



Use of plant-derived drugs in the prevention and treatment of dairy cow mastitis

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Abstract

Dairy cow mastitis is one of most seriously diseases affecting dairy herds. The prevention and treatment of this pathology is especially done through antimicrobials, but the increasing antimicrobial resistance of pathogens to this disease may affect the efficiency of conventional drugs. Plant extracts are increasingly being valued by livestock producers because of their wide sources, low toxic and side effects, and high environmental affinity. Thereby, a lot of research has been conducted on the control of dairy cow mastitis by plant-derived drugs in recent years. This review summarizes the current of the plant types, main active ingredients, and the mechanism of action of plant extracts for preventing and treating dairy cow mastitis. Finally, a review was carried out to prospect the future development of plant extracts in the treatment of dairy cow mastitis.

Key words: Dairy cow mastitis, Plant-derived drugs, Chemical composition, Antimicrobial.

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1. Introduction

Mastitis is the most important disease in dairy farming. It is not only affects the quality of milk, but also brings serious economic losses to the dairy industry. Dairy cow mastitis is the inflammatory response of the mammary gland caused by the physical, chemical or biological stimulation of the cow mammary gland after and the body interacts with the environment and pathogenic microorganisms (Seegers et al., 2003). With the continuous improvement of people's living standards, milk, as the best source of human calcium, has become an indispensable drink every day, making the dairy farming industry in our country have developed rapidly. Although scholars from all over the world have conducted unremitting research on the prevention and treatment of mastitis for more than 100 years, so far there has not been a method that can effectively prevent mastitis in cows (Gomes

& Henriques, 2016). At present, there are multiple treatments for dairy cow mastitis, including antibiotic treatment, traditional Chinese medicine treatment, biological treatment, laser treatment, etc. Among them, antibiotics are the main means of controlling mastitis in dairy cows. However, after antibiotic treatment, a large amount of antibiotics and toxins will remain in the milk, which will cause pathogens to mutate and reduce the efficacy, but also cause harm to human health, and gradually become a bottleneck restricting the prevention and treatment of cow mastitis (Swinkels et al., 2015). As a natural substance, plant-derived drugs contain a variety of effective biologically active ingredients. It has the characteristics of antibacterial, anti-inflammatory, anti-drug resistance, low toxicity and low residue (Tamiris et al., 2020), and has the dual functions of medicine and nutrition. In recent years, experts at home and abroad have conducted a lot of research on the use of plant-derived drugs to treat

dairy cow mastitis, playing an irreplaceable role in preventing and treating dairy cow mastitis, achieving green farming, and producing animal products and related products without drug residues (Jin-Lun et al., 2017). It can be seen from the examination and approval of preparations for cow mastitis in China that plant-derived pharmaceutical products have a place (Lai et al., 2017).

The author summarizes the action mechanism of the plant-derived plants, main active ingredients, and plant extracts for preventing and treating cow mastitis in recent years, and prospects for the future development of traditional Chinese medicine treatment of cow mastitis.

2. Results and discussion

1. Types of plant-derived medicines and their chemical components. Published literature shows that more than 30 kinds of plant extracts have an inhibitory effect on dairy cow mastitis in vivo or in vitro, such as, musk, stevia, scutellaria, rhubarb, astragalus, dandelion, honeysuckle, forsythia, licorice and so on. Many active ingredients in plants have strong bactericidal effects. For example, phenolic acids, alkaloids, flavonoids, terpenes, volatile oils and other drugs. They can directly or indirectly inhibit pathogenic bacteria killing and exert anti-inflammatory effects. Finding new anti-pathogenic bacteria ingredients from plant extracts is great significance to scientific research.

1.1. Phenolic acids. The phenolic acid extracts of various plants have protective effects on different types of dairy cow mastitis, which mainly include chlorogenic acid, caffeic acid, tea polyphenol compounds and so on. Ruifeng G. et al. (2014) have reported that anti-inflammatory effects of chlorogenic acid against LPS-induced mastitis may be due to its ability to inhibit TLR4-mediated NF- κ B signaling pathway. CGA significantly reduced TNF- α , IL-1 β and IL-6 production compared with LPS group. Liu M. et al. (2014) showed that the protective effect of caffeic acid on LPS-induced inflammation injury in bMEC was at least partly achieved by the decreased by the effect of reducing the κ B inhibitor α degradation and p65 phosphorylation in the NF- κ B pathway. The use of caffeic acid would be beneficial in dairy cows during *Escherichia coli* mastitis as a safe and natural anti-inflammatory drug. Total phenol extract from *Clerodendranthus spicatus* could effectively scavenge DPPH free radicals, reduced the production of NO and TNF- α in RAW264.7 cells induced by LPS, down-regulated the expression of IL-1 β and IL-2, up-regulated the expression of IL-10, and increased cell viability of the breast epithelium under oxidative stress (Wang et al., 2015).

