Application Prospects of Lonicera japonica Extract for Oxidative Stress and Inflammation in Transition Dairy Cows (Postprint)

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Abstract

Perinatal dairy cows undergo metabolic and physiological alterations due to increased energy requirements coupled with reduced dry matter intake, which precipitates negative energy balance, oxidative stress, and inflammatory responses. Oxidative stress constitutes a significant contributor to inflammation and immunosuppression, potentially elevating the incidence of various perinatal diseases. Therefore, enhancing health management of perinatal dairy cows is imperative for safeguarding their well-being and optimizing lactation performance. Previous research has demonstrated that honeysuckle extract, as a natural plant-derived extract, exhibits dual medicinal and nutritional properties alongside diverse physiological and biochemical activities, including anti-inflammatory and antioxidant effects. However, applications of honeysuckle extract in perinatal dairy cows remain unreported to date. Accordingly, this article reviews oxidative stress, inflammatory responses, and immunosuppression in perinatal dairy cows, together with the physiological effects of honeysuckle extract, aiming to provide a reference for further investigation into the role of honeysuckle extract in perinatal dairy cows.

Full Text

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

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Abstract

During the perinatal period, dairy cows experience metabolic and physiological changes due to increased energy demands coupled with reduced dry matter intake, leading to negative energy balance, oxidative stress, and inflammatory responses. Oxidative stress represents a critical factor underlying inflammation and immunosuppression, potentially increasing the incidence of various peripartum diseases. Therefore, strengthening health management during this period is essential for ensuring cow health and optimizing lactation performance. Previous research has demonstrated that honeysuckle extract, as a natural plant extract, possesses both medicinal and nutritional properties with multiple physiological activities, including anti-inflammatory and antioxidant effects. However, applications of honeysuckle extract in perinatal dairy cows have not yet been reported. This review examines oxidative stress, inflammatory responses, and immunosuppression in perinatal dairy cows, along with the physiological effects of honeysuckle extract, to provide a reference for further investigation of its potential benefits.

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

1. Overview of Important Physiological Disorders in Perinatal Dairy Cows

The perinatal period, encompassing the three weeks before and after parturition, represents a critical physiological stage for dairy cows. Dramatic metabolic and physiological changes during this phase can trigger a series of abnormalities, including negative energy balance (NEB), inflammatory responses, oxidative stress, and immunosuppression, which fundamentally underlie the high incidence of metabolic and infectious diseases in peripartum cows. Consequently, enhancing management and maintenance during the perinatal period to reduce the occurrence of NEB, inflammation, oxidative stress, and immunosuppression is crucial for preserving cow health and production performance.

1.1 Oxidative Stress and Its Hazards

Under normal conditions, the continuous generation of free radicals from physiological activities is balanced by their clearance through the antioxidant system, maintaining homeostasis. However, when free radical production exceeds the capacity of endogenous antioxidant defenses, oxidative stress occurs. Free radicals are independent molecules, atoms, ions, or atomic groups characterized by unpaired electrons that can seize electrons from other atoms or molecules, conferring strong oxidizing capacity. In biological systems, these primarily include reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS encompass superoxide anion radicals, hydrogen peroxide, hydroxyl radicals, and singlet oxygen, while RNS include nitric oxide, nitrogen dioxide, and peroxynitrite radicals. ROS exhibit strong oxidative properties toward numerous biomolecules, damaging proteins, DNA, and nucleotides while inducing lipid peroxidation of biological membranes, thereby altering normal physiological and metabolic states.

The radical scavenging system comprises two categories: enzymatic antioxidants, such as superoxide dismutase (SOD), and non-enzymatic antioxidants, including vitamin-based antioxidants, trace elements, bioactive substances, and natural plants with active components. This system is closely associated with various nutrients, such as vitamins and reduced glutathione, which serve as low-molecular-weight radical scavengers, while 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, preventing energy intake from meeting the requirements for fetal development and milk production, thus creating negative energy balance. NEB not only enhances lipid metabolism but also impairs the antioxidant system. The resulting surge in metabolic activity and dramatic physiological changes during the perinatal period cause ROS production to increase sharply, inducing oxidative stress. Research has identified oxidative stress as a significant contributor to immunosuppression and inflammatory responses in peripartum cows, increasing the incidence of retained placenta, mastitis, and other peripartum diseases, which in turn further exacerbate oxidative stress. Therefore, improving oxidative stress status through proper management is essential for enhancing cow health. Numerous studies have investigated antioxidant supplementation, which can alleviate oxidative stress by scavenging free radicals, thereby improving neutrophil phagocytic and bactericidal capacity and reducing the risk of mastitis and retained placenta. Evidence indicates that supplementing peripartum cows with antioxidants such as vitamin E and selenium significantly enhances the immune function of neutrophils and macrophages.

