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RESEARCH ARTICLE

Nanoparticles of selenium as high bioavailable and non-toxic supplement alternatives for broiler chickens

Sheeana Gangadoo[1,2,3,4] · Ivan Dinev[5] · Nicky-Lee Willson[1,6] · Robert J. Moore[2,4] · James Chapman[4] · Dragana Stanley[1,2]

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Abstract

Selenium is commonly used in the poultry industry as an additive in broiler feed to improve immunity and overall health. The selenium comes in different forms, inorganic and organic selenium, as sodium selenite and selenomethionine, respectively. This study proposes the use of nanoparticles of selenium (nanoSe) for improved delivery and absorption of the trace element while causing no toxicity. Previous studies have shown the success in utilizing nanoSe in broiler feed, with increased absorption and diffusion of material into organs and tissues, and increased antioxidant capacity. However, the mechanism of nanoSe conversion remains unknown, and the gut microbiota is believed to play a significant role in the process. The use of inorganic selenium in poultry feed demonstrated a lower bioavailability in breast ($P \leq 0.01$) and duodenum tissue ($P \leq 0.05$), and increased accumulation in organs involved in detoxification processes as compared to organic selenium and selenium nanoparticle supplementation. Histopathological analysis showed that nanoSe did not cause any damaging effects to the tissues analysed, revealing intact epithelial cells in the digestive system and neuronal bodies in brain tissue. The results indicate that nanoparticles of selenium operate a similar way to organic selenium and could potentially be used in poultry feed as a trace element additive.

Keywords Selenium · Nanoparticle · Poultry · Additives · Histology · Toxicity

Introduction

The presentation of compounds as nano-sized particles can result in new properties, change the interactions with other materials, and alter uptake and retention in biological systems, compared with presentation of compounds as larger particles or in solution. The novel properties of nanomaterials have been exploited for a range of applications, particularly in food (Gangadoo et al. 2016), sensing (Power et al. 2018), the environment (Rajapaksha et al. 2018), materials (Chapman and Regan 2012) and health (Gangadoo and Chapman 2015). Trace elements have also been delivered for nutritional supplementation using a nanomaterial (< 100 nm), representing a novel and effective method to deliver essential metals to support immunity and health (Gangadoo et al. 2016).

Nano-sized particles have already demonstrated a number of benefits such as enhanced absorption, bioavailability, antimicrobial activity (Chapman et al. 2013; Chapman and Regan 2012; Chapman et al. 2010; Regan et al. 2012; Sullivan et al. 2012), and excretion of the nano-materials (Pan et al. 2002; Schäfer-Korting et al. 2007; Shaikh et al. 2009). Nanoparticle delivery of minerals and vitamins has essentially been shown to be effective in improving feed conversion ratio, promote growth and development of muscle cells, improve the gut microbial environment, treat common parasitic disease such as coccidiosis and reduce mortality in poultry (Gangadoo et al. 2018; Gangadoo et al. 2016).

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✉ Sheeana Gangadoo
sgangadoo@gmail.com

[1] Institute for future farming, Central Queensland University, Rockhampton, Queensland 4702, Australia

[2] Poultry Cooperative Research Centre, University of New England Armidale, New South Wales 2315, Australia

[3] Central Queensland University, Rockhampton, QLD 4701, Australia

[4] RMIT University, School of Science, Melbourne, Victoria 3083, Australia

[5] Faculty of Veterinary Medicine, Trakia University, Stara Zagora, Bulgaria

[6] School of Animal and Veterinary Sciences, The University of Adelaide, Roseworthy, South Australia 5371, Australia

Selenium (Se) is an essential micronutrient that is routinely added to the feed of production animals to promote the optimal functioning of the immune system (Surai 2002b). It is currently delivered in two distinct forms, either inorganic (selenite) and organic (selenomethionine) (Surai 2002a). There has also been a recent focus in micronutrient uptake efficiency using nanomaterials (Gangadoo et al. 2016), which has also shown to modulate gut microbiota (Gangadoo et al. 2018), improve immune and musculoskeletal function, and growth performance (Beski et al. 2015; Lin et al. 2015; Wang et al. 2011). The delivery of Se in the form of a nanoparticle is appealing as it does not need to be metabolized before being incorporated into selenoproteins and can be taken up by the body at a much faster rate than inorganic Se (Gangadoo et al. 2016; Suzuki and Ogra 2002).

