Biological Activity of Sanguinarine and Application of Macleaya cordata Extract in Animal Production: Postprint

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Abstract

Sanguinarine, as the principal active constituent of Macleaya cordata extract, exhibits multiple pharmacological effects including anti-inflammatory, antibacterial, and antitumor activities. The Ministry of Agriculture has also approved Macleaya cordata extract as a Class II new traditional Chinese veterinary medicine for application in animal production. This article reviews the biological activities of sanguinarine—including anti-inflammatory, antioxidant, intestinal health-promoting, antitumor, and antibacterial effects—and their mechanisms, as well as the application status of Macleaya cordata extract in animal production, thereby providing some theoretical references for its practical application in animal production.

Full Text

Biological Activities of Sanguinarine and Application of Macleaya Cordata Extract in Animal Production

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Abstract

Sanguinarine, the principal active component of Macleaya cordata extract, exhibits diverse pharmacological effects including anti-inflammatory, antibac-

terial, and antitumor activities. The Ministry of Agriculture has approved Macleaya cordata extract as a Class II new veterinary traditional Chinese medicine for use in animal production. This review summarizes the biological activities of sanguinarine—including anti-inflammatory, antioxidant, intestinal health-promoting, antitumor, and antibacterial effects—and their underlying mechanisms, as well as the application of Macleaya cordata extract in animal production, providing theoretical references for its practical utilization.

Keywords: Macleaya cordata extract; sanguinarine; biological activities; application in animal production

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Macleaya cordata (Willd.) R. Br. is a perennial herb belonging to the Papaveraceae family and a traditional Chinese medicinal material rich in alkaloids. Commonly known as "hao tong gan" or "shan hao tong," it is widely distributed and abundant in China. Its main bioactive components are isoquinoline alkaloids, including sanguinarine, chelerythrine, protopine, and allocryptopine. Macleaya alkaloids exhibit multiple biological activities such as antibacterial, insecticidal, antiviral, antitumor, analgesic, anti-inflammatory, hepatoprotective, and immune-enhancing effects, with sanguinarine playing a crucial role as the primary alkaloid in Macleaya cordata extract (MCE). Recent research both domestically and internationally has demonstrated that sanguinarine-rich MCE promotes growth and improves performance in livestock, poultry, and aquatic species. Internationally, sanguinarine-based MCE has been used as a feed additive in livestock and poultry since 2000 and is currently approved in over 40 countries and regions including the EU, United States, and Japan, with its efficacy widely recognized. Although sanguinarine was once listed in China' s feed additive catalog, it was removed by the Ministry of Agriculture in 2008. Consequently, sanguinarine-based MCE was subsequently developed and registered in China as a Class II new veterinary traditional Chinese medicine [Certificate No. (2011) New Veterinary Medicine 34] and obtained a veterinary additive approval number [Veterinary Additive No. (2012) 180415250], permitting its use as a medicated feed additive. It has become one of the alternatives to antibiotic feed additives and is gradually being promoted in the market. As the main component of this nationally approved Class II veterinary medicine, sanguinarine possesses extensive biological activities, which are reviewed herein along with the applications of MCE in animal production.

1 Molecular Structure and Physical Properties of Sanguinarine

Sanguinarine is a benzophenanthridine benzylisoquinoline alkaloid first purified in 1829 [1]. Its molecular formula is $C_{20}H_{14}NO_4$ with a relative molecular mass of 332 and a melting point of 265–267°C. The molecular structure is shown in [Figure 1: see original paper]. Free sanguinarine base is unstable and typically exists in salt form as an orange-yellow powder with a bitter taste. It is readily

soluble in organic solvents such as ethanol, chloroform, acetone, ethyl acetate, and methanol, but only slightly soluble in water. Sanguinarine is primarily found in the whole plant of Chelidonium majus, the whole plant of Macleaya cordata, the roots of Sanguinaria canadensis, and the aerial parts of Eomecon chionantha [2].

2 Biological Activities of Sanguinarine

2.1 Anti-inflammatory Activity

Sanguinarine exhibits potent anti-inflammatory properties [3] and acts as a strong inhibitor of nuclear factor- B (NF- B) [4]. It reduces lipopolysaccharide (LPS)-induced tumor necrosis factor-α (TNF-α) and nitric oxide (NO) levels in peritoneal macrophages, decreases LPS-induced phosphorylation of p38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase 1/2 (ERK1/2), and lowers serum TNF-α levels in LPS-challenged mice. Thus, sanguinarine effectively inhibits inflammatory mediator expression and systemic inflammation both in vitro and in vivo, while also suppressing MAPK activation [5]. In sanguinarine-pretreated cells, LPS-stimulated expression of chemokine ligand 2 (CCL-2) and interleukin-6 (IL-6) mRNA is significantly reduced; even when administered 8 hours after LPS stimulation, sanguinarine still markedly decreases CCL-2 mRNA expression, producing effects similar to prednisone [6]. When used in toothpaste and mouthwash, sanguinarine protects teeth and alveolar bone through mechanisms involving NF- B and ERK signaling pathways [7]. Sanguinarine solid lipid nanoparticles also demonstrate excellent anti-inflammatory effects by reducing LPS-induced inflammatory factors TNF-α, IL-6, and NO in mouse serum [8].

