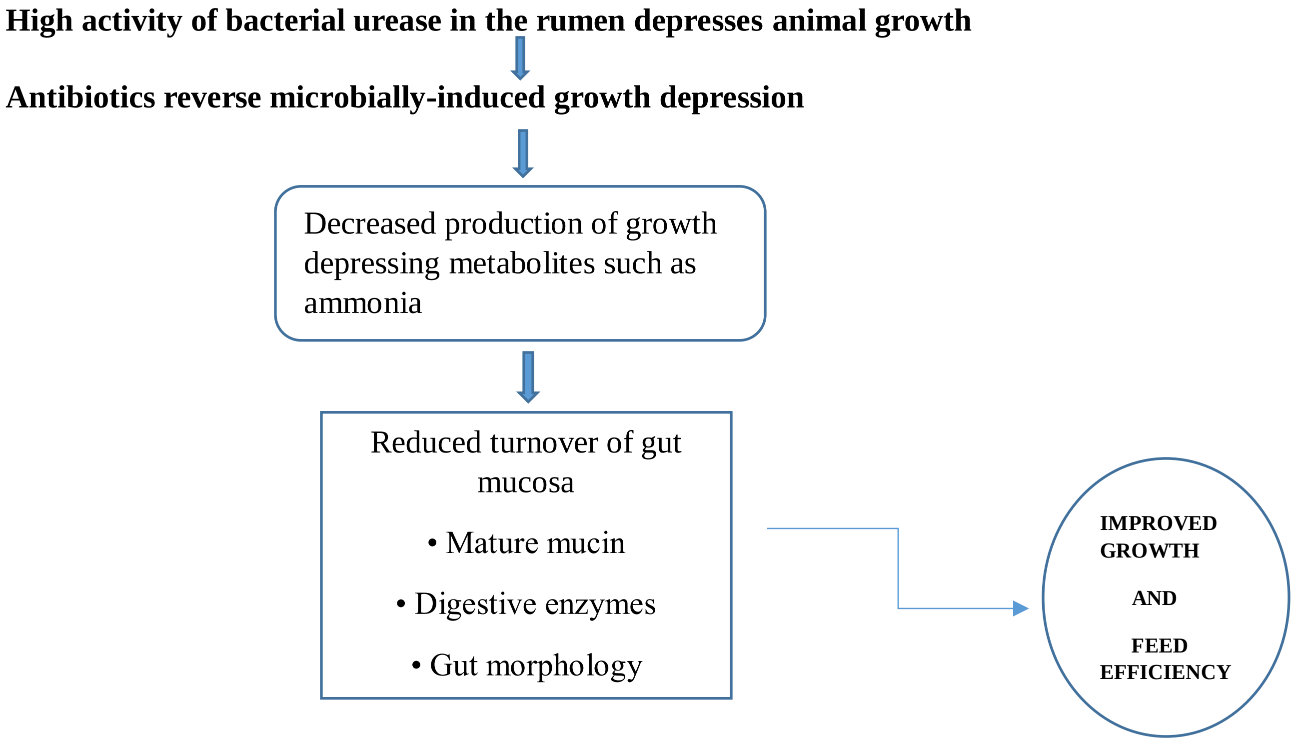
Literature search: Presenting evidence that urease inhibition is leading to enhanced animal health resulting in accelerated growth.

Background Information

Urease is an enzyme that catalyzes the breakdown of urea into ammonia, which can be used by rumen microorganisms for the synthesis of amino acids [1]. Amino acids are essential for the growth of animals and plants. However, the high activity of urease in the rumen can also decrease the efficiency of urea utilization, because the rate of ammonia release from urea is much faster than the rate of its assimilation by rumen microbes for the synthesis of amino acids [2]. Moreover, if the concentration of ammonia exceeds a certain limit, it causes toxicity to the animals [3]. Their bodies have to detoxify the excess ammonia. The detoxification process requires energy. When this process can be more balanced, the energy can be used for increasing body weight [4]. An overload of ammonia induce several toxic effects in animals. It has been shown that the ammonia produced in the colon reduces the life span of the colonic mucosal cells. These cells are high in protein and their sloughing into the colon accounts for a significant portion of the obligant protein loss from animals. Decreasing the conversion of urea to ammonia in the colon would prevent the loss of colonic mucosal cells and their protein from the gastrointestinal tract. Moreover, the liver would be spared, the core of driving the futile cycle between ammonia and urea which is energy consuming. It would also lead to increased use of ingested protein in farm animals improving their growth [5].

