Weight gain by gut microbiota manipulation in productive animals

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ABSTRACT

Antibiotics, prebiotics and probiotics are widely used as growth promoters in agriculture. In the 1940s, use of Streptomyces aureofaciens probiotics resulted in weight gain in animals, which led to the discovery of chlortetracycline. Tetracyclines, macrolides, avoparcin and penicillins have been commonly used in livestock agriculture to promote growth through increased food intake, weight gain, and improved herd health. Prebiotic supplements including oligosaccharides, fructooligosaccharides, and galactosyl-lactose improve the growth performance of animals. Probiotics used in animal feed are mainly bacterial strains of Gram-positive bacteria and have been effectively used for weight gain in chickens, pigs, ruminants and in aquaculture. Antibiotics, prebiotics and probiotics all modify the gut microbiota and the effect of a probiotic species on the digestive flora is probably determined by bacteriocin production. Regulations governing the introduction of novel probiotics and prebiotics vary by geographical region and bias is very common in industry-funded studies. Probiotic and prebiotic foods have been consumed for centuries, either as natural components of food, or as fermented foods and it is possible to cause the same weight gain effects in humans as in animals. This review presents the use of growth promoters in food-producing animals to influence food intake and weight gain.

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1. Introduction

The gut microbiota plays an important part in the harvesting, storage, and expenditure of energy obtained from the diet [1]. Over the last few years, new technologies have been developed that have enabled researchers to attempt more systematic studies on intestinal bacterial flora and have provided more reliable information about its composition [2]. Indeed, an increasing number of studies have connected imbalances in the composition of the gut microbiota with obesity and its associated diseases [3]. Data from agriculture, laboratory animals and humans show that manipulating gut microbiota results in weight modifications and that further investigation of the effects of routinely adding high amounts of bacteria to food is required [4]. The role of digestive microbiota is still largely unknown, but gut flora bacteria do contribute enzymes that are absent for food digestion [5,6].

In the last century, it became obvious that the incorporation of growth promoters into animal feed made it possible to improve animal health conditions and to decrease food production costs significantly [7]. An increase in the growth rate normally reduces the cost of producing meat and a wide range of techniques are now known to be effective in increasing the growth rate and lean deposition in animals. The use of growth promoters is also being enhanced by the shortage of resources, such as animals, feed, water, and land. Animal gut microbiota have been manipulated through diet by means of feed additives, including antibiotics, probiotics and prebiotics. All these agents are typically ingested via feed or water, targeting the gut microbiota, where they initially play an antagonistic or barrier role in reducing the proliferation of pathogenic, opportunistic bacteria, preventing colonization and increasing energy intake [1]. As a result, livestock performance and feed efficiency are closely interrelated with the qualitative and quantitative microbial load of the animal’s gut, the intestinal wall’s morphological structure and immune system activity.

This review focuses on the use of growth promoters in animals and the possible mechanisms of action of these supplements.

2. Probiotics

Probiotics are live microorganisms, generally bacteria, but also yeasts that, when ingested live in sufficient quantity, have a positive effect on health in addition to the well-known nutritional effects [8]. The word “probiotics” is the antonym of the term “antibiotics”, which was introduced by Lilly and Stillwell in 1965, and indicates the substances produced by microorganisms that encourage the growth of other microorganisms [9]. Microorganisms used in animal feed are mainly bacterial strains of Gram-positive bacteria [9]. While a substantial number of microbial species have been reported to exhibit potential probiotic properties, established after in vitro and preclinical research and/or after full-scale clinical trials, only the most documented and robust strains make it to the market. A good probiotic agent should be nonpathogenic and nontoxic, should tolerate gastric acid, should adhere to gut epithelial tissue, and should produce antibacterial substances. Moreover, it should persist and withstand for short periods in the gastrointestinal tract.

2.1. The history of probiotics

Probiotic foods have been consumed for centuries before microbes were discovered, either as natural components of food or as fermented foods. Scientists in the 1800s mentioned the apparent effect on health of ingesting quantities of fermented milk products, but the reason for these effects on health remained unknown. In 1905, Nobel Prize winner Iila Metchnikoff was the first to study the addition of lactic acid bacteria in food scientifically [11] (Fig. 1). He proved that it is possible to make edible fermented milk products by using pure cultures of Lactobacillus bulgaricus, and suggested that lactobacilli were able to eliminate pathogenic toxin-producing bacteria from the colon. In 1906, Henry Tissier isolated Bifidobacterium from an infant and claimed it could displace pathogenic bacteria in the gut and in 1922, Lactobacillus acidophilus was reported to improve chronic constipation, diarrhea and eczema in patients. L. acidophilus was also confirmed in 1932 in patients with constipation and mental illnesses [11]. In the 1940s, the use of Streptomyces aureofaciens probiotics resulted in weight gain in animals, which led to the discovery of chlorotetacycline [1].

