The Zinc Oxide ban: What led to it, what are the alternatives?

*By **Dr.** Inge **Heinzl**, Editor, EW Nutrition*

In June 2017, the European Commission decided to ban the use of veterinary drugs containing high doses of zinc oxide (3000mg/kg) from 2022. The use of zinc oxide in pig production must then be limited to a maximum level of 150ppm. Companies have been on the lookout for effective alternative strategies to maintain high profitability.

Modern pig production is characterised by its high intensity. In many European countries, piglets are weaned after 3-4 weeks, before their physiological systems are fully developed (e.g. immune and enzyme system). Weaning and thus separation from the mother, as well as a new environment with new germs, means stress for the piglets. Besides, the highly digestible sow's milk, for which the piglets are wholly adapted, is replaced by solid starter feed.

This, associated with the above-mentioned stressors, can result in reduced feed intake during the first week after weaning and therefore in a delayed adaptation of the intestinal flora to the feed. Since the immune system of animals is not yet fully functional, pathogens such as enterotoxic *E. coli* can colonize the intestinal mucosa. This can possibly develop into a dangerous dysbiosis, leading to an increased incidence of diarrhea. Inadequate absorption results in suboptimal growth with worse feed conversion. The consequences are economic losses due to higher treatment costs, lower yields, and animal losses.

Diarrhea is one of the most common causes of economic losses in pig production. In the past, this was the reason antibiotics were prophylactically used as growth promoters. Antibiotics reduce antimicrobial pressure and have an anti-inflammatory effect. In addition to reducing the incidence of disease, they eliminate competitors for nutrients in the gut and thus improve feed conversion.

However, the use of antibiotics as growth promoters has been banned in the EU since 2006 due to increased antimicrobial resistance. As a result, zinc oxide (ZnO) appeared on the scene. A study carried out in Spain in 2012 (Moreno, 2012) showed that 57% of piglets received ZnO before weaning and 73% during the growth phase (27-75 days).

Zinc oxide: the disadvantages outweigh the advantages

What made the use of zinc oxide so attractive? Zinc oxide is inexpensive, available in many EU countries, and as a trace element it can be used in high doses through premixing. In some countries, however, a veterinary prescription is needed; in others, the use is already banned.

Zinc is a trace element involved in cell division and differentiation, and it influences the efficacy of enzymes. Since defence cells also need zinc, a supplementation that covers the demand for zinc strengthens the body's defences. Through a positive effect on the structure of the gut mucosa membrane, zinc protects the body against the penetration of pathogenic germs.

If ZnO is used in pharmacological doses, it has a bactericidal effect against e.g. staphylococci (Ann et al., 2014) and various types of *E. coli* (Vahjen et al., 2016). Thus, prophylactic use prevents the incidence of diarrhea and the consequent decrease in performance. But the use of zinc oxide also has "side effects".

Accumulation in the environment

Zinc belongs to the chemical group of heavy metals. For the use as a performance enhancer, it has to be administered in relatively high doses (2000–4000ppm). These high amounts are far above the physiological needs of the animals. With relatively low absorption rates (the bioavailability amounts to approximately 20% (European Commission, 2003)) and subsequent accumulation in manure, zinc can cause substantial contamination of the environment.

Encouraging the development of antibiotic resistance

In addition to the accumulation of zinc in the environment, another aspect also plays an important role: according to Vahjen et al. (2015), a dose of ≥2500mg/kg of food increases the presence of tetracycline and sulfonamide resistance genes in bacteria. In the case of *Staphylococcus aureus*, the development of resistance to zinc is combined with the development of resistance to methicillin (MRSA; Cavaco et al., 2011; Slifierz et al., 2015). A similar effect can be observed in the development of multiresistant *E. coli* (Bednorz et al., 2013; Ciesinski et al., 2018). The reason for this is that the genes that encode antibiotic resistance, i.e. the ones that are "responsible" for the resistance, are found in the same plasmid (a DNA molecule that is small and independent of the bacterial chromosome).

Consequence: no more zinc oxide in the production of piglets from 2022 onwards

The negative effects on the environment and the promotion of antibiotic resistance led to the European Commission's decision in 2017 to completely ban zinc oxide as a therapeutic agent and as a growth promoter in piglets within five years.

