Novel zinc sources as antimicrobial growth promoters for monogastric animals: A review

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ABSTRACT: The essentiality of zinc for animals has been recognized over 80 years. Zinc is a n essential trace element that is a component of many enzymes and is associated with the vario us hormones. Apart from the nutritional function, zinc has antimicrobial property and often be supplemented in diets in the quantities greater than which is required to meet the nutritional re quirement, especially for weaning pigs. This review will focus on the application of pharmacol ogical zinc and its mechanisms which may be responsible for the effects of zinc on performan ce and health of monogastric animals. Various novel sources of zinc in non-ruminant animal p roduction will also be discussed. These should assist in more precisely formulating feed to ma ximize the production performance and to maintain the health condition of monogastric animal s.

Key words: novel zinc source; pharmacological zinc; monogastric animals

INTRODUCTION

Zinc, an essential trace element, is a component of many metalloenzymes including DNA and RNA synthetases and many digestive enzymes [1]. The essentiality of zinc for animals has been recognized in 1933 [2]. Besides, zinc has a regulatory role in the immune system and deficiency in zinc may impair the proper immune function [3]. The concentration of zinc in body increases during the initial period of postnatal ontogenesis (2 weeks for chicks and 4 weeks for piglets), after which it remains approximately constant. Apart from the nutritional function, unlike most other minerals, copper and zinc have antimicrobial properties. Therefore, they are often supplemented in diets in the quantities greater than which is required to meet the nutritional requirement, especially for weaning pigs [4]. In practice, the use of pharmacological levels of zinc ranging from 2,000 to 4,000 mg/kg (that this "practice" is forbidden in the EU) in the form of zinc oxide is a common recommendation to reduce post-weaning diarrhea and improve growth performance in weaning pigs [5]. However, the use of high doses zinc oxide has raised serious concern related to microbial resistance development [6-8]. Moreover, due to its low absorption, high amount of zinc excretion has motivated environmental concerns [9-11]. Those provoke the question about the reasonability of pharmacological levels of zinc supplementation as a solution of the ban of antimicrobial growth promoters.

To improve the bioavailability of zinc, several efforts have been made including: changing conventional zinc oxide powder into porous particles or nanoparticles, organic zinc (eg, zinc lactate, zinc amino acid, zinc chelate), and the application of enteric coating method [12-17]. Phytate from whole grains and some vegetables, by forming indigestible complexes with zinc in intestine strongly interferes with zinc absorption [18]. Therefore, it is suggested that supplementation of phytase in the diet can be a useful strategy to improve bioavailability of

zinc [19]. This review will focus on the application of pharmacological zinc and its mechanisms which may be responsible for the effects of zinc on performance and health of monogastric animals. various novel sources of zinc in non-ruminant animal production will also be discussed. These should assist in more precisely formulating feed to maximize the production performance and to maintain the health condition of monogastric animals.

PHARMACOLOGICAL ZINC

Traditionally, antibiotics are included in the diet of young animals for the prevention of post-weaning diarrhea and enhancement of growth performance in the worldwide. However, the use of in-feed antibiotics has been fully or gradually banned by many countries including European countries, United States of America, South Korea and China due to the development of antibacterial resistance and antibiotic residues [20-23]. Supplementation of pharmacological doses of zinc in the form of zinc oxide has been proposed as one of the most effective feed additives to replace antibiotics and is already widely commercialized in several countries [24-27]. Pharmacological levels of zinc oxide have shown antimicrobial properties and are used to fight against post-weaning infections and improve growth performance [28-31].

The exact mechanisms regarding pharmacological doses of zinc oxide exert beneficial effects on alleviating post-weaning diarrhea and promoting growth performance are unknown, but potential theories proposed include: (1) pharmacological doses of zinc oxide may reduce intestinal permeability and improve intestinal morphology and appetite [32,33]. Carlson [34] observed that zinc oxide reduced the intestinal mucosal susceptibility to secretagogues which activate chloride secretion. In addition, it is suggested that zinc oxide may increase insulin-like growth factor-1, 2 expressions in the small intestinal mucosa [35]. (2) pharmacological doses of zinc oxide have a antimicrobial effects on gram negative bacteria and beneficial effects on the stability and diversity of gastrointestinal microbial balance, especially coliforms [36, 37].

