# **Marine Polysaccharides and Pigs Weaning**

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Weaning is the most crucial event in commercial pig farms in terms of animal productivity and health. The newly weaned pig not only transits from milk to a solid and more complex diet, but is also subjected to additional stressors including separation from sow and littermates, co-mingling with unknown pigs, adaptation to new environmental settings, and increased pathogen exposure. All these stressors result in reduced feed intake, lasting up to 48 h post-weaning, which is the main driver of the observed gastrointestinal dysfunction, poor performance, and post-weaning diarrhoea (PWD). Marine polysaccharides from macroalgae and chitin provide an interesting source of novel bio-actives and are interesting group of natural dietary supplements for use in pig nutrition due to their prebiotic, antibacterial, and immunomodulatory activities. Hence, they offer great potential as preventatives and prophylactics in pig diets.

Keywords: pig ; weaning ; marine polysaccharides ; dietary supplement

### 1. The Negative Biological Effects Associated with Weaning

Weaning is a critical period in pig husbandry. In the wild, pigs naturally wean at 10-12 weeks of age, which coincides with the almost complete development and maturation of the gastrointestinal tract (GIT); in contrast, commercial weaning occurs at 2-4 weeks of age. Commercial weaning induces transient alternations to the gastrointestinal tract (GIT). These morphological and physiological changes are most likely driven by the post-weaning reduction in feed intake. As feed intake resumes, the GIT undergoes a period of intestinal maturation [1]. The villi and crypts that line the epithelium of the small intestine are essential for the digestive and absorptive processes <sup>[2]</sup>. Dietary composition has marginal effects on the small intestinal morphology of weaned pigs, with the level of feed intake found to be the most important determinant of mucosal function and integrity [3]. Food deprivation leads to a lack of luminal stimulation. This results in a rapid decrease in villous height <sup>[2]</sup>. Villous height is at its lowest after 2-5 days post-weaning, resulting in a reduced ability to absorb nutrients <sup>[4]</sup>. Villous height starts to recover in feed deprived piglets 4 days after feeding is restarted and can take more than 10 days to completely recover [5]. The villus surface area is also altered in the post-weaning period. Pre-weaning, villi are dense and finger-like, while the weaning transition changes the villi into predominantly smooth, compacted, and tongue-shaped villi <sup>[6]</sup>. As well as the intestinal morphology being affected by weaning, gastrointestinal functionality is also impaired as indicated by the reduction in brush border enzymes such as lactase, sucrase, and peptidases, and the disturbances in nutrient absorption and electrolyte secretion with the latter also contributing to the weaning-associated diarrhoea [4][5][7]. The resulting maldigestion and malabsorption leads to the weight loss observed during the first 4–5 days post-weaning [8][9].

A compromised intestinal barrier characterised by increased paracellular permeability, reduced transepithelial resistance, and reduced gene expression of tight junction proteins is additionally observed at the immediate post-weaning period and may lead to overstimulation of the immune system due to the increased presence of dietary and microbial antigens <sup>[10][8]</sup> <sup>[11]</sup>. The activation of the immune system further contributes to the reduced intestinal barrier function and diarrhoea in newly weaned pigs. Several studies have reported infiltration of immune cells such as lymphocytes, macrophages, and mast cells in the lamina propria <sup>[12][10]</sup>, increased expression of genes encoding for inflammatory cytokines such as tumour necrosis factor (*TNF*), interferon gamma (*INFG*), and interleukins *IL1B* and *IL6* <sup>[11][13]</sup>, and activation of several pathways associated with immune responses <sup>[9]</sup> in the small and large intestine of pigs in the immediate post-weaning period.

The composition of the GIT microbiota is also altered in response to the weaning stress, diet alteration, reduced feed intake, and gastrointestinal dysfunction. Several studies have investigated the weaning-induced compositional and functional changes in the GIT microbiota of pigs <sup>[14][15][16][17][18]</sup>. *Lactobacillus* spp. are amongst the intestinal bacterial populations that are frequently monitored during the post-weaning period due to their high abundance in pigs and known beneficial effects. A significant reduction of this population, as well as shifts of the dominant strains, has been observed in the ileum of pigs post-weaning <sup>[19][20]</sup>. The decrease in the *Lactobacillus* spp. is transient, as seen in the ileum and faeces

