The use of herbal medicine as an alternative antimicrobial in the feed of post-weaning piglets: A field trial

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Abstract

The present study was performed to evaluate the effect of 3 antimicrobial substances on average daily feed intake (ADFI), average daily gain (ADG), feed conversion ratio (FCR), mortality rate and number of *Escherichia coli* (*E. coli*) and *Bacillus* sp. in feces and on mucosal epithelium of the small intestine. The experiment was performed in a pig farm using a total number of 651 weaned piglets with an average initial weight of 5.8 kg and 24 ± 2 days of age. Two repetitions of the experiment were performed and the piglets in each repetition were randomly divided into 3 groups with 3 administration programs; piglets in group 1, 2 and 3 were fed with colistin sulfate, halquinol and an herbal medicine, berberine, respectively. All piglets were housed in the same barn until 9 weeks of age. ADG, ADFI and FCR were measured. The mean of the ADFI was lowest in the piglets that received halquinol. The group received colistin or berberine was significantly heavier at 9 weeks of age than that of the group receiving halquinol (20.4, 20.4 and 19.0, $P<0.001$). Piglets receiving colistin or berberine grew significantly faster than those treated with halquinol (344.1, 348.6 and 304.9 g/d, $P<0.05$). Piglets receiving berberine had a lower FCR than those receiving halquinol (1.5 versus 1.7, $P<0.05$). The mortality rate of piglets in all groups was less than 2.0% and did not differ significantly. Piglets that received colistin or berberine treatment had a lower retarded growth than those receiving the halquinol treatment ($P<0.05$). The feces from piglets that received colistin or berberine had less *E. coli* than that receiving halquinol ($P<0.05$). The number of *Bacillus* sp. did not significantly differ among the groups but tended to be diminished in the piglets that received colistin. The number of *E. coli* and *Bacillus* sp. on duodenal and jejunal mucosa did not differ significantly among the groups. The tendency of *E. coli* numbers in groups treated with halquinol was highest, whereas the *Bacillus* sp. number was highest in piglets that were treated with herbal medicine. In conclusion, in one farm condition, the piglets treated with colistin and the herb product grew faster, and heavier at 9 weeks of age and had a lower number of deaths and retarded growths than those treated with halquinol. Furthermore, the use of herbal medicine was able to control the number of *E. coli* overgrowth, as effective as the use of colistin, whereas the side effect on the reduction in the number of *Bacillus* sp. was less than the use of colistin.

Keywords: pig, *Escherichia coli,* berberine, colistin, halquinal

การใช้สมุนไพรเป็นสารต้านจุลชีพแทนยาปฏิชีวนะในอาหารของลูกสุกรหย่านม: การทดลองในภาคสนาม

