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Review

Impacts of rare earth elements on animal health and production: Highlights of cerium and lanthanum

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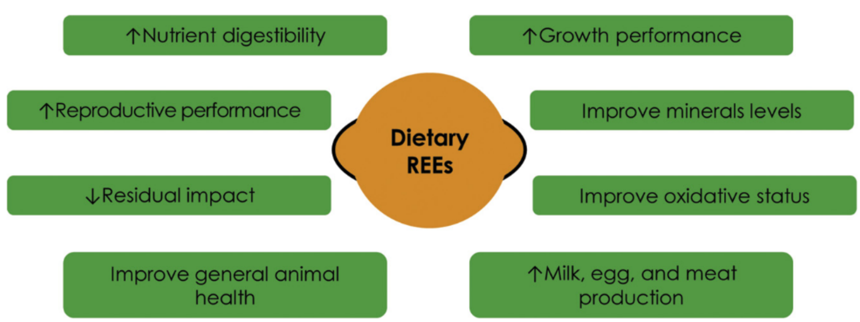
HIGHLIGHTS

- REEs promote growth and reproductive performance.
- REEs enhance feed intake, nutrient digestibility, and feed conversion rate.
- REEs improve oxidative status through decreasing MDA and increasing SOD levels.
- REEs increase milk, egg, and meat production.
- REEs have low residual levels in liver and muscles.

GRAPHICAL ABSTRACT



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ABSTRACT

Because the use of antibiotics as growth promoters was banned due to global health concerns, researchers are focusing on exploring alternative safe and effective feed additives. Rare earth elements (REEs) are located in group III of the periodic table, which includes cerium (Ce), lanthanum (La), and other elements. Recently, REEs have been involved in many medical, industrial, zootechnical, and agricultural applications. They play a pivotal role in functional and structural molecules in the biological system. Currently, in veterinary practice, REEs have been introduced as new feed additives to improve animal health and production. Based on the previous literature, REEs reportedly enhance milk, egg, and meat production. However, the controversy between adverse (e.g., toxicological and ecotoxicological) and favourable REE-associated effects has not been fully discussed. This review summarizes the relevant literature on the impacts of REEs on animal production and health; specifically, this review emphasizes the application of REEs as alternative safe feed additives used to promote animal growth and performance.

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1. Introduction

In 2006, all in-feed growth-promoting antibiotics were banned by the European Union because of public concerns about the transmission and development of multi-resistant bacteria, which are hazardous to human health. Such restrictions provoked the need to explore new safe, efficient, and cheap feed additives as alternative sources of growth promoters. During the last few decades, rare earth elements (REEs) have been introduced as feed additives due to their efficacy in improving the body weight, feed conversion rate (FCR), and milk and egg production in a variety of farm animals, including cattle, poultry, and swine. They predominantly exist in the Earth's crust (Redling, 2006) and contain group III elements from the periodic table, including cerium (Ce), lanthanum (La), scandium (Sc), yttrium (Y), and 14 La-like elements called lanthanoids (IUPAC, 2005). In China, REEs are utilized for improving the performance of both animal and crop production, and their safety and effectiveness were assessed prior to their commercial application (Redling, 2006). However, the growth-promoting potential of REEs was not documented until 1999 (Rambeck et al., 1999).

Among REEs, Ce and La have been commonly used as feed additives in organic or inorganic forms for poultry and swine (Pagano et al., 2015). The addition of organic REEs (e.g., REE-enriched yeast (RY) and REE-citrate) to non-ruminant diets significantly increased the serum concentration of 3,5,3′ triiodothyronine, nutrient digestibility, and growth performance (Cai et al., 2018; Forster et al., 2008; Kraatz et al., 2006) compared to the use of inorganic REEs (e.g., chlorides) (He and Rambeck, 2000; He et al., 2010). Yang et al. (2009) concluded that in vitro REE supplementation improved the microflora proportions in the rumen; therefore, REEs may be an efficient substitute for antibiotics. Furthermore, there were no safety problems or residues in non-ruminant animals fed <100 mg/kg of Ce or La (Han and Thacker, 2010; He et al., 2010; Wang and Xu, 2003). During fermentation, yeast absorbs REEs and forms organic REE compounds (RY) (Andres et al., 2003).

A growing body of evidence has suggested that administering REEs to farm animals results in growth-promoting effects (Redling, 2006), which may manifest as increased milk yield in cows and egg production in laying hens (Schuller, 2001). In female rabbits, dietary supplementation with cerium oxide (CeO) at a dose of 200 mg/kg improved the average daily feed intake (ADFI), FCR, average daily weight gain (ADWG), and health status without having any negative effects on the serum biochemical parameters (Adua et al., 2015). Bölükbaşı et al. (2016) reported that dietary supplementation of CeO at 300 mg/kg dose in laying hens increased the shell breaking strength, egg production, shelf-life of eggs, and FCR. The authors attributed these improvements to the CeO-enhanced oxidative stability of eggs. On the other hand, several studies have investigated the toxic effects of REEs on different body organs and functions, as well as their eco-toxicological impacts on soil microflora.

A large body of data has accumulated concerning REEs supplementation as an alternative potential growth promoter. This review aimed to summarize relevant studies regarding the potential of dietary REEs on growth performance, blood biochemical parameters, antioxidant status, rumen fermentation, and nutrient digestibility in different animal species; additionally, it summarizes the application of REEs as growth promoters in animal diets and evaluates their impacts on animal production, including milk yield and growth performance in livestock and poultry. Moreover, we discuss the toxicological and eco-toxicological evidence related to the use of REEs.

2. Physical and chemical properties of rare earth elements

Despite their name, REEs are a group of chemical elements that represent the 15th most abundant component of the Earth's crust (Weber and Reisman, 2012). Based on their atomic weight, they are classified into light REE (LREE), or the cerium subgroup from lanthanum ($Z = 57$) to samarium ($Z = 62$), and heavy REE (HREE), or the yttrium subgroup from europium ($Z = 63$) to lutetium ($Z = 71$). Scandium ($Z = 21$) and yttrium ($Z = 39$) are included among REEs because of their similar chemical properties (Zhuang et al., 2017).

According to the periodic table, the atomic radius of Ce and La is analogous to that of Ca or other metallic ions; therefore, they may act as cofactors to supersede Ca or other metallic ions in the growth metabolism of livestock (Martin and Richardson, 1979). Rare earth oxides are the most stable rare earth compounds. The common formula RE_2O_3 is applied to oxides of the trivalent REEs, while the dioxides, CeO_2, with Ce being quadrivalent, are also a characteristic member. A wide range of mixed oxides, many with commercial uses, are known. The ones containing La, Ba, Sr, or Cu, which provide superconductivity at and even above liquid nitrogen temperature, are of great interest for industrial use (Richter, 1996). REEs are soft, malleable, ductile, and chemically very active. When they are freshly cut, their smooth surfaces have silvery white lustre that changes to chestnut and dark brown as a result of the formation of RE oxides in the presence of air. They all react directly with water, slowly at low temperatures and rapidly at elevated temperatures, by expelling hydrogen and thus producing insoluble hydrous oxide or hydroxide. Fast reactions also occurred with C, N2, Si, P, S, halogens, and other non-metals at higher temperatures (Redling, 2006). The two-stage precipitation process was used to prepare CeO nanocrystalline powders from Ce nitrate solution with the subsequent production of weakly agglomerated powders with small-sized crystallite (>5 nm) (Martin and Richardson, 1979).

