Research Progress on Pathogenesis and Treatment Targets of Chloasma Based on Network Pharmacology

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Abstract. In recent years, with the deepening research on biological networks, drug action targets and their relationships, it has been found that many chemical drugs with single chemical components and clear targets have multi-target microscopic action mechanisms from the perspective of biological regulatory networks. Therefore, the concept of network pharmacology has been put forward and has become one of the important methods for studying the action mechanisms of traditional Chinese medicine compounds. Neuro-endocrine-immune network (NEI) is an important system for the overall maintenance of the body's steady state. At present, the research on the mechanism of neuro-endocrine-immune network is also one of the frontier fields of modern medicine. Under the guidance of network pharmacology, this paper analyzes the pathogenesis of chloasma from the perspective of NEI by using modern medical technology, summarizes the channels and related targets for drug treatment of chloasma, provides new ideas for the treatment of chloasma, and also provides reference for exploring the significance and value of network pharmacology theory in the research of the mechanism of action of traditional Chinese medicine and drug targets.

Introduction

Chloasma is a common acquired hyperpigmentation skin disease, with light brown to dark brown patches, which are generally symmetrically distributed in the forehead, cheek, eye, mouth and other parts, with different sizes, shapes, no conscious symptoms, and will be deepened by sunlight [1]. It is more common in young and middle-aged women with darker skin color than in male patients. There are many factors affecting the occurrence of chloasma and its pathogenesis is complex. Its treatment is one of the difficult problems in dermatology. Neuro-endocrine-immune network, as a multi-dimensional and three-dimensional network regulation mechanism, is interconnected, coordinated and restricted to maintain the body's steady state and normal physiological functions [2]. The skin and the central nervous system (CNS) have the same neuroectoderm source. The skin is densely covered with complex nerves and expresses various hormones and their receptors. There is a complex interaction between skin, neuroendocrine and immune inflammation. There is sufficient theoretical basis for the treatment of skin diseases by using neuroendocrine-immune network. Now there are many related methods for the treatment of skin diseases. This article analyzes the application and effect of traditional Chinese medicine in the treatment of chloasma, discusses the pathogenesis of chloasma from the perspective of NEI regulation, provides ideas for the regulation and treatment of chloasma by traditional Chinese medicine, and provides theoretical basis for the diagnosis and treatment of skin diseases by network pharmacology.

Modern Pathogenesis

Ultraviolet Radiation

Ultraviolet rays or thermal stimulation in sunlight can cause oxidative damage to sulphhydryl (SH) in skin, increase tyrosinase activity in skin, and further activate melanocytes, thus accelerating their division and activity, increasing melanocytes per unit area, increasing secretion of melanosomes,
accelerating movement and diffusion, and causing skin pigmentation. The ultraviolet radiation in summer is strong, and it weakens in winter. Therefore, chloasma patients usually show a change from summer to winter. Liu Bangmin and others analyzed the pathogenic factors of 217 female chloasma patients. The results showed that 146 (67.28%) of the 217 patients had skin lesions or aggravation of skin lesions after solarization. 137 cases felt that the severity of color spots was related to seasons, 111 cases (81.02%) of which had aggravation in summer [3].

Endocrine Disorders

Endocrine imbalance is another important factor in the occurrence of female chloasma.

**Abnormal Thyroid Function.** Thyroid hormone can promote the synthesis of tyrosinase and melanosomes and reduce SH in epidermis, thus increasing melanin formation. Thyroxine and free thyroxine in female patients with chloasma are higher than those in normal group, which indicates that the occurrence of female chloasma may be related to thyroid dysfunction [4, 5].

**Hormone Abnormality.** Sex hormone may promote the onset of chloasma. Estrogen with a certain concentration can improve tyrosinase activity and promote melanin cell to synthesize pigment [6]. Gu Jinzhang compared 67 patients with chloasma and 47 healthy women. The levels of serum estradiol (E2), follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone (P) and other sex hormones in the two groups were detected. It was found that FSH, E2 and LH in patients with chloasma were significantly higher than those in healthy women [7, 8].

Imbalance of Skin Antioxidant System

Under normal circumstances, there are many oxygen free radical scavengers in the body, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (CSH-PX), glutathione (GSH), etc. Under the protection mechanism of gene regulation, the generation and elimination of free radicals in the body are in dynamic equilibrium. The early research results showed that the contents of lipid peroxide (LPO) and malondialdehyde (MDA) in the blood of chloasma patients increased significantly, and the SOD activity decreased significantly, suggesting that the balance between in vivo oxidation and oxidation resistance was broken, accelerating the oxidation reaction and excessive melanin formation, which is one of the important factors for the pathogenesis of chloasma [9-10]. Zhang Hui and others further confirmed that oxidative stress reaction has important clinical significance in the occurrence and development of chloasma by detecting the contents of GSH-PX, SOD, MDA and advanced oxidation protein products (AOPP) in serum of chloasma patients [11, 12].

Local Microecological Imbalance

The skin has the ability to maintain its own micro ecological stability, and the flora are antagonistic and interdependent. If the dynamic balance among the host's skin, environment and flora is broken, it will cause pathological damage to the skin. Some studies have found that the possibility of pigmentation in patients with acne and chloasma is significantly increased [13]. Bai Jie compared the facial flora of chloasma patients and normal people, and found that the number of live bacteria of propionibacterium acnes in the skin lesion area of chloasma patients was significantly lower than that of normal people, while the number of live bacteria of Micrococcus pigmentosus and Gram-negative bacteria was significantly higher than that of normal people, indicating that the onset of chloasma was related to the change of skin flora, that is, the disturbance of micro ecology [14].

