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review article

Zeolite clinoptilolite nanoporous feed additive for animals of veterinary importance: potentials and limitations

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Abstract

In the past two decades many substances of natural or synthetic origin were studied as potential alternatives to antibiotic growth promoters (AGP) and some of them, particularly immunomodulators (IMs) and nutraceuticals (NCs), have shown to be capable of stimulating functions of the immune system and improving general health. At the same time, they were shown to be harmless for animals and the environment. Promising results have been obtained with natural clay minerals, zeolites among which clinoptilolite (CPL) is the best known as zootechnical and biomedical feed ingredient widely reported in scientific literature and used in farm animal nutrition. CPL has a potential to replace AGP due to its unique anti-bacterial properties, safety and efficacy as dietary supplement in food animals unifying potentials of an IM and NC. Currently, there are many reasons for CPL utilization in animal biotechnology and veterinary medicine because of its detoxificating, antioxidant, hemostatic, anti-diarrheic, growth-promoting and immunostimulating properties. Also, in human medicine it is an adjuvant in immunodeficiency states, oncology (after chemotherapy and radiotherapy) or reducer of radioactive elements. The aims of this review were to compile and discuss scientific data on safety and efficiency of nutritive modulation by dietary CPL (and other zeolites) as an alternative to AGP in animals of veterinary importance. In particular the aim is to analyse its potentials and limitations in cattle regarding metabolic and endocrine status, oxidative stress and systemic/local inflammatory responses involved in reproductive and metabolic disorders of dairy cows. Altogether, these analyses will contribute to objective validation of practical significance of CPL as a novel feed additive able to maintain and improve health, fertility and performance in cattle production.

INTRODUCTION

The phrase „survival of the fittest" as an alternative to „natural selection" has been adopted and published in 1868 by Charles Darwin (*1*), and nowadays is becoming so true because of the rapid emergence of antibiotic resistant strains of pathogenic microbes of biomedical, particularly veterinary importance. This is a consequence of non-clinical use and misuse of dietary antibiotics for more than sixty years to prevent bacterial infections and to enhance performance in livestock production, mostly in chickens and pigs (*2*). Namely, the increased sanitary problems in intensive farming of food animals have been overcome thus far by adding sub-therapeutic doses of antibiotic growth promoters (AGP) in-feed to enhance production efficiency by increasing growth rate, improving feed utilization and reducing mortality from clinical disease is well documented particularly in swine production systems (*3*). However, the consumers especially in developed countries are becoming increasingly concerned about drug residues in meat and other animal products (*4*). In addition, it has been suggested that the continuous use of antibiotics may contribute to a reservoir of drug-resistant bacteria (*5*) which may be capable of transferring their resistance to pathogenic bacteria in both animals and humans (*6*). As a result, many countries have banned or are banning the inclusion of antibiotics in diets as a routine means of growth promotion. The first experience of an AGP ban in Sweden in 1986 indicated a reduction in growth and an increase in morbidity and mortality rates in weaned pigs, which emphasized the importance of antibiotic use in intensive swine production(*7*). The total ban of dietary AGP in the EU countries since January 1, 2006 (EU Regulation No. 1831/2003) and the elimination of their use in animal feed and water in the USA effective January 1, 2017 (FDA, CVM 2012, VFD Basics 2017) has had a serious influence on both health and performance of food animals underlining the need to develop alternative dietary and non-dietary strategies to evaluate the potential antimicrobial agents for their replacement (*8*). According to the World Health Organization, most antibiotics will not be effective in the control of microbial infections of both animals and humans beyond 2020 and, thus, crucial questions arise „is host innate and adaptive immunity the answer", „what are novel anti-infective strategies", and „can immunomodulators play a role as alternatives to antibiotics"? (*9*). Such global concerns over the use of AGP in diets of food animals and increasing emergence of antibiotic resistant pathogenic bacteria has led researchers to look for alternatives to conventional antimicrobials in livestock production (*10*). In the past two decades, a significant amount of research has been focused on immunomodulators (IMs) and nutraceuticals (NCs), substances which are capable of stimulating functions of the immune system and the bioactive components of feed that have shown positive impact on gut health and performance, and were harmless for the animal and the environment (*4, 8, 11, 12*). Promising results have been obtained with natural, synthetic or modified clay minerals, zeolites (*13*) among which clinoptilolite (CPL) is the best known as zootechnical and biomedical feed ingredient widely reported in the scientific literature and used in farm animal nutrition as candidate to replace AGP in farm animals (*14, 15*) due to its unique antibacterial properties, safety and efficacy as dietary supplement, particularly reported for swine (*16-19*). So far, CPL has been successfully used in animal biotechnology and veterinary medicine as the agent which is capable to ameliorate mycotoxicosis, maintain gut health by acting favorably on intestinal microbiota, reduce, prevent and treat diarrheal disease in farm animals, decrease the level of toxic heavy metals and ammonia, improve immunity, general health and growth performance in animals of veterinary and biomedical importance, and thus exhibiting potentials of both an IM and NC (*4, 20-24*). In human medicine, the experiments *in vitro* and *in vivo* have suggested that CPL could be used as an adjuvant in immunodeficiency states and anticancer therapy, antioxidative agent or reducer of the levels of radionuclides (*25-28*). This review article intended to summarize and discuss the published reports on safety and efficiency of beneficial nutritive modulation by dietary CPL (and other zeolites) as an alternative to AGP in animals of veterinary importance, and in particular to analyse its potentials and limitations in dairy cattle regarding metabolic and endocrine status, oxidative stress and systemic/local inflammatory responses involved in reproductive and metabolic disorders of dairy cows.