Se is added in poultry feed as inorganic Se (0.5 ppm) or organic Se (0.3 ppm), the latter demonstrating improved bioavailability, with multiple studies focusing on using selenium-enriched yeast and wheat as feed additives (Fisinin et al. 2008; Surai and Fisinin 2014; Utterback et al. 2005). Previous studies showed that nanoSe increased daily weight gain of broilers, and resulted in improvement in antioxidant functions (Cai et al. 2012; Fuxiang et al. 2008). Despite the promising results, some concerns have also been raised, with a few recent reports of unexpected nanoparticle toxicity (Ahmadi and Branch 2012; Ahmadi and Kurdestany 2010; Pinget et al. 2019), some specific to the gut (Ruiz et al. 2017). For example, the use of silver nanoparticles (nanoAg), while effective against aflatoxins in poultry nutrition (Gholami-Ahangaran and Zia-Jahromi 2014), was found to accumulate in the liver and muscle tissues of livestock and therefore, discontinued (Jennifer and Maciej 2013). Histopathology studies have shown that nanoAg can cause lesions in hepatocytes contributing to liver inflammation and necrosis (Loghman et al. 2012). In a previous study, we investigated the ability of nanoSe to control poultry pathogens (Gangadoo et al. 2018). Here we extended the study to investigate nanoparticle tissue bioaccumulation and histopathological toxicology, producing findings that are relevant to both chicken and human consumer health.

The aim of the current study was to examine the tissue distribution of Se supplemented to broiler chicken in the form of inorganic, organic and three different concentrations of nanoparticles. Trace elements from biological tissues were extracted using a simple, standard, acid digestion at high temperatures and pressures using a microwave oven. The digests were analysed on an ICP-MS instrument, and concentrations as low as parts per billion were determined (Liang et al. 2000). Additional histopathological analysis was carried out to corroborate and to assess the integrity of tissues exposed to the different sources of Se.

Materials and methods

Reagents

Nitric acid (concentrated HNO_3) and hydrogen peroxide (30% (w/w) H_2O_2) were purchased from Sigma, Aldrich, Australia and used without further purification. A high purity standard of selenium (Se), 1000 μg/mL in 2% HNO_3 was purchased from Choice Analytical Pty Ltd., NSW, Australia. A Dogfish Liver Certified Reference Material for Trace Metals and other Constituents (DOLT-5) was purchased from NRC-CNRC. Milli-Q water was used to perform dilutions throughout the digestion protocol.

NanoSe synthesis and characterization

NanoSe was prepared as previously described by Gangadoo et al. (2017); briefly, metal salt, selenium tetrachloride ($SeCl_4$), was chemically reduced with ascorbic acid, and a stabilizing agent, poly (sodium 4-styrenesulfonate), was added to obtain stabilized and monodispersed nanoparticles. NanoSe parameters, size, shape, crystallinity and presence of elemental selenium, were characterized using UV-vis spectroscopy, dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), x-ray diffraction and energy dispersive spectroscopy (EDS).