1.2. Alkaloids. Alkaloids plays an important role in the treatment of many chronic diseases and exhibits strong antibacterial and anti-inflammatory activity. A study reported that, chelerythrine isolated from root of *Toddalia asiatica* (Linn) Lam possesses antibacterial activities through destruction of bacterial cell wall and cell membrane and inhibition of protein biosynthesis. Chelerythrine showed strong antibacterial activities against Gram-positive bacteria, *Staphylococcus aureus* (SA), Methicillin-resistant *S. aureus* (MRSA), and extended spectrum β -lactamase *S. aureus* (ESBLs-SA) (He et al., 2018). Lai J. et al. (2017) Found that indirubin can inhibit the expression of TLR4 in a dose-dependent manner, and play a therapeutic role in LPS-induced MMECs inflammation and mouse mastitis. *Staphylococcus epidermidis* (*S. epidermidis*) is an opportunistic

pathogen with low pathogenicity and a cause of the repeated outbreak of bovine mastitis in veterinary clinical settings. Li X et al. (2016) suggested that total alkaloids of *Sophora alopecuroides* has an inhibitory effect on biofilm formation of clinic *S. epidermidis*, which may be a potential agent warranted for further study on the treatment prevention of infection related to *S. epidermidis* in bovine mastitis.

1.3. Flavonoids. It has been reported that flavonoids possess a number of biological properties, such as anti-inflammatory, anti-virus, anti-bacteria, anti-tumor, and immunosuppressive properties. Astragaloside, a main flavonoid component isolated from Chinese herbs, which has several medical functions including treating allergy, antiatopic dermatitis, and anti-inflammatory effects. Li F. Y. et al. (2014) showed that astragaloside suppressed the expression of TNF- α , IL-6 and NO in a dose-dependent manner in mouse mammary epithelial cells (mMECs), the expression of inducible nitric oxide synthase and cyclooxygenase-2 was also inhibited. Besides, astragaloside efficiently decreased LPS-induced TLR4 expression, NF- κ B activation, I κ B α degradation, and the phosphorylation of p38, extracellular signal-regulated kinase in BMECs. It may be a potential therapeutic agent for bovine mastitis. Baicalin, one of the major flavonoids in *Scutellaria baicalensis*, has natural antioxidant and anti-inflammatory properties in various cell types. Baicalin exerts protective antioxidant effects on bovine mammary cells, which suggests that it could be used to prevent oxidative metabolic disorders in dairy cows (Perruchot et al., 2019). Emodin is an anthraquinone derivative from the Chinese herb *Radix et Rhizoma Rhei*. Emodin has protective effect against lipopolysaccharide (LPS)-induced mastitis in a mouse model by reduced MPO, IL-6, IL-1 β and TNF- α . It acts on mastitis through the NF- κ B pathway like other flavonoids (Li et al., 2013).

1.4. Terpenoids. Geniposide is a medicine isolated from *Gardenia jasminoides* Ellis. Song X. et al. (2014) use a lipopolysaccharide (LPS)-induced mouse mastitis model and LPS-stimulated primary mouse mammary epithelial cells (mMECs) to explore the anti-inflammatory effect and the mechanism of action of geniposide. The results showed that geniposide significantly reduced the infiltration of inflammatory cells and downregulated the production of TNF- α , IL-1 β , and IL-6. Then, geniposide exerted its anti-inflammatory effect by regulating TLR4 expression, which affected the downstream NF- κ B and mitogen-activated protein kinase (MAPK) signaling pathways. Stevioside is isolated from *Stevia rebaudiana*, which reduced the expression of TNF- α , IL-1 β , IL-6 and TLR2 by inhibiting the phosphorylation of proteins in the NF- κ B and MAPK signaling pathways dose-dependently in the *S. aureus*-infected mouse mammary gland and mouse mammary epithelial cells (MMECs), as well as caspase-3 and Bax (Wang et al., 2014).

2. The mechanism of plant-derived medicines on dairy cow mastitis.

2.1. Preventive and therapeutic effects. Dairy cow mastitis has a huge impact on the dairy industry. The key to its treatment is prevention. Its preventive measures mainly include scientific feeding management, excellent hygienic conditions, scientific milking methods, nipple medicine baths, and vaccine prevention. The studies found that mammary gland epithelial cells will repair themselves by fine-tuning death caused by pathogenic bacteria and other factors. According to further research, cell apoptosis is the

