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ZINC: THE POULTRY INDUSTRY'S PRODIGIOUS TRACE ELEMENT!

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ABSTRACT
In 2006, the European Union, Switzerland and other countries around the world banned the use of antibiotics as growth-promoters (AGPs) in poultry feed. This is due to the fact that excessive use of AGPs would generate antibiotic resistance at dangerously high levels. compromising the capacity to treat common infectious diseases in humans such as pneumonia, tuberculosis, sepsis, ... This fact implies the urgency of banning the use of AGPs in poultry farms and the obligation to substitute them with alternatives that can match their effects in terms of growth performance but also can improve intestinal health such as Zinc. In fact, Zinc in organic or inorganic form has multiple effects, like improving growth parameters in broilers and production in layers and breeders, stimulating the immune system and maintaining the balance of the intestinal microbiota. Zinc is thus a broad-spectrum substitute for AGPs in poultry and its potential should be further explored.

Keywords: Zinc, poultry, alternative, growth promoter, immune system.

1. INTRODUCTION
In the quest of public health improvement, several substances have been incriminated to be harmful to human being in several industrial sectors, including poultry production. In fact, this sector is pointed out as one of the major causes leading to antibiotic resistance in human and animal health through an overuse of antimicrobials as growth promoters (AGP).
Indeed, the use of AGPs at sub-therapeutic doses in poultry feed, for several decades, has contributed to the selection of antibio-resistant bacteria by reducing the number of susceptible bacteria in the animal's gut microbiota (Sanders et al. 2017), although, they have the advantage of enhancing growth rate, decreasing the feed conversion ratio (FCR) and consequently, improving broiler performances (Gayatri et al. 2017). Moreover, it has been estimated that by the year 2030, a total of 105,596 tons of anti-pathogens will be used globally in feed manufacturing (Van Boeckel et al. 2015) which is far from negligible. Hence, in order to lead, in terms of public health, the giant McDonald's Cop announced in June 2003 that it will prohibit its direct suppliers from using AGPs used in curative treatments in humans, starting in 2004, and has created a purchasing preference for companies that minimize the use of these substances (Ferket, 2004).
Nevertheless, considering the production benefits of AGPs and their dramatic consequences on public health, it is imperative to reconsider their use in chicken feed to substitute them with safe alternatives such as zinc (Zn).

Zinc is a trace element that influences immune function, gene expression, cell proliferation, growth and fertility in poultry. As a key element in the synthesis of more than 300 enzymes and 2000 transcription factors, zinc is directly involved in metabolism and is a major link in the cytosolic Cu/Zn Superoxide Dismutase (Cu/Zn SOD) necessary for cellular defense against oxidative stress (Ivanišinová et al. 2016; Broom et al. 2021). Therefore, adequate Zn intake and absorption are paramount for several metabolic and biological functions, including growth, production, meat quality, and immune response in chicken (Salim et al. 2008). Indeed, Zn supplementation at the dose of 40 mg/kg of feed, as recommended by the National Research Council (NRC, 1994) did significantly reduce the impact of coccidiosis in broilers (Troche, 2012). Similarly, Zn supplementation of 35 mg/kg of feed alone or combined with 250 mg vitamin C/Kg in laying hens did significantly improve egg production (Gerzilov et al. 2015). Furthermore, in a necrotic enteritis (NE) challenge model in chickens, Zn supplementation of 90 mg/kg of feed reduced lesions and mortality following NE (Bortoluzzi et al. 2019a). However, Zn deficiency causes losses in the poultry industry, namely, decreased egg production in layers and reduced growth rate in chicks as well as shortening and thickening of long bones and poor feather development (Naz et al. 2016). Thus, and because drinking water is not generally considered the major leavening of minerals, feed and supplements are the primary mineral sources for poultry. However, due to potentially inadequate levels of micronutrients and variability in their bioavailability among grains, low-cost mineral supplementation has become a common practice on farmers (Broom et al. 2021). The bioavailability of zinc depends primarily on whether the mineral is present in organic or inorganic form (Bao and Choct, 2009). Recently, organic sources of Zn have been introduced in animal feed, such as Zn-methionine (ZnMet) and Zn-lysine (ZnLys) (Naz et al. 2016), due to their potentially higher bioavailability as compared to the traditionally used inorganic forms (Ivanišinová et al. 2016) namely ZnO (72% Zn) and ZnSO4H2O (36% Zn) (Naz et al. 2016). Zn-picolinate, on the other hand, is an excellent source of Zn, efficiently absorbed by the gut and bioavailable in blood. Indeed, the use of organic Zn in poultry feed can prevent formation of non-digestible complexes with certain dietary compounds as well as with reciprocal mineral antagonisms in the gut, which may reduce their absorption rate (Swiatkiewicz et al. 2014). Thus, given its high bioavailability and better absorption, the doses used in poultry feed are lower, without compromising the performance of the chicken, consequently its excretion in the environment is reduced (Mohammadi et al. 2015).