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บทคัดย่อ

การทดลองนี้มีวัตถุประสงค์เพื่อศึกษาผลของการใช้ยาต้านจุลชีพ 3 ชนิด ต่ออัตราการกินอาหารเฉลี่ยต่อวัน (ADFI) อัตราการเจริญเติบโตต่อวัน (ADG) ประสิทธิภาพการใช้อาหาร (FCR) อัตราการตายและสูญเสีย ปริมาณของเชื้อ เอสเชอริเชีย โคลัย (อี.โคลัย) และเชื้อบาซิลลัสในอุจจาระและในเยื่อบุผนังลำไส้ของลูกสุกร การทดลองทำในฟาร์มสุกรแห่งหนึ่งโดยใช้ลูกสุกรหย่านม 615 ตัว น้ำหนักเฉลี่ย 5.8 กก. และ อายุเฉลี่ย 24 ± 2 วัน แบ่งการทดลองเป็น 2 ซ้ำ แต่ละซ้ำลูกสุกรถูกแบ่งเป็น 3 กลุ่ม แต่ละกลุ่มได้รับยาผสมอาหารต่างกัน 3 ชนิด โดยกลุ่มที่ 1 2 และ 3 ได้รับโคลิสติน ฮาลควินอล และสมุนไพรที่มีส่วนประกอบของสารเบอเบอรีน ผสมในอาหาร ตามลำดับ สุกรทั้ง 3 กลุ่มถูกเลี้ยงภายในโรงเรือนเดียวกันจนกระทั่งอายุ 9 สัปดาห์ ชั่งน้ำหนักสุกรเป็นรายตัวในวันที่รับสุกรเข้าและในวันที่สุกรออกจากโรงเรือนอนุบาล ทำการวัดและคำนวณ ADG ADFI FCR ในแต่ละกลุ่ม ผลการทดลองพบว่าปริมาณอาหารที่กินได้ต่อตัวต่อวันต่ำที่สุดในสุกรกลุ่มที่ได้รับยาฮาลควินอลในอาหารในทั้ง 2 ซ้ำ ลูกสุกรที่ได้รับโคลิสติน หรือเบอเบอรีนมีน้ำหนักตัวเมื่ออายุ 9 สัปดาห์สูงกว่าสุกรที่ได้รับฮาลควินอลอย่างมีนัยสำคัญ (20.4 20.4 และ 19.0 กก.; *P*<0.001) ในการทดลองซ้ำที่ 2 สุกรที่ได้รับโคลิสตินหรือเบอเบอรีนผสมอาหาร มีอัตราการเจริญเติบโตที่ดีกว่าสุกรที่ได้รับฮาลควินอลอย่างมีนัยสำคัญ (344.1 348.6 และ 304.9 กรัม/วัน; *P*<0.05) สุกรที่ได้รับเบอเบอรีนมีประสิทธิภาพการใช้อาหารดีกว่าสุกรที่ได้รับยาฮาลควินอลอย่างมีนัยสำคัญ (1.5 กับ 1.7; *P*<0.05) อัตราการตายในลูกสุกรทั้ง 3 กลุ่ม ต่ำกว่า 2.0% และไม่แตกต่างกันอย่างมีนัยสำคัญ (*P*>0.05) สุกรที่ได้รับโคลิสตินหรือเบอเบอรีนมีสัดส่วนของสุกรที่ตายและโตช้าน้อยกว่าสุกรกลุ่มที่ได้รับฮาลควินอลอย่างมีนัยสำคัญ (*P*<0.05) ลูกสุกรที่ได้รับอาหารผสมโคลิสตินหรือเบอเบอรีนตรวจพบปริมาณเชื้อ อี.โคลัย ในอุจจาระต่ำกว่าลูกสุกรที่ได้รับ ฮาลควินอลอย่างมีนัยสำคัญ (*P*<0.05) ในขณะที่ปริมาณของเชื้อบาซิลลัสไม่แตกต่างกันระหว่างกลุ่มเมื่อถึงสัปดาห์สุดท้ายของการทดลองแต่มีแนวโน้มต่ำในกลุ่มที่ได้รับโคลิสติน ปริมาณของ เชื้อ อี.โคลัย ในลำไส้ส่วนดูโอดีนัมและเจจูนัม ของลูกสุกรทั้ง 3 กลุ่มไม่แตกต่างกัน โดยลูกสุกรที่ได้รับฮาลควินอลมีแนวโน้มที่จะมีปริมาณของเชื้ออี.โคลัยสูงกว่ากลุ่มอื่นๆ ลูกสุกรที่ได้รับเบอเบอรีนพบปริมาณของเชื้อบาซิลลัสในลำไส้ส่วนดูโอดีนัมและเจจูนัมมากกว่ากลุ่มอื่น โดยสรุปการศึกษานี้พบว่าในฟาร์มสุกรแห่งนี้ลูกสุกรที่ได้รับโคลิสตินหรือสมุนไพรเบอเบอรีนในอาหารมีอัตราการเจริญเติบโตสูงกว่า น้ำหนักเมื่ออายุ 9 สัปดาห์สูงกว่า และมีสัดส่วนของสุกรที่ตายและโตช้าน้อยกว่าลูกสุกรที่ได้รับฮาลควินอล และแสดงให้เห็นว่าภายในฟาร์มแห่งนี้สารสมุนไพรเบอเบอรีนมีประสิทธิภาพในการควบคุมปริมาณของเชื้อ อี.โคลัย ได้ไม่แตกต่างจากโคลิสติน และไม่มีผลต่อปริมาณเชื้อบาซิลลัส

