, 1999), and 0.1 ppm (Mahan and Parrett, 1996) are included in the diet, regardless of the source used. However, OSe seems to have less bioavailability to favor GPH-Px activity in serum, when compared to sodium selenite (inorganic selenium) (Mahan and Parrett, 1996). Meta-analysis is a statistical method that summarizes and quantifies the knowledge acquired through the analysis of already published research results (Sauvant, Schmidely, Daudin, and St-Pierre, 2008). This tool allows researchers to access the values resulting from combined effects with higher precision than the ones in individual studies acquired through systematic review, and therefore, greater statistical data (Catalá-López and Tobías, 2014). Accordingly, Se supplementation in the diet of pigs would favor serum GPH-Px activity. The aim of this paper was to determine the effect of Se supplementation (inorganic and organic) on GPH-Px activity in blood serum (liquid portion of blood without clots or coagulation factors) in pigs, and the possible impact of other factors on this response variable, using meta-analysis.

MATERIALS AND METHODS

Source of information (data)

A search of online scientific papers was conducted (between January and March, 2018), in double-blind peer-review indexed journals, to avoid predatory journals, based on the methodology set up by Bougouin *et al.* (2014), in Elsevier, Google Scholar, MEDLINE, PubMed, Science Direct, Scopus, CAB Abstract, Directory of Open Access Journals, Cambridge University Press (Fig. 1). The key word combination used was, selenium, Se, diet, food, nutrition, organic, inorganic, pigs, glutathione peroxidase, and GPH-Px, with no date limit. This research paper did not follow the protocols established by PRISMA-P (Moher *et al.*, 2015), since they were designed for studies in humans. This meta-analysis study follows its own methodology for animal science studies, as was detailed in various published papers on meta-analysis of swine nutrition (Apple *et al.*, 2007; Kiefer and Sanches, 2009; Sales, 2011; Andretta *et al.*, 2012; Létourneau-Montminy, Jondreville, Sauvant, and Narcy, 2012; Remus *et al.*, 2015; Hung, Hanson, Shurson, and Urriola, 2017; Metzler-Zebeli *et al.*, 2017; Torres-Pitarch *et al.*, 2017; Zeng, Shurson and Urriola, 2017; Torres-Pitarch, Manzanilla, Gardiner, O'Doherty, and Lawlor, 2019).



Electronic database	Articles
Scopus	67
PubMed	12
Elsevier	11
Google Scholar	11
Science Direct	10
Directory of Open Access Journals	9
CAB Abstract	5
Medline	2
Cambridge University Press	1
TOTAL	128

Fig. 1. Flow diagram of rejection and selection of papers

Inclusion criteria

Articles referring to the only inclusion of selenium through the diet of healthy animals, and the selection and rejection of articles is shown in Fig. 1. The scientific articles should include information regarding the number of experimental farms (EF) per treatment (repetitions), the number of animals per EF, and the number of screened animals per EF. The experiments should have at least 2 treatments (including the control group, CG), the sources of selenium used for supplementation (inorganic: sodium selenite; organic: selenium-yeast), and amounts of Se, Zn, Cu, and vitamins A and E supplemented in the diet (nutrients supplied via commercial feedstuffs, which are detailed in the formulation of each diet. GPH-Px activity in the papers chosen was determined by the methods combined, according to Lawrence and Burk (1976). Regarding the dose or levels of Se supplemented through the diet, only values of 0.5 ppm or below, were considered, since higher values have negative effects on food consumption by pigs, and they favor interaction with other minerals in the food (National Research Council, 2012; PIC, 2016; Rostagno *et al.*, 2017), in addition to being sparsely used by industrial practice. The studies should have been done in non-reproductive stages of pigs (suckling, growing, finishing). Besides, the articles selected were expected to include the mean values (average), and some variation measurement, standard deviation (SD), standard error (SE), of the variable studied, to perform the corresponding estimations; otherwise, they would be rejected. The authors of the articles were never contacted throughout the redaction of this paper.