There are effective alternatives to zinc oxide

By the 2022 deadline, the EU pig industry must find a solution to replace ZnO. It must develop strategies that make future pig production efficient, even without substances such as antibiotics and zinc oxide. To this end, measures should be taken at different levels, such as farm management and biosecurity (e.g. effective hygiene management). The promotion of intestinal health for high animal performance is most important, however.

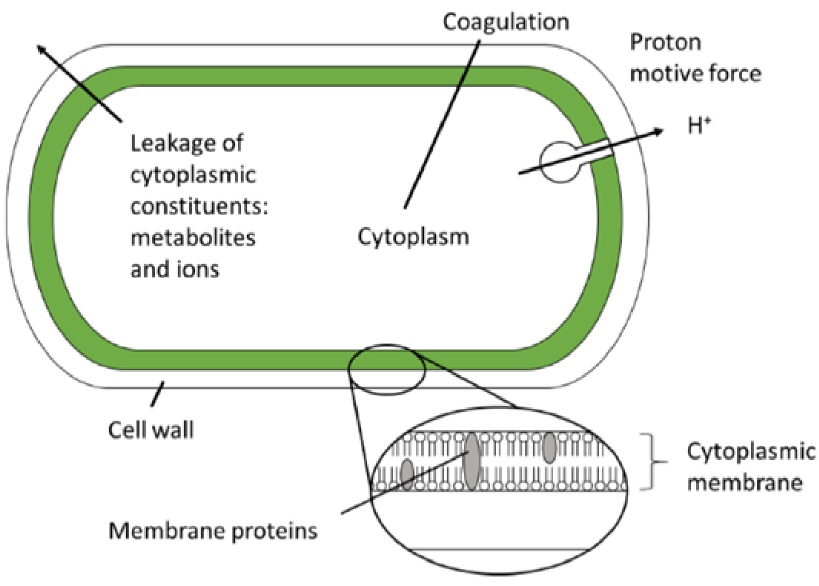
Promotion of gut health through stable gut microbiota

The term eubiosis denotes the balance of microorganisms living in a healthy intestine, which must be maintained to prevent diarrhea and ensure performance. However, weaning, food switching, and other external stressors can endanger this balance. As a result, potentially pathogenic germs can "overgrow" the commensal microbiome and develop dysbiosis. Through the use of functional supplements, intestinal health can be improved.

Phytomolecules – potent compounds created by nature

Phytomolecules, or secondary plant compounds, are substances formed by plants with a wide variety of properties. The best-known groups are probably essential oils, but there are also bitter substances, spicy substances, and other groups.

In animal nutrition, phytomolecules such as carvacrol, cinnamon aldehyde, and capsaicin can help improve intestinal health and digestion. They stabilize the intestinal flora by slowing or stopping the growth of pathogens that can cause disease. How? Phytomolecules, for example, make the cell walls of several bacteria permeable so that cell contents can leak. They also partially interfere with the enzymatic metabolism of the cell or intervene with the transport of ions, reducing the proton motive force. These effects depend on the dose: all these actions can destroy bacteria or at least prevent their proliferation.



Another point of attack for phytomolecules is the communication between microorganisms (quorum sensing). Phytomolecules can prevent microorganisms from releasing substances known as autoinducers, which they need to coordinate joint actions such as the formation of biofilms or the expression of virulence factors.

Medium-chain triglycerides and fatty acids

Medium-chain triglycerides (MCT) and fatty acids (MCFA) are characterised by a length of six to twelve carbon atoms. Thanks to their efficient absorption and metabolism, they can be optimally used as an energy source in piglet feeding. MCTs can be completely absorbed by the epithelial cells of the intestinal mucosa and hydrolysed with microsomal lipases. Hence they serve as an immediately available energy source and can improve the epithelial structure of the intestinal mucosa (Hanczakowska, 2017).

In addition, these supplements have a positive influence on the composition of the intestinal flora. Their ability to penetrate bacteria through semi-permeable membranes and destroy bacterial structures inhibits the development of pathogens such as salmonella and coliforms (Boyen et al., 2008; Hanczakowska, 2017; Zentek et al., 2011). MCFAs and MCTs can also be used very effectively against gram-positive bacteria such as streptococci, staphylococci, and clostridia (Shilling et al., 2013; Zentek et al., 2011).

