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PREVENTING POST WEANING DIARRHEA IN PIGS BY USING BIOACTIVE COMPOUNDS

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ABSTRACT

Post-weaning diarrhea (PWD) is a significant challenge in pig production, driven by physiological, immunological, and microbiological disruptions during the weaning transition. Conventional management strategies, such as antibiotics and zinc oxide, face increasing regulatory and environmental constraints, highlighting the need for alternative solutions. Tannins, plant-derived polyphenols with antimicrobial, gut-modulating, and anti-inflammatory properties, have emerged as a promising tool for mitigating PWD. In vitro studies demonstrate tannins' ability to enhance intestinal barrier integrity, reduce pathogenic bacterial adhesion, and suppress inflammatory responses, addressing key drivers of PWD. Additionally, their modulation of gut microbiota fosters a healthier microbial balance. While experimental and mechanistic studies support tannins' efficacy, further research is needed to optimize their application and address variability in their effects. Tannins offer a sustainable, natural alternative to conventional prophylactics, potentially improving piglet health and productivity while aligning with environmental and regulatory goals.

INTRODUCTION

The weaning phase is one of the most critical periods in a pig's life, where significant physiological, nutritional, and environmental changes occur. This transition from a milk-based diet to solid feed is often accompanied by disruptions in gut physiology, immunity, and microbiota, resulting in post-weaning diarrhea (PWD) (Guevarra et al., 2018; Tang et al., 2022). The condition is characterized by frequent watery faces, weight loss, and dehydration, leading to high piglet mortality rates. Traditionally, PWD has been managed using antibiotics and pharmacological levels of zinc oxide. However, the growing global concerns regarding antimicrobial resistance and the environmental impact of zinc oxide have necessitated the development of alternative solutions. Bioactive compounds, particularly tannins, have emerged as a promising strategy for mitigating PWD. These plant-derived polyphenols exhibit antimicrobial, gut-modulating, and anti-inflammatory properties, providing a natural and sustainable alternative to conventional prophylactic measures (Girard & Bee, 2020).

This short review synthesizes findings from experimental studies and mechanistic investigations to evaluate the potential of tannins in PWD prevention. The discussion integ-

rates evidence from recent research, including studies on chestnut tannins and harmonized in vitro digestion models, with practical insights into their application in piglet diets.

PATHOPHYSIOLOGY OF POST-WEANING DIARRHEA

Post-weaning diarrhea has a multifactorial etiology, encompassing physiological, immunological, and microbiological disturbances. This complexity renders its effective management a significant challenge. The weaning process introduces significant and abrupt changes to the gastrointestinal tract (GIT) as piglets undergo a dietary transition from a predominantly milk-based diet to one based on solid feedstuffs. This dietary shift occurs concurrently with social and environmental stressors, which collectively place substantial demands on the digestive and immune systems of the piglets. Consequently, the physiological adjustments that are necessary during this phase frequently exceed the capacity of the piglets to maintain intestinal homeostasis, thereby creating an environment favorable to diarrhea.

One of the most significant changes that occurs following weaning is the disruption of intestinal morphology and function. The small intestine, which plays a critical role in digestion and nutrient absorption, undergoes transient structural alterations, including villous atrophy and crypt hyperplasia. The reduction in absorptive surface area caused by villous atrophy impairs the intestine's ability to effectively process nutrients. Concurrently, crypt hyperplasia, which involves an increase in the number of immature cells in the intestinal crypts, represents a compensatory mechanism to replace the damaged villous cells. However, this regeneration often occurs at the expense of functional maturity, resulting in an immature epithelial layer that cannot fully support digestive or absorptive processes (Tang et al., 2022).

In addition to these structural changes, there is a marked reduction in the activity of brush border enzymes, which are essential for nutrient digestion. The diminished activity of enzymes such as lactase and sucrase aggravates malabsorption, leading to the accumulation of undigested nutrients in the intestinal lumen (Heo et al., 2013). This accumulation creates an osmotic imbalance, where water is drawn into the gut lumen, contributing to the watery feces characteristic of PWD. The presence of undigested nutrients serves to further encourage microbial fermentation in the hindgut, thereby contributing to increased production of toxic by-products, including branched-chain fatty acids, indole, phenols, ammonia, and biogenic amines, within the GIT (Heo et al., 2013).

The difficulties associated with nutrient absorption are worsened by disturbances in intestinal permeability, which is frequently referred to as "leaky gut." During the weaning period, the intestinal epithelial barrier becomes compromised, allowing the translocation of toxins and antigens into the bloodstream. This increased permeability is associated with a reduction in the expression of tight junction proteins, such as Zonula Occludens and Claudin, which are critical for maintaining the integrity of the intestinal barrier. As the barrier function weakens, the risk of systemic inflammation and secondary infections rises, further complicating the clinical management of PWD (Hu et al., 2013).