Animal trial

The animal trial was conducted as described in Gangadoo et al. (2018). Briefly, 70 one-day-old Ross 308 broiler male chicks (Bond Enterprises, Toowoomba Qld, Australia), were randomly divided among five treatment groups; two control groups: organic Se (Alkosel 3000 inactivated whole cell yeast, selenomethionine, containing elevated levels of organic selenium, min. 98%), inorganic Se (sodium selenite), and nanoSe supplementation given at three different concentrations, 0.3, 0.9 and 1.5 ppm. For the nanoparticle manipulated feed, the nanoSe was homogenized in a poultry remix (Rabar, PTY, LTD) which had no selenium concentrations. The poultry remix had been manufactured to possess no basal selenium content, as determined by the manufacturer (Nestel and Nalubola 2002). To be able to experimentally compare the standard poultry remix containing the standard selenium forms: organic selenium and inorganic selenium (sodium selenite) with concentrations of 133 ppm, versus the synthesized nanoparticle selenium feed system, feeds were homogenized in an Ozito CMX-125 mixer (Ozito Industries Pty. Ltd., Bangholme, Australia) at a revolution of 200 rpm and air-dried for 24 h. This homogenisation method is a standard method for commercial poultry remix formulation where many commercial

manufacturers mix vitamins, trace minerals, medicaments, feed supplements, and diluents (Armstrong and Behnke 1996, Monsalve 2006, Nestel and Nalubola 2002). The birds were fed twice daily in a light- and temperature-controlled room and were euthanised at 29 days post-hatch by CO_2 asphyxiation. Tissue samples were taken from the following organs: breast, liver, spleen, duodenum, ileum and brain, and were stored at − 80 °C until analysed.

Tissue preparation

Tissue samples ($n = 5$ per treatment group) were thawed in a fridge overnight and dried at 105 °C for 24 h. The percentage moisture was calculated using the following formula: [1 − ((dry sample weight/wet sample weight) × 100)]. Dried samples of 0.5 g were digested using a TANK PRO Microwave Digester with 6 mL of concentrated HNO_3 and 2 mL of concentrated H_2O_2 using the method shown in Table 1. The sample was reconstituted in Milli-Q water prior to analysis on the ICP-MS.

Preparation of standards and quality control

External calibration standards were prepared using the Se standard with a stock solution of 100 ppm, and standards were prepared at the start of each ICP-MS run, at concentrations of 0.05, 0.1, 0.5, 1, 2, 5 and 10 ppm with Milli-Q water. The limit of detection (LOD) and limit of quantitation (LOQ) were evaluated using digestion blanks ($n = 10$) consisting of 6 mL of conc. HNO_3, 2 mL of conc. H_2O_2 and 2 mL of Milli-Q water. Reference materials and blanks were prepared, digested and analysed, along with the dried tissue samples, for quality control. The dogfish liver certified reference material (DOLT-5 CRM) is a tissue standard with known elements and concentrations, provided by the National Research Council Canada, and was used to calculate recoveries of Se from the digestion procedure.

ICP-MS instrument settings

Sample analysis was performed on a Shimadzu ICPMS-2030 instrument, and the method parameters used by the instrument are as described in Table 2.

Table 2 Instrument settings for ICPMS-2030 and measurement parameters

Parameter	Setting
Radio frequency power	1200 W
Plasma gas	8 L/min
Auxiliary gas	1.1 L/min
Carrier gas	0.7 L/min
Nebuliser	Coaxial
Sampling depth	5 mm
Spray chamber temperature	5 °C
Collision cell gas flow (He)	6 mL/min
Internal standard tube	Mini torch

LOD and LOQ values were calculated as 3 and 10 times the standard deviation, respectively, using ten measurements of acidic blank solutions (HNO_3 and H_2O_2) divided by calibration curve

Tissue sample histology

For histological analysis, tissue samples ($n = 5$) of approximately 100–500 mg were collected from organs: breast, liver, spleen, brain, duodenum and ileum, and washed using phosphate-buffered saline. The tissues were cut at 4 μm and fixed in 10% buffered formalin and stained with haematoxylin and eosin (H&E) dyes, which allows for the differentiation of the nucleus and cytoplasmic components respectively (Cardiff et al. 2014; Wu and Zhou 2013). The histological images were scanned at the Translational Research Institute Microscopy Core Facility (Brisbane, Australia) using a Nikon Brightfield, Olympus VS120 slide scanner and analysed using Olympus microscopy software, Olivia.