Prebiotics

Prebiotics are short-chain carbohydrates that are indigestible for the host animal. However, certain beneficial microorganisms such as lactobacilli and bifidobacteria can use these substances as substrates. By selectively stimulating the growth of these bacteria, eubiosis is promoted (Ehrlinger, 2007). In pigs, mannan-oligosaccharides (MOS), fructooligosaccharides (FOS), inulin and lignocellulose are mainly used.

Another element of prebiotics' positive effect on intestinal health is their ability to agglutinate pathogens. Pathogenic bacteria and MOS can bind to each other through lectin. This agglutination prevents pathogenic bacteria from adhering to the wall of the intestinal mucosa and thus from colonizing the intestine (Oyofo et al., 1989).

Probiotics

Probiotics can be used to regenerate an unbalanced gut flora. To do this, useful bacteria such as bifido or lactic acid bacteria are added to the food. They must settle in the gut and compete with the harmful bacteria.

There are also probiotics which target the communication between pathogens. In an experiment, Kim et al. (2017) found that the addition of probiotics that interfere with quorum sensing can significantly improve the microflora in weaned piglets and thus their intestinal health.

Organic acids

Organic acids show strong antibacterial activity in animals. In their undissociated form, the acids can penetrate bacteria. Inside, the acid molecule breaks down into a proton (H^+) and an anion ($HCOO^-$). The proton reduces the pH value in the bacterial cell and the anion interferes with the bacteria's protein metabolism. As a result, bacterial growth and virulence are inhibited.

Conclusion

Today there are several possibilities in piglet nutrition to effectively support the young animals after weaning. The main objective is to maintain a balanced intestinal flora and therefore to sustain intestinal health – its deterioration often leads to diarrhea and hence to reduced returns. Intestinal health is promoted by stimulating beneficial bacteria and by inhibiting pathogenic ones. This can be achieved through feed additives that have an antibacterial effect and/or support the intestinal mucosa, such as phytomolecules, prebiotics, and medium-chain fatty acids. Through a combination of these possibilities, additive effects can be achieved. Piglets receive optimal support and the use of zinc oxide can be reduced.

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How can you compensate an activated immune system in piglets?

By Technical Team, EW Nutrition

As pig production specialists, we understand that our animals are under constant challenge during their life. Challenges can be severe or moderate, correlated to several factors – such as, for instance, stage of production, environment, and so on – but they will always be present. To be successful, we need to understand how to counter these challenges and support the healthy development of our pigs.

Factors for successful pig production

For years we have been increasing our understanding of how to formulate diets to support a healthy intestine through the optimal use of the supplied nutrients. Functional proteins, immune-related amino acids, and fiber are now applied worldwide for improved pig nutrition.

What lies beyond formulation adjustments?

However, pig producers have also realized that these nutritional strategies alone are not always fully efficient in preventing an "irritation" of the immune system and/or in preventing diseases from happening.

Immune nutrition is gaining a strong foothold in pig production, and the body of research and evidence grows richer every year. At the same time, we see **genetics** continually evolving and bringing production potential to increasingly higher levels. We are also constantly increasing our understanding of the importance of **farm and feed management**, as well as **biosecurity** in this process.

Finally, the importance of a **stable microflora** is now uncontested. Especially around weaning, a stable microflora is necessary to prevent the proliferation of pathogens such as *E.coli* bacteria. Such pathogens can degrade the lysine (the main amino acid for muscle protein production) we have added to our formulations, rendering it useless.

Single molecules (or additives) are able to support the development of gut microflora, boost its integrity, and therefore help the animals use "traditional nutrients" in a more effective way.

The impact of immune system activation on the performance of pigs

Animal performance is influenced by complex processes, from metabolism to farm biosecurity. Environmental conditions, diet formulation and feed management, and health status, among others, directly affect the amount of the genetic potential that animals can effectively express.