of weaned pigs and is followed by restoration or even an increase in its numbers and dominance of strains that utilise complex carbohydrates <sup>[14][15][18][20][21]</sup>. *Enterobacteriaceae* is an important indicator of dysbiosis in the faeces of newly weaned pigs, as an increase in the counts of this bacterial family was associated with higher incidence of diarrhoea <sup>[22]</sup>. Nevertheless, the increase in *Enterobacteriaceae* relative abundance is transient under normal circumstances, as this bacterial population and its members (*Escherichia/Shigella*) are minor constituents of the maturing GIT microbiota <sup>[15][16]</sup> <sup>[20][21]</sup>. The reduction in *Bacteroides* spp. and increase in *Prevotella* spp. is another common change in the faecal microbiota of weaned pigs that is probably associated with the transition from milk mono- and oligo-saccharides to plant-derived polysaccharides <sup>[14][15][17]</sup>. Weaning-induced gastrointestinal dysbiosis is considered a key contributor to the development of diarrhoea and predisposes pigs to PWD <sup>[23]</sup>. The most common causative agent of PWD is the  $\alpha$ -haemolytic Gram-negative enterotoxigenic *E. coli* (ETEC) that colonises the epithelium of the small intestine via F4 (ab, ac, ad) and F18 (ab, ac) fimbriae and non-fimbrial AIDA (adhesin involved in diffuse adhesion) <sup>[24][25]</sup>.

### 2. Traditional and Alternative Dietary Interventions

Dietary interventions are one strategy with which to prevent or alleviate dysbiosis and its associated impact on the growth and health of pigs. A diverse range of feed additives have been studied as preventatives and prophylactics in pig diets. An array of natural compounds have been investigated as alternative strategies to AGPs and ZnO such as yeast  $\beta$ -glucans <sup>[26][27]</sup>, mannan-oligosaccharides <sup>[28]</sup>, prebiotics such as galacto-oligosaccharides <sup>[29]</sup>, organic acids <sup>[30][31]</sup>, probiotics <sup>[32]</sup>, spray dried plasma proteins <sup>[33]</sup>, exogenous feed enzymes <sup>[34]</sup>, and essential oils <sup>[35]</sup>. These compounds can support the microbial composition, health, and growth performance of pigs. However, there is only a limited number of compounds that result in a similar improvement in growth performance and reduced the occurrence of diarrhoea compared to in-feed AGP or ZnO. Therefore, there is still a need to identify natural bio-actives with growth promoting and immunomodulatory properties as suitable substitutes to AGPs and ZnO. It is also critical to explore the underlying mechanisms when evaluating the functional properties of feed ingredients and feed additives <sup>[36]</sup>. Key components of GIT function that should be considered include absorptive capacity (villi architecture and nutrient transporters expression), digestive capacity (activity of pancreatic and brush-border enzymes), physical and chemical barriers, microbial load, microbial diversity, and immune function.

### 3. Marine Polysaccharides

Marine macroalgae, broadly classified into brown, red, and green seaweeds, are a major source of novel bio-actives with potential benefits on animal health. While they consist of  $\geq$ 94% water, they also contain varying concentrations of non-digestible polysaccharides, polyphenols, minerals, vitamins, proteins, and lipids <sup>[37]</sup>. Of particular interest are the non-digestible polysaccharides of brown seaweeds, namely alginate and fucoidan which, along with cellulose, are structural components of the algal cell wall, while laminarin and mannitol are located in the cytoplasm <sup>[37][38][39]</sup>. Feeding intact or whole macroalgae has attracted considerable interest in recent years as potential substitutes for AGP and ZnO to maintain performance and health in weaner pigs, due to their prebiotic, antibacterial, antioxidative, and immunomodulatory activities <sup>[40][41]</sup>.

The supplementation with crude seaweed extracts containing both laminarin and fucoidan have been shown to be effective in post-weaned pig diets [42][43][44][45], however, the supplementation of intact seaweed has been less successful in the immediate post-weaned pig diet, as presented in **Table 1**. In a recent large commercial experiment in Denmark, Satessa et al. [46] could not obtain any positive effects of intact macroalgae on piglet health and performance. Previous studies with intact brown macroalgae also reported similar results in weaned pigs [47][48] or reduced performance when fed to finishing pigs [49]. The application of the intact macroalgae in a dry meal, means that the nutritional value of the final product is dependent on the seaweed variety, season of harvest, geographic location, and environmental and climatic conditions, all of which influence chemical composition [50][51][52][53]. The extraction methodologies and conditions used to extract polysaccharides (i.e., combination of parameters such as solvent, pH, temperature, time, solvent to seaweed ratio) are also an important contributing factor to the quantitative, structural, and functional variability of seaweed polysaccharides [51][52][54].