Treatment Pathway and Target

The treatment of chloasma with traditional Chinese medicine has the characteristics of multi-component, multi-target and multi-pathway. the network pharmacology method is used to analyze the target in the treatment process of chloasma, and the network diagram of the target is obtained, as shown in Fig. 1. In view of the pathogenesis of chloasma, the treatment of chloasma is currently carried out from the angles of oxidation resistance, endocrine regulation, micro ecology.
improvement, etc. The combination of acupuncture auricular points scraping and other traditional Chinese medicine therapies with modern medical therapies has made remarkable progress in treating chloasma both internally and externally.

![Network Diagram of Chloasma Action Targets](image)

Figure 1. Network Diagram of Chloasma Action Targets.

The treatment of chloasma mostly reduces pigment production by inhibiting the action of enzymes related to pigment formation. Attenuate ultraviolet effect and reduce melanocyte activity; Removal of existing excess pigments, etc.

**Antioxidant Therapy with Oxidation Factor as Therapeutic Target**

The balance between in vivo oxidation and oxidation resistance is broken. Abnormal scavenging of oxygen free radicals leads to tissue aging and pigment formation, which is one of the important factors for the pathogenesis of chloasma. Therefore, maintaining the balance of in vivo free radicals and adjusting the oxidative stress state are one of the main approaches for the treatment of chloasma [15, 16]. Liang Wei and other studies found that the extracts of Chrysanthemum morifolium, Angelica sinensis and Salvia miltiorrhiza have ideal effects on inhibiting chloasma formation, which can effectively reduce tyrosinase (TYR) level, reduce MDA level, improve the body's antioxidant capacity and inhibit melanin formation [17]. Glutathione has the functions of activating redox system, activating sulfhydrylase, detoxifying, etc., can effectively eliminate free radicals, reduce pigmentation, achieve the purpose of treating chloasma, and has better effect when combined with vitamin C or traditional Chinese medicine [18].

**Endocrine Regulation Therapy with Hormones as Therapeutic Targets**

Modern medicine believes that the pathogenesis and mechanism of chloasma are complex, and endocrine disturbance is generally considered as the main cause of the disease. Therefore, the levels of hormones and related enzymes in vivo are often used as therapeutic targets [19]. There are many neuropeptides (SP, MSH) in the nervous system. Adverse mental factors may cause pigmentation by releasing related neuropeptides such as melatonin (MSH) from hypothalamus-pituitary system. Weng Lili explored the effect of Bushen Quban Decoction on substance P (SP), melatonin (MSH) and quality of life in serum of patients with chloasma. It was found that SP and MSH in serum of patients with chloasma were significantly lower than those before treatment. The mechanism of improving chloasma patients was related to the changes of SP and MSH content in serum [20, 21].

**Microecological Improvement Therapy with Flora as Therapeutic Target**

The study found that compared with healthy people, the number and isolation rate of propionibacterium acnes, pigment-producing micrococcus and gram-negative bacilli in chloasma lesions were significantly higher than those of healthy people, and with the increase of temperature and time, the number of viable bacteria increased and the pigment produced by them deepened significantly. Clinically, micro ecological therapy for adjusting skin bacteria groups is often used to promote the regression of chloasma. Skin immunity can regulate the growth of skin microbial flora,
keratinocytes recognize microorganisms on the skin surface, activate immune response, release antibacterial peptides, cytokines, chemokines, etc., and regulate the balance of skin microorganisms [22]. Needle rollers can directly stimulate the skin in a large area and improve the expression levels of skin cells interleukin 12, cluster of differentiation 80, major histocompatibility complex II and vimentin, thus improving the immune function of skin cells.

In addition, the dysfunction of skin barrier leads to amplification of external stimulation effect, and the skin micro inflammation produced at the same time will lead to pigmentation. Therefore, the reconstruction of skin barrier function is also a new target for chloasma treatment.

**Outlook**

At present, there is no single therapy with 100% satisfactory effect, so combination therapy is the trend of chloasma treatment. After the combination of drugs, the active ingredients of the drugs are more complex, and the corresponding target points are also increased, which brings difficulties to the research of the mechanism of action. At present, the pathogenesis of chloasma is unclear, and the related factors include endocrine factors, solarization, mental factors, free radicals, micro ecology, etc. In the nervous system, negative mental factors may cause pigmentation and endocrine disturbance by releasing related neuropeptides such as melatonin (MSH) from hypothalamus-pituitary system. Skin immunity can regulate the growth of skin microbial flora. When skin damage causes micro ecological imbalance, pigment-producing micrococcus multiply in large numbers, adhere to and colonize the epidermis, causing pigmentation on the epidermis. Chloasma can be treated by improving skin immunity and regulating flora.

There are many treatment methods for chloasma, mainly including western medicine treatment, traditional Chinese medicine treatment and integrated traditional Chinese and western medicine treatment. Modern medicine has made a thorough analysis of its pathogenic mechanism, but the breadth and depth of development are not enough. New representative drugs need to be found. With the help of network pharmacology theory and modern advanced technology, the mechanism of action and therapeutic targets are explored from the perspective of NEI. In addition, the development of optical technology has prompted the gradual development of new drugs and various laser therapies. With the development of genetic engineering technology, gene therapy is also trying to be applied to chloasma patients, bringing new hope to chloasma patients.

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**References**