Between the 1950s and the 1980s, probiotic research focused on screening potential probiotic strains from isolates in nature or from human hosts, and defining the mechanisms of actions for probiotic strains. The term “probiotic” was first used by Lilly and Stillwell in 1965 to describe substances secreted by one microbe that stimulated the growth of another [12]. In 1966 a drug containing bifidobacteria was designed, and its industrial production began in 1972 [13]. The first proposed South African regulations regarding probiotics also appeared in 1972. The term probiotic, meaning food or drugs containing beneficial bacteria for a healthy lifestyle, appeared in world literature much later, in the 80s, following a renewed interest in these beneficial bacteria [14]. In 2001, the U.N. Food and Agriculture Organization redefined probiotics as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host”. In 2008, it was proposed that probiotics may have the same growth-promoting effects in human as in animals [4]. In 2013, the World Gastroenterology Organization published its global guidelines on probiotics and prebiotics, and confirmed that the efficacy of probiotics is strain-specific and dose-specific, dispelling the myth held by many that any yogurt can be considered a probiotic. To date, there are three broad categories of probiotics: (1) those with no health claims, (2) those which are food supplements with a specific health claim and (3) those considered as a probiotic drug [15]. Moreover, it was proposed that probiotics may have various biological effects and should be treated as medicinal products before they can be approved [1].

2.2. Regulations and biases of probiotics

The regulations governing introduction of novel probiotics and prebiotics vary by geographical region [16]. In the EU, the introduction of novel foods that were not used in the EU before 15 May 1997 is governed by the Novel Food Regulation 285/97/EC. The Novel Food Regulation of 1997 is currently under revision and a proposed new regulation was published in December 2013. For bacteria added to foods, a list of microbes intentionally added to foods is updated annually (QPS, Qualified Presumption of Safety of Microorganisms in Food and Feed) and this list forms the basis of organisms at the species level which are considered safe for foods and feeds in the European Union (EFSA 2013 update). A novel probiotic or prebiotic can be a potential component of conventional foods, food supplements or foods for particular nutritional uses. When designated as a novel food, a safety assessment follows the European Novel Foods Regulation [17], and an evaluation is needed for the EC to make a decision on the safety of the novel component. However, the line between nutrition, pharma and cosmetics is often unclear [18]. While debates and controversies within the scientific community generally stimulate further research, there is a
risk that lay people may find it difficult to place these controversies in context.

One of the considerations of evidence-based medicine and in the use of probiotics as food supplements is methodologic bias [19]. Bias is the introduction of one or more external factors that then interfere with the measurement or interpretation of the results of a clinical trial. Studies with probiotics have been difficult to assess, because many of the earlier studies were not statistically analyzed, experimental protocols were not clearly defined, microorganisms were not identified, and viability of the organisms was not verified. In many cases, the environmental and stress status of the birds was neither considered nor reported. Large amounts of money have been invested in probiotic products, but food-related research is subject to less stringent controls and protocols than pharmaceutical research. Indeed, probiotics are a very important economic issue, and much scientific research has been conducted in association with the agrifood industry. A transparent declaration of conflict of interest is important for publication in medical literature and it was found that the publication of studies financed by industries was associated with an increase in the journal’s impact [20]. 67% of the 63 randomized trials published regarding nutrition and obesity were sponsored by the food industry [21]. Some species were linked to weight gain, whereas others species were associated with weight loss. Meta-analyses revealed that Lactobacillus acidophilus, Lactobacillus fermentum and Lactobacillus ingluviei administration resulted in significant weight gain whereas Lactobacillus plantarum and Lactobacillus gasseri are associated with weight loss [26]. To date, L. acidophilus, L. fermentum, L. johnsonni, L. paracasei, L. plantarum, L. reuteri, L. rhamnosus and L. salivarius are the most commercialized Lactobacilli [27]. Concentrates of these bacteria are usually freeze-dried, spray-dried, or micro-encapsulated and are typically incorporated into dairy products in humans or in water in animals. Lactobacillus probiotics have been successfully used for the treatment of diarrhea, for irritable bowel syndrome, inflammatory bowel disease, and pouchitis [28]. Many commercial Lactobacilli probiotics products are currently available on the market worldwide and are rapidly gaining in popularity [29,30].