Chitin is a natural polysaccharide found in the exoskeletons of arthropods. Chitosan is formed by partial deacetylation of chitin under alkaline conditions or by enzymatic hydrolysis. Chitosan has exhibited antimicrobial activities against many bacteria, fungi, and yeasts, with a high killing rate for both gram-positive and gram-negative bacteria and low toxicity towards mammalian cells, indicating its suitability as an antimicrobial supplement <sup>[55]</sup>. The antimicrobial activities of chitosan are dependent on several factors including pH, the species of the microorganism, pKa, molecular weight, degree of deacetylation, and the presence or absence of metal cations <sup>[56]</sup>. This review will focus on the feeding of laminarin,

fucoidan, chitosan, and chitosan derivatives and their ability to alter the composition of the GIT microbiota, inhibit intestinal pathogens, modulate the immune system, and enhance performance and health in the post-weaned pig.

 Table 1. Effect of seaweed supplement on growth performae, diarrhoea scores and parameters of gastro intestinal functionality.

Pig Age	Dietary Supplement	Dose	Time and Duration of Supplementation	Effect on Growth Performance and Diarrhoea Scores	Effect on Parameters of GIT Functionality and Health	Ref.						
Weaned pigs												
24-day- old	Laminarin ( <i>Laminari</i> a spp.) Fucoidan ( <i>Laminaria</i> spp.) Laminarin + Fucoidan	300 mg/kg 240 mg/kg 300 mg/kg + 240 mg/kg	After weaning for 21 days	+ ADG and G:F in pigs fed laminarin- supplemented diets + ADG in pigs fed with diet supplemented solely with fucoidan (interaction) - diarrhoea score in pigs fed laminarin- supplemented diets	- faecal <i>E. coli</i> in pigs fed laminarin-supplemented diets + faecal <i>Lactobacillus</i> spp. in pigs fed with diet supplemented solely with fucoidan (interaction)	[42]						
24-day- old	Laminarin ( <i>Laminaria</i> spp.) Fucoidan ( <i>Laminaria</i> spp.) Laminarin + Fucoidan	150 or 300 mg/kg 240 mg/kg 150 or 300 mg/kg + 240 mg/kg	After weaning for 35 days	+ ADG in pigs fed 300 mg/kg laminarin- supplemented diets + G:F in pigs fed with diet supplemented solely with 300 mg/kg laminarin or fucoidan (interaction) - FS in pigs fed 150 or 300 mg/kg laminarin- supplemented diets and in pigs fed with diet supplemented solely with fucoidan (interaction)	+ faecal <i>Lactobacillus</i> spp. in pigs fed fucoidan- supplemented diets 0 faecal <i>E.</i> <i>coli, Bifidobacterium</i> spp.	[43]						
28-day- old	65% laminarin-rich extract (Laminaria spp.)	300 mg/kg	After weaning for 14 days	+ ADG, ADFI 0 diarrhoea score	<ul> <li>+ VH in duodenum and jejunum and CD in jejunum</li> <li>- Enterobacteriaceae in caecum</li> <li>+ Lactobacillus spp. in colon</li> <li>+ butyrate in colon</li> <li>+ gene expression of nutrient transporters in small intestine and colon</li> <li>- gene expression of tight junction proteins, mucins and immune markers in small intestine and colon</li> </ul>	[44]						
35-day- old	Dried seaweed (Ocean Harvest Technology) containing laminarin, fucoidan, alginate, mannitol, fucoxanthin and rhamnose sulphate.	1500 mg/kg	After weaning for 52 days	0 ADG, ADFI, G:F 0 diarrhoea score	– VH in jejunum	[46]						
35-day- old	Dried sea weed (Ascophyllum nodosum)	2.5 g/kg 5 g/kg 10 g/kg	After weaning for 28 days	- ADG	ND	[48]						

