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Review

Potato protein concentrate: a possible alternative to the use of antibiotics in diets for weaned piglets. Review

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Abstract:

The weaning period is critical in the life of piglets and can cause gastrointestinal disorders and low growth, which are lessened with the use of antibiotics in starter feeds. However, due to the need to eliminate antibiotics from animal nutrition, some possible alternatives to their use are mentioned. In this literature review, antimicrobial peptides and plant-derived protease inhibitor compounds are described, especially those from potatoes, which have traditionally been recognized for their potential biomedical application and activity against pathogenic bacteria and fungi. The characteristics and applications of potato protein concentrate (PPC) from the starch industry, which is distinguished by its amino acid profile and high digestibility, were reviewed. Molecules that are present in the protein fraction and that can contribute to the intestinal health of piglets stand out in PPC, so it is emerging as an ingredient with potential to be used in antibiotic-free diets. However, it is necessary to have more bibliographic information on PPC to verify whether the health response is consistent or not, and to recommend its inclusion in starter diets for newly weaned piglets as an alternative to antibiotics.

Key words: Piglets, Weaning, Antimicrobial peptides, Protease inhibitors, Potato.

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Introduction

The newborn piglet has a low intestinal capacity to digest and absorb solid feeds, especially those of vegetable origin, so its digestive system must mature quickly to ensure its survival(1,2). Enteral nutrition (colostrum and milk) plays a fundamental role in the maturity of the piglet(1); however, milk soon ceases to cover the nutritional demand of the piglet and it begins a gradual consumption of other feeds, allowing the gradual maturity of the nervous, immune and digestive systems. This maturation process of the digestive tract is stimulated by the colonization of different bacterial genera(3.4), which use some nutrients and produce enzymes(2,5) and, through competitive exclusion, prevent the adhesion of pathogens(4).

Under natural conditions, piglet weaning occurs between weeks 10 to 22 of life(6,7). However, under commercial conditions, weaning is carried out between 21 and 28 d of age in order to allow the maximum productive efficiency of the female; higher number of births and piglets per sow per year, reduce the cost of facilities, etc.(6). Commercial weaning, unlike natural weaning, is not gradual but an abrupt and sudden event, which is extremely stressful for the still immature piglet. This fact is characterized by the separation of the mother, the environmental change and from a dairy diet to a solid one (mainly composed of cereals). All this, added to the presence of new pathogens, causes neuroendocrine, immunological and digestive complications(2,7), with piglets showing in the first 24 to 48 h after weaning a low, and even zero, feed consumption, weight loss, atrophy of the intestinal structure and with it of the digestive and absorption capacity, as well as an increase in the incidence of post-weaning diarrheas(6,8).

The presence of post-weaning diarrheas is widely related to the sudden change in diet, as well as gastrointestinal infections. Both factors promote rapid dysbiosis, that is, an imbalance in the composition of bacterial populations, with an increase in *E. coli*, which contributes to the loss of intestinal structure(9), as well as an abrupt reduction of *Lactobacillus* spp. The incidence of these post-weaning digestive disorders generates great economic losses(10). To combat these gastrointestinal complications, antibiotics have been used as growth promoters (GPAs) in diets in recent years, since their use in animal feed favors the growth rate and reduces the incidence of diseases and mortality(11,12). These molecules decrease the number of pathogens and with it the atrophy of the intestinal villi and hypertrophy of the crypts are prevented. This leads to a greater and early consumption of feed, adequate digestive capacity and better feed efficiency, thus increasing the retention of nitrogen and energy from the diet(13,14). However, in recent years, the inclusion of GPAs in animal diets has been questioned, and even banned in some countries, since they represent a serious problem for public health, due to the development of bacterial resistance to antibiotics, which can potentially reduce the treatment of diseases in animals and possibly in humans. Therefore, the search for substitutes or alternatives to antibiotics is of great relevance for pig farming(15,16).

With the growing human population, the demand for safe food resources by the pig industry has increased dramatically in recent years(17). Due to its nutritional and possibly therapeutic characteristics, potato protein concentrate (PPC), obtained after starch extraction, seems to be a good choice as a protein source. Therefore, the present work aims to review some characteristics of this protein ingredient, which place it as a nutritional alternative with potential to improve the intestinal health of newly weaned piglets.

