Mechanism of Action and Application Effects of Sanguinarine in Animal Nutrition (Postprint)

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Abstract

Sanguinarine is a benzophenanthridine isoquinoline alkaloid that exhibits antibacterial, antioxidant, and anti-inflammatory effects, is utilized for schistosome control, and additionally possesses antitumor properties. As a feed additive, sanguinarine has demonstrated favorable efficacy in replacing antibiotics in swine and poultry production management. This review summarizes the primary effects of sanguinarine and their underlying mechanisms, along with its applications in animal nutrition.

Full Text

Sanguinarine: Mechanisms of Action and Its Application Effects in Animal Nutrition

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Abstract: Sanguinarine is a benzophenanthridine isoquinoline alkaloid that exhibits antimicrobial, antioxidant, and anti-inflammatory properties. It has been used to control schistosomiasis and also demonstrates antitumor characteristics. As a feed additive, sanguinarine has achieved promising results as an antibiotic alternative in swine and poultry production. This paper reviews the primary biological functions of sanguinarine, its underlying mechanisms, and its applications in animal nutrition.

Keywords: sanguinarine; biological functions; mechanism; animal nutrition; application

Alkaloids are a class of structurally complex and diverse natural products derived from microorganisms, plants, and animals. Due to the presence of a ni-

trogen atom (proton acceptor) and one or more imine ions (proton donors), alkaloids readily form hydrogen bonds with proteins, enzymes, and receptors, thereby exerting unique biological effects [?]. Sanguinarine ($C_{20}H_{15}O_5N$) is a benzophenanthridine isoquinoline alkaloid [?] found primarily in *Macleaya cordata*, *Chelidonium majus*, *Eomecon chionantha*, and *Corydalis* species [?]. It is synthesized through the oxidation of dihydrosanguinarine by dihydrobenzophenanthridine oxidase [?]. The purified solid appears as a reddish-yellow powder with a relative molecular mass of 332. The chemical activity of sanguinarine is based on the nucleophilicity of its imine group, which enables participation in oxidant scavenging and/or oxidase inhibition [?]. Sanguinarine possesses antimicrobial, antioxidant, and anti-inflammatory activities, and is used to control schistosomiasis while also exhibiting antitumor properties [?]. Currently, sanguinarine has been applied clinically in both human and veterinary medicine, and was approved as a national Class II veterinary drug in China in 2011. Macleaya cordata powder (trade name: Meiyouzhuang; English name: Sangrovit), with sanguinarine as its main active component, was approved in 2012 as China' s first traditional Chinese veterinary medicine feed additive. As a feed additive, sanguinarine has demonstrated excellent efficacy as an antibiotic substitute in swine and poultry management. This paper reviews the primary biological functions and mechanisms of sanguinarine and its applications in animal nutrition.

1.1 Antimicrobial Effects

Sanguinarine exhibits sustained antimicrobial activity in antibacterial assays [?]. With strong cellular permeability, sanguinarine and its derivatives demonstrate resistance against *Staphylococcus aureus*, *Escherichia coli*, *Salmonella gallinarum*, *Klebsiella pneumoniae*, *Mycobacterium smegmatis*, and *Candida albicans* at a minimum inhibitory concentration (MIC) of 6.25 g/mL [?]. Additional studies have reported MIC values of 1.6–6.3 g/mL against Gram-positive bacteria [?]. In human clinical applications, benzophenanthridine alkaloids are commonly used to treat periodontal diseases, with water-soluble sanguinarine chloride present at 0.3% concentration in antimicrobial toothpastes and mouthwashes. Furthermore, sanguinarine effectively inhibits the production of volatile sulfur compounds that cause halitosis [?]. Regarding antifungal activity, sanguinarine inhibits various fungal strains including *Trichophyton*, *Microsporum canis*, *Epidermophyton floccosum*, and *Aspergillus fumigatus* [?]. Compared to chlortetracycline, sanguinarine shows stronger inhibitory effects against pathogenic bacteria such as *Salmonella*, *S. aureus*, and *E. coli*, while exhibiting weaker inhibition against probiotic bacteria like *Bacillus subtilis*. Additionally, sanguinarine demonstrates potent clearance of biofilms formed by these pathogens, offering a novel solution to problems arising from antibiotic abuse in aquaculture, including drug resistance and environmental pollution [?].