Pioneer research on natural zeolite clinoptilolite in biomedicine in Croatia

Natural, synthetic and modified zeolites, particularly CPLs that are found mainly in sedimentary rocks of volcanic origin are crystalline, hydrated aluminosilicates and cations clustered to form micro aggregates with three-dimensional structures comprising multiple micro pores. The nanopore sizes modulate their unique catalytic properties. Such inorganic molecules with pore sizes ranging from less than 2 nm to 50 nm, can absorb gas and water molecules, facilitate ion exchange and acts as „molecular sieves" with long-term chemical and biological stability (*29-31*). The positively charged metal ions (*i. e.* Na^+, K^+, Ca^{2+}, Mg^{2+}) are positioned in cavities of aluminosilicate skeleton which are termed as micro- (2-20 A°), meso- (20-50 A°), and macro (50-100 A°) – pores. These ions are readily exchangeable in contact with aqueous solution of other positively charged ions, and this structural characteristic of zeolites is the base of their cation-exchange property (*32*). Therefore, zeolites have been recognized as interesting nanoporous materials and became subjects of research in different areas of chemistry, and are now widely used in industrial, agricultural, environmental and biological technologies (*13, 33*), but have also attracted interest for use in molecular medicine (*26*). Several toxicological studies as well as hematological, biochemical and histopathological analyses of a natural CPL proved that this compound is non-toxic and safe for use in human and veterinary medicine (*19, 25, 31, 34-36*). The CPL utilization in veterinary medicine showed that it is capable to act as detoxificating (including mycotoxins and heavy metals), antioxidant, hemostatic, anti-diarrheic, growth-promoting and immunostimulating agent (*22-24*). In human medicine it is an adjuvant in immunodeficiency states, oncology (after chemotherapy and radiotherapy), reducer of radioactive elements or as an IM and antioxidant (*26-28, 37, 38*). The pioneer biomedical study in Croatia using natural CPL demonstrated that the agent affects tumor cells proliferation *in vitro*. Data obtained on several cancer cell lines indicated that CPL treatment might affect cancer growth by attenuating survival molecular signals of protein kinase B and by inducing expression of tumor suppressor proteins and, thus might act as an adjuvant in cancer therapy (*25*). This finding was confirmed by Katić et al. (*39*) who reported that CPL influences tumor cell viability, division and stress response, which resulted in antiproliferative effect and apoptosis induction *in vitro*. Such inhibitory effect of CPL on tumor cells growth might be a consequence of its adsorptive and ion-exchange characteristics that cause adsorption of some serum components by the agent. Moreover, CPL exhibited antiviral effects *in vitro* and a potential in antiviral therapy either against herpesvirus infections or systemic adenovirus/enterovirus infections (*40*). The antiviral mechanism was probably non-specific and based on adsorption of viral particles on surface cavities of CPL rather than a consequence of its ion-exchange properties. The immunostimulating activity of CPL was firstly observed by Pavelić et al. (*37*) in mice fed for 28 days with micronized zeolite as lymphocytes from these animals exhibited a significantly higher allogeneic graft-versus-host reaction than did cells in the controls. Also, the number of peritoneal macrophages increased significantly following CPL were administered intraperitoneally. These *in vitro* and *in vivo* studies clearly showed that CPL has also potential as an IM and suggested that this could be a possible mechanism of its antimetastatic ability. Such, immunomodulatory properties of CPL were encouraging for the first human trials performed by oral zeolite supplementation therapy in order to enhance the primary treatment of a variety of immunodeficiency disorders (*28*). More recently, biomedical applications of natural and synthetic zeolites have been established as detoxicants, antibacterial and antidiarrheal agents, vaccine and antitumor adjuvants, contrast in magnetic resonance and biosensors, and also for hemodialysis and hemoperfusion, diabetes mellitus/enzyme mimetic, delayed release drug delivery and bone formation/external application (*32*). Furthermore, zeolites have been successfully utilized for wound and surgical incision healing (*31*), including skin burns (*41*), for hemorrhage control (*32*) and dental treatment (*26*). However, recently it was recognized that previously observed positive biological effects of various colloidal silicic acids (various hydrated silica gels) as well as of some zeolites, such as zeolite A and CPL might be partially ascribed to their ortho-silicic acid (OSA)-releasing property (*26, 32, 42, 43*). Namely, numerous biologically active silicon compounds such as some types of zeolites, particularly CPL, are major natural sources of the OSA as documented so far.

Health and performance promoting zeolites in veterinary medicine

Among 140 types of natural zeolites, CPL is the most widespread scientifically studied substance that incorporates biologically active nanoporous structures spontaneously formed by self-assembly at the molecular level without any human intervention. Therefore it is a very interesting compound in the medical market and has recently been approved in the EU as a feed additive for use as a mycotoxin binder in veterinary medicine, particularly for livestock and poultry industry (70/524/EEC). Also, it has been approved by the FDA for usage in different agricultural related applications such as an anticaking agent in animal feeds (21 CFR 582-2727). Accordingly, natural zeolites are inert and nontoxic minerals which are classified as „Generally Recognized As Safe“ in most applications as previously mentioned and exempted from regulations and reporting when used in accordance with good agricultural and veterinary practice (*23*). As feed additives, zeolites including CPL have been extensively used in farm animals to positively influence growth and reproductive performance, but most of all to improve gut health and general health status (*14*), and to improve welfare for other domestic animals, such as companion animals and horses (*22*).

Companion animals and horses

During the last two decades of the twentieth century a variety of *in vitro* and *in vivo* studies have been performed on animal models, mostly using laboratory rodents (mice and rats), but also Beagle breed of dogs (*25, 44-46*) as well as Quarter breed of horses (*42, 47*) as the most common companion animal species in order to evaluate the effects of orally applied CPL on their health status and performance (Table 1).

