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The Mechanism and Clinical Application of Licorice in the Treatment of Recurrent Aphthous Ulcers

Chengrui Li

School of Stomatology, North China University of Science and Technology, Tangshan, China
lcrsincere@gmail.com

Abstract. Recurrent Aphthous Ulcer (RAU), a common type of oral mucosal disease, has a significant impact on the quality of the general public. It is urgently to explore safe and effective treatment strategies. By comprehensiving description of traditional Chinese medicine and modern research basis, the article summarizes the main pathogenesis of RAU, including immune imbalance, inflammatory reaction, oxidative stress and so on. As a traditional and widely used rug, Licorice has multiple roles including anti-inflammatory effects, immunomodulation, promoting mucosal repair, anti-bacterial and anti-viral effects. Based on the above, licorice and its compounds, such as Licorice Heart-Draining Decoction, can not only relieve pain effectively but also accelerate wound healing and reduce the recurrence rate. Also, licorice and its compounds have high safety of topical application. Therefore, licorice has its own unique advantages and broad prospects in the treatment of RAU. To promote the standardized and international application of licorice and its compounds, researchers should further improve the preparation form of licorice and conduct higher-quality clinical trials.

Keywords: Recurrent Aphthous Ulcer, Licorice, anti-inflammatory effects

1. Introduction

Recurrent Aphthous Ulcer (RAU), one of the common ulcerative lesions of oral mucosa, is also known as aphthous ulcer and oral chyme. With the characteristics of periodicity, recurrence and self-limitation, RAU has a high incidence rate and long course. RAU not only seriously affects the patients' eating, speech and quality of life, but also may increase the risk of mucosal malignant transformation after long-term repetition.

In the classics of traditional Chinese medicine, oral ulcer has long been recorded. According to the Inner Canon of Huangdi, "if the heart is hot, the mouth and tongue will become sore", the cause of the disease, pyroptosis was pointed out. The synopsis of the Golden Chamber mentions that "the fox bewilders and erodes in the mouth", and believes that the pathogenesis is related to damp heat and evil toxin. Based on the General Treatise on the Cause and Symptoms of Diseases, people with aphthous ulcer usually steam up their mouth due to the accumulation of heat in the spleen and stomach." According to the Standards of Diagnosis and Treatment, the theory of “deficiency fire and inflammation” is put forward [1]. Compendium of Materia Medica also contains the treatment of mouth erosion and throat ulceration. Based on the understanding of doctors in the past dynasties, the

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pathogenesis of oral ulcer is mostly attributed to the accumulation of heat in the heart and spleen, deficiency of fire and inflammation, and is closely related to the imbalance of Qi and blood, Yin and Yang [2]. Licorice, which has been recorded in herbal works, is known as the medicine of "national elders". Sheng Nong's herbal classic lists it as the top grade, saying that "it is the main evil Qi of cold and heat in the five zang organs, strengthening muscles and bones, and growing muscles." Compendium of Materia Medica says that it "replenishes spleen and Qi, relieves pain, clears heat and detoxifies, and reconciles various drugs", especially used to treat aphthous ulcer, throat ulcer and other diseases. Modern pharmacological studies revealed that Licorice contains Glycyrrhizin (GL), Glycyrrhetinic Acid (GA), Licochalcone A (Glabridin), Glycyrrhiza polysaccharide and other active ingredients, which have anti-inflammatory, immune regulatory, antioxidant, antibacterial and antiviral effects [3].

At present, western medicine treatment of RAU mainly relies on local hormones, antibacterial gargle and analgesics. Although western medicine treatment can relatively quickly relieve symptoms, it is difficult to cure the diseases, and the recurrence rate is high. Long-term application may also leads to oral flora imbalance, mucosal atrophy, secondary infection and so on. In contrast, traditional Chinese medicine pays attention to the overall regulation and multi-target effects, with few side effects and a low recurrence rate. Because of its effects of tonifying middle Qi, clearing heat and detoxification, relieving pain in a hurry, and harmonizing hundreds of drugs, Licorice shows unique advantages and broad application prospects in modern RAU treatment [4]. This article aims to systematically analyze the mechanism and clinical efficacy of licorice in the treatment of RAU and provide a theoretical basis for optimizing its application.

