Mycotoxins as contributors to antibiotic resistance?

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Antibiotic resistance is a growing global health concern, making infections more complicated to treat and increasing the risk of disease spread, severe illness, and death. While overuse and misuse of antibiotics are the primary causes, recent research has uncovered another unexpected contributor: mycotoxins. Among these, deoxynivalenol (DON), a toxin commonly found in contaminated grains, has been shown to significantly alter gut microbiota and promote antibiotic resistance. This article examines how DON impacts gut bacteria, influences antibiotic resistance, and highlights why this issue warrants urgent attention.

Mycotoxins – originators of antimicrobial resistance?

Actually, it would be logical…

Alexander Fleming discovered Penicillin when he returned after the summer holidays and saw that a mold had grown on the agar plate he had prepared. Around the mold, Staphylococcus was unable to proliferate. The reason was a substance produced by the mold – penicillin, which, like other toxins produced by molds, is a mycotoxin. In his article about the origin of antibiotics and mycotoxins, Shier (2011) stated that antibiotics and mycotoxins share considerable similarities in structure, metabolic roles, and biosynthesis.

A short excursus to antimicrobial resistance

In general, the primary mechanisms of resistance involve the prevention or limitation of the antimicrobial substance's uptake, modifying the drug target, inactivating the drug, or facilitating its discharge with efflux pumps.

There are two types of resistance: natural resistance, which is further divided into intrinsic and induced resistance, and acquired resistance.

Intrinsic resistance is a "characteristic" of a bacterial species and is not dependent on antibiotic exposure. An example is the reduced permeability of the outer membrane of gram-negative bacteria, which prevents certain antibiotics from entering.

Induced resistance, however, needs to be initiated by antibiotics. Here, multidrug-efflux pumps can be mentioned.

The third one, acquired resistance, refers to the process by which bacteria acquire genetic material, the resistance genes, from other bacteria that are resistant. The mechanisms include vertical transfer to daughter cells and horizontal transfer, such as the transfer from dead bacteria to living ones, by viruses, or the transfer of plasmids (Reygaert, 2018).

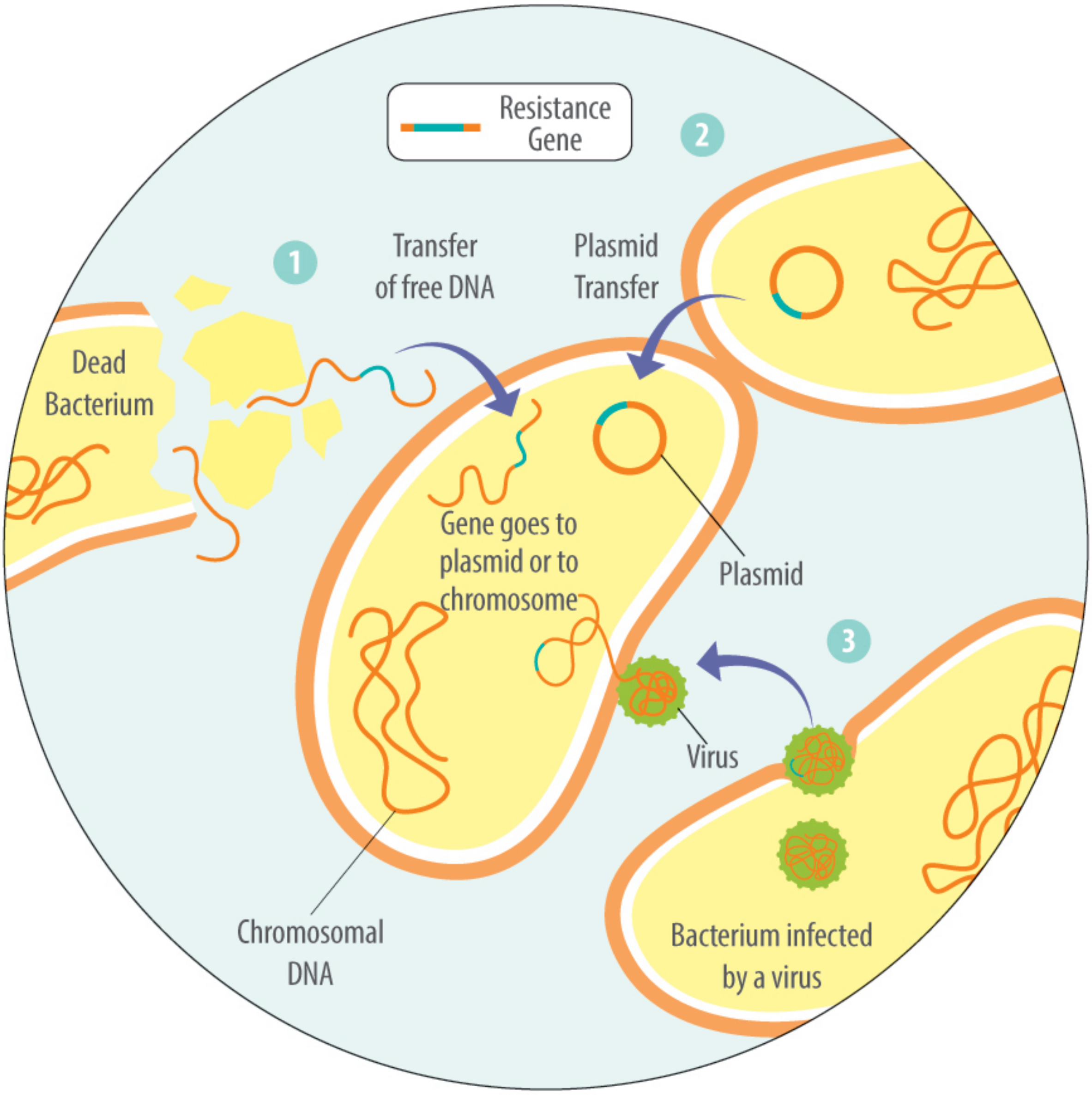

Figure 1: Different possibilities of transfer of resistance genes

Deoxynivalenol (DON) promotes resistance in gut microbiota

A Chinese group of researchers (Deng et al., 2025) examined for the first time the influence of DON on the intestinal microbiota of chickens. One of the most alarming findings is DON's ability to enhance antibiotic resistance. It contributes to this issue in several ways:

1. Encouraging resistant bacteria – By disrupting microbial balance, DON provides a survival advantage to bacteria that carry resistance genes.
2. Activating resistance genes – Studies suggest that DON can increase the expression of genes that help bacteria withstand antibiotics.
3. Enhancing gene transfer – Bacteria can share resistance genes through horizontal gene transfer. DON appears to promote this process, making antibiotic-resistant strains spread more rapidly.
4. Weakening antibiotic effectiveness – DON-induced changes in the gut environment can reduce the effectiveness of antibiotics, making treatments less successful.

A further indication that mycotoxins can enhance resistance is the significant overlap in the geographical distribution of antimicrobial-resistant bacteria and genes with that of mycotoxins, as noted by Deng et al.

Which protection mechanisms do bacteria have against mycotoxins?

In the case of mycotoxins, bacteria employ similar molecular mechanisms to those used against antibiotics. In an in vitro experiment, Hassan et al. (2019) challenged *Devosia mutans*, a gram-negative bacterium, with DON in the growth medium. DON inhibits protein synthesis, induces oxidative stress, and compromises cell membrane integrity in eucaryotic cells. Hassan et al. asserted three adaptive mechanisms as the response to the challenge:

1. Activation of cellular membrane proteins (adenosine 5'-triphosphate-binding cassette -ABC-transporters) responsible for the unidirectional transport of substrates, either outward or inward. These ABC transporters can work as drug efflux pumps.
2. Production of DON-specific deactivation enzymes, thereby engaging a toxin-specific pyrroloquinoline quinone-dependent detoxification pathway. This enables the bacterial isolate to transform DON to a non-toxic stereoisomer.
3. Upregulation of auxiliary coping proteins, such as porins (transmembrane proteins involved in metabolite exchange), glutathione S-transferases, and phosphotransferases, both of which are likely involved in the detoxification of xenobiotics.

Public health implications and preventive measures

Given the widespread presence of DON in food and animal feed, its potential role in antibiotic resistance poses a serious threat. The combination of increased bacterial resistance and weakened antibiotic efficacy could lead to more difficult-to-treat infections. This is particularly concerning in hospital settings, where antibiotic-resistant infections already cause high mortality rates.

To address the issue, several strategies can be implemented:

1. Reducing DON contamination: Implementing improved agricultural practices, such as crop rotation, the use of fungal-resistant crop varieties, and maintaining proper storage conditions, can help limit fungal growth and DON production.
2. Monitoring food and feed supply – Strict regulations and testing for DON contamination in grains and animal feed are essential to minimize human and animal exposure.
3. Effective mycotoxin risk management at feed mill and farm levels: Using tools such as MasterRisk and effective products combatting mycotoxins.
4. Maintaining gut health: A healthy diet rich in fiber, probiotics, and gut health-supporting feed supplements, such as Ventar D or products from the Activo line, may help counteract some of the adverse effects of DON on gut microbiota.
5. Developing new treatments: Research into alternative therapies and new antibiotics is crucial to combat the rise of antibiotic resistance.

Antimicrobial resistance: Be aware of the mycotoxins!

The connection between mycotoxins, such as DON, and antibiotic resistance underscores the need for a broader perspective on public health and food safety and once again brings the "One Health Concept" into focus. While antibiotic overuse remains the primary driver of resistance, environmental factors, such as exposure to mycotoxins, should not be overlooked. By increasing awareness, enhancing food safety regulations, and investing in research, we can take steps to mitigate this emerging threat and safeguard the effectiveness of antibiotics for future generations.

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Piglet rearing – there is still room for improvement!

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Optimal rearing conditions for piglets are crucial for ensuring their healthy growth, reducing mortality, and enhancing productivity. These conditions include proper temperature, nutrition, housing, hygiene, and care. Here are the key aspects:

1. Temperature and ventilation

Piglets are sensitive to cold because they cannot regulate their body temperature effectively in the first few days after birth. Proper temperature control is essential to prevent chilling, possibly leading to illness and death. Additionally, regulating the temperature would cost energy, which otherwise could be spent for growth.
Signs of a too-cold environmental temperature are piling on top of one another, tucking the legs under the body, being unable to get up, laying near a corner or wall, or shivering, which may stop if the conditions worsen. Measuring the body temperature shows less than 35°C in the case of chilling.