Alternatives to growth-promoting antibiotics (GPAs)

The crisis of bacterial resistance to antibiotics shows no signs of a solution in the short term and the lack of new antimicrobial drugs, as well as the few companies that invest in this area, threatens the ability to treat and prevent infections. One reason for the shortage of new antibiotics is that typical points of action, such as cell wall and protein synthesis, as well as that of DNA/RNA, have perhaps been overexploited. Currently, thanks to access to complete bacterial genomes, strategies based on new molecular targets are sought; however, this approach has not been fully developed(18).

However, the antibiotic crisis demands measures that contemplate a new approach and different therapeutic strategies(18). There are many literature reviews on the different alternatives to GPAs. Among the most studied alternatives the following stand out: plant extracts, chicken egg antibodies, organic acids and enzymes(12), as well as essential oils(10), probiotics(19), prebiotics(20), minerals such as copper and zinc(11), as well as animal plasma(21) and plant proteins such as potato protein concentrate(22).

Among the most successful alternatives for the control of post-weaning digestive disorders, animal proteins stand out, such as animal plasma and fishmeal, which, due to their high digestibility and amino acid profile, favor feed consumption and growth rate(23,24). However, ingredients of animal origin are expensive and inadequate handling during storage could favor the transmission of some pathogens. Fishmeal is the essential protein in piglet feeds, but marine overfishing has caused a vertiginous increase in prices, reducing its availability.

The results of including these ingredients in piglet diets can sometimes be inconsistent and hardly able to match the effect of antibiotics in productive terms, however, benefits to intestinal health are reported, which should be considered when using antibiotic-free diets. Plant-based antimicrobial peptides (AMPs) are an alternative to GPAs that have shown potential use(12).

Plant-based antimicrobial peptides

AMPs are developed by different plants and tubers as a defense mechanism and in response to microbial aggressions and infections(25-27). These peptides are expressed and stored in different plant tissues(25). AMPs are encoded by genes that have a wide range of activity against Gram-negative, Gram-positive bacteria, fungi and bacilli of the genus *Mycobacterium*. They have been isolated and characterized from tissues and organisms that represent practically all kingdoms and phyla(28). These peptides play an important role in the mechanisms responsible for eliminating or preventing the growth of pathogens, both inside and outside plant organisms(29). AMPs exist in different molecular forms, the most common are linear, although there are also cyclic forms. Most AMPs have 2 to 6 cysteine residues(26), which give them high thermal, enzymatic and chemical stability(30). They are polypeptides with less than 200 amino acids (AAs), commonly less than 50 AAs, of low molecular weight (approximately 10 kDa), basic character and are generally cations at physiological pH due to their residues loaded with arginine and lysine(25).

Cystine-rich AMPs are classified into families according to their sequence similarity, cysteine motifs, that is, the cysteine combinations that accumulate in the tertiary structure of the peptide and disulfide bond patterns. Families of cystine-rich plant AMPs include thionines, defensins, hevein-type peptides, knottin-type peptides (linear and cyclic), lipid transfer proteins, α-hairpinines and snakins(25,26). It should be clarified that there are AMPs rich in other amino acids (glycine, histidine). The ability of plant AMPs to organize into families with conserved structural characteristics allows the variation of the sequence of residues that are not cysteine in the same structure within a particular family to perform multiple functions(26).

Plant AMPs have activity against bacteria, fungi, viruses and parasites. The mechanism of action of AMP is generally believed to be related to membrane lysis or peptide penetration followed by attack on intracellular targets. The cationic nature and amphipathic capacity of AMPs allows interaction with the (anionic) wall and phospholipid membrane of microorganisms(25,26). Mechanisms of action such as pore formation and membrane depolarization, disruption of bacterial energy metabolism and interference with biosynthetic pathways for the antimicrobial activity of several AMPs that contain disulfide bridges(31) have been suggested. The aforementioned characteristics profile them as an important alternative for the development of antibiotic and anti-inflammatory molecules(25). These characteristics, in addition to cysteine residues, are classic of the families of thionines and defensins. Other families of AMPs such as hevein-type peptides bind to chitins, and lipid transfer proteins bind to cell membrane lipids to disrupt microbial penetration into cells(26).