Statistical analysis

All statistical tests were conducted using the SPSS Statistics package and the results are reported as mean values ± standard error of mean (SEM). Normality tests, Kolmogorov-Smirnova and Shapiro-Wilk, and Levene's Test of Equality of Error Variances were conducted to confirm equal variances and normal distribution across datasets of treatment groups ($P > 0.05$). The differences between the Se supplementation groups were analysed by a one-way analysis of variance (ANOVA), followed by a post hoc Tukey multiple comparison test when a statistically significant ($P < 0.05$) result was observed among the different treatment groups.

Table 1 Digestion protocol settings using the TANK PRO Microwave digester

Step (N)	Temperature (T)/°C	Pressure (psi)	Heating up time (t)/min	Keep time (t)/min
1	150	400	8	3
2	180	400	3	10

Animal ethics statement

Animal ethics approvals were obtained from the Animal Ethics Committee at Central Queensland University with the approval number A15/07-333.

Results

NanoSe synthesis & characterization

The synthesized nanoSe were an average of 45 ± 0.17 nm and demonstrated a polydispersity index value of 0.04 ± 0.01 nm, indicating the nanoparticles were well dispersed and did not induce aggregation. As shown in Fig. 1, the EDS analysis confirmed the presence of selenium, while TEM & SEM confirmed the shape and size of nanoparticles to be spherical and less than 100 nm respectively. The size distribution of the nanoSe was further supported from additional analysis with DLS, showing the size of nanoSe to be below 100 nm.

Se concentration varied among treatment groups and different types of tissues

A linear calibration curve ($R^2 = 0.9999$) was obtained from the external Se calibration standards Se, with a LOD of 2.69 ppb and a LOQ of 7.81 ppb. The DOLT-5 CRM Se concentration obtained from the digestion procedure was 8.49 ± 0.38 ppm, showing a 102% Se recovery. The concentration of Se, from the different supplementation sources varied, as did the concentration of Se in the different tissue types, as shown by Fig. 2.

The highest average concentration of Se within all treatment groups was found in the spleen, followed by duodenum, brain, ileum, liver and breast (spleen>duodenum>brain>ileum>liver>breast). Inorganic Se supplementation exhibited the highest Se concentrations in the spleen, liver and brain, and the lowest concentration in duodenum, ileum and breast (spleen>liver>brain>duodenum>ileum>breast). Organic Se demonstrated higher Se concentrations in spleen, duodenum and ileum, showing higher Se absorption in the gastrointestinal tract, while lower Se concentrations were found in the brain, liver and breast (spleen>ileum>duodenum>brain>liver>breast). NanoSe supplementation showed comparable results with organic Se, with 0.9 ppm nanoSe treatment producing the best result, with higher concentrations in the spleen, duodenum and ileum, and lower concentrations in brain, liver and breast tissues. Additionally, 0.9 ppm nanoSe showed improved absorption in the duodenum, and lower retention in the brain tissue, than the low and high nanoSe concentration, confirming that there was no indication of a dose-response effect in the tissue concentrations produced by the different supplementation levels of nanoSe.

The differences in the Se concentration were not significant among treatment groups in the brain ($P = 0.051$), liver ($P = 0.182$), spleen ($P = 0.449$) and ileum ($P = 0.092$) but differed significantly in breast ($P = 0.01$) and duodenum ($P = 0.013$), with higher concentrations observed in birds supplemented with nanoSe. A similar trend was observed in the ileal tissue, with a higher Se content observed with nanoSe than inorganic Se. There was an opposing trend observed with the liver, spleen and brain tissues, with inorganic Se displaying the highest Se content.