3. Mechanisms of REEs

Ou et al. (2000) suggested four possible REE mechanisms, including enhanced enzyme activity, improved protein metabolism, suppressed bacterial growth, and promoted secretion of digestive fluids in the stomach. The anti-inflammatory and immunostimulating actions of REEs have also been proposed to promote growth in animals (Flachowski, 2003). Furthermore, effects on hormone activity as well as on cell proliferation have been considered as possible mechanisms for enhancing the effects of REEs (He et al., 2010).

Several studies have investigated the mechanisms underlying REE-enhanced ruminal degradability of feeds, but they are still unclear. The possible mechanisms of action of REEs in the digestive tract have been well investigated in monogastric animals. Ou et al. (2000) concluded that REE supplementation can improve the digestion and absorption of nutrients through the induction of digestive enzyme secretion in the intestine as well as the destruction of infectious bacteria. Recently, REEs have been described to have antibacterial activities by selectively affecting the growth of some bacterial species in the gastrointestinal tract. H. Zhang et al. (2000) and Peng et al. (2004) observed that REEs suppressed the growth of several bacteria in a dose-dependent manner. Similarly, REEs can modulate digestive microorganisms and enzymes (Xun et al., 2014). The mechanistic actions of REEs were profound in relation to high nutrient absorption and enhanced digestive enzyme secretions, thereby improving the digestion process and growth performance (Azer, 2003).

4. Influences of rare earth elements

Fig. 1 shows the proposed mechanisms of the dietary inclusion of REEs in the diets of different animal species. Fig. 2 shows the sources, applications, benefits, and health risks of high-technology REEs. Table 1 summarizes the major experimental findings for REE dietary inclusion in the diets of different animal species.

4.1. Growth performance

Recently, REEs have gained more attention due to their biological properties. Adua et al. (2015) reported that ADWG and ADFI were significantly improved after supplementation with different dietary

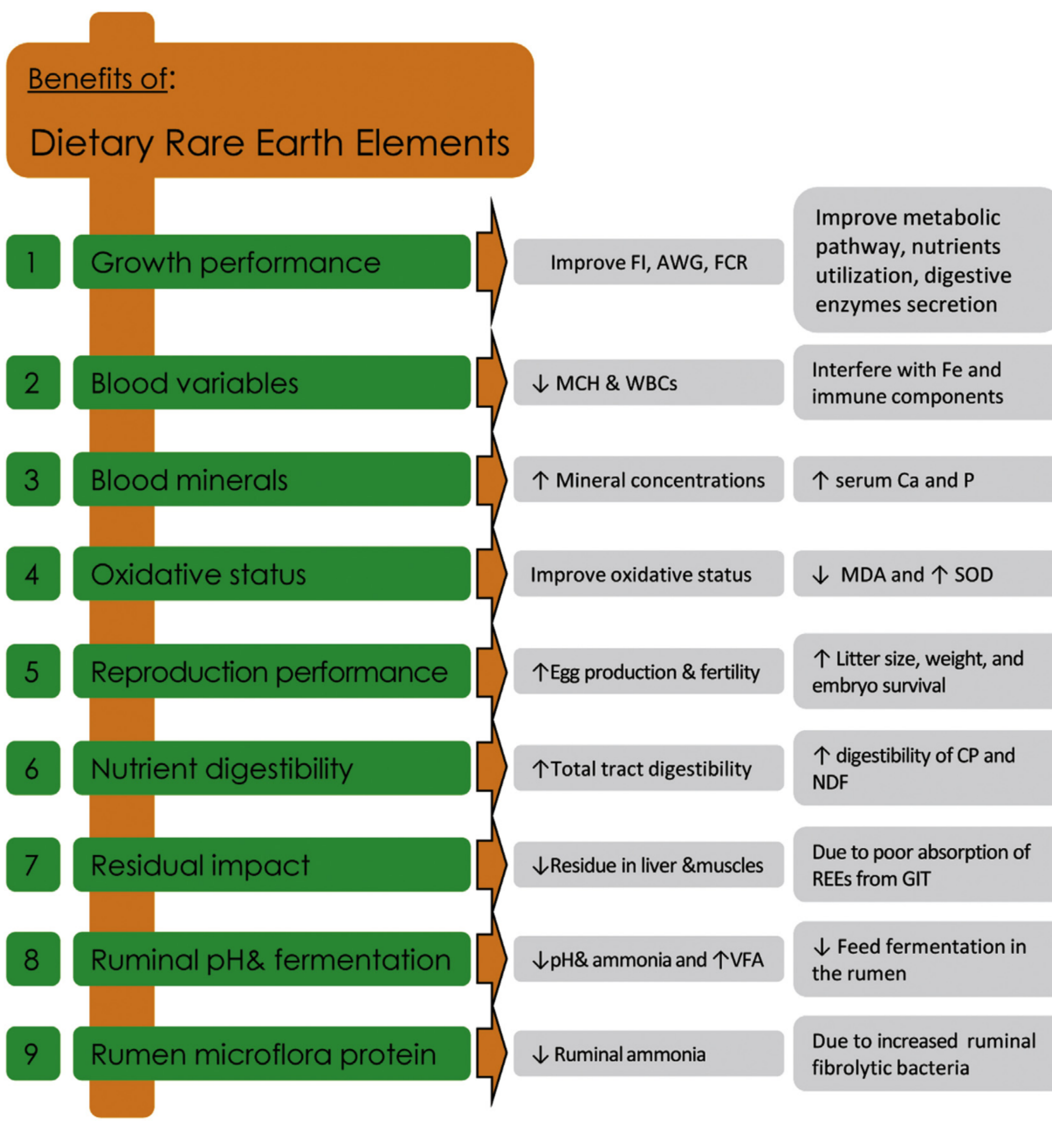

Fig. 1. Possible explanations for the effect of dietary inclusion of REEs in different animal species diet.