2. MECHANISM OF ACTION OF ZINC

One of the major objectives of nutritionists is to enhance feed digestibility in order to improve zootechnical performances of chicken and that makes the choice of nutritional supplements crucial. Out of these elements, Zinc (a mineral cofactor of several enzymes) seems to play multiple roles in metabolism and utilization of nutrients in poultry.

Indeed, Zn, a multifaceted trace element, acts on panoply of parameters, namely:

- Maintenance of normal growth, including skeletal and feather developments as well as skin and leg health (Kierończyk et al. 2017);

- Improvement of the immune system by increasing the level of immunoglobulins (IgG, IgM and IgY) as well as the cellular response of the individual (Feng et al. 2010);

- Modification of carbohydrate, protein and lipid metabolisms by increasing glutamic dehydrogenase, alcohol dehydrogenase, alkaline phosphatase and RNA polymerase (Abd El-Hack et al. 2017a),
- Reduction of lipid peroxidation in poultry meat (Saleh et al. 2018);
- Improvement of antioxidant capacities by increasing cytosolic Cu/Zn Superoxide Dismutase (Cu/Zn SOD) and zinc metallo-enzyme (Saleh et al. 2018) and
- Influence of gene expression by altering DNA and chromatin structures (Huang et al. 2019).

3.EFFECTS OF ZINC ON GROWTH PERFORMANCE AND NUTRIENT DIGESTIBILITY

Zinc plays an important role in growth and development of poultry. In fact, Zn deficiency is associated with several clinical and biochemical manifestations including delayed growth, loss of appetite and increased mortality in chickens. As un example, Zn deficiency causes decreased egg production in the layer industry, delayed hatchability, and chicks produced by parents lacking Zn often have skeletal abnormalities and die shortly after hatching (Naz et al. 2016).

In Broilers

Zn contributes to improved growth performance (Liu et al. 2011) and skeletal development of broilers. Indeed, Zn supplementation during the start-up and growth periods at 40 and 32 mg/kg of feed, improves growth performance and decreases Zn excretion in the environment, respectively (Zhang et al. 2018). Combining Zn with an amino complex in a wheat- and rye-based diets at 60 mg/kg of feed also increased digestibility and the ratio of villi length to crypt depth and contributed to improve the feed conversion ratio/phase start (De Grande et al. 2020). In heat-stress conditions, Zn-methionine (Zn-M) supplementation at 50 and 100 mg/kg of feed significantly improved the Daily Average Gain (DAG) (51.45 and 51.24 g, respectively), decreased feed conversion index and total feed intake, and increased the wishbone weight compared to the negative control (DAG: 47.60 g) as well as to the group fed 25 mg/kg of feed with Zn-M (Saleh et al. 2018). During the first 4 weeks of growth, the average daily gain increases in broilers supplemented with 20, 50, or 80mg Zn/Kg of feed compared to the control group as Zn content is increased till 50 mg/kg of feed (Azad et al. 2017). In addition, 0.01% organic Zn in broiler feed results in higher weight gain and lower feed conversion index (Sarvari et al. 2015). Similarly, combining Zn with oligosaccharide pectin (Zn-PO) at 600 mg/kg of feed resulted in a significant increase in average daily gain and average daily feed intake compared to the control group and those supplemented with 300 or 900 mg/kg (Wang et al. 2016). In broilers, increasing the zinc level to 100 mg/kg of feed resulted in a significant improvement of bone strength and a reduction in the risk of locomotor disorders which do, indirectly, affect growth performance as an integrated locomotor system allows smoother movements for better feed intake (Štofaníková et al. 2011). At 60, 120, or 180 mg Zn/Kg of feed, an increase in average daily feed intake and average daily gain during the start-up and growth periods as well as a reduction in the conversion index during the growth period were noted (Liu et al. 2011). Indeed, nano-ZnO supplementation at 50 mg/kg of feed ranks this molecule in the first position with respect to body weight gain, feed conversion ratio as well as protein utilization. Followed by the combination of Zn-M and nano-ZnO (Zn-mix) at 25 mg/kg of feed each and in the last position the supplementation with 50 mg/kg of feed with Zn-M (Zinc-Methionine) compared to the feed enriched with inorganic ZnO. The weight gain towards the end of the trial was approximately 15.5; 12.5 and 4.3% for the nano-ZnO, Zn-mix and Zn-M, respectively (Ibrahim et al. 2017). Incorporation of 60 or 45 mg of the zinc polysaccharide complex/Kg of feed improved final body weight, total body gain, conversion index, protein efficiency ratio, energy utilization efficiency and performance index of broiler compared to Zn-O or even supplementation below 30 or 15 mg Zn/Kg of feed (El-Katcha et al. 2017).