main method in the early onset of mastitis. When mastitis is aggravated, cell necrosis is the main method. Therefore, in order to avoid the occurrence and development of inflammation, the body increases the apoptosis of epithelial cells in the inflammatory reaction of breast, which is a self-protection mechanism to protect the integrity of the breast to the maximum extent. [Chen G. et al. \(2002\)](#) found that astragalus polysaccharide (APS) has the effect of inducing apoptosis of tumor cells, which can reduced the number of cells in S phase and increased the number of cells in G0-G1 and G2-M phases. The increased of polysaccharide dose stayed in the G2-M phase, indicating that inducing apoptosis of tumor cells is an anti-tumor way of astragalus polysaccharides. [Zhong K. et al. \(2007\)](#) studied the effect of astragalus polysaccharides on *E. coli* endotoxin (LPS) – induced experimental mastitis in goats, cows and rats. The results showed that local infusion of APS in the breast or feeding animals can alleviate the effect of LPS on animal breast tissue. Briefly, the destruction has a certain protective effect on animal breast tissue. The traditional Chinese medicine and prescriptions for the treatment of mastitis were: synthetic *Houttuynia cordata*, propolis mixture, Xianfang Huoming Yin, Gongying Shanjia Tang, Erhua Zaozi Yin, Ruyan San, etc ([Wang et al., 2013](#)). Studies by [Zhang Z. \(2009\)](#) have confirmed that the use of plant-derived drugs with honeysuckle and dandelion as the main components to treat diseased cows can play a good therapeutic effect, and its effect is significantly better than cefazolin sodium. [Geng M. et al. \(2006\)](#) have shown that the extract of the plant-derived medicine *Ulmus pumila* is better than cefalexin in the treatment of dairy cow mastitis. [Zhang M. et al. \(2001\)](#) selected Chinese herbal medicines such as angelica, chuanxiong, astragalus, dandelion, salvia miltiorrhiza, motherwort to feed dairy cows with latent mastitis, and detected the lymphocyte stimulation index (SI) and neutrophil phagocytosis of dairy cows. The results showed that the additive directly strengthens the phagocytic power of neutrophils and stimulates the proliferation of lymphocytes. Through the action of antibodies and complements, the phagocytic power of neutrophils is further strengthened. It had obvious therapeutic effect. Therefore, Chinese traditional plant-derived drugs and their active ingredients have great advantages and potential in clinical treatment of cow mastitis.

2.2. Inhibition of pathogenic bacteria. According to the reports, there are more than 130 pathogenic microorganisms that can cause mastitis in dairy cows, and even more than 20 kinds are common. The pathogens with the highest detection rate are *Staphylococcus aureus*, *Streptococcus* and *Escherichia coli*. Mastitis caused by a variety of pathogens can account for 90 %. Therefore, the antibacterial activity of plant-derived drugs is the important indicator of their effectiveness ([Rebhun, 2003](#)). [Luan Y. et al. \(2005\)](#) used eight Chinese herbal medicines, including Daqingye and Coptis, to detected their resistance to β -lactamase-producing *E. coli*. Inhibition screening study found that *Scutellaria baicalensis* had the most obvious inhibitory effect, followed by Coptis and Daqingye. [Liu P. et al. \(2006\)](#) used five Chinese herbal medicines to test the drug resistance inhibition screening of drug resistant strains producing extended-spectrum β -lactamase and sustained high yield AmpC enzyme, such as *Forsythia suspensa*, *Senecio*, *Scutellaria baicalensis*, etc. As a result, it was found that 5 kinds of traditional Chinese medicines inhibited the production of extended-spectrum β -

lactamase and AmpC enzyme strains to varying degrees. Among them, the effect of *Scutellaria baicalensis* was more obvious, followed by *Coptis chinensis* and *Senecio*. Honeysuckle is known as “Chinese medicine penicillin” and has inhibitory effects on a variety of bacteria, including *S. aureus*, *E. coli*, *Vibrio cholerae*, and *hemolytic streptococcus*, etc ([Song et al., 2003](#)). In vitro antibacterial experiments of 10 Chinese herbal medicines showed that, the antibacterial effects of Chinese herbal medicines on *E. coli* were: Myrobalan, *Viola* and *Houttuynia cordata*, which were moderately sensitive; *Prunella vulgaris*, *Scutellaria*, *Senecio*, *Astragalus*, *Gorgon*, *Teasel* were followed by low sensitivity. The antibacterial effect on *S. aureus* were: Myrobalan, *Scutellaria*, *Pomegranate Peel* and *Rhubarb* had the best effects, which were the highly sensitive; *Forsythia*, *Chuanxiong* and *Shegan* were second, and were the moderately sensitive; *Prunella vulgaris*, *Xanthium grass*, *Fried gardenia*, and *Rhubarb* were low sensitivity. The antibacterial effect of *Streptococcus agalactiae* were: *Astragalus* and *pomegranate peel* were the highly sensitive; *Ligusticum chuanxiong*, *Shegan*, *Phellodendron amurense* and *Houttuynia cordata* were moderately sensitive; *Forsythia*, *Myrobalan*, *Radix Scutellariae*, *Viola Ding*, *Rhubarb* and *Wangbu Staying* were low sensitivity ([Luo et al., 2002](#)). In summary, Chinese herbal medicine has a good inhibitory effect on *E. coli*, *S. aureus* and *Streptococcus agalactiae*.

