Application Prospects of Lonicera japonica Extract in Oxidative Stress and Inflammation in Periparturient Dairy Cows: A Postprint

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Abstract

Perinatal dairy cows experience metabolic and physiological alterations due to increased energy demands but reduced dry matter intake, thereby triggering negative energy balance, oxidative stress, and inflammatory responses. Oxidative stress is a significant cause of inflammation and immunosuppression in the body, which may increase the incidence of various perinatal diseases. Therefore, strengthening health management of perinatal dairy cows is essential for ensuring their health and optimizing lactation performance. Previous studies have shown that Lonicera japonica extract, as a natural plant extract, possesses both medicinal and nutritional properties, and exhibits multiple physiological and biochemical activities, such as anti-inflammatory and antioxidant effects. However, to date, no reports have been published on the application of Lonicera japonica extract in perinatal dairy cows. Therefore, this article reviews oxidative stress, inflammatory response, and immunosuppression in perinatal dairy cows, as well as the effects of Lonicera japonica extract on these physiological aspects, aiming to provide a reference for further investigation into the role of Lonicera japonica extract in perinatal dairy cows.

Full Text

Application Prospects of Honeysuckle Extract in Oxidative Stress and Inflammation of Perinatal Dairy Cows

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Abstract

During the perinatal period, increased energy demand coupled with reduced dry matter intake in dairy cows leads to metabolic and physiological changes that trigger negative energy balance, oxidative stress, and inflammatory responses. Oxidative stress is a major contributor to inflammation and immunosuppression, potentially increasing the incidence of various perinatal diseases. Therefore, strengthening health management of perinatal dairy cows is essential for ensuring their well-being and optimizing lactation performance. Previous studies have demonstrated that honeysuckle extract, as a natural plant extract, possesses both medicinal and nutritional properties, exhibiting multiple physiological and biochemical activities such as anti-inflammatory and antioxidant effects. However, the application of honeysuckle extract in perinatal dairy cows has not yet been reported. This paper reviews oxidative stress, inflammatory responses, and immunosuppression in perinatal dairy cows, along with the physiological effects of honeysuckle extract, to provide a reference for further research on its potential role in perinatal cattle.

Keywords: honeysuckle extract; perinatal period; dairy cows; inflammation; oxidative stress; mechanism

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The perinatal period is a critical physiological stage for dairy cows, encompassing the three weeks before and after parturition. The physiological status of cows during this period largely determines their health and productive efficiency throughout the subsequent lactation cycle [1]. Perinatal cows undergo dramatic metabolic and physiological changes that increase susceptibility to various metabolic and infectious diseases, including milk fever, fatty liver, ketosis, laminitis, retained placenta, and mastitis. These conditions can lead to compromised body condition, reduced immunity and performance, and even culling [2]. Currently, enhancing perinatal cow management to improve health status and extend productive lifespan represents an urgent challenge for China' s dairy industry.

Previous research has shown that dietary supplementation with appropriate additives during the perinatal period can effectively alleviate oxidative stress and inflammation while regulating physiological status. For an extended period, antibiotics were commonly used as feed additives in ruminant production to prevent metabolic diseases and enhance performance. However, with rising living standards, increasing concerns have emerged regarding antibiotic residues and their potential to cause carcinogenic, teratogenic, and mutagenic effects. Consequently, the European Union banned antibiotic feed additives in 2006 [3]. Honeysuckle (*Lonicera japonica* Thunb.) extract, as a natural plant extract, offers both medicinal and nutritional benefits, exhibiting diverse physiological and biochemical activities including anti-inflammatory, antioxidant, antiviral, antimicrobial, hypoglycemic, lipid-lowering, hepatoprotective, and diuretic effects, while being non-toxic and residue-free, thus holding significant medicinal value. Nevertheless, applications of honeysuckle extract in perinatal dairy cows remain unreported. Therefore, this review examines oxidative stress, inflammatory responses, and immunosuppression in perinatal dairy cows, along with the effects of honeysuckle extract under these physiological conditions, to provide a foundation for further investigation of its potential benefits in perinatal cattle.

