Effects of Tributyrin on Animal Growth and Intestinal Barrier Function and Its Mechanism of Action: Postprint

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Abstract

Tributyrin (TB) is a short-chain fatty acid ester composed of four carbon atoms, existing as a white, near-oily liquid with a slight fatty odor. It can smoothly traverse the gastrointestinal tract and be slowly hydrolyzed into butyric acid, thereby reaching the posterior intestine to exert its physiological effects. Research has reported that TB promotes intestinal villus growth, enhances nutrient digestion, maintains intestinal microbiota balance, strengthens tight junctions, promotes mucin secretion, and improves immunity, consequently enhancing animal production performance. Therefore, dietary supplementation with TB has become a nutritional strategy for improving animal intestinal barrier function and promoting growth, and is widely applied in livestock farming. This article primarily elaborates on the effects of TB in promoting animal growth and maintaining intestinal barrier function, as well as the potential mechanisms of action.

Full Text

Effects of Tributyrin on Growth and Intestinal Barrier Function of Animals and Its Mechanism

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Abstract

Tributyrin (TB) is a short-chain fatty acid ester composed of four carbon atoms, appearing as a white, oily liquid with a slight fatty aroma. It can pass smoothly

through the gastrointestinal tract, where it is slowly hydrolyzed into butyric acid that reaches the distal intestine to exert physiological effects. Studies have reported that TB promotes intestinal villus growth, enhances nutrient digestion, maintains intestinal flora balance, strengthens tight junctions, promotes mucin secretion, and improves immunity, thereby enhancing animal production performance. Consequently, dietary TB supplementation has become a nutritional strategy to improve intestinal barrier function and promote animal growth, and is widely applied in livestock production. This review primarily elaborates on the effects of TB on animal growth and intestinal barrier function and its potential mechanisms of action.

Keywords: tributyrin; animal growth; intestinal barrier function

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With the expansion of intensive livestock production, disease has become a major challenge for farmers. To address the negative effects of antibiotics, the European Union implemented a complete ban on antibiotic growth promoters in January 2006 [**?**]. Consequently, researchers have increasingly focused on developing green and safe novel feed additives for widespread application in production. Tributyrin (TB) is a short-chain fatty acid ester composed of four carbon atoms that can be hydrolyzed by pancreatic lipase in the gastrointestinal tract into butyric acid and glycerol, which are then transported via blood to various tissues and organs for utilization. Compared with butyrate, TB is widely used in livestock production due to its fatty aroma and advantages such as resistance to gastric acid decomposition and slow metabolism. Studies have reported that TB promotes healthy animal growth by maintaining intestinal flora balance in pufferfish (*Takifugu flavindus*) [**?**], improving intestinal immunity in piglets [**?**], and enhancing intestinal antioxidant capacity in Jian carp (*Cyprinus carpio* var. Jian) [**?**]. This review primarily addresses the effects of TB on animal growth and intestinal barrier function and its underlying mechanisms.

1.1 Physicochemical Properties

Tributyrin is a short-chain fatty acid ester composed of three butyric acid molecules and one glycerol molecule, with the molecular formula C H O and a relative molecular mass of 302.41. It is a colorless, oily liquid with a fatty aroma. TB is insoluble in water but readily soluble in organic solvents such as ether and ethanol, and exhibits a low melting point (-75°C) and high boiling point (305-310°C). These physicochemical properties remain essentially unchanged under high temperature, light exposure, and pelleting conditions, making it suitable for various current feed processing technologies.

1.2 Metabolism

Butyrate is rapidly absorbed in the stomach and upper small intestine during metabolism, with minimal amounts reaching the distal intestine to exert physio-

logical effects. In contrast, TB is not easily decomposed by gastric acid and can pass smoothly through the stomach. In the intestine, TB is slowly hydrolyzed by pancreatic lipase into butyric acid and glycerol [?]. On one hand, butyric acid is readily absorbed by colonic mucosal epithelial cells, where most of it is oxidized into ketone bodies to synthesize ATP, providing energy for intestinal cells [?]. On the other hand, butyric acid is converted into butyryl-CoA under the action of butyrate-CoA synthetase, then undergoes a series of chemical reactions to generate acetyl-CoA, which participates in -oxidation for energy metabolism [?].

2.1 TB Promotes Animal Growth

Dietary supplementation with varying levels of TB can promote animal growth (Table 1). In terrestrial animals, studies have shown that adding 5 g/kg TB to diets increased average daily gain (ADG) by 13.64% in 1–28-day-old weaned piglets [?]; supplementation with 1 g/kg TB increased ADG by 237.93% in 7–21-day-old intrauterine growth-retarded (IUGR) piglets [?] and by 10.65% in weaned piglets [?]; and 2 g/kg TB increased ADG by 6.47% in 1–42-day-old broilers [?] and by 6.67% in Avian broilers [?]. Similar findings have been reported in aquatic animals: 1 g/kg TB increased percentage weight gain (PWG) by 13.2% in Jian carp [?], while 0.1 g/kg TB increased PWG by 28.12% in *Takifugu flavindus* [?].