Dry matter digestibility, on the other hand, was significantly elevated upon Zn-M supplementation of 50 and 100 mg/kg of feed while crude protein utilization was better with 50mg Zn-M/Kg of feed compared to the other groups (Saleh et al. 2018). Indeed, Zn-POS (pectin oligosaccharide) supplementation at 600 mg/kg of feed increased apparent digestibility of dry matter, raw protein as well as metabolic energy and this compared to the groups supplemented with 300 or 900 mg/kg of feed and the control groups (Wang et al. 2016). Therefore, incorporation of Zn may optimize nutrient utilization most likely as a result of increased digestive enzyme activity and improved individual welfare (Abd El-Hack et al. 2017a).

In laying hens and breeders

Towards the end of the laying period, sudden changes did occur in some farms, decreased reproductive rate (8% loss) and larger and heavier eggs with poor quality shells. These alterations caused large economic losses in the laying hen industry (Abdallah et al. 2009). Thus, in the quest to improve eggshell quality, use of zinc is highly recommended as it is a component of the carbonic anhydrase enzyme (CA), involved in eggshell formation by providing carbonate ions (Yildiz et al. 2010). Supplementation with MHA- Zn (organic Zinc) at 40 and 60 mg/kg of feed provides better shell strength and density between 66 and 72 weeks and 62 and 72 weeks, respectively, in addition to a significant improvement of egg weight at 62 weeks, as compared to inorganic Zn supplemented group (Min et al. 2018). Indeed, Zn deficiency affects directly the quality of the oviduct epithelium due to the reduction of protein synthesis and indirectly the structure of the epithelium and epithelial secretions during the formation of the shell membrane, which, undeniably, leads to poor shell quality (Tabatabaie et al. 2007). Therefore, Zn plays an essential role in albumin deposition in the magnum and shell membrane formation in the isthmus (Nys et al. 2004). Moreover, cracking, reduced strength or presence of defects in the shell can lead to the penetration of pathogens such as Salmonella (Innocenti et al. 2004). Zn-Met supplementation at 25 and 50 mg/kg and 75 and 100 mg/kg of feed significantly increases shell thickness (Abd El-Hack et al. 2017b). Incorporation of 80 mg/kg of MHA-Zn in the diet improves the shell calcium concentration at 62, 70 and 72 weeks as well as the shell Zn concentration at 66, 70 and 72 weeks (Min et al. 2018). In another register, the incorporation of 50 mg of ZnO (Zinc oxide) as well as 100 mg of Zn-Met increased the egg production rate revealingly compared to the control group with 86.76 and 86.66% respectively between 22 and 34 weeks. Egg weight also increased with 73.14g for the supplemented group and 67.90g for the control group (Abd El-Hack et al. 2018). In addition, Zn-Met supplementation at 100 mg/kg of feed significantly increased daily feed intake and the number of eggs laid/month as well as egg weight and mass between 22 and 34 weeks with 26.03 eggs/month, 73.14g and 63.48g/day/hen respectively in contrast to the control group with 22.90 eggs/month, 67.90g and 51.80g/day/hen during the same period (Abd El-Hack et al. 2017b).

Vol. 07, No. 02; 2022

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For flesh-type breeding males, Zn supplementation at 50-100 mg/kg of feed improves semen quality with an increased spermatocrit (5-7%), ejaculate volume (0.2-0.3 ml) as well as a 10% individual sperm motility improvement along with a 7% and 2-7% decreases of dead and abnormal spermatozoa, respectively (Amem and Al-Daraji, 2011). The effects of Zn on semen quality are subsequent to a serial of chemical interactions. Indeed, lipids are an integral component of the sperm cell membrane and are sensitive to lipid peroxidation. Moreover, oxidative stress decreases sperm motility and increases the percentage of dead spermatozoa in poultry (Surai et al. 1998). Therefore, Zn, as an essential component of the Cytosolic Cu/Zn Superoxide Dismutase (Cu/Zn SOD) and metallo-thionines (MT) in semen, protects the sperm cell membrane and increases their viability (Surai et al. 2000). Thus, Zn supplementation at a rate of 100 mg/kg of feed effectively improves sperm quality by increasing sperm cell viability (Gallo et al. 2003).
It should also be noted that growth and development of embryos and hatchability are closely influenced by mineral deposition in the egg (Richard, 1997). Therefore, Zn deficiency in breeding hens can alter the physiological status of the offspring and then influence chicks' body weight, meat quality, and antioxidant and immune status thereafter (Zhu et al. 2017). Indeed, a soy protein-based diet with Zn intake between 8 and 10 mg/kg in laying hens resulted in severe zinc-deficient hatching chicks with weak and poor plumage as well as an inability to stand up, drink or feed. These chicks developed hyperpnea, leading to high incidence of mortality (Zhu et al. 2017). On the other hand, Zn supplementation in laying hens or in ovo (Hassan, 2018) not only reduces chick mortality but improves post-hatching performance also (Zhu et al. 2017).