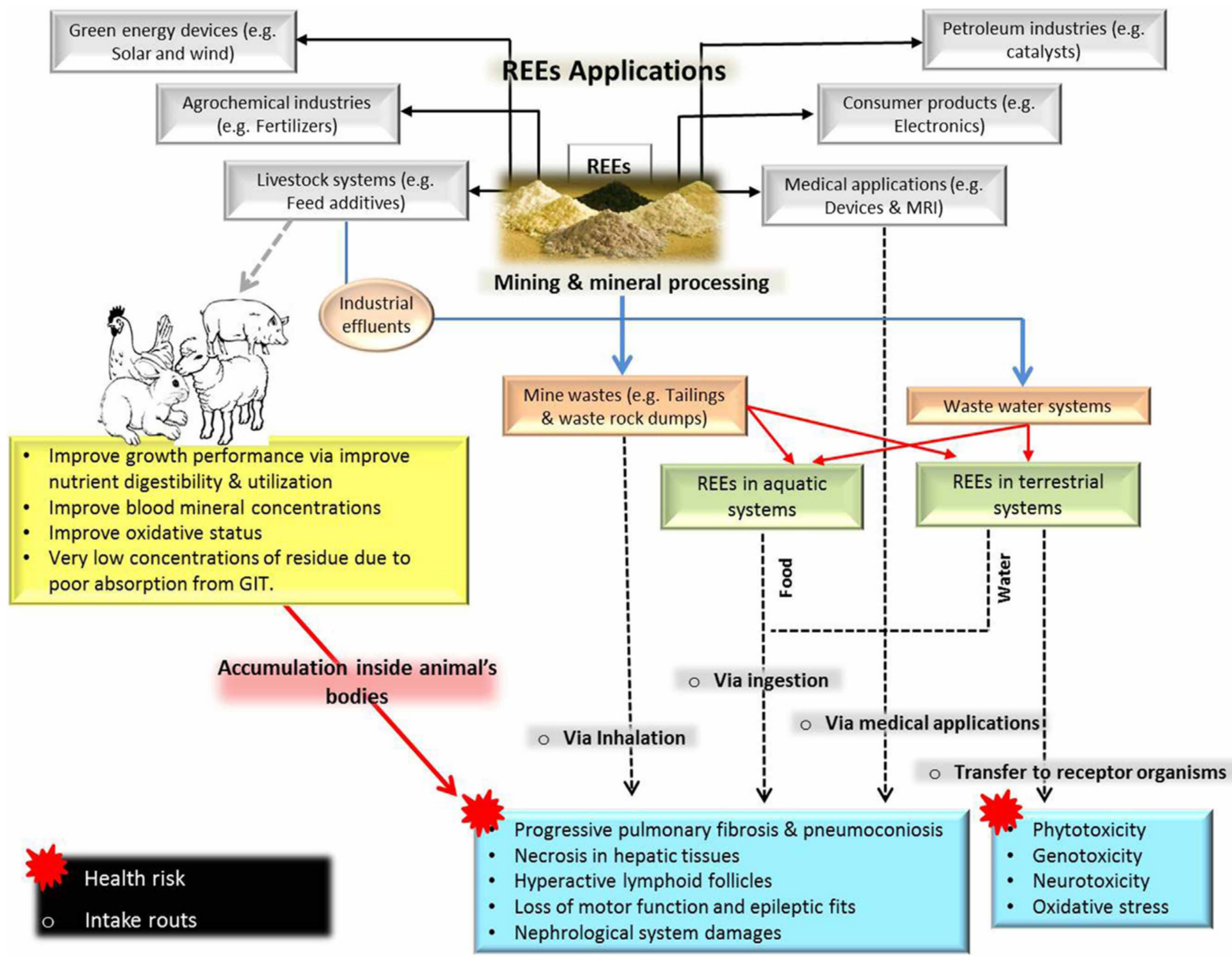

Fig. 2. Source, applications, benefits, and health risk of high technology REEs.

concentrations of CeO (100, 200, and 300 mg/kg) in rabbits. Similar findings were reported by He et al. (2010) and Xu et al. (1999); these findings could be explained by the fact that dietary REEs improved nutrient utilization and enhanced digestive enzyme secretion (He et al., 2010; Xu et al., 2004). Furthermore, REEs helped to stabilize the intestinal microflora and thereby had the potential to promote growth performance (H. Zhang et al., 2000; Zhao et al., 2002). The performance-enhancing effects of REEs in animals are supported by their anti-bacterial and anti-inflammatory properties (Redling, 2006). However, few studies have concluded there were few or no effects of dietary supplementation with REEs in animals (Gebert et al., 2005). This variation in results might be attributed to the difference in investigated REEs, the concentration of each REE and the animal species used in the different experimental studies. Although many REEs exhibit similar chemical properties, there are some variations among these elements. For example, Ce is different from La because La is a cation with missing unpaired f-electrons, while Ce exhibits two oxidation states, Ce^{3+} and Ce^{4+}.

Zhang and Shao (1995) reported that the optimum concentration of rare earth nitrate on the growth performance of 10-day-old broilers after 60 days was 300 mg/kg feed. The addition of rare earth nitrates (38.7% rare earth oxides; mainly containing La_2O_3, Ce_2O_3, Nd_2O_3) at 300, 400, and 600 mg/kg feed improved the body weight gain by 20.3% ($p < 0.01$), 18.6% ($p < 0.01$) and 6.6% ($p < 0.05$), respectively, compared to the control group. Final body weights increased by 7% in chickens after organic rare earth compounds were supplemented in the diet (Redling, 2006). However, these positive effects could not be replicated in another study, in which inorganic rare earth compounds were added to the feed of broilers and Japanese quails (Redling, 2006), thus indicating the importance of the chemical compound that is applied. He et al. (2010) demonstrated that both organic and inorganic rare earth compounds were able to improve the growth performance of broilers after oral administration at low dosages. However, neither La chloride nor the mixture of rare earth chlorides was able to enhance performance (Schuller et al., 2002). On the other hand, a slight reduction in performance was demonstrated in quails receiving high-supplemented diets (300 mg/kg) during the first half of the experiment. The absence of positive effects may be attributed to differences in concentrations because only distinct amounts of REEs supplemented in the diet may cause effects. In addition, variations in animal species, fattening periods, or keeping and feeding conditions may also play a role. Therefore, further investigations using different breeds at different growth stages and intensities are recommended. In accordance with Schuller et al. (2002), no positive effects of REEs on the fattening performance of turkeys were revealed in another feeding trial (Redling, 2006). However, studies using organic compounds at very low concentrations instead of inorganic compounds, as in Schuller (2001), were able to prove significant performance-enhancing effects in chickens (He et al., 2010).

Body weight increases of 7%, 5.6%, 2%, and 5% were achieved in animals whose feed was supplemented by rare earth ascorbate, citrate, nitrate, and La chloride, respectively (Flachowski, 2003). Thus, the best performance was achieved in chickens treated with either rare earth ascorbates or citrates. Based on these results, both the chemical form

Table 1
Major experimental findings for REEs dietary inclusion in different animal species diet.