2.3. Probiotics as growth promoters in agriculture

Much of the information on the use of probiotics for farm animals comes from experimental trials performed by commercial organizations producing or selling probiotics. Although claims regarding the efficacy of probiotics are made for a wide variety of animals, including pets, horses and farm animals, most consumption is in chicken, pigs and cattle (Fig. 2). Different compositions may be more suitable for different animals and the type of probiotic can also be related to the age of the animal.

2.3.1. Lactobacillus sp. probiotics

Following the Metchnikoff studies of Lactobacilli and their use as probiotics, Lactobacilli are now the most commonly used probiotic bacterial strains. Several experiments have shown significant effects of Lactobacillus probiotic on weight in animals and humans, and these effects vary according to the species [25,26]. Some species were linked to weight gain, whereas others species were associated with weight loss. Meta-analyses revealed that Lactobacillus acidophilus, Lactobacillus fermentum and Lactobacillus ingluviei administration resulted in significant weight gain whereas Lactobacillus plantarum and Lactobacillus gasseri are associated with weight loss [26]. To date, L. acidophilus, L. fermentum, L. johnsonni, L. paracasei, L. plantarum, L. reuteri, L. rhamnosus and L. salivarius are the most commercialized Lactobacilli [27]. Concentrates of these bacteria are usually freeze-dried, spray-dried, or micro-encapsulated and are typically incorporated into dairy products in humans or in water in animals. Lactobacillus probiotics have been successfully used for the treatment of diarrhea, for irritable bowel syndrome, inflammatory bowel disease, and pouchitis [28]. Many commercial Lactobacilli probiotics products are currently available on the market worldwide and are rapidly gaining in popularity [29,30].

2.3.2. Poultry

The effect of different probiotics on chicken has been extensively investigated. Several Lactobacillus strains have been shown to decrease the population of Salmonella sp., Campylobacter sp. and some other non-beneficial bacterial groups in chicken guts [31].
The most common probiotics used for chickens are yeasts (Saccharomyces boulardii), and bacteria (Lactobacillus spp., Enterococcus spp., Pediococcus spp., Bacillus spp.) targeting the hindgut (caecum, colon) which harbors an abundant and very diverse microbial population, mainly composed of bacteria and archaea. Studies on the beneficial impact on poultry performance have indicated that probiotic supplementation can have positive effects. Probiotics can increase feed efficiency and productivity of laying hens [32], and an improvement in egg quality (decreased yolk cholesterol level, improved shell thickness, egg weight) has also been reported [32]. In some studies, it was found that the growth-promoting effects of probiotic bacteria were equal to or better than treatment with antibiotics in chickens [33–35]. Indeed, following treatment with Lactobacillus sp. probiotics, there was equal weight gain in animals treated with the antibiotic avilamycin [35,36], and better weight gain than in animals treated with chloroxytetracycline [34]. Moreover, live weight gains were significantly higher in experimental birds as compared to controls [37,38] (Fig. 3).

### Ruminants

The most commonly marketed products for ruminants are live yeast (Saccharomyces cerevisiae) preparations. In dairy ruminants, live yeasts have been shown to improve performance, the most consistent effects being an increase in dry matter intake and milk production. Ruminal acidosis is a common digestive disorder in high-producing dairy or beef cattle and is responsible for a decrease in animal performance. In vitro studies have reported that live yeasts could influence the balance of lactate-metabolizing bacteria, by limiting lactate production by Streptococcus bovis and favoring lactate uptake by Megasphaera elsdenii or Selenomonas ruminantium [39]. Moreover, S. cerevisiae could prevent pH decrease by stimulating certain populations of ciliate protozoa [40]. Feed efficiency can also be significantly improved after probiotic feeding [41]. The carcass-based gain/feed ratios also tended to be better for animals receiving the probiotic treatment [42]. Lactobacillus sp. treatment also resulted in higher metabolic activity, lower levels of non-esterified fatty acids, triglycerides, urea, and an increase in alkaline phosphatase and creatine kinase levels [43].

### Piglets

During the weaning period, the most promising effects of the use of probiotics are related to the competitive exclusion of pathogenic bacteria. The post-weaning period is characterized by a marked reduction in voluntary feed intake, poor growth and development, diarrhea and an increased risk of disease, particularly from Escherichia coli and Salmonella. Feed intake in pigs is highly variable following weaning. A relationship between feed intake after weaning and villus height has been reported and it was speculated that this relationship may affect the overall efficiency of nutrient capture and utilization [44]. Compared to control groups, weight gain has been reported in piglets after supplementing daily feed with L. casei subsp. casei, L. reuteri, or L. acidophilus (Table 1). The feed conversion rate in animals fed with Lactobacillus sp. was also better as they consumed less [46]. Piglets fed with Lactobacillus sp. also had significantly higher Lactobacillus sp. cell counts in their fecal samples [46,47].
Moreover, the higher *Lactobacillus* sp. and lower *E. coli* counts in animal feces was associated with a higher animal productivity [48].

### 2.3.5. Aquaculture

A wide variety of Gram-negative bacteria play a role as putative probiotics in aquaculture [49]. Probiotic administrations have been widely applied via water routine or feed additives with either single or a combination of probiotics or even a mixture with prebiotics or other immunostimulants. Probiotic administration varies from direct oral/water routine or feed additives, in which the former is considered the most practical method for prawn probiotics. Normally, probiotics can be added directly into culture water as water additives, bathed in bacterial suspension [50]. Endospore-forming members of *Bacillus* genera including *Bacillus subtilis* are commonly used in aquaculture [50]. Moreover, several yeasts have been proven to provide benefits to aquatic animals. *Saccharomyces cerevisiae* has been recognized to have potential as a substitute for live feed production of fish whereas the marine yeast *Yarrowia lipolytica* has improved the survival and growth of pearl oysters [50]. However, appropriate probiotic levels depend on the probiotic species, fish species and their physiological status, rearing conditions and specific goal of the applications.

### 2.4. Possible actions of probiotics

Various mechanisms have been proposed by which probiotics modify the gut microbiota, including competition for substrates, production of toxic compounds that inhibit pathogens, and competition for attachment sites. As a result, large differences are seen among strains belonging to the same species, as they may exhibit distinct phenotypes and properties that can trigger various clinical effects [1,25]. Research-based evidence largely confirms that probiotic activity mechanisms are diverse and strain-specific rather than conserved within a species or genus. The mechanisms by which probiotics exert their effects may involve modification of gut pH, competition for pathogen binding and receptor sites, as well as for available nutrients and growth factors, which antagonize pathogens through the production of antimicrobial compounds that stimulate immunomodulatory cells and lactase production. Comparative genomics has revealed the unusual diversity of the genus *Lactobacillus* at structural and functional levels and a recent genome analysis revealed significant differences between *Lactobacillus* spp. that are associated with weight modifications with respect to the genes involved in transcription, replication, recombination and repair, lipid metabolism, carbohydrate transport and metabolism, and bacteriocin production [25]. Indeed, *Lactobacillus* associated with weight gain lack enzymes involved in the catabolism of fructose, but these strains encode several enzymes that participate in the conversion of sucrose into glucose and fructose and enzymes that promote fructose production. Moreover, thiols were only encoded in *Lactobacillus* associated with weight gain which is thought to potentially help these bacteria to participate in lipid digestion in the upper gastrointestinal tracts of humans through the degradation of dietary fats (acylglycerols) [25]. In addition, LAB probiotics can modulate the innate and adaptive immune defence mechanisms by improving the human intestinal microbiota [51]. Studies suggest that LAB promotes and maintain gastrointestinal motility, prevent inflammation, and act protectively against cancer development by binding to mutagens, inactivating them through the production of antioxidants, and by enhancing the human immune system [52]. Indeed cytokine production, antibody production and NK cell population have been

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Animal</th>
<th>Bacteria inoculation</th>
<th>Duration of treatment</th>
<th>Weight gain increase</th>
<th>Feed intake</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination of <em>L. acidophilus</em>, <em>L. salivarius</em>, <em>L. paracasei</em> subs. <em>paracasei</em>, <em>Calves</em></td>
<td>1 $\times 10^9$</td>
<td>8-weeks</td>
<td>Significant</td>
<td>Feed efficiency significantly improved</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>L. acidophilus</em></td>
<td>Cattle</td>
<td>5$x10^7$</td>
<td>6-weeks</td>
<td>Not significant</td>
<td>Not significant</td>
<td></td>
</tr>
<tr>
<td><em>L. acidophilus</em></td>
<td>Calves</td>
<td>3$x10^9$</td>
<td>49 days</td>
<td>Significant</td>
<td>Higher than for the control group</td>
<td></td>
</tr>
<tr>
<td><em>L. acidophilus</em>, <em>L. salivarius</em>, and <em>L. reuteri</em></td>
<td>Goats</td>
<td>1 $\times 10^{11}$</td>
<td>—</td>
<td>Significant</td>
<td>Feed efficiency significantly improved</td>
<td></td>
</tr>
<tr>
<td><em>L. reuteri</em></td>
<td>Piglets</td>
<td>1 $\times 10^6$ or 1 $\times 10^8$</td>
<td>28 days</td>
<td>Significant</td>
<td>Feed conversion was better</td>
<td></td>
</tr>
<tr>
<td><em>L. acidophilus</em></td>
<td>Piglets</td>
<td>3$x10^8$</td>
<td>Suckling period</td>
<td>Significant</td>
<td>No effect on feed conversion</td>
<td></td>
</tr>
<tr>
<td><em>L. casei</em> subsp. <em>casei</em></td>
<td>—</td>
<td>—</td>
<td>Significant</td>
<td>No difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>L. acidophilus</em> a mixture of 12 <em>Lactobacillus</em> strains</td>
<td>Piglets</td>
<td>1 $\times 10^9$</td>
<td>—</td>
<td>Significant</td>
<td>Feed-to-gain ratios decreased</td>
<td></td>
</tr>
<tr>
<td><em>L. fermentum</em> <em>Lactobacillus</em> subsp.</td>
<td>Chicks</td>
<td>1 $\times 10^7$</td>
<td>1 inoculation</td>
<td>Significant</td>
<td>Feed conversion efficiency improved</td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus</em> sp.</td>
<td>Chicks</td>
<td>1 g/kg</td>
<td>42 days</td>
<td>Significant</td>
<td>Better food efficiency</td>
<td></td>
</tr>
<tr>
<td>Combination of <em>L. reuteri</em>, <em>E. faecium</em>, <em>B. animalis</em>, <em>P. acidilactici</em>, and <em>L. salivarius</em></td>
<td>Chicks</td>
<td>2 $\times 10^{12}$</td>
<td>—</td>
<td>Significant</td>
<td>Feed conversion rate improved</td>
<td></td>
</tr>
<tr>
<td><em>L. acidophilus</em> and <em>L. salivarius</em> subsp. <em>salicinius</em> mix</td>
<td>Chicks</td>
<td>1 $\times 10^6$</td>
<td>40 days</td>
<td>Significant</td>
<td>Not mentioned</td>
<td></td>
</tr>
<tr>
<td><em>L. casei</em></td>
<td>Chicks</td>
<td>0.1% (L. casei)</td>
<td>3 weeks</td>
<td>Significant</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td><em>L. casei</em> and <em>L. acidophilus</em></td>
<td>Chicks</td>
<td>“Low and high” dose respectively</td>
<td>6 weeks</td>
<td>Significant</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus</em> sp.</td>
<td>Turkey</td>
<td>1 $\times 10^9$</td>
<td>3 days</td>
<td>Significant</td>
<td>Feed conversion ratio decreased</td>
<td></td>
</tr>
<tr>
<td><em>L. acidophilus</em></td>
<td>Mongrel pups</td>
<td>2 $\times 10^7$</td>
<td>13 weeks</td>
<td>Not significant</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td><em>L. acidophilus</em>, <em>B. subtilis</em>, or both</td>
<td>Tilapia</td>
<td>1 $\times 10^7$</td>
<td>—</td>
<td>Significant</td>
<td>Feed conversion ratio decreased</td>
<td></td>
</tr>
</tbody>
</table>
shown to increase with yogurt consumption and the per os administration of *Lactobacillus* probiotics, can stimulate macrophage activity [53]. Stimulation of macrophage activity is unlikely to affect the composition of the gut microbiota, but there is evidence of influx in the intestine of systemically produced antibody [51]. Recently, it was indicated that probiotics and prebiotics affect type 2 diabetes and cardiovascular diseases by changing gut microbiota, regulating insulin signaling, and lowering cholesterol [54].

Recently, it was also suggested that the bacteriocins produced by probiotic bacteria can play an important role in the modification of the gut microbiota [1,55]. Bacteriocins are peptides produced by bacteria that are active against other bacteria [56] and are beneficial to probiotics because they facilitate colonization in the competitive gastrointestinal environment. Many bacteriocins are produced by lactic acid bacteria (LAB). The antibacterial activity of bacteriocins produced by probiotic bacteria has been extensively demonstrated *in vitro* [57] (Fig. 4). Moreover, it was recently found that *Lactobacillus* spp. associated with weight gain encoded more bacteriocins than *Lactobacillus* spp. associated with weight loss [25].

### 2.5. Same probiotics used in human and animals

Over the last few years, there has been an increasing trend towards the use of the same probiotic strains in humans and in animals. Indeed, humans and animals may obtain the same effects from the use of the same probiotic strains in humans and in animals. Indeed, humans and animals may obtain the same effects from the use of the same probiotic strains in humans and in animals [6,59]. Similarly, as in animals, probiotic bacteria have been used to harvest energy from the human diet that could lead to the development of new treatments for malnutrition [60]. This weight gain is probably due to the use of *Lactobacillus* spp that produces bacteriocins [60]. Many probiotics for human consumption that are also present in obese humans are also used as growth promoters in animals and are selected by antibiotics that promote weight gain in animals and humans.

In contrast there are studies indicating that probiotics indicated that probiotics have limited efficacy in terms of decreasing body weight and BMI and were not effective for weight loss [61]. Indeed a recent meta-analysis indicated that probiotics are not effective in decreasing body weight and BMI [61]. In contrast, other meta-analysis revealed that although probiotics had heterogeneous effects across different comparisons studies, it is possible that these products might be useful for weight loss in adults [58]. Similarly, other studies show that the overweight and obese patients that receive probiotics and symbiotics present a significant reduction in the abdominal adiposity and BMI, and also, probiotic supplementation produce an improvement in the metabolism of carbohydrates, as well as a reduction in the metabolic stress in patients with type 2 diabetes and insulin resistance syndrome [62].

Taken together, there is evidence that of potential weight implications that accompany the use of probiotics. However there are contradictory effects in the reported studies that might be related to inappropriate design such as diversity, the use of several strains, and the small number of individuals receiving some interventions. As a result, future studies should explore this concept, as well as weight change, after probiotic and antibiotic interventions.

### 3. Prebiotics

Prebiotics were initially defined as “nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already in the colon, and thus attempt to improve host health” [63]. The U.N. Food and Agriculture Organization (FAO) defines ‘prebiotic’ as “a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well-being and health” [64]. The dominant prebiotics are fructooligosaccharide products (FOS, oligofructose, inulin). However, many food components, especially many food oligosaccharides and polysaccharides (including dietary fiber), have been claimed to have prebiotic activity without due consideration to the criteria required. Today, only two dietary, nondigestible oligosaccharides...
fulfill all the criteria for prebiotic classification. The daily dose of the prebiotic is not a determinant of the prebiotic effect, which is mainly influenced by the number of bifidobacteria/g in feces before diet supplementation with the prebiotic begins.

3.1. Prebiotics as growth promoters

Several types of oligosaccharides have been suggested to have specific functionalities in calves. The addition of galactosyl-lactose in milk replacers was previously found to have beneficial effects on the growth and health of dairy calves [65]. Moreover, supplementation with oligosaccharides, fructooligosaccharides, and galactosyl-lactose may improve the growth performance of calves in either the pre- or post-weaning stage; however, modifications to the activities of microbial fermentation by these sugars have not yet been examined in detail [66]. An in vivo study indicated that cell oligosaccharide feeding improved daily gain and feed efficiency in calves during the post weaning period, but not during the pre-weaning period [67]. The addition of fermentable carbohydrates to the diet of weaning piglets is regarded as a comparatively straightforward way to improve microbiota composition and functionality in both the small and large intestines of piglets. Instead, a high dietary level of lactose favors bifidobacteria and lactobacilli while decreasing E. coli [68]. Moreover, the addition of insulin to different basal diets affects the proportion of piglets with detectable levels of bifidobacteria, while lactobacilli are unaffected [69]. In poultry, prebiotics are commonly used to decrease Salmonella that causes diarrhea [70] and dietary supplementation with fructooligosaccharides also decreased C. perfringens and E. coli, and increased Lactobacillus diversity in chicken guts [71]. Moreover, it was found that broiler chicks treated with fructooligosaccharide products presented an improvement in their growth, as well as increases in cecal lactobacilli [72]. Inulin and fructooligosaccharides are considered selective, because they are fermented by certain lactic acid bacteria and bifidobacteria [73]. Moreover, it was demonstrated that many Lactobacillus and Bifidobacterium were capable of fermenting fructooligosaccharides [74]. Therefore, it may be possible to explain the growth-promoting effects of prebiotics on animals by the selective increase of the population of Lactobacillus and Bifidobacterium in their gut microbiota.

4. Antibiotics

In combination with dietary changes, antibiotic administration has been associated with changes in the population structure of the gut microbiota. In the 1940s, the use of Streptomyces aureofaciens probiotics resulted in weight gain in animals, which led to the discovery of chlorotetracycline. Since then and for more than 60 years, antimicrobials have been used to maintain or improve health and feed efficiency in productive animals. The oral administration of antibiotics, in either feed or water, suggests that the microbiota of the gastrointestinal tract is a major target [74]. Although modifications to gut microbiota revert following short-term antibiotic therapy, long-term therapy can result in pervasive alterations [75]. Many different classes of antibacterial agents, including macrolides, tetracyclines, and penicillins, promote animal growth. In poultry, for growth promotion and prevention of infectious diseases, several classes of antimicrobial agents, such as glycolipids (bambermycin), polypeptides (bacitracin), ionophores (salinomycin), ß-lactams (penicillin), streptogramins (virginiamycin), and tetracyclines (chlorotetracycline) [76] are used. In contrast, these growth-promoting effects have not been demonstrated as antifungals or antivirals [77]. The glycopeptidetides avoparcin and bacitracin, the macrolides spiramycin and tylosin, and the streptogramin virginiamycin were withdrawn as growth promoters in the European Union between 1995 and 1999. In the United States, antibiotics and related antimicrobial substances increase weight gain by as much as 15% [78]. To date, growth promoters loosely defined as antibiotics used in healthy animals at concentrations below 200 g per ton of feed for more than 14 days. It is estimated that the amount of growth promoters used in U.S. animal production ranges from 3.1 million pounds to approximately 25 million pounds annually [79]. It has been estimated that antibiotic growth promoters in animals, through unspecific and poorly-defined mechanisms, improve body weight by 5–6% and feed efficiency by 3–4%, with the most pronounced effects observed in young animals [78]. Early studies, conducted between 1950 and 1960, showed mean increases in body weight of 8.5%–8.8% using penicillin and 10.2%–12.3% using tetracyclines [79]. Between 1968 and 1980, median body weight increase was found to be 11% for penicillin and 8%–10% for tetracyclines [79]. A meta-analysis of more than 1000 growth experiments performed in swine over a 25-year period demonstrated that antibiotics improved growth rate in starter pigs (7–25 kg) by an average of 16% and feed efficiency by 7% [80]. Antimicrobial growth promoters are no longer permitted in the European Union, but they are still used in North America and other countries.

5. Conclusions

Probiotics, prebiotics and antibiotics alter the intestinal microbiota and immune system to reduce colonization by pathogens under certain conditions. Moreover, given recent international legislation and pressure from domestic consumer groups to withdraw growth-promoting antibiotics and limit antibiotics available for the treatment of bacterial infections, probiotics can offer alternative options. New advances in the application of probiotics aim to produce significant changes in gut physiology and provide even better health conditions, as well as increasing performance parameters in different animals. Evidence now suggests that some antibiotics are also associated with weight gain in humans, including malnourished children [81], neonates [82] and adults [74,83,84]. Probiotics have also been associated with weight gain in humans [60]. Human beings have used probiotics for many years, but most experimental data are confined to animal models and, until now, most human studies have been limited to fairly small populations. Many of the studies concerned Lactobacillus spp interventions and data from agriculture, laboratory animals and humans show that manipulating gut microbiota results in weight modifications. As in animals, the long-term effects of probiotic interventions should be investigated in humans and the regulations established by the European Food Safety Authority and the U.S. Food and Drug Administration for probiotics should be based on high-level data from good-quality studies. The probiotics used for growth promotion in the farming industry should be examined to determine if they cause the same effects in humans.

In conclusion, probiotics and prebiotics show promise as alternatives for antibiotics for growth promotion in agriculture, but much research is still needed to understand the effects on host weight by routinely adding large quantities of bacteria to our food.

Conflict of interest

None.

Acknowledgments

None.

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