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Review Article

Research Progress of Baicalin Interactions with the Animal Gut Microbiome

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ABSTRACT

Homeostasis of the animal gut microbiome is essential for maintaining intestinal health and normal growth and development. Baicalin is an O-glucuronidated flavonoid that possesses strong anti-bacterial, anti-inflammatory and antioxidant activities. Its addition to animal feed can alter gut microbial community composition, diversity and production of bacterial metabolites while decreasing production of pro-inflammatory cytokines and other factors that compromise the integrity of the epithelial cell barrier. This review thus summarizes the research progress of baicalin and regulation of the gut microbiota to provide guidance for the potential application of this compound for animal production as an antibiotic alternative.

Keywords: Baicalin, Gut microbiota, Mechanism, Intervention treatment, Intervention environment, Function, Structure.

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INTRODUCTION

The intestinal flora plays critical roles in animal nutritional, metabolic and immune health and is an indispensable part of normal host physiology.[1,2] Beneficial intestinal bacteria can limit reproduction of pathogenic bacteria via antimicrobial compounds and through nutrition and adhesion site competition. These bacterial functions have evolved with the host and are key obstacles in collective resistance to bacterial pathogens. Residence in the gastrointestinal tract also entails interactions with host digestive processes and food and drugs can alter intestinal flora composition that affects digestion and nutrient absorption as well as oral drug absorption and metabolic disposal.[3,4]

Traditional Chinese Medicines (TCM) can also exert effects on the gut microbiome. Upon oral administration, traditional Chinese medicine exerts a regulatory effect on the structure and abundance of gut microbiota, The gut microbiota has been found to produce metabolic enzymes that play a crucial role in the material metabolism and chemical structure remodeling of effective components of Traditional Chinese Medicine. This leads to diverse pharmacological and toxicological activities of the said components. Baicalin is a TCM flavonoid extracted from *Scutellaria baicalensis* (Baikal skullcap, Lamiaceae) that has displayed a variety of biological effects as an antibacterial, anti-inflammatory and antioxidant. This compound exerts its beneficial effects through the regulation of intestinal flora populations especially in the fasting state. Baicalin has been used as a green feed additive in food animal production and is a potential antibiotic substitute. When fed to livestock and poultry, it improved production performance and was successfully applied to treat mastitis, endometritis and diarrhea.[5,6] However, the mechanisms of its action such as the identification of interacting metabolic pathways are not clear.

The essential roles that the intestinal microbiome plays in animal health are currently the subjects of intense research that involves numerous aspects of the topic. In the current review we document research progress on the *in vivo* metabolism of baicalin and its

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effects on the composition, structure, diversity and metabolites of intestinal flora. This work provides a scientific basis for the application of baicalin in animal production.

Physicochemical properties of baicalin

Baicalin (astragalin) is a flavonoid that is present in the roots, stems and leaves of *S. baicalensis*. It is a small organic molecule ($C_{21}H_{18}O_{11}$; 446.34 g mol^{-1}) composed of the 3-membered ring baicalein ($C_{15}H_{16}O_5$; 270.24 g mol^{-1}) that is O-glucuronidated. It is typically found in the form of a light-yellow powder that is soluble in N-dimethylformamide and pyridine and insoluble in water, ether, benzene and chloroform. The therapeutic applications of baicalin are wide-ranging and include antibacterial, anti-inflammatory, antiviral, antioxidant, anti-tumor and immunity enhancement functions. Its primary use is in the prevention and treatment of respiratory and gastrointestinal inflammation, diarrhea and dysentery and has shown good therapeutic effects as an antiviral and lung protectant.[7-9]

Baicalin *in vivo* metabolism

The intestinal microbiota plays essential roles in both health and disease and can alter *in vivo* drug pharmacodynamics including absorption and metabolism by direct cleavage, reduction or other pathways such glucuronidase and glucosidase modifications. For example, glycosidase action can alter the effects the cardiac glycoside digoxin, salicin (aspirin) and other drugs that are readily modified by intestinal bacteria.[10,11] The active drug baicalein is the aglycone of baicalin formed by the action of intestinal microorganisms and is the form that is readily absorbed. Oral administration to rats indicated its aglycone baicalein was present in high amounts in the intestine and in blood 1-2 hr later and only low levels were present in blood 2 hr following administration to aseptic rats.[12] Baicalin is rapidly converted to the aglycone baicalein by the intestinal microbiota and this action results in a significant increase in its biological activity.[13] Baicalein can also be metabolized by intestinal flora *in vitro* to form wogonin, the less polar O-methylated version of baicalein that is absorbed more readily through intestinal walls.[14] Interestingly, glucuronosyltransferase activity in blood can also convert baicalein to baicalin.[15] Baicalin used in combination with the antibiotics (cefadroxil, oxytetracycline and erythromycin) significantly altered maximal absorption C_{max}, $T_{½}$ β elimination and Area Under the Concentration time curve (AUC) values of baicalin in plasma. This also implicated the intestinal microflora in the oral Pharmacokinetics (PK) of baicalin and the intestinal microflora increase baicalin efficacy through their metabolic activities.[16]

Baicalin and the intestinal microbiome

Effects on microbiome composition and structure

Baicalin is a potential antibiotic substitute for livestock and poultry but its therapeutic profile must also be balanced with potential alterations to microbiome composition, diversity and metabolism. Baicalin can reduce metabolic inflammation by reducing the Gram-negative/Gram-positive bacterial ratio in the intestinal tract and reduce endotoxin levels and associated secretion of inflammatory cytokines such as TNF-α and IL-6. Baicalin administration also reduced the ratio of thick-walled bacteria/*Bacteroides*, increased lactobacilli and reduced clostridial numbers and enhanced intestinal barrier functions.[17] It also enriched for the beneficial bacterial groups *Bacteroidales S24-7group_norank, Parasutterella, Prevotellaceae UCG-001, Ruminiclostridium* and *Ruminiclostridium-9* and reduced *Escherichia coli* and *Shigella* spp. numbers.[18] Baicalin used as a feed additive for chickens increased the cecal abundance of beneficial bacteria while reducing *Salmonella enteritis* levels that effectively reduced intestinal inflammation and improved chicken production performance. Direct feeding of the parent plant *S. baicalensis* also increased levels of lactic acid bacteria and decreased *Enterobacteriaceae* representation in the ileocecum of broiler chickens and these effects were age-dependent. For instance, at 1-21 days of age, lactic acid bacteria were increased and *Enterobacteriaceae* were reduced but no significant effects were produced in at 22-42 days of age.[19] In addition, baicalein could regulate the fecal flora in the Chemotherapy-induced Intestinal Mucositis (CIM) mouse model and reduced the abundance of *Bacteroides, E. coli, Shigella, Parabacteriodes Enterococcus* and *Clostridium*.[20] *S. baicalensis* used as a feed supplement in mice increased *Lactobacillus* abundance and reduced levels of the pathogenic *Lactococcus.* These results indicated that the beneficial effects of Baicalin on ulcerative colitis are most likely via regulation of the intestinal flora structure.[21] However, intragastric administration of Baicalin at high (100 mg/kg) levels decreased *Bifidobacterium, Lactobacillus* and *E. faecalis* and increased *E. coli* presence while lower doses increased *E. coli* and decreased *E. faecalis* with no effect on *Bifidobacterium* and *Lactobacillus*.[22] High levels of 500 mg/kg baicalin in feed administered to mice also resulted in floral imbalances and intestinal injury similar to that seen in mice receiving 5 g/L lincomycin in drinking water. The use of lower baicalin doses also resulted in community disruptions but the effects occurred the later stages of the experiment.[23] These studies suggested that long-term heavy use of baicalin may have a destructive effect similar to that of lincomycin that include diarrhea, inflammatory bowel disease and pseudomembranous colitis. Lower doses of baicalin did not alter the structure of the intestinal flora and the number of beneficial bacteria increased while conditional pathogens such as *Enterococcus* decreased slightly. These data also

suggested that baicalin could induce the emergence of new flora and stabilize intestinal microfloral structures.

Baicalin therefore can enhance or inhibit beneficial intestinal flora and this effect is dose-dependent. An optimal dosage increases abundance of beneficial bacteria such as short-chain fatty acid producers, rumen cocci and bile acid decomposing bacteria while reducing levels of harmful bacteria including *Bacteroides, E. coli* and *Shigella*.

Baicalin and intestinal microflora diversity

Baicalin exerts its pharmacological activity by increasing the abundance of probiotics in the intestinal tract, reducing the abundance of harmful bacteria and adjusting the microecological balance of the intestinal tract. It may therefore provide effective treatment for intestinal disease states by increasing abundance of lactic acid bacteria and total anaerobes and increasing butyric acid levels. Baicalin can significantly increase abundance of thick-walled bacteria, *Bifidobacterium, Lactobacillus* and *Rosella* and inhibit *Bacteroides, Proteus* and *Staphylococcus* growth and provide a protective effect against pathological injury to the colon.[24] Its regulation of the intestinal microbiota includes increasing the abundance of the beneficial *Lachnoclostridium, Alistipes, Roseburia* and *Lactococcus* and reducing the levels of quasi-*Bacteroides, Parasutterella* and *unidentified_Clostridiales*. Baicalin displayed a very good protective effect against inflammatory injury caused by *Mycoplasma gallisepticum* and could restore the abnormal intestinal flora imbalance caused by this infection. It significantly increased the abundance of symbiotic bacteria *Bacteroides fragilis* and reduced the pulmonary inflammatory damage caused by mycoplasma infection in chickens.[25] Baicalin can reduce the inflammatory damage of hypertension, increase the abundance of bacteria producing unsaturated fatty acids, change the structure of intestinal microflora, reduce intestinal permeability and protect against intestinal barrier damage caused by inflammatory reactions.[26] These studies have indicated that baicalin regulates intestinal flora diversity and maintains the balance of intestinal microecology.

Effects of baicalin on intestinal flora metabolism

The intestinal flora can regulate host metabolic processes via production of Short-Chain Fatty Acids (SCFA), bile acids, amino acids, vitamins and polyamines.[27] These effects have also been documented for baicalin. For instance, baicalin could inhibit experimental Enteropathogenic *E. coli* (EPEC) infection by increasing production of the SCFAs acetic (C2), propionic (C3) and butyric (C4) acids.[28] The presence of acetic acid in the intestine can result in its circulation to the lungs to activate the Free Fatty Acid Receptor 2 (FFAR2) to diminish susceptibility toward EPEC, *Klebsiella pneumonia*, *Citrobacter rodentium* and *Staphylococcus aureus* infections.[29] Baicalin administration significantly reduced ATP and increased ADP and AMP levels that were traced to activation of the key enzymes of SCFA synthesis; acetate kinase, methylmalonyl-CoA decarboxylase, butyryl-CoA: acetate-CoA transferase and butyrate kinase. In particular, the peroxisome proliferator-activated receptor-gamma coactivator (PGC-1 α) - Uncoupling Protein-2 (UCP-2) signaling pathway was activated to increase mitochondrial biogenesis.[30] The anti-inflammatory effects of baicalin have also been traced to the activation of the anti-inflammatory cascade that included Akt / NF-κB. Baicalin treatment significantly increased serum levels of anti- *M. pneumoniae* IgM and decreased C-Reactive Protein (CRP) expression in lung tissue during experimental *Mycoplasma pneumoniae* infections. In this infection model, baicalin administration decreased levels of the pro-inflammatory cytokines IL-1 β, IL-6, IL-18 and TNF- α in bronchioalveolar lung fluid. Lung tissue inflammatory infiltrates were also reduced as were pathological changes in lung tissue that included reduced apoptosis and TLR4, MyD88 and NF-κB protein levels. Interestingly, baicalin down-regulated expression of the microRNA miR-221 and overexpression of the latter weakened the positive effects of baicalin administration.[31]

Baicalin has also been examined using a chronic gastritis model and was found to be a binding partner of both Akt and NF-κBp65.[32] It could improve the outcomes in cases of hyperglycemia and hyperlipidemia by regulating the interaction between intestinal flora and bile acid metabolism. This action involved activation of hepatic cholesterol 7 α-hydroxylase (CYP7A1) via inactivation of the Farnesoid X (bile acid) Receptor (FXR) in the intestine rather than liver.[33] Baicalin has a synergistic effect on cholesterol lowering by increasing excretion of bile acids in feces. This process is accompanied by the activation of FXR and low-density lipoprotein receptor genes and the inhibition of HMG CoA reductase, the rate limiting enzyme of liver cholesterol biosynthesis. Baicalin was also found to restore order to the intestinal microbiome in an Azoxymethane (AOM) model of induced colitis. The effects of baicalin were traced to altered metabolites that were are almost all involved in lipid metabolic pathways.[25] Baicalin can also prevent release of pro-inflammatory cytokines and counter membrane injury by inhibiting Lipopolysaccharide (LPS) and Toll-Like Receptor 4 (TLR4) signaling.[34-36] It has very strong antibacterial activity and can alter the abundance, composition and diversity of animal intestinal flora by altering patterns of metabolites produced by the intestinal flora. These include activation of the Nucleotide Oligomerization Domain (NOD)-like receptors and TLR signaling pathways by altering levels of peptidoglycan, flagellin and bacterial polysaccharides contained in intestinal flora.[37] It can thus regulate the secretion of intestinal inflammatory factors from the microflora and lessen intestinal inflammation.

CONLUSION

Baicalin can balance the intestinal microecological environment by regulating the composition, structure and diversity of the intestinal flora and thereby alter the functioning of their metabolites. This compound can increase intestinal health, physiological functions, immune ability and production performance in animals. Therefore, it provides a theoretical basis for research and development of antibiotic alternatives and the rational application of baicalin as a new green feed additive in animal production. Currently, understanding the mechanisms of baicalin regulation of animal intestinal flora in different physiological states is only beginning. Future research combining multi-group techniques, fecal bacteria transplantation and gene knockout animal models can give a comprehensive view of key intestinal flora members and metabolites regulated by baicalin. These will facilitate discovery of its molecular mechanism of action and enhance its potential as an antibiotic alternative.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

TCM: Traditional Chinese medicines; **AOM:** Azoxymethane; **AUC:** Area under the concentration time curve; **PK:** Pharmacokinetics; **CIM:** Chemotherapy-induced intestinal mucositis; **EPEC:** Enteropathogenic Escherichia coli; **FFAR:** Free fatty acid receptor; **SCFA:** Short-chain fatty acids; **ADP:** Adenosine diphosphate; **AMP:** Adenosine monophosphate; **CRP:** C-reactive protein; **CYP7A1:** Cholesterol 7α-hydroxylase; **TLR:** Toll-like receptor.

SUMMARY

The intestinal flora, which is the largest endocrine organ in the body, produces numerous bioactive metabolites that significantly impact the physiological and pathological processes of the host. Baicalin has been shown to have a regulatory effect on the intestinal flora. It promotes the growth of beneficial bacteria and regulates the secretion of the intestinal flora. Additionally, the intestinal flora is capable of transforming baicalin, making it easier to absorb and reducing any potential adverse reactions.

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