Parameters	Reference	Species	Treatment	Findings
Growth performance	Adua et al. (2013) Xu et al. (1999) He et al. (2010)	Rabbits Pig Broiler	Dietary CeO (100, 200, and 300 mg/kg diet)	• Significant improvement in ADFI • Significant improvement in BWG
	Gebert et al. (2005)	Pig		• No significant effects of dietary supplementation with REE
	Bölükbaşı et al. (2016)	Laying hens	Dietary CeO (200 and 300 mg/kg diet)	• Significant improvement in FCR • Significant increase in egg production • Significant increase in egg shell breaking strength
	Cai et al. (2018)	Pig	RY	• ADG and FCR increased linearly with increasing level of RY in diet
	Ladipo et al. (2015)	Rabbits	Dietary CeO (0, 50, 100, 150 mg/kg diet)	• Significant improvement in ADFI, BWG and FCR
	Durmuş and Bölükbaşı (2015)	Laying hens	LaO (100, 200, 300, 400 mg/kg diet)	• No significant differences in feed intake and egg weight between all groups. • Significant improvement in egg production and FCR at (400 mg) • Significantly increased shell breaking strength of egg at (200 mg)
Blood variable	Adua et al. (2013)	Rabbits	CeO at (0, 100, 200 and 300 mg/kg diet)	• Significant improvement of blood means corpuscular haemoglobin, differential leukocyte counts, and urea. • Non-significant differences in serum biochemical parameters
		Laying hen	La and Ce (250 mg/kg diet)	• Non-significant effect on total protein, albumin, and globulin
	He et al. (2001) Adu (2005)	Pig Rabbits	Dietary REE	• No negative effects of REE on blood parameters of animals
	Jones et al. (2004) He et al. (2009)	Rabbits Broiler	Dietary REE	• Significant decreased in MCH, leukocytes, lymphocytes, neutrophils, and eosinophils counts
	Adu et al. (2009)	Rabbits	LaO (0, 100, 200, 300, and 400 mg/kg diet)	• Non-significant effect on blood erythrocytes and leukocytes counts
	Cai et al. (2018)	Pig	RY	• Non-significant effect on RBC and WBC • Linear increase in blood lymphocyte counts with increasing level of RY in diets
	Ladipo et al. (2015)	Rabbits	CeO (50, 100, and 150 mg/kg diet)	• No significant influence on serum biochemical parameters and haematology (except for packed cell volume, white blood cell, and monocyte)
	Durmuş and Bölükbaşı (2015)	Laying hens	LaO (100, 200, 300, 400 mg/kg diet)	• Non-significant difference in serum ALT, AST, glucose, TG, total cholesterol, LDL, and HDL
Blood minerals	Reka et al. (2018)	Laying hens	(La and Ce) (250 mg/kg diet)	• Significant increase in plasma Ca and P levels in first and second month
			(500 mg/kg diet)	• Significant increase in plasma Ca and P in first month • No significant changes were reported in second month of the trial
	Bölükbaşı et al. (2016)	Laying hens	CeO (100 mg/kg diet)	• Significant increase in serum Ca and P concentrations
	Zohravi (2006)	Japanese quails	REE supplements (50 and 100 mg/kg diet)	• Significant increase in concentration of serum Ca
	He et al. (2010)	Broilers	REE	• No significant effect on the concentration of serum Ca
	Durmuş and Bölükbaşı (2015)	Laying hens	LaO (100, 200, 300, 400 mg/kg diet)	• Non-significant difference in serum Ca and P concentrations
Immunity responses (oxidative/anti-oxidative status)	Bölükbaşı et al. (2016)	Egg yolk	Dietary CeO	• Significant decrease in SOD and MDA
	Wang et al. (1999) Xie and Wang (1998)	Fish Chickens	Dietary REE	• Significant increase in SOD levels
	Kawagoe et al. (2005)	Rats	Dietary Ce	• Non-significant effect on plasma LPO • Significant decrease in SOD activity of plasma
	Durmuş and Bölükbaşı (2015)	Laying hens	LaO (300 mg/kg)	• Non-significant impacts on SOD and GPx values, • Significant decrease in serum MDA value
Reproductive performance	Akinmuyisitan et al. (2015)	Rabbits	Various concentrations of CeO	• Significant improvement in litter size (8.45–19.86%) • Litter weight and total litter weight (3.57–11.31% and 12.45–33.57%) • Embryo survival rate (8.29% at 200 mg/kg) • Non-significant effect on conception rate (3.13–6.25%)
	Redling (2006)	Rabbits	REE (100–200 mg/kg diet)	• Enhancement of reproductive performance • Improvement in litter size and embryo survival rate
	Wu et al. (1994)	Poultry	Dietary REE	• Enhanced egg production, fertilization and rate of hatching eggs
	Chen and Xiong (1994)	Laying hen & pig	Dietary REE	• Improvement in the laying rate (8.18%). Enhancement of egg embryo development • Significant improvement in embryo survival rate.
Ruminal pH and fermentation	Xun et al. (2014)	Sheep	REE-citrate (100–300 mg/kg DM)	• Significant decrease in ruminal pH (6.72 to 6.53) • Ruminal ammonia content was quadratically decreased with increasing REE supplementation. • Negative effect on growth of several rumen bacteria
	Liu et al. (2008)	Simmental steers	La (0, 450, 900 to 1800 mg per head per day)	• Linear and quadratic increase of total VFA and propionate with increasing supplementation

(continued on next page)

Table 1 (*continued*)

Parameters	Reference	Species	Treatment	Findings
	Yang et al. (2009)	Sheep	REE (400 and 800 mg/kg DM)	• No impacts on ruminal VFA concentration
Nutrients digestibility	Xun et al. (2014)	Sheep	REE (300 mg/kg DM)	• Linear increase in nutrients digestibility with increasing REE supplementation • Non-significant influence on digestibility of nutrients
	Liu et al. (2008)	Steers, Pigs	$LaCl_3$ (450, 900, and 1800 mg/day)	• Linear increase in NDF
	Ming et al. (1995)	Pigs	Dietary REE	• Significant improvement in digestibility of CP
	Hu et al. (1999)	Sheep		
	Halle et al. (2003)	Steers and pigs	Dietary REE	• Enhancement of nutrients digestibility, growth, and feed efficiency
	Shen et al. (1991)	Beef cattle		
	He et al. (2003)	Rats		
	Cai et al. (2018)	Pig	RY1500 diet	• Significant increase in total tract digestibility
	Han and Thacker (2010)	Pig	RY	• Total tract digestibility of DM, CP, and GE was significantly increased
Rumen microbial protein synthesis	Xun et al. (2014)	Sheep	REE (100–300 mg/kg diet)	• Significant decrease in ruminal ammonia concentration • Improved ruminal microbial protein synthesis
Residual impacts	He et al. (2009)	Broiler	La and Ce	• Residual concentrations in liver and muscles were very low, accounting for 0.11–0.76 and 0.02–0.30 mg/kg
	He et al. (2001)	Piglets	La and Ce	• Lower concentration of REE was found

REE, rare earth element; CeO, cerium oxide; LaO, lanthanum oxide; ADFI, average daily feed intake; BWG, body weight gain; FCR, feed conversion rate; ADG, average daily gain; RY, REE-enrich yeast; DM, dry matter; LPO, lipoperoxide; SOD, superoxide dismutase; MDA, malondialdehyde; NDF, neutral detergent fiber; CP, crude protein.

and the concentration of REEs seem to have great impacts on their efficiency because no effects on final weight were noticed after the supplementation of 50 mg rare earth nitrates per kg feed (Halle et al., 2002). In accordance with Halle et al. (2004), better results were achieved after the application of organic rare earth compounds. Significantly improved feed intake and body weight gain up to 5.4% and 5.0%, respectively, were noticed over the entire experimental period after rare earth citrates were applied.

Cai et al. (2015) studied the effects of REE-enriched yeast (RY) on meat quality, nutrient digestibility, growth performance, excreta microflora, and relative organ weight in broiler chickens. The authors reported that meat nutrient quality and digestibility were slightly improved in broiler chickens supplemented with 1500 mg/kg of RY.

In laying hens, the dietary inclusion of CeO had no marked improvement in terms of egg weight and feed intake; however, it markedly enhanced egg production and improved FCR (Bölükbaşı et al., 2016). A considerable improvement in eggshell breaking strength was observed when CeO was added at doses of 200 and 300 mg/kg diet. This improvement may be attributed to the enhanced absorption of Ca and REEs (Bölükbaşı et al., 2016). The application of REEs at 120 mg/kg could improve the total egg production and laying rate of 75-week-old laying hens (Beijing White T.) by 8.18% and 6.4%, respectively (Chen and Xiong, 1994). In hen farming, RCT - 3 (organic rare earth compounds) supplementation at a dosage of 100 mg/kg for one month increased the laying rate by 3.4%, decreased the feed egg ratio and significantly improved both the fertility and the hatching rates. Furthermore, the fertilization and hatching rates as well as the percentage of healthy chickens increased. On the other hand, improvements in laying rates of 7.1% ($p < 0.01$) and 3.6% ($p < 0.05$), respectively, were reported when REEs were applied at concentrations of 0.03% and 0.04%, respectively, to 53-week-old laying hens (Beijing White) for seven weeks. Moreover, individual egg weight was significantly enhanced (Zhang et al., 1996).