Statistical analysis

MIX 2.0 Pro, Microsoft Excel (Bax, 2016) was used for statistical processing of data. The extent of the effect of supplementation (EE) of Se on GPH-Px activity (units.mL^{-1}) by mean differences (MD), was determined with confidence intervals (CI) of 95%. Heterogeneity was evaluated through the index of inconsistency (I^2) (Higgins and Thompson, 2002). The publication bias was evaluated through the funnel plot, and Egger regression (Egger *et al.*,1997). A model of randomized effects was used as recommended by Borenstein *et al.* (2011) and Sauvant *et al.* (2008). A number of 8 meta-analyses including 66 comparison records and 1 624 animals, were made. (Mahan and Parrett, 1996; Marin-Guzman, Mahan, Chung, Pate and Pope, 1997; Mahan *et al.*, 1999; Mahan and Peters, 2004;). The productive stages were 2: (1) suckling and (2) growing-finishing pigs. The source of selenium was split into 2 categories: (1) inorganic and (2) organic; no selenium type was included in this work, because after the selection of articles, the organic source had used sodium selenite, and the organic source included selenium-yeast only. The pigs used in the individual studies were crossbreds Yorkshire-Landrace and Duroc x Yorkshire-Landrace. Various meta-regressions were performed to explain study heterogeneity, using covariables number of EF per treatment (repetitions), number of animals per EF, number of screened animals per EF, level of supplementation with Se, Cu, Zn, and vitamins A and E.

RESULTS AND DISCUSSION

Dietary supplementation of Se significantly increased GPH-Px activity in all the meta-analyses made (Table 1): general-general (MD= 0.326; IC= 0.282 to 0.371; P <0.00001); general-inorganic (MD= 0.327; IC= 0.269 to 0.385; P <0.00001), general-organic (MD= 0.325; CI= 0.255 to 0.396; P <0.00001), suckling-general (MD= 0.261; CI= 0.234 to 0.288; P <0.00001), suckling-inorganic (MD= 0.261; CI= 0.234 to 0.288; P <0.00001). During growing-finishing (GF) a significant difference was found after meta-analyses: general (MD = 0.328; CI = 0.281 to 0.375; P < 0.00001), inorganic (MD = 0.331; CI = 0.265 to 0.396; P < 0.00001), and organic (MD = 0.325; CI = 0.255 to 0.396; P < 0.00001). The analysis of subgroups showed no difference between ISe supplementation and OSe supplementation (MD= 0.00185; CI= -0.126 to 0.130; P= 0.997) on GPH-Px activity. During the productive stage, no significance was found in GPH-Px following Se supplementation in suckling (S) vs GF pigs (MD= 0.0666; CI= -0.007 to 0.140; P=0.07857). Moreover, (Table 1) shows a summary of GPH-Px activity, in absolute values between the treatment and control groups. The effect of supplementation on enzymatic activity was not consistent among the studies, as shown by high values of heterogeneity: general-general (I^2= 96.06 %; CI= 95.48 to

96.57 %), general-inorganic (I^2= 95.71 %; CI= 94.77 to 96.48 %), general-organic (I^2= 96.48 %; CI= 95.73 to 97.09 %).(> 97.09 %). The productive stage L, did not have as many studies, and I^2 produced 0%. In the GF stage, high values of general were found (I^2= 96.16 %; CI= 95.59 to 96.65 %), inorganic (I^2= 95.91 %; CI= 95 to 96.66 %), and organic (I^2= 96.48 %; CI= 95.73 to 97.09 %). The analysis of meta-regression determined that GPH-Px activity was significantly affected by factors linked to experimental design and nutritional content of the diets used in individual studies, as shown in Fig. 2-5 A funnel graph (Fig. 6), and Egger regression (Fig. 7), suspecting the presence of publication bias. The funnel graph shows that most studies piled up on the right side of 0 in the mean differences (MD), indicating the existence of a trend toward the publication of studies with positive results. Accordingly, the inverted funnel is not showing, indicating the absence of a publication bias, which was later confirmed by Egger regression (Intercept=3.74, P=0.03; Slope=0.17, P=0.005).

