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Research Progress on the Therapeutic Efficacy of Astragalus and Coptis Combined Therapy for Non-alcoholic Fatty Liver Disease from the Perspective of Immune-inflammation Mechanisms

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Abstract

The pathogenesis of non-alcoholic fatty liver disease is linked to immune-mediated inflammation; therefore, the joint treatment of Astragalus and Coptis shows promising therapeutic value in affecting this pathological process. In this study, we comprehensively investigate the significant role of immune inflammation in the occurrence and development of the disease, analyse the features of the Astragalus-Coptis drug combination in modulating the immune-inflammatory network, and concentrate on reviewing the possible mechanisms by which this herbal formula can control immune inflammation to prevent or treat the disease. It has been found that the Astragalus-Coptis combination can alleviate hepatic inflammatory responses via several pathways: blocking the function of the TLR4/NF-κB signalling pathway, regulating the formation and secretion of NLRP3 inflammasome and decreasing the amount of endotoxin translocation in the enterohepatic circulation. This drug combination, using a method which combines both cold- and warm-working pharmacological effects together with comprehensive regulation of qi and blood, possesses special advantages in dealing with the complicated pathophysiology of this disorder. These results offer important theoretical guidance for deeper understanding of the molecular pharmacological mechanisms behind this therapeutic method and for its reasonable clinical application.

Keywords

Immune-inflammation, Astragalus-Coptis herbal formulation, Non-alcoholic fatty liver disease

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) has become one of the main types of chronic liver disease; during its development, continuous immune-inflammatory activation is thought to be the principal factor causing the worsening of the disease. In recent years, the research on the application of the Astragalus-Coptis medicinal combination, which is usually used in the therapeutic process of liver diseases accompanied by metabolic disorders, has made notable progress in the prevention and treatment of NAFLD, especially regarding its immunomodulating and anti-inflammatory effects. The present paper intends to give an overall view from three aspects, i.e., the significance of immune inflammation, the features of the medicinal formula, and its possible working principles, for future reference.

2. The Significance of Immune-inflammation in the Pathogenesis and Progression of Non-alcoholic Fatty Liver Disease

2.1 Hepatic Lipotoxicity-induced Initiation of Inflammation

The excessive lipid accumulation in the liver causes a strong stimulation of inflammatory responses. Firstly, when the free fatty acids and their related metabolites are improperly stored in hepatocytes, there occurs a stress reaction in the endoplasmic reticulum and a malfunction of the mitochondrial oxidative phosphorylation subsequently, which results in a substantial increase in the generation of reactive oxygen species [1,2]. These signaling processes, originating from the unbalanced redox conditions, are transferred through the stress kinase pathway to the nuclear transcription factors, finally activating the gene expression for the proinflammatory cytokines. At the same time, the lipid toxic metabolites can also directly influence both the hepatocyte and organelle membranes, changing the membrane permeability and causing the release of damage associated molecular patterns [3]. After leaving the hepatocytes, these substances are recognized by the pattern recognition receptors on the surfaces of adjacent Kupffer cells and dendritic cells, thus initiating an intrinsic defensive inflammatory response. Consequently, the stress generated by the simple lipid overload is gradually transformed into an inflammatory microenvironment with the involvement of various immune cells, providing the basic condition for the development of the disease towards necrotic inflammation and fibrosis.

2.2 Kupffer Cell Polarization-mediated Inflammatory Amplification

Kupffer cells are a part of the intrinsic macrophage population in the liver and their functions are greatly influenced by the high lipid levels [4]. When the resting Kupffer cells have their surface Toll-like receptors and clearance receptors blocked by a lot of free fatty acids or injury-causing substances, they take up debris and maintain the tissue's tolerance; at the same time, the intracellular signal transduction pathways induce a change in the transcriptional programs, leading to the transformation of the cells into a typical pro-inflammatory activated state [5]. Polarized Kupffer cells secrete a variety of chemokines and adhesion molecules extensively; these secreted substances not only enhance their own ability to attract inflammatory monocytes but also promote the entrance of monocytes derived from bone marrow into the liver and their differentiation into inflammatory macrophages, thus increasing the local number of

immune effector cells. Furthermore, the upregulation of co-stimulatory molecules and the increased expression of major histocompatibility complex on Kupffer cells remarkably improve their antigen-presenting ability to T lymphocytes, which connects the innate and adaptive immunity [6-7]. The collaborative effect of these multiple mechanisms strengthens the initial short-term and limited inflammatory reaction, causing a continuous rise of inflammatory mediators in the liver tissue and worsening the paracrine damage to the adjacent hepatocytes, and eventually forming an inflammatory amplification loop based on Kupffer cells.