Pig Age	Dietary Supplement	Dose	Time and Duration of Supplementation	Effect on Growth Performance and Diarrhoea Scores	Effect on Parameters of GIT Functionality and Health	Ref.
Finisher pigs	Dried seaweed extract (Ascophyllum nodosum) containing laminarin, fucoidan, alginate, mannitol, fucoxanthin and rhamnose sulphate.	3 g/kg 6 g/kg 9 g/kg	After weaning for 28 days	– ADG 0 ADFI, G:F	ND	[49]
28-day- old	65% laminarin-rich extract (Laminaria spp.)	300 mg/kg	After weaning for 14 days	+ ADG, ADFI 0 diarrhoea score	<ul> <li>abundance of OTUs assigned to</li> <li>Enterobacteriaceae</li> <li>abundance of OTUs assigned to the genus</li> <li>Prevotella</li> </ul>	[ <u>57]</u>
24-day- old	Laminarin ( <i>Laminaria</i> spp.) Fucoidan ( <i>Laminaria</i> spp.) Laminarin + Fucoidan	300 mg/kg 240 mg/kg 300 mg/kg + 240 mg/kg	After weaning for 8 days	ND	<ul> <li>Enterobacteriaceae</li> <li>population in pigs offer</li> <li>fucoidan (interaction).</li> <li>AEEC strains in pigs offer</li> <li>laminarin (interaction).</li> <li>VH and VH:CD ratio in pigs</li> <li>offered laminarin or fucoidan (interaction).</li> <li>IL-6, IL-17A and IL-1b</li> <li>mRNA expression in pigs</li> <li>offered laminarin</li> </ul>	[ <u>58]</u>
24-day- old	Laminarin (Laminaria spp.)		After weaning for 8 days	+ ADG and ADFI – diarrhoea score	ND	[ <u>59]</u>
24-day- old	Laminarin ( <i>Laminari</i> a spp.)	0 mg/kg 240 mg/kg ZnO	After weaning for 32 days	+ ADG and G:F, similar effect to ZnO	+ digestibility of GE + the expression of glucose transporters in small intestine compared with the basal diet.	[ <u>60</u> ]
24-day- old	44% fucoidan-rich extract (Laminaria spp.)	0 mg/kg 125 mg/kg 250 mg/kg	After weaning for 14 days	– diarrhoea score 0 ADG, ADFI and G:F	0 effect on VH – abundance of Prevotella and Lachnospiraceae + the abundance of Helicobacter	[ <u>61</u> ]

+: increase; 0: no effect; -: reduction; N/D: not determined; ADG = average daily gain, ADFI = average daily feed intake, G:F = gain to feed ratio, VH = villous; height, CD = crypt depth, AEEC = attaching effacing *E coli*; GIT = gastrointestinal tract.

## 4. Laminarin

Laminarins are low molecular weight  $\beta$ -glucans consisting of a linear backbone of (1,3)- $\beta$ -linked glucopyranose residues with a varying level of  $\beta$ -(1,6)-branching <sup>[62]</sup> (**Figure 1**). Water solubility of laminarin depends on the level of branching <sup>[63]</sup>. Laminarin accumulates in the vacuoles of algal cells during summer and early autumn to support survival and growth during the winter and early spring when it reaches its lowest levels <sup>[62][64][65]</sup>. In terms of laminarin quantity, *Laminaria hyperborea* and *L. digitata* were reported to have the highest laminarin concentration among the different seaweed species, indicating that *Laminaria* spp. are an important source of this polysaccharide <sup>[63]</sup>.



Figure 1. Reported chemical structure of laminarin extracted from Laminaria digitata [52].

#### 4.1. Antibacterial Activity

Crude laminarin-rich seaweed extracts (*Laminaria* spp.) have exhibited antibacterial activity against *E. coli*, *S.* Typhimurium, *Listeria monocytogenes*, and *Staphylococcus aureus* in vitro <sup>[66]</sup>. Similar results were observed with purified laminarin (*Laminaria* spp., *Eisenia* spp., *Cystoseira* spp.) from various seaweed species, while it is also evident that laminarin is more effective against Gram-negative than Gram-positive bacteria <sup>[67][68]</sup>. Dietary supplementation with crude or highly purified laminarin-rich extracts (*Laminaria* spp.) reduced *Enterobacteriaceae* <sup>[44][57]</sup> and/or the subpopulation of attaching-effacing *Escherichia coli* (AEEC) <sup>[58][59]</sup> in the caecum and colon of weaned pigs. Similar reductions in ileal and colonic coliform counts were observed in growing <sup>[69][70][71]</sup> and finishing pigs <sup>[72]</sup> supplemented with highly purified laminarin-rich extracts (*Laminaria* spp.). In a dextran sodium sulphate (DSS)-induced colitis porcine model, the DSS-challenged pigs supplemented with crude <sup>[73]</sup> or highly purified <sup>[74]</sup> laminarin-rich extracts (*Laminaria* spp.) had reduced *Escherichia/Shigella* relative abundance and colonic *Enterobacteriaceae* counts, respectively, compared to DSS-challenged control pigs.