The following temperatures are recommended for successful piglet rearing:

Farrowing unit (for newborns)	32 – 35°C (90–95°F) during the first few days
After the first week	The temperature can gradually decrease by about 1.5-2.0°C per week until it reaches 25°C (77°F)

For supplemental heating, heat lamps, heated floors, or creep areas (a designated warm spot) can be used to maintain the ideal temperature, especially in cooler climates.

Temperature is often closely related to ventilation. Ventilation is essential to reduce dust, humidity, ammonia, and other harmful substances occurring in the air. However, if fresh/cold air enters the pigsty, the temperature decreases, which can get dangerous for the piglets. Suitable ventilation means finding a good balance between providing fresh air and maintaining temperature to prevent energy losses and chilling of the piglets.

Comfort zones can be a solution. They are an effective way to keep the piglets warm and ventilation rates where needed to maintain proper air exchange and humidity levels.

2. Nutrition

Nutrition is critical for piglet growth and immune system development. Most important after birth is the access to colostrum. Piglets are born with an immature immune system, and the maternal antibodies ingested with the colostrum are vital for their survival. They should consume colostrum within the first 6 hours after birth.

It will take 5 to 7 days for piglets to stabilize and get regular on suckling schedule.

At around seven days of age, it is recommended to introduce a highly digestible, nutrient-dense creep feed that helps transition piglets from milk to solid food. Fresh and clean water of the best quality must always be available.

Never forget most important nutrient, beside sow´s love and care – water. Allow piglets free access to the excellent quality water.

3. Housing and Space

A well-designed, clean, and dry environment is critical for reducing stress and promoting health. Farrowing crates help prevent sows from accidentally crushing the piglets during the first few weeks. However, these farrowing crates should provide enough space for the sow to nurse the piglets while allowing piglets to move freely.

Separate warm and clean areas (creep spaces) for the piglets within the farrowing pen are helpful to help the piglets escape from cooler or potentially dangerous parts of the crate. Straw, sawdust, or rubber mats should be provided to keep the piglets warm and comfortable, and good drainage is essential to maintain dryness.

4. Hygiene and Health

Hygiene is crucial to prevent disease and promote the health of piglets. For this purpose, pens and farrowing units should be thoroughly cleaned. Regular removal of waste and keeping bedding dry helps control pathogens. It is essential to clean and disinfect the farrowing unit from one farrowing to the other to reduce disease risks.

Health: After birth, the piglets' umbilical cord stump should be disinfected to prevent infections. A further essential precautionary measure to prevent anemia is an oral supplementation or an iron injection within the first three days of life, as piglets are born with low iron levels.

For further health monitoring and management, it should be ensured that the piglets are vaccinated against common diseases, such as E. coli, Mycoplasma, and Porcine Circovirus. Additionally, deworming protocols and monitoring for signs of parasites should be implemented for parasite control.

5. Weaning Practices

Piglets are typically weaned between 3 and 4 weeks of age, but early weaning (around 21 days) can be practiced in intensive systems. Optimal weaning requires gradual adaptation to solid feed and a stress-free environment.

If the piglets are weaned at 21 to 28 days, a high-quality starter diet after weaning is essential to maintain growth rates and minimize post-weaning stress.

6. Minimizing Stress

Stress management is essential to prevent disease and poor growth. For this purpose, minimize handling to the minimum during the first few days and, if necessary, handle the piglets gently to reduce stress.

A new environment also means strain for the piglets, so keep the litter groups together during weaning to reduce fighting and social stress.

7. Supportive functional feed ingredients

Depending on veterinary and managing practices, the availability of feed, and the possible use of antimicrobials or other medicals as prophylactics, there can be high variability in rearing conditions in diverse areas of the world. In the following, two functional feed ingredients with entirely different modes of action are presented that support piglets at different rearing conditions.

7.1 Egg immunoglobulins (IgY) support piglets under poor rearing conditions

Egg immunoglobulins are beneficial if piglets are not raised under the best conditions, meaning lower hygienic standards and higher pathogenic pressure. With egg immunoglobulins coming from hens having been in contact with pathogens relevant to piglets, it is possible to support the young animals. What is the background? Hens are able to transfer maternal antibodies against diseases that they are confronted with to the egg. With this mechanism, they can provide their progeny with a starter kit for the first time after hatching. However, the best thing is that these antibodies are also helpful for mammals.

A trial conducted on a commercial farm in Spain shows the weight development of piglets fed an IgY-containing egg powder product (EP) compared to a negative control. The weaned piglets were fed a two-phase feeding (15 days prestarter, 22 days starter). The control (n=51) received no additional functional feed ingredient, whereas the EP group was fed 2 kg of the product/t of feed during the prestarter phase. The animals were weighed individually on days 16 and 37.

The results are shown in Figures 1 and 2.

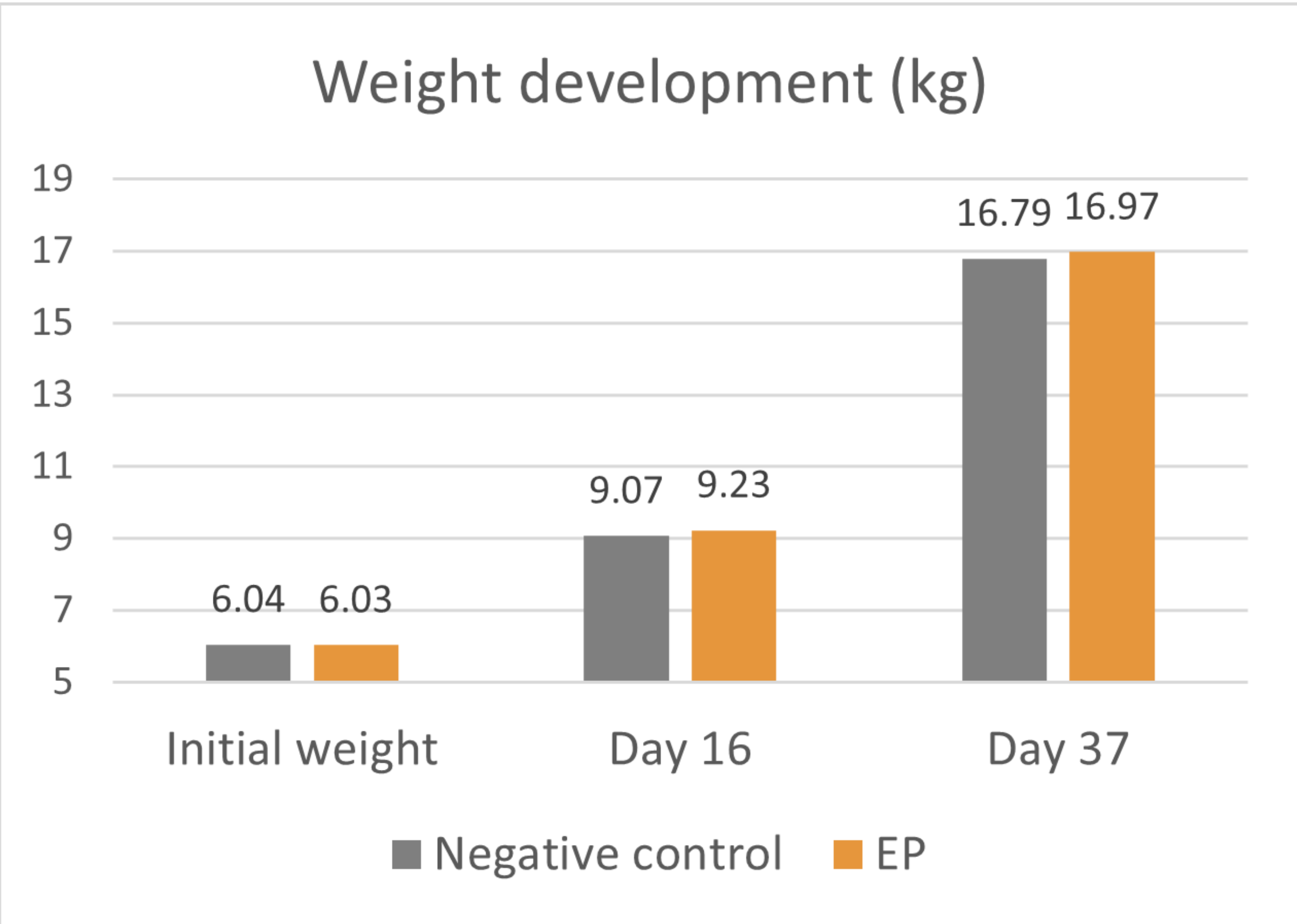


Figure 1: Weight development of piglets receiving an IgY-containing egg powder product compared to a negative control