Regarding the improvement of REE absorption, Cai et al. (2018) reported that RY (*Pichia kudriavzevii* LA30) could be used as a substitute for antibiotics in pigs, and they detected the linear elevation of FCR and ADWG with increasing levels of dietary RY; these improvements in FCR and ADWG may be explained by the improved digestibility of gross energy (GE) and dry matter (DM). Second, Ce and La may affect some metallic ion channels that influence the metabolic pathways (e.g., magnesium is an important cofactor in the tricarboxylic acid cycle; Ca^{2+} is essential in signal transduction and cellular metabolism) (Adu et al., 2009; Cai et al., 2018; Peng et al., 2004). Because the atomic radius of Ce and La resembles that of some metallic ions (Cai et al., 2018), it was supposed that Ce and La may affect cell metabolism by altering metallic ion (e.g., Ca^{2+}) channels on organelles or plasma membranes.

In rabbits, supplementation with dietary CeO (50, 100, and 150 mg/kg feed) significantly improved ADWG, ADFI, and FCR (Adua et al., 2015). In another study, laying hens that were supplemented with four different levels of LaO (100, 200, 300, and 400 mg/kg diet) showed non-significant differences in feed intake and egg weight among all groups, while egg production and FCR were significantly improved at the level of 400 mg/kg compared with the control group. In addition, the shell breaking strength of eggs was significantly increased at a dose of 200 mg/kg (Durmuş and Bölükbaşı, 2015). In a Chinese study, improvements in both body weight and FCR could be observed in six-month-old fattening cattle (average body weight of 219 kg) after their feed was supplemented with rare earth nitrates containing ≥38% rare earth oxides (mainly La (22%), Ce (45%), and Nd (15%) oxides) at a concentration of 600 mg/kg (5 mg/d/kg body weight) for 76 days (Zhang and Yang, 1994). In dairy cattle, dietary supplementation of REEs improved performance in terms of increased milk production. The addition of rare earth nitrates consisting of ±38% rare earth oxides (22% La_2O_3, 45% Ce_2O_3, and 15% Nd_2O_3) to the feed of nine lactating dairy cows increased both total and individual milk production as well as milk fat percentage (Shen, 1991). The best results were obtained at 800 ppm.

Meyer et al. (2006) reported increases in body weight gain and total feed intake of 14.6% and 7.8% ($p > 0.05$), respectively, after the addition of 200 mg/kg rare earth citrates to a milk substitute of veal cattle (initial body weight of 44 kg, one-week-old). On the other hand, no effects were reported after REE application in another feeding trial performed on veal cattle (initial body weight of 83 kg, average age of 44 days) (Miller, 2006). However, due to the different age classes addressed in these two trials, the results are not completely comparable with each other.

4.2. Blood variables

In female rabbits, dietary supplementation with CeO (100, 200, and 300 mg/kg) significantly decreased blood mean corpuscular haemoglobin (MCH), blood mean corpuscular haemoglobin concentration (MCHC), and differential leukocyte counts. However, non-significant differences were observed in packed cell volume (PCV), haemoglobin (Hb) concentration, RBCs count, and serum biochemical parameters except urea (Adua et al., 2015). Similar results were reported by Adu et al. (2009) and He et al. (2001), where they found no negative effects of REEs (100, 200, 300 and 400 mg/kg) on blood parameters of animals. MCH is an indicator of the average haemoglobin content in each RBC (Schalm et al., 1975). Decreased MCH may be caused by the interaction of dietary REEs with Fe metabolism; however, the decreased eosinophil, neutrophil, and lymphocyte counts might indicate interference of dietary REEs with the immune system (Adua et al., 2015). Leukocytes are important parts of the body's defence and protection systems, and alterations in the total leukocyte counts affect animal immunity. Shen (1991) suggested that the oral administration of Ce in drinking water at low and moderate doses could enhance the immunity of male rats by significantly increasing the WBC and the total lymphocyte counts. However, Cheng et al. (2014) reported a depletion in WBC counts after the administration of La at high doses, indicating its adverse effect on mouse immunity. Moreover, they noted a significant reduction in platelet (PLT) content and reticulocyte percentage after treatment with 20 mg/kg of Ce, while there were no significant changes in the RBC and Hb contents. These changes in blood indices implied that La exposure affects blood counts after entering the blood.

In laying hens, globulin, albumin, and total protein were not changed in REE-treated hens (with Ce and La at 250 mg/kg diet) compared to those in the control group. Similarly, in broilers, dietary REEs had no significant effect on serum biochemical parameters (He et al., 2010).

Cai et al. (2018) stated that RY exerted no changes in the WBC and RBC counts, which agrees with the previous observations by Adu et al. (2009), who mentioned that the administration of La oxide (LaO) (100, 200, 300, and 400 mg/kg diet) did not affect the WBCs and RBCs counts in rabbits. However, the results of the investigation conducted by Cai et al. (2018) revealed a linear increment between the lymphocytic counts and increased levels of RY dietary supplementation, which may be attributed to the use of different animal models, proper dose gradients of RY, and chemical forms of REEs. Ladipo et al. (2015) reported non-significant alterations in serum biochemical and haematological parameters (except for PCV and WBCs) during dietary supplementation with CeO (50, 100, 150 mg/kg diet). In another study, the addition of LaO (100, 200, 300, and 400 mg/kg diet) did not reveal marked differences in aspartate aminotransferase (AST), alanine aminotransferase (ALT), triglyceride (TG), glucose, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol concentration of laying hens (Durmuş and Bölükbaşı, 2015).

4.3. Blood minerals

Reka et al. (2018) showed that the dietary supplementation of REEs (Ce and La) at a dosage rate of 250 mg/kg diet in laying hens significantly increased plasma Ca and P levels in the first and second months, while a 500 mg/kg diet significantly increased plasma Ca and P concentrations in the first month, but no significant changes were found in the second month. Moreover, the serum Ca and P concentrations were significantly increased in a 22-week-old laying hen at a supplementation rate of 100 mg/kg CeO (Bölükbaşı et al., 2016). Zohravi (2007) reported a marked increase in the serum Ca in Japanese quail, and this increase was accompanied by a low dietary supplementation of REEs (50 and 100 mg/kg). On the other hand, He et al. (2010) detected no influence on the serum Ca after the oral administration of REEs in broiler chickens. Similarly, the supplementation of LaO (100, 200, 300, and 400 mg/kg diet) in laying hens did not show significant differences in the serum mineral levels, including Ca and P (Durmuş and Bölükbaşı, 2015).