คำสำคัญ : สุกร อี.โคลัย เบอเบอรีน โคลิสติน ฮาลควินอล

Introduction

The use of certain antibiotics in livestock production has been officially banned due to the incidence of widespread antimicrobial resistant. Nowadays, the use of herbal medicine for disease prevention, treatment or as growth promoters has become an alternative in the pig industry, and many recent researches have been taken into consideration (Cuellar *et al.,* 2001; Schinella *et al.,* 2002; Stermitz *et al.,* 2002). Many types of herbal medicine have been studied but only a few trials have been completed.

Berberine is a plant extract using as herbal medicine that has been studied for a long time. Commercial version of berberine is now available for both human and animals. However, an application of this product as a preventive medicine in pig has never been performed. Berberine is a plant alkaloid that can be extracted from many types of plant, such as *Hydrastis canadensis* (goldenseal), *Coptis chinensis* (Coptis or goldenthread), *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry) and *Berberis aristata* (tree turmeric). It has been demonstrated that berberines produce antimicrobial activity against a variety of organisms including bacteria, viruses, fungi, protozoa and helminths. The predominant clinical uses of berberine include bacterial diarrhea, intestinal parasite infections, and ocular trachoma infections (Birdsall and Kelly, 1997). Diarrhea caused by *Escherichia coli (E. coli)* has been the focus of numerous berberine studies, and results indicate several mechanisms, which may explain its ability to inhibit bacterial diarrhea. The therapeutic dosage for most clinical situations is 200 mg orally two to four times on a daily basis (Birdsall and Kelly, 1997).

As feed additives, antibiotics have been widely used as growth promoters in pig. The use of herbal products is an alternative to prevent antimicrobial resistance. However, to our knowledge, there have been no field trials performed to evaluate the efficiency of herbal medicine compared with the routine use of antibiotic such as colistin or halquinol. The present study was performed to investigate the effect of berberine on average daily feed intake (ADFI), average daily gain (ADG) and mortality rate in nursery pigs. In addition, the efficacy of the natural compound for controlling *E. coli* and monitoring *Bacillus* sp. in feces and in small intestine was also evaluated and compared with the use of colistin and halquinol.

Materials and Methods

Animals

A total of 615 weaned pigs (crossbred Landrace x Yorkshire x Duroc) with an average initial weight of 5.8 kg and average age of 24 days was used. The trial was carried out in 2 replications with a 2-week interval (300 piglets in the first batch and 315 piglets in the second batch). The piglets were housed in an environmentally controlled nursery facilitated with an evaporative cooling system. The pigs were grouped according to their body weight and sex. Each pen (2.5 x 2.5 m) was equipped with a manual feeder and two nipple drinkers to allow ad libitum consumption of feed and water. In the first batch, 100 piglets were assigned into 10 pens per group and each group had 100 piglets (10 piglets/pen). In the second batch, 150 piglets were assigned to 7 pens per group and each group had 105 piglets (15 piglets/pen). The piglets were fed with 3 feed rations, the starter feed contained 23% protein, 3,600 kcal ME, 1.96% fiber, 6.2% fat and 1.45% lysine. The second feed contained 22% protein, 3,450 kcal ME, 2.5% fiber, 5% fat and 1.35% lysine. The third feed contained 20.5% protein, 3,450 kcal ME, 2.6% fiber, 4% fat and 1.35% lysine.