1.2 Inflammation, Immunosuppression and Their Hazards

Dairy cows possess a dynamic immune system comprising three lines of defense, encompassing both innate and acquired immunity. This system must maintain a delicate balance, as insufficient immune responses fail to clear pathogens while excessive responses can damage host tissues. Inflammatory responses represent a form of innate immunity that eliminates harmful substances and initiates tissue healing. While appropriate inflammation rapidly clears microbial pathogens and prevents self-damage, excessive inflammatory responses often cause diseases such as colitis and septic shock.

The perinatal period subjects cows to substantial metabolic and physiological changes, particularly metabolic shifts in late gestation and parturition stress. These changes generate large quantities of ROS, causing oxidative stress, and trigger the release of hormones such as corticosteroids that severely impair immune function by reducing lymphocyte responsiveness and immune capacity. This immunosuppression predisposes cows to peripartum diseases like mastitis and retained placenta, which subsequently induce further oxidative stress. The relationships among energy metabolism, inflammation, immunosuppression, and oxidative stress in peripartum cows are illustrated in Figure 1 [Figure 1: see original paper].

Research by Sagone et al. demonstrated that hydrogen peroxide inhibits lymphocyte differentiation, while other studies confirmed that free radicals affect lymphocyte proliferation, cellular immunity, and responsiveness to stimuli. In peripartum cows, increased inflammatory responses directly correlate with altered concentrations of inflammatory cytokines. Haddad et al., using fetal lung type II epithelial cells as a model, investigated the effects of superoxide anion radicals on the release of interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- (TNF-) under specific oxygen pressures, finding that superoxide anion radicals significantly induced release of these three cytokines in a concentration-dependent manner. These findings demonstrate that oxidative stress can trigger inflammatory responses and immunosuppression.

Furthermore, studies have shown that polymorphonuclear neutrophil function is compromised during the peripartum period, affecting migration, phagocytosis, and bactericidal capacity. Neutrophils constitute the first line of defense against mammary infections, and their functional impairment directly contributes to the development of mastitis and metritis. Neutrophil maturation is closely associated with pro-inflammatory cytokine release, and inflammatory responses during the peripartum period have also been linked to decreased milk production, thereby affecting overall productivity.

2. Potential Applications of Honeysuckle Extract in Perinatal Dairy Cows

Honeysuckle (*Lonicera japonica* Thunb.), also known as "Ren Dong," was first documented in *Compendium of Materia Medica*. Its name derives from the color transformation of its flowers from white to yellow during growth. The medicinal material consists of dried flower buds or newly opened flowers from *Lonicera* plants. Widely used in China, Korea, and Japan for treating common colds, fever, enteritis, pain, and swelling, honeysuckle has been found to contain active components including organic acids, volatile oils, flavonoids, and triterpenoids, with chlorogenic acid being the primary active ingredient.

2.1 Antioxidant Effects

Honeysuckle is a natural herbal plant whose extract exhibits strong free radical scavenging and antioxidant capacity. Fu et al. conducted a study with 20 Jinjiang yellow cattle under high summer temperatures, dividing them into four groups receiving 0%, 0.2%, 0.4%, and 0.6% honeysuckle extract in concentrate.

