Physiological Functions of Berberine and Its Application in Animal Production Postprint

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Abstract

Berberine exhibits abundant physiological functions and unique pharmacological properties, representing a potential alternative to antibiotics. This article introduces the fundamental characteristics and pharmacokinetic profiles of berberine, summarizes its primary physiological regulatory functions, explores its applications in animal production, and provides a scientific rationale for its utilization in livestock practice.

Full Text

Preamble

Berberine, also known as coptisine, is one of the main components of the traditional Chinese medicine *Coptis chinensis*. Initially used in human clinical practice as an antipyretic, detoxifying, and antibacterial agent, berberine has been documented in traditional Chinese medicine for over 3,000 years for the prevention and treatment of gastroenteritis, dysentery, and trachoma. Recent research has revealed its pharmacological effects in treating tumors, cancer, diabetes, cardiovascular disease, hyperlipidemia, inflammation, bacterial and viral infections, cerebral ischemic injury, mental disorders, neurological dysfunction, Alzheimer' s disease (AD), and osteoporosis. These therapeutic effects demonstrate that berberine possesses diverse physiological functions including antibacterial, anti-inflammatory, lipid-regulating, glucose-lowering, antitumor, antioxidant, blood pressure-reducing, antithrombotic, analgesic, smooth muscle-stimulating, and immunomodulatory activities [1]. Currently, most studies on berberine' s efficacy and mechanisms have focused on animal pathological models and human clinical treatment, with limited reports on its use as a feed additive in livestock and poultry. Wang et al. [2-3] added different doses of berberine hydrochloride to the diets of growing meat rabbits, revealing that berberine' s unique pharmacological properties make it a promising candidate for development as a

novel green feed additive. This review introduces the basic characteristics and pharmacokinetic features of berberine, summarizes its main physiological regulatory functions, and explores its applications in animal production to provide a scientific basis for its use in livestock practice.

1. Types and Characteristics of Berberine

Berberine has long been utilized in Ayurvedic medicine in India and traditional Chinese medicine. It is a quaternary ammonium isoquinoline alkaloid and an active component found in the roots, stems, and bark of many important medicinal plants. Berberine exists in various plant families including Berberidaceae, Papaveraceae, Ranunculaceae, Rutaceae, Menispermaceae, and Rhamnaceae, commonly found in species such as *Coptis chinensis*, *Phellodendron amurense*, *Berberis aquifolium*, *Berberis vulgaris*, and *Berberis aristata*. Among these, *Berberis aristata* is a thorny shrub up to 3 meters tall, widely distributed in the Himalayan region at altitudes of 2,000-3,000 meters and in the Nilgiri hills of southern India, with active components including berberine, berbamine, and palmatine [4].

The molecular formula of berberine is C20H19NO4, with a melting point of 145°C. It is odorless, extremely bitter in taste, soluble in methanol, slightly soluble in water and ethanol, and poorly soluble in benzene, ether, and chloroform, forming yellow needle-like crystals in ether. Its salts have relatively low solubility in water; for example, the hydrochloride salt has a solubility of 1:500, while the sulfate salt is 1:30. Treatment with different bases yields three forms of berberine: quaternary ammonium, aldehyde, and alcohol forms, with the quaternary ammonium form being the most stable. In recent years, berberine has been primarily obtained through chemical synthesis, with its hydrochloride or sulfate salts commonly used in clinical practice.

2.1 Absorption

In the intestinal tract, berberine is primarily taken up and transported by small intestinal mucosal epithelial cells through passive diffusion. The oral bioavailability of berberine is extremely low, mainly due to two factors: (1) its poor water solubility and dissolution characteristics. The solubility of berberine hydrochloride in water is positively affected by temperature and pH. For instance, at 25°C and 37°C, its solubility in water is $(5.27\$\pm0.29)and(8.50\pm0.40)mmol/L, respectively, whileinpH7.0phosphatebuffer, thesolubilityis(4.05\pm0.29)$
mmol/L, respectively. (2) Efflux pump systems on the cell membrane can pump berberine absorbed by intestinal mucosal epithelial cells back out of the cells, reducing intracellular concentration and consequently decreasing systemic absorption [4-6]. Therefore, improving berberine' s water solubility in the intestine, enhancing its dissolution, and promoting absorption by mucosal epithelial cells can increase its oral bioavailability. Gui et al. [7] reported that the bioavailability of an oral berberine microemulsion was