(3) pharmacological doses of zinc oxide can improve animals' defense function indicated as improved immune and anti-inflammatory responses [38]. Nevertheless, the use of high doses of zinc is criticized due to the developing bacterial resistance and the excretion of a large amount zinc which may raise environmental concerns [39, 40]. Although the use of pharmacological doses of zinc oxide are allowed be in most countries and regions, the European legislation limits the use of zinc oxide in animal production to a maximum of 150 mg/kg [41]. Thus, considerable efforts have been made to improve the bioavailability of zinc, including organic zinc, nanosized zinc oxide, coated zinc oxide, and porous zinc oxide.

COATED ZINC OXIDE

Enteric coating is a common technology used to protect oral medications against the influence of stomach juices in the field of pharmacy [42]. In feed additives production, enteric coating technology also has been used for a long time [43,44]. Under the protection of outer enteric coating, the inner targeted component can safely pass through the stomach. Whereas, the coating materials can be gradually degraded in the gastrointestinal tract, and the inter zinc oxide will be released slowly within the intestine [13]. Park et al. [9] suggested that the physiological level (100 mg/kg) of zinc from coated zinc oxide showed the similar growth promoting effects as pharmacological zinc oxide, but activities of maltase and sucrase in the intestinal mucosa and pancreatic tissue and small intestinal mucosal morphology were not affected by dietary treatments in weaning pigs. However, the effects of coated zinc oxide in pigs were not consistent. Byun et al. [45] indicated that inclusion of coated zinc had no effects on growth performance, intestinal mucosal morphology, and fecal consistency in weaning pigs. Song et al. [46] observed that sub-pharmacological levels (100, 200, or 400 mg/kg) zinc from coated zinc oxide had no effects on growth performance and fecal consistency but reduced

villus height and the ratio of villus height to crypt depth in weaning pigs. Shen et al. [18] concluded that low concentrations (380 or 570 mg/kg) of zinc from coated zinc oxide or 2,250 mg/kg zinc from conventional zinc oxide could alleviate the occurrence of diarrhea by promoting intestinal morphology, protecting intestinal mucosal barrier from damage, stimulating mucosal immune system, and regulating microbial composition. Moreover, pigs offered diets with coated zinc oxide excreted less zinc in feces compared with those fed those fed conventional zinc oxide. In enterotoxigenic *Escherichia coli* challenged weaning pigs, Kwon et al. [47] found that both low dose (100 mg/kg) of coated zinc oxide and high dose (2,500 mg/kg) of conventional zinc oxide improved growth rate, reduced *Escherichia coli* shedding, increased goblet cell density in small intestine, and decreased gastrointestinal tract pH values in post-challenge period. In a recent study, Upadhaya et al. [48] indicated that use of coated zinc oxide in lower doses (250, 500, 750, and 1000 mg/kg) was possible to substitute high dose of conventional zinc oxide in improving growth performance, nutrient digestibility, and intestinal microbial balance in weaning pigs. Importantly, compared with high level of conventional zinc oxide, the zinc excretion was decreased by use of low doses of coated zinc oxide. To our best knowledge, no information is available on the application of coated zinc oxide in poultry, at least for broilers and layers. Thus, researches are required to determine the effects of coated zinc oxide in poultry.

ORGANIC ZINC OXIDE

Organic mineral sources for dietary supplementation, such as proteinate and amino acid chelate, have become popular in feed industry in the past 2 decades due to their higher bioavailability [49]. In weaning pigs, Wang et al. [50] observed that low levels (50 and 100 mg/kg) of zinc from zinc glycine chelate could improve growth rate and serum alkaline