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. supplemented 10 beef cattle with 0.2% honeysuckle extract 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. found through in vitro experiments that honeysuckle extract and chlorogenic acid possess strong scavenging capacity against hydroxyl radicals, superoxide anion radicals, and diphenyl picrylhydrazyl radicals, with the chlorogenic acid content largely determining this scavenging ability. Hu et al. also examined the effects of different chlorogenic acid concentrations on three ROS types (hydroxyl radicals, superoxide anion radicals, and hydrogen peroxide) and lipid peroxidation, demonstrating that chlorogenic acid effectively scavenged all three ROS types and inhibited lipid peroxidation in a concentration-dependent manner. Beyond chlorogenic acid, other honeysuckle components show potent antioxidant activity, with phenolic compounds from the extract significantly alleviating oxidative damage in mouse liver microsomes and human umbilical vein endothelial cells. Additionally, honeysuckle extract is rich in flavonoids whose chemical structures contain numerous phenolic groups that can donate highly unstable protons. When free radicals combine with these protons, they form stable structures that inhibit oxidative processes. These findings confirm that honeysuckle extract possesses strong antioxidant and free radical scavenging capabilities, suggesting considerable potential for alleviating oxidative stress in peripartum dairy cows.

2.2 Heat-Clearing, 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 investigated these properties in various animal models. Cui et al. demonstrated 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, while 15 days of continuous administration markedly suppressed macrophage phagocytic capacity, indicating strong immunosuppressive activity. Hou et al. examined the effects of honeysuckle extract on T lymphocyte proliferation and differentiation and its therapeutic efficacy against sepsis in mice, finding that it inhibited lymphocyte activation and proliferation while enhancing peritoneal macrophage phagocytic function and effectively suppressing thymus and spleen cell apoptosis in sepsis induced by *E. coli*. Liu et al. observed that honeysuckle polysaccharides at concentrations of 10–250 g/mL significantly promoted mouse spleen lymphocyte proliferation, with maximal effect at 100 g/mL, suggesting that polysaccharide components can enhance immune function and potentially inhibit S180 tumor growth through immunomodulation. These results demonstrate that honeysuckle possesses immunomodulatory functions.

Additional studies have investigated the anti-inflammatory mechanisms of honeysuckle extract. Park et al. used a lipopolysaccharide (LPS)-induced RAW 264.7 cell inflammation model to show that honeysuckle polyphenols effectively inhibited LPS-induced inflammatory responses. Kang et al. 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 including TNF- , interleukin-8 (IL-8), and IL-6. These findings indicate that honeysuckle extract exerts anti-inflammatory effects by suppressing nuclear factor- B (NF- B) and mitogen-activated protein kinase (MAPK) signaling pathways, thereby reducing pro-inflammatory cytokine release.

3. Summary

In summary, increased metabolic activity and dramatic physiological changes during the peripartum period trigger oxidative stress and inflammatory responses that severely impact cow health and production performance throughout the peripartum and subsequent lactation periods. Researchers increasingly recognize the importance of alleviating oxidative stress and inflammation in peripartum dairy cows. Dietary supplementation represents an effective strategy for improving peripartum health, and honeysuckle, as a natural herbal plant rich in proteins, carbohydrates, fats, and trace elements, contains bioactive components including organic acids, volatile oils, flavonoids, and triterpenoids. Its non-toxic, non-residual properties ensure animal safety and product quality, making it highly suitable for animal production. Although numerous studies have demonstrated the anti-inflammatory and antioxidant effects of honeysuckle extract, its application in peripartum dairy cows remains unexplored. Future research should investigate the effects of honeysuckle extract on oxidative stress and inflammation in peripartum dairy cows to elucidate its efficacy and provide effective strategies for improving peripartum health.

References

[1] DRACKLEY J K. Biology of dairy cows during the transition period: the final frontier?[J]. Journal of Dairy Science, 1999, 82(11): 2259–2273.

[2] DAI Yingchun. Comparative study on the variation patterns of antioxidant enzyme activities and copper, zinc, manganese, and magnesium contents in serum of periparturient dairy cows[D]. Master's thesis. Hohhot: Inner Mongolia Agricultural University, 2007.

[3] WEI Qingtian. Effects of *Enterococcus faecalis* as a substitute for feed antibiotics on production, immunity, intestinal development, and intestinal microbiota in weaned piglets[D]. Master’ s thesis. Nanjing: Nanjing Agricultural University, 2014.

[4] ZHOU, BULGARI O, VAILATI-RIBONI M, et al. Rumen-protected methionine compared with rumen-protected choline improves immunometabolic status in dairy cows during the peripartal period[J]. Journal of Dairy Science, 2016, 99(11): 8956–8969.