Histopathological effect of Se sources

A histological examination was performed on the tissues obtained from the five treatment groups. All Se treatment groups showed normal histological structure of breast tissue,

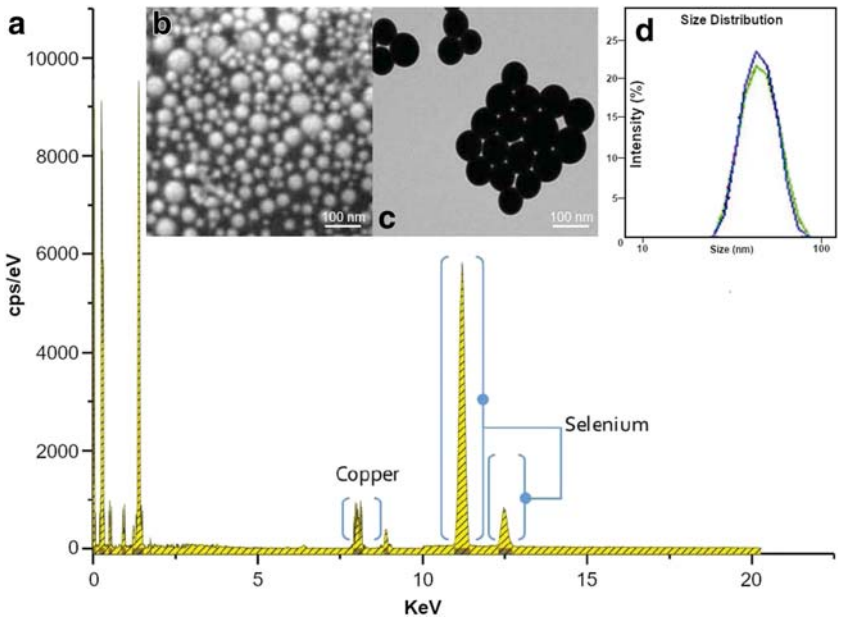

Fig. 1 NanoSe characterization obtained from **a**: EDS; **b**: SEM; **c**: TEM; **d**: DLS