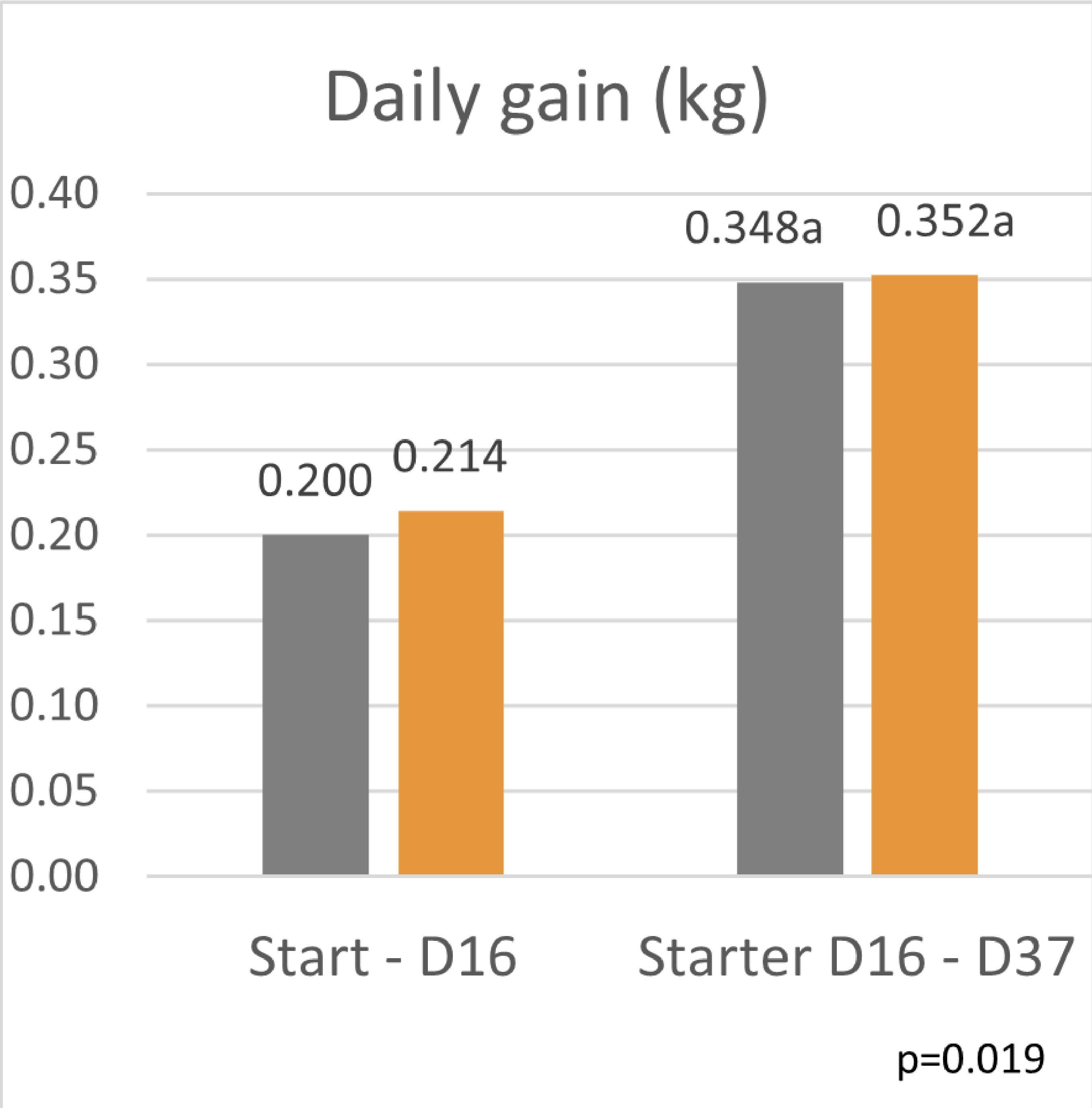


Figure 2: Daily gain of piglets receiving an IgY-containing egg powder product compared to a negative control

Explanation of the results: Under poor hygienic conditions, the pathogenic pressure is relatively high, and everything lowering this pressure helps to improve gut health, the utilization of nutrients, and performance. Egg immunoglobulins positively influence the gut microbiome, thus helping reduce diarrhea. By lowering the pathogenic pressure, the organism's energy can be used for growth and must not be employed for the body's defense.

7.2 Phytomolecules can even show improvement under optimum conditions

Phytomolecules generally show diverse gut health-promoting effects, from driving the intestinal microbiome in the right direction and strengthening the intestinal barrier to acting as antioxidants or antiinflammatories or increasing the secretion of digestive juices and, therefore, improving digestion. Which mode of action is relevant if the piglets are raised under already optimal conditions (best hygiene, no prophylactic antibiotics or zinc oxide) and show the highest growth? Is there still room for improvement? Yes, it is. A trial conducted in Germany adduces evidence.

In this trial, 220 piglets weaned on average at 26 days and weighing around 8 kg were housed in 20 pens of 11 castrated males or gilts each. Piglets were blocked by body weight and fed a two-phase feeding program (phase 1 from day 1 to day 13 and phase 2 from day 17 to day 40; pelleted diet). Neither feed or water medication nor therapeutic levels of ZnO were used.

The results of this piglet trial can be seen in Figures 3 and 4.

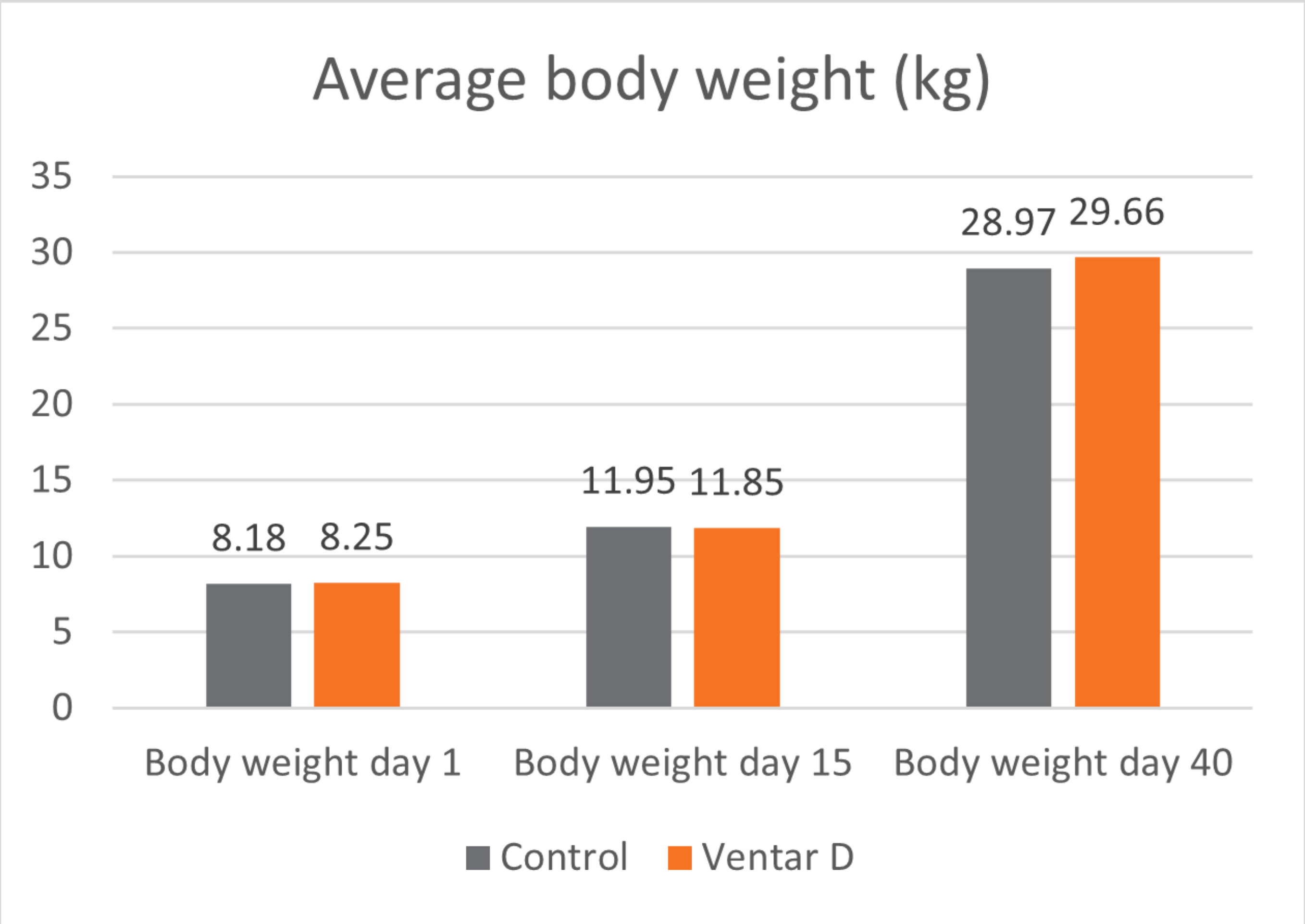


Figure 3: Weight development of piglets fed Ventar D compared to a negative control

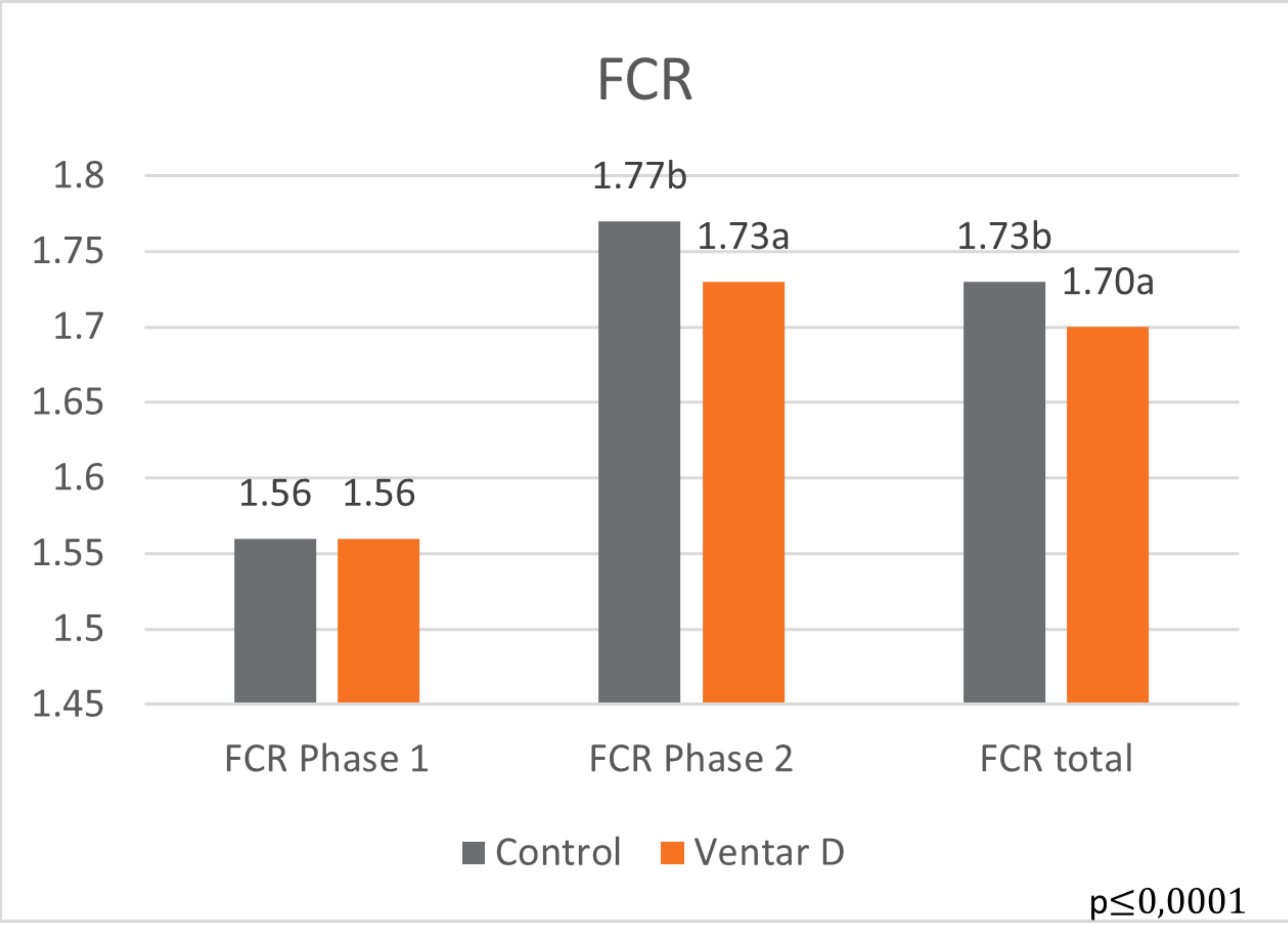


Figure 4: Feed conversion rate in piglets fed Ventar D compared to a negative control

Explanation of the results: The figures show that the piglets in the control already have an extremely high weight compared to those of a similar age in the previous trial, indicating the best rearing conditions in this trial. But, even here, Ventar D has the capacity to improve performance. Why? High-performing animals stress their body more than low-performing ones. Anabolic processes increase oxidative stress and non-infectious inflammation and burden the immune system. The relevant mode of action of Ventar D is not the gut health-promoting or the antimicrobial one because there is no issue. The relevant modes of action in this case are antioxidant and anti-inflammatory. With these two characteristics, Ventar D still has the capacity to improve the performance of piglets that are already at the top level.