3. The Characteristics of the Astragalus-Coptis Medicinal Pair in Modulating the Immune-inflammatory Network

3.1 The Combination of Cold and Warm Therapies is Consistent with the Complicated Pathogenesis of Liver Diseases

The mechanisms of non-alcoholic fatty liver disease (NAFLD) include fat accumulation, oxidative stress, inflammatory responses and hepatic fibrosis; its special point is the qi deficiency and internal blockage due to pathological influences. Astragalus, a sweet and warm drug, can enter the Spleen and Lung channels and has the properties of replenishing qi and raising yang, thus promoting body metabolism and substance transformation. It also regulates the condition of spleen qi deficiency which is often seen in this disease. Coptis, a bitter and cold drug, can enter the Heart, Liver and Large Intestine channels; its function of clearing heat and drying dampness can expel the damp-heat turbid pathological factors produced by liver lipid toxicity and has an inhibitory effect on the inflammatory microenvironment at the beginning of the disease. The characteristics of these two drugs, one warm and the other cold, and their different actions, one ascending and the other descending, constitute a bidirectional regulatory system. If used separately, Astragalus is not sufficient to warm and tonify, which may lead to the retention of damp-heat; if used separately, Coptis may have too much clearing and purging effect, which might impair the spleen and stomach qi. However, when used together, the warm drug is controlled by the cold drug without increasing the heat, while the cold drug is moderated by the warm drug without harming yang, therefore a balanced treatment is achieved which supports the vital qi and eliminates the pathogenic factors. This combined use not only meets the need of tonifying the body in the qi deficiency stage of the disease but also satisfies the requirement of eliminating dampness, heat, turbidity and stagnation at the level of excess. Thus, this therapeutic method is suitable to the complex pathophysiological structure of the disease and provides a reasonable theoretical basis for the subsequent pharmacodynamic explanation based on immune-inflammatory regulatory pathways.

3.2 Simultaneous Regulation of Qi and Blood to Maintain Immune-metabolic Homeostasis

The progression of non-alcoholic fatty liver disease is closely related to the disturbance of energy metabolism and the abnormality of immune responses; from the viewpoint of Traditional Chinese Medicine (TCM), the state of Middle Qi and Blood matches exactly with the two main systems in the body, i.e., the material metabolism system and the immune regulation system. The efficacy of Astragalus

root mainly enhances the transformation and transportation functions of the zang-fu organs and promotes the diffusion of refined substances; its therapeutic effect acts on the energy production and lipid utilization stages of metabolic processes. On the other hand, the function of Coptis root to eliminate damp-heat from the blood system concentrates on removing the excess inflammatory mediators and metabolic waste products in the circulatory system; its therapeutic result acts on the release of excessive effector molecules and the abnormally activated cell populations during the immune response [8]. These two parts work together: strong Qi promotes smooth blood circulation and substance transformation, while blood ensures that the ascending, descending, entering and exiting movements of Qi are not hindered by pathogenic factors, thus forming a reinforcing relationship where Qi governs blood and blood supports Qi [9]. Under pathological circumstances, this co-regulation mechanism appears at two levels, namely, the activity of key enzymes in metabolic pathways and the main transcription factors involved in immune signalling, to achieve the balance between the rates of lipid synthesis and degradation; furthermore, it guarantees the appropriate ratio of the production of inflammatory cytokines and the expression of anti-inflammatory mediators. This synergistic regulation of Qi and blood prevents either the unilateral adjustment of metabolism at the cost of immune function, which may cause recurrent inflammation, or the emphasis on controlling inflammation without considering the underlying metabolic causes, thus only treating the symptoms rather than curing the root of the disease. Therefore, this method achieves coordination and stability at the whole systemic level between the metabolic microenvironment and the immune response state.