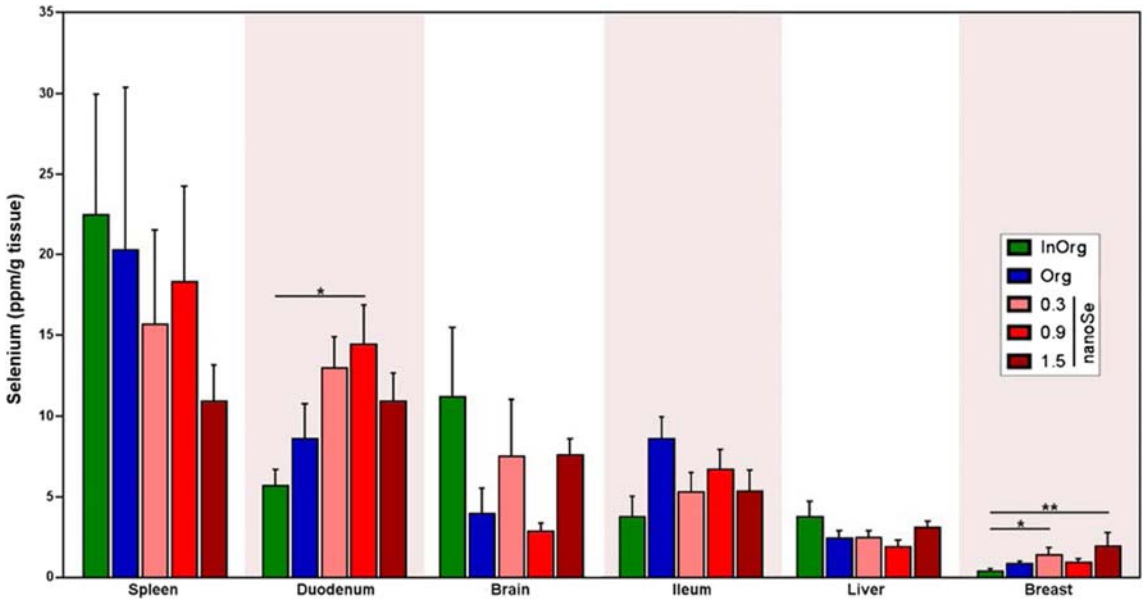

Fig. 2 Se concentration among treatment groups in different tissue types

demonstrated by the relatively uniform diameter of the cross-cut myofibrillar bundles and intermyofibrillar spaces of the muscle fibres. The integrity of the muscle fibres was demonstrated by the well-defined cross-striation, as shown in Fig. 3(a), and preserved nuclei of the myofibril (b). The cross-striation of myofibrils was less expressed in inorganic Se than the other Se groups. There was no pathological damage observed in brain samples, with neuronal bodies between the neuroglia and blood vessels of brain substance shown to be normally distributed in all Se treatment groups. Figure 3(c) shows basophilically stained Nissl bodies/tigroid clustered mainly in the area around the nucleus/pericarion and in the periphery of the cell. An initial to moderate degree of fat infiltration in liver epithelial cells was observed in liver tissue.

Hepatocytes and Kupffer cells pictured in Fig. 4 (a) and (b), respectively, showed no damage in any of the Se treatment groups. Spleen samples across all Se treatment groups showed normal structural characteristics, with minor to moderate amounts of erythroblasts observed in the spleen pulp as pictured in Fig. 4(c).

There was no histopathological damage observed in either the duodenal or ileal tissue across any of the five Se treatments. The intestinal villi of the mucosa in the duodenum were covered by a monolayer prismatic epithelium. Single goblet cells (Fig. 5(b)) were located between the normal intestinal cover cells. The epithelial cells covering the crypts showed preserved microvilli (Fig. 5(a)). The intestinal crypts of the ileum are shown in Fig. 5(c), with the villi evenly covered by a monolayer prismatic epithelium and a common density of goblet cells observed. The ileum tissue also showed densely located, mucous-associated, accumulations of lymphoid cells forming Peyer's patches, pictured in Fig. 5(d).

Discussion

Selenium is an important micronutrient and is a constituent of the immune system (Rayman 2000). Selenium nanoparticles were synthesized using a typical bottom-up approach, allowing the control and formation of stable and defined crystals, and delivered to a chicken model to improve the uptake and absorption rate of the trace element. The model used was a broiler chicken model with a rationale to investigate whether nanoSe supplementation would induce toxicity and/or alter bioavailability, compared to the two commonly used Se supplementation products by the poultry industry (organic and inorganic selenium). Previous studies utilizing nanoSe for improvement of poultry's health and performance only investigated concentration levels of the nanoparticle rather than its parameters such as size, surface charge and crystallinity. The nanoparticle size was an average of 80 nm and studies showed levels exceeding 2.0 ppm resulted in a decline in the immune system (Gangadoo et al. 2016). This trial included the common concentration of Se used in poultry industry, 0.3 ppm as a minimum level and a maximum concentration level of 1.5 ppm. However, there was no correlation observed with the concentration of nanoSe and effects presented in this study, indicating further studies with a wider range of concentration levels to be beneficial.

The histopathological analysis of the sampled tissues indicated that there were no damaging effects from any of the Se sources, however, significant differences in Se concentration between the nanoSe and inorganic Se treated birds were observed. The tissues from birds with nanoSe supplementation displayed higher Se concentration in breast and intestinal tissues than the birds treated with inorganic Se, indicating its