4. EFFECTS OF ZN ON GUT MORPHOLOGY AND MICROBIOTA

Appropriate micronutrient supplementation is essential for several physiological functions and overall health to end into an optimal growth in poultry. The gastrointestinal tract of the chicken is home for a diverse and complex microbiota responsible for several important functions, out of which: protection against pathogens (Pickard et al. 2017), detoxification and stimulation of the immune system (Shang et al. 2018) as well as the breakdown of polysaccharides to produce energy, synthesize vitamins, amino acids and other micronutrients (Rowland et al. 2018). Zn is a critical link in the dynamic interactions between the host and the gut microbiota to shape a healthy gastrointestinal environment (Read et al. 2019). Indeed, Zn-glycine supplementation at 50 mg/kg of feed significantly improves gut wall histological parameters and caliciform cell counts (Chand et al. 2019). In addition, incorporation of 30 and/or 60 mg/kg of feed of $ZnSO_4$ under heat stress increases intestinal morphological characteristics in broilers (Shah et al. 2020). Incorporation of a Zn-chelate amino acid complex into a wheat and rye diets at 60 mg/kg of feed in broilers increases the ratio of villi length/crypt depth, reduces the abundance of some genera of proteobacteria phyla compared to the Zn sulfate group (De Grande et al. 2020). Zn supplementation at 30 mg/kg of feed did increase the height of villi in the duodenum: 1242 µm, as compared to the control: 970 µm while a concentration of 60 mg/kg of feed had this same effect in the ileum. As for the ratio of villi height/crypts depth (VH:CD), a Zn content of 30 mg/kg of feed resulted in the highest ratio in the duodenum compared to the control with 6.88 and 5.32 respectively. In the jejunum, the increase in the number of caliciform cells is consequent to Zn dosage of 30 and 60 mg/kg of feed while in the ileum the use of 60 mg Zn/kg of feed has a favorable effect on the number of these intestinal cells (Shah et al. 2018). In a context of challenge by coccidiosis and *Clostridium perfringens*, the incorporation of 90 mg/kg of feed of ZnSO4 or Zn-P (Zinc-Proteinate) significantly reduces the lesion score characteristic of necrotic enteritis with 1.29 and 0.92, respectively, compared to the challenged negative control whose score is 1.46 (Bortoluzzi et al. 2019a). Applying cyclic heat stress at D22 namely 35 ± 1°C and 75 ± 5% relative humidity (RH) from 09:00 am to 05:00 pm (8 h per day) followed by 26°C and 65 ± 5% RH for 16 h for the following 3 weeks, the use of Zn at 60 mg/kg of feed increased the VH:CD ratio from 2.93 in the control group to 4.57 (Shah et al. 2019). Subjected to cyclic heat stress namely 19.8°C ± 1.1°C from 03 to 11 pm and 33.7°C ± 0.6°C from 11 am to 03 pm at D35 for 3 days, incorporation of 50 mg/kg of organic Zn feed in broiler chicken diet, increased the VH:CD ratio to 3.96 at the duodenum from 3.86 in the control and to 2.78 at the ileum from 1.94 in the control (Abuajamieh et al. 2020).

Despite the well-known use of Zn in poultry production, its effects on the intestinal bacterial population remains poorly understood. Zn-Pro supplementation at a rate of 90 mg/kg of feed decreases the relative abundance of *Lactobacillus* in the ileum and cecum with 72.10 and 25.86%, respectively compared to the control (95.71 and 30.82%). On the other hand, the same assay decreases the abundance of *Clostridia* at the cecum from 12.55% in the non-supplemented control to 6.34% (Bortoluzzi et al. 2019a). Also, nano zinc supplementation at a dose of 0.1 g/kg of feed generates a significant increase in Coliforms, Lactobacilli and *Salmonella* except for *E. coli* and *Enterococcus spp*. However, the use of nano zinc at 0.2 or 0.4 g/kg of feed results in a decrease in the number of the same microbial population except for *Enterococcus* at 0.4 g/Kg of feed. However, with 0.4 g/kg of feed in nano Zinc, the number of *Salmonella spp*. is reduced to 4.18 log (UFC)/g compared to the control which is 6.41 log (UFC)/g (Reda et al. 2021).