Experimental design

The piglets were randomly assigned to three groups and three preventive medical programs were applied to each group. In group 1, the piglets received colistin 200, 120 and 120 ppm in the three stages of the feeding program, respectively. In group 2, the piglets received halquinol 120 ppm in the three stages of feeding program. In group 3, the piglets received a 1 kg of a commercial herbal medicine product per ton of feed, containing berberine 120 ppm (Bicmax®, BIC Chemical Co. Ltd., Nonthaburi, Thailand). Each kilogram of the herbal product contained berberine 120 g, Glycyrrhizin and Flavonoid 300 g, Gambirines 120 g, Limonene 120 g and mixture of phenol 100 g. All piglets were housed in the same barn until 9 weeks of age (40-42 days in nursery). The individual weight of the piglet was determined at entry and at 40 days after entering the nursery house. The feed intake of piglets was measured in each group. All dead piglets were weighed and taken into account. ADG, ADFI and FCR were calculated.

Measurements of ADFI, ADG and FCR

The ADFI of piglets was an average amount of feed intake per day divided by the number of lived piglets each day. ADG was calculated by the subtracted body weight at the end of the experiment or the bodyweight of dead piglets with the body weight at entry divided by number of days that the piglets still in the experiment. FCR was calculated by dividing the amount of feed intake per day by ADG. All data from dead piglets were also included in the calculation.

Sample collection and enumeration of *E. coli* and *Bacillus* sp.

Fecal samples were collected randomly in every 20 piglet that was weighed at entry. Afterwards, feces were collected from the same piglets at the 2^{nd} week and 6^{th} week after the entry. About 10 grams of feces were collected directly from the rectum. They were kept at $4^{o}C$ and brought to the microbiology laboratory within 12 h. The samples were ten-folded diluted and were determined according to the method of ISO: 6877-1 (1999). The enumeration of *E. coli* was determined according to the standard method (ISO: 7251, ISO: 4832) and was reported as most probable number (MPN/g). According to ISO: 7932 (1993), *Bacillus* sp. was enumerated. At the end of each batch, 3 piglets were randomly selected for post-mortem examination. Parts of small intestine (duodenum and jejunum) and intestinal contents were collected for both histological examination and bacterial culture. A mucosal content was scraped from duodenum and the distal part of jejunum, and performed as same as that of the fecal samples.

Histological examination

The duodenum and the distal part of jejunum were fixed with 10% buffered formalin, embedded in paraffin, cut and stained with Haematoxylin and Eosin. The tissue sections were examined under light microscope. Ten microscopic fields of each section were determined. Pathological changes such as an infiltration of inflammatory cells and the colonization of bacteria on microvilli of enterocytes were verified.

Statistical analyses

The statistical analyses were carried out by using SAS (SAS Inst. Inc. V 6.12, Cary, NC, USA). The descriptive statistics (number of observation, general means, standard deviation, minimum and maximum value of the data) were performed by using Means procedure. Analysis of variance (ANOVA) was conducted by the General Linear Model (GLM) procedure of SAS. Average body weight at the end of the trial (9 weeks of age) (BW), ADG and FCR were assigned as dependent variable. The statistical model for BW included the effect of batch (1 and 2), sex (male vs female), treatments (group 1, 2 and 3), interaction among batch, treatments and the regression of body weight at entry. For ADG and FCR traits, the analyses were performed by batch and the model included effect of sex, treatment and the regression of body weight at entry. The mortality rate and proportion of piglets with a body weight below 16 kg at 9 weeks of age, called retarded growth, was analyzed using Chi-square test.

The number of *E. coli* and *Bacillus* sp. counted (log10) in feces of the piglets at 3, 5 and 9 weeks of age and in the small intestine (duodenum and jejunum) at 6 weeks after treatment were regarded as dependent variables. The statistical model for the fecal bacterial count included the effect of batch (1 and 2), treatments (group 1, 2 and 3), age (3, 5 and 9 weeks) and the interaction between treatments and age. The statistical model for the intestinal bacterial count included the effect of batch (1 and 2), treatments (group 1,2 and 3), parts of the small intestine (duodenum and jejunum) and the interaction between treatments and part of the intestine. The difference between the value with *P*<0.05 were considered statistical significance.