Although, considerable efforts have been devoted to the understanding of infectious diseases of bacterial etiology, including the biology of pathogens, host resistance and therapy in companion animals and horses, by contrast very little is known on the prevention of such diseases through dietary and non-dietary strategies. Namely, these problems have been overcome thus far by antibiotics. However, their prolonged use or misuse pose the risk for developing cross-resistance and multiple-antibiotic resistance in bacterial strains pathogenic for both animals and humans which has been strongly related to the therapeutic, metaphylactic or prophylactic administration of antibiotics in human and veterinary medicine (*15*). The dietary strategy of using zeolites in animal studies have shown the possibility of zeolite A as a viable source of silicon for dogs and horses (*42, 43, 50*) due to its property to breaks down into bioavailable OSA, (H_4SiO_4) in the digestive system (*32*). Thus, it provides additional source of silicon to the organism resulting in decreased skeleton injury rates and better training performances in young racing horses (*47*). However, increased bone formation was observed in randomized controlled studies on broodmare horses (*51*), but not in yearling horses (52). Additionally, dietary CPL showed antitumor activity in dog models, particularly against skin cancers (25) and mammary gland carcinoma (*48*).

Table 1. *The summarized in vivo effects of CPL and other natural, artificial (modified) or synthetic zeolites on companion animals and horses as obtained and reported in the studies referred.*

Dietary rate (%) or dose per (kg) of dry matter (DM)	Breed/species (N)	Effect	Reference
Zeolite A: – 30 mg/kg Na aluminosilicate: – 16 mg/kg Mg aluminosilicate: – 20 mg/kg in diet for a total of 24 hours	Beagle breed of dogs (N =12)	Zeolite A significantly increased Si plasma level (9.5 + 4.5 mg h/L±SD; P < 0.05) and, thus increased bioavailability of Si.	Cefali et al. (*45*)
CPL: – 0.5, 5 or 50 mg/mL for human carcinoma cell lines *in vitro* – 600 to 3600 mg/dog per day for anticancer studies *in vivo* – 60 to 1000 mg/mouse or rat per day (in diet) for toxicity studies	Different dog breeds (N = 14)	*In vivo* treatment of variety of tumors in dogs with dietary CPL resulted in improvement of their general health status, prolongation of survival and decrease in tumor size, particularly of skin cancers. Additionally, toxicology studies in mice and rats showed no adverse effects of CPL treatment. *In vitro* treatment showed that CPL inhibited protein kinase B, induced expression of tumor suppressor proteins and blocks growth of several human carcinoma cell lines.	Pavelić et al. (*25*)
CPL: – 100 to 200 mg/kg per day/dog for 3.5 to 5.5 weeks	Cocker Spaniel breed of dogs (bitch and 2 puppies)	In addition to standard treatment of the burns (caused by fire after gas explosion) the use of CPL was evaluated. Application of CPL hastened the recovery and complete healing was achieved in spite that 50% of the skin of dogs was severely burned.	Bedrica et al. (*41*)
CPL: – 100 mg/kg per day for a total of 3 months	Bitches of different dog breeds (N = 20)	The effectiveness of orally applied CPL treatment on mammary gland tumors varied in size from 3 to 100 mm. The therapy resulted in reduction of the bigger tumors for two thirds of their diameters, whereas smaller (≤ 20 mm) completely disappear.	Bedrica et al. (*48*)
Sodium zeolite A in daily diet: – 0.66% – 1.32% – 2.00% for a total of 12 months	Quarter breed of horses (N = 53)	Whether or not dietary sodium zeolite A fed to horses since 6 months of age would result in an increase of plasma silicon level which may improve bone calcification and connective tissue characteristics in order to prevent racing related injuries. There was correlation (R^2) of 0.54 between plasma silicon level and the distance traveled before injury in the group of horses which was prone to injury, and thus feeding Na-zeolite supplement may help prevent injury by providing bioavailable silicon to the horse.	Nielsen et al. (*47*)
Sodium zeolite A in daily diet: – 2.00% for a total of 21 days	Quarter breed of horses (N = 27)	The addition of Na- zeolite A to the feeding rations resulted in increased plasma silicon concentration and in increased radiographically measured density of third metacarpal which may prevent race training injuries in weanling horses.	Frey et al. (*42*)
Sodium zeolite A in daily diet: – 200 g OSA in daily diet: – 28.6 mL for a total of 13 days	Arabian breed of horses (N = 8)	The OSA tended to increase retention, apparent digestion and also increased plasma Si, and thus appears to be a promising option for Si supplementation/bone health in horses.	O'Connor et al. (*43*)
CPL in daily diet: – 0.5% – 0.75% – 1.0% for a total of 42 days	Different cat crossbreds (N = 21)	Feeding regimes with addition of two higher CPL rates showed to be effective in both reducing odor (R^2 = 96.39) and increasing fecal texture (R^2 = 99.63), showing a quadratic pattern for these variables.	Roque et al. (*49*)

Food animals

Since the EU (and recently the USA) regulations prohibited the use of AGP in production of food animals, among numerous natural substances rather scientifically tested than translated to practice, the natural zeolites, particularly CPL are widely used by livestock farmers as feed additives for beef cattle, dairy cows, sheep, goats, pigs, poultry (broilers and egg production), rabbits, turkeys due to their detoxifying/decontaminating properties and abilities to act as reducers of heavy metals, organic pollutants, radionuclides and antibiotics (*31*). More recently, zeolite CPL was tested as a feed supplement for the treatment of infected honeybee colonies in order to be evaluated as a potential alternative to antimicrobials (*53*). The objective assessment of various natural or synthetic substances (*8, 54*) as potential alternatives to in-feed AGP in food animals must impact positively on their health and performance, and on their products in order to be fully accepted by producers, consumers and to be environmental friendly. Among a vast variety of such substances tested, zeolite CPL has been suggested as an alternative feed additive for use in farm animals (Table 2).