Gastric function also plays a significant role in the pathophysiology of PWD. The transition from liquid to solid feed is associated with a reduction in gastric acid production, leading to an elevated gastric pH. The elevated pH environment reduces the stomach's ability to prevent ingested pathogens from surviving, creating favorable conditions for their proliferation. Gastric stasis or the slowing of stomach emptying, is another challenge during this period. The delayed passage of food through the stomach can lead to bacterial overgrowth and fermentation, increasing the microbial load of pathogens that enter the small intestine (Heo et al., 2013).

Microbiological changes during weaning are another critical component of PWD. The gut microbiota, which is responsible for maintaining a healthy microbial balance and protecting against pathogens, is significantly altered. Beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* are often diminished, while opportunistic pathogens, including enterotoxigenic *Escherichia coli* (ETEC), proliferate. Enterotoxigenic *Escherichia coli* is particularly problematic, as it adheres to intestinal epithelial cells using fimbrial adhesins such as F4 and F18. Once adhered, ETEC secretes heat-labile and heat-stable enterotoxins, disrupting the normal electrolyte transport. These toxins stimulate the secretion of chloride ions while inhibiting sodium absorption, leading to excessive water secretion into the intestinal lumen and the onset of diarrhea (Buddle & Bolton, 1992; Pluske et al., 2002).

The immunological impact of weaning also plays a critical role in the development of PWD. The removal of maternal antibodies provided through milk leaves piglets immunologically vulnerable. The immature immune system struggles to respond effectively to the sudden influx of environmental and dietary antigens, resulting in increased susceptibility to infection. This is further complicated by the upregulation of pro-inflammatory cytokines, which contribute to the inflammation and damage observed in the intestinal epithelium (De et al., 2017; Hu et al., 2013). The inflammatory response impairs gut permeability, creating a vicious cycle where the compromised barrier allows further infiltration of pathogens, perpetuating the condition.

In regions where pathogenic pressures are high, such as on farms with suboptimal hygiene practices, the prevalence of ETEC-related PWD is particularly concerning. Studies have shown that ETEC is responsible for up to 43% of PWD cases in Swiss pig farms, highlighting the pathogen's significant role in disease prevalence (Schubnell et al., 2016). The high shedding rates of ETEC in infected piglets contribute to its rapid spread within herds, emphasizing the need for targeted interventions that can interrupt its pathogenesis.

In conclusion, the pathophysiology of PWD is a multifaceted process involving disruptions to intestinal structure, function, and microbiota, compounded by immune system immaturity and stress-induced vulnerabilities. These changes collectively create an environment that supports the proliferation of pathogens like ETEC, whose toxins drive the electrolyte imbalances and fluid loss that characterize PWD. Understanding these interconnected mechanisms is essential for developing effective prevention and treatment strategies that address the root causes of the condition.

THE ROLE OF TANNINS IN THE PREVENTION OF POST-WEANING DIARRHEA

Due to their diverse chemical composition, tannins, which are plant-derived polyphenolic compounds, have received considerable attention in recent years. Their potential for alleviating the challenges associated with PWD in piglets has become an area of significant interest. Their multifunctional properties, including antimicrobial, antioxidant, and gut-modulating effects (Maugeri et al., 2022; Mueller-Harvey, 2006), position them as a promising alternative to antibiotics and pharmacological levels of zinc oxide in the prevention of PWD. By targeting multiple aspects of the condition's pathophysiology, tannins offer a comprehensive approach to maintaining gut health and reducing the impact of pathogens such as ETEC.

The antimicrobial effects of tannins are among their most well-documented properties, rendering them especially valuable in environments susceptible to pathogenic challenges. Tannins exert their antimicrobial action through three primary mechanisms: disruption of bacterial cell membranes, denaturation of bacterial proteins, and interference with microbial enzymatic activity (Scalbert, 1991). In the context of ETEC-related PWD, tannins have been demonstrated to be particularly effective at preventing bacterial adhesion to the intestinal epithelium. As previously mentioned, ETEC relies on fimbrial F4 or F18 adhesins to attach to glycoprotein receptors on the intestinal brush border. Tannins have been shown to bind to these receptors or fimbrial structures, preventing ETEC from adhering to the epithelial cells and thereby interrupting its pathogenesis and reducing the bacterial load in the gut (Girard & Bee, 2020).