Several pharmacological or biochemical properties of REEs, such as coagulation inhibition (Jakupec et al., 2005), muscle contraction (Triggle and Triggle, 1976), transmission of nervous impulses (Vaccari et al., 1999), hormonal response influences (Enyeart et al., 2002) or the release of histamine from mast cells (Beaven et al., 1984), are ascribed to their high resemblance to Ca. Interactions of REEs with cellular and subcellular processes in animal systems in terms of their calcium substitutions have been reviewed previously by Brown et al. (1990). The processes included, among others, cell communication through junctional membranes, actinomyosin contraction, activation of phosphorylase kinase in muscle, hormone-cell interactions, determination of cellular permeability, and stabilization of cellular membranes (Mikkelson, 1976).

4.4. Oxidative status and immune responses

It has been documented that dietary supplementation of CeO significantly decreased the concentration of serum malondialdehyde (MDA) and activity of superoxide dismutase (SOD) in egg yolk (Bölükbaşı et al., 2016). In contrast, other studies reported increased activity of SOD in plants (An and Chen, 1994), chickens (Xie and Wang, 1998), and fish (Wang et al., 1999). Kawagoe et al. (2005) detected that the inclusion of Ce in rat's diets caused significant reduction in plasma SOD activity, while it had no effect on plasma lipoperoxide (LPO) concentration. Moreover, Redling (2006) suggested that the immunostimulant activity of dietary REEs has the potential to improve the animal's health status. Therefore, a low or slight high oral intake of REEs might enhance the immune system. In vitro studies revealed that Ce and La affect the production of blood cells within the bone marrow and lowers production of WBCs in a dose-dependent manner (Redling, 2006). In addition, feeding laying hen with a diet rich in LaO positively influenced immune responses and had no significant effect on SOD and glutathione-peroxidase (GPx) activities, however, it significantly decreased value of serum MDA (Durmuş and Bölükbaşı, 2015).

Far from the indirect effect of REEs-associated anti-oxidative properties on the immune system, the REEs were reported to have other immunomodulating abilities (He et al., 2003). They can enhance histamine secretion by mast cells (Foreman and Mongar, 1973) and induce the immunological responses (Ni, 1995) in a dose-dependent manner. Lazar et al. (1985) observed that the application of $GdCl_3$ in mice was able to protect against anaphylactic death, while the oral application of La nitrate at low concentrations transformed splenic lymphocytes (Wang et al., 2003). Also, marked elevations in the phagocytic activity of polymorphonuclear leucocytes were detected in mice two days after intraperitoneal application of rare earth citrates at 0.1 mg per kg body weight (Wang et al., 2003). it may conclude that oral intake of slightly more or less content of REEs may enhance the immune system. Positive influences for REEs application on the immune system could share in the explanation of the good performance of animals (Redling, 2006). Moreover, recent studies revealed a correlation between high doses of Ce and La and decreased production of WBCs (Flachowski, 2003). Therefore, difference in spleen or thymus weight could be expected between control and REE-administrated rats; but actually no difference was detected (He et al., 2003).

On the other hand, Zhang et al. (2006) reported that the long-term oral administration of yttrium (Y^{3+}) had negative effects on cellular immunity of male rats, where the CD^{4+}/CD^{8+} ratio was elevated and CD^{8+} and CD^{3+} cells were markedly lowered. Identically, Cheng et al. (2014) noticed the marked decrease in CD^{8+}, CD^{4+}, CD^{3+} cells, and CD^{4+}/CD^{8+} ratio were reported after administration of La in mice, suggesting that La destroyed CD^{4+} and CD^{8+} cells. Furthermore, CD^{19} is considered the marker of the entire B cell series because it expressed on their membranes so, the low expression of CD^{19} indicated adverse influence of La on B-lymphocyte immunity. Moreover, Tu et al. (2005) detected marked stimulation of NK cells in mice by intragastric administrations of 10, 50 mg/kg BW Ce citrate for successive 7 days, indicating that Ce citrate could enhance immunity in mice. However, Cheng et al. (2014) observed that treatment with La for one month markedly suppressed NK cells of mice. This conflict between previous investigations could be explained by the variations in the exposure time, indicating that subchronic exposure to La may suppress the cellular immunity in mice.

IgM is an antimicrobial antibody of high competence and one of the most diffused membrane immunoglobulins in human B cells. Cheng et al. (2014) observed a marked decrease in level of serum IgM after the administration of La, indicating its effects on humoral immunity.

However, Zhang et al. (2006) detected that La has dual influences on the serum immunoglobulin depending on its dose; for instance, long-term exposure to low oral dose of Y^{3+} could markedly elevate the levels of serum IgM and IgG, however the high-dose exposure lowered the immunoglobulins levels. Additionally, Liu et al. (2001) reported that oral administration of La at a dose of 2 mg/kg elevated the spleen plaque-forming cell (IgM-PFC), while it is reduced at doses of 20 and 200 mg/kg in pregnant mice.

Collectively, although the mechanisms responsible for the changes of immunophenotype and blood indices are obscure, it can be proposed that REEs have an inhibitory and stimulatory influence on the immuno-regulation relying on dose after entering the body. The data on the influence of REEs on the immune responses were still restricted and need further investigation in the future.

4.5. Reproductive performance

Akinmuyisitan et al. (2015) concluded that dietary CeO at various concentrations significantly enhanced the reproductive parameters in female rabbits, such as litter size (8.45–19.86%), litter weight (3.57–11.3%), total litter weight (12.45–33.57%), and embryo survival rate (8.29%) at 200 mg/kg level of inclusion. Moreover, the conception rate was improved by 3.13–6.25% across the treatments but it was not significantly affected. Redling (2006) mentioned that lower concentrations of REEs enhanced the reproductive performance in different species and the best results were recorded between 100 and 200 mg/kg diet. In addition, Wu et al. (1994) reported that dietary REEs improved the rate of eggs hatching, fertilization, and egg production in poultry. Dietary REEs have been also reported to enhance the laying rate of hen (8.18%), chicken embryo development, and embryo survival rate (Chen and Xiong, 1994).

4.6. Ruminal pH and fermentation

Ruminal pH is a pivotal indicator to rumen microbial ecosystem. Low ruminal pH (<5.7) has disadvantages such as lowering fiber ruminal digestibility (Cheng et al., 1984). Addition of REE-citrate per kg DM lowered ruminal pH (from 6.72 to 6.53) with elevating REEs from 100 to 300 mg (Xun et al., 2014). This change in ruminal pH provided the ideal range for cellulolytic bacterial activity (Russell and Wilson, 1996; Xun et al., 2014).

An experiment conducted by Xun et al. (2014) showed that increased supplementation of REEs led to decreasing of ruminal ammonia content, this lower level of ammonia was detected also by Liu et al. (2008). Previous investigations reported that animal growth was promoted by REEs through enhancing the development of bacterial microflora in the gastrointestinal tract (Rambeck and Wehr, 2005). Another investigation reported that high dose of REEs supplementation (300 mg/kg dry matter) decreased utilization of ammonia as a result of the inhibition of several rumen bacteria (Shen, 1991). Moreover, rumen fermentation state was turned from acetate to propionate as revealed by the decrease in the ratio of acetate to propionate with elevating dietary supplementation of REEs (Xun et al., 2014). Moreover, there was an increase in the concentration of propionate in response to the increased concentration of total volatile fatty acids (VFA) and decreased acetate to propionate ratio. These findings are in the same line with that obtained by Liu et al. (2008) who observed a quadratic and linear increase of propionate and total VFA with increasing La supplementation from 0, 450, 900 to 1800 mg/head/day in Simmental steer. In conflict to the former investigation, the addition of REEs at level 400 and 800 mg/kg DM in diluted rumen fluid had no effect on ruminal VFA concentration in continuous culture trial (Yang et al., 2009). Moreover, the administration of REEs in higher dose did not improve feed fermentation in the animal rumen. However, the bacterial growth was enhanced by REEs in a low dosage. Therefore, it was concluded that the difference in REEs dosages was closely related to changes in ruminal fermentation patterns (Xun et al., 2014; Yang et al., 2009).