2. Pathogenesis of RAU

The pathogenesis of RAU is complex, involving the interaction of multiple internal and external factors. Immune imbalance is the core point. Patients often exhibit abnormal CD4+/CD8+ ratio, disturbed Th1/Th2/Th17 balance, and high expression of pro-inflammatory factors, such as TNF-α, IL-1β, IL-6, and IFN-γ, which ultimately leads to an exacerbated inflammatory response [5]. Oxidative stress is also an important mechanism. Local ROS accumulation causes lipid peroxidation, decreases the activities of antioxidant enzymes (SOD, GSH-Px), and increases the level of malondialdehyde (MDA), thus damaging the cellular structure of the oral mucosa and delaying the repair [6].

Moreover, the imbalance of oral flora (such as Streptococcus, Candida albicans hyperproliferation) and reactivation of herpesvirus also induces or aggravates RAU [7]. Meanwhile, genetic susceptibility, mental stress, local trauma, nutrient deficiency (vitamin B12, iron, zinc) and other factors can further aggravate the risk of disease. Behcet's disease, inflammatory bowel disease and other systemic diseases are also closely related to RAU. These complex pathological mechanisms provide a theoretical basis for the multi-target treatment of Licorice.

3. The mechanism of licorice in treating RAU

Licorice, a traditional Chinese Medicine, has multiple biological activities, which is widely used in the treatment of RAU. The therapeutic mechanism of licorice covers anti-inflammatory, immune regulation, antioxidant, antibacterial, antiviral and other aspects. The therapeutic effect of licorice mainly comes from its rich active ingredients, including Glycyrrhizin (GL), Glycyrrhetinic Acid (GA), Licochalcone A (Glabridin), Glycyrrhiza polysaccharide and other active ingredients. These components work together to treat RAU through multiple pathways.

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3.1. Anti-inflammatory mechanisms

Mechanism of licorice in anti-inflammatory effect is depends on the regulation of a broad range of important signal pathways. The main mechanisms are as follows: Inhibiting the activation of N-κB and MAPK signal pathway; Down-regulating the expression of the proinflammatory factor; Reducing the production of inflammatory mediators.

NF-κB is one of the most important inflammatory mediators in human body and it takes part in the process of many kinds of immune and inflammatory response. NF-KB pathway will be activated and this will result in the release of many pro-inflammatory cytokines, which will aggravate the response of the local tissue inflammation. It was demonstrated experimentally that GL is able to suppress the activation of NF-K B significantly and relieve an inflammatory reaction [3]. GL has the capability of inhibiting the translocation of the NF-kB in the cytoplasm to the nucleus and activates the levels of proinflammatory factor by blocking the phosphorylation of IkB kinase (IKK) and p65 [6]. Moreover, MAPK (mitogen-activated protein kinase) signal pathway is also a significant mediator of immune response and inflammatory response of RAU. The association of MAPK signal pathway will trigger numerous types of biological reactions in the cells such as the synthesis of inflammatory factors, the proliferation and differentiation of cells, et cetera. GL inhibited the phosphorylation of MAPK, thus, dropping away the inflammatory reaction of the local tissue [6]. Moreover, there are two types of enzymes, closely related to the process of inflammatory response, COX-2 (cyclooxygenase 2) and iNOS (inducible nitric oxide synthase) as well [6]. COX-2 and iNOS are generally highly expressed in immune mediated disease. The inflammatory response can be catalyzed by them via the synthesis of the prostaglandins (like PGE 2) and nitric oxide (NO). Licorice has a great potential to reduce the local pain and inflammatory response of RAU patients by down-regulating expression of COX-2 and iNOS, decreasing the synthesis of PGE2 and NO, and decreasing the synthesis and release of inflammatory mediators [4].