Beyond their direct antimicrobial effects, tannins also modulate the gut microbiota, fostering a healthier balance of microbial populations. Studies have shown that tannins reduce the abundance of pathogenic bacteria such as ETEC and *Clostridium perfringens* while promoting beneficial species like *Lactobacillus* and *Bifidobacterium*. This modulation of the microbiota contributes to enhanced gut resilience, as beneficial microbes compete with pathogens for nutrients and adhesion sites, produce antimicrobial metabolites and stimulate the host's immune response. The ability of tannins to shift the gut microbiota toward a more favorable composition is particularly important during the weaning period when disruptions to the microbial ecosystem are common (Puljula et al., 2020).

Another crucial function of tannins in preventing PWD is their potential to alleviate the inflammatory response in the intestinal tract. Tannins have anti-inflammatory properties due to their ability to inhibit the production of pro-inflammatory cytokines, including tumour necrosis factor-alpha and interleukin-6 (Ekambaram et al., 2022). These properties help maintain the structural and functional integrity of the intestine, thereby facilitating a more rapid recovery from disturbances caused by the weaning process and pathogen exposure.

The benefits of tannins extend to their influence on the digestibility and utilization of nutrients. Although tannins have been the subject of criticism due to their protein-binding properties, which can reduce protein digestibility, recent studies indicate that these effects are dose-dependent and can be managed through the formulation of a care-

fully designed diet. Furthermore, the interaction of tannins with dietary proteins may result in a reduction in the availability of nutrients for pathogenic bacteria, thereby limiting their growth and activity in the gut. This selective inhibition of pathogenic bacteria without disturbing beneficial microbes highlights the potential of tannins as a dietary tool. One of the most compelling demonstrations of tannins' efficacy is evidenced by studies examining the effects of chestnut tannin extracts on weaned piglets. In an experiment conducted by Girard et al. (2020), the effects of dietary supplementation with chestnut tannin extracts were investigated in piglets experimentally infected with ETEC F4. This study found that piglets receiving a chestnut extract rich in hydrolysable tannins exhibited significantly lower fecal scores, indicative of reduced diarrhea severity, compared to untreated controls (Figure 1). Additionally, ETEC shedding in the feces was markedly reduced in the tannin-supplemented group, demonstrating the antimicrobial properties of tannins against key pathogens associated with PWD. Beyond their impact on diarrhea, tannin supplementation was associated with improved growth performance, as evidenced by a 20% increase in feed intake and a 34% improvement in average daily gain compared to the control group (Figure 2). These findings underscore the dual benefits of tannins in enhancing health outcomes and supporting productivity in weaned piglets.