Antibiotics improve animal health and growth decreasing gastrointestinal ureolytic activity

Antimicrobial growth promoters enhance nutrient and energy availability for animals, while decreasing toxic molecules in the gut like ammonia, resulting in reduced turnover in the colon epithelium. Studies have shown that animals given antimicrobial growth promoter supplemented feeds grow faster and more uniformly than controls. Most feeds for broilers, pigs, and veal calves are supplemented with antimicrobial growth promoters, with beef cattle receiving 1/3 of these supplements. Currently, certain antibiotics such as avilamycin, flavomycin, lasalocid, monensin, and salinomycin are allowed with permitted doses around 20 g/t feed [6]. The mechanism behind enhanced animal growth involves [7];



Increased weight gain in rats and chicks concurrently with decreased gastrointestinal ureolytic activity has been demonstrated with antibiotics, an organic arsenical and cyclic urea derivatives [8] [9] [10] [11]. This indicates a causality between an excess of ammonia production and weigh gain. Obviously this is an indirect measure, as not only urease producing bacteria die from antibiotic use. Harbers and his colleagues found that chicks showed enhanced growth of 17% with barbituric acid and 25% with chlortetracycline. When the chicks were killed, they had lowered gastrointestinal ammonia concentrations [11].

Application of chemical Urease inhibitors improves animal health to a limited extent

Various chemicals have also been used to inhibit urease activity aiming to improve animal health. It has been shown that N-(n-butyl) thiophosphoric triamide (NBPT) and hydroquinone improves nitrogen utilization and decreases NH3 production in growing lamb and sheep decreasing urease activity [12] [13] [14]. The major disadvantage is that the chronic use of chemicals may cause ruminal microflora to adapt, limiting their practical use in enhancing dietary urea utilization. A study has shown that the depression in urea degradation induced by NBPT was diminished with its chronic use. The maximum response to NBPT was occurred on day 2 but diminished by day 15 of the experiment. They concluded that while NBPT can temporarily inhibit ruminal urease, chronic administration may cause ruminal microflora to adapt, limiting its practical use [14]. Cinnamon extracts have also been used to reduce nitrogen loss through ammonia production. A study investigated the role of cinnamon extracts in reducing urease activity and increasing growth performance in broilers. It was found that adding 250 mg/kg of cinnamon extracts to broiler diets significantly improve the growth performance of broilers and reduce nitrogen loss via ammonia production [15]. Yucca schidigera extract also help reducing ammonia production in livestock housing. A study found that Yucca schidigera extract decreases nitrogen production may by inhibiting urease and improves nutrient utilization and gut barrier function in weaned piglets [16]. Similarly, essential oil mixtures are found important in reducing ammomia emissions. A study found that 10 ppm cinnamaldehyde, 20 ppm thymol and 200 ppm carvacrol mixture inhibited the activity of urease and enhanced nitrogen digestibility of 85.4%, decreasing ammonia production in pigs [17].

Feeding animals antiurease antibodies improves their feed conversion and growth

Feeding animals antibodies against urease improves the performance of animals [4]. It has been studied that passively administered antiurease antibody enhances feed conversion efficiency in mammals. A study found that mammals, such as swine show 9 to 15 points enhanced feed conversion efficiency when fed a diet containing anti-urease antibodies for three to four consecutive weeks at a dose of 25 to 500 mg of antibody extract per ton of feed, preferably 25 to 100 mg/ton. Sheep and cows also grow with enhanced feed conversion when fed with a diet containing anti-urease antibodies. Similarly, chickens and turkeys also grow faster when fed with diet containing anti-urease antibodies. Anti-urease antibodies can be produced by injecting animals with urease and collecting their blood serum, but this procedure is costly and invasive. However, alternative ways to prepare antibodies should be considered. Repeated injections of urease antigens to hens, increase the average yield of anti-urease in the eggs [18].

It has been found that body weight of mammals increases when purified antiurease antibody is added to the feed of mammals. A study found that body weight of piglets increased when antiurease antibody treated feed at dose of 50 mg/kg was supplied for four weeks. Similarly, body weight of weaned pigs increased 24 % when they were fed antiurease antibody containing diet for 6 weeks. Another way to prepare active, stable, and functional antiurease antibody is spray drying the egg containing a urease specific antibody. In an experiment, body weight of pigs increased from 93.95 kg to 99.74 kg when they were fed with diet containing 250 mg/kg of spray dried egg containing antiurease antibody for 17 weeks [18].