Two antimicrobial mechanisms of sanguinarine have been elucidated: disruption of Z-ring formation and inhibition of cell division. Specifically, sanguinar-

ine binds to the bacterial cell division protein filamentous temperature-sensitive protein Z (FtsZ), thereby inhibiting Z-ring formation and inducing cell elongation without affecting DNA replication or bacterial nucleoid segregation [**?**].

1.2 Anti-inflammatory Effects

Inflammation represents a defensive response of vascularized living tissue to injurious agents, and sanguinarine exhibits strong anti-inflammatory activity. Sanguinarine hydrochloride also demonstrates direct inactivation effects against phage types 1017 and T2 acting on *E. coli* [**?**]. Nuclear factor-kappa B (NF- B) is a well-known regulator involved in the expression of over 200 genes, and its activity has been associated with numerous inflammatory diseases, including cancer [**?**]. NF- B exists as an inactive heterotrimeric complex in the cytoplasm, composed of P50, P65, and I Bα subunits. Upon activation, the I Bα subunit undergoes sequential phosphorylation, ubiquitination, and degradation, releasing the P50-P65 heterodimeric complex that subsequently translocates to the nucleus. Stimulated by pro-inflammatory factors such as lipopolysaccharide, tumor necrosis factor (TNF), and interleukin-1, this process generates inflammatory responses [**?**]. Treatment of human myeloid ML-1a cells with TNF rapidly activates NF- B, and this activation is completely inhibited by sanguinarine in a dose- and time-dependent manner. Rather than inhibiting NF- B protein binding to DNA, sanguinarine suppresses the activation pathway by preventing I Bα phosphorylation [**?**].

1.3 Antitumor Effects

Cancer stands as the most prominent life-threatening disease affecting humans, representing the leading cause of mortality worldwide [**?**]. Over recent decades, extensive global research efforts have yielded comprehensive understanding of cancer and led to the successful development of chemotherapeutic agents for cancer treatment [**?**]. Sanguinarine has attracted significant research attention due to its potent antitumor properties. In vitro data indicate that sanguinarine exerts antitumor effects at concentrations below 10 mol/mL in most cases, inducing cell cycle arrest at various phases or apoptosis in multiple cancer cell lines [**?**]. Clinical studies have also demonstrated that combined administration of cyclooxygenase-2 (COX-2) inhibitors and sanguinarine can treat prostate cancer [**?**]. Furthermore, sanguinarine can be developed as an agent for treating ultraviolet radiation-induced lesions such as skin cancer [**?**].

The primary antitumor mechanisms of sanguinarine can be summarized as follows: (1) Direct interaction with glutathione, which substantially depletes intracellular glutathione and induces reactive oxygen species (ROS) production [**?**, **?**]; (2) Inhibition of tumor-promoting cytokines or enzyme activities to promote tumor cell apoptosis. Sanguinarine is a selective inhibitor of mitogen-activated protein kinase phosphatase 1 (MKP-1), which is overexpressed in many tumor cells [**?**]. Its anticancer effects are also attributed to disruption of microtubule assembly dynamics [**?**], impairment of nucleocytoplasmic transport of cyclin D1

and topoisomerase II [?], and induction of DNA damage. Signal transducer and activator of transcription 3 (STAT-3), which plays important roles in cancer development and progression, represents a significant therapeutic target. Sanguinarine acts as a potential inhibitor of STAT-3 activation, suppressing the growth, migration, and invasion of prostate cancer cells by inhibiting STAT-3 phosphorylation at tyrosine 705 and serine 727 [?]. Additionally, sanguinarine effectively inhibits NF- B activation induced by TNF, interleukin-1, phorbol esters, and okadaic acid [?]; (3) Induction of tumor cell apoptosis. Apoptosis is a physiological process of cell death and an effective control mechanism for maintaining genome stability and preventing tumorigenesis. Sanguinarine kills human epidermoid carcinoma A431 cells by inducing apoptosis [?]. Numerous in vitro studies have demonstrated that sanguinarine inhibits the growth of various cancer cells by inducing apoptosis, including squamous cell carcinoma, lung, breast, pancreatic, prostate, and colon cancers, as well as osteosarcoma [?]; (4) Induction and stabilization of G-quadruplex structures in telomeric DNA. The single-stranded overhang of telomeric DNA can form G-quadruplex structures, whose formation can prevent cancer development by blocking oncogene overexpression, tumor suppressor gene loss, and abnormal expression of other genes. Sanguinarine induces G-quadruplex formation in single-stranded human telomeric DNA, thereby inhibiting telomerase activity and suppressing tumor cell proliferation [?]. These mechanisms collectively explain the anticancer activity of sanguinarine from different perspectives. However, potential dose-dependent effects require careful consideration, as sanguinarine-induced DNA damage and cytotoxicity increase with dosage in mouse primary spleen cells and L1210 cells [?].