129 phosphatase and copper/zinc superoxide dismutase activities as 3,000 mg/kg of zinc as
130 conventional zinc oxide. But zinc excretion in feces was decreased in pigs offered zinc glycine
131 chelate diets compared with pigs receiving diet supplemented with high level conventional
132 zinc oxide. Case and Carlson [51] indicated that weaning pigs fed 500 mg/kg zinc in the form
133 of an organic zinc-polysaccharide complex had comparable production performance but
134 excreted less zinc in feces compared with pigs fed 3,000 mg/kg zinc as zinc oxide. Buff et al.
135 [52] indicated that supplementation of 300 or 450 mg/kg zinc from zinc-polysaccharide
136 allowed pigs obtained similar growth performance as 2,000 mg/kg zinc from conventional
137 zinc oxide, but 300 mg/kg zinc as zinc-polysaccharide reduced 76% of fecal zinc compared
138 with 2,000 mg/kg zinc as conventional zinc oxide. Cheng et al. [53] suggested that both 100
139 mg/kg of zinc from zinc lysine complex and zinc sulfate were equally effective in maintaining
140 production performance and zinc absorption of weaning pigs. In sows, Payne et al. [54] found
141 that supplementation of zinc from organic zinc (zinc amino acid complex) could improve the
142 development of fetuses during gestation, thus resulting in increased piglets weight at birth and
143 weaning. Moghaddam and Jahanian [55] replaced 75% inorganic zinc with dietary zinc-
144 methionine and observed improvement in both cellular and humoral functions of the immune
145 system in broilers. Ao et al. [56] reported that chelated zinc proteinate could be used as a zinc
146 source. 12 mg/kg of zinc from chelated zinc proteinate allowed broilers obtained optimal
147 growth performance, whereas when inclusion of phytase in the diet, the optimal dose of zinc
148 from chelated zinc proteinate to meet the requirement of broiler was 7.4 mg/kg. Rossi et al.
149 [57] supplemented graded levels (0, 15, 30, 45, or 60 mg/kg) of organic zinc (chelated zinc
150 proteinate) in male chicks did not affect production performance but improved carcass quality
151 by increasing resistance of skin to tearing. Using the same organic zinc oxide-chelated zinc
152 proteinate, Salim et al. [58] reported that inclusion of 25 mg/kg chelated zinc proteinate had

no effect on growth performance and skin quality of broiler chickens, but increased the zinc content in thigh meat and calcium content in plasma.

NANOSIZED ZINC OXIDE

Nanotechnology has revolutionized the commercial application of nanosized minerals in the areas of engineering, food, biological, and pharmacological applications [11]. Due to better antibacterial property than conventional zinc oxide, nanosized zinc oxide is the third highest produced nanosized metal after nanosized silicon dioxide and nanosized titanium dioxide [59,60]. Reducing the size of the material to the nano scale may modify the physico-chemical properties compared to the same material at larger-size scales, such as much larger surface to mass ratio, improved surface reactivity or increased ion release [61]. The nanosized zinc oxide may expose more molecules of zinc oxide to interact with the gastrointestinal tissues and microbial population. In Hendrix laying hens, Tsai et al. [62] observed that supplementation of 20 mg/kg zinc from nanosized zinc oxide (40 mg/kg zinc in basal diet) enhanced zinc retention and serum zinc, eggshell thickness, growth hormone, and carbonic anhydrase activity. Mao and Lien [63] reported that compared with conventional zinc oxide, supplementation with 100 mg/kg nanosized zinc oxide in Hendrix laying hens showed better effects on feed intake, serum zinc, ghrelin, metallothionein, immunoglobulin G (IgG), and eggshell strength. Zhao et al. [14] indicated that addition of 20 and 60 mg/kg nanosized zinc oxide improved growth performance (body weight gain) and antioxidant capacity (increased catalase activity and total antioxidant capacity in serum and reduced malondialdehyde in serum and liver) compared with 60 mg/kg conventional zinc oxide, whereas 100 mg/kg nanosized zinc oxide impaired growth rate. Although growth performance were unaffected, Li et al. [64] suggested that supplementation of 120 mg/kg both conventional zinc oxide and nanosized zinc oxide