Among these so-called *non-genetic* variables, health status is one of the most decisive factors for the optimal performance from a given genotype. Due to the occurrence of (sub-) clinical diseases, the inflammatory process can be triggered and may result in a decrease in weight gain and feed efficiency.

Not so long ago, pig producers believed that a maximized immune response would always be ideal for achieving the best production levels. However, after decades spent researching what this "maximized immune response" could mean to our pigs, studies from different parts of the globe proved that an activated immune system could negatively affect animal performance. The perception is nowadays common sense within the global pig production industry.

That understanding led us to increasingly search for production systems that will yield the best conditions for the pigs. This means minimum contact with pathogens, reduced stress factors, and therefore a lower need for an activated immune system.

How immune system stimulation works

The immune system has as main objective to identify the presence of antigens – substances that are not known to the body – and protect the body from these "intruders". The main players among these substances are bacteria and viruses. However, some proteins can also trigger an immunological reaction. Specific immune cells are responsible for the transfer of information to the other systems of the body so that it can respond adequately. This response from the immune system includes metabolic changes that can affect the demand for nutrients and, therefore, the animals' growth.

The stimulation of the immune system has three main metabolic consequences:

- behavioral responses
- direct connection with the endocrine system and regulation of the secretions
- release of leukocytes, cytokines, and macrophages

In general, the immune system responds to antigens, releasing cytokines that activate the cellular (phagocytes) and humoral components (antibody), resulting in a decreased feed intake and an increased body temperature/heat production.

When feed formulation is concerned, possibly even more important is to understand that the activation of the immune system leads to a change in the distribution of nutrients. The basal metabolic rate and the use of carbohydrates will have completely different patterns in such an event. For instance, some glucose supplied through the feed follows its course to peripheral tissues; however, part of the glucose is used to support the activated immune system. As a consequence, the energy requirement of the animal increases.

Protein synthesis and amino acid utilization also change during this process. There is a reduction of body protein synthesis and an increased rate of degradation. The nitrogen requirement increases because of the higher synthesis of acute-phase proteins and other immunological cells.

However, increased lysine levels in the diets will not always help the piglets compensate for this shift in the protein metabolism. According to Shurson & Johnston (1998), when the immune system is activated, there is further deamination of amino acids and increased urinary excretion of nitrogen. Therefore we need to understand better which amino acids must be supplied in a challenging situation.

In pigs, the gastrointestinal tract is, to a large extent, responsible for performance. This happens because the gut is the route for absorption of nutrients, but also a reservoir of hundreds of thousands of different microorganisms – including the pathogenic ones.

Understanding Gut Health

Gut health and its meaning have been the topic of several peer-reviewed articles in the last few decades (Adewole et al., 2016, Bischoff, 2011, Celi et al., 2017, Jayaraman and Nyachoti, 2017, Kogut and Arsenault, 2016, Moeser et al., 2017, Pluske, 2013). Despite the valuable body of knowledge accumulated on the topic, a clear and widely-accepted definition is still lacking. Kogut and Arsenault (2016) define it in the title of their paper as “the new paradigm in food animal production”. The authors explain it as the “absence / prevention / avoidance of disease so that the animal is able to perform its physiological functions in order to withstand exogenous and endogenous stressors”.

In a recently published paper, Pluske et al. (2018) add to the above definition that gut health should be considered in a more general context. They describe it “a generalized condition of homeostasis in the GIT, with respect to its overall structure and function”. The authors add to this definition that gut health in pigs can be compromised even when no clinical symptoms of disease can be observed. Every stressful factor can undermine the immune response of pigs and, therefore, the animals’ performance.

All good information on this topic leads us to the conclusion that, without gut balance, livestock cannot perform as expected. Therefore, balance is the objective for which we formulate our pigs’ feed.

Current nutritional strategies for a stable gut microbiota

Feeding: quality of raw materials

The photos included here were taken in the field and show that taking action against this reality is a must for keeping animals healthy.

Much of this action is related to farm management. The most effective way to minimize such situations is to implement a strict control system in the feed production sites, including controlling raw material quality.

Additives can be used to improve the safety of raw materials. As already extensively discussed, everything that goes into the intestine of the animals will affect gut health and performance. Therefore, the potential harmful load of mycotoxins should be taken into account. Besides careful handling at harvest and the proper storage of grains, mycotoxin binders can be applied to further decrease the risk of mycotoxin contamination.

