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Research Progress on the Role of *Rubia cordifolia* in the Treatment of Lichen Planus

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Abstract: Lichen planus is a chronic inflammatory skin disease. Due to its unclear etiology, the treatment is slow and complicated. *Rubia cordifolia* is a drug with a long history, with the effects of cooling blood and removing blood stasis, promoting blood circulation, and dredging meridians. Modern research suggests that the components of *Rubia cordifolia* have the effects of immune regulation, anti-inflammation, liver protection, and antioxidation. It may be a potential drug for the treatment of lichen planus. However, the specific mechanism of *Rubia cordifolia* in the treatment of this disease is still under study. This article reviews the mechanism of *Rubia cordifolia* in the treatment of lichen planus, in order to provide references for the clinical application of the drug.

Keywords: *Rubia cordifolia*; Lichen planus; Immune regulation; Anti-inflammation; Liver protection; Antioxidation

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1. Introduction

Lichen planus (LP) is a chronic inflammatory skin disease of unknown cause, clinically manifested as small, discrete, irregularly shaped, flat-topped purplish-red papules, which may coalesce to form rough, scaly plaques, and are often accompanied by lesions of the oral cavity, fingernails/toenails, and genitalia. The etiology of the disease has not been clarified by modern medicine, but most scholars believe that LP is mainly a T-cell-mediated autoimmune reaction, in addition, there are other theories, such as liver function impairment and carcinoma, etc. LP has a global incidence, accounting for about 0.5–1.2% of new dermatologic cases, affecting more females than males, and is rare in children [1]. Currently, there is still no specific treatment for LP, the first choice for clinical treatment is topical corticosteroid drugs such as clobetasol and dieldrin, while oral drugs are mainly corticosteroids and retinoids. Therefore, clinical treatment of LP is characterized by long treatment, large differences in prognosis, and many adverse reactions, which bring great physical and mental harm and economic burden to patients and families. In the face of the difficulty in identifying the cause of the disease and the lack of effective treatments, TCM (traditional Chinese medicine) can recognize the pathogenesis of LP from another perspective and propose effective treatments. Chinese medicine believes that LP is mostly caused by

exogenous wind-dampness-heat-pathogen, liver and qi stagnation, and blood stasis. It is treated by the method of drying dampness and regulating qi, activating and cooling the blood, and *Rubia cordifolia* may be a potential therapeutic drug in the treatment of LP blood heat and blood stasis syndrome.

Rubia cordifolia, also known as Indian madder or blood-activating grass, is mainly produced in Anhui, Shandong, and other places; *Shennong Bencaojing* recorded "bitter flavor, cold; mainly used for treating wind-cold and dampness paralysis, jaundice, and tonifying the middle"; in *Chinese Materia Medica*, *Rubia cordifolia* can cool the blood, stop bleeding, activate blood circulation, and remove blood stasis, and it is suitable for treating vomiting and epistaxis, menstrual leakage and occlusion, bruises, rheumatism, paralysis, and pain. Modern research has concluded that *Rubia cordifolia* has immunosuppressive, leukocyte-boosting, anti-inflammatory, hepatoprotective, and antioxidant effects. In this paper, we reviewed the mechanism of *Rubia cordifolia* in the treatment of LP, with a view to providing references for the further clinical application of *Rubia cordifolia*.

2. Traditional Chinese medicine

Although there is no clear record of LP in Chinese medicine, according to clinical observation, the skin manifestation of LP is similar to the "purpura" described by Chinese medicine; and Chinese medicine believes that this kind of disease is mostly caused by exogenous wind-dampness-heat-pathogen, liver and qi stagnation, and blood stasis. Therefore, the treatment of this disease is mostly based on the drying of dampness, activating blood circulation, eliminating blood stasis, and dredging up the liver. In the *Yilin Gaicuo*, "purpura, blood stasis in the skin, treatment according to the vitiligo, the effect can be applied by hand," it can be seen that blood stasis is Qingren Wang's main understanding of the disease and thus put forward blood stasis as the treatment method. With continuous medical advancement, the knowledge and treatment of LP in Chinese medicine have also gradually improved. Xia and Wu [2] summarized the idea of treatment from the liver through clinical experience; Zhu *et al.* [3] put forward the treatment direction of "the disease is located in the liver, and its pathogen is dampness" according to the clinical observation of the onset site of LP, the color of the lesions, and analysis of the medication used. In addition, other scholars in China have also carried out detailed dialectical typing of LP, such as spleen and stomach heat type, liver stagnation and fire type, and blood stasis type, etc. [4,5], and these researches have far-reaching significance for the treatment of LP.