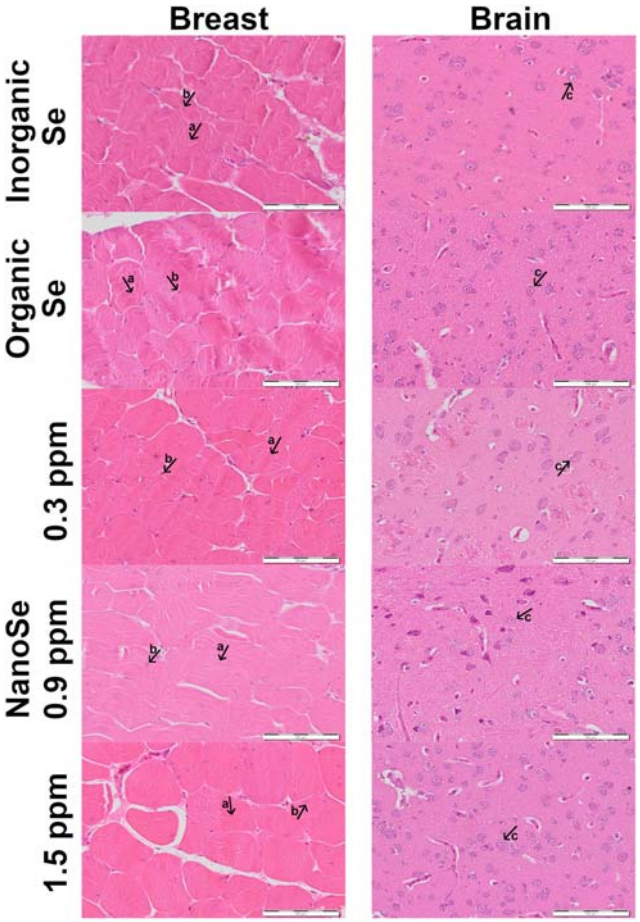

Fig. 3 Histological assessment of 55 Se treatment on breast tissue showing myofibrils (**a**) and cell nuclei (**b**); and brain with Nissl bodies (**c**)

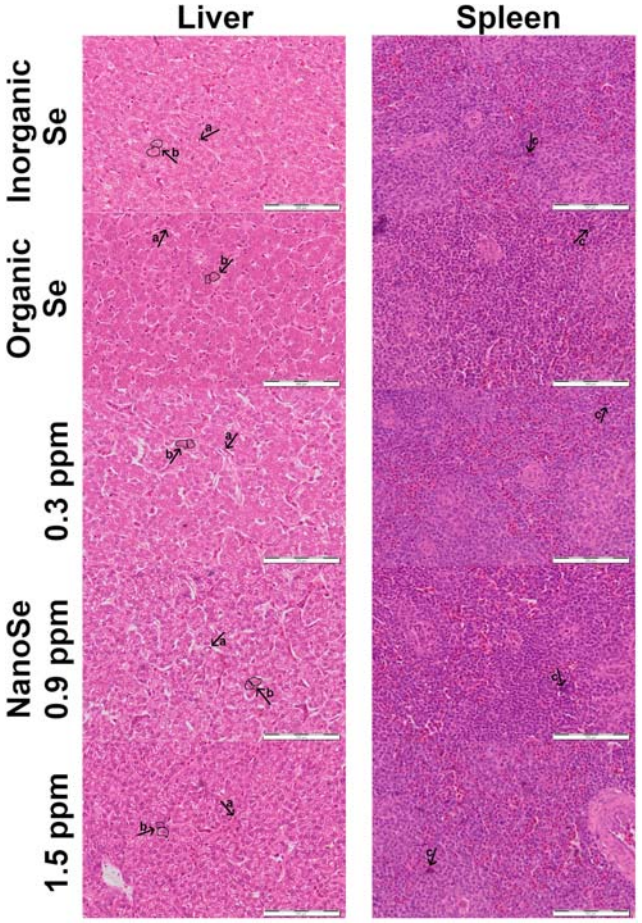

Fig. 4 Histological assessment of Se treatment on liver tissue showing hepatocytes (**a**) and Kupffer cells (**b**); spleen tissue with minor to moderate amounts of erythroblasts (**c**)

superior bioavailability and suggesting an active transport mechanism similar to organic Se (Shi et al. 2011). Se species differ within the treatment groups, affecting its bioavailability and absorption. Inorganic Se combines with other food components during digestion and form insoluble complexes, reducing its absorption, while the Se form in organic Se undergoes amino-acid uptake mechanisms in the intestine, increasing its transportation across the intestinal wall (Constantinescu-Aruxandei et al. 2018; Mahima et al. 2012), and this has been observed from greater bioavailability of organic Se in broilers and egg-laying hens from organic Se than inorganic Se (Dobrzański et al. 2003; Jiakui and Xiaolong 2004; Payne and Southern 2005). NanoSe is consequently elemental Se and its transportation across the biological body is determined by its physicochemical properties, including size and shape (Constantinescu-Aruxandei et al. 2018). This study demonstrated the higher bioavailability of nanoSe obtained through a spherical and non-crystalline morphology, with an average size of 46 nm.