Some authors(28,32,33) suggest that PPC may be an alternative to feeds medicated with antibiotics, because it showed antimicrobial activity by effectively reducing the population of coliform bacteria. It is suggested(33) that potato protein may have an additional potential advantage over antibiotics by selectively inhibiting the *in vitro* growth of pathogenic bacteria (*Staphylococcus aureus*, *Salmonella gallinarum* and *E. coli*). The explanation of the antimicrobial effects of PPC could be related to the action of certain antimicrobial peptides that can be found in the protein of the tuber *Solanum tuberosum*(34), since peptides with antimicrobial activity are produced by the potato in its defense against pathogens.

Antimicrobial potato peptides

Potato proteins are divided into three groups: patatin, protease inhibitors (PIs) and other proteins that are also involved in the defense of the potato, as they all have antifungal or antimicrobial actions(35). PIs represent a high proportion of the total potato protein(36), and are a structurally heterogeneous group (Table 1) with a wide range of antifungal and antimicrobial activities(35).

Table 1: Potato protease inhibitors(35)

Protease inhibitor	Molecular mass (kDa)	Isoelectric point	SU	Inhibited enzyme
Protease inhibitor l	7.68 - 7.87	5.1–6.3–7.2–7.8	5	T, Q
Protease inhibitors ll	20.02 - 20.68	5.5–5.8–5.9–6.0–6.1–6.5–6.9	2	T, Q
Aspartate protease inhibitor	19.87 - 22.03	6.2–7.5–8.2–8.4–8.6–8.7	1	T, Q, CD
Cysteine protease inhibitor	20.1 - 22.7	5.8–6.6–6.7–7.1–8.0–8.3–>9	1	T, Q, Pap.
Kunitz-type protease inhibitor	20.19 - 20.24	8.0–9.0	1	T, Q
Other serine protease inhibitors	21.03 - 21.80	7.5-8.8	1-2	T, Q
Carboxypolypeptidase inhibitor	4.20	not determined	1	CA

SU= subunits. T = trypsin; Q= chymotrypsin; CD= cathepsin D; Pap= papain; CA= carboxypolypeptidase A.

In the past, PIs were only considered antinutritional factors; however, they have recently aroused interest because they have multiple biological activities. Potato PIs have been studied for their antimicrobial effect, anticancer activity and regulation of feed consumption related to the modulation of cholecystokinin through trypsin inhibition(35).

The high stability of antifungal activity of potato PIs I and II at high temperatures opens a new market for starch producers, due to the potential use of these peptides in the food, pharmaceutical or agricultural industry(27).

In some experiments(35,37), potato PIs I and II reduced the growth of several fungi; while members of the Kunitz family (proteins Potide-G, AFP-J, Potamin-1 and PG-2) inhibited pathogenic bacteria (*Staphylococcus aureus*, *Listeria monocytogenes*, *Escherichia coli* or *Candida albicans*). In an *in vitro* study(37), Potamin-1 inhibited the growth of different plant pathogens, and also had inhibitory activity against the enzymes trypsin, chymotrypsin and papain. The peptide Potamin-1 is currently the most mentioned in the literature to explain the mechanism of action of PPC in animals(38).

Other potato proteins

Within the group called “other potato proteins”, cysteine-rich peptides such as thionines, defensins, lectins and snakins are included(39). Thionines base their antimicrobial activity on the interaction with the phospholipid membrane of pathogenic microorganisms. Defensins seem to act on specific membrane receptors, however, information on these peptides is limited(35).

Snakin peptides are part of an independent group. They are within the classification of other potato proteins due to their practically zero similarity to any other type of potato peptide(35,40). Snakins are involved in biological processes such as cell division, elongation, and growth and signaling in potato defense. Two types of snakin peptides are found [snakin-1 (SN1) and snakin-2 (SN-2)] and although they only share 38 % of their structure, they have similar functions. Both are peptides rich in cysteine residues with reported activity against Gram-negative and Gram-positive bacteria (*C. michiganensis*, *R. solanacearum*, *E. chrysanthemi* and *R. meliloti*), as well as against some fungi(35,39). Their spectrum of antimicrobial activity against bacterial and fungal pathogens is quite similar to each other and different from that of defensin peptides from the same tissues. However, the expression of the SN2 gene is induced in the potato by a local wound and shows differential responses to infection by pathogens. The expression patterns and antimicrobial activities of SN2 are consistent with its participation in the constitutive and inducible defense barriers of the potato(41).

Potato protein concentrate in the feed of weaned piglets

There are about 5,000 varieties of potato, originating mainly from the Andes, with variants in size, shape, color, texture, as well as nutritional profile. About 10 varieties are cultivated, and the most cultivated variety worldwide is the species *Solanum tuberosum*. China is responsible for 80 % of the world’s production of this variety. The chemical composition of the potato is modulated by different factors such as geographical area and cultivation practices; its protein content in the fresh state varies between 0.49 and 2.7 %(42,43).

In addition to consumption in fresh form, the potato is also used to obtain starch, fiber and juice. In the European Union alone, 8 million tonnes of potatoes are processed annually. PPC is a coproduct of the starch industry, by recovering the liquid fraction that remains after its extraction(44). The process is based on thermal coagulation followed by protein separation and drying(27,45). Potato proteins are typically classified according to their molecular mass and electrophoretic separation into three large groups: patatins, protease inhibitors and other proteins(35). Patatins represent about half of potato proteins and are glycoproteins with molecular weights of 39 to 43 kDa, with enzymatic activities (hydrolases, phospholipases and glucanases)(35).

The potato has some antinutritional factors such as glycoalkaloids of solanines (927 – 2,632 mg/kg) and trypsin inhibitors (0.97 - 3.70 mg/kg), where the concentration can be variable according to the conditions of processing(44). Thermal processing (100°/15 min) before drying is capable of inactivating up to 48 % of protease inhibitors and up to 89 % of glycoalkaloids(46).

PPC is an ingredient that contains adequate amounts of essential amino acids, which can replace animal protein in piglet diets(47), as it has been characterized by a highly balanced amino acid profile and is especially rich in lysine, methionine, threonine, tryptophan and valine. In piglets that received a diet with PPC with the same level of inclusion as fishmeal, an improvement in the growth rate of piglets was observed(48), which can be attributed to the quality of its amino acid profile. Thus, the nutritional value of PPC is related to the concentration and availability of amino acids since it has a profile similar to that of soybean(49) and some animal proteins(50). The proportion of eight essential amino acids (threonine, valine, methionine, isoleucine, leucine, phenylalanine, lysine and tryptophan) corresponds to 40.7 % of the PPC protein(42). The amino acid profile of potato protein completes or exceeds the ideal protein profile, except for tryptophan and lysine with 64.5 and 89.75 % of the requirement, respectively.

In 2008 and 2009, three articles were published (28,32,33) in which a refined potato protein (RPP or PP) purified at laboratory level from a special variety of potato (*Solanum tuberosum* L. cv. Golden valley) was used. This protein fraction showed an inhibitory effect on the *in vitro* growth of pathogenic bacteria, so they studied the incorporation of RPP or PP at different levels in the diet of newly weaned piglets and compared it with a control diet with antibiotics. Results varied between studies, and an advantage of using the diet with antibiotics was observed in the three studies.

When the authors(33) used diets with 0, 200, 400 and 600 ppm of RPP, it was reported that the increase in levels of inclusion in the diets linearly improved the productive performance and reduced the populations of total bacteria, coliforms and *Staphylococcus* spp. in the contents of the colon and rectum and in feces. The apparent fecal digestibility of dry matter and crude protein, as well as apparent ileal digestibility of amino acids, did not differ between pigs fed the control diet (0 ppm) with antibiotics and diets with RPP(33).

With higher levels of inclusion (0.0, 2.5, 5.00 and 7.50 g PP/kg of diet), researchers(28) also observed a linear improvement in feed efficiency during the 28 experimental days and an increase in the apparent fecal digestibility of dry matter in phase II (0 to 14 days post-weaning) with the increase in the level of inclusion of PP. A linear decrease in fecal bacteria was also observed on days 21 and 28 with the increase in the level of inclusion of PP. Piglets that consumed the diets with PP had a linear reduction of total bacteria, coliforms and *Staphylococcus* spp. in the cecum and rectum. The apparent ileal digestibility of amino acids and the morphology of intestinal villi and crypts were not affected by the consumption of experimental diets(28).