6.47 times higher than that of a tablet suspension. Sut et al. [8] found that co-administration of natural deep eutectic solvents with berberine at a dose of 50 mg/kg increased blood drug concentration in mice by 2-20 fold. Additionally, an anhydrous reverse micelle system prepared by a water-in-oil emulsion freeze-drying method can also improve berberine' s bioavailability and anti-diabetic effects. P-glycoprotein (P-gp) can pump various drugs including verapamil, daunorubicin, rhodamine, and berberine out of cells. However, when the aforementioned three drugs are present intracellularly, they can inhibit berberine efflux, suggesting that regulating P-gp expression or interfering with efflux pump systems could promote berberine absorption [5].

2.2 Distribution

Despite berberine' s bioavailability being less than 1%, it is rapidly distributed throughout the body after absorption. Following oral administration, the concentration of berberine and its active metabolites in blood is very low, significantly lower than that in tissues and organs. Among tissues and organs, berberine is most abundant in the liver, followed by the kidneys, muscles, lungs, brain, heart, and pancreas, with the lowest concentration in adipose tissue. Moreover, berberine can maintain relatively stable levels in these tissues and organs for at least 48 hours [9]. Additionally, berberine can easily cross the blood-brain barrier (BBB), rapidly accumulating in the hippocampus after intravenous injection and subsequently being slowly eliminated [9].

2.3 Metabolism

Berberine is metabolized in the liver, undergoing Phase I demethylation and Phase II conjugation with glucuronic acid or sulfate, with the final metabolites being readily excreted. The primary metabolic modifications occur at the 2,3-OCH2O and 9,10-OCH3 groups. Phase I metabolites include thalifendine, berberrubine, jatrorrhizine, columbamine, palmatine, 3,9-demethylpalmatine, demethyleneberberine, hydroxylated berberine, and hydroxylated demethyleneberberine. After conjugation with glucuronic acid or sulfate, Phase II metabolites are formed. Kumar et al. [1] reported that after oral administration of berberine hydrochloride at doses of 100 and 300 mg/kg to male Wistar rats and adult men, respectively, both Phase I and Phase II metabolites could be detected in bile, urine, and feces within 72 hours, indicating that these metabolites may represent the active forms of berberine after oral administration.

2.4 Excretion

Kumar et al. [1] found that after oral administration of 200 mg/kg berberine to rats, both berberine and its metabolites were excreted in bile, urine, and feces within 48 hours. The total recovery rate of berberine was 22.83%, with berberine accounting for 19.07% and metabolites for 3.76%. Specifically, 9.2$\times$$10-6%

was recovered from bile within 24 hours, while 0.0939% and 22.74% were recovered from urine and feces within 48 hours, respectively, demonstrating that berberine is primarily excreted through feces. Of the berberine excreted in bile, approximately 83% was thalifendine, while in urine, approximately 78% was thalifendine and berberrubine [1].

3.1 Oxidative Regulation

Berberine can scavenge free radicals including 1,1-diphenyl-2-picrylhydrazyl, 2,2' -azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), nitric oxide, and superoxide anion, exhibiting antioxidant properties in the prevention and treatment of diabetes, hypercholesterolemia, central nervous system disorders, and various inflammatory conditions, with effects showing concentration dependence. In vitro studies using human bone marrow neuroblastoma cell lines demonstrated that berberine can reduce cytochrome C (Cyt C) release and promote B-cell lymphoma/leukemia-2 gene expression, thereby inhibiting reactive oxygen species generation induced by high glucose concentrations [1]. Berberine can downregulate insulin-like growth factor-1 and nuclear factor erythroid 2-related factor 2 (Nrf2) gene expression, block phosphatidylinositol-3 kinase (PI3K)/protein kinase B (Akt) phosphorylation, thereby stimulating Nrf2-dependent neurite outgrowth and preventing reactive oxygen species generation [10]. Rats with cerebral ischemia orally administered 5, 10, or 20 mg/kg berberine for 19 consecutive days showed improved activities of mitochondrial complexes I, II, and IV [11].