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1 Overview of Important Physiological Disorders in Dairy Cows During the Perinatal Period

The perinatal period represents a critical physiological stage in dairy cows. Due to increased energy requirements and reduced dry matter intake, cows may experience various physiological and metabolic abnormalities during this phase, including negative energy balance (NEB), inflammatory responses, oxidative stress, and immunosuppression [4]. These metabolic disturbances constitute the fundamental cause of the high incidence of metabolic and infectious diseases in perinatal dairy cows. Therefore, strengthening feeding management and health maintenance to reduce the occurrence of negative energy balance, inflammation, oxidative stress, and immunosuppression is crucial for preserving cow health and productive performance.

1.1 Oxidative Stress and Its Hazards

Under normal physiological conditions, the continuous production of free radicals from metabolic activities is balanced by their elimination through the antioxidant system, maintaining homeostasis. However, when excessive free radicals overwhelm the antioxidant capacity, dairy cows develop oxidative stress. Free radicals are independent molecules, atoms, ions, or atomic groups characterized by unpaired electrons that can capture electrons from other atoms or molecules, exhibiting strong oxidizing capacity [5]. The primary free radicals in biological systems include reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS comprise superoxide anion radicals, hydrogen peroxide, hydroxyl radicals, and singlet oxygen, while RNS include nitric oxide, nitrogen dioxide, and peroxynitrite radicals [6]. ROS exhibit strong oxidizing effects on numerous biomolecules, damaging proteins, DNA, and nucleotides, while also inducing lipid peroxidation of biological membranes, thereby altering normal physiological and metabolic states [7]. The free radical scavenging system prevents such damage and consists of two categories: enzymatic antioxidants, including superoxide dismutase (SOD) and other antioxidant enzymes, and non-enzymatic antioxidants, comprising vitamin antioxidants, trace element antioxidants, bioactive antioxidant compounds, and natural plants with active components [8]. This scavenging system is closely associated with various nutrients, such as vitamins and reduced glutathione, which serve as low-molecular-weight free radical scavengers [9], and the activity of many antioxidant enzymes depends on specific trace elements.

During late pregnancy, parturition, and the onset of lactation, nutritional demands increase dramatically. However, fetal growth occupies substantial abdominal space, and hormonal changes gradually reduce feed intake, making energy intake insufficient to meet the requirements for fetal development and milk production, resulting in negative energy balance. Negative energy balance promotes lipid metabolism and increases metabolic activity while simultaneously impairing the antioxidant system [10]. The markedly elevated metabolic activity and dramatic physiological changes during the perinatal period cause a sharp increase in ROS production, leading to oxidative stress. Research has identified oxidative stress as a critical factor triggering immunosuppression and inflammatory responses in perinatal dairy cows [11], increasing the incidence of perinatal diseases such as retained placenta and mastitis, which in turn further exacerbate oxidative stress. Therefore, improving oxidative stress status through proper feeding management is essential for enhancing perinatal cow health. Numerous studies have investigated oxidative stress mitigation, demonstrating that antioxidant supplementation can scavenge free radicals, enhance neutrophil phagocytic and bactericidal capacity, and reduce the risk of mastitis and retained placenta. Research indicates that supplementing perinatal cows with antioxidants such as vitamin E and selenium significantly improves the immune function of neutrophils and macrophages [12-13].

1.2 Inflammation, Immunosuppression and Their Hazards

Dairy cows possess a dynamic immune system comprising three lines of defense, encompassing both innate and adaptive immunity. This system must maintain a delicate balance, as inadequate immune responses fail to eliminate pathogens, while excessive responses can damage host tissues [14]. Inflammatory responses represent a form of innate immunity that clears detrimental substances and initiates tissue healing. Appropriate inflammatory reactions rapidly eliminate microbial pathogens and prevent self-inflicted tissue damage, whereas excessive inflammation often causes diseases such as colitis and septic shock [15-16].