Figure 1. Grain storage in a home pig farm

Figure 2. Feed mixer in a home mixer pig farm

The effect of nutrition on microflora: commercial weaning diet after focusing on gut health

The gut-health-focused formulation of diets must take into account the following essentials:

- decrease of gut pH
- gut wall integrity
- minimization of (pathogenic) microbial growth
- microflora modulation with consequently improved colonization resistance

Gut pH

A lower pH in the stomach slows the passage rate of the feed from the stomach to the small intestine. A longer stay of the feed in the stomach potentially increases the digestion of starch and protein. The secretion of pancreatic juices stimulated by the acidic stomach content will also improve the digestion of feed in the small intestine.

For weaned pigs, it is essential that as little as possible of the substrate will reach the large intestine and be fermented. Pathogens take advantage of undigested feed to proliferate. Lowering these “nutrients” will decrease the risk of bacterial overgrowth.

The same is true where protein sources and their levels are concerned. It is essential to reduce protein content as much as possible and preferably use synthetic (essential) amino acids. The application of such sources of amino acids has been proven long ago, and yet in some cases, it is still not fully utilized. Finally, using highly digestible protein sources should, at this point, be a matter of mere routine.

All these strategies have the same goal: the reduction of undigested substances in the gut. Additionally, the reduction of the protein levels can also decrease the costs of the diets.

Further diet adjustments

Further diet adjustments, such as increasing the sulfur amino acids (SAA) tryptophan and threonine to lysine ratio, must also be considered (Goodband et al., 2014; Sterndale et al., 2017). Although the concept of better balancing tryptophan and threonine are quite clear among nutritionists, SAA are sometimes overestimated. Sulfur amino acids are the major amino acids in proteins related to body maintenance, but not so high in muscle proteins. Therefore, the requirement of SAA must also be approached differently. Unlike lysine, the requirements of SAA tend to be higher in immunologically stimulated animals (Table 1).

Pig weight (kg)	ISA*	SID Lysine (%)	SAA (%)	SAA:Lys
9	High	1,34	0,64	0,48
	Low	1,07	0,59	0,55
14	High	1,22	0,62	0,51
	Low	0,99	0,57	0,58

Table 1. Effect of the immune system activation on the demand for lysine and sulfur amino acids in pigs (Stahly et al., 1998)

*ISA – immune system activation

Vitamins and minerals are classic nutrients to be considered when formulating gut health-related diets. Maybe not so extensive as the amino acids and protein levels, these nutrients have, however, been found to carry benefits in challenging situations. In the past several years, a lot was published on the requirements of pigs facing an activation of the immune system. Stahly et al. (1996) concluded that when the immune system is activated, the phosphorous requirements change.

Parameters	ISA*	
	High	Low
Feed intake (g/d)	674	833
Weight gain (g/d)	426	566
Available P (%)	0,45	0,65

Table 2. Effect of the immune system activation on the performance and phosphorous requirements of pigs (Stahly et al., 1998)

*ISA – immune system activation

Another example is vitamin A. It is involved in the function of macrophages and neutrophils. Vitamin A deficiency decreases the migratory and phagocytic abilities of the immune cells. A lower antibody production is observed in vitamin A deficiency as well. Furthermore, vitamin A is an important factor in mucosal immunity, because this vitamin plays a role in lymphocyte homing in the mucosa (Duriancik et al., 2010).

Phytomolecules: key additives to support gut health

Phytomolecules are currently considered one of the top alternatives to in-feed antibiotics for pigs worldwide. Programs sponsored by the European Union are once more evaluating the effectiveness of these compounds as part of a strategy to produce sustainable pigs with low or no antibiotic use. The EIP-Agri (European Innovation Partnership "Agricultural Productivity and Sustainability") released a document with suggestions to lower the use of antibiotics in feed by acting in three areas:

- improving pig health and welfare
- changing attitudes and human habits
- finding specific alternatives to antibiotics

Under the last topic, the commission recommends plant-based feed additives to be further examined.