#### 4.2. Prebiotic Activity

In weaned and grower pig studies, dietary supplementation with crude or highly purified laminarin-rich extracts (*Laminaria* spp.) led to increases and compositional changes in the colonic and faecal *Lactobacillus* spp. populations <sup>[44]</sup> <sup>[60][71]</sup>. An in-depth investigation of the effects of a crude laminarin-rich extract (*Laminaria* spp.) on the composition of the colonic and caecal microbiota of weaned pigs showed an increased relative abundance in *Prevotella* spp. while its family, *Prevotellaceae*, was positively correlated with improved pig performance <sup>[57]</sup>. Supplementation with crude or highly purified laminarin-rich extracts (*Laminaria* spp.) also altered the short chain fatty acid (SCFA) production and profile of the gastrointestinal microbiota in pigs <sup>[44][70][72]</sup>, particularly altering butyrate production.

#### 4.3. Immunomodulatory Activity

Dietary supplementation with crude or highly purified laminarin-rich extracts (*Laminaria* spp.) exerted an anti-inflammatory effect on the small intestine and colon of weaned and growing pigs evidenced by the decreased expression of proinflammatory cytokine genes including tumour necrosis factor (*TNF*), transforming growth factor beta 1 (*TGFB1*), interleukins *IL1A*, *IL1B*, *IL6*, *IL17A*, and *IL10*, pattern recognition receptors such as toll-like receptor 2 (*TLR2*) and Dectin-1/C-type lectin domain containing 7A (*CLEC7A*), and the transcription factor nuclear factor kappa B subunit 1 (*NFKB1*) <sup>[44]</sup> <sup>[58][70]</sup>. An immunosuppressive effect due to laminarin was also observed in the colon, more specifically related to the down-regulation of genes associated with the Th17 pathway <sup>[75]</sup>. The influence of dietary supplementation with highly purified laminarin-rich extracts on the immune response of the porcine intestinal tissue towards a bacterial stimulus was evaluated in an ex vivo LPS challenge model. Here, the colonic tissue of pigs supplemented with highly purified laminarin-rich extracts (*Laminaria* spp.) had higher expression of *IL6* and C-X-C motif chemokine ligand 8 (*CXCL8*) following the LPS challenge, indicating that laminarin might provide improved protection against intestinal bacterial infection via enhanced activation of the immune system <sup>[69][70]</sup>.

#### 4.4. Effects of Laminarin-Rich Extracts on Pig GIT Functionality

Several studies have demonstrated the benefits of laminarin-rich extracts as a dietary supplement during the postweaning period in pigs, as presented in **Table 1**. Performance parameters such as final bodyweight, daily gain, feed intake, and gain to feed ratio were positively influenced in weaned pigs supplemented with crude or highly purified laminarin-rich extracts (*Laminaria* spp.) <sup>[42][43][44][59][60]</sup>. Furthermore, dietary supplementation with crude or highly purified laminarin-rich extracts (*Laminaria* spp.) led to improved villus architecture in the small intestine, mainly characterised by increased villus height (VH) and VH: Crypt depth (CD) ratio and increased expression of nutrient transporter genes, indicating enhanced nutrient digestion and absorption, both of which are impaired in the immediate post-weaning period <sup>[44][58][60]</sup>. Diarrhoea, a common characteristic of weaning stress, was reduced by dietary supplementation with highly purified laminarin-rich extracts (*Laminaria* spp.) as indicated by the lower faecal scores in the supplemented weaned pigs <sup>[42][43][58]</sup>. In a recent study, Rattigan et al. <sup>[45]</sup> showed that under hygienic sanitary conditions, laminarin-rich extracts reduced the incidence of diarrhoea in weaned pigs, while under unsanitary conditions, laminarin reduced the incidence of diarrhoea and improved daily gains. Therefore, laminarin-rich extracts seem to be a promising dietary alternative to antibiotic growth promoters and ZnO to alleviate PWD.

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