The perinatal period presents unique challenges as cows undergo substantial metabolic and physiological changes. The metabolic demands of late gestation and the stress of parturition generate large quantities of ROS, causing oxidative stress, while also triggering the release of hormones such as corticosteroids that severely impact immune function. Corticosteroids reduce lymphocyte responsiveness and immune capacity, predisposing cows to perinatal diseases like mastitis and retained placenta, which themselves can induce oxidative stress [8]. The relationship among energy metabolism, inflammation, immunosuppression, and oxidative stress in perinatal dairy cows is illustrated in Figure 1 [Figure 1: see original paper].

Figure 1 Relationship between energy metabolism, inflammation, immunosuppression and oxidative stress of cows during perinatal period. The direction of arrow represents acceleration.

Sagone et al. [17] found that hydrogen peroxide inhibits lymphocyte differentiation. Experimental studies have confirmed that free radicals affect lymphocyte proliferation, cellular immunity, and responsiveness to stimuli [18-19]. The increased inflammatory response in perinatal cows directly results from altered concentrations of inflammatory cytokines. Using fetal lung type II epithelial cells as a model, Haddad et al. [20] investigated the effects of superoxide anion radicals on the release of inflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) under specific oxygen pressures. The results demonstrated that superoxide anion radicals significantly induced release of these three cytokines in a concentration-dependent manner. These findings indicate that oxidative stress can trigger inflammatory responses and immunosuppression. Additionally, research has shown that polymorphonuclear neutrophil function is impaired during the perinatal period, affecting migration, phagocytosis, and bactericidal capacity [21-22]. Neutrophils constitute the first line of defense against mammary infections, and their functional impairment directly contributes to the development of mastitis and metritis [23]. Neutrophil maturation is closely associated with pro-inflammatory cytokine release [24]. Furthermore, inflammatory responses during the perinatal period can reduce milk yield [25], compromising productive performance.

2 Potential Applications of Honeysuckle Extract in Perinatal Dairy Cows

Honeysuckle, also known as Lonicera japonica, was first mentioned in the *Compendium of Materia Medica* as "honeysuckle" because its flowers initially appear white before turning yellow as they mature [26]. Medicinal honeysuckle consists of dried flower buds or newly opened flowers from *Lonicera japonica* Thunb. and related species in the Caprifoliaceae family. In Asian countries including China, Korea, and Japan, honeysuckle has been widely used to treat common colds, fever, enteritis, pain, and swelling. Phytochemical studies have identified its primary active components as organic acids, volatile oils, flavonoids, and triterpenoids, with chlorogenic acid being the principal bioactive compound among the organic acids [27].

2.1 Antioxidant Effects

Honeysuckle is a natural herbal plant whose extract exhibits strong free radical scavenging and antioxidant capacities. Fu et al. [28] conducted a study with 20

Jinjiang yellow cattle under high summer temperatures, dividing them into four groups supplemented with 0%, 0.2%, 0.4%, and 0.6% honeysuckle extract in concentrate. The results showed that honeysuckle extract supplementation increased serum total antioxidant capacity (T-AOC) and activities of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) while reducing malondialdehyde (MDA) concentrations. Similarly, Song et al. [29] supplemented 10 beef cattle with 0.2% honeysuckle extract in concentrate under high temperature and humidity conditions, observing increased serum T-AOC and GSH-Px activity along with decreased MDA levels. Both studies demonstrate that honeysuckle extract can enhance antioxidant capacity in cattle.

Additional animal studies have investigated the antioxidant and free radical scavenging abilities of honeysuckle and its active components. Guan et al. [30] found through in vitro experiments that both honeysuckle extract and chlorogenic acid possess strong scavenging capacity against hydroxyl radicals, superoxide anion radicals, and diphenyl picrylhydrazyl radicals. The chlorogenic acid content in honeysuckle extract largely determines its free radical scavenging efficacy [31]. Hu et al. [32] also examined the effects of different chlorogenic acid concentrations on three ROS types (hydroxyl radicals, superoxide anion radicals, and hydrogen peroxide) and lipid peroxidation in vitro. The results indicated that chlorogenic acid exhibits strong scavenging activity against all three ROS types and effectively inhibits lipid peroxidation, with these effects increasing in a concentration-dependent manner. Beyond chlorogenic acid, other components in honeysuckle extract also demonstrate potent antioxidant activity. Studies have shown that phenolic compounds in honeysuckle extract can alleviate oxidative damage in mouse liver microsomes and human umbilical vein endothelial cells [33]. Furthermore, honeysuckle extract is rich in flavonoids, whose chemical structures contain multiple phenolic groups that can donate highly unstable protons. When free radicals combine with these protons, they form stable structures that inhibit oxidative processes [34]. These findings confirm that honeysuckle extract possesses strong antioxidant and free radical scavenging capabilities, suggesting considerable potential for alleviating oxidative stress in perinatal dairy cows.

2.2 Heat-Clearing and Detoxifying, Anti-inflammatory, and Immunomodulatory Effects

Honeysuckle extract contains numerous pharmacologically active components, such as chlorogenic acid and flavonoids, that confer significant heat-clearing, detoxifying, and anti-inflammatory effects. Previous studies have explored the anti-inflammatory and immunomodulatory activities of honeysuckle extract. Cui [35] conducted experiments using various animal models, demonstrating that daily oral administration of honeysuckle extract to Wistar rats for five days significantly inhibited carrageenan-induced paw edema and croton oil-induced granuloma formation. Moreover, continuous administration for 15 days markedly suppressed macrophage phagocytic activity in normal mice, indicating strong immunosuppressive activity. Hou [36] investigated the effects of honeysuckle extract on T lymphocyte proliferation and differentiation and its therapeutic efficacy against sepsis in mice. The results showed that honeysuckle extract inhibited lymphocyte activation and proliferation in vitro, blocked lymphocyte differentiation, enhanced peritoneal macrophage phagocytic function, and effectively suppressed thymus and spleen cell apoptosis in mice with *Escherichia coli*-induced sepsis. Liu et al. [37] examined the effects of honeysuckle polysaccharides on mouse splenic lymphocyte proliferation, finding that concentrations of 10–250 g/mL significantly promoted lymphocyte proliferation, with maximal effect at 100 g/mL. These results suggest that polysaccharide components in honeysuckle extract can enhance immune function and potentially inhibit S180 tumor growth through immunomodulation. Collectively, these findings demonstrate that honeysuckle possesses immunomodulatory functions.

Additional studies have investigated the anti-inflammatory mechanisms of honeysuckle extract. Park et al. [38] used a lipopolysaccharide (LPS)-induced RAW 264.7 cell inflammation model to test honeysuckle polyphenols, finding they effectively suppressed LPS-induced inflammatory responses. Kang et al. [39] isolated luteolin from honeysuckle and applied it to phorbol 12-myristate 13-acetate (PMA) and A23187-activated mast cell cultures, observing significant reductions in release of inflammatory cytokines TNF-α, interleukin-8 (IL-8), and IL-6. These results demonstrate the anti-inflammatory properties of honeysuckle extract. Moreover, these studies reveal that the anti-inflammatory activity of honeysuckle and its active components involves inhibition of nuclear factor- B (NF- B) and mitogen-activated protein kinase (MAPK) signaling pathways, leading to reduced release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [38-39].

3 Summary

In summary, increased metabolic activity and dramatic physiological changes during the perinatal period trigger oxidative stress and inflammatory responses in dairy cows. Inflammation and oxidative stress severely affect cow health and productive performance during both the perinatal period and subsequent lactation. Researchers worldwide increasingly recognize the importance of mitigating oxidative stress and inflammation in perinatal dairy cows. Dietary supplementation represents an effective strategy for improving perinatal cow health. As a natural herbal plant rich in proteins, carbohydrates, fats, and trace elements, honeysuckle extract contains bioactive compounds including organic acids, volatile oils, flavonoids, and triterpenoids. Its non-toxic, non-residue, and non-resistance properties ensure animal safety and product quality, making it highly suitable for animal production. Numerous studies have investigated honeysuckle extract applications in animal production, and its anti-inflammatory and antioxidant effects hold considerable potential for alleviating inflammation and oxidative stress in perinatal dairy cows. However, its efficacy during the perinatal period remains unreported. Future research should investigate the effects of honeysuckle extract on oxidative stress and inflammation in perinatal dairy cows to elucidate its mechanisms and provide effective strategies for improving perinatal cow health.

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