3.3 Active Ingredient-targeted, Multi-pathway Synergistic Effect

The influences of Astragalus membranaceus and Coptis chinensis on the immune-inflammatory regulation pathway are different, leading to a combined effect via multiple pathways [10-11]. The polysaccharides, astragaloside and isodaphnotriene from Astragalus membranaceus mainly regulate the differentiation of macrophages, reduce endoplasmic reticulum stress and inhibit the activation of nuclear transcription factors; whereas the alkaloids like berberine, pharmacogenin and coptisine from Coptis chinensis affect the respiratory chain activity of mitochondria, decrease the production of nitric oxide and suppress the expression of pro-inflammatory cytokines. When these two substances exist together in the body, they bind to different receptor proteins or enzyme molecules respectively and exert their regulatory action on several aspects including transmembrane signal transduction, cytoplasmic kinase cascades and nuclear gene transcription [12-14]. During this procedure, the components of Astragalus membranaceus can improve the energy sensing and redox balance in the related metabolic signal pathways, while those from Coptis chinensis concentrate on blocking the inflammatory signal transduction after the recognition of immune receptors. These two herbs do not act on the same location but offer complementary spatial and temporal coverage, enabling the simultaneous inhibition of some important nodes in the inflammatory network which cannot be regulated by a single pathway alone, thereby enhancing the overall regulatory efficiency. This multiple-target synergistic characteristic is an important difference between the Astragalus-Coptis herb mixture and single-herb preparations.

4. The Astragalus-Coptis Medicinal Pair: The Mechanism by which it Regulates Immune-inflammatory Responses for the Prevention and Treatment of This Disease

4.1 Inhibition of TLR4/NF-κB Signaling Pathway Activity

The TLR4/NF-κB signaling pathway is crucial in transmitting information from metabolic stimulation to inflammatory responses. In non-alcoholic fatty liver disease, the high level of free fatty acids in the blood and the release of damage-associated molecular patterns (DAMPs) into hepatocytes can be recognized as endogenous ligands which bind to TLR4 receptors on the hepatic parenchymal cells and immune cells. After the receptors are activated, two signal transduction pathways - MyD88-dependent and MyD88-independent are successively initiated, leading to the activation of the IκB kinase complex and the phosphorylation and degradation of the NF-κB inhibitor protein. As a result, the NF-κB dimers are rapidly transported into the nucleus where they activate the transcription of many pro-inflammatory cytokine and chemokine genes. This continuous activation of the pathway plays an important role in maintaining the long-term local hepatic inflammatory responses. Some active components in the herbal formula containing *Astragalus membranaceus* and *Coptis chinensis* can regulate the signaling pathway at different levels. On one hand, some components can compete with the binding sites of TLR4 receptors and thus decrease the binding capacity of the endogenous ligands to their receptors, weakening the upstream signal transmission [15]. On the other hand, other components inhibit the recruitment of MyD88 or interfere with the phosphorylation process of its downstream kinases, preventing the efficient nuclear transport of signals. Additionally, these pharmacological agents can also slow down the degradation rate of IκB proteins, keeping the NF-κB in the cytoplasm in the inactive state for a longer time and reducing the frequency of its nuclear transport. A decrease in the nuclear NF-κB content will affect the transcriptional activity of pro-inflammatory genes, resulting in a corresponding decrease in the production of effect molecules like tumor necrosis factor-α and interleukin-6. By using this multi-layered blocking strategy, the amplification of inflammatory signals through the pathway is effectively controlled, the persistent inflammatory condition in the liver tissue is relieved and the tendency towards necrotizing inflammation is correspondingly reduced.