1.4 Antioxidant Effects

Reactive oxygen species (ROS) are normal metabolic products in aerobic organisms. Under normal physiological conditions, the body maintains dynamic ROS balance, which positively regulates cellular signaling, gene transcription, and tissue growth and development. Low-dose ROS enhances cell proliferation, moderate doses inhibit cell growth, while excessive ROS overwhelm endogenous antioxidants, causing oxidative damage including protein oxidation, lipid peroxidation, and DNA damage [?], which may trigger carcinogenesis through persistent DNA damage and p53 mutations as observed in skin, liver, and colon cancers [?]. To mitigate oxidative damage, natural antioxidants such as vitamin C, resveratrol, and tea polyphenols have attracted widespread attention [?]. Sanguinarine also exhibits strong antioxidant activity, effectively scavenging free radicals and protecting against protein oxidative and carbonylation damage while significantly inhibiting lipid and DNA oxidation [?]. Sanguinarine also inhibits phorbol ester-induced oxidative cleavage [?], a process in which the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex plays a crucial role. Sanguinarine likely exerts its antioxidant function by inhibiting NADPH oxidase activity, consistent with Qin et al. [?], suggesting that sanguinarine acts as an enzyme inhibitor rather than a ROS scavenger. Since

NADPH oxidase is important for ROS generation induced by angiotensin II (Ang II), sanguinarine may suppress ROS production by reducing NADPH oxidase expression [**?**].

1.5 Parasiticidal Effects

Sanguinarine has been reported to exhibit effective killing activity against various parasites. It demonstrates excellent efficacy against the fish parasite *Dactylogyrus intermedius*, with a 100% effective concentration (EC_{50}) of 0.37 mg/L under laboratory conditions. Additionally, sanguinarine shows antimalarial, antitrypanosomal, and anti-amoebic activities, as well as leptospiricidal effects [**?**]. Schistosomiasis, a neglected tropical disease caused by blood-dwelling trematodes of the genus *Schistosoma*, ranks as the second most important human parasitic disease after malaria, affecting over 200 million people and placing approximately 800 million at risk across more than 70 countries. Natural product-derived antischistosomal drugs have gained increasing attention, with major plant metabolites including terpenes, alkaloids, phenolic compounds, and peptides being investigated for their in vitro and/or in vivo antischistosomal properties [**?**]. Sanguinarine has been reported to possess potent antischistosomal activity, with an effective concentration of 10 mol/L against adult *Schistosoma mansoni* in vitro. Scanning electron microscopy studies have revealed that sanguinarine causes severe tegumental erosion and disruption in worms [**?**]. The molluscicidal mechanism of sanguinarine may involve alterations in hepatic glycogen content and key enzyme activities in snails, leading to liver function damage [**?**, **?**]. Sanguinarine also damages the body surface and ultrastructure of *Dactylogyrus* while affecting the antioxidant enzyme system and reducing antioxidant capacity in the parasites [**?**].

2.1 Growth Performance Enhancement

The application of sanguinarine as a feed additive in animal nutrition primarily focuses on its role as an antibiotic alternative. The extensive long-term use of antibiotics has created numerous problems, including increased drug-resistant bacteria, induction of microbial variation, and disruption of microecological balance, while drug residues pose growing threats to human health. Sanguinarine is metabolized in vivo into non-hazardous dihydrosanguinarine, which cannot be reoxidized to sanguinarine under physiological conditions [**?**]. Dietary supplementation with 0.75 mg/kg sanguinarine has shown optimal effects in weaned piglets, increasing body weight and daily gain while improving feed conversion ratio [**?**]. Rao et al. [**?**] evaluated sanguinarine as an antibiotic substitute in weaned "Landrace × Large White" piglets using chlortetracycline as a positive control. Compared with the blank control group, the sanguinarine group showed significantly improved average daily feed intake and average daily gain, along with better feed conversion ratio. While these growth parameters did not differ significantly from the positive control group, feed conversion ratio was significantly improved, indicating that sanguinarine enhances growth performance

more effectively than chlortetracycline. Similar conclusions were drawn in studies with (65$±$2)-day-old weaned "Duroc × Landrace × Large White" piglets [?] and 25-kg "Duroc × Landrace × Large White" growing pigs [?]. In poultry research, broilers fed diets supplemented with 0.30 and 0.75 mg/kg sanguinarine showed significantly improved final body weight, average daily gain, and feed conversion ratio compared to those fed a basal diet [?]. Dietary sanguinarine supplementation also improved growth performance in turkeys [?]. Furthermore, studies in common carp confirmed that dietary sanguinarine supplementation significantly enhanced growth performance compared to control groups [?].