Fig. 2. Meta-regression general analysis: GPH-Px activity in blood serum, and number of repetitions
Regression coefficient= -0.009 (P < 0.001)

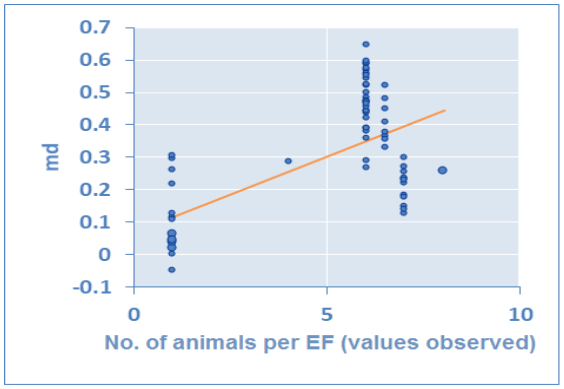


Fig. 3. Meta-regression general analysis: GPH-Px activity in blood serum, and number of animals per experimental farm
Regression coefficient= 0.047 (P < 0.001)

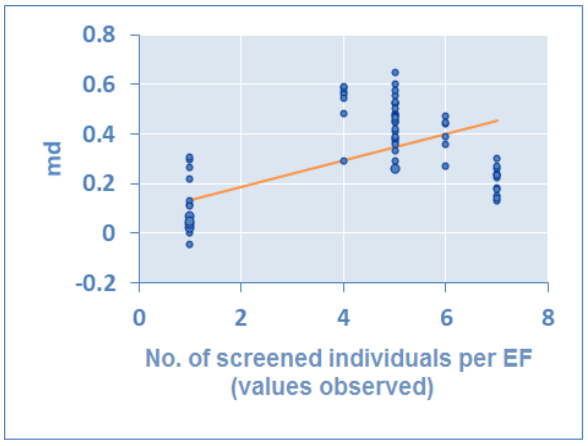


Fig. 4. Meta-regression general analysis: GPH-Px activity in blood serum, and number of screened individuals per experimental farm

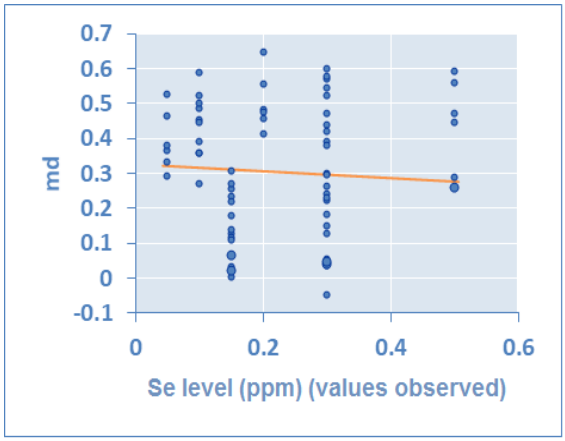


Fig. 5. Meta-regression general analysis: GPH-Px activity in blood serum, and level of selenium in the diet

Regression coefficient= 0.053 (P < 0.001)	Regression coefficient= -0.1 (P < 0.002)