8. Conclusion

For high piglet performance, providing the best possible rearing conditions is essential. However, there are differences concerning these conditions in different areas of the world. Depending on them, different feed strategies can be used. Egg immunoglobulins show the best effects if there is a certain pathogenic pressure. Phytomolecules, however, due to their various modes of action, can be beneficial under different levels in rearing conditions. In a low standard, the antimicrobial and gut health-promoting effect is more relevant; in the case of best conditions, the anti-oxidant and anti-inflammatory effects are decisive.

In summary, it could be said that functional feed ingredients have significant advantages in piglet rearing, but the right choice must be made depending on the prevailing conditions.

The crucial role of short-chain fatty acids and how phytomolecules influence them

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

For optimum health, the content of short-chain fatty acids (SCFAs) is decisive. On the one hand, they act locally in the gut, on the other hand, they are absorbed via the intestinal mucosa into the organism and can affect the whole body. Newer studies in humans show a connection between the deficiency of SCFAs and the occurrence of chronic diseases such as diabetes type 2 or chronic inflammatory gut diseases.

SCFAs – what are they, and where do they come from?

SCFAs consist of a chain of one to six carbon atoms. They are crucial metabolites primarily generated through the bacterial fermentation of dietary fiber (DF) in the hindgut. However, SCFAs and branched SCFAs can also arise during protein fermentation. Short-chain fatty acids predominantly include acetate, propionate, and butyrate, which together account for over 95% of the total SCFAs, typically in a 60:20:20 ratio.

Acetate is produced in two different ways, via the acetyl-CoA and the Wood-Ljungdahl pathways where Bacteroides spp., Bifidobacterium spp., Ruminococcus spp., Blautia hydrogenotrophica, Clostridium spp. are involved. Additionally, acetogenic bacteria can synthesize acetate from carbon dioxide and formate through the Wood-Ljungdahl pathway (Ragsdale and Pierce, 2021). Acetate counts for more than 50% of the total SCFAs in the colon and is the most abundant one.

Propionate can also be produced in two ways. If it is produced via the succinate pathway involving the decarboxylation of methyl malonyl-CoA, the essential bacteria are Firmicutes and Bacteroides. In the acrylate pathway, lactate is converted to propionate. Here, only some bacteria, such as Veillonellaceae or Lachnospiraceae, participate.

Butyrate is produced from acetyl-CoA via the classical pathway by several Firmicutes. However, also other gut microbiota such as Actinobacteria, Proteobacteria, and Thermotogae, which contain essential enzymes (e.g., butyryl coenzyme A dehydrogenase, butyryl-CoA transferase, and butyrate kinase) can be involved. Butyrate can also be produced via the lysine pathway from proteins.

Besides the production of SCFAs from dietary fiber, there is another possibility for the synthesis of SCFAs as well as branched SCFAs – the fermentation of protein in the hindgut. This is something we want to avoid, since it´s clear signal of incorrect animal nutrition. It tells us that there is either oversupply of protein or decrease in protein digestion and absorption.

Which roles do SCFAs play?

SCFAs play a crucial role in the maintenance of gut health. Some benefits originate from these substances' general character, while others are specific to one acid. If we talk about the benefits of all SCFAs, we can mention the following:

1. Primarily, SCFAs are absorbed by the intestine and serve enterocytes as an essential substrate for energy production.
2. By lowering the pH in the intestine, SCFAs inhibit the invasion and colonization of pathogens.
3. SCFAs can cross bacterial membranes in their undissociated form. Inside the bacterial cell, they dissociate, resulting in a higher anion concentration and bactericidal effect (Van der Wielen et al., 2000)
4. SCFAs repair the intestinal mucosa
5. They mitigate intestinal inflammation by G protein-coupled receptors (GPRs).
6. They enhance immune response by producing cytokines such as IL-2, IL-6, IL-10, and TNF-α in the immune cells. Furthermore, they enhance the differentiation of T-cells into T regulatory cells (Tregs) and bind to receptors (Toll-like receptor, G protein-coupled receptors) on immune cells (Liu et al., 2021).
7. SCFAs are involved in the modulation of some processes in the gastrointestinal tract, such as electrolyte and water absorption (Vinolo et al., 2011)

After seeing the general characteristics of short-chain fatty acids, let us take a closer look at the specialties of the single SCFAs.

Acetate might play a crucial role in the competitive process between enteropathogens and bifidobacteria and help to build a balanced gut microbial environment (Liu et al., 2021). Additionally, acetate promotes lipogenesis in adipocytes (Liu et al., 2022).

Concerning general health, acetate inhibits, e.g., lung inflammatory response and the reduced air-blood permeability induced by avian pathogenic E. coli-caused chicken colibacillosis (Peng et al., 2021).

Propionate is thought to be involved in controlling intestinal inflammation by regulating the immune cells assisting and, consequently, in maintaining the gut barrier. Furthermore, propionate regulates appetite, controls blood glucose, and inhibits fat deposition in broiler chickens (Li et al., 2021).

In a trial conducted by Elsherif et al. (2022), birds fed a diet with 1.5 g sodium propionate/kg showed considerably ($P<0.05$) longer and wider guts, higher counts of lactobacillus($P<0.05$) and no colonization of Clostridium perfringens. The immunological state improved significantly ($P<0.05$), which could be seen by the higher antibody titers when the birds were vaccinated against Newcastle disease or avian influenza.

Butyrate additionally improves the function of the intestinal barrier by regulating the assembly of tight junctions (Peng et al., 2009) and stimulating cell renewal and differentiation of the enterocytes. Butyrate-producing microbes on their side prevent the dysbiotic expansion of potentially pathogenic E. coli and Salmonella (Byndloss et al., 2017; Cevallos et al., 2021) by stimulating PPAR-γ signaling. This leads to the suppression of iNOS synthesis and a significant reduction of iNOS and nitrate in the colonic lumen. Furthermore, the microbiota-induced PPAR-γ-signaling inhibits dysbiotic Enterobacteriaceae expansion by limiting the bioavailability of oxygen and, therefore, respiratory electron acceptors to Enterobacteriaceae in the colon.

In a trial conducted by Xiao et al. (2023), sodium butyrate enhanced broiler breeders' reproductive performance and egg quality due to the regulation of the maternal intestinal barrier and gut microbiota. Additionally, it improved the antioxidant capacity and immune function of the breeder hens and their offspring.

SCFAs' production can be managed

The extent of production depends on the diet and the composition of the intestinal flora. Nutritional strategies can be taken to regulate the production of short-chain fatty acids by providing dietary fiber and prebiotics, the respective bacteria but also additives in the diet or, on the other, negative way, use of antibiotics.

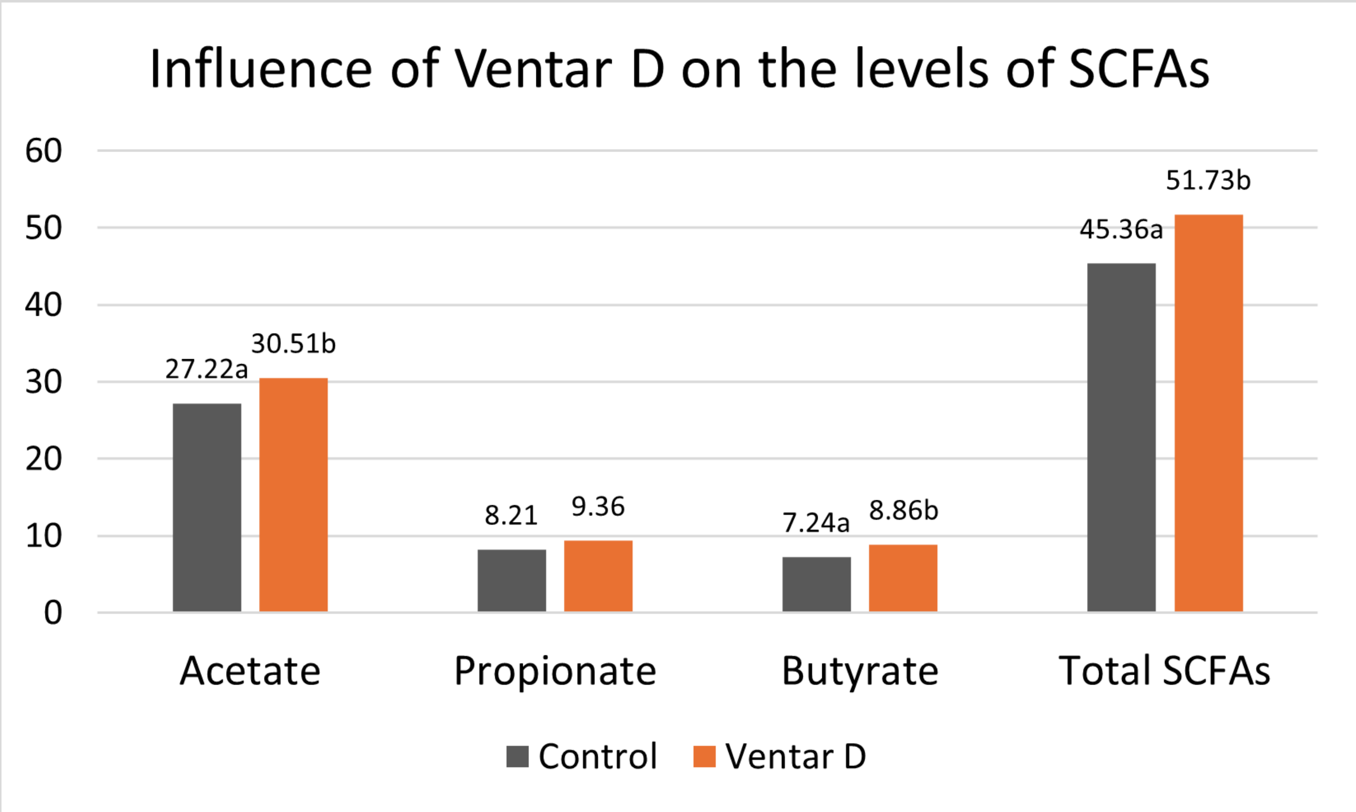
One example of SCFA-promoting additives is phytomolecules. Ventar D, a blend of diverse gut health-promoting phytomolecules, shows its SCFAs-increasing effect in a trial with Ross 308 broilers.