Antibiotics have been used for many years for supporting performance in animal production, especially in critical moments. The mode of action consists of the reduction of pathogen proliferation and inflammation processes in the digestive tract. These (soon-to-be-) banned compounds therefore reduce the activation of the immune system, helping keep pigs healthy through a healthy gastrointestinal tract. As potential alternatives to antibiotic usage, phytomolecules should be able to do the same.

The mode of action of phytomolecules

Antimicrobial

Most phytomolecules used nowadays aim to control the number and type of bacteria in the gut of animals. According to Burt (2004), the antimicrobial activity of phytomolecules is not the result of one specific mode of action, but a combination of effects on different targets of the cell. This includes disruption of the membrane by terpenoids and phenolics, metal chelation by phenols and flavonoids, and protective effects against viral infections for certain alkaloids and coumarins (Cowan, 1999).

Digestion support

The antimicrobial efficacy is one of the most important activities of secondary plant compounds, but it also impacts digestion. Windisch et al. (2008) states that growth-promoting agents decrease immune defense stress during critical situations. They increase the intestinal availability of essential nutrients for absorption, thus promoting the growth of the animal.

Indeed, phytomolecules are a good tool for stabilizing the gut microbiota. But more can be expected when adding this class of additives into your formulation and/or farm operations. Mavromichalis, in his book "Piglet Nutrition Notes – Volume 2", brings attention to the advantages of using phytomolecules such as capsaicin, which is often related to increased feed intake. Recent research has demonstrated that capsaicin increases the secretion of digestive enzymes that may result in enhanced nutrient digestibility. According to Mavromichalis, this can lead to a better feed conversion rate as more nutrients are available to the animal. Indirectly, this also helps control the general bacterial load in the gut.

Antioxidant support

This results from the polyphenols' capacity to act as metal-chelators, free radical scavengers, hydrogen donators, and inhibitors of the enzymatic systems responsible for initiating oxidation reaction. Furthermore, they can act as a substrate for free radicals such as superoxide or hydroxyl, or intervene in propagation reactions.

This variety of benefits explains at least partially the high level of interest in this group of additives for pigs under challenging conditions. For the production of effective blends, it is crucial to understand the different modes of action of the phytomolecules and the probable existing synergies. Furthermore, the production technology must be considered. For instance, microencapsulation techniques that prevent losses during feed processing are an important consideration.

Not to be discarded: Biosecurity

The recent outbreak of African Swine Fever focused our attention on something that is sometimes neglected on the farm: biosecurity rules. According to the report "Good Practices For Biosecurity In The Pig Sector" (2010), the three main elements of biosecurity are:

- segregation
- cleaning
- disinfection

In general terms, the following steps must be adopted with the clear goal of reducing the challenges that the pigs are facing.

- Farms must be located far from other farms (regardless of the species) and ideally must be protected with natural (forest/woods) or physical barriers.
- Only one entrance must be used to go into the farm (for both vehicles and people) and a disinfection procedure must be in place, either by an automatized system or by manual application of disinfectants. Equipment disinfection systems must also be in place.
- Workers and any other person that enters the facility should adhere to strict biosecurity measures 24/7. The farms must have a visitors' book including relevant data on previous visits

to farms (regardless of the species).
- Trucks and visitors should not have been in contact with other pigs recently (at least 48 hours previous to the visit).
- Only farm workers are allowed to go into the barns unless special approval is given (followed by strict biosecurity measurements prior to the visit).
- The use of clothing and footwear that are worn only in the pig unit (and certainly not during visits to other pig farms) is recommended.
- No materials (e.g. tools) can be moved from one barn to another barn. People that enter a barn should change footwear and wash their hands with soap for at least 10 seconds.

These simple actions can make a big difference to the performance of the pigs, and as a consequence to the profitability of a swine farm.

Take-home messages

Different formulations and reassessed nutritional level recommendations have been on the radar for a couple of years. It is high time to consider using efficient additives to support the pigs' gut health. Phytomolecules appear as one of the most prominent tools to reduce pathogenic stress in pig production. Either via feed or water, phytomolecules are proven to reduce bacterial contamination and therefore reduce the need for antibiotic interventions. Furthermore, a more careful look at our daily activities in the farm is crucial. Paying attention to biosecurity and to feed safety should be standard tools to improve performance and the success of pig production operations.