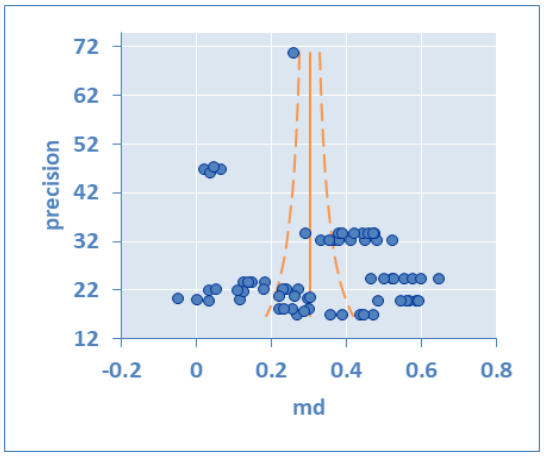


Fig. 6. Funnel graph

Fig. 7. Egger regression graph

Table 1. Enzymatic activity of GPH-Px (absolute values), and extent of the effect of enzyme GPH-Px on the blood serum of pigs

Meta-analysis		Summary of response variable and extent of the effect (Units.mL^{-1})							
		Treatment		Control		Extent of the effect			P
		Mean	SD	Mean	SD	MD	CI		
General	General	0.823	0.22	0.496	0.178	0.326	0.282	0.371	< 0.00001
	Inorganic	0.812	0.23	0.484	0.19	0.327	0.269	0.385	< 0.00001
	Organic	0.834	0.22	0.508	0.168	0.325	0.255	0.396	< 0.00001
Suckling	General	0.75	0.08	0.1	0.056	0.261	0.234	0.288	< 0.00001
	Inorganic	0.75	0.08	0.1	0.056	0.261	0.234	0.288	< 0.00001
Growing-finishing	General	0.837	0.21	0.508	0.166	0.328	0.281	0.375	< 0.00001
	Inorganic	0.839	0.2	0.508	0.168	0.331	0.265	0.396	< 0.00001
	Organic	0.834	0.22	0.508	0.168	0.325	0.255	0.396	< 0.00001

SD= standard deviation P= probability value

This work clearly shows that Se supplementation significantly favors the EE of GPH-Px vs GC in all the analyses. The enzymatic activity was higher when the source supplemented was ISe, similar to the reports made of broiler chicken, where sodium selenite was more bioavailable for production, and GPH-Px activity (Almad *et al.*, 2012), when compared to OSe, thus favoring the antioxidant capacity of the animal, at lower final food costs, because ISe is less expensive than OSe. There is a tendency of sodium selenite to improve GPH-Px activity, and it has been found that though OSe is mostly retained in body tissues, it does not favor GPH-Px activity. However, the meta-regression analysis showed that the Se level (dose) in the diet (Fig. 5) significantly affects enzymatic activity (Regression coefficient= -0.1; P=0.002). Analysis by subgroups (Se source), revealed that this effect is caused by ISe (Regression coefficient -0.17; P < 0.001),

but different from OSe (0.09; P = 0.123). A meta-analysis performed to broiler chicken showed that the activity of GPH-Px is not linked to the concentration of Se in the diet supplement (Zoidis, Demiris, Kominakis, and Pappas, 2014).

Importantly, the supplementation level of Se in the diet of pigs varies between 0.15 and 0.3 ppm, according to the National Research Council (2012). No statistically significant difference (P<0.05) was reported in GPH-Px activity with the supplementation of ISe vs OSe to pigs. The productive stage did not determine any difference (L vs GF), which was economically important, since ISe is less costly than OSe, and cheaper diets can be formulated. The above might lead to the assumption that supplementation with ISe is sufficient for pigs during rearing (weaned sucklings), growth, and finishing. However, close attention should be paid to pigs during the reproductive stage (gestation and lactation, and boars), as they require tissue reserves of Se due to their Se-demanding physiologies, which OSe can meet (Surai and Fisinin, 2015, 2016).

A study conducted by Aaron and Hays (2004) highlighted the importance of considering the number of repetitions, and the number of individuals per EF before starting research. This is the way to detect significant differences should they exist, preventing the loss of valuable information. These meta-regression studies helped determine that the number of repetitions per treatment, the number of individuals per EF, and the number of screened individuals on each EF, significantly affect GPH-Px activity in blood serum (Fig. 2-4). The more repetitions per treatment, the lower response variable; whereas, when there is an increase in the number of individuals per repetition, and the number of screened individuals per EF, the variable evaluated increases as well. The previous are important elements to be considered for the experimental design of these works, clearly showing that not only the number of repetitions should be foreseen, but also the number of pigs in each repetition.