2.3. Mechanism of action on inflammation. In recent years, the role of non-professional immune cells such as dairy cow mammary epithelial cells in resisting pathogens from invading the cow’s mammary gland has received attention. When pathogenic bacteria invaded the mammary gland of dairy cows, epithelial cells would first synthesize and secrete a variety of immunologically active substances to resisted the infection of pathogenic bacteria and reduced or even relieved the inflammatory response. After pathogenic microorganisms were infected, its lipoteichoic acid, peptidoglycan and lipopolysaccharide could trigger the natural immune system of the mammary gland, activated intracellular signal transduction pathways such as NF- κ B, MAPKs and JAK/STAT, and finally led to chemokines and inflammation factor release. Most scholars use pathogenic microorganisms or their products to stimulate breast tissue or breast epithelial cells, established in vivo and in vitro models of mastitis, and use Chinese herbal medicine or its main active ingredients to detect inflammatory factors such as IL-1 β , IL-6 and TNF- α , TLRs, NF- κ B, MAPKs and JAK/STAT signal pathway changes. Studies have shown that chlorogenic acid ([Ruifeng et al., 2014](#)) and caffeic acid ([Liu et al., 2014](#)) in honeysuckle and dandelion, emodin in rhubarb ([Li et al., 2013](#)), thymol in musk ([Wei et al., 2014](#)), indirubin in *Indigo Naturalis* ([Lai et al., 2017](#)), and berberine hydrochloride in *Coptis* ([Ye, 2007](#)), *Astragalus glycosides* in *Astragalus vulgaris* ([Li et al., 2014](#)), *Geniposide* in *Gardenia* ([Song et al., 2014](#)), *flavonoids baicalin* ([Perruchot et al., 2019](#)), *Kidney tea total phenols* ([Wang et al., 2015](#)), *Dandelion sterols* ([San, 2014](#)), *Astragalus polysaccharides* ([Perruchot et al., 2019](#)), all of them could inhibited NF- κ B, MAPKs and JAK/STAT pathways, reduced the expression level of inflammatory factors and played a protective effect on breast cells or animals.

2.4. Improve immune function. The mammary glands of dairy cows contained the necessary components for immune response to invading pathogenic microorganisms. When the low content of immunoglobulin and complement

in breast secretions and the existence of certain inhibitory factors, the immune function of the breast was suppressed (Hu, 1997). According to the reports, a traditional Chinese medicine consisting of astragalus, angelica, salvia, dandelion, etc. can increase animal antibody production and promote lymphocyte transformation (Ma, 1986). Zhang Y. et al. (2001) added Chinese herbal medicine added to the diets of normal dairy cows at the early stage of lactation, and the results showed that the addition of Chinese herbal medicines in the early stage of lactation can significantly increase the milk production of dairy cows by 7.4 ($P < 0.01$), it also improved the milk composition, and increased the milk fat rate by 11.7 ($P < 0.05$). That means the Chinese herbal medicine can reduce the incidence of non-clinical mastitis, and enhance the immunity of dairy cattle. Another study has found that Astragalus polysaccharides can enhance the ability of phagocytes, activate macrophages, promote cell differentiation and the secretion of IL-2, thereby enhancing the ability of macrophages to kill bacteria and disease, and enhance the immune system of dairy cows. It could stimulate the release of cytokines, affect the neuroendocrine-immune system (Liu et al., 2011).

3. Conclusions

The use of Chinese herbal medicine to prevent and treat dairy cow mastitis has the advantages of no drug residues and high economic benefits, and has broad application prospects in the dairy industry. Although the prevention and treatment of mastitis by traditional Chinese medicine was indeed effective, the current research and development efforts were not strong. It was manifested that there were few varieties of traditional Chinese medicine preparations for the prevention and treatment of mastitis. Most of them were powders and decoctions. The effective ingredients, content and structure have not been researched clearly, which restricts its wide application in clinic and application effect. Further research is needed on the method of separating and extracting the active ingredients of traditional Chinese medicine, the efficacy and mechanism of traditional Chinese medicine. On this basis, we will develop efficient, safe and stable Chinese medicine preparations so that Chinese medicine can play a greater role in the prevention and treatment of cow mastitis.

Author's contributions

All authors participated in this article design. Ping Xu participated and performed writing and data collection. All authors read and approved the final manuscript. All authors contributed to the draft of the manuscript. All authors gave final approval for publication.

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Conflict of interest

Author does not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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