Trial design: The 41-day research study was conducted at an R&D farm in Turkey, with 3200 Ross 308 broilers in total. The day-old broiler chicks were randomly divided into two groups with 8 replicates in 16-floor pens (6.5×2 m each), each of 200 chicks (100 males and 100 females). One group was managed as a control group with regular feed formulation, and the other group was supplemented with Ventar D. All the birds were provided feeds and water ad libitum. Temperature, lighting, and ventilation were managed as per Ross 308 recommendation.

Groups	**Application dose**	
	Starter (crumbles)	**Grower & Finisher – 1 & 2 (pellet)**
Control	No additive	
Ventar D	100 gm/MT	100 gm/MT

All the birds and feed were weighed on days 0, 11, 23, and 41. Dead birds were also weighed, and the feed consumption was corrected accordingly. At the end of the experiment, one male and one female chicken close to the average weight of each pen were separated, weighed, and slaughtered. Short-chain fatty acid (SCFA) concentration in the caecum was measured by gas chromatography (Zhang et al. 2003). Statistical analysis of the data obtained in this study was carried out in the Minitab 18 program using the T-test following the randomized block trial design ($P \leq 0.05$). The research results were subjected to statistical analysis on a pen basis. Mortality results were evaluated with the Chi-square test.

Results: Ventar D significantly increased the levels of acetate, butyrate, and total SCFAs. The level of propionate was numerically higher. Additionally, higher final body weights (on average 160 g), improved feed efficiency (6 points), a higher EPEF (33 points), and lower mortality (0.5%) could be asserted in this experiment.



One explanation could be the microbiota-balancing effect of Ventar D. Meimandipour et al. (2010), for example, saw in their study that increased colonization of Lactobacillus salivarius and Lactobacillus agilis in cecum significantly increased propionate and butyrate formation in caeca.

Phytomolecules: Balancing intestinal microbiome and increasing healthy SCFAs

By promoting beneficial intestinal bacteria and fighting the harmful ones, phytomolecules drive the microbiome in the right direction and promote the production of short-chain fatty acids. Their gut health-protecting effect, in turn, provides for adequate digestion and absorption of nutrients, leading to optimal feed conversion and growth rates. The support of the immune system and the promotion of the antioxidant capacity additionally enhance the health of the animals. Healthy animals grow better, which ultimately leads to a higher profit for the farm.

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Consistency in performance: a decisive factor in choosing feed additives

*by **Madalina Diaconu**, Global Manager Gut Health, EW Nutrition*

In practical poultry production, multiple stress factors occur simultaneously: nutrition, management, environment, etc.. The effects of these factors are additive, leading to chronic stress, a condition in which animals cannot regain homeostasis and continuously deviate the use of resources to inflammation and restoring the gut barrier-function (Das et al., 2011). As a result, the gut microbiome is altered and oxidative stress ensues (Mishra et al., 2019). In this situation, health and productivity are compromised.

The feed supplied to production animals is designed to help them express their genetic potential. However, some feed components are also continuous inflammatory triggers. Anti-nutritional factors, oxidized lipids, and mycotoxins induce a low-grade inflammatory response (Cardoso Del Pont et al., 2020). Other factors that trigger gut health issues include the environment, management, and pathogens.

Feed interventions have shown to increase productivity and improve gut-related biomarkers, demonstrating a mitigation effect over the challenge factors (Deminicis et al., 2020; Latek et al., 2022).

Meta-analysis of broiler studies shows consistent results

As broilers are continuously challenged during the production period, the effects of an in-feed phytogenic (Ventar D – EW Nutrition GmbH) were extensively researched in broiler meat production. 21 trials in different locations (7 in Europe, 6 in the USA, 4 in Japan, 3 in Middle East, and 2 in India), with different production levels (grouped by EPEF) and challenges were analyzed to establish Ventar D's benefits for the broiler production industry in terms of performance and sustainability. In all trials, the treatment group consisted of a supplementation of the basal feed with Ventar D at a dose 100 g/ton. The control groups were not supplemented with any gut health improvement feed additive.

Of these 21 trials, 14 had corn/soybean meal-based diets and 7 had high fiber diets (based on wheat and rye, which constituted a challenge as no NSP-enzymes were included). Reused litter (by 12 to 14 flocks, previous to the trial) also was used as a challenge. 18 trials were performed in research facilities and 3 in commercial farms.

Consistency in the results from Ventar D could be demonstrated as 19 out of 21 trials showed an improvement in FCR, lowering 3.4 points on average; 18 /21 trials showed higher body weight, with an average of 64 grams more; and 17 trials showed lower mortality than the control group, averaging 1.19 percentual points of reduction. The phenolic compounds included in Ventar D, such as thymol, possess antioxidant, anti-inflammatory, and antibacterial activities, which account for improving gut health and thus increasing performance in production animals.

The European Poultry Efficiency Factor (EPEF) was used to establish the performance level of each flock. This index is based on the average daily weight gain, mortality, and feed conversion, and takes in consideration the age of the flock at collection, allowing to make comparisons on performance within and between farms.

Of the 21 trials, 10 control groups had an EPEF lower than 375, and were considered of low performance level, in 8 the EPEF was between 375 and 425 and considered of medium performance, and for 3 the performance was considered high having an EPEF of 425 or more.

Ventar D increased performance at all levels (Figure 1). However, the effects were challenge-dependent: Low performing flocks averaged an 8% increase in EPEF, and high performing flocks increased 4%, indicating that Ventar D can help broilers to overcome challenges commonly found in poultry production, and boost performance even with excellent farm and management conditions. These results concur with a meta-analysis by Valle Polycarpo and collaborators (2022), finding that a microbial challenge can influence the performance of phytogenic feed additives.

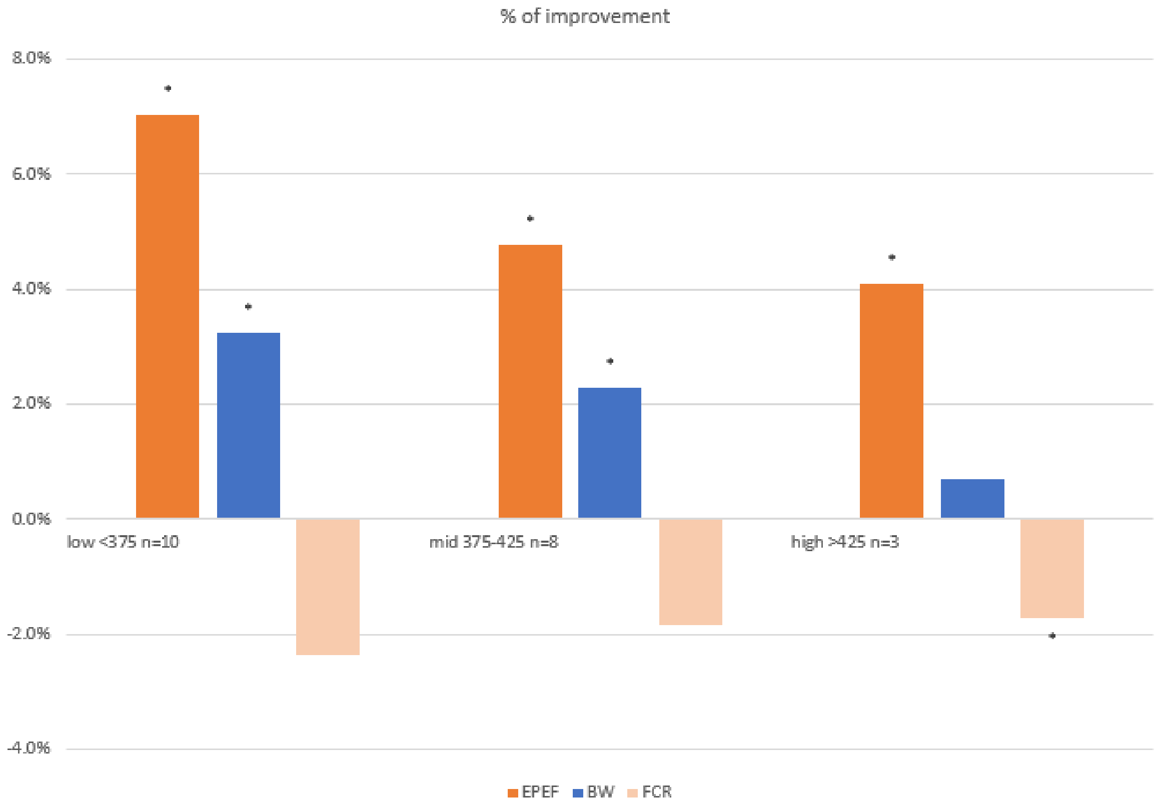

Figure 1: % of improvement in EPEF, body weight (BW) and Feed Conversion Rate (FCR) against a non-suplemented control group of IFI suplemented flocks with low (<400), mid (400 – 450) and high (>450) EPEF levels. Significant differences ($p<0.05$) against a control group (not shown as the improvements against it are depicted) are indicated by (*).

Overall, this analysis demonstrates that effective nutritional interventions can give consistent results and constitute effective tools to help production animals overcome stress and enhance productivity.

Managing gut health – a key challenge in ABF broiler production

*By **Dr. Ajay Bhoyar**, Global Technical Manager Poultry, EW Nutrition*

Gut health is a critical challenge in antibiotics-free (ABF) production as it plays a vital role in the overall health and well-being of animals. Antibiotics have long been used as a means of preventing and treating diseases in animals, but their overuse has led to the development of antibiotic-resistant bacteria. As a result, many farmers and producers are shifting towards antibiotics-free production methods. This shift presents a significant challenge as maintaining gut health without antibiotics can be difficult. It is, however, not impossible.