The capacity of antioxidant defense in the organism depends on the combined work of enzymes and other non-enzymatic factors, such as vitamins (Halliwell, 1994). The superoxide dismutase in the body (SOD) is another important enzyme along the chain of chemical reactions to control free radicals or pro-oxidant factors. The cofactors of the enzyme are Cu and Zn (Collins, 2016; Ighodaro, and Akinloye, 2018). That study found that the two minerals affect GPH-Px activity significantly. GPH-Px activity decreases for every Cu unit added in the diet (regression coefficient= -0.076; P < 0.001), whereas the opposite takes place for every Zn unit increased, which raises the enzymatic activity (regression coefficient = 0.0035; P < 0.001). A similar situation takes place in vitamins, which have an antioxidant role (vitamins A (Chew, 1996) and E (Wang, Xu, Su, Shi, and Shan, 2017). As vitamin A increases in the diet, GPH-Px activity raises (regression coefficient = 0.00006; P < 0.001). The opposite occurs in vitamin E, a greater inclusion reduces enzymatic activity (regression coefficient = -0.011; P < 0.001). This effect may be caused by a larger amount of vitamin E in the diet, which can lead to a higher protective effect of the cell membrane, compared to pro-oxidant factors, and diminishing the role of enzyme GPH-Px. A study done in sows by Chen *et al.* (2016a, 2016b) found no interaction between vitamin E and Se supplemented in the diet, on GPH-Px activity. However, Urso *et al.* (2015), in a study on chicken, found that vitamin E favors the production of GPH-Px. Studies evaluating the enzymatic antioxidant activity in pigs, using diets with different supplementation levels of Cu, Zn, and vitamins A and E, are fundamental. Equally important is to determine the existence of possible interactions during intestinal absorption.

The publication bias found (P<0.05) shows that only the scientific articles with positive results in GPH-Px activity after supplementation of Se, would be favored. However, though the control animals were not Se supplemented, the macro ingredients present in the diet (corn, soybean, sorghum, etc.) contribute with some levels of Se to the basal diet (0.067 ± 0.027 ppm). The above would stimulate enzymatic activity of GPH-Px. Because of limitations with the software used, no evaluation was made on the impact of possible lost studies on the extent of the effects achieved. Neither was it possible to correct the estimated effect through the trim and fill test. Furthermore, a bias was found in relation to the origin of the articles used in this paper, since all belong to the same author, Mahan *et al.*, (Mahan and Parrett, 1996; Marin-Guzman, Mahan, Chung, Pate and Pope, 1997; Mahan *et al.*, 1999; Mahan and Peters, 2004;). Nevertheless, the use of Se in pigs is the work line of this well-known research group in the world. Further research should

evaluate the effect of Se supplementation on GPH-Px activity against health challenges, as this selenoprotein is one of the weapons of the immune system of pigs (Dalgaard *et al*., 2018). Although some authors state the hypothesis that supplementation may potentially stimulate cell immunity, because Se can increase the expression of IL-2R (interleukin receptors 2) in the T cells, and improve the response of T cells (McKenzie, Rafferty, and Beckett, 1998). No study was found to analyze GPH-Px activity and the link to glutathione levels, a reductor molecule during the reaction (Bansal and Simon, 2018).

CONCLUSIONS

Diet supplementation of Selenium (Se) favors the activity of enzyme Peroxidase Glutathione in Blood Serum. There are several factors linked to the experimental design that affect the response variable studied, which must be considered thoroughly before conducting further research. Other nutrients with antioxidant function, like Cu, Zn, and vitamins A and E, are also associated to GPH-Px activity, so it is important to improve quality control of premixes and feedstuffs.

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CONFLICT OF INTERESTS

None