2.2 Possible Mechanisms of TB in Promoting Animal Growth

Animal growth is closely related to the intestinal capacity for nutrient digestion [?, ?]. Studies in pigs [?], chickens [?], and fish [?] have demonstrated that amylase, protease, and lipase are important digestive enzymes, and increasing their activities can enhance intestinal digestive capacity. Research in pigs [?] and pufferfish [?] has found that dietary TB supplementation can increase ileal lipase activity, jejunal and ileal trypsin activity, and intestinal amylase activity. Furthermore, intestinal digestive capacity is regulated by intestinal growth and development, which is closely associated with villus height and crypt depth [?]. Studies have shown that TB supplementation increases ileal villus height in weaned piglets [?]; increases duodenal and jejunal villus height in broilers without significantly affecting crypt depth [?]; increases duodenal and jejunal villus height while decreasing crypt depth in 1–14-day-old broilers [?]; increases anterior and posterior intestinal villus height in *Takifugu flavindus* [?]; and decreases ileal crypt depth in broilers challenged with lipopolysaccharide (LPS) [?]. The mechanism by which TB promotes intestinal growth and development remains unclear, but we speculate it may be related to its metabolites serving as the primary energy source for intestinal epithelial cells. Rapid intestinal mucosal growth and development require an effective energy source. Macfarlane et al. [?] reported that butyric acid is readily absorbed by colonic mucosal epithelial cells and oxidized into ketone bodies to synthesize ATP, providing energy for intestinal cell growth and development.

These findings demonstrate that TB promotes healthy animal growth by enhancing intestinal growth and development, thereby improving digestive capacity.

3 TB Maintains Animal Intestinal Barrier Function

The intestine serves as both a crucial site for nutrient digestion and absorption and an important barrier against external environmental stimuli (toxic substances in the environment and feed, bacteria, etc.). The intestinal barrier primarily comprises the microbial barrier, physical barrier, chemical barrier, and immune barrier [**?**]. When intestinal barrier function is compromised, it can lead to immune system disorders, increased susceptibility to pathogenic bacteria, and ultimately reduced production performance.

3.1 TB Maintains Intestinal Microbial Barrier Function

Billions of microorganisms colonize the animal gastrointestinal tract, and changes in their composition are critical for maintaining gastrointestinal health and homeostasis [**?**, **?**]. External factors such as dietary composition changes, lifestyle modifications, and invasion of toxic substances can affect intestinal microbial composition, disrupt flora balance, and trigger disease [**?**, **?**]. In broilers, dietary TB supplementation has been shown to increase beneficial *Lactobacillus* populations and reduce harmful *Escherichia coli* populations in the cecum [**?**], increase *Lactobacillus* while decreasing *E. coli* in the duodenum and cecum [**?**], and reduce cecal *Salmonella* populations [**?**]. Research on TB' s effects on aquatic animal intestinal flora is limited, with only one report in *Takifugu flavindus* showing that dietary TB increased aerobic heterotrophic bacteria and *Lactobacillus* while reducing *Vibrio* populations [**?**]. The mechanism by which TB modulates intestinal flora remains unclear, but we speculate it may be related to hydrogen ion accumulation altering pH. Studies have reported that TB is slowly hydrolyzed by pancreatic lipase into butyric acid and glycerol. Butyric acid entering the distal intestine dissociates into butyrate ions and hydrogen ions, and high concentrations of hydrogen ions can lower pH, thereby killing harmful bacteria such as *E. coli* and *Salmonella* while allowing acid-tolerant beneficial bacteria like *Lactobacillus* to proliferate and modulate intestinal flora composition [**?**].

These findings demonstrate that TB maintains intestinal microbial barrier function by increasing beneficial bacteria and reducing harmful bacteria to modulate intestinal flora composition.

3.2 TB Maintains Intestinal Physical Barrier Function

Intestinal physical barrier function is closely related to tight junctions between epithelial cells [**?**]. Tight junctions are protein complexes composed of multiple proteins, primarily including transmembrane proteins (claudin family and occludin) and cytoplasmic proteins (ZOs), which play crucial roles in maintaining intestinal mucosal epithelial cell polarity and regulating intestinal barrier

permeability [?]. Increasing tight junction protein expression enhances intercellular tight junction formation, thereby preventing macromolecules such as bacteria and toxins from entering the body and maintaining intestinal physical barrier function [?]. Studies have reported that dietary TB supplementation enhances ZO-1 and occludin protein expression in mouse ileum and colon [?]. Additionally, dietary sodium butyrate supplementation increases occludin gene expression in the anterior intestine of gilthead sea bream (*Sparus aurata*) [?] and claudin-1 and occludin gene expression in broiler intestine [?].