improved nutrient (crude protein, crude fat, phosphorus, and zinc) digestibility, blood IgG, and γ-globulin concentrations in weaning pigs. Moreover, pigs fed diet supplemented with nanosized zinc oxide had greater digestibility of phosphorus and zinc, blood phytohemagglutinin skin challenge, IgG, and γ-globulin values, growth hormone, carbonic anhydrase activity, and zinc concentrations in serum, compared with those fed diet with conventional zinc oxide. Milani et al. [10] suggested that low doses (15, 30, and 60 mg/kg) nanosized zinc oxide were not effective in improving production performance and controlling post-weaning diarrhea of weaning piglets, although increasing nanosized zinc oxide levels increased gain to feed ratio and reduced diarrhea occurrence during first week post-weaning. In addition, supplementation of low doses of nanosized zinc oxide increased dry matter and crude protein digestibility. More recently, Wang et al. [65] showed that supplementation of 800 mg/kg nanosized zinc oxide had comparable effects to 3,000 mg/kg conventional zinc oxide on improving growth rate, alleviating diarrhea, and improving intestinal morphology in weaning pigs. Importantly, fecal zinc was lower in pigs fed diets supplemented with low doses nanosized zinc oxide than those fed high dose of conventional zinc oxide.

TETRABASIC ZINC CHLORIDE

Tetrabasic zinc chloride is produced through a reactive crystallisation process in which zinc chloride is reacted with ammoniated zinc chloride and water. Tetrabasic zinc chloride is intended to supply zinc in final feed for all species [66]. In weaning pigs, Mavromichalis et al. [67] found that with or without antibacterial compound (carbadox), at pharmacological levels, tetrabasic zinc chloride was an effective source of zinc for enhancing growth performance. Zhang and Guo [68] conducted an experiment to evaluate pharmacological doses of zinc from tetrabasic zinc chloride (1500, 2250, and 3000 mg/kg) and conventional zinc oxide (2250 and

3000 mg/kg) in weaning pigs. The results reported that supplementation with both tetrabasic zinc chloride and conventional zinc oxide increased daily gain, feed intake, and gain to feed ratio, but decreased fecal scores in weaning pigs. The relative bioavailability of zinc from tetrabasic zinc chloride was 159%, 125%, and 128%, 123%, and 122%, respectively, compared with conventional zinc oxide in broilers [68]. In New Hampshire × Columbian female chicks, Batal et al. [69] suggested that tetrabasic zinc chloride provided same bioavailable zinc as that of analytical-grade zinc sulfate. However, to promote the growth performance, tetrabasic zinc chloride has to be included at pharmacological levels, and therefore, the problem of high zinc excretion is still present.

POROUS ZINC

High porosity zinc oxide is a novel form of zinc oxide with enhanced surface area and more importantly greater porosity (as much as ten times higher than conventional zinc oxide) and this allows it even stronger efficacy than nanosized zinc as it further increases the possible sites of the interaction among the molecules of zinc oxide, the animals, and microbial population in the gastrointestinal tract (Animine, Sillingy, France) [70]. Vahjen et al. [71] reported that porous zinc oxide exhibited higher *ex vivo* bacterial growth depressing effects than conventional zinc oxide. In weaning pigs, Morales et al. [72] suggested that pigs fed diet supplemented with 110 mg/kg zinc from porous zinc oxide increased growth rate and gain to feed ratio compared with pigs offered diet with 3,000 mg/kg conventional zinc oxide during 42 to 63 days of age. Long et al. [73] compared the effects of the zinc from nanosized zinc oxide (400 mg/kg), porous zinc oxide (400 mg/kg), and conventional zinc oxide (2,400 mg/kg) in weaning pigs. The results indicated that dietary supplementation with low dose of porous and nanosized zinc oxide had similar effects on improving production performance and

intestinal morphology and reducing diarrhea and intestinal inflammatory as high level of conventional zinc oxide in weaning pigs. In addition, compared with zinc oxide, porous zinc oxide had better effect on reducing diarrhea. Also, no information is published regarding the effects of application of porous zinc oxide in poultry.

CONCLUSIONS

Supplementation of pharmacological doses (2,000 to 4,000 mg/kg) of zinc, especially zinc oxide, is an effective method to improve growth performance and alleviate diarrhea post-weaning. However, the use of pharmacological doses zinc is criticized due to the large amount of zinc excretion and microbial resistance. To improve the bioavailability of zinc, several novel zinc sources have been developed. However, contradictory effects of those novel zinc sources in animal production have been reported. Therefore, further studies are required to explore the exact mechanisms involved in the antibacterial functions of zinc.

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