4.7. Nutrients digestibility

Xun et al. (2014) reported a linear positive correlation between REEs levels in diet and nutrients digestibility in sheep. Digestibility of neutral detergent fiber (NDF) was linearly and quadratically increased by supplementing 450, 900 and 1800 mg $LaCl_3$ per steer per day (Liu et al., 2008). Moreover, REEs supplementation markedly enhanced the apparent digestibility of crude protein (CP) in pigs (Hu et al., 1999; Ming et al., 1995) and sheep (Xun et al., 2014). The improvement of nutrients digestibility, growth, and feed efficiency due to addition of REEs were detected in steers (Liu et al., 2008), pigs (Halle et al., 2003), beef cattle (Shen, 1991), and rats (He et al., 2003). Cai et al. (2018) concluded an elevation of the GE and DM total tract digestibility in pigs fed RY1500 diet, which agrees with Han and Thacker (2010) who observed that total tract digestibility of GE and DM was increased in weanling pigs fed with RY. On the other hand, Han and Thacker (2010) detected increased CP digestibility in pigs fed with RY when compared with the control group. In contrast, Xun et al. (2014) and Schwabe et al. (2011) observed no marked effect on nutrients digestibility following the REEs supplementation at level 300 mg/kg DM. This conflict may be due to animal age and the chemical forms of REEs utilized.

In contrast to ameliorations in digestibility, Prause et al. (2006) and Böhme et al. (2002) did not detect any marked effect of various REEs (rare earth citrates, rare earth nitrates, La chloride and rare earth ascorbates supplemented at 100 mg/kg feed as the total amount of La and Ce) on the digestibility of crude nutrients in nutritional balance tests performed on 40 pigs. Mainly, better utilization of crude fiber was detected in rare earth ascorbate-administrated animals, but this was under 1%. However, REEs did not improve the performance in this investigation. Other authors attributed the performance improving influences to the alteration of phosphorous compounds by REEs (Fleckenstein et al., 2004). Moreover, several studies have reported the phosphate binding properties of REEs (Albaaj and Hutchison, 2005; Evans, 2013). Furthermore, REEs were detected to form insoluble phosphate RE compounds, which affect the phosphate metabolism in bacteria (Wurm, 1951). However, the REEs application did not induce any change in serum phosphate concentrations of rats (He et al., 2003).

The mechanism responsible for these performance-improving influences may be attributed to enhancements of nutrient availability and digestibility (Azer, 2003). As well, REEs had the ability to improve the digestibility of both total protein and energy in pigs (Ming et al., 1995). Consistently, Hu et al. (1999) detected marked improvement in energy, crude protein digestibility, and total essential and non-essential amino acids in pigs whose diet was enhanced with REEs. Furthermore, many other studies related the performance-improving influences of REEs to the enhanced utilization and digestibility of nutrients (Li et al., 1992; Xu et al., 1998; Zhu et al., 1994). In addition, some authors reported marked improvement in utilization of dietary nutrients (crude fat, crude protein, and total energy) in animals supplemented with a REE diet ($p > 0.05$) (Xie and Wang, 1998). Additionally, after feeding trials in quails and pigs under Western conditions, better utilization of nutrients was detected, in which elevated body weight gain was detected with decreased feed consumption (Flachowski, 2003). Moreover, Knebel (2004) did not detect any difference in Zn absorption because of REEs supplementation between the control group and REEs-supplemented pigs suggesting that REEs may not affect the absorption of other trace elements. On the other hand, studies on the influences of REEs on nitrogen, carbohydrate, and energy balance (Prause et al., 2004) reported elevated nitrogen uptake (14% ($p = 0.054$)) in animals supplemented with rare earth citrates at 150 mg/kg feed when compared to control animals, but there were no influences after the addition of REEs at high concentrations (300 mg/kg feed) (Prause et al., 2006). Moreover, improved fat acquirement was detected in pigs supplemented with REEs, which contributed with elevated protein accretion to improve feed intake (Bikker et al., 1995; Tomé and Bos, 2000).

4.8. Rumen microbial protein synthesis

Microbial protein has a relevant role in ruminant's diets with high-fiber content and low nitrogen levels. Sometimes, it is the only protein source for animals (Rodríguez et al., 2007). Likely, Xun et al. (2014) concluded that the REEs supplementation at a level of 100–300 mg/kg of sheep diet resulted in significant decrease in ruminal ammonia concentration with further sustained improvement in ruminal microbial protein synthesis. This lowering in ruminal ammonia concentration may attribute to the cellulolytic bacteria, where they obtain their nitrogen exclusively from ammonia (Russell et al., 1992). Apparently, it has been suggested that REEs inclusion may improve the activity of ruminal fibrinolytic bacteria.

5. Residual impacts

It has been suggested that residual concentrations of Ce and La in the liver and muscles tissues were low due to poor gastrointestinal absorption of REEs in broiler (He et al., 2010) and piglets (He et al., 2001).

REE feed additives were examined for their safety on two million animals after analysis of their products in the inner Mongolian state technical inspection departments (IMSTID). It was concluded that REEs and their additives were non-poisonous to either humans or animals (Rosewell, 1995). Consistently, Ming et al. (1995) concluded that there were no negative impacts of REEs supplementation on the quality of carcass and animal feedstuffs. Another trials were conducted by Xie and Wang (1998) and Liu (2005); authors illustrated that pigs supplemented with REEs showed non-significant alteration in slaughter indexes including body length, carcass weight and thickness, back fat, eye muscle area, meat color and marbling, pH value, as well as rate of lean meat, water holding, water loss, and cooked meat vs control one.

Ming et al. (1995) reported that REEs were highly concentrated in pig's bone, suggesting their high bone affinity. Additionally, rabid elimination of REEs from liver tissue as well as preserved meat quality were reported after supplementation of chicken with REEs; where no significant REEs accumulation was discovered in either chicken liver or muscle (Xie and Wang, 1998). Likewise, in meat breed ducks, REEs residues in meat and liver tissues were ranged from 0.1 to 0.2 mg/kg, while only trace amounts were reported in eggs (Zhou, 1994). Shi et al. (1990) concluded that REEs were detected in low safe concentrations in chickens, pigs, and fish, the highest concentrations were reported in bone, gill, and fin; however this accumulation was easily to depilate.

Based on these facts, it could be concluded that the application of REEs feed additives at low concentrations seem to be safe either for animals or humans. On these bases, application of REEs-containing feed additives to farming animals became largely safe and acceptable.