These findings demonstrate that TB strengthens intestinal physical barrier function by promoting tight junction protein expression to maintain intercellular tight junctions.

3.3 TB Maintains Intestinal Chemical Barrier Function

The intestinal chemical barrier is primarily composed of the mucus layer covering the intestinal epithelium [?]. Mucin (Muc) is the most abundant molecule in the mucus layer, secreted by specialized epithelial cells, and can prevent macromolecules (such as bacteria and toxins) from entering the epithelial cell layer [?]. Studies have reported that dietary sodium butyrate increases Muc13 and Muc2 gene expression in gilthead sea bream intestine [?] and Muc2 gene expression in grass carp [?] and broiler intestine [?]. As an enzymatic hydrolysis product of tributyrin, butyric acid can increase Muc1, Muc2, Muc3, and Muc4 gene expression in mouse colon [?].

These findings demonstrate that TB strengthens intestinal chemical barrier function by promoting Muc secretion.

3.4.1 TB Enhances Intestinal Immunity

Animal immunity depends on a series of immune substances, such as complement factors, immunoglobulins, and antimicrobial peptides [?]. Zhang et al. [?] found that increasing complement factor 3 (C3) and complement factor 4 (C4) contents and upregulating antimicrobial peptide hepcidin and -defensin gene expression enhanced grass carp immunity. Studies have shown that dietary TB supplementation increases IgG gene expression and secretory IgA (sIgA) and IgG contents in IUGR piglet ileum [?], and increases serum IgA, IgM, and IgG contents in weaned piglets [?]. Dietary sodium butyrate supplementation increases serum C3, IgG, and IgM contents and intestinal mucosal plasma cell IgA+ content in piglets [?], increases serum IgG and jejunal IgA+ content in weaned piglets [?], and increases grass carp intestinal lysozyme and acid phosphatase activities, C3 and C4 contents, and hepcidin and -defensin-1 gene expression [?]. Furthermore, dietary butyrate increases cathelicidin B1, -defensin 9, and -defensin 14 gene expression in chicken jejunum and ileum [?]. The mechanism by which TB modulates intestinal immune substances may be related to promoting immune cell growth. Studies have reported that animals contain abundant mucosa-associated lymphoid tissues rich in immune cells such

as lymphocytes, macrophages, neutrophils, and eosinophils [?]. Immune cells can secrete immune substances including lysozyme, complement factors, and immunoglobulins [?]. In mice and pigs, TB increases intestinal macrophage and T cell numbers and cecal mononuclear and B cell numbers [?], and increases blood lymphocyte and neutrophil numbers in pigs [?]. In broilers, dietary butyrate supplementation increases duodenal, jejunal, and ileal mast cells, lymphocytes, and goblet cells [?] and small intestinal mast cell numbers [?].

3.4.2 TB Enhances Intestinal Immunity by Alleviating Inflammatory Responses

Studies have shown that alleviating intestinal inflammatory responses can enhance animal immunity [?]. Wang et al. [?] reported that inflammatory responses are primarily mediated by a series of cytokines, including pro-inflammatory and anti-inflammatory cytokines. Elevated pro-inflammatory cytokine levels and reduced anti-inflammatory cytokine levels can exacerbate inflammatory responses and disrupt intestinal health homeostasis [?, ?]. In a dextran sulfate sodium-induced mouse colitis model, TB increased transforming growth factor- (TGF-) and interleukin-10 (IL-10) contents [?]. Li et al. [?] induced intestinal injury in broilers with LPS and then fed TB-supplemented diets, finding that TB decreased IL-1 and IL-6 contents in the duodenum and jejunum and IL-1 content in the ileum. In mice fed long-term high-fat diets, TB supplementation decreased macrophage tumor necrosis factor (TNF)- , IL-1 , and IL-6 contents [?]. Zhang et al. [?] found that TB increased serum IL-2 content in weaned piglets. Additionally, sodium butyrate decreased grass carp intestinal TNF- , interferon- 2 (IFN- 2), IL-6, and IL-8 while increasing IL-4/13A and IL-4/13B gene expression [?]; decreased carp intestinal IL-1 and TNF- while increasing TGF- 1 gene expression [?]; and in human peripheral blood mononuclear cells, butyrate inhibited LPS-induced TNF production and decreased TNF- , TNF- , and IL-6 gene expression [?]. The mechanism by which TB suppresses intestinal inflammatory responses may involve the nuclear factor- B (NF- B) signaling pathway. NF- B plays an important role in regulating inflammatory cytokine expression [?]. Inhibiting NF- B can downregulate pro-inflammatory cytokines IL-6 and IL-8 [?] and upregulate anti-inflammatory cytokines TGF- and IL-10 [?]. Studies in human peripheral blood mononuclear cells [?] and mouse neutrophils [?] have shown that butyrate inhibits LPS-induced NF- B nuclear translocation. Additionally, I B kinase (IKK) can phosphorylate nuclear factor of B inhibitor protein (I B), causing its dissociation from NF- B and allowing NF- B to translocate into the nucleus to regulate downstream target gene expression [?]. Studies have shown that butyrate promotes I B phosphorylation in Caco-2 cells [?] and HT-29 cells [?]. Tian et al. [?] found that sodium butyrate decreased IKK and IKK gene expression and upregulated I B gene expression in grass carp intestine.