Berberine can positively regulate related anti-apoptotic factors and intervene in cellular redox reactions. Daily oral administration of 50 and 100 mg/kg berberine inhibited the increase in glial fibrillary acidic protein (GFAP) in streptozotocin (STZ)-induced diabetic rats [11]. Oral administration of 50 mg/kg berberine for 11 consecutive days restored the activities of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in STZ-induced diabetic rats and cyclophosphamide-induced hepatotoxic rats, alleviating lipid peroxidation damage [12]. Through its antioxidant activity, berberine exhibits hepatoprotective and nephroprotective functions. Studies have reported that berberine protects against hydrogen peroxide (H2O2)-induced apoptosis by inhibiting the expression of the apoptosis-related protein SIRT1 in diet-induced obese mice, thereby eliminating berberine-mediated autophagy enhancement and hepatic steatosis to exert protective effects on the liver [13]. STZ-induced diabetic rats orally administered 75, 150, and 300 mg/kg berberine for 16 weeks showed increased cyclin-dependent kinase (Cdk) 9 activity in liver tissue, promoted cyclin T1 mRNA and protein expression, and enhanced catalase, SOD, and GSH-Px activities [11]. Cisplatin-induced nephrotoxic mice orally administered 1, 2, and 3 mg/kg berberine for 2 consecutive days showed inhibited expression of 4-hydroxynonenal, 3-nitrotyrosine, Cyt P450 E1, and heme oxygenase in the kidneys, thereby alleviating oxidative/nitrative stress and providing renal protection [1].

Berberine can negatively regulate oxidative substances, inhibit lipid peroxidation, and alleviate oxidative stress. Intraperitoneal injection of 200 mg/kg berberine for 14 consecutive days in bleomycin-induced pulmonary fibrosis rats inhibited inducible nitric oxide synthase (iNOS) gene expression and stimulated Nrf2 gene expression [14]. Rats with atherosclerotic renovascular disease orally administered 150 mg/kg berberine daily for 12 weeks showed reduced renal iNOS gene expression and restored SOD activity [15]. Berberine can improve blood-brain barrier permeability by activating the Akt/glycogen synthase kinase (GSK) signaling pathway and promoting tight junction protein 5 antibody expression, block neuronal potassium channels in the hippocampal CA1 region, reduce neuronal malondialdehyde (MDA) concentration, and restore SOD activity, thereby exerting neuroprotective effects against aluminum trichloride-induced acute brain injury in rats and improving cognitive dysfunction and hippocampal damage [16]. Oral administration of berberine at 100 and 200 mg/kg for 21 consecutive days reduced serum MDA concentration and enhanced SOD and GSH-Px activities in alloxan-induced diabetic rats [17].

3.2 Immunomodulation

Berberine can exert different effects on immune cells including lymphocytes, leukocytes, astrocytes, and microglia, demonstrating immunomodulatory and neuroprotective functions. It can inhibit the activation of lymphocytes and leukocytes, exerting immunosuppressive effects. Berberine at 25-100 mol/L showed time- and dose-dependent inhibition of activation antigen cluster of differentiation (CD) 69 and CD25 expression in isolated human T-lymphocytes stimulated with phytohemagglutinin alone or in combination with phorbol dibutyrate and ionomycin, and also blocked cell cycle progression [15]. Non-obese diabetic mice orally administered 200 mg/kg berberine for 2 weeks activated extracellular signal-regulated kinase (ERK) 1 and ERK2, inhibited p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase, thereby hindering T helper cell (Th) 17 and Th1 differentiation, suggesting that berberine may be an ideal drug for treating autoimmune diabetes [12]. Diabetic retinopathy patients orally administered berberine at 0.25 g twice daily for one month could prevent the diabetes-induced increase in leukocyte-mediated killing of retinal endothelial cells, thereby improving diabetic retinopathy symptoms [18]. Intraperitoneal injection of 200 mg/kg berberine for 14 consecutive days in bleomycin-induced pulmonary fibrosis rats reduced inflammatory cell infiltrates, collagen accumulation, and hydroxyproline concentration in bronchoalveolar lavage fluid, and decreased tumor necrosis factor-α (TNF-α), nuclear factor- β (NF- β), and transforming growth factor-$ $1 expression [14]. STZ-induced diabetic rats orally administered 50 and 100 mg/kg berberine for 8 weeks reduced the number of GFAP-immunopositive astrocytes in the hippocampus [19].