Results

The ADFI in each group of the piglets is demonstrated in Fig 1. The ADFI of piglets that received colistin was highest in batch 2 (Fig. 1) and the ADFI of piglets that received berberine was highest in batch 1 (Fig. 1).

Piglets that received colistin or berberine had a significantly heavier bodyweight at 9 weeks of age than those received halquinol (20.4, 20.4 and 19.0, respectively; *P*<0.001). Body weight at 9 weeks of age did not differ significantly between colistin and berberine (*P*>0.05).

On average, piglets in the first batch grew faster than those in the second batch (362.4 versus 322.7 g/d, *P*<0.05). In the first batch, ADG did not differ significantly among groups (*P*>0.05), but in the second batch, piglets treated with colistin or berberine grew significantly faster than those treated with halquinol (344.1, 348.6 and 304.9 g/d, respectively) (Fig. 2).

FCR did not differ significantly between batches (1.4 and 1.6 in batch 1 and 2, respectively, *P*>0.05). In the second batch, piglets treated with berberine had a significantly lower FCR than those treated with halquinol (1.5 versus 1.7, *P*<0.05).

The mortality rate of the piglets treated with colistin, halquinol and berberine were 2.0% (4/205), 1.5% (3/205) and 1.5% (3/205) (*P*>0.05), respectively. The proportion of dead piglets in combination with those with body weight below 16 kg at 9 weeks of age (retarded growth) was significantly different among the treatment groups (*P*<0.05). Piglets treated with colistin or berberine had a lower proportion of deaths and retarded growth piglets than those treated with halquinol (11.2, 14.6 and 22.9%, respectively; *P*<0.05).