One of the main challenges in antibiotics-free production is the prevention of bacterial infections in the gut. The gut microbiome plays a crucial role in the immune system and overall health of animals. When the balance of microbes in the gut is disrupted (dysbiosis), it can lead to poor nutrient absorption which subsequently results in reduced live bird performance including feed efficiency and weight gain in broiler chicken. In the absence of antibiotics, farmers and producers must rely on other methods to maintain a healthy gut microbiome.

Antibiotic reduction – a major global trend

The trend in recent years has been for poultry producers to reduce their use of antibiotics to promote public health and improve the sustainability of their operations. This has been driven by concerns about the development of antibiotic-resistant bacteria and the potential impact on human health, as well as by consumer demand for meat produced without antibiotics. Many countries now have regulations in place that limit the use of antibiotics in food and animal production.

Challenges to antibiotics-free poultry (ABF) production

1. **Disease control**. Antibiotic-free poultry production requires farmers to rely on alternative methods for controlling and preventing diseases, such as stepped-up biosecurity practices. This can be more labor-intensive and costly.
2. **Higher mortality rates.** Without antibiotics, poultry farmers may experience higher mortality rates due to disease outbreaks and other health issues. This can lead to financial losses for the farmer and a reduced supply of poultry products for consumers.
3. **Feeding challenges.** Antibiotic growth promotors (AGPs) are often used in feed to promote growth and prevent intestinal disease in poultry. Without AGPs, poultry producers can find alternative ways to ensure expected production performance.
4. **Increased cost.** Antibiotic-free poultry production can be more expensive than conventional production methods, as farmers must invest in additional housing, equipment, labor, etc.

Phasing out AGPs will likely lead to changes in the microbial profile of the intestinal tract. It is hoped that strategies such as infectious disease prevention programs and using non-antibiotic alternatives minimize possible negative consequences of antibiotic removal on poultry flocks (Yegani and Korver, 2008).

Gut health is key to overall health

A healthy gastrointestinal system is important for poultry to achieve its maximum production potential. Gut health in poultry refers to the overall well-being and functioning of the gastrointestinal tract in birds. This includes the balance of beneficial bacteria, the integrity of the gut lining, and the ability to digest and absorb nutrients. Gut health is important for maintaining the overall health and well-being of the birds. A healthy gut helps to improve feed efficiency, nutrient absorption, and the overall immunity of the birds.

The gut is host to more than 640 different species of bacteria and 20+ different hormones. It digests and absorbs the vast majority of nutrients and makes up for nearly a quarter of body energy expenditure. It is also the largest immune organ in the body (Kraehenbuhl and Neutra, 1992). Consequently, 'gut health' is highly complex and encompasses the macro and micro-structural integrity of the gut, the balance of the microflora, and the status of the immune system (Chot, 2009).

Poultry immunity is mediated by the gut

The gut is a critical component of the immune system, as it is the first line of defense against pathogens that enter the body through the digestive system. Chickens have a specialized immune system in the gut, known as gut-associated lymphoid tissue (GALT), which helps to identify and respond to potential pathogens. The GALT includes Peyer's Patches, which are clusters of immune cells located in the gut wall, as well as the gut-associated lymphocytes (GALs) that are found throughout the gut. These immune cells are responsible for recognizing and responding to pathogens that enter the gut.

The gut-mediated immune response in chickens involves several different mechanisms, including the activation of immune cells, the production of antibodies, and the release of inflammatory mediators. The GALT and GALs play a crucial role in this response by identifying and responding to pathogens, as well as activating other immune cells to help fight off the infection.

The gut microbiome also plays a critical role in gut-mediated immunity in chickens. The gut microbiome is made up of a highly varied community of microorganisms, and these microorganisms can have a significant impact on the immune response. For example, certain beneficial bacteria can help to stimulate the immune response and protect the gut from pathogens.

Overall, the gut microbiome, GALT, and GALs all work together to create an environment that is hostile to pathogens while supporting the growth and health of beneficial microorganisms.

Dysbiosis/Dysbacteriosis impacts performance

Dysbiosis is an imbalance in the gut microbiota because of an intestinal disruption. Dysbacteriosis can lead to wet litter and caking issues. Prolonged contact with the caked litter can lead to pododermatitis (feet ulceration) and hock-burn, resulting in welfare issues as well as degradation of the carcass (Bailey, 2010). Apart from these issues, the major economic impact comes from reduced growth rates, FCR, and increased veterinary treatment costs. Coccidiosis infection and other enteric diseases can be aggravated when dysbiosis is prevalent. Generally, animals with dysbiosis have high concentrations of *Clostridium* that generate more toxins, leading to necrotic enteritis.

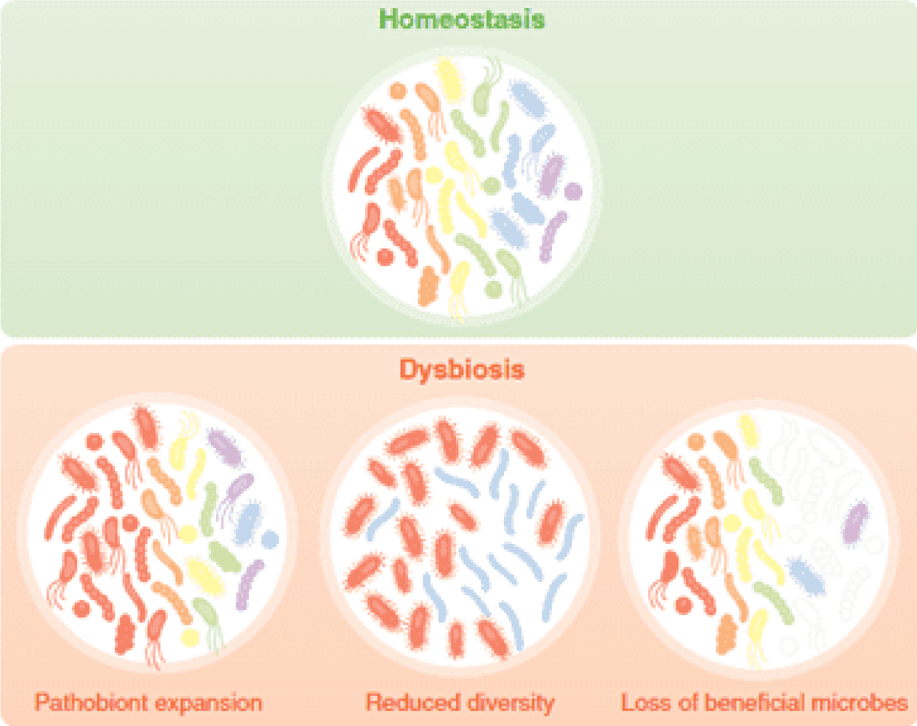

Fig.1: Dysbiosis – a result of challenging animal's microbiome. Source: Charisse Petersen and June L. Round. 2014

It is believed that both non-infectious and infectious factors can play a role in dysbacteriosis (DeGussem, 2007). Any changes in feed and feed raw materials, as well as the physical quality of feed, influence the balance of the gut microbiota. There are some risk periods during poultry production when the bird will be challenged, for example during feed change, vaccination, handling, transportation, etc. During these periods, the gut microbiota can fluctuate and, in some cases, if management is sub-optimal, dysbacteriosis can occur.

Infectious agents that potentially play a role in dysbacteriosis include mycotoxins, *Eimeria* spp., *Clostridium perfringens*, and other bacteria producing toxic metabolites.

Factors affecting gut health

The factors affecting broiler gut health can be summarized as follows:

1. **Feed and water quality**: The form, type, and quality of feed provided to broilers can significantly impact their gut health. Consistent availability of cool and hygienic drinking water is crucial for optimum production performance.
2. **Stress**: Stressful conditions, such as high environmental temperatures or poor ventilation, can lead to an imbalance in the gut microbiome and an increased risk of disease.
3. **Microbial exposure**: Exposure to pathogens or other harmful bacteria can disrupt the gut microbiome and lead to gut health issues.
4. **Immune system**: A robust immune system is important for maintaining gut health, as it helps to prevent the overgrowth of harmful bacteria and promote the growth of beneficial bacteria.
5. **Sanitation**: Keeping the broiler environment clean and free of pathogens is crucial for maintaining gut health, as bacteria and other pathogens can easily spread and disrupt the gut microbiome.
6. **Management practices**: Proper management practices, such as proper feeding and watering, and litter management can help to maintain gut health and prevent gut-related issues.

Fig. 2. Key factors affecting broilers' gut health

Key approaches for managing gut health without antibiotics

Two key approaches for managing gut health in poultry without the use of antibiotics are outstandingly successful.

Proper nutrition and management practices

Ensuring the birds have access to clean water, high-quality feed, and a stress-free environment is crucial for ABF poultry production. A balanced diet in terms of protein, energy, and essential vitamins and minerals is essential for maintaining gut health.

The environment in which birds have kept plays a major role in maintaining gut health. Proper sanitation and ventilation, as well as the right temperature and humidity, are crucial to prevent the spread of disease and infection. There is no alternative to the strict implementation of stringent biosecurity measures to prevent the spread of disease.

Early detection and treatment of diseases can help to prevent them from becoming more serious problems affecting the profitability of ABF production. It is important to keep a close eye on birds for signs of disease, such as diarrhea, reduced water, and feed consumption.

Gut health-promoting feed additives

Another approach to maintaining gut health in antibiotics-free poultry production is using gut health-supporting feed additives. A variety of gut health-supporting feed additives including phytochemicals/essential oils, organic acids, probiotics, prebiotics, exogenous enzymes, etc. in combination or alone are used in animal production. Particularly, phytogenic feed additives (PFAs) have gained interest as cost-effective feed additives with already well-established effects on improving broiler chickens' intestinal health.

Plant secondary metabolites and essential oils (generically called phytogenics, phytochemicals, or phytomolecules) are biologically active compounds that have recently garnered interest as feed additives in poultry production, due to their capacity to improve feed efficiency by enhancing the production of digestive secretions and nutrient absorption. This helps reduce the pathogenic load in the gut, exert antioxidant properties and decrease the microbial burden on the animal's immune status (Abdelli et al.

2021).