The mechanisms underlying sanguinarine' s growth-promoting effects include: (1) Irreversible inhibition of L-amino acid decarboxylase activity in the gastrointestinal tract, which reduces aromatic amino acid degradation and improves the utilization efficiency of tryptophan and phenylalanine in the small intestine, thereby increasing protein retention [?]. Additionally, increased feed intake through the tryptophan-serotonin pathway promotes animal growth [?]; (2) Antimicrobial and anti-inflammatory effects that effectively alleviate weaning stress, maintain intestinal health, and reduce diarrhea incidence in piglets, which may be the primary reason for improved growth performance; (3) Altered intestinal morphology, as dietary sanguinarine increases the relative length of the jejunum and ileum while decreasing relative jejunum weight [?], thereby promoting efficient nutrient absorption and improving diet digestibility; and (4) Antioxidant function that reduces muscle oxidation reactions [?] and decreases oxidative stress, consequently improving growth performance. These mechanisms likely act synergistically to promote animal growth.

2.2 Tryptophan Replacement

Beyond its shared characteristics with other alkaloids, sanguinarine specifically influences tryptophan metabolism. This effect likely stems from its similar nitrogen-containing ring structure, allowing it to bind key enzymes in aromatic amino acid metabolism and competitively inhibit tryptophan decarboxylase activity, thereby reducing tryptophan catabolism. In low-protein diets without tryptophan supplementation, sanguinarine addition increases net absorption of total amino acids and essential amino acids in the portal vein without affecting net absorption of portal plasma urea nitrogen [?]. Moreover, dietary sanguinarine in low-protein diets tends to increase serum tryptophan content, affects intestinal tryptophan decarboxylase activity, and significantly reduces skatole content [?]. Skatole, a bacterial degradation product of L-tryptophan, poses hazards to livestock production. Reducing skatole content not only improves the rearing environment and animal growth performance but also decreases environmental pollution, aligning with sustainable development requirements for animal agriculture.

3 Safety Assessment

Some alkaloids exhibit strong toxicity, with numerous human poisoning incidents reported [**?**]. Toxicity studies of sanguinarine have shown that intravenous injection of 2 mg sanguinarine hydrochloride causes 100% mortality in 100-g rats, and sanguinarine can induce blindness in albino rats. It also exhibits toxicity toward certain enzyme systems by inhibiting oxidation of pyruvate, lactate, and succinate. In vivo toxicity can be prevented by injecting ethylene glycol 15–20 minutes beforehand, while in vitro enzyme system damage, though irreparable, can be prevented from progressing [**?**]. Additionally, excessive dosage (10 mg/kg) shows hepatotoxicity and induces concentration-dependent calcium influx in cardiomyocytes, causing cardiac contracture [**?**]. However, studies have demonstrated that oral administration at 5 mg/kg body weight daily is safe in animals [**?**].

As feed additives, antibiotics provide health benefits and growth promotion for livestock. However, with the rapid development of animal production and increasing disease complexity, the long-term extensive use of antibiotics has led to drug residues and resistance issues that affect food safety from animal sources and pose growing threats to human health. Developing efficient, non-residual, non-resistant, and non-polluting feed additives represents an important direction for animal husbandry development. Natural plant extracts, with their natural origin, multifunctionality, low toxicity, and lack of resistance, have gradually become ideal substitutes for antibiotics, hormones, and chemical synthetics. As a major component of natural plants, sanguinarine exerts broad and potent physiological activities in humans, animals, and agricultural pests. Its chemical activity is based on the nucleophilic properties of its imine group, enabling participation in oxidant scavenging and/or oxidase inhibition. The aforementioned studies demonstrate that sanguinarine can replace antibiotics in practical production to improve animal growth performance and enhance disease resistance. However, comprehensive antibiotic replacement requires extensive further research. Notably, most studies have been conducted in monogastric animals, with no reports on ruminant applications. Furthermore, these studies have primarily focused on phenotypic observations, with limited investigation into internal mechanisms, which warrants detailed in-depth research.

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