In another study(32) with piglets fed diets with 0.0, 0.25, 0.50 or 0.75 % potato protein (PP) during phase I (0 to 14 d post-weaning) and phase II (14 to 28 days post-weaning), the authors observed that increasing levels of PP linearly improved daily weight gain, daily feed consumption and feed efficiency in both phases (I and II); in addition to increasing the digestibility of the dry matter in phase II. Consumption of diets with increasing levels of PP linearly reduced bacterial populations in feces and contents of the cecum, colon and rectum. The height of the villi and the depth of the intestinal crypts did not vary with the increase in the level of PP in the diet. These three studies(28,32,33) opened an area of opportunity for the use of potato protein concentrate generated in the starch industry in animal feed.

The use of PPC of commercial origin(22) in growing pigs (25 kg live weight) showed a high ileal digestibility of nitrogen, both standardized (93.0 %) and apparent (85.8 %). The apparent ileal digestibility and the digestibility of most AAs were similar to the digestibility of soybean protein concentrate and isolate, with the highest standardized and apparent ileal digestibility of leucine (96.3 and 94.7 %, respectively) and threonine (94.7 % and 86.9 %, respectively) standing out in PPC(22).

In another study(47) with growing pigs (21 kg live weight), the inclusion in the diet of 17.5 % PPC with a low concentration of glycoalkaloids and low trypsin inhibitory activity did not affect daily weight gain, daily feed consumption or the relative weight of stomach, duodenum and jejunum, as well as other aspects of intestinal morphology. Protein digestibility was lower in pigs fed the diet with PPC than with the diet with casein, however, the apparent ileal digestibility of fat was better in piglets with PPC. The authors conclude that the diet with a high level of PPC was well used by growing pigs(47).

The good results to the consumption of PPC observed in growing pigs are probably related to its nutritional characteristics; however, due to the reported antimicrobial properties, the use of PPC is more recommended for its inclusion in diets for newly weaned piglets.

In 2005, it had already been observed(48) that piglets fed diets with 6 % PPC had a greater daily weight gain in the first 1-21 and 21-50 d post-weaning than piglets fed diets in which they included fishmeal, sunflower meal and gluten meal in similar amounts. Mortality in the period was low (about 4 %) and the severity of diarrheas was slight (1.6 points) in all piglets(48).

Some authors(51), using PPC with a low level of glycoalkaloids (PPCLG) in diets of newly weaned pigs, found no differences in the productive behavior with respect to diets with animal plasma. The authors observed a quadratic response in weight gain and feed consumption in weaned piglets when using increasing levels of inclusion of PPCLG, replacing 25, 50, 75 and 100 % of animal plasma in the diet. Feed efficiency improved linearly with the inclusion of PPCLG. It was concluded that PPCLG may be an effective substitute for a part of the pig plasma in diets for weaned piglets(51).

During the first week after weaning(52), it was observed that daily weight gain and feed efficiency were also not different between piglets that consumed dehydrated porcine plasma or PPC in their diets. During the second week post-weaning and in the total experimental period, the daily feed consumption was similar among all animals. The apparent ileal digestibility of crude protein was higher in piglets fed antibiotic and PPC. The apparent total digestibility of dry matter and energy was higher for piglets fed PPC than the other diets. The severity index of diarrheas in piglets fed the PPC diet was similar among piglets fed the control diet with antibiotic(52). These results demonstrate a potential use of PPC for newly weaned piglets.

Conclusions

In recent years, the search for alternatives to the use of antibiotics in feeds as promoters of growth and intestinal health in newly weaned piglets has increased. The potato is some food rich in antimicrobial peptides (AMPs) and other proteins that are involved in its defense system, which have already been purified at the laboratory level. The industry of starch extraction from the potato generates a large amount of a protein concentrate, which probably preserves these AMPs. In this context, potato protein concentrate could exert a positive effect on the productive development of pigs due to its nutritional value, in addition to the possible benefits of its AMPs on intestinal health. However, for it to be considered as an alternative to the use of antibiotics in starter diets, it is necessary to have more bibliographic evidence on the presence of these peptides in commercial products based on potato protein concentrate available on the market, and if their beneficial effects persist at the gastrointestinal level, decreasing post-weaning diarrheas.

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