Plant extracts – Essential oils (EOs) /Phytomolecules

Phytochemicals are naturally occurring compounds found in plants. Many phytomolecules have been found to have antimicrobial properties, meaning they can inhibit the growth or kill microorganisms such as bacteria, viruses, and fungi. Examples of phytomolecules with antimicrobial properties include compounds found in garlic, thyme, and tea tree oil. Essential oils (EOs) are raw plant extracts (flowers, leaves, roots, fruit, etc.) whereas phytomolecules are active ingredients of essential oils or other plant materials. A phytomolecule is clearly defined as one active compound. Essential oils (EOs) are important aromatic components of herbs and spices and are used as natural alternatives for replacing antibiotic growth promoters (AGPs) in poultry feed. The beneficial effects of EOs include appetite stimulation, improvement of enzyme secretion related to food digestion, and immune response activation (Krishan and Narang, 2014).

A wide variety of herbs and spices (thyme, oregano, cinnamon, rosemary, marjoram, yarrow, garlic, ginger, green tea, black cumin, and coriander, among others), as well as EOs (from thyme, oregano, cinnamon, garlic, anise, rosemary, citruses, clove, ginger), have been used in poultry, individually or mixed, for their potential application as AGP alternatives (Gadde et al., 2017).

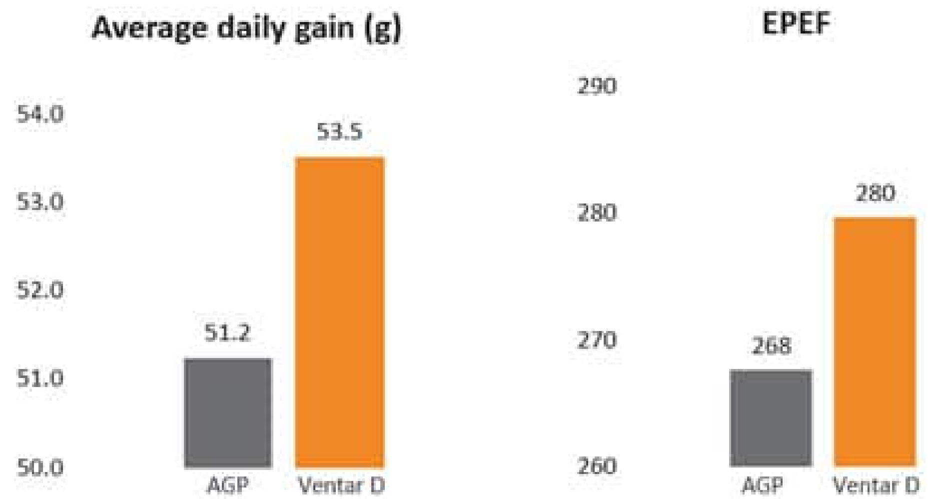

Fig. 3: Phytomolecule-based feed additive outperforms AGPs with improved broiler performance (42 Days field study)

One of the primary modes of action of EOs is related to their antimicrobial effects which allow for controlling potential pathogens (Mohammadi and Kim, 2018).

Phytomolecule blend	*Clostridium perfringens*	*Enterococcus caecorum*	*Enterococcus hirae*	*Escherichia coli*	*Salmonella typhimurium*	*Staphylococcus aureus*
Ventar D	1250	2500	5000	2500	5000	2500

Fig. 4: Effectivity of phytomolecule-based feed additive (Ventar D) against enteropathogenic bacteria (MIC value in PPM)

Phytomolecules have been shown to have anti-inflammatory properties. These compounds include flavonoids, polyphenols, carotenoids, and terpenes, among others. One of the ways in which phytomolecules exhibit anti-inflammatory effects is through their ability to inhibit the activity of pro-inflammatory enzymes and molecules. For example, polyphenols have been shown to inhibit the activity of nuclear factor-kappa B (NF-kB), a transcription factor that plays a key role in regulating inflammation.

Phytomolecules also have antioxidant properties, which can help to protect cells from damage caused by reactive oxygen species (ROS) and other reactive molecules that can contribute to inflammation. Plant extracts are also proposed to be used as antioxidants in animal feed, protecting animals from oxidative damage caused by free radicals. The presence of phenolic OH groups in thymol, carvacrol, and other plant extracts act as hydrogen donors to the peroxy radicals produced during the first step in lipid oxidation, thus retarding the hydroxyl peroxide formation (Farag et al., 1989, Djeridane et al., 2006). Thymol and carvacrol are reported to inhibit lipid peroxidation (Hashemipour et.al. 2013) and have strong antioxidant activity (Yanishlieva et al., 1999).

Overall, the anti-inflammatory effects of phytomolecules are thought to be due to a combination of their ability to inhibit the activity of pro-inflammatory enzymes and molecules, their antioxidant properties, and their ability to modulate the immune system. Plant extracts (i.e. carvacrol, cinnamaldehyde, eugenol. etc.) inhibit the production of pro-inflammatory cytokines and chemokines from endotoxin-stimulated immune cells and epithelial cells (Lang et al., 2004, Lee et al., 2005, Liu et al., 2020). It has been indicated that anti-inflammatory activities may be partially mediated by blocking the NF-κB activation pathway (Lee et al., 2005).

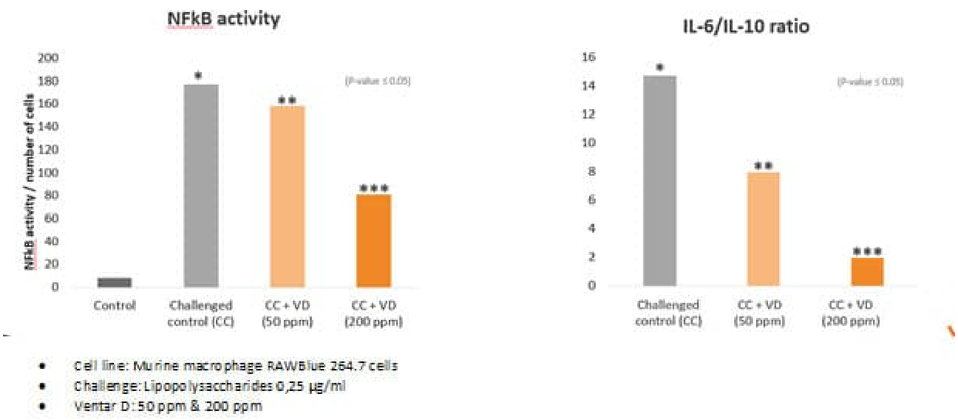

Fig. 5: Anti-inflammatory effect of phytomolecule-based feed additive (Ventar D) – the reduced activity of inflammatory cytokines

Proper protection of EOs/Phytomolecules is key to optimum results

Several phytogenic compounds have also been shown to be largely absorbed in the upper GIT, meaning that without proper protection, the majority would not reach the lower gut where they would exert their major functions (Abdelli et al. 2021). The benefits of supplementing the broiler diet with a mixture of encapsulated EOs were higher than the tested PFA in powdered, non-protected form (Hafeez et al. 2016). Novel delivery technologies have been developed to protect PFAs from the degradation and oxidation process during feed processing and storage, ease the handling, allow a slower release, and target the lower GIT (Starčević et al. 2014). The specific protection techniques used during the commercial production of an EO/phytomolecule blend are crucial in delivering on all the objectives with remarkable consistency.

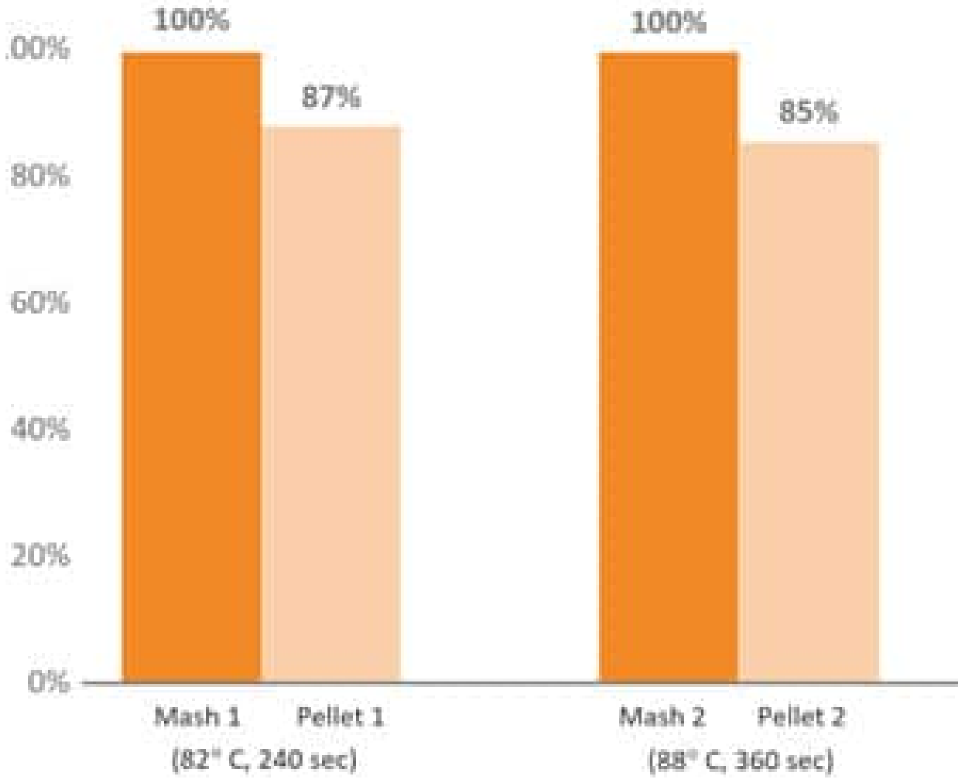

Fig. 6: Pelleting stability of phytomolecule – based feed additive (Ventar D) at high temperature and longer conditioning time

Phytomolecule blend optimizes production performance

Removal of antibiotics in poultry production can be challenging for controlling mortality and maintaining the production performance of the birds. Phytogenic feed additives have been shown to [improve production performance](#) of chicken due to their antimicrobial, anti-inflammatory, antioxidant, and digestive properties. Possible mechanisms behind improved nutrient digestibility by phytogenic feed additives (PFAs) supplementation could be attributed to the ability of these feed additives to stimulate appetite, saliva secretion, intestinal mucus production, bile acid secretion, and activity of digestive enzymes such as trypsin and amylase as well as to positively affect the intestinal morphology (Oso et al. 2019). EOs are perceived as growth promoters in poultry diets, with strong antimicrobial and anticoccidial activities (Zahi et al., 2018). PFAs have positive effects on body weight gain and FCR in chickens (Khattak et al. 2014, Zhang et el. 2009).

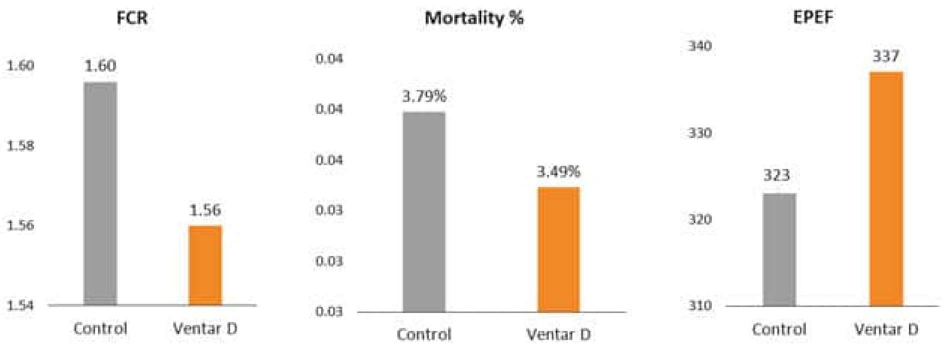

Fig. 7: Phytomolecule-based feed additive improved broiler FCR and mortality in field trial

Conclusion

In conclusion, managing gut health is a significant challenge in ABF broiler production that must be addressed to achieve optimal performance and welfare of the birds. The use of antibiotics as a preventative measure in broiler production has been widely used, but with the increasing demand for antibiotic-free products, alternative methods to maintain gut health must be implemented. These include using gut health-supporting feed additives, and proper management practices such as implementing biosecurity measures, maintaining optimal environmental conditions, providing adequate space and ventilation, and reducing stress. However, it is essential to note that there is no one-size-fits-all solution for gut health management in ABF broiler production. It is important to continuously monitor and assess their flock's gut health and make adjustments as necessary. Additionally, research and development in this field should be encouraged to identify new and innovative ways to maintain gut health in ABF broiler production.

Overall, managing gut health is a critical challenge that requires a multi-faceted approach and ongoing monitoring and management. By implementing the appropriate strategies and utilizing new technologies, poultry operators can ensure the health and well-being of their flocks while meeting the growing demand for antibiotic-free products sustainably.

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How to develop phytogenic feed

additives

By Technical Team, EW Nutrition

Modern feed additives are now commonly used as a critical tool to improve animal health. Among these, phytogenic feed additives are increasingly widely adopted. Consequently, more and more products are entering the market, leaving producers to wonder how these products differ from one another and which product performs best. To better understand the benefits that phytogenic feed additives can bring to operations, one must understand the development process feed additives undergo.

Not all feed additives are born equal

Feed additives are products that are added into an animal feed to improve its value. They are typically used to improve animal performance and welfare and consequently to optimize profitability for livestock producers.

Their purpose should not be confused with that of veterinary drugs. Feed additives provide additional benefits *beyond* the physiological needs of the animals and should be combined with other measures to improve production efficiency. Those measures include improvements in management, selection of genetics, and a constant review of biosecurity measures.

Several categories of feed additives exist. They all have in common that they are mixed into the feed or premix or the drinking water in relatively low inclusion rates to serve a *specific* purpose. Examples of feed additives are organic acids, pre- and probiotics, short and medium chained fatty acids, functional yeast products, and phytogenic feed additives. Modern feed additives also blend those different additives into combination products, increasing the value of the final products.

Phytogenic feed additives are a sub-category of additives containing phytomolecules, active ingredients which originate from plants and provide a unique set of characteristics. These molecules are produced by plants to protect themselves from molds, yeasts, bacteria, and other harmful organisms. Depending on the type of molecule, phytomolecules have different properties, ranging from antimicrobial to antioxidant and anti-inflammatory.

EW Nutrition’s approach to developing Ventar D: 6 steps

The development of best-in-class phytogenic feed additives is a complex process. For Ventar D, EW Nutrition divided the process into the following steps, which can serve as a template for a successful development process:

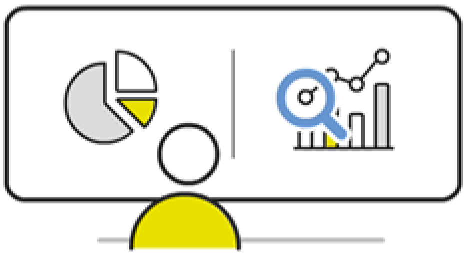
1. Reviewing customer needs
2. Active ingredient selection
3. Technical formulation
4. Application development and scale-up
5. Performance tests
6. Safety and regulatory validation

Understanding customer needs

The most important point in developing a feed additive is customer-centricity. Understanding the challenges and needs of producers is crucial to developing feed additive solutions.

In a first step, additive producers need to evaluate and *quantify* customer needs wherever possible. This is achieved through communication and literature review: Producers, key opinion leaders, and research partners are interviewed, and their challenges are listed. In the next step, those challenges are further analyzed using scientific literature. In a final step, the customer needs are ranked according to their impact on the customer’s profitability.

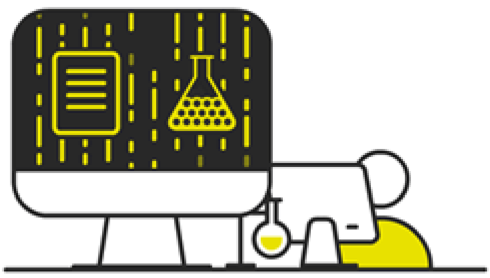
Subsequently, the *minimum requirements* for the new feed additive are derived. For phytogenic feed additives, this might be, for instance, something like “Improving animal performance and reducing antibiotic use while increasing profitability”. The selected key performance parameters might be, for example, feed efficiency improvements in broilers.



Market research

Meeting unmet needs

Once the customer needs have been understood, the next phase of the development starts. Based on the intended mode of action, certain phytomolecules are chosen based on their described properties. In our example, this might be an antimicrobial mode of action that targets enteropathogenic bacteria in broilers, supporting gut health.



Laboratory research

In this *in-vitro* process, the selected individual compounds will be tested for their respective antimicrobial efficacy using MIC and MBC testing. Those tests are run using high-purity compounds.

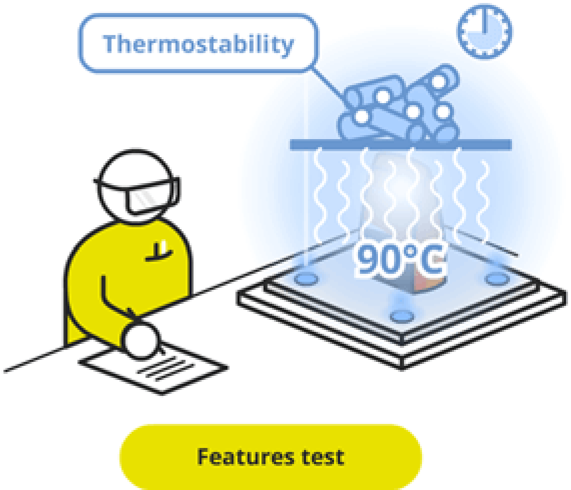
Features test

The tests will be conducted using various relevant field strains like *E. Coli, S. enterica* or *C. perfringens*. In the next step, the testing will be repeated with commercially available ingredients. The most promising compounds will be tested in more complex mixtures.

Modern phytogenic feed additives are based on the concept of combining different phytomolecules to attack bacteria in diverse ways, with their antimicrobial effects being multi-modal. This mode of action is crucial because it makes it very unlikely that bacteria can develop resistance to combinations of phytomolecules, as they do to antibiotics.

Selecting the right form of application

Feed processing is often a challenge for additives. Many phytomolecules are highly volatile and prone to volatilization and high temperatures. Especially non-protected phytogenic products are negatively affected by high pelleting temperatures and long retention times of the feed in the conditioner. The results are losses in activity.

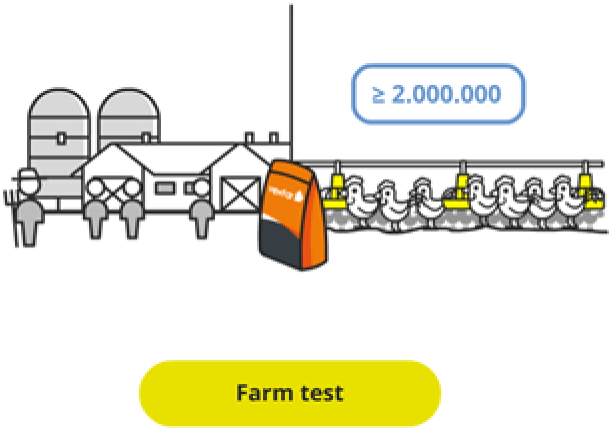


Therefore, the development of appropriate delivery systems is a preemptive method to ensure the release of the effective compounds where they should be released – in the gut of the animals. Those delivery systems can utilize emulsifiers when applying the additive via the water for drinking, or encapsulation technologies when the new additive is administered via feed.

Due to the importance of mixability, flowability, and pelleting stability for the performance of the feed additives, the exact types of emulsifiers, carrier, and technologies used in their production is often considered corporate intellectual property.

The importance of *in-vivo* evaluations

In one of the last steps of the development, the newly developed feed additive prototype needs to prove its safety and efficacy in the animal. Hence the need to run evaluation studies to confirm the mode of action chosen in the initial lab phase. Typically, the additive will be tested in the target species in in-house and external research institutes.



For a phytogenic feed additive, that might entail comparing its effect on body weight gain, feed efficacy, and gut health against different control groups. Additionally, the newly developed feed additive might be compared to existing additives to get a better understanding of its capabilities.

Dose-finding studies are conducted to verify the chosen dose recommendation and additional overdosing studies are conducted to prove the safety of the additive for both animals and consumers. In certain markets or regulatory environments, additional studies might be required. Those can contain environmental safety assessments or proof that the new additive does not create residues in animal products.

Case study: Ventar D

For Ventar D, the process followed these steps meticulously, in agile iterative development loops that went from the customer need to formulation, testing, scale-up, in-house and external trials, and finally production.

These steps ensured that the final product that reaches the customer’s doorstep delivers on the expectations – and more.

Scale-up & Distribution

Choose your phytogenic products wisely

The plethora of (phytogenic) feed additives in the market leaves producers with many options to choose from. However, only scientifically developed feed additives can be relied upon to optimize both animal health and production profitability. It is important to select reliable feed additive producers who developed their phytogenic product with the customers’ challenges in mind and went through all the steps necessary to create a high-performing and safe additive.