[5] HAI Chunxu. Free Radical Medicine[M]. Xi’ an: Fourth Military Medical University Press, 2006.

[6] BENZ C C, YAU C. Ageing, oxidative stress and cancer: paradigms in parallax[J]. Nature Reviews Cancer, 2008, 8(11): 875–879.

[7] TREVISAN M, BROWNE R, RAM M, et al. Correlates of markers of oxidative status in the general population[J]. American Journal of Epidemiology, 2001, 154(4): 348–356.

[8] GU Juan, ZHANG Chungang, LIU Zhen, et al. Relationship between oxidative stress and peripartum diseases in dairy cows and its mechanism[J]. China Dairy Cattle, 2015(10): 31–36.

[9] XIONG Guilin. Study on antioxidant effects of lipoic acid in periparturient dairy cows[D]. Doctoral thesis. Yangzhou: Yangzhou University, 2009.

[10] OSORIO J S, TREVISI E, LI C, et al. Supplementing Zn, Mn, and Cu from amino acid complexes and Co from cobalt glucoheptonate during the peripartal period benefits postpartal cow performance and blood neutrophil function[J]. Journal of Dairy Science, 2016, 99(3): 1868–1883.

[11] SORDILLO L M, AITKEN S L. Impact of oxidative stress on the health and immune function of dairy cattle[J]. Veterinary Immunology and Immunopathology, 2009, 128(1/2/3): 104–109.

[12] HOGAN J S, SMITH K L, WEISS W P, et al. Relationships among vitamin E, selenium, and bovine blood neutrophils[J]. Journal of Dairy Science, 1990, 73(9): 2372–2378.

[13] POLITIS I, HIDIROGLOU N, WHITE J H, et al. Effects of vitamin E on mammary and blood leukocyte function, with emphasis on chemotaxis, in periparturient dairy cows[J]. American Journal of Veterinary Research, 1996, 57(4): 468–471.

[14] SORDILLO L M, CONTRERAS G A, AITKEN S L. Metabolic factors affecting the inflammatory response of periparturient dairy cows[J]. Animal Health Research Reviews, 2009, 10(1): 53–63.

[15] BURVENICH C, BANNERMAN D D, LIPPOLIS J D, et al. Cumulative physiological events influence the inflammatory response of the bovine udder

to *Escherichia coli* infections during the transition period[J]. Journal of Dairy Science, 2007, 90(Suppl. 1): E39-E54.

[16] HILL A W. Factors influencing the outcome of *Escherichia coli* mastitis in the dairy cow[J]. Research in Veterinary Science, 1981, 31(1): 107-112.

[17] SAGONE A L Jr., KAMPS S, CAMPBELL R. The effect of oxidant injury on the lymphoblastic transformation of human lymphocytes[J]. Photochemistry and Photobiology, 1978, 28(4/5): 909-915.

[18] METZGER Z, HOFFELD J T, OPPENHEIM J J. Macrophage-mediated suppression. I. Evidence for participation of both hydrogen peroxide and prostaglandins in suppression of murine lymphocyte proliferation[J]. Journal of Immunology, 1980, 124(2): 983-988.

[19] FISHER R I, BOSTICK-BRUTON F. Depressed T cell proliferative responses in Hodgkin' s disease: role of monocyte-mediated suppression via prostaglandins and hydrogen peroxide[J]. Journal of Immunology, 1982, 129(4): 1770-1774.

[20] HADDAD J J E, SAFIEH-GARABEDIAN B, SAADÉ N E, et al. Chemioxyexcitation (ΔpO /ROS)-dependent release of IL-1 , IL-6 and TNF- : evidence of cytokines as oxygen-sensitive mediators in the alveolar epithelium[J]. Cytokine, 2001, 13(3): 138-147.

[21] KEHRLI M E Jr., NONNECKE B J, ROTH J A. Alterations in bovine neutrophil function during the periparturient period[J]. American Journal of Veterinary Research, 1989, 50(2): 207-214.

[22] GUIDRY A J, PAAPE M J, PEARSON R E. Effects of parturition and lactation on blood and milk cell concentrations, corticosteroids, and neutrophil phagocytosis in the cow[J]. American Journal of Veterinary Research, 1976, 37(10): 1195-1200.