References are available upon request.

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How phytomolecules support antibiotic reduction in pig production

by Merideth Parke, Regional Technical Manager, EW Nutrition

To contain and reverse antimicrobial resistance, consumers and government regulators expect changes in pork production with the clear goal to reduce antibiotic use. For healthy, profitable pig production with simultaneous antibiotic reduction, a holistic strategy is required: refocusing human attitudes and habits, optimal pig health and welfare, and applying potential antibiotic alternatives.

Corn is often contaminated with Aspergillus fungi that can produce poisonous mycotoxins

Pig producers need to manage

pathogenic pressure while reducing antibiotics

Intensive pig production has stress points associated with essential husbandry procedures such as weaning, health interventions, and dietary modifications. Stress is widely accepted to have a negative impact on immune system effectiveness, enhancing opportunities for pathogenic bacteria to invade at a local or systemic level. The gastrointestinal and respiratory systems are highly susceptible to developing disease as a result of these combined factors. Interventions such as antibiotics are commonly implemented to reduce the impact of pathogens and manage pig health. Processes that minimize the number of pathogens in the environment are the foundation for a successful antibiotic reduction plan. The challenge is to smartly combine strategies to keep the gastrointestinal and respiratory tract intact and robust.

Phytomolecules, the specific active defense compounds found in plants, have been identified as capable of enhancing pig health through antimicrobial (Cimanga et al., 2002, Franz et al., 2010), antioxidative (Katalinic et al., 2006, Damjanovic-Vratnica et al., 2007, Lee et al., 2011), digestion-stimulating and immune-supportive functions. As many thousands of phytomolecules exist, laboratory research has focused on identifying those with the capability of microbial management, facilitating the end goal of reducing the reliance on antibiotics for pig health and welfare and the production of safe pork (Zhai et al., 2018).

Which roles can phytomolecules play in reducing antibiotics?

The gastrointestinal tract benefits from applying phytomolecules such as capsaicin, carvacrol, and cinnamaldehyde, as they:

- support a balanced and stable biome,
- prevent dysbiosis, maintain tight junction integrity (Liu et al., 2018),
- increase secretion of digestive enzymes, and
- enhance gut contractility (Zhai et al., 2018).

Pigs most susceptible and in need of phytomolecule gastrointestinal supportive actions are piglets at weaning and pigs of all ages undergoing stress, pathogen challenges, and/or dietary changes.

Porcine respiratory disease is a complex multifactorial disorder. It frequently requires antibiotics to manage infection pressure and clinical disease to maintain pig health, welfare, and production performance. Causal pathogens may be transmitted by direct contact between pigs in saliva (Murase et al., 2018) or bioaerosols (LeBel et al., 2019), via the nasal or oral cavities (inhalation directly into the airways and lungs), or via an unhealthy gut. Phytomolecules such as carvacrol and cinnamaldehyde have antimicrobial properties. Hence, they may help contain respiratory pathogens in their natural habitat (the upper respiratory tract) or during transit through the oronasal cavity and gastrointestinal tract (Swildens et al., 2004, Lee et al., 2001).

In addition to supporting the gastrointestinal and respiratory systems, phytomolecules such as menthol and 1,8-cineole have been shown to enhance the physical and adaptive immune systems in multiple species (Brown et al., 2017, Barbour et al., 2013). When applied via drinking water, adherence to the oronasal mucosa facilitates the inhalation of the active phytomolecule compounds into the respiratory tract. There, they act as mucolytics, muscle relaxants, and enhancers of the mucociliary clearance mechanism (Başer and Buchbauer, 2020). Phytomolecules have also been documented to positively influence the adaptive immune system, promoting both humoral and cell-mediated immune responses (Awaad et al., 2010, Gopi et al., 2014, Serafino et al., 2008).

How phytomolecules feature in the holistic approach to antibiotic reduction

Antibiotic reduction programs positively enact social responsibility by reducing the risk to farmworkers of exposure to antimicrobial-resistant bacteria. They also help maintain or increase efficiency in safe pork production – pork with minimal risk of antibiotic residues.