Rubia cordifolia is bitter and cold in nature, it can cool the blood and it has a more reliable potential therapeutic effect for LP with blood heat; *Rubia cordifolia* expels blood stasis, dredges channels, activates blood circulation, and removes blood stasis, it can be used to treat LP with blood stasis; *Rubia cordifolia* enters into the liver meridian, it can be used to carry out further clinical therapeutic research based on the idea of "treating from the liver."

3. Modern medicine

Although the etiology of LP has not been clarified by modern medicine, most scholars believe that the disease is caused by abnormal immune function and is accompanied by chronic inflammatory reactions. In addition, some scholars have found that lichen planus is related to liver function damage and cancer. In the following, we will discuss the four aspects of immune regulation, anti-inflammation, liver function regulation, and antioxidation in conjunction with the active ingredients of *Rubia cordifolia* and their effects (**Table 1**).

Table 1. Summary of active ingredients and therapeutic effects of *Rubia cordifolia*

	Active ingredients	Therapeutic effects
Immune regulation	Alizarin I Alizarin II *Rubia* diester Arborane triterpenes *Rubia cordifoli*a-containing serum	Regulation of immune function and increasing white blood cell levels
Anti-inflammation	Rubiacin *Rubia* total anthraquinone	Inhibition of some IL and TNF
Regulation of liver function	*Rubia* aqueous-methanol extract *Rubia cordifolia* essential oil Methylisorubicin	Liver protection
Antioxidation	*Rubia cordifolia* polysaccharide QC *Rubia cordifolia* polysaccharide QA2	Free radical scavenging, antioxidant

3.1. Immune regulation

LP is often accompanied by a T-cell-mediated process at the onset of the disease, with a large number of T cells infiltrating the locally diseased tissues. As the disease progresses, there is an autoimmune response with an increased number of T cells and a lowered level of B cells, which is accompanied by a decrease in the natural growth rate of the peripheral blood lymphocytes [6].

In response to this autoimmune response, *Rubia* diester, arborane triterpenes, and *Rubia cordifolia*-containing serum can effectively inhibit T cell proliferation. Yang and Liu [7] demonstrated that *Rubia* diester could reduce delayed hypersensitivity reaction and T cell proliferation by inhibiting phagocytosis of macrophages and neutrophils; He *et al.* [8] found that arborane triterpenoids could effectively inhibit the proliferation of T cells but had no effect on the proliferation of B cells when its concentration ranged from 30 to 100 μg/ml; Liu *et al.* [9] found that *Rubia cordifolia*-containing serum could significantly inhibit the expression of cell surface activation molecule CD69 and effectively downregulate the secretion of IFN-γ, IL-2, and TNF-α, and inhibit the proliferation of T cells. The immune regulation effect of *Rubia cordifolia* is also manifested in the elevation of leukocytes, alizarin I, II, and *Rubia* diester have a good effect on increasing the peripheral blood leukocyte level, as evidenced by Ma *et al.* [10]. *Rubia* diester also has an obvious effect of elevating leukocytes [11]; Song and Ding [12] gave oral administration of 2.5 mg of *Rubia* diester to each mouse, drew blood from the tail vein after drug administration to measure the leukocyte level, which was obviously elevated after 8 hours, reaching 151.9% of the control group, and then recovered to normal; when each dog was orally administered with 200 mg of *Rubia* diester, the peak was reached 18–24 hours after the drug administration, which was 196–209% of the pre-drug level. It indicates that *Rubia* diester can promote the proliferation and differentiation of hematopoietic stem cells and increase the peripheral blood leukocytes. Su and Zhou [13] obtained the water-extracted and alcohol-precipitated dry paste of *Rubia cordifolia* by extracting its active ingredients and found that the substance also had a high leukocyte-boosting effect. Therefore, *Rubia cordifolia* plays a therapeutic role in LP by regulating the immune system.