These findings demonstrate that TB alleviates intestinal inflammatory responses by inhibiting NF- B nuclear translocation, thereby decreasing pro-inflammatory

cytokine expression and increasing anti-inflammatory cytokine expression.

3.4.3 TB Enhances Intestinal Immunity by Improving Antioxidant Defense Function

Oxidative stress can damage animal intestinal immunity [**?**]. Malondialdehyde (MDA) content is a sensitive indicator for evaluating lipid peroxidation [**?**]. Dietary TB supplementation decreases MDA content in IUGR piglet liver [**?**] and in broiler duodenum, jejunum, and ileum [**?**]. Additionally, Zhang et al. [**?**] reported that animals have developed their own antioxidant defense systems to combat oxidative stress, including enzymatic and non-enzymatic antioxidants. In IUGR piglets, TB increased liver superoxide dismutase (SOD), glutathione peroxidase (GPx), reduced glutathione (GSH) activity, total antioxidant capacity (T-AOC), and liver mitochondrial manganese-superoxide dismutase (Mn-SOD) activity [**?**]. Leonel et al. [**?**] found that TB increased SOD and catalase (CAT) activities while decreasing hydroperoxide content in a dextran sulfate sodium-induced colitis model. In broilers, TB increased duodenal, jejunal, and ileal CAT and jejunal GPx activities [**?**]. Perfusion with 100 mmol/L butyrate increased GSH content in human colonic mucosa [**?**]. The mechanism by which TB improves intestinal antioxidant capacity may involve increased antioxidant gene expression. Song et al. [**?**] reported that antioxidant enzyme activity partially depends on antioxidant enzyme gene expression, which is regulated by the Kelch-binding protein 1 (Keap1)/nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway. Studies have reported that butyrate increases glutathione reductase (GR) gene expression in gilthead sea bream intestine [**?**], glutathione S-transferase P1 (GSTP1) gene expression in human lung cancer cells [**?**], GPx1, GPx3, and GR gene expression in human colonic mucosa [**?**, **?**], GSTP1, GSTA4, GSTM2, and GSTM5 gene expression in human colon cancer cells [**?**], and GSTA1 and GSTA2 gene expression in Caco-2 cells [**?**]. Sodium butyrate inhibits Keap1 expression in RAW264.7 cells [**?**] and promotes Nrf2 nuclear translocation in IEC-6 cells [**?**] and HepG2 cells [**?**].

These findings demonstrate that TB enhances intestinal immune barrier function by: (1) inhibiting NF- B transcriptional activation to regulate cytokine expression and alleviate inflammatory responses, and (2) promoting the Nrf2 signaling pathway to upregulate antioxidant enzyme GST gene expression and increase antioxidant enzyme activity, thereby alleviating oxidative damage.

4 Summary

The evidence indicates that dietary TB supplementation enhances intestinal barrier function and promotes animal growth by improving intestinal digestive capacity, modulating flora balance, strengthening tight junctions, promoting Muc secretion, and enhancing immunity. Specifically, TB improves digestive capacity by increasing digestive enzyme activities (amylase, protease, lipase) and promoting intestinal villus growth; enhances microbial barrier function by promoting beneficial bacteria (*Lactobacillus*) and inhibiting harmful bacteria (*E.*

coli); strengthens physical barrier function by increasing tight junction protein expression; enhances chemical barrier function by increasing Muc secretion; and improves immune barrier function by inhibiting the NF- B signaling pathway to alleviate inflammatory responses and promoting the Nrf2 signaling pathway to enhance antioxidant capacity. As a novel, green feed additive, TB has attracted considerable attention and shows broad market application prospects. However, current research is limited to piglets, broilers, and a few aquatic species, and more systematic and in-depth studies are needed.

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Note: Figure translations are in progress. See original paper for figures.