Intestinal permeability, on the other hand, was assessed by the passage of the FITC-d marker into the circulatory system and revealed that Zn-Pro supplementation at 90 mg/kg of feed increases the integrity of the intestinal-blood barrier compared to the control with serum FITC-d of 409.3 and 485.1 ng/ml, respectively (Bortoluzzi et al. 2019a).

5.EFFECT OF ZN ON THE IMMUNE SYSTEM

Stimulation of the immune system by trace elements is considered a practical and effective way to improve gut health and performance in poultry (Zhang et al. 2009). Zinc is a trace element with many physiological functions in the body (Wellinghausen et al. 1997). It is involved in gene expression, DNA and protein synthesis, cell signaling and division, immune system maturation and development, and antioxidant processes. Deficiency in this element in poultry results in decreased lymphocyte levels, mainly Th (T helper) and NK (Natural Killer) cells (Eguchi et al. 1986), titer of specific antibodies against Newcastle virus and Marek's disease as well as reduced reactivity of B cells to T cells and bacterial lipo-polysaccharides (Amitava at al. 2014). Indeed, supplementation of 90 mg/kg of feed with organic Zn down-regulated IL-8 expression in the jejunum while IL-10 and INF- γ were up-regulated when challenged with a combination of *Eimeria maxima* and *Clostridium perfringens* and this was compared to ZnSO4. IgA expression in the same intestinal portion was up-regulated during the same challenge conditions and this during organic Zn supplementation compared to the group with znso4 with and 4.22 and 1.87 genes, respectively (Bortoluzzi et al. 2019b). The incorporation of 40 mg/kg of feed also significantly increases phagocytic activity and index and total lymphocyte number with 43.6, 2.85 and 24.9 respectively compared to the control group with 38.4, 1.83 and 20.7 respectively (Hafez et al. 2019). Furthermore, in response to supplementation up to 400 mg/kg of feed with Zn, total sheep red blood cell (SRBC) and IgG titers increase linearly and hypersensitivity 24 hours after sheep blood injection improves with increasing Zn incorporation level from 200 to 400 mg/kg of feed (Kakhki et al. 2018). In a similar way, the incorporation of 40 mg of Zn-Met/kg of feed to broilers inoculated at D13 with Newcastle virus generates a significant increase in antibody (Ab) titers against these diseases at D6 post-challenge, as compared to the group supplemented with the same dose of Zn-S with log24.64 and log23.86 respectively. Also, the immune response to vaccination at D18 and D23 against bronchitis and infectious bursal disease (IB), allows to conclude that this trace element increases the titers of Ab against avian corona and IB at D12 post-vaccination with respectively log103.62 and log103.38 compared to Zn-S (log103.15 and log103.22) (Moghaddam and Jahanian, 2009). Indeed, Zinc-Glycine (Zn-Gly) supplementation at 100 mg/kg of feed amplifies the relative expression of IL-2, IL-4, IL-10, IL-17 as well as IFN-γ at D42 with 0.03, 0.2, 1.2, 0.015 and 0.015 compared to the ZnSO4 group respectively. This combination of Zn with the same assay also enhances IgA and IgG expression at D20 and D42 compared to the ZnSO4 supplemented group (Jarosz et al. 2017a). The incorporation of 100 mg of Zn-Gly/kg feed combined with phytase increased the percentage of CD3+ lymphocyte with 35.22%, CD4+ and CD8+ with 36.48% at D20 and D42 as well as that of CD25+ T cells with a value of 48.52% and this compared to the control group (Jarosz et al. 2017b). Moreover, under heat stress and with 50 and 100mg Zn-Met/Kg of feed dosage, the titers of Ab against infectious bursal disease virus detected by ELISA are significantly higher with 3.36 and 3.97 respectively compared to the control (2.81) (Saleh et al. 2018).

6. CONCLUSION

As part of several basal reaction cascades, Zn, in its organic or nanoparticle form, must be included in the diet of broilers, breeders, and layers at doses recommended by the NRC. Therefore, Zn is a powerful alternative to growth-promoting antibiotics because of its ameliorative effect on zootechnical and production performances, immune system, microflora of the digestive tract and architecture of the intestinal epithelium.

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