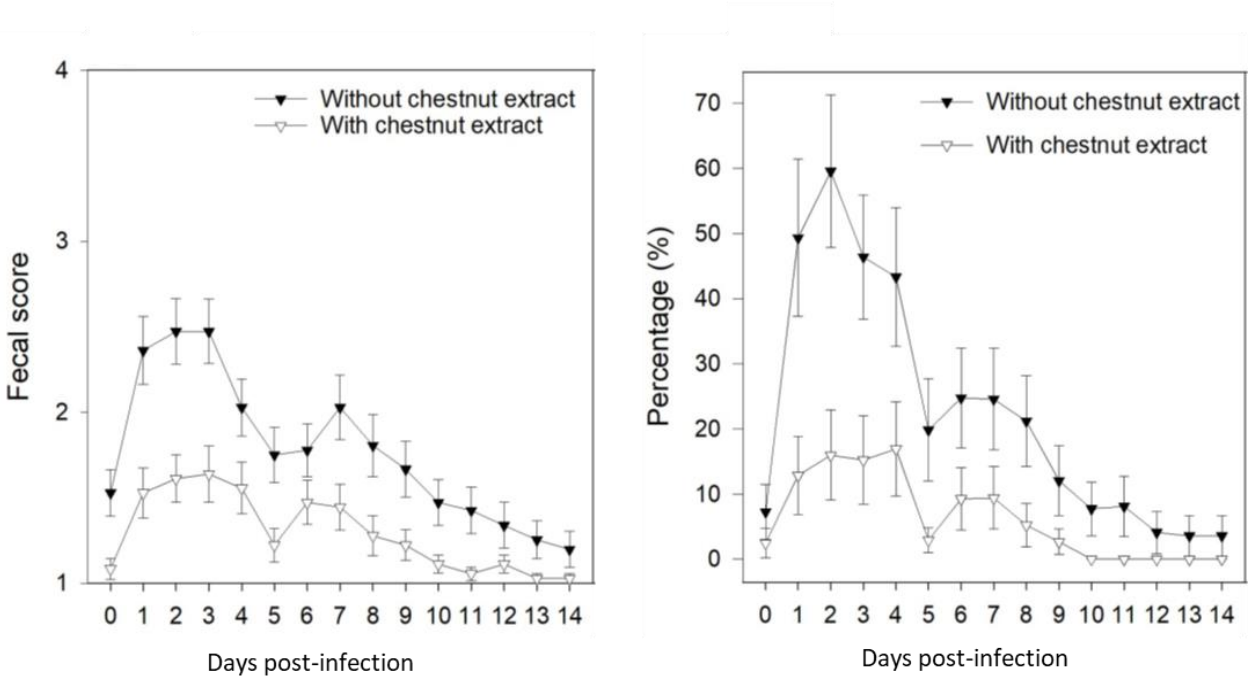

Figure 1 Effects of chestnut extract supplementation on the fecal score and the percentage of piglets with diarrhea from days 0–14 post-infection. Fecal scores ≥ 3 were termed diarrhea. Pigs (N = 36) in the unsupplemented group had *ad libitum* access to a control standard starter diet, which was formulated according to the Swiss feeding recommendations for pigs (Agroscope, 2017). Pigs (N = 36) in the chestnut extract supplemented group had *ad libitum* access to the chestnut extract supplemented diet, in which wheat straw in the unsupplemented diet was substituted for with 2% chestnut extract (Silvafeed Nutri P/ENC for Swine; Italy). P-values for the main effects: chestnut extract supplementation: P<0.001; Time: P < 0.001 for each; source: Girard et al. (2020)

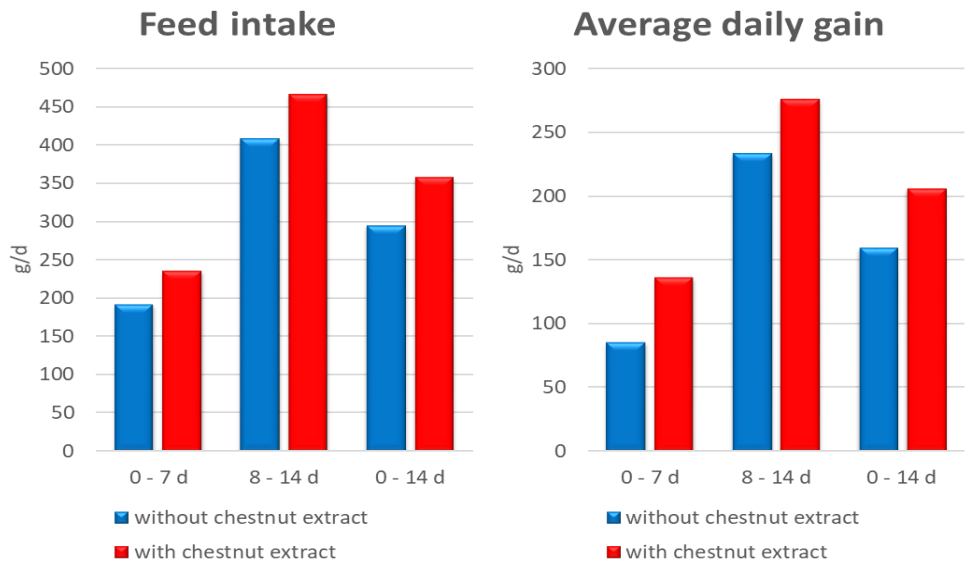

Figure 2 Feed intake (g/day/pen) and average daily gain (g/day) from days 0–7, 8–14, and 0–14 post-infection of piglets with *ad libitum* access to an unsupplemented starter diet or a starter diet supplemented with 2% chestnut extract. In the chestnut extract-supplemented diet, 2% chestnut extract (Silvafeed Nutri P/ENC for Swine, Italy) replaced wheat straw from the unsupplemented diet. P-values for the main effects: chestnut extract supplementation: $P \leq 0.04$; Time: $P < 0.001$ for each; source: Girard et al. (2020)

In conclusion, tannins play a multifaceted role in the prevention of PWD by targeting its key pathophysiological mechanisms. Through their antimicrobial effects, modulation of gut microbiota, enhancement of intestinal barrier function, and anti-inflammatory properties, tannins can provide comprehensive protection against the disruptions caused by weaning. Their ability to simultaneously address pathogen load, gut health, and nutrient utilization makes them an invaluable tool in the pursuit of sustainable and effective PWD management strategies.

MECHANISTIC INSIGHTS FROM *IN VITRO* STUDIES

The mechanistic effects of tannins on GIT health and pathogen mitigation have been extensively studied using *in vitro* models. These controlled experimental setups, including harmonized digestion models and Ussing chambers, offer critical insights into how tannins interact with the GIT and their potential to prevent PWD (Reggi et al., 2020; Yu et al., 2020). By simulating the physiological environment of the piglet's gut, these studies provide valuable data on tannins' impact on intestinal integrity, and their role in modulating gut function.