Table 2. *The summarized in vivo effects of CPL and other natural, artificial (modified) or synthetic zeolites on food animals as obtained and reported in the studies referred.*

Dietary rate (%) or dose per (kg) of dry matter (DM)	Breed/species (N)	Objective and Effect	Reference
CPL in daily diet: – 2% for a total of 180 days (from weaning at 4 weeks until the next reproductive cycle)	Crossbred (Large White x Landrace) swine (sows/gilts) (N = 240)	No adverse effects of the CPL use were observed during critical periods of pregnancy and lactation in sows, whereas their reproductive parameters, such as increased litters and body weights of pigs at birth/weaning were improved and the impact of zearalenone-contaminated diets on reproduction efficiency was ameliorated.	Kyriakis et al. (*16*)
CPL in daily diet: – 50 g/kg for a total of 28 days	Laying hens, three breeds (N = 120)	Dietary CPL significantly increased number of lay eggs, thickness of the shells, utilization of the feed and on the humidity of excrements.	Oliver (*55*)
CPL in daily diet: – 0.5% – 1.0% for a total of 35 days	Broiler chickens (Hubard JV breed) one-day-old (N = 200)	The CPL fed broilers had reduced gut microbiota and enteric infections, positive impact on performance (increased body weight), organoleptic meat parameters and elevated level of n-3 polyunsaturated fatty acids.	Mallek et al. (*56*)
Natural and modified CPL (NCPL and MCPL) in daily diet: – 2% for a total of 42 days	Broiler chickens (Arbor Acres breed) one-day-old (N = 240)	Both zeolites had no effect on growth performance and relative weights of organs. The activity of nitric oxide synthase was decreased in MCPL fed group, whereas total antioxidant capacity, glutathione peroxidase, catalase, total superoxide dismutase activities were increased in NCPL/MCPL groups. In both supplemented groups the content of malondialdehyde was decreased.	Wu et al. (*57*)
Natural and modified CPL (NCPL and MCPL) in daily diet: – 2% for a total of 42 days	Broiler chickens (Arbor Acres breed) one-day-old (N = 240)	Both supplements were associated with increased jejunal/ileal villous height, had no effect on crypt depth, but improved activities of total protease and amylase.	Wu et al. (*58*)
Natural and modified CPL (NCPL and MCPL) in daily diet: – 2% for a total of 42 days	Broiler chickens (Arbor Acres breed) one-day-old (N = 240)	Both supplements reduced total viable counts of *Escherichia coli* and increased the number *Lactobacillus acidophilus.*	Wu et al. (*59*)
CPL in daily diet: – 5 g for a total of 20 days	Honeybee (*Apis mellifera*) homologous colonies (N = 24)	Honeybees originated from colonies naturally infected by microsporidium *Nosema cerane* and fed with CPL had decreased number of spores after 20, 30 and 40 days of feeding which is indicative for its preventive/therapeutic use against nosemosis.	Tlak-Gajger et al. (*53*)
CPL in daily diet: – 1.5% – 3.0% for a total of 42 days (for 3 weeks before after weaning)	Balouchi sheep breed, newborn lambs (N = 30)	None of hematological parameters tested differed, and severity of diarrhea and fecal consistency score were lower in the 3% CPL fed lambs and daily weight gain was higher in these animals.	Norouzian et al. (*60*)
CPL in daily diet: – 2.5% for a total of 420 days (from 8 weeks before parturition)	Crossbred Sannen dairy goats (N = 72)	The CPL fed dairy goats had increased percentage of milk fat and reduced somatic cell counts without any adverse effects on serum vitamins (A, E), microelements/trace elements, β-hydroxibutyrate and hepatic enzymes (AST, GGT) activity.	Katsoulos et al. (*61*)
CPL in daily diet: – 0.5% for a total of 35 days	Crossbred (Topigs®) weaned pigs (N = 40)	The CPL fed pigs had significantly higher body weight, the control pigs had higher average daily feed intake whereas the principals had lower feed conversion ratio. The sum of diarrhea severity score in CPL-treated pigs was lower as well as a total bacterial load in jejunum (19 x 10^7 *vs.* 19 x 10^8 CFU/mL). With exception of $CD8^+$ T cells, the proportions of lymphoid cell subsets tested were significantly higher in CPL-treated pigs. These pigs had an increased recruitment of $CD45RA^+$ cells in interfollicular, but not in follicular areas of ileal Payer's patches.	Valpotić et al. (*24*)
CPL in daily diet: – 0.5% for a total of 35 days	Crossbred (Topigs®) weaned pigs (N = 60)	The CPL supplement only sporadically induced lymphopaenia and granulocytosis, decreased CK and total protein and increased urea and creatinine levels, indicating that the agent was not associated with any harmful side effects on monitored blood and gut histological parameters as well on impairment in general health status of pigs.	Valpotić et al. (*19*)