6. Toxicity of rare earth elements

According to the EC regulation No 1831/2003, a new European food safety authority (EFSA) has been released in 2004, which indicated that the feed additives allowed on the European market were exposed to several comprehensive restraint. Lancer, which consisting mainly of two REEs, La and Ce in their citrate forms - is available in market as REEs feed additive, with recommended concentrations range between 150 and 300 mg/kg feed. It has been concluded that Lancer is neither genotoxic nor irritant to eyes and skin; where it didn't induce skin sensitisation. However, La might be toxic for some relevant environmental species based largely on speciation (Redling, 2006).

Recently, several studies concerning REEs toxicity in income-generating animals were conducted; it was established that Lancer is reported as safe for the treated piglets when it is used at maximum does equal to 250 mg/kg ration (FEEDAP, 2013). However, the presence or absence of REEs toxic impacts on consumer's health are still important research point among scientists. Additionally, the great increase in medical and industrial use of lanthanides resulted in elevating their environmental levels, with in turn increasing in animals and humans exposure rate (FEEDAP, 2016).

Toxicological studies concerning REEs influences on humans and animals health are relatively scarce and mostly focused on effect of Ce and La. For instant, in a recent study conducted by Benedetto et al. (2018); authors suggested that the REEs dosage represents a pivotal factor for switching the biological effects from down- to up-regulation of cell growth. Increased concentrations of REEs also able to exert higher cytotoxic and anti-proliferative impacts. Moreover, exposure of REEs either in vivo or in vitro found to be associated with lipid peroxidation, ROS formation, proinflammatory mediators production, and antioxidant enzymes activation such as glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) (Pagano et al., 2015).

Following Hodge-Sterner classification system, REEs are generally identified as less toxic additive (Haley, 1979). Several studies has concluded mild REEs-associated oral toxicity in various animal species such as mice, rats, and guinea pigs (Ji et al., 1985). Following investigations illustrated that the oral intake of La carbonate for 4 years are safe in concentration up to 3 g/person/day (Ritz, 2004). As well, level of 2 μg/l was recommended for safety inclusion in drinking water (De Boer et al., 1996). It has been well established that subcutaneous or intramuscular injection of lanthanides might lead to mild absorption. As a result, mild acute toxicity might be reported, for instance, minimal lethal doses of 100–1000 mg/kg (with LD50 values of 50–500 mg/kg b.w.) were reported for subcutaneous injection. However, intraperitoneal injection of lanthanides was usually more toxic particularly in guinea pigs, which is more susceptible than mice and rats. Likewise, few immediate impacts are produced via inhalation, however the chronic exposure is more toxic due to accumulation of rare earth particles, which causing pneumonitis, bronchitis, pulmonary fibrosis, and emphysema.

Previously, it was reported that lanthanides is able to bind to DNA and RNA in vivo (Pennick et al., 2004) and in vitro (Evans, 2013). However, genotoxicity did not reported after exposure to La carbonate in high plasma and tissue levels. Consistently, Ji et al. (1985) reported negative mutagenicity tests for La carbonate; authors concluded that oral supplementation of La carbonate yield no increase in chromosome aberration rates in bone marrow cells. However, high doses induced significant increase in spermatocytes chromosomal translocation when compared to low dose.

Although oral administration of REEs did not revealed any genotoxic, teratogenic, or carcinogenic effects, the intravenous and other applications methods showed contradicted results; so further toxicological studies are need based on median lethal dose. Taken together, administration of REEs either orally, intra-peritoneally, intravenously, or subcutaneously might consider of low toxicity. Thus, the few reported toxicological alterations based on the affected organ were briefly showed (Redling, 2006).

In lung, toxicological aspect of REEs administrated via inhalation or via intra-tracheal injection have been assessed (Evans, 2013; Haley, 1979). Authors concluded that REEs-associated pulmonary toxicity is represented by occurrence of progressive pulmonary fibrosis (pneumoconiosis), which could be promoted by the radioactive materials contamination. The pathologic potential of inhaled lanthanides particles was affected by several factors such as type, dose, exposure duration, and physicochemical form (Haley, 1991; Nemery, 1990). However, such pathologic potential of REEs may be evaluated as minimum toxicity when it compared to other well-established fibrogenic dusts including quartz and silica (Richter, 2003).

In liver, injection of REEs resulted in reversible increase in the levels of liver enzymes including ALT and AST, where those levels reversed to normal after 6 to 10 days with the aid of phenobarbital, spironolactone, pregnenolone, and α carbonitrile (Tuchweber et al., 1976). Additional trial concluded that subcutaneous and intravenous injection of REEs induced hepatic necrosis (Salonpää et al., 1992).

In spleen, Stineman et al. (1978) reported that subcutaneous administration of Ce citrate to mice resulted in hypertrophy, hyperactive lymphoid follicles, and reticuloendothelial hyperplasia. However, oral administration contributed in focal neutrophil infiltration, as well as gastric necrosis and hemorrhages.

In brain, administration of lanthanides resulted in several deleterious effects on nerve cells such as release of neuronal transmitter and interaction with Ca^{2+} involved in transport processes. However, lanthanides are unable to pass the blood brain barrier; and so does not enter the central nervous system (Evans, 2013). In an additional trial, oral supplementation of La carbonate for long-term had no deleterious impact on the central nervous system (Jones and Webster, 2004).

7. Ecotoxicology of rare earth elements

Now, it is became well established that REEs have the potential to influence a great variety of microorganisms. Thus, the possible effect of REEs on soil micro-flora became of increased concerns (H. Zhang et al., 2000; J. Zhang et al., 2000). The soil micro-flora are largely responsible for great portion of earth nutrient cycles, and act as a key word in the living pool of soil organic matter (Jenkinson, 1981). Interestingly, using of moderate levels of La led to increased soil microbial biomass and bacterial populations including azotobacter, actinomyces, nitrifying bacteria. However, excessive application implicated in the prevention of all soil microbial properties (Chu et al., 2001). Similarly, the excessive dose-related inhibitory effects of La on the total number of soil bacteria were concluded by Xu and Wang (2001) and Redling (2006) when REEs accumulated at 5 to 50% of absorption capacity.

8. Conclusions

This review summarized the impacts of REEs on animal health and production. REEs have emerged as possible substitutes for antibiotics and novel natural feed additives. Several studies have shown the ability of REEs to enhance ADWG, ADFI, and FCR with no negative effect on blood biochemical parameters. In addition, REEs are able to increase the plasma concentrations of Ca and P, improve reproductive performance, and enhance the oxidative/antioxidative status. Besides, REEs have played a pivotal role in reducing ruminal pH and increasing nutrient digestibility and microbial protein synthesis, with low acceptable residual concentrations in the liver and muscle. Even though several experimental and field trials concerning the enhancement effect of REEs on general health and performance parameters have been designed, further experimental confirmation still needed on increasing number of animals. Moreover, numerous questions concerning the optimal application of REEs to animals are still searching suitable answers such as the proper concentrations and relationship between the applicable doses and the obtained effects. As well, the possibility of different REEs combinations and their effects on metabolism, immunity, and ruminal microflora also need more in depth investigations. In addition, the deleterious effects of REEs on human and animals health remain less elucidated. Thus, additional toxicological studies are necessary to clearly identify the mechanistic actions of REEs toxicosis and their effect on environmental components. Finally, clarification for the underlying mechanisms discussed the growth promoting action and the adverse effect of REEs particularly in ruminant is still urgently required.

Conflict of interests

All authors declare that they have no conflict of interest.

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