The use of Ussing chambers has illuminated how tannins affect intestinal barrier function. These models allow researchers to measure parameters such as trans-epithelial electrical resistance (TEER), which is an indicator of epithelial barrier integrity. In experiments involving digested chestnut tannins, we observed a significant increase in TEER values, suggesting that tannins strengthen the intestinal barrier (Figure 3; Tretola et al. (2022)). A tighter epithelial barrier is crucial in preventing the translocation of pathogens, toxins, and other harmful substances from the gut lumen into systemic circulation.

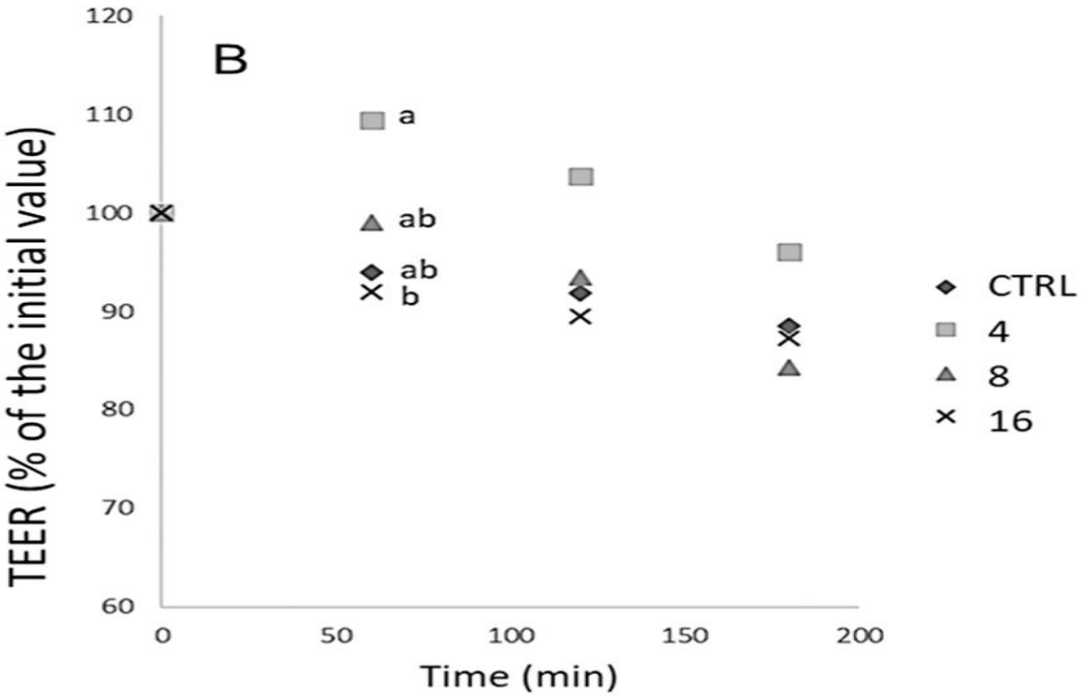

Figure 3 Changes in trans-epithelial resistance (TEER; expressed as % of the basal TEER) induced by luminal application of three dilutions (4 = 1:4; 8 = 1:8; 16 = 1:16) of digested chestnut extracts (v/v) (sample to apical Kreb's Ringier buffer) to the porcine intestinal mucosa. Different letters indicate a significant ($P < 0.05$) statistical difference. Data for each dilution were obtained in five ($n = 5$) independent experiments (source: Tretola et al. (2022)

The ability of tannins to modulate tight junction proteins, such as Zonula Occludens 1 and Occludin, has also been confirmed through *in vitro* studies (Yu et al., 2020). These proteins are essential for maintaining the cohesion of epithelial cells, forming a selective barrier that regulates the passage of molecules between the gut lumen and the blood-stream. When intestinal tissues are exposed to digested tannin extracts, an upregulation of tight junction protein expression is observed, correlating with improved barrier integrity (Figure 4). This effect is particularly evident in tissues compromised by stressors such as indomethacin, a nonsteroidal anti-inflammatory drug known to weaken tight junctions. In the presence of tannins, the damage caused by indomethacin is mitigated, demonstrating the restorative potential of tannins under adverse conditions (Figure 5; Tretola et al. (2022)). The digestion and bioavailability of tannins have also been explored using the harmonized *in vitro* digestion model INFOGEST (Brodkorb et al., 2019). This model simulates the digestive processes that occur in the stomach and small intestine allowing researchers to assess how tannins are broken down and their metabolites are formed. Studies have shown that tannins undergo significant degradation during digestion, with the majority of their bioactivity localized to the gut. The polyphenolic metabolites produced during tannin degradation retain gut-modulating properties, suggesting that even after partial breakdown, tannins continue to exert beneficial effects (Tretola et al., 2023).