4.2 Regulation of NLRP3 Inflammasome Assembly and Secretion

The NLRP3 inflammasome is a protein complex consisting of several proteins; its orderly combination and the release of proinflammatory factors are very important during the inflammatory enhancement phase of non-alcoholic fatty liver disease (NAFLD). The combination process includes two stages: initiation and activation. The activation stage is mainly influenced by different metabolic stimulants such as elevated intracellular reactive oxygen species (ROS) levels, damage to the lysosomal membrane, decrease of cytoplasmic potassium ion content and so forth. These stimulants cause conformational changes and self-oligomerization of NLRP3 receptor proteins, which subsequently, through homotypic associations, bring about apoptosis-related speckled proteins. These proteins link up to form filaments and finally attract the precursors of caspase-1, thus completing the combination process [16-17]. After the combination, the inflammasome mediates the self-processing of caspase-1 producing the active caspase-

1 which immediately cleaves the inactive precursors of interleukin-1β (IL-1β) and interleukin-18 (IL-18) transforming them into their mature forms and secreting them outside the cell. In the situation of liver lipid overload, these combination and secretion processes are significantly intensified, becoming a main factor in the persistent liver inflammation. The active parts of the herbal formula made from Astragalus and Coptis have regulatory effects on multiple points in the inflammasome combination pathway. Some components act on the upstream of the activated signal transduction pathway and inhibit the oxidative stimulation of NLRP3 by decreasing the production of ROS through blocking the abnormal translocation of mitochondrial electron transfer chain. Another component stabilizes the lysosomal membrane structure, reduces the release of cathepsins into the cytoplasm and prevents the non-specific activation of the inflammasome. Some active substances located near the core of the complex can directly disturb the binding site between NLRP3 and apoptosis-related speckles and reduce the aggregation efficiency, thereby decreasing the activation level of caspase-1. The reduction in the activated caspase-1 level is directly reflected in the decrease of mature interleukin-1β and interleukin-18 production; consequently, the secretion of these effectors molecules outside the cell is also decreased.

4.3 Improvement of Endotoxin Translocation Levels in the Enterohepatic Circulation

Intestinal endotoxins enter the liver through the portal venous system and play an important role as an exogenous driving force in the sustained hepatic inflammation that occurs in non-alcoholic fatty liver disease. Normally, the tight junction structure of the intestinal epithelial barrier and the mucus layer on its surface can prevent the penetration of endotoxins released by Gram-negative bacteria in the intestinal cavity into the submucosal tissues. However, under physiological conditions, metabolic harmful factors such as a high-fat diet may change the composition of the gut microbiota and weaken the function of the intestinal epithelial barrier, resulting in a large amount of endotoxins passing through the intestinal mucosa into the mesenteric lymphatic circulation and portal venous blood flow. These endotoxins are then recognized by Kupffer cells and the TLR4 receptors on the surface of hepatocytes in the hepatic sinusoids, initiating downstream inflammatory signaling pathways and promoting the production of pro-inflammatory cytokines in the liver. The herbal combination of Astragalus and Coptis has a multifunctional inhibitory effect on the above mentioned endotoxin translocation process in the enterohepatic circulation. On the one hand, the bioactive alkaloid parts of Coptis can adjust the composition of the gut microbiota and decrease the relative abundance of endotoxin-producing bacterial strains, thus reducing the overall endotoxin level in the intestinal cavity [18]. On the other hand, the active polysaccharides and saponins in Astragalus affect the expression and distribution of tight junction proteins in intestinal epithelial cells, improving the physical integrity of the intestinal mucus barrier and decreasing the flux of endotoxins through the paracellular pathway across the epithelium. Therefore, this herbal combination can also target the existing endotoxins in the portal venous blood; some components of these endotoxins, after binding directly to the lipid A moiety, decrease their binding capacity to the surface receptors on hepatic sinusoidal immune cells. After the above multiple level inhibition and blockage, the total amount of endotoxins needed to activate sinusoidal and inflammatory signaling

pathways is reduced and the intensity of the endotoxin-induced intrahepatic inflammatory response is correspondingly weakened.

5. Summary

The Astragalus-Coptis medicinal mixture shows a clearer pharmacological basis for its effect on the prevention and treatment of non-alcoholic fatty liver disease (NAFLD) by regulating the multi-targeted intