Yellow catfish; chicken meal; fish meal; growth performance; feed utilization; antioxidant capacity; postprint

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Abstract

This article summarizes the additives reported domestically and internationally that can improve intestinal health in livestock, poultry, and aquatic animals, including functional amino acids, zinc, fatty acids, probiotics, polysaccharides, etc., reviews their effects on animal intestinal structure and function, and elaborates on some mechanisms of action, aiming to provide references for improving intestinal health in aquatic animals.

Full Text

Research Advances: Intestinal Health and Feed Additives in Aquatic Animals

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Abstract: Intestinal health is a critical determinant of overall animal health and represents one of the key factors ensuring rapid growth in animals. Certain exogenous feed additives can improve intestinal health in animals. This paper summarizes reported feed additives that improve intestinal health in livestock, poultry, and aquatic animals, including functional amino acids, zinc, fatty acids, probiotics, and polysaccharides. We review their effects on intestinal structure and function and elucidate some of the underlying mechanisms, providing a reference for improving intestinal health in aquatic animals.

Keywords: intestinal health; feed additives; aquatic animals

The intestine is the primary site for nutrient digestion and absorption in animals, with a structure comprising four layers: the mucosa, submucosa, muscularis, and serosa. The mucosal layer, being the outermost, directly contacts nutrients and intestinal microorganisms, making the intestinal mucosal barrier system essential for preventing invasion by toxins and bacteria in the intestinal lumen. Normal morphological structure and function of the intestinal mucosa are crucial for the organism. However, numerous factors can cause mucosal damage, including malnutrition, various enteritides, parenteral nutrition, and endotoxin infection [1]. Once normal intestinal function is compromised—such as through disruption of normal mucosal integrity, disturbance of intestinal barrier function, or dysregulation of the intestinal immune system—numerous diseases can develop, including reduced appetite, low feed intake, slow growth, and decreased nutrient digestion and absorption capacity [2].

In aquatic animals, intestinal health is influenced by feed composition, aquaculture water environment, and intestinal microbiota [1]. For example, high levels of soybean meal in feed can cause oxidative damage and structural destruction in fish intestine due to antinutritional factors, thereby inducing enteritis [3]. Typical symptoms of fish enteritis include: (1) thinning of mucosal folds, with absorptive cells showing nuclear vacuolation or disappearance; (2) thickening of the lamina propria of mucosal folds, with massive infiltration of inflammatory cells (macrophages or eosinophils) in the lamina propria and mucosal epithelium; and (3) increased goblet cells in the mucosal epithelium [3]. Therefore, nutritional intervention through external measures to improve intestinal function in aquatic animals is particularly necessary. This paper focuses on reviewing the effects of feed additives on intestinal health in aquatic animals to provide references for improvement strategies.

1 Functional Amino Acids

Functional amino acids are those that serve special functions beyond protein synthesis. They are essential for normal growth and maintenance of bodily functions and for synthesizing various bioactive substances. Nutritionally, they may be either non-essential or essential amino acids, including glutamine, arginine, branched-chain amino acids, tryptophan, proline, glycine, histidine, aspartic acid, asparagine, and sulfur-containing amino acids [4]. Evidence indicates that amino acids such as arginine, glutamine, threonine, tryptophan, and lysine can promote intestinal development and facilitate repair after mucosal injury.

1.1 Glutamine

Glutamine is an aliphatic neutral amino acid and the most abundant amino acid in animals. It serves as a critical energy substrate for rapidly proliferating cells (such as epithelial cells, lymphocytes, tumor cells, and fibroblasts) and is an important precursor for synthesizing proteins, nucleotides, and amino sugars [5]. Glutamine is the primary energy source for small intestinal mucosa and an important metabolic substance in the small intestine, with content far exceeding that of glucose and fatty acids. It is a crucial precursor for synthesizing polyamines, glutathione, and other compounds that maintain mucosal structure and function [5]. Numerous studies have shown that glutamine can be catabolized and utilized by small intestinal mucosa and is an essential nutrient for maintaining structural integrity and function [6-7]. Under pathological conditions, supplementation via oral or intravenous routes can promote improvement and recovery of intestinal damage caused by various conditions, including multiple organ system failure, endotoxemia, skin burns, weaning, and cancer [7-8]. Studies on rodents and pigs have shown consistent effects; for example, adding 2% glutamine can improve growth performance and intestinal function in weaned piglets [9], while adding 3% glutamine to the diet of rats with penetrating brain injury can reduce intestinal damage [10].

Due to its instability in aqueous solutions and poor tolerance to high-pressure sterilization, direct utilization of monomeric glutamine is limited in clinical medicine and practical production. In recent years, artificially synthesized glutamine-containing dipeptides such as alanine-glutamine (Ala-Gln) and glycine-glutamine (Gly-Gln) have been applied in various fields because of their good aqueous stability, tolerance to high-pressure sterilization, and rapid release of glutamine after entering the body. In weaned piglets fed plant-based diets, supplementation with 1.01 g/kg BW of alanyl-glutamine for 14 days significantly improved immune function, intestinal structure, and growth compared to controls [11]. In mice with malnutrition-induced enteritis, administration of drinking water containing 111 mmol/L alanyl-glutamine for 21 days significantly improved intestinal function [12]. Similar results have been confirmed in studies on mouse intestinal epithelial cells [13] and porcine intestinal epithelial cells [14]. These studies all demonstrate beneficial effects of glutamine-containing dipeptides on intestinal function.

Glutamine was the first amino acid discovered to activate key kinases in intestinal cell signaling pathways. It enters cells through various transporters, primarily via sodium-dependent amino acid transporters such as amino acid/carnitine transporters B^0,$^+$ (ATB^0,$^+$) and neutral amino acid transporter B(0)-like (ASCT2), and can maintain high glutamine influx into small intestinal epithelial absorptive cells by regulating transporter levels [15]. The role of glutamine in nutritional diseases (such as chronic diarrhea, short bowel syndrome, enteritis, and multiple organ system failure) has been extensively studied. Its mechanisms of action against diarrhea and enteritis include: (1) glutamine transport being coupled with sodium absorption, and (2) glutamine’s effect on sodium absorption complementing that of glucose [7]. Glutamine enters cells through sodium-dependent transporters ASCT2 or ATB^0,$^+$; ASCT2 is a high-affinity neutral amino acid transporter for glutamine that plays an important role in cellular glutamine uptake and can maintain high glutamine influx by regulating transporter levels. ASCT2 functions as an antiporter [15]. Other studies suggest that glutamine is an important factor mediating the mitogen-activated protein kinases (MAPKs) signaling pathway for intestinal cell proliferation in pigs, serves as a signal for improving cell survival rates in the intestine and other vital organs, and can inhibit intestinal cell apoptosis, thereby exerting anti-inflammatory effects [7].

Studies on the effects of glutamine on intestinal health in aquatic animals have also been reported. Pohlenz et al. [16] supplemented glutamine in feed for channel catfish (*Ictalurus punctatus*) for 10 weeks and found that while glutamine did not affect growth or plasma amino acid content, 2% dietary glutamine improved intestinal structure and enterocyte migration. In Jian carp (*Cyprinus carpio* var. Jian), dietary supplementation with 1.2% glutamine improved growth performance, feed utilization, intestinal weight, villus length, and digestive enzyme activity [17]. In cell studies, addition of 4 mmol/L glutamine to culture medium improved antioxidant capacity in Jian carp intestinal cells [18]. Applications of glutamine-containing dipeptides in fish have also been reported. In Jian carp, dietary supplementation with 0.36% alanyl-glutamine significantly improved growth, feed utilization, and muscle protein content [19]. In larval taimen (*Hucho taimen*), dietary supplementation with 0.75% alanyl-glutamine enhanced growth performance and antioxidant capacity [20].

1.2 Arginine

Beyond serving as an essential precursor for protein synthesis, arginine and its metabolites (ornithine, citrulline, and nitric oxide) play important roles in immune regulation and in maintaining and protecting intestinal mucosal structure and function [21]. In studies on humans and other terrestrial animals, arginine has been recognized as an essential nutrient for tissue repair and an immune nutrient, considered a primary amino acid precursor for polyamines required for intestinal repair [7]. For example, oral administration of 2% arginine solution improved ischemia-induced intestinal mucosal injury in rats [22]; dietary supplementation with 0.7% arginine improved microvillus development in the small intestine of weaned piglets [23]; and dietary supplementation with 0.6% arginine improved growth performance, health status, and intestinal function in piglets [24]. These effects may occur because arginine promotes proliferation and growth of intestinal mucosal cells, thereby enhancing intestinal mechanical barrier function, reducing intestinal damage from diseases, maintaining internal environmental stability, and ensuring mucosal integrity. However, studies have shown that arginine is a “double-edged sword” : at a dose of 4 mmol/L (the “intestinal physiological level”), it benefits cell migration, while doses >10 mmol/L are harmful [25].

In fish, arginine is an essential amino acid. Currently, reports on arginine’ s effects on intestinal function in aquatic animals are limited. Dietary supplementation with 1% arginine and 1% glutamine improved intestinal function in red drum (*Sciaenops ocellatus*) [26], while dietary supplementation with 1.85% arginine reduced lipopolysaccharide-induced intestinal injury in Jian carp [27].

The mechanisms underlying arginine' s role in intestinal repair are generally believed to involve promoting reactive oxygen species production and enhancing nitrotyrosylation of the intestinal mucosa, making it a potent stimulator of intestinal cell migration and epithelial recovery. Additionally, arginine can enhance cell migration rates and activate downstream ribosomal protein S6 kinase 1 (S6K1) of the mammalian target of rapamycin (mTOR) pathway [7].

1.3 Other Amino Acids

Threonine is a major component of plasma γ-globulin and intestinal mucin, with approximately 70% of threonine intake metabolized by intestinal tissue in infants [28]. When dietary threonine is deficient, the number of mast cells and goblet cells in piglet intestinal tissue decreases, and intestinal mucin content declines significantly; intravenous threonine supplementation cannot fully reverse this inhibition [29]. Restricting dietary threonine significantly reduces mucin synthesis capacity in all segments of the rat small intestine [30]. Studies have found that adding 0.89% threonine to piglet diets can improve intestinal function [31]. During inflammatory responses in piglets, threonine deficiency weakens intestinal barrier function, while increased threonine supply promotes mucin synthesis and restoration of intestinal mucosal function [32].

Leucine is considered a functional amino acid with important roles in intestinal function. Approximately 42-48% of leucine intake is utilized by intestinal tissue in infants [33], compared to only 20-30% in adults [28]. Lysine is also used in the intestine to synthesize intestinal mucosal proteins and can provide energy for the intestine through catabolism. Studies have found that 35% of dietary lysine is retained by the intestine in piglets, with only 18% used for synthesizing intestinal mucosal proteins [34].

In fish studies, appropriate levels of tryptophan improved immune status in the anterior, mid, and posterior intestine of mid-term grass carp (*Ctenopharyngodon idella*), enhanced intestinal antioxidant capacity, and maintained intestinal barrier structure integrity [35]. Microencapsulated threonine effectively improved intestinal health in juvenile Jian carp, thereby enhancing nutrient digestion and absorption capacity [36].

2.1 Zinc

Zinc is an important factor affecting intestinal cell division and regeneration and regulating intestinal amino acid and protein metabolism [37-38]. Dietary supplementation with 3,000 mg/kg zinc in weaned piglets promoted intestinal development [37] and reduced stem cell factor mRNA and protein expression levels in the jejunum [38], thereby preventing enteritis. Dietary zinc oxide supplementation enhanced antioxidant stress capacity and inhibited intestinal cell apoptosis in weaned piglets, preventing enteritis in newborn piglets [39]. Appropriate zinc supplementation in juvenile Jian carp feed promoted intestinal development, increased activities of digestive enzymes and intestinal brush border enzymes, thereby improving nutrient digestion and absorption capacity and enhancing production performance [40].

2.2 Fatty Acids

Polyunsaturated fatty acids (PUFAs) have been confirmed to benefit enteritis prevention and treatment. Dietary supplementation with C18:3n-3 in young mice with colitis reduced inflammatory responses [41], and n-3 PUFAs reduced the incidence of necrotizing enterocolitis in mice [42]. Adding eicosapentaenoic acid (EPA) to culture medium of human colon adenocarcinoma cells affected tight junctions and permeability of intestinal monolayer cells [43], suggesting that n-3 PUFAs may prevent enteritis by improving intestinal barrier function [44]. Adding free fatty acids to primary culture of porcine intestinal mucosa promoted development of brush border lipid raft microdomains [45]. Dietary supplementation with 0.3% mixed medium-chain fatty acids in piglets affected gastric microbial populations and intestinal bacterial metabolite production [46], possibly related to the immune-enhancing and antibacterial functions of medium-chain fatty acids. When fish meal content was reduced, dietary supplementation with 0.02% plant essential oils improved growth performance and intestinal health in Pacific white shrimp (*Litopenaeus vannamei*) [47].

2.3 Probiotics

Probiotics interact with various cellular components in the intestine and can affect intestinal cell function in multiple ways. Studies have shown that major cellular signaling regulatory pathways and cytokines, such as nuclear transcription factors, MAPKs, heat shock proteins, and peroxisome proliferator-activated receptors, are targets of probiotics or their products, and these pathways and cytokines can be modified and regulated by probiotics through different mechanisms [48]. Currently, probiotics have been widely applied in aquaculture, with confirmed benefits for promoting aquatic animal growth by enhancing intestinal digestive enzyme activities, maintaining bacterial balance, and strengthening immune capacity [49-50].

2.4 Carbohydrates

Carbohydrates that can improve animal intestinal function include oligosaccharides and polysaccharides. Studies have found that intraperitoneal injection of peptidoglycan in tumor-bearing mice significantly inhibited colon cancer cell growth [51]. Research shows that plant oligosaccharides can regulate intestinal microflora in livestock and poultry, inhibit proliferation of harmful microorganisms, and promote proliferation of *Bifidobacterium* and *Lactobacillus* [52]. The regulatory effect of oligosaccharides on intestinal flora in livestock and poultry is achieved mainly by proliferating beneficial bacteria such as *Bifidobacterium*, inhibiting harmful bacteria such as *Escherichia coli*, and preventing pathogen colonization to promote their elimination [53]. Polysaccharides primarily resist pathogen invasion by enhancing intestinal immune function, maintaining normal function of intestinal mucosal microcirculation, promoting proliferation of intestinal mucosa-associated immune cells, improving intestinal mucosal antioxidant capacity, and regulating secretion and expression of cytokines and inflammatory mediators [54]. In tilapia, dietary supplementation with astragalus polysaccharide increased villus length and the number of intestinal mucus cells and intraepithelial lymphocytes [55].

In summary, intestinal health is one of the key factors ensuring rapid growth in aquatic animals. Some additives can promote intestinal development, maintain normal intestinal structure and function, and enhance nutrient transport and absorption capacity. Therefore, adding additives that improve intestinal health to feed can increase utilization of relatively inexpensive feed sources by aquatic animals, though the mechanisms underlying their enhancement of digestion and absorption capacity require further investigation.

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