CPL in daily diet: – 2.00% for 2 and 14 days	Holstein breed of calves (N = 30)	Serum plasma fibrinogen, total albumin, beta and gamma globulins were significantly higher after 14 days of dietary CPL application and, thus may be effective in prevention of the mycotoxins intoxication.	Mohri et al. (*62*)
CPL in daily diet: – 15 g/kg for a total of 42 days	Broiler chickens (N = 576)	The number of affected chickens and the organs degeneration were decreased in the CPL fed chickens indicating its effectiveness against aflatoxins.	Ortatatli et al. (*63*)
CPL: – 2.0% for a total of 136 days	Crossbred weaned pigs, 25 days of age (N = 720)	From day 25 to day 70, weight gain and feed conversion were increased in the CPL fed pigs, but less than those obtained in growing and finishing pigs fed the antibiotics.	Papaioannou et al. (*21*)
CPL in daily diet: – 2.0% for a total of 136 days	Crossbred sows (Large White x Landrace) (N = 450)	Farrowing rate and percentage of sows returning to estrus were increased and with inappetence, pyrexia, and mastitis were decreased in the CPL fed sows, but vaginal discharge was lower in the controls.	Papaioannou et al. (*64*)
Artificial zeolite (AZ) in daily diet: – 0.5% for a total of 90 days	Crossbred weaned pigs (Landrace x Yorkshire x Duroc), 2-months-old (N = 48)	No significant differences in average daily gain, feed intake or feed conversion ratio were observed. The IgG level (but not IgM and IgA levels) increased in the AZ fed pigs. Reduction in *Bacilus spp.* in growing and *E. coli* in both growing and finishing pigs were recorded, and also AZ reduced fecal NH_3, SO_2 and H_2S noxious gas emission, but had no effect on fecal yeast and *Lactobacillus spp.* concentrations.	Islam et al. (*65*)
Natural zeolite (NZ) in daily diet: – 0.3% for total of 15 days (3 before and 12 after weaning)	Crossbred weaned pigs (PIC c-22 female x PIC line 337 male) (N = 128)	The NZ treatment did not affect growth rate of the pigs, but in F18$^+$ *E. coli* challenged subgroup reduced diarrhea score for the overall period, ratio of β-hemolytic and total coliforms at days 9 – 12, total white blood cells (WBC) at day 6 and alleviated experimentally induced diarrhea.	Song et al. (*66*)
CPL in daily diet: – 1.25% – 2.5% – 5.0% for a total of 148 days	Crossbred steers (N = 48)	No differences were detected in average daily gain, feed intake and feed conversion rate. Total DM digestibility was higher for the 1.25% than for 2.5% and 5.0% diets, but not from the control diet. The 2.5% CPL diet produced level of propionic acid, and the 5.0% diet had the lowest rumen ammonia level. Rumen pH was decreased by the 2.5% CPL diet and no differences in rumen volume/fluid flow rates were observed.	McCollum and Galyean (*67*)

The CPL utilization in animal biotechnology and veterinary medicine are as detoxificating, anti-diarrheic, hemostatic and immunostimulating agent. The CPL has shown to be effective as growth-promoting (*68*), immunostimulating (*24*) and gut health restoring anti-bacterial (*21*) dietary supplement in food animals, particularly in swine. The natural zeolite supplement did not affect growth rate of weaned pigs, but alleviated experimentally induced diarrhea (*66*). Similarly, the AZ-fed pigs didn't show differences in weight gain and feed conversion ratio, but their serum IgG levels were increased and they had reduced *E. coli* count (*65*). An early study of McCollum and Galyean (*67*) in the steers showed no effect of CPL on growth performance and feed efficiency. Also, in poultry there is conflicting data regarding beneficial effects on growth performance in broiler chickens fed with either natural or modified CPL (*57*). However, these authors observed that both CPL sources increased total antioxidant capacity and the activity of three antioxidative enzymes tested (Table 2). Interestingly, dietary CPL exhibited the potential to stimulate systemic and local immunity by increasing recruitment of circulating and intestinal lymphoid cell subsets with exception of CD8$^+$ T cells (*24*). In the functional study using the CPL-fed mice as the immune cell donors immunostumulatory effect of the agent was also observed (*37*). Regarding limited reports on potential adverse effects of CPL as a feed supplement, tested in pigs (*19*) it has been shown that the agent was not associated with any harmful side effects on monitored blood and gut histological parameters as well on impairment of general health status of pigs.

Aquaculture industry

Recently published review by Ghasemi et al. (*23*) summarized the application of natural, synthetic and modified zeolites, particularly CPLs found mainly in sedimentary rocks of volcanic origin from South Africa, New Zealand, Iran and USA in aquaculture industry as adsorbents for ammonia removal from fish farming ponds/transportation tanks (*69, 70*), as cation-exchanger for removal of different toxic heavy metals from fresh water and sea water cultures (*71*), and as feed supplement to enhance fish growth and promote their health and nutritional parameters (*72*). However, despite lower efficiency of natural CPL to remove ammonia from saline fish and shrimp farms due to its limited cation exchange capacity in salt waters, it possesses tremendous potential of applications in aquaculture industry (Table 3).

Despite of all beneficial and promising effects of many natural zeolites, particularly CPL, and few synthetic zeolites as reported by abovementioned authors, there are few

Table 3. *The summarized effects of CPL and other natural, artificial (modified) or synthetic zeolites on aquatic animals and/or aquaculture systems as obtained and reported in the studies referred.*

Dietary rate (%) or dose per (L^{-1} or kg^{-1}) of dry matter (DM)	Species/fish culture system	Objective and/or effect	Reference
CPL: – 15 g/L – 12 g/L	– Beluga (*Huso huso*) – Persian sturgeon (*Acipenser persicus*) cultures	Prevention of acute ammonia toxicity and increasing survival rate	Asgharimoghadam et al. (*73*), Farhangi et al. (*74*), Farhangi and Rostami-Charati (*75*)
CPL: – 10 g/L	Angel fish (*Pterophyllum scalare*) in freshwater aquarium	Reduction of ammonia and hardness level of water	Ghiasi and Josour (*76*)
CPL: – 15 g/L	Rainbow trout (*Oncorhynchus mykiss*) culture	Prevention of mortality rate by reducing ammonia lethal concentration	Farhangi and Hajimoradloo (*77*)
CPL: – 10%	Common carp (*Cyprinus carpio*) closed breeding system	Absorption of nitrogenous compounds and decreased ammonia values	Motesharezadeh et al. (*78*)
Artificial zeolite product „Zestec-56“: – 10 mg/L	Culture of rainbow trout juveniles	Decreasing ammonia concentration for 23 days, but then the process was reversed due to decomposition of feed remains	Ferreiro Almeda et al. (*79*)
CPL: – 10 g/L	Common carp culture	Reducing of cadmium toxicity in tissues	Ghiasi et al. (*71*)
CPL: – 0.5 g/L – 2.0 g/L – 4.0 g/L	Prussian carp (*Carassius gibelio*) culture	Reducing of water and tissue bioaccumulation of cadmium in the rate related to the dose applied	Nicula et al. (*80*)
Natural and sythetic zeolite: – 10 g/L	Stinging catfish (*Heteropneustes fossilis*) culture	Protection from poisoning by adsorption of lead and reduction of fish exposure to its toxicity for 35 or 120 days	Jain et al. (*81*)
CPL: – 25.8 g/kg	Culture of gilt-head sea bream (*Sparus auurata*) juveniles	Improvement of final body weight, growth rate, feed conversion and protein efficiency ratio	Kanyilmaz et al. (*72*)
CPL: – 5%	Common carp culture	Beneficial effects on dry matter, protein apparent digestibility coefficients and growth rate	Khodanazary et al. (*82*)
CPL: – 1% – 2% – 3%	Rainbow trout culture	Elevated fatty acid profiles	Danabas (*83*)
CPL: – 1% – 2%	Culture of redbelly tilapia (*Tilapia zillii*) juveniles	Improved growth performance and feed conversion ratio	Yildirim et al. (*84*)
CPL: – 4 g/L – 10 g/L – 15 g/L	Angel fish in freshwater aquarium	Improvement in growth and nutritional parameters	Ghiasi and Josour (*76*)

reports showing contradictory results (for review see Ghasemi et al. (*23*)). Generally, it seems that zeolites are not sufficiently effective to remove ammonia from salt water ponds, especially from large-scale systems due to the fact that sea water comprises large amount of cations that are competing with ammonia, and that their application for ammonium and nitrite reduction in large-scale freshwater aquacultures is not feasible with the amount of zeolite used in target-oriented studies as yet. However, it seems more likely that zeolites, such as natural CPL can be used as filters to remove ammonia from small-scale systems, for transportation of live fish and as a feed additives for aquatic animals.

Zeolites as dietary supplements in beef and dairy cattle production

Findings that zeolites may improve the energy status of dairy cattle in early lactation could be translated that CPL supplementation might also have beneficial effects on the reproductive efficiency in dairy cattle. Reproductive efficiency is key for profitability of the dairy herds, and is frequently affected by numerous factors such as negative energy balance (NEB), age, milk yield, breed, health status and herd management, including nutrition and housing (*85, 86*). Recent study that long term use of (Day 210 of gestation until the end of the first lactation period) CPL supplementation to pregnant heifers improved rumen fermentation and energy status, resulting in a milder form of NEB, and consequently increased reproductive efficiency and milk production in the first lactation of the studied animals. Consequently, it is assumed that CPL might modulate metabolic, endocrine and antioxidative status in dairy cows and thus improve their health, fertility and milk production (*87*).

Nutritional requirements of dairy cows are rapidly increasing following parturition due to rising milk production and inevitably the animals enter NEB which indirectly affects ovarian function causing failure of regular ovarian activity during puerperium and consequently decreases fertility. The NEB could not be avoided by any known treatments but it is possible to decrease its duration and severity. Energy imbalance occurs due to increased milk production following parturition, low feed intake, peripartal stress and/or puerperal diseases. Such diseases have a significant negative economic impact, during puerperium and afterwards by decreased fertility (*88, 89*). One of the most important puerperal diseases is mastitis which causes large economic losses particularly due to difficulties in diagnosis of its subclinical form (*90*).

The use of zeolites in animal nutrition has increased in the past 20 years, mainly to protect against mycotoxins, but also to improve performance (*14, 91*). The high affinity of zeolites for water and osmotically active cations may facilitate ruminal fermentation, and osmotic activity may regulate rumen pH by buffering against hydrogen ions of organic acids. In addition, zeolite supplementation in dairy rations may improve nitrogen (N) utilization, because it gradually releases excess ammonia (NH_3) and allows rumen microorganisms to efficiently capture the NH_3 into microbial protein (*33*). Research results suggest that both natural and synthetic zeolites may have some influence on energy metabolism, because when they were fed to cattle, there were changes in rumen fermentation patterns, which affected the molar proportions of volatile fatty acids. Some researchers have observed that CPL increases the proportion of propionate in the rumen (*67*), whereas others have recorded increased ruminal pH and acetate (*92*). In other studies, Grabherr et al. (*93*) observed increased molar proportions of acetate, but decreased propionate and valerate proportions in the rumen following supplementation with synthetic zeolite A, while Dschaak et al. (*94*) reported a decrease in production of all volatile fatty acids with no negative implications on milk yield. Recently, Đuričić et al. (*95*) evaluated the effects of dietary CPL, a novel vibroactivated and micronized modification (Vibrosorb) of the natural mineral, in lactating dairy cows on milk composition, somatic cell counts (SCC) and the incidence of mastitis from the third to the seventh month of gestation. No significant differences were observed in the content of milk components, and only the chemical composition of milk was found to be more stable in the CPL-fed cows. Also, the SCC in milk did not differ significantly between the groups. However, the control cows had a 21-fold higher odd of intramammary infections than the CPL-fed cows as these cows had a decreased incidence of intramammary infections during the dry period, parturition and early lactation. The authors concluded that such indicative and beneficial outcome of CPL-supplementation could be attributed to its antibacterial, detoxifying and immunostimulating effects on the incidence of mastitis and general udder health in dairy cows.

Dietary CPL as an alternative to antibiotic growth promoters

The use of natural zeolites and their modified forms, especially those micronized to microparticles has numerous advantages such as safety for animals and humans, low cost, abundance in many parts of the world, and are environmentally friendly although there are still challenges if their future applications are to be successful (*96*). Based on a huge body of literature on this issue, it appears that the observed beneficial effects of natural zeolites, particularly CPL as a possible alternative to antimicrobials by increasing performance and reproductive efficiency in dairy cows, improving health status and reducing morbidity and mortality rates have shown inconsistent results regarding growth performance and their influence on pig immunity remains inconclusive (*97*). Although, the majority of these natural substances, particularly activated or micronized zeolites (*4, 18*) showed promising results regarding their impact on the immune and nutritive modulation, gut health and physiology and the development of intestinal immunity in early weaned pigs (*24*), it does not appear that any one natural remedy could completely replace antimicrobials in dairy production. In spite that many dietary zeolites showed ability to act beneficially on energy status, reproductive efficiency and milk yield it is not likely that CPL when solely applied could completely replace conventional AGP in improving reproductive functions, maintaining general health status and promoting productivity of dairy cows (*87*). However, further research is needed in this field, alternative methods have been identified and non-antibiotic bioactive substances have been tested in effectively controlling bacterial infections in dairy cows (*10*). All of the alternative substances tested as potent NCs and IMs pose no known threat to animal and human health and a combination of the most potent, and at the same time synergistic can probably lead to the adequate replacement of antibiotics in cattle pro-

Table 4. *The summarized in vivo effects of CPL and other natural, artificial (modified) or synthetic zeolites on dairy cows and their calves as obtained and reported in the studies referred.*

Dietary rate (%) or dose per (kg) of dry matter (DM)	Breed of dairy cow and their calves	Effect	Reference
CPL in daily diet: – 1.25% – 2.50% for a total of 350 days (28 days before expected calving until the end of lactation)	Holstein breed of dairy cows (N = 52)	Protective effects of CPL against clinical ketosis. Significantly reduced ketosis with both concentrations of CPL applied.	Katsoulos et al. (*99*)
CPL in daily diet: – 1.25% – 2.50% for a total of 350 days (4 weeks before expected calving until the end of lactation)	Holstein breed of dairy cows (N = 52)	Dietary CPL did not induce any adverse effects on serum levels of trace elements, such as Cu, Zn and Fe, and thus, did not affect their bioavailability.	Katsoulos et al. (*100*)
CPL in daily diet: – 1.25% – 2.50% for a total of 350 days (from 30 days before expected calving until the end of lactation)	Holstein breed of dairy cows (N = 52)	Both supplementations of CPL had no adverse effects on the hematological parameters, such as packed cell volume (PCV), hemoglobin (Hb) or WBC count, and thus, the long-term applications of CPL in the levels tested should be safe for dairy cows.	Katsoulos et al. (*101*)
Zeolite A (ZA) in daily diet : – 0.7 kg for a total of 14 days (last 2 weeks of pregnancy)	Crossbred pregnant dry dairy cows (N = 31)	Significantly increased the plasma Ca level on the day of calving, but Mg and P levels were decreased. Serum vitamin D was increased 1 week before the expected calving while the excretion of the bone metabolite deoxypyridinoline was not affected. Feed intake was decreased in the ZA fed cows during the last 2 weeks of pregnancy, but milk yield, milk fat and protein were not affected.	Thilsing-Hansen et al. (*102*)
CPL in daily diet: – 5 g/L – 20 g/L for a total of 180 days (with colostrum following parturition)	Romanian Black and White breed of newborn calves (N = 26)	The incidence of diarrhea was decreased in both groups of calves fed colostrum supplemented with CPL. Body weight was increased in the CPL fed calves receiving 5 g/L at age of 45 days, but at 90 days differences for either treatment were not significant.	Zarcula et al. (*103*)
CPL in daily diet: – 200 g for a total of 70 days	Holstein breed of dairy cows (N = 34) vaccinated (days 210-240 of gestation) with multivalen *E. coli* vaccine	The CPL fed cows (and particularly in combination with Se) had increased specific antibody titers against *E. coli* in their serum/colostrum and in the serum of their calves. The incidence of diarrhea in calves was not different among treatments.	Karatzia (*97*)
CPL in daily diet: – 200 g for a total of 84 days	Hostein breed of dairy cows (N = 16) with a rumen fistula	The CPL supplementation had no significant effect on ruminal and blood serum concentrations of Al and P, but CPL increased ruminal pH and acetate, and decreased ruminal propionate and valerate.	Karatzia et al. (*92*)
CPL in daily diet: – 200 g for a total of 380 days (from day 210 of gestation until the end of the first lactation)	Holstein breed of pregnant dairy heifers (N = 80)	Body condition score and blood serum level of glucose were significantly increased while level of ketone bodies was decreased in CPL fed heifers. Also, CPL improved the reproductive parameters evaluated and increased milk production.	Karatzia et al. (*87*)
Zeolite A (ZA) in daily diet: – 10 g/kg – 20 g/kg for a total of 21 days	Holstein breed of double fistulated (rumen and proximal duodenum) dairy cows (N = 8)	The ZA supplementation reduced ruminal DM digestibility and fermentation of organic matter, proportion of acetate increased, and propionate as well as valerate decreased, whereas the total fatty acids and ruminal pH were not affected. No effects on fecal digestion of DM, organic matter nor on Ca and Mg digestion were observed. The level of P in rumen fluid correlated negatively with the mean ZA intake (r^2=75; p = 0.0003), and a lower digestibility of P resulted in decreased level of inorganic P in serum. The ZA fed cows showed a higher Al level already in rumen fluid (14.31 and 13.84 mmol/L *vs* 6.33 mmol/L).	Grabherr et al. (*93*)
Natural zeolite (NZ) in daily diet: – 1.40% for a total of 84 days	Holstein breed of dairy cows (N = 30)	Feeding the NZ did not affect milk fat level, but resulted in a tendency of increased milk protein level. Feed N efficiency for milk N did not differ, and milk urea N level was not influenced by dietary NZ. Level of ammonia N did not differ as well as molar proportions of acetate/propionate were not affected by NZ. The agent may cost-effectively replace Na-bicarbonate as a ruminant buffer additive in a lactating dairy diet in order to prevent subacute acidosis.	Dschaak et al. (*94*)