Berberine can promote heme oxygenase-1 gene expression through the PI3K/Akt pathway in a dose-dependent manner, reduce astrocyte numbers, and thereby inhibit astrocyte-mediated oxidative damage [17]. Berberine

can regulate microglial activity by blocking the PI3K/Akt, MAPK, and AMP-activated protein kinase pathways [20]. Therefore, by inhibiting astrocyte and microglial proliferation, berberine exerts positive effects on central nervous system diseases.

3.3 Enzyme Activity Regulation

Numerous reports have addressed berberine' s effects on GSK and matrix metalloproteinases (MMPs), both of which critically regulate numerous physiological signaling pathways. GSK-3β is the primary kinase for phosphorylating amyloid precursor protein and microtubule-associated protein tau. Treatment of tau-transfected human embryonic kidney cells HEK293 with 20 g/mL berberine for 24 hours reversed GSK-3β activation and restored protein phosphatase 2A activity [21]. Berberine increased the levels of phosphorylated glycogen synthase kinase-3β antibody Ser9, an inactive form of GSK3, in the brains of AD transgenic mice [1]. Inhibition of GSK-3β by berberine can improve amyloid pathology, gliosis, and cognitive dysfunction [22]. When oxygen and glucose supply to organotypic hippocampal slices cultured in vitro was stopped, berberine enhanced GSK-3β phosphorylation and inhibited apoptosis factor generation, demonstrating neuroprotective effects during cerebral ischemia [23].

MMPs constitute a large family that can degrade various protein components in the extracellular matrix and represent the primary proteolytic enzymes in tumor invasion and metastasis. Berberine can inhibit periodontal tissue degradation by regulating MMP activity (mainly pro-MMP2, MMP2, and MMP9) [24]. Berberine can also inhibit MMP1 and MMP9 activity, induce apoptosis and cell cycle arrest in the human in situ ER-positive breast cancer cell line MCF7 and highly metastatic malignant breast cancer cell line MDAMB231, thereby hindering cancer cell metastasis [24].

Berberine can inhibit major nervous system enzymes including acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and monoamine oxidase (MAO) through hydrophobic interactions. Kumar et al. [1] reported that the 50% inhibitory concentration (IC50) values of berberine for AChE, BChE, MAO-A, and MAO-B were 0.44, 3.44, 126, and 98.2 mol/L, respectively. Inhibition of MAO-A can alleviate depression, while inhibition of AChE and BChE can relieve dementia caused by AD and cerebral ischemia.

3.4 Neurotransmitter Regulation

Neurotransmitter modulation represents a primary mechanism by which berberine treats diseases such as AD, Parkinson's disease (PD), anxiety, and depression. Both single and 15-day consecutive intraperitoneal injections of 5 mg/kg or oral administration of 10 and 20 mg/kg berberine increased concentrations of norepinephrine (NE), dopamine (DA), and serotonin in the striatum, hippocampus, and cortex of mice, demonstrating antidepressant effects [6]. Berberine can inhibit hypothalamic corticotropin-releasing hormone secretion and alleviate mor-

phine withdrawal symptoms in rats, exhibiting anti-addiction properties [23]. In vitro culture of PC-12 cells with 10 and 30 mol/L berberine for 48 hours, or intraperitoneal injection of rats with 5 and 30 mg/kg for 21 consecutive days, both reduced DA and NE levels and alleviated 6-hydroxydopamine-induced neurotoxicity, indicating that berberine can interfere with DA biosynthesis [24]. Intraperitoneal injection of 20 and 50 mg/kg berberine for 4 consecutive days prevented 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced damage to dopaminergic neurons in the mouse brain striatum, thereby exerting therapeutic effects on PD [24]. Berberine can promote presynaptic acetylcholine release and stimulate neurogenic contraction responses in rats [13]. These studies demonstrate that berberine participates in the regulation of major neurotransmitters involved in various neurological conditions.

3.5 Molecular Target Regulation

Berberine exerts anti-inflammatory, anticancer, and antimicrobial effects through regulation of molecular targets, including inflammatory mediators, topoisomerases (Topo), cyclins, tumor suppressor genes, calmodulin, and telomerase. Berberine can directly regulate the expression of inflammatory mediators such as TNF-α, NF- β, prostaglandin E2, and cyclooxygenase-2. It can inhibit Topo I and II activity, with protoberberine showing particularly strong inhibition of Topo I activity. At low concentrations, protoberberine exhibits camptothecin-like properties, selectively inhibiting the binding of Topo I-DNA complexes and preventing re-ligation of broken DNA strands, thereby blocking DNA replication and RNA synthesis. At high concentrations, protoberberine directly binds to plasmid DNA, preventing Topo I from accessing the plasmid DNA and thus inhibiting Topo I relaxation activity [25].

Berberine is non-toxic to normal cells but exhibits anticancer properties by arresting the cell cycle in various cancer cell lines. It can inhibit Cdk2, Cdk4, Cdk6, and cyclin expression, induce G1 phase arrest, and thereby suppress proliferation of human prostate cancer cell lines (DU145, PC3, LNCaP), human bladder cancer cell lines (BIU-87, T24), and human lung cancer cell lines (A549) [26]. Both in vivo and in vitro studies have shown that berberine can alleviate damage caused by cell cycle arrest induced by cerebral ischemia in rats by mediating cyclin D and p53 gene expression [27]. For mitoxantrone-induced cellular senescence, berberine can effectively reduce senescence marker levels, providing a potential option for treating age-related diseases [28]. Calmodulin can inhibit calmodulin kinase II phosphorylation and block MAPK 1 activation in human hepatocellular carcinoma cells Bel7402. Synergistic use of berberine with calmodulin inhibitors can induce G1 phase growth arrest in Bel7402 cells [29]. Berberine can inhibit post-translational maturation of H1N1 influenza A virus with an IC50 of 0.01 mol/L. For five multidrug-resistant diarrheagenic *Escherichia coli* strains isolated from hemorrhagic diarrhea cattle, the minimum inhibitory concentration range of berberine was 1.75-3.60 mol/L [30]. During the intraerythrocytic stage of *Plasmodium falciparum*, berberine selectively

binds to DNA G-quadruplexes, exhibits high DNA binding affinity, and inhibits telomerase activity [28].

4. Application of Berberine in Animal Production

Berberine' s unique pharmacological properties and effects on various diseases demonstrate its diverse physiological functions and biological activities. As a feed additive in livestock and poultry diets, berberine can enhance animal health and produce beneficial effects, which have been fully confirmed in human clinical studies, model animals, and food animal research. Additionally, berberine demonstrates other application effects in animal production.

4.1 Growth Promotion

Berberine effectively promotes animal growth and development with dose-dependent effects. Wang et al. [2] suggested that berberine can improve growth and fattening performance and promote gastrointestinal development in meat rabbits, with an appropriate dietary supplementation level of 20 mg/kg for growing meat rabbits. Li [31] reported that berberine significantly increased 7-week body weight, average daily feed intake, and average daily gain of Avian broiler chickens, substantially improving production performance. Liu et al. [32] found that dietary supplementation with 500 mg/kg of *Berberis sargentiana* extract (equivalent to 99 mg/kg berberine) produced better growth-promoting effects in weaned piglets than levels of 1,000 mg/kg and 200 mg/kg (equivalent to 198.0 and 39.6 mg/kg berberine, respectively). Zhang et al. [33] reported that oral administration of 30 and 120 mg/kg berberine and 300 mg/kg *Coptis chinensis* water extract (equivalent to 29.7 mg berberine) to weaned SD rats resulted in comparable growth-promoting effects between 30 mg/kg berberine and 300 mg/kg *Coptis chinensis* water extract, both superior to 120 mg/kg berberine. Wang et al. [34] and Ding et al. [35] fed 1-day-old Avian broiler chickens diets supplemented with 0.5, 2.0, 3.5, and 5.0 g/kg *Berberis sargentiana* extract (equivalent to 99, 396, 693, and 990 mg/kg berberine, respectively) for 7 weeks, showing that feed intake first increased then decreased, with 3.5 g/kg being the turning point. Wang et al. [2] found that, without affecting major organ function in growing meat rabbits, berberine diverted more dietary nutrients to the growth and development of other tissues and organs, manifested as increased carcass weight, improved dressing percentage, and promoted gastrointestinal development. Sun et al. [36] suggested that berberine improved breast muscle percentage in broilers by regulating endogenous hormone metabolism.

4.2 Digestive Metabolism Improvement

Appropriate dietary supplementation with berberine can effectively improve animal digestive metabolism. Berberine can dual-regulate smooth muscle, with excitatory effects at low concentrations and inhibitory effects at high concentra-

tions. Therefore, appropriate amounts of berberine can inhibit gastrointestinal motility, increase chyme retention time in the gastrointestinal tract, and facilitate nutrient digestion and absorption. Reports indicate that with increasing berberine supplementation levels, the apparent digestibility of dietary dry matter, organic matter, crude fiber, gross energy, and nitrogen in growing meat rabbits first increased then decreased, demonstrating a dose-dependent effect of berberine on nutrient utilization efficiency. Liu et al. [32] found that compared with higher or lower supplementation levels, appropriate addition of *Berberis sargentiana* extract (500 mg/kg, equivalent to 99 mg/kg berberine) improved apparent digestibility of dietary nutrients in weaned piglets.

The effect of berberine on pancreatic enzyme secretion shows dose dependence, promoting secretion at low concentrations and inhibiting it at high concentrations. Wang et al. [34] and Ding et al. [35] reported that supplementation with 2.0 g/kg *Berberis sargentiana* extract (equivalent to 396 mg/kg berberine) increased duodenal chyme amylase activity in Avian broiler chickens, while 3.5 and 5.0 g/kg (equivalent to 693 and 990 mg/kg berberine) had the opposite effect. Berberine has weak inhibitory effects on beneficial resident bacteria in the gastrointestinal tract but strong inhibitory effects on harmful bacteria, helping maintain gastrointestinal microflora balance. Wang et al. [2] reported that dietary supplementation with 20 and 30 mg/kg berberine reduced diarrhea rate and mortality in growing meat rabbits, while 10 mg/kg showed poorer effects. Rong [37] found that berberine improved cecal fermentation in rabbits, mainly due to enhanced activity of beneficial cecal microorganisms. Wang et al. [38] noted that oral berberine increased intestinal butyrate-producing bacteria abundance in mice, thereby improving intestinal microflora composition.

4.3 Product Quality Improvement

Reports on berberine' s effects on animal product quality are limited. Wang et al. [2-3] suggested that berberine only affected lipid content and gross energy concentration in rabbit longissimus dorsi muscle, with minimal impact on other nutrients. Li [31] reported that berberine reduced lipid content including crude fat, triglycerides, and total cholesterol in broiler thigh and breast muscles. Wang et al. [2] found that berberine increased pH and cooking yield of rabbit longissimus dorsi muscle while decreasing water loss rate, drip loss, and shear force, indicating that berberine can improve meat physical properties, particularly at dietary supplementation levels of 10 and 20 mg/kg.

5. Summary

Berberine plays an important role in preventing and treating numerous human diseases. Consequently, extensive research has been conducted on its absorption and metabolism, pharmacological properties, physiological functions, and biological activities. However, deeper animal experiments and clinical observations are needed to elucidate its mechanisms of action in various diseases, expand its clinical applications from new perspectives, and establish a solid foundation

for developing novel disease-resistant drugs. Research on berberine' s application in animal production remains limited, and both chemically synthesized products and *Berberis sargentiana* extract products are currently in the preliminary stages. Further studies are needed, particularly regarding different animal species and physiological stages, various dietary types, supplementation levels, and supporting application technologies. Therefore, comprehensive evaluation of berberine' s efficacy and potential in animal production, in-depth exploration of its biological functions, and close attention to its rare side effects are necessary to ensure safety.

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