3.2. Anti-inflammation

As a chronic inflammatory skin disease, the pathogenesis of LP is characterized by the production of local cytokines that play an important role in the progression of the disease. Studies have shown that the development of LP is accompanied by elevated levels of IL-6 and granulocyte-macrophage colony-stimulating factor, and further studies have demonstrated that keratinocytes in oral LP tissues are capable of producing IFN-α, IL-6,

and TNF-α, and are positively correlated with the condition of skin lesions [14]. In recent years, it has also been found that the occurrence of LP may be related to IL-17 and IL-23 [15].

For the abnormal elevation of inflammatory mediators, *Rubia* total anthraquinone and rubiacin can effectively inhibit the release of inflammatory mediators, especially IL and TNF. Xu *et al.* [16] found experimentally that *Rubia* total anthraquinone could significantly reduce the levels of IL-1, IL-2, IL-6, and TNF in the serum of rats; Zhu and Jin [17] utilized rubiacin to interfere with lipopolysaccharide-treated mice and found that rubiacin could significantly inhibit the release of IL-1β and IL-6. The *Rubia cordifolia*-containing serum involved above can also effectively downregulate the secretion of relevant inflammatory mediators. It is thus clear that *Rubia cordifolia* can play a therapeutic role in LP by inhibiting the release of inflammatory mediators and reducing the inflammatory response.

3.3. Regulation of liver function

In recent years, some scholars have found a link between LP and liver disease, but the pathological mechanism has not yet been proven. Monk [18] suggested in 1985 that patients with LP had liver dysfunction along with the onset of the disease. In 1991, the occurrence of oral LP was first reported to be associated with HCV (hepatitis C virus) [19]. Another study showed that the risk of LP in patients with hepatitis B is twice as high compared to normal subjects [20].

It was found that *Rubia* aqueous-methanol extract, *Rubia cordifolia* essential oil, and methylisorubicin had good alleviating and therapeutic effects on liver injury. Experiments proved that oral administration of *Rubia* aqueous-methanol extract to mice had a significant alleviating effect on liver injury mediated by acetaminophen and CCl_4 [21]; Quan and Tian [22] also experimentally found that *Rubia cordifolia* essential oil significantly reduced hepatotoxicity induced by CCl_4; and Rao *et al.* [23] found that methylisorubicin had a strong therapeutic effect on liver injury induced by CCl_4 in mice. It can be seen that *Rubia cordifolia* may have a potential therapeutic role in the treatment of LP through the protection and regulation of liver function.

3.4. Antioxidation

Experiments have shown that *Rubia cordifolia* polysaccharides have significant antioxidant and free radical scavenging effects. Wang *et al.* extracted QA2 and QC from *Rubia cordifolia* and found that QA2 had a strong free radical scavenging effect with a scavenging rate of 94.59%, and the scavenging rate of QC was 93.24% [24,25]. Therefore, *Rubia cordifolia* can repair and regenerate skin and mucous membranes by scavenging free radicals and reducing oxidative damage. This effect can be applied during the recovery period of LP.

4. Conclusion

LP is a T-cell-mediated chronic inflammatory skin disease of unknown cause, which may be associated with liver function impairment, and most TCM diagnosis is based on the treatment from the liver. *Rubia cordifolia*, which enters the liver meridian, can cool the blood, dispel blood stasis, activate blood circulation, and dredge channels, and has great potential for the treatment of LP with blood heat and blood stasis. Modern medicine has proved that *Rubia cordifolia* can regulate immune function, inhibit inflammatory response, improve liver function, and reduce oxidative damage. However, the specific mechanism of action of *Rubia cordifolia* in the treatment of LP, especially from the perspective of modern medicine, is still being explored and developed.

Disclosure statement

The authors declare no conflict of interest.

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