Another study found that body weight and feed conversion efficiency of animals increase when they are fed with an effective dose of antibodies against anti-nutritional factors, such as urease. The antibody administered to animals can be present in unfractionated whole egg or egg yolk, and can be freeze dried, spray dried, or suspended in a suitable liquid. Feeding an effective amount of anti-urease antibody to animals such as cats, dogs, pigs and other companion animals, that may suffer a weight loss due to disease or malnutrition, increases their weight. It was found that body weight of chickens was increased from 348 g to 377 g when they were fed with the diet including a preparation of dried egg yolk containing anti-urease antibodies for three weeks [4].

Urease vaccination improves animal health and growth

Studies have shown that urease vaccination improves animal health and growth by reducing urease activity and ammonia toxicity through the production of antiurease antibodies. Interestingly similar results have been obtained during the 4 weeks following active immunization with crystalline jackbean urease commensurate with demonstrable circulating urease antibody. A study investigated the effect of urease vaccination on body weights of rats and chicks. It was observed that immunized chicks experienced a weight gain of 905 g, compared to the 777 g gained by the control group. Similarly, the immunized rats exhibited slightly accelerated growth and statistically significant difference in feed efficiency [19]. Another study investigated the effect of urease immunity upon rats given controlled vitamin A intakes. They found reduced ammonia production and ureolytic activity in the gastrointestinal tract of rats immunized with crystalline jackbean urease. Moreover, immunized rats experienced 17% to 31% accelerated growth and displayed 40% more feed consumption and utilization [20]. Researchers have also studied the effect of urease immunization of growing pigs upon their performance and intestinal ureolysis. It was found that urease prepared from jackbean meal when injected intraperitoneally, stimulates the production of urease antibody (antiurease) and reduces intestinal urease activity. The average daily gain was 1.64 lb in immunized pigs when injected with 10 unit urease [21].

Pros and Cons of Urease vaccination

One major disadvantage of urease immunity is the need for repeated immunologic challenges in order to maintain the required levels of antibody activity. However, it may be possible to develop slow release depot preparations containing urease and other antigens, which could potentially eliminate the need for multiple injections. Immunization offers several distinct advantages. Its specificity allows for control of the targeted process through normal bodily secretions, with minimal risk of altering bacterial populations. In contrast to antibacterial agents or other chemicals, urease immunization specifically control the required process without causing adverse effects to the host or other non-target processes. Additionally, most antigens are easily destroyed through processing methods, and antibodies are proteins that are naturally consumed. As a result, residues that often contaminate meat or animal products treated with chemical agents can be avoided [22].

Table of findings with respect to improved health and accelerated growth

References	Source of Inhibition	Animal	Positive health effects or growth rate
Harbers et al (1963a)	Barbituric acid and chlortetracycline	Chicks	Enhanced growth of 17% with barbituric acid and 25% with chlortetracycline
Ludden et al (2000)	N-(n-butyl) thiophosphoric triamide (NBPT)	Lambs	Improved nitrogen utilization and decreased NH3 toxicity
Zhang et al (2002)	Hydroquinone	Lambs	Improved nitrogen utilization and decreased NH3 toxicity
Zhang et al (2002)	Hydroquinone	Sheep	Improved nitrogen utilization and decreased NH3 toxicity
Chen et al (2009)	Cinnamon extracts	Broilers	Reduced urease activity and ammonia toxicity resulting in increased growth performance
Fan et al (2022)	Yucca schidigera extract	Weaned piglets	Improved nutrient utilization and gut barrier function
Hsu et al (2022)	Cinnamaldehyde, thymol and carvacrol mixture	Pigs	Enhanced nitrogen digestibility of 85.4%, decreasing ammonia toxicity
Pimentel, 1998	A diet containing anti-urease antibodies	Swine	9 to 15 points enhanced feed conversion

Pimentel, 1998	Antiurease antibody treated feed at dose of 50 mg/Kg supplied for six weeks	Weaned pigs	24 % increase in body weight
Pimentel, 1998	A diet containing 250 mg/kg of spray dried egg containing antiurease antibody fed for 17 weeks	Pigs	Body weight increased from 93.95 kg to 99.74 kg
Pimentel, 2009	A diet including a preparation of dried egg yolk containing anti-urease antibodies fed for three weeks	Chickens	Body weight increased from 348 g to 377 g
Dang and Visek, 1960	Urease vaccination	Rats and Chicks	Weight gain of 905 g, compared to the 777 g gained by the control group
Harbers et al (1963b)	Immunization with crystalline jackbean urease	Rats	17% to 31% accelerated growth and 40% more feed consumption and utilization
Kornegay et al (1964)	Urease immunization	Pigs	Average daily gain was 1.64 lb when injected with 10 unit urease

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