Implementation of a successful health program with reduced antibiotic use will require:

- application of strict internal and external biosecurity processes;
- evaluation and monitoring of AMR bacteria;
- partnerships with specialist nutritionists to target a lifetime healthy gut biome; and
- phytomolecule-assisted health management (Figure 1).

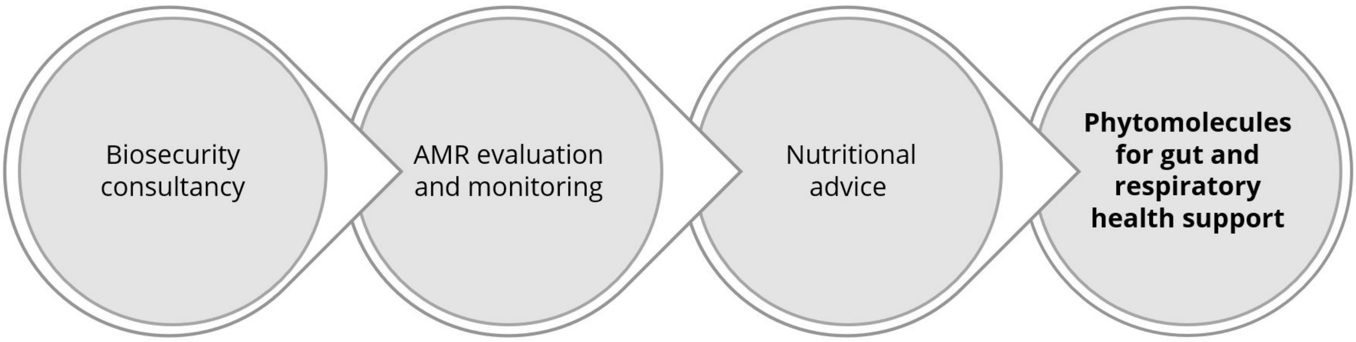

Figure 1: The role of phytomolecules within EW Nutrition's holistic Antibiotic Reduction program

A combination of *in vitro* and *in vivo* studies provides evidence that specific phytomolecules can support both enteric and respiratory systems through biome stabilisation and pathogen management (Bajabai et al., 2020). Antimicrobial activity of thymol, carvacrol, and cinnamaldehyde has been reported against respiratory pathogens including *S. suis, A. pleuropneumoniae*, and *H. parasuis* (LeBel et al., 2019)*;* multi-drug resistant and ESBL bacteria (Bozin et al., 2006); enteric pathogens including *E. coli*, *Salmonella enteritidis*, *Salmonella cholerasuis*, and *Salmonella typhimurium* (Penalver et al., 2005); *Clostridium* spp., *E. coli* spp., *Brachyspira hyodysenteriae* (Vande Maelle et al., 2015); and *Lawsonia intracellularis* (Draskovic et al., 2018). These results have shown phytomolecules to be effective antimicrobial alternatives for incorporation into holistic pig health programs.

Additionally, the inclusion of phytomolecules into pig production systems also enhances production performance by reducing the negative impact of stress on the pig and increasing the positive effects on gut health and nutrient utilization (Franz et al., 2010). Phytomolecules that directly impact digestive actions include capsaicin, which optimizes the production of digestive enzymes and increases serotonin for gut contraction maintenance and improved digesta mixing (Zhai et al., 2018). Cineol's antioxidative activities provide support during times of stress (Cimanga et al., 2002).

Phytomolecules are key to reducing antibiotics in pig production

The pig industry searches for alternatives to therapeutic, prophylactic, and growth-promoting antibiotic applications to keep available antibiotics effective for longer – and to address the social responsibility of mitigating AMR. This search for ways to produce safe pork has made it clear that only a combination of management and antibiotic alternatives can achieve these aligned goals.

Biosecurity, hygiene, stress reduction, and husbandry and nutritional advances form the foundation for the strategic application of specific phytomolecules (Zeng et al. 2016). Supporting pig production and health, this complete holistic solution (EIP-AGRI) moves the pig industry into a future where antibiotic reduction or removal, with equivalent or increased production of safe pork, becomes a reality.

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