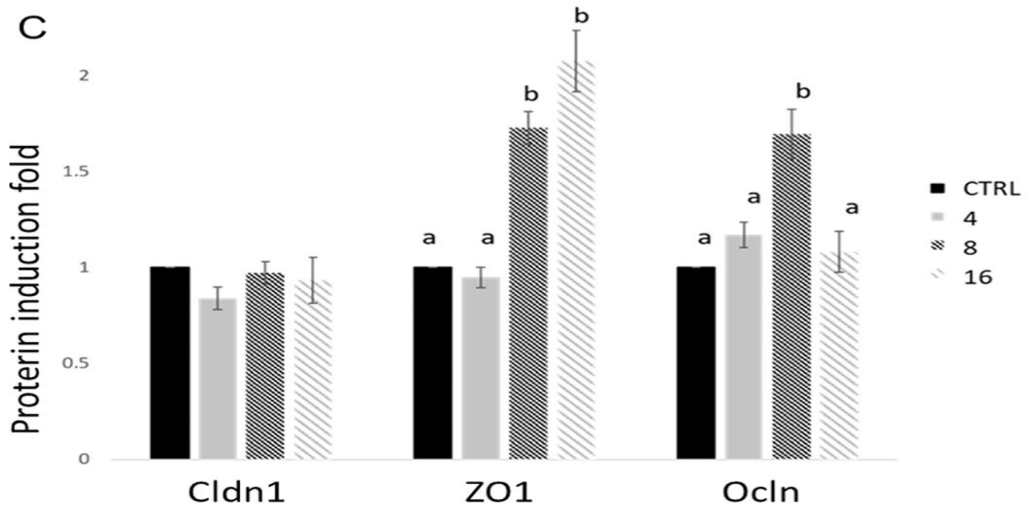

Figure 4 Tight junction protein induction fold in tissue incubated for 180 min with three digested chestnut extracts (CHEs) dilutions (4 = 1:4; 8 = 1:8; 16 = 1:16 v/v sample to apical Kreb's Ringier buffer). CLDN1: claudine-1; ZO1: zonula occludens-1; OCLN: occludin. Data are LS-means ± standard deviations. Data were obtained by at least five independent experiments. [ab] Different superscripts indicate a significant ($P < 0.05$) statistical difference (source: Tretola et al., 2022)

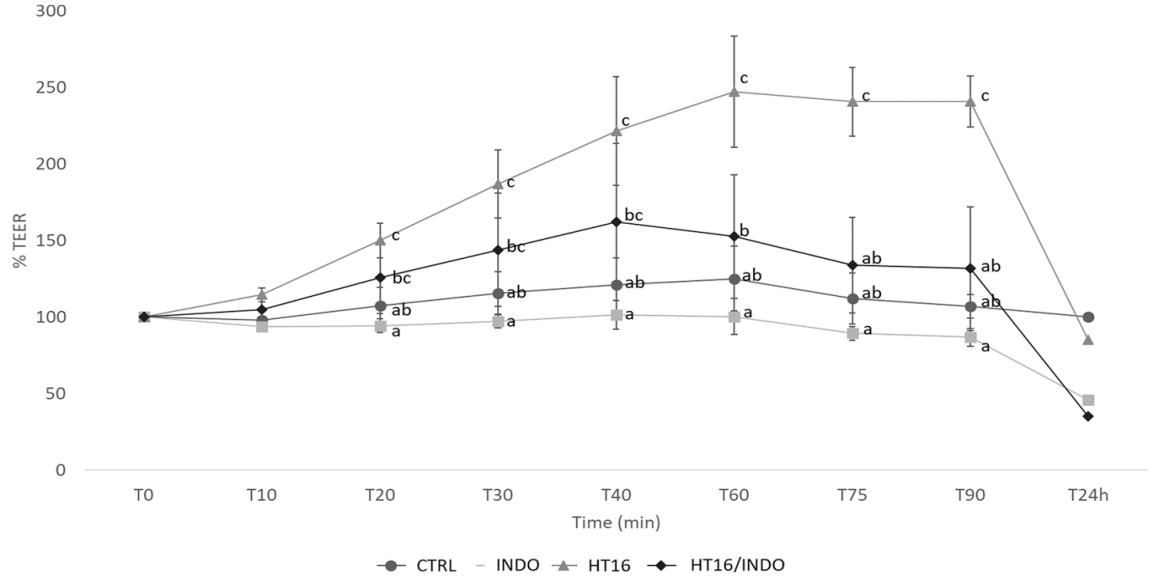

Figure 5 Effect of indomethacin (INDO, 250 µM) on the barrier function of pig jejunum and protection by digested CHE at a 1:16 dilution (v/v) (sample to apical Kreb's Ringier buffer). 16/INDO = digested CHE diluted 1:16 (v/v) (sample to apical Kreb's Ringier buffer) in the presence of indomethacin; 16 = digested CHE diluted 1:16 (v/v). [abc] Different superscripts indicate a significant ($P < 0.05$) statistical difference (source: Tretola et al., 2022)