The proinflammatory cytokines like TNF-a, IL-1b, IL-6 etc will increase in the trend with the occurrence of RAU. These cytokines are also essential in the local tissue inflammatory response and over-production of pro-inflammatory cytokines will not only enhance the inflammatory response, but could also result in tissue damage. Licorice compound is one which can particularly prevent the production of these cytokines, and which provides a good effect in the treatment of the RAU symptoms [4]. Oxidative stress is another significant elicitor of RAU inflammatory response. The surplus formation of ROS (reactive oxygen species) will trigger the inflammatory process and stimulate the freeing of the inflammatory factors. Licorice is capable of scavenging the free radical and reducing the ROS buildup, and subsequently reducing the number of factors which cause inflammation. Such that, licorice has its indirect anti-inflammatory effect in improving the local redox and alleviate the inflammatory reaction in the ultra [5].

3.2. Immunomodulatory effect

Within the context of immune regulation, licorice can restore the immune homeostasis of RAU and rectify T cell subsets, increase the activity of Treg and mimic the action of corticosteroids. The Cd4 +/Cd8 + ratio has been reported to imbalance in the RAU patients and inappropriate activation of T cell subsets, CD4+ [1].

Licorice is able to increase the normal differentiation of the CD4+ T cell and suppress the overgrowth of the CD8+T cell. Licorice is also capable of reducing excessive stimulation of immune response and further regulates the immune balance of body. The common types of cells that are involved in the mechanism of induction and control of the immune response are Treg cells. Treg is

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able to sustain the balance of the immune system by suppressing the hyper immune response. Treg cell purposely becomes severe in the procedure of immune mediated diseases and causes the imbalance of immune response [3]. GL is viewed as the primary element which contributes to the improvement of the action of Treg cell. Licorice can enhance the function of Treg cell by promoting the differentiation of Treg cell and alleviating the activity of Th1 and Th17 cell [3]. In addition, Licorice can inhibit the activity of 11β-HSD2 to enhance the effect of corticosteroids in vivo, and inhibit the excessive immune effect, and further alleviate the inflammatory response caused by immune dysregulation [3].

3.3. Other mechanisms of action

Licorice has a certain antioxidant effect, which can scavenge free radical, decrease oxidative damage, increase the activities of the antioxidant ex- tremases, such as superoxide dismutase (SOD) and glutathione prexi- dolase (GSH-PX), and decrease the content of malondialdehyde (MDA), protect oral mucosa from damage [8]. In terms of repair, licorice can promote the expression of EGF and VEGF, accelerate the rapid pro- liferation of epithelial cells and the process of angiogenesis, and en- dure ulcer healing time [2]. Licorice can inhibit the ordinary oral pathogen and can generate certain inhibitory effect on herpes virus (HSV), sup- press the virus reactivation, and decrease the recurrence of RAU, the above multi-target effects are the pharmacological basis of licorice together in the treatment of RAU.

4. Clinical effect of licorice

In recent years, a large number of basic and clinical studies have confirmed the effectiveness and safety of licorice and its compounds in the treatment of recurrent aphthous ulcer (RAU). Animal experiments showed that licorice could significantly shorten the healing time of oral ulcers, improve mucosal repair and reduce tissue inflammatory response in the guinea pig model [9]. Foreign pharmacological experiments further found that licorice extract could promote complete epithelial regeneration, increase collagen synthesis and angiogenesis, and significantly reduce TNF-α levels in a rat traumatic ulcer model [8]. Clinical studies further verified the efficacy of licorice. Several randomized controlled trials showed that the topical application of licorice preparation could effectively relieve pain, reduce ulcer area and shorten healing time [8]. The application of a compound gargle containing licorice and diphenhydramine in RAU patients showed that compared with the simple control group, the ulcer area and pain of patients were significantly decreased [10].

Licorice Heart-Draining Decoction is widely used in RAU patients. Wangwenying et al. observed that the prescription can improve clinical symptoms, shorten the healing period and reduce the recurrence rate [11]. Liulianfang and other researchers pointed out that Licorice Heart-Draining Decoction gargle combined with G-CSF local application had faster healing speed and lower ulcer pain score than the single treatment group [12]. Wanghaijian and other clinical studies also showed that Licorice Heart-Draining Decoction Combined with chlorhexidine gargle can significantly improve the clinical symptoms of RAU patients with mixed cold and heat syndrome, significantly reduce the recurrence frequency, significantly increase the expression of EGF and VEGF in animal experiments, promote wound healing and reduce inflammation [2]. The exploration of new formulations also showed positive results. The licorice aqueous extract hydroxyethyl cellulose (HEC) hydrogel developed by Moussa et al., has good adhesion and slow-release characteristics [8]. The compound gingival coating of licorice showed inhibitory effect on Staphylococcus aureus, Streptococcus mutans and Candida albicans in vitro test, and had no obvious toxicity. The above

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researches illustrate that licorice has potential application prospects in the prevention and treatment of oral ulcers [13]. These studies provide strong evidence for the clinical transformation of licorice.

5. Discussion

Licorice has multi-target and multi-mechanism advantages in RAU treatment, which can significantly improve symptoms and reduce recurrence rate. Also, Licorice has good safety in tropical applications. However, not only does the taste and compliance of the licorice preparation still need to be improved, but the safety of systemic medication needs to be strictly controlled. Topical preparations of licorice are generally safe and have few side effects. Nevertheless, long-term or high-dose oral administration of Glycyrrhiza may cause pseudo-aldosterone-like side effects such as water and sodium retention, hypokalemia, hypertension, etc. Therefore, when using licorice preparations, the dosage and course of treatment should be strictly controlled. At the same time, although the multi-component and multi-target synergistic effect of licorice has been significant, the specific molecular network mechanism of licorice still needs further study. Ranging from tropical preparation and compound decoction to new preparation, Licorice preparations have shown great potential in multiple randomized controlled trials. While paying attention to safety, researchers should pursue a better curative effect. While reducing the pain of patients, researchers should pay more attention to overall regulation and improve the immune defence system of the body, thereby reducing the recurrence and malignant transformation risk of RAU.

6. Conclusion

With the development of molecular biology and modern pharmacology, the multi-target and multi-mechanism effects of licorice in the treatment of RAU have been proven by a large number of theories and practices. By inhibiting NF-κB and MAPK signaling pathways, reducing the production of inflammatory factors, regulating immune cell balance, scavenging free radicals and other pathways, Licorice and its active components achieve anti-inflammatory, immunomodulatory, antioxidant and repair-promoting effects. Meanwhile, Licorice and its active components improve the oral microenvironment, enhancing the immune defense system of the host, and reduce the recurrence rate of RAU. For its multi-component, multi-target and multi-mechanism treatment of RAU, Licorice provides a new research idea and clinical choice for the follow-up treatment of combined Traditional Chinese Medicine and Western medicine. The rich pharmacological activity and high safety of Licorice preparation make Licorice one of the core medicines for the treatment of RAU, providing a more efficient solution for the overall regulation and comprehensive treatment of oral mucosal lesions. To deserve to be mentioned, the international innovation in new preparations has provided new technologies and ideas for compound preparations, which promote further innovative research on drug stability and sustained release. Future research should deeply analyze the pharmacodynamic mechanism and signal pathway network of licorice ingredients, and develop new drug delivery systems to improve the efficacy and increase the acceptance of patients. At the same time, scientists should carry out high-quality clinical research and determine the optimal dosage and long-term efficacy of Licorice to promote the modernization and international application of licorice and its compound preparations. Starting with the ingredients of the compound preparation of licorice, researchers can also search for more significant synergistic effects of traditional Chinese medicine ingredients, or combined drugs, and the combined application of traditional Chinese medicine compounds.

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