[23] CAI T Q, WESTON P G, LUND L A, et al. Association between neutrophil functions and periparturient disorders in cows[J]. American Journal of Veterinary Research, 1994, 55(7): 934-943.

[24] BURTON J L, MADSEN S A, CHANG L C, et al. Gene expression signatures in neutrophils exposed to glucocorticoids: a new paradigm to help explain "neutrophil dysfunction" in parturient dairy cows[J]. Veterinary Immunology and Immunopathology, 2005, 105(3/4): 197-219.

[25] HUZZEY J M, MANN S, NYDAM D V, et al. Associations of peripartum markers of stress and inflammation with milk yield and reproductive performance in Holstein dairy cows[J]. Preventive Veterinary Medicine, 2015, 120(3/4): 291-297.

[26] WAGNER W L, HERBST D R, SOHMER S H. *Colocasia*[M]//Manual of the Flowering Plants of Hawaii. Honolulu, Hawaii: University of Hawaii Press, 1999: 1356-1357.

[27] XING Xiangwei. Study on honeysuckle and mountain honeysuckle in traditional Chinese medicine preparations[D]. Master’ s thesis. Zhengzhou: Henan University of Traditional Chinese Medicine, 2011.

[28] FU Yunbin, HUANG Tao, QU Mingren, et al. Effects of honeysuckle extract on serum hormones and antioxidant indices in heat-stressed beef cattle[J]. Chinese Journal of Animal Nutrition, 2016, 28(3): 926–931.

[29] SONG Xiaozhen, FU Yunbin, HUANG Tao, et al. Effects of honeysuckle extract on antioxidant indices and skeletal muscle fiber structure in beef cattle under high temperature conditions[J]. Chinese Journal of Animal Nutrition, 2015, 27(11): 3534–3540.

[30] GUAN Bingfeng, TAN Jun, ZHOU Zhidi. Correlation between antioxidant activity of honeysuckle extract and its chlorogenic acid content[J]. Science and Technology of Food Industry, 2007, 28(10): 127–129.

[31] LI Rongwei. Study on antioxidant activity and chromatographic analysis of honeysuckle and propolis[D]. Master’ s thesis. Xi’ an: Northwest University, 2008.

[32] HU Zongfu, YU Wenli, ZHAO Yaping. Study on chlorogenic acid scavenging reactive oxygen species and anti-lipid peroxidation[J]. Food Science, 2006, 27(2): 128–130.

[33] PALÍKOVÁ I, VALENTOVÁ K, OBORNÁ I, et al. Protectivity of blue honeysuckle extract against oxidative damage to human endothelial cells and rat hepatocytes[J]. Journal of Agricultural and Food Chemistry, 2009, 57(15): 6584–6589.

[34] ZHU Guodong, CHEN Yunbo, PAN Feng, et al. Research progress on flavonoids in honeysuckle[J]. Guangdong Chemical Industry, 2017, 44(15): 184–185.

[35] CUI Xiaoyan. Anti-inflammatory and immunological effects of honeysuckle extract[J]. China Pharmacy, 2011, 20(23): 8–9.

[36] HOU Huina. Effects of honeysuckle extract on T cell behavior and immunomodulation in sepsis in mice[D]. Master’ s thesis. Guangzhou: Jinan University, 2008.

[37] LIU Bei, LIU Yuhong. Effect of honeysuckle polysaccharides on spleen lymphocyte proliferation[J]. China Practical Medicine, 2013, 8(11): 244–245.

[38] PARK K I, KANG S R, PARK H S, et al. Regulation of proinflammatory mediators via NF- B and p38 MAPK-dependent mechanisms in RAW 264.7 macrophages by polyphenol components isolated from Korea *Lonicera japonica* Thunb[J]. Evidence-Based Complementary and Alternative Medicine, 2012, 2012: 828521.

[39] KANG O H, CHOI J G, LEE J H, et al. Luteolin isolated from the flowers of *Lonicera japonica* suppresses inflammatory mediator release by blocking NF-

B and MAPKs activation pathways in HMC-1 cells[J]. Molecules, 2010, 15(1): 385-398.

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