An opposing trend was observed in liver and spleen tissue, with the birds from the inorganic Se treatment group showing higher Se concentrations, while nanoSe and organic Se showed comparable results. The liver is a major organ of Se accumulation (Surai 2002a), where selenides, from inorganic Se sources, are incorporated into seleno-proteins before being distributed throughout the body (Pilarczyk et al. 2011; Suzuki 2005). The spleen is the largest lymphoid tissue and is important in regulating immune functions around the body (Attia et al. 2010; Chen et al. 2014). This suggests that inorganic Se contributes to higher Se retention and accumulation in organs involved with detoxification processes.

Although our data indicates that there is no Se toxicity occurring in the tissues and no direct damaging effects on the intestinal morphology, more toxicity studies such as immunogenicity, cytotoxicity, NP accumulation and excretion kinetics, would be required prior to engaging in nanoSe supplementation to livestock on an industrial scale. The determination of selenium concentrations in tissue samples and histological analysis of multiple broiler tissues showed nanoparticles of selenium to be non-toxic, while exhibiting higher absorption in intestines and a lower retention in tissues involved in detoxification as compared to selenium additives

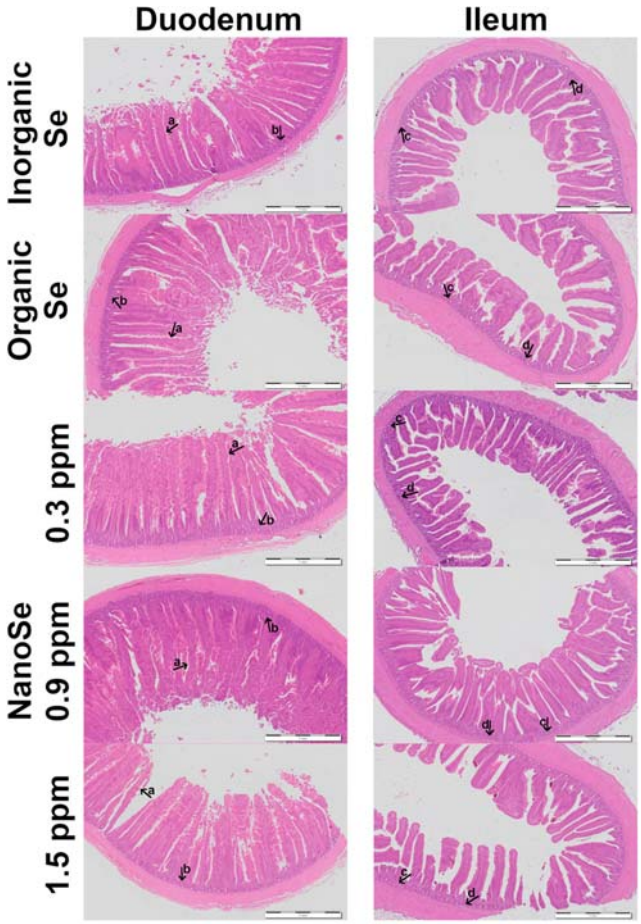

Fig. 5 Histological assessment of Se treatment on duodenum with microvilli (**a**) and goblet cells (**b**); and ileum showing intestinal crypts (**c**) and accumulation of lymphoid cells forming Peyer's patches (**d**)

commonly used in the poultry industry, such as sodium selenite and selenomethione (selenium yeast).

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Compliance with ethical standards

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

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