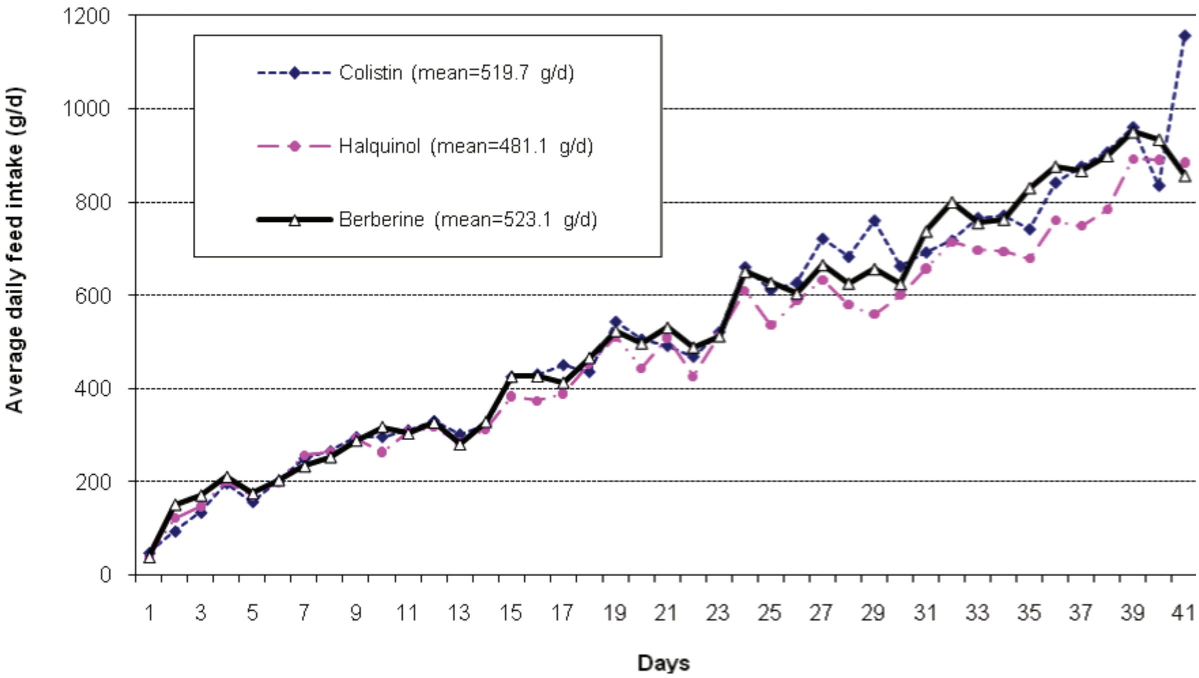

Fig. 1 Average daily feed intake (g/d) in piglets receiving 3 treatments, i.e., colistin, halquinol and herbal medicine (berberine) 205 piglets/treatment

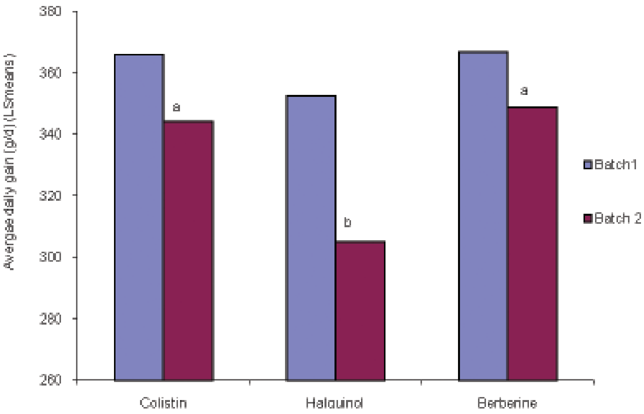

Fig. 2 Average daily gain (g/d) from weaning (3 weeks) to 9 weeks of age in piglets receiving 3 treatments, i.e., colistin, halquinol and herbal medicine (berberine); different letters indicate significant difference (P<0.01)

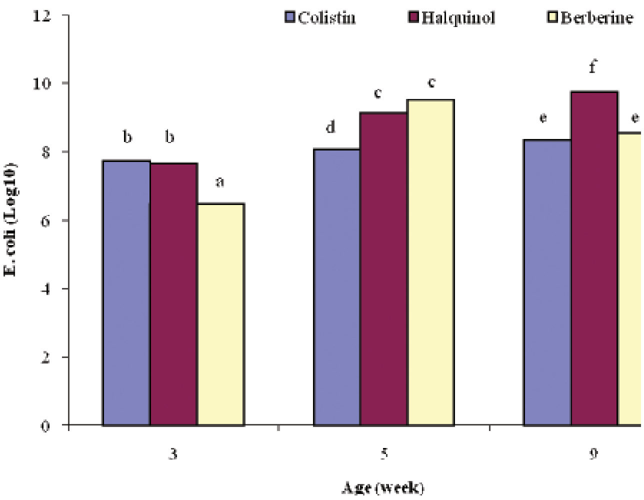

Fig. 3 Number of *Escherichia coli* counted in feces of the piglets treated with colistin, halquinol and herbal medicine (berberine) at 3, 5 and 9 weeks of age, a and b, c and d, e and f, differ significantly (P<0.05)

Body weight at entry influenced BW at 9 weeks of age and ADG (P<0.001). Regression analysis revealed that a 100-g increase in body weight at entry resulted in 160 g increase in BW at 9 weeks of age and 2.6 g/d increase in ADG. BW at 9 weeks of age, ADG and FCR of females and castrated males did not differ significantly (19.9 vs 20.0 kg; 339 vs 346 g/d; 1.6 vs 1.5, P>0.05).

During the second week of administration, the number of *E. coli* in the feces of piglets in group 1 and 2 was 1x10^9 and 5x10^9 MPN/g, which was significantly higher than that in group 3 (10^8 MPN/g) (P<0.05). During the sixth week of administration, the number of *E. coli* in groups 1 and 3 (3x10^8 and 5x10^8 MPN/g) was significantly lower than group 2 (7 x 10^9 MPN/g) (P<0.05) (Fig. 3).

Among the treatment groups, the number of *Bacillus* sp. in group 1 at the second week was lowest (5 x 10^{10} CFU/g) and significantly differed from that in group 2 and 3 (9 x 10^{11} and 6 x 10^{11} CFU/g). However, the number of Bacillus sp. did not differ significantly among the groups at sixth week after treatment (P<0.05) (Fig. 4).

The number of *E. coli* on duodenal mucosa collected at 6[th] week after treatment in group 1, 2 and 3 was 3 x 10^4, 7 x 10^3, and 4 x 10^4 MPN/g, respectively. Those from jejunal mucosa in group 1, 2 and 3 was 8 x 10^4, 1 x 10^5, and 8 x 10^4 MPN/g, respectively. Statistical analysis revealed that MPN/g of *E. coli* between duodenum and jejunum was not significantly different (P>0.05). The number of *Bacillus* sp. in group 1, 2 and 3 was 2 x 10^5, 9 x 10^5 and 4 x 10^6 CFU/g, respectively. The results indicated a tendency in the increase of *Bacillus* spp in group 3 in both duodenum and jejunum (group1: 10^6, group2: 10^7 and group3: 3 x 10^7 CFU/g).

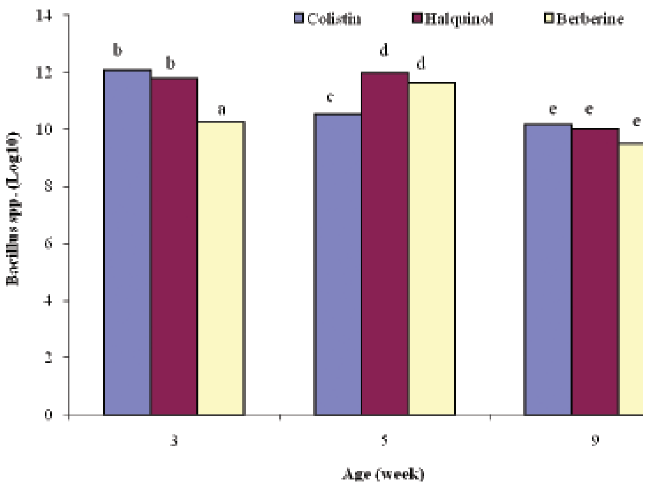

Fig. 4 Number of *Bacillus* sp. counted in feces of the piglets treated with colistin, halquinol and herbal medicine (berberine) at 3, 5 and 9 weeks of age, a and b, c and d differed significantly (P<0.05)

For the histological examination, some pathological changes were observed in the jejunum but not in the duodenum. No obvious colonization of bacteria on duodenal and jejunal epithelia was found and this was closely related to health status of the pigs that they had no intestinal disorders during the experiment.

Discussion

The present study demonstrated the growth performance, the feed intake of the piglets, the intestinal bacteria and the pathological changes after applying an herbal medicine in the feed of the nursery pigs. It was found that the herb did not decrease ADFI as well as FCR of the nursery compared with the common antibiotics used for controlling diarrhea i.e., colistin and halquinol. Furthermore, this herbal medicine increased BW at 9 weeks of age and ADG, and reduced the percentage of deaths and retarded growth pigs. Under field conditions, many factors such as BW at entry, temperature and humidity, sex and number of piglets per pen, might influence feed intake as well as the growth performance of the piglets. In the present study, these factors had been controlled; all piglets were reared in the same house and the evaporative cooling system was used to optimize temperature. The number of piglets per pen was equal among the treatment groups. However, the first batch had a lower numbers of piglets per pen than the second batch (10 and 15 piglets/pen, respectively), which might result in a lower ADG in the second batch compared with the first batch.

Berberine has been recommended for treament and control of bacterial diarrhea, intestinal parasite infections, and ocular trachoma infections (Amin *et al.,* 1969; Birdsall and Kelly, 1997). Studies have shown that berberine directly inhibits some *E. coli* enterotoxins, reduces smooth muscle contraction and intestinal motility and delays intestinal transit time in humans (Akhter *et al.,* 1979; Sack and Froelich, 1982; Yuan *et al.,* 1994). An *in vitro* study indicated that berberine sulfate was capable of inhibiting bacterial adherence to mucosal or epithelial surfaces, which is the first step for the infective process (Sun *et al.,* 1988). In the present study, a 120 ppm of berberine was added to the feed of the nursery pigs for 6 weeks. During this period, the ADFI for both batches was 523.1 g/d, which means the piglets received berberine, on average, 62.8 mg/day. Therefore, dosage used in this trial is relatively low, whereas therapeutic dosage for most clinical situations of berberine is 200 mg orally by two to four times daily (400-800 mg/d) (Birdsall and Kelly, 1997). Side effects of berberine may include gastrointestinal discomfort, dyspnea, lowered blood pressure, flu-like symptoms and cardiac damage which can result from high dosage application. Berberine usage should be avoided in pregnant animals, due to the potential in causing uterine contractions and miscarriage, and jaundiced neonates because of its bilirubin displacement properties (Chan, 1993). However, the adverse effect was not observed in the present study. The efficiency of berberine to prevent bacterial diarrhea might partly enhance growth as well as feed efficiency in the piglets.

In addition, the herbal medicine used in the present study included any other substance such as flavoniod. Flavonoid-derived natural products in plants are well-known as the floral pigments that also function as pollen fertility factors, signal molecules for beneficial plant-microbe symbiosis in the rhizosphere and anti-microbial defense compounds. Flavonoid compounds have cancer chemopreventive, antioxidant and antiasthmatic properties. There has been an explosion of interest in their use as health-promoting components of the human diet. Flavonoid has been used for the treatment of gastric disorders and gastric ulcers as a prescribed drug (Fukai *et al.,* 2002). However, the use of flavoniod as feed additive has never been studied in pig. In the present study, the additive effect of flavoniod might be involved.

In the present study, the group of piglets treated with the herbal medicine was able to control the number of *E. coli* in intestines as good as the treatment with colistin. Moreover, the use of herbal medicine did not inhibit the growth of any other beneficial flora such as *Bacillus* sp. The manipulation of gut flora during and after weaning should be keenly considered because weaned piglets are usually stressed by many factors, which might result in an imbalance of microbials in the microenvironment. The number of lactobacilli in the gut tends to decrease while *E. coli* increases at the upper region of the small intestine and subsequently cause diarrhea. To prevent fatal diarrhea caused by *E. coli*, a promotion of the beneficial flora for minimizing the digestive function such as *Saccharomyces* sp., *Bacillus subtilis, Lactobacillus* sp. or antimicrobial feed additive is useful (Fuller, 1989). Furthermore, Gedek et al. (1993) demonstrated that an increase of *Bacillus* sp. could reduce the adhesion and colonization of pathogenic bacteria on villous epithelia such as *E. coli*. Berberine not only reduced the number of pathogenic bacteria, but also hazardous effects from their enterotoxins in the jejunum of the piglets (Zhu and Ahrens, 1982).

In conclusion, the present study indicated the possibility of using an herbal medicine to treat and control diarrhea in the nursery without any negative effect on ADFI, ADG, FCR and mortality rate compared with the use of colistin and halquinol. The efficacy of the herbal medicine to control the number of *E. coli* was nearly resembled to that of colistin, and it had no adverse effect for *Bacillus* sp. population in all likelihood. Therefore, herbal-extracted product might be an alternative for reducing the overuse of antimicrobial agents for prevention and control of post-weaning diarrhea in piglets.

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