In a mouse model of acetic acid-induced ulcerative colitis, sanguinarine pretreatment significantly reduces mortality, weight loss, lesion severity, and colonic wet weight. It effectively inhibits p65 NF- B protein expression and myeloperoxidase (MPO) activity accumulation in a concentration-dependent manner, while decreasing TNF-α and IL-6 levels in colonic tissue and serum [9]. In an LPS-induced murine endotoxic shock model, sanguinarine pretreatment at doses of 1, 5, and 10 mg/kg increases survival rates from 25% to 58%, 75%, and 91%, respectively. It significantly suppresses cyclooxygenase-2 (COX-2) mRNA expression and prostaglandin E2 (PGE2) production in LPS-induced peritoneal macrophages, while reducing COX-2 protein expression [10].

2.2 Antioxidant Activity

Reactive oxygen species (ROS) are normal metabolic byproducts maintained in dynamic equilibrium in healthy organisms. Under stress conditions, excessive ROS production causes oxidative damage including protein oxidation, lipid peroxidation, and DNA damage. Sanguinarine exerts antioxidant effects by inhibiting reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity [11]. It also suppresses angiotensin II (Ang II)-induced NADPH

oxidase 2 (NOX2) mRNA expression and ROS generation in rat cardiomyocyte H9c2 cells, significantly reducing Ang II-induced apoptosis and caspase-3 and -9 levels, likely by restoring ROS-mediated decreases in mitochondrial membrane potential (MMP) [12]. Heme oxygenase-1 (HO-1) serves as an antioxidant defense enzyme, and sanguinarine induces nuclear accumulation of nuclear factor erythroid 2-related factor 2 (Nrf2), increases Hmox1 gene expression, and elevates HO-1 protein levels in murine macrophage RAW264.7 cells [13]. Additionally, sanguinarine exhibits concentration-dependent scavenging of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals and protects against copper ion (Cu^{2+})/hydrogen peroxide (H_2O_2)- and 2,2'-azobis(2-methylpropionamidine) dihydrochloride (AAPH)-induced oxidative and carbonylation damage to bovine serum albumin at concentrations of 1–100 mol/L. It also significantly inhibits ferrous sulfate ($FeSO_4$)-induced lipid peroxidation and AAPH-induced DNA oxidative damage [14]. However, some studies report that while sanguinarine demonstrates significant antioxidant effects at low concentrations, it can induce ROS and malondialdehyde (MDA) production, cause oxidative damage, inhibit growth, and reduce viability in rat intestinal smooth muscle cells (ISMC) at high concentrations [15]. Thus, the pro-oxidant and antioxidant effects of sanguinarine may be concentration-dependent.

2.3 Effects on Intestinal Health

Ex vivo small intestine experiments confirm that sanguinarine inhibits the frequency and amplitude of intestinal smooth muscle activity in a concentration-dependent manner, significantly suppressing contractions induced by acetylcholine, histamine, and calcium chloride. It also enhances the blocking effects of atropine on M receptors, promethazine on H1 receptors, and nifedipine on L-type calcium channels (Ica-L) [16]. Treatment of rat ISMC with 1 mol/L sanguinarine for 24 hours significantly inhibits M2 and M3 receptor expression, with sanguinarine's inhibitory effects on ISMC contraction being associated with protein kinase C (PKC)-mediated signal transduction and intracellular calcium ion (Ca^{2+}) concentration [17]. High concentrations of sanguinarine (0.25–4.00 g/mL) inhibit porcine intestinal epithelial cell (IPEC-1) proliferation, whereas low concentrations (0.00625–0.01000 g/mL) significantly promote IPEC-1 proliferation, with peak promotional effect observed at 0.0125 g/mL [18]. Macleaya cordata extract (primarily sanguinarine) also attenuates dextran sulfate sodium (DSS)-induced colonic mucosal damage and colitis lesions in rats, reducing DSS-induced COX-2 mRNA expression, colonic MPO activity, and erythrocyte reduced glutathione levels while improving intestinal mucosal and villus repair [19]. Furthermore, as an aromatic amino acid decarboxylase inhibitor [20], sanguinarine can enhance amino acid utilization in feed.

2.4 Anticancer Activity

Sanguinarine inhibits growth and induces apoptosis in various cancer cells by generating ROS and endoplasmic reticulum (ER) stress [21-22] or by inactivat-

ing the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway [23-24]. It demonstrates significant inhibitory effects on human gastric cancer BGC-823 cells and human hepatocellular carcinoma SMMC-7221 cells, with enhanced antiproliferative and proapoptotic effects observed with increasing concentrations, prolonged treatment duration, and lower cell densities. As sanguinarine concentration increases, expression of antiapoptotic proteins B-cell lymphoma 2 (Bcl-2) and Bcl-2-associated X protein (Bax) decreases [25]. Sanguinarine inhibits prostate cancer cell activity in a dose-dependent manner, increasing DNA damage and altering apoptosis while inducing cyclin-dependent kinase inhibitors P21Waf1/Cip1 and p27Kip1 in prostate cancer cells [26]. Overexpressed mitogen-activated protein kinase phosphatase-1 (MKP-1) protects tumor cells from apoptosis induced by DNA-damaging agents and cellular stress in many human tumors, and sanguinarine acts as a potent and selective MKP-1 inhibitor that blocks this protective effect [27]. Additionally, sanguinarine inhibits cervical cancer HeLa cell proliferation by interfering with microtubule assembly dynamics [28].

2.5 Antibacterial Effects

Sanguinarine exhibits strong antibacterial activity and has long been used in toothpaste and mouthwash for its antimicrobial effects against oral microorganisms [29]. It demonstrates antibacterial activity or significant bacteriostatic effects against both Gram-positive and Gram-negative bacteria isolated from poultry, with stronger activity against Salmonella than penicillin [30]. Sanguinarine shows the strongest inhibitory effects against Staphylococcus aureus and Enterococcus, without cross-resistance to existing antibiotics [31]. Combined use of sanguinarine with antibiotics such as streptomycin, vancomycin, ampicillin, oxacillin, norfloxacin, and ciprofloxacin demonstrates synergistic antibacterial effects against many Gram-positive and Gram-negative bacteria, including methicillin-resistant Staphylococcus aureus (MRSA), while reducing the effective antibacterial concentrations of each drug [32-35]. In both Gram-negative and Gram-positive bacteria, sanguinarine blocks bacterial cell division by interfering with cytokinetic Z-ring formation and inhibiting FtsZ protein assembly dynamics in Escherichia coli [36]. Against MRSA strains, sanguinarine induces release of membrane-bound cell wall autolytic enzymes, causing bacterial lysis and altering cell membrane morphology [33]. Sanguinarine more effectively inhibits biofilm formation by Salmonella paratyphi A, invasive E. coli, and Staphylococcus aureus than chlortetracycline hydrochloride, reducing alginate content within biofilms and significantly decreasing polysaccharide content while altering biofilm structure and morphology [37]. Additionally, sanguinarine possesses antifungal activity and inhibits fungal biofilm formation [38-39].

2.6 Effects on Reproductive System

Sanguinarine has no effect on follicular cell proliferation or progesterone production but significantly reduces estradiol production at high concentrations

(100 and 300 nmol/L). It inhibits vascular endothelial growth factor (VEGF) production in ovarian granulosa cells while increasing peroxidase and catalase activities, with high concentrations also elevating superoxide dismutase activity [40]. In porcine follicular granulosa cells, sanguinarine inhibits VEGF production and VEGF-induced protein kinase activation [41]. Other studies report that sanguinarine causes apoptosis in mouse blastocyst cells, impairs embryo implantation, disrupts oocyte maturation, and inhibits embryonic development [42-43]. Therefore, sanguinarine may negatively affect ovarian granulosa cell development and embryonic growth, warranting careful consideration when used as a feed additive.

3 Application of Macleaya Cordata Extract in Animal Production

Recent studies have demonstrated that sanguinarine-rich Macleaya cordata extract improves growth performance and treats gastrointestinal disorders including abdominal pain, diarrhea, and intestinal inflammation in livestock and poultry production.

3.1 Swine

Dietary supplementation with Macleaya cordata extract in weaned piglets significantly increases average daily feed intake and average daily gain while reducing feed-to-gain ratio. It effectively prevents diarrhea, improves apparent crude protein digestibility, and produces growth-promoting effects comparable to chlortetracycline or oxytetracycline [44-45]. Macleaya cordata extract enhances serum immunoglobulin G (IgG) levels and lysozyme activity, increases macrophage phagocytic index, and improves immune function, thereby enhancing disease resistance and growth performance in weaned piglets [44-46]. It also significantly reduces serum haptoglobin and serum amyloid A levels, improving stress resistance [47]. In low-protein diets without tryptophan supplementation, sanguinarine increases portal plasma flow rate and net absorption of essential and total amino acids without affecting portal plasma urea nitrogen net absorption [48]. In finishing pigs, dietary Macleaya cordata extract improves feed conversion efficiency, reduces acute and chronic pathological damage caused by Lawsonia intracellularis infection [49], and enhances meat color and pH while reducing drip loss when administered before slaughter.

In lactating sow diets, Macleaya cordata extract improves stress status, increases milk production, and enhances piglet weaning weights.

3.2 Poultry

Dietary supplementation with Macleaya cordata extract in broilers improves average daily gain, feed conversion ratio, and average daily feed intake. In low-crude protein diets (18.8%), Macleaya cordata extract supplementation achieves similar average daily gain and feed intake as normal crude protein diets (19.7%)

[50]. It also improves relative organ weights, serum cholesterol levels, intestinal microflora, and meat quality [51]; reduces overall feed-to-gain ratio and jejunal nitric oxide synthase expression; decreases abdominal fat content [52]; enhances immune system function; increases Newcastle disease antibody levels; improves slaughter weight and leg muscle ratio [53]; and reduces pathogenic bacteria in the digestive tract while improving intestinal health [54]. Combined use of Macleaya cordata extract with organic acids shows better efficacy in improving broiler growth performance [55]. As a feed additive in yellow-feathered broilers, it improves digestive performance, increases average daily feed intake and gain, reduces feed-to-gain ratio, enhances European Efficiency Index, increases jejunal Lactobacillus counts, improves villus height-to-crypt depth ratio, increases breast and leg muscle ratios, reduces MDA content in breast muscle after cold storage, and improves carcass quality and shelf life [30]. In laying hens fed low-protein diets, sanguinarine enhances cellular and humoral immunity, inhibits ileal E. coli and Salmonella populations, and increases villus height-to-crypt depth ratio, thereby improving intestinal health [56].

3.3 Aquatic Animals

Macleaya cordata extract promotes growth in red tilapia, common carp, and Caspian roach by increasing average daily gain, reducing feed-to-gain ratio, and improving condition factor, with synergistic effects observed with vitamins A, D_3, and E in common carp [57-59]. Sanguinarine reduces total bacterial and E. coli counts in carp intestines and enhances resistance to Aeromonas hydrophila [60]. In crucian carp, sanguinarine improves immunity and disease resistance by upregulating interleukin-8 (IL-8), IL-1β-1, IL-1β-2, TNFα-1, and TNFα-2 expression in gills, kidney, and spleen while decreasing CCL-1 mRNA expression in gills and increasing it in kidney and spleen; sanguinarine treatment also elevates transforming growth factor-β (TGF-β) levels [61]. In Pacific white shrimp, the anti-inflammatory and antibacterial activities of Macleaya cordata extract improve survival rates [62].

3.4 Ruminants

Dietary supplementation with Macleaya cordata extract in dairy cows improves nitrogen utilization efficiency, partly by enhancing rumen microbial activity, reducing ammonia nitrogen degradation, and strengthening rumen nitrogen digestion [63]. It also improves mastitis conditions. In sheep, Macleaya cordata extract ameliorates growth performance decline caused by heat stress, likely through anti-inflammatory effects and enhanced nutrient absorption [64]. However, Macleaya cordata extract has not yet been approved for use in ruminants in China.

4 Summary

Antibiotic feed additives have been widely used in animal production for disease prevention, feed conversion improvement, and growth enhancement, with nearly half of China' s antibiotic consumption occurring in animal husbandry. However, long-term, low-dose usage has led to increasing problems including drug-resistant strains and residues, posing serious threats to public health and animal production. Consequently, many developed countries have legislated restrictions on antibiotic feed additives, with the EU implementing a complete ban in 2006, followed by South Korea in 2011, while the US and Japan have strengthened usage limitations. China has also tightened regulations, revoking colistin sulfate' s veterinary additive approval in 2017 to reduce public health threats from antibiotic misuse. Developing safe, green, environmentally friendly, and efficient alternatives has become a research priority. Traditional Chinese veterinary medicines and natural plant extracts represent ideal antibiotic substitutes due to their natural origin, multifunctionality, low toxicity, minimal residues, and lack of drug resistance. These contain diverse bioactive components such as alkaloids, ketones, and polysaccharides that exhibit various biological activities including antimicrobial, antiviral, antitumor, analgesic, anti-inflammatory, and immunomodulatory functions. With the Ministry of Agriculture' s 2016 release of the "General Technical Requirements for Traditional Chinese Veterinary Medicine and Natural Medicine Premixes (Draft for Comment)," sanguinarine-based Macleaya cordata extract (Class II new veterinary medicine) serves as a starting point for developing new premix formulations with disease-preventing and growth-promoting functions to support healthy, environmentally sustainable, and efficient animal production in China.

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