Interestingly, the ability of tannins to complex with dietary proteins has implications for their activity in the gut. *In vitro* experiments assessing protein digestibility have demonstrated that tannins reduce the enzymatic breakdown of proteins (Figure 6) by binding to them and/or inhibiting proteolytic enzymes (Tretola et al., 2022). While this interaction may reduce protein digestibility, it may also, as previously suggested, limit the availability of proteins to pathogenic bacteria, effectively starving them and inhibiting their growth.

Finally, the anti-inflammatory properties of tannins have been elucidated through *in vitro* experiments measuring cytokine production. In response to inflammatory stimuli,

including bacterial toxins, tannins reduce pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), alleviating epithelial inflammation. This anti-inflammatory effect reduces the damage to intestinal tissues caused by excessive immune activation, allowing for faster recovery of gut homeostasis (Piazza et al., 2022).

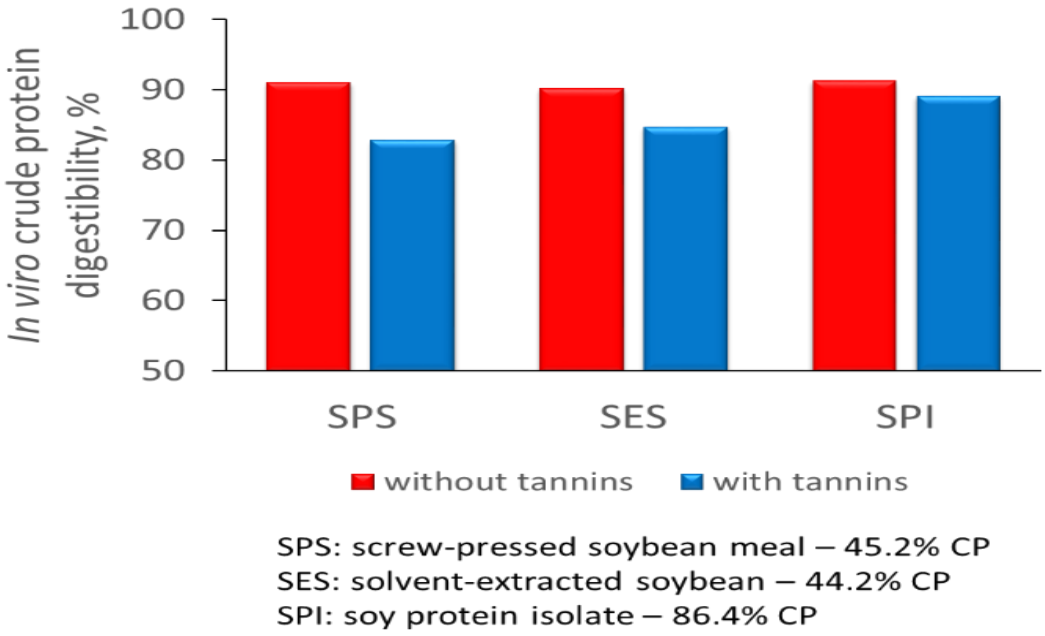

Figure 6 Effects of 30 g/kg as-fed supplemented chestnut extract on *in vitro* digestibility of the crude protein of soybean meal products and soy protein isolate (source: Tretola et al. (2022)

In summary, *in vitro* studies have provided critical mechanistic insights into how tannins mitigate the key drivers of PWD. Tannins enhance intestinal barrier integrity by increasing TEER and upregulating tight junction proteins, while also mitigating stressor-induced damage. During digestion, tannins are broken down into metabolites that inhibit pathogen growth by limiting protein availability. Additionally, tannins reduce inflammation by suppressing pro-inflammatory cytokines, promoting gut homeostasis and recovery. These findings highlight tannins' potential to protect and restore gut health.

PRACTICAL CONSIDERATIONS

The incorporation of tannins into piglet diets must consider their bioavailability and potential interactions with other dietary components. Although tannins exhibit low systemic bioavailability due to degradation in the digestive tract, their localised effects in the gut are sufficient to confer health benefits. The cost of tannin supplementation ranges from 0.14 to 0.43 euros per piglet for a 19-day feeding period, making it an economically viable alternative to antibiotics and zinc oxide. However, their protein-binding properties can reduce nutrient digestibility, necessitating careful diet formulation.

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Despite significant advancements in understanding the role of tannins in preventing PWD, several knowledge gaps remain that must be addressed to optimize their application in pig nutrition and health management. Addressing these gaps is critical for refining the use of tannins as an alternative to antibiotics and zinc oxide, ensuring their efficacy, sustainability, and economic feasibility in commercial pig production systems.

One of the most pressing gaps is the variability in tannin efficacy between studies: there is a need for a deeper understanding of how different tannin types, sources and chemical structures affect their biological activity. Hydrolysable tannins and condensed tannins have different chemical properties and mechanisms of action, but their comparative efficacy under different production conditions is not fully understood. In addition, the impact of variability in tannin source - such as chestnut, quebracho or grape extracts - on antimicrobial activity, digestibility and gut modulation remains underexplored. Standardisation of tannin formulations and the development of reliable metrics to assess their bioactivity are essential to ensure consistent results in commercial applications.

The interaction of tannins with other dietary components represents another area of uncertainty. Tannins are known to bind proteins and other macronutrients, which can reduce nutrient availability. However, this protein-binding property also limits nutrient availability to pathogenic bacteria, contributing to tannins' antimicrobial effects. Striking a balance between these competing outcomes is critical for optimizing diet formulation. Research is needed to explore how tannins interact with various protein sources, feed additives, and bioactive compounds, such as organic acids, probiotics, and essential oils. Understanding these interactions could pave the way for synergistic combinations that enhance the overall efficacy of tannins while minimizing potential drawbacks.

A significant knowledge gap also exists regarding the bioavailability and metabolism of tannins within the gastrointestinal tract. *In vitro* digestion models have provided valuable insights into the degradation of tannins and the formation of bioactive metabolites, but *in vivo* validation of these findings is limited. It remains unclear how these metabolites interact with intestinal tissues, microbiota, and immune cells, particularly in the lower gut. Research should focus on elucidating the fate of tannins during digestion, the bioactivity of their metabolites, and their contribution to the observed health benefits in piglets.

Another area requiring attention is the mechanistic understanding of how tannins modulate the gut microbiota. While evidence suggests that tannins selectively inhibit pathogenic bacteria while promoting beneficial microbes, the underlying mechanisms driving these changes are not fully understood. Advanced techniques, such as metagenomics and metabolomics, could be employed to investigate how tannins influence microbial community structure, function, and metabolic activity. These studies could also explore the potential for tannins to promote the production of beneficial metabolites, such as short-chain fatty acids, which are known to support gut health and barrier integrity.

The anti-inflammatory properties of tannins present another promising avenue for research. While *in vitro* studies demonstrate their ability to suppress pro-inflammatory cytokines, the translation of these findings to *in vivo* contexts remains underexplored. Understanding how tannins influence systemic and localized immune responses in weaned piglets could reveal new applications for tannins in managing not only PWD but also other inflammatory gut disorders. Investigating the dose-dependent effects of tannins on immune modulation and identifying the optimal concentrations for achieving therapeutic benefits without compromising growth performance are crucial steps forward.

Economic and environmental considerations also warrant further investigation. While tannins are increasingly recognized as a sustainable alternative to conventional prophylactics, comprehensive life cycle assessments are needed to quantify their environmental impact relative to antibiotics and zinc oxide. These assessments should account for factors such as tannin extraction, production, transportation, and on-farm use. Additionally, economic analyses should evaluate the cost-effectiveness of tannin supplementation under varying market conditions, production systems, and regulatory frameworks. Identifying strategies to reduce production costs and improve the scalability of tannin-based solutions will be critical for their widespread adoption.

Finally, there is a need for field trials that replicate real-world farming conditions. Most current research is conducted under controlled experimental setups, which may not fully capture the complexities of commercial pig farming. Field studies could provide valuable insights into the practical challenges of incorporating tannins into weaning diets, such as variability in feed intake, differences in baseline gut health, and interactions with farm-specific management practices. These trials could also evaluate the impact of tannin supplementation on herd-level outcomes, including disease incidence, antibiotic use, and overall productivity.

In conclusion, while tannins hold significant promise as a natural and sustainable solution for managing PWD, addressing the existing knowledge gaps is essential for unlocking their full potential. Future research should prioritize long-term studies, standardization of tannin formulations, exploration of dietary interactions, and in-depth mechanistic investigations into their effects on the gut and immune system. By advancing our understanding of tannins and refining their application strategies, we can contribute to the development of more sustainable and effective approaches to pig health management.

CONCLUSIONS

The growing restrictions on antibiotics and zinc oxide in pig production underscore the need for alternative strategies that are both effective and sustainable. Tannins offer a promising solution for managing PWD through their antimicrobial, gut-modulating, and barrier-enhancing properties. By addressing knowledge gaps and optimizing their application, tannins could play a pivotal role in the future of sustainable swine production, ensuring animal health and welfare while meeting environmental and regulatory goals.

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