CPL in daily diet: – 1.25% – 2.50% for a total of 650 days (from 1 months before expected parturition until the next non-lactating period)	Holstein breed of dairy cows (N = 52)	The cows fed with 2.5% of CPL supplement had significantly lower incidence of parturient paresis. Serum levels of total Ca, PO_4^{-2}, Mg^{2+}, K^+ and Na^+ were not affected by long-term supplementation with CPL. Such dietary treatment could be used as a cost-effective during non-lactating period for prevention of parturient paresis.	Katsoulos et al. (*104*)
Treated calves were fed via a nipple pail during the first day of life with 3 L of maternal colostrum containing 5 g/L CPL. Control animals were fed with the same amount of colostrum. The first feeding was 2 hours after birth.	Black and white spotted breed of newborn calves (N = 26)	The CPL fed calves (3 L + 15 g CPL) had 50% higher IgG level 6 hours after birth but differences were not statistically significant. However, 24 and 48 hours after birth differences between groups were significant (P<0.001)	Stojić et al. *(105)*
CPL in daily diet (colostrum: 0.75 L+, 1.5 L+, 0.75 L–, 1.5 L–): – 5 g/L – 5 g/L – 0 g/L – 0 g/L for a total of 2 days (after birth)	Holstein breed of newborn cows (N = 60)	The CPL fed calves (0.75 L + 5 g/L) had higher IgG level 6 hours, but not 24 and 48 hours after birth. The calves fed 1.5 L + 5 g/L of CPL had higher IgG levels after 6, 24 and 48 hours after birth. The dose of 5 g/L of CPL, as a mineral adsorber in colostrum significantly elevated absorption rate of colostral IgG in newborn calves.	Fratric et al. (*106*)

duction (*24*). With further research it is highly likely that a technologically applicable, cost and health effective alternatives could and will be found.

Safety and efficacy of CPL in dairy cows and their calves

Several toxicological studies proved that certain natural zeolites, *e. g.* CPL are non-toxic and completely safe for use in human and veterinary medicine (*25*). The best known and the most thoroughly tested for its safety and efficacy as feed additive for animal species of veterinary importance is CPL of sedimentary origin containing at least 80% of CPL and a maximum of 20% clay minerals (*98*) (Table 4).

Reproductive efficiency is a key factor for the dairy herd's profitability. Among various parameters for estimating the reproductive efficiency, calving to the first heat interval, calving to the first service interval, calving to new conception interval, number of services per conception and calving interval are the most prominent (*88*). These parameters are affected by a significant number of factors such as energy balance (*107*), age (*108*), milk yield (*109*), cattle breed (*110*), health status and herd management, including nutrition and housing (*109*). Findings that zeolites improve the energy status of dairy cattle, especially in early lactation (*99*), could be interpreted that the dietary inclusion of CPL might have beneficial effects on the reproductive efficiency of dairy cattle. Numerous biological activities of some types of zeolites, and previously observed positive biological effects documented so far might probably be attributed to their OSA-releasing property. Namely, the group of authors that performed pioneer research of zeolites (CPL) on animal models and humans in Croatia (*32*), critically reconsidered their previous observations and those of the other authors as well the most recent findings on biological effects of Si and OSA on animals (particularly dogs, horses and calves), and propose that such effects of various colloidal silicic acids (various hydrated silica gels) and of some zeolites, *e.g.* zeolite A and CPL, might be at least partially attributed to their OSA-releasing properties.

CONCLUDING COMMENTS

The inconsistency observed in different studies on the use of natural CPL and other zeolites as feed additives in companion animals (dogs and cats) and horses, farm animals (pigs, poultry, small and large ruminants and honeybees) and farmed fish might be attributed to the differences in type of zeolite tested, particle size, pretreatment and the dosages that were used in these studies. According to numerous scientific and practical data that are discussed in this review, natural and modified zeolites, in particular CPL should be considered as nanoporous materials possessing tremendous potential for applications in veterinary medicine, especially in livestock production. Thus, it is logical that considerable amounts of research are under way to evaluate novel approaches for application of CPL in dairy cows. Namely, our current research is focused on the effects of nutritive modulation by dietary CPL on NEB, fertility, productivity and incidence of subclinical mastitis for early diagnosis of oxidative stress and systemic/local inflammatory responses involved in reproductive and productive disorders in dairy cows. The expected outcomes of this study will include well defined beneficial effects of nutritive modulation by dietary CPL on: (1) NEB, fertility and productivity regarding body condition and parity during transition period and late puerperium, and on (2) incidence/severity of subclinical mastitis in dairy cows. Altogether, the obtained findings will contribute in scientifically and practical aspects and could improve health and economical parameters in cattle production in Croatia and abroad.

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Authors' contributions

Among coauthors of this manuscript the following researchers: Hrvoje Valpotić, Damjan Gračner, Ljiljana Bedrica, Nino Maćešić, Tomislav Dobranić and Marko Samardžija had experience working with zeolites (clinoptilolite) in animals of veterinary importance. Beside, Hrvoje Valpotić designed and developed the overall manuscript, studied literature search, presented data, critically discussed obtained results and drafted the manuscript. Damjan Gračner, Romana Turk, Dražen Đuričić, Silvijo Vince, Ivan Folnožić, Martina Lojkić, Ivona Žura Žaja, Ljiljana Bedrica, Nino Maćešić, Iva Getz and Tomislav Dobranić studied literature search, presented data, critically discussed obtained results and drafted the manuscript. Marko Samardžija is the principal researcher and the project leader, search and reviewed the literature data, performed final critical manuscript revision and approved the final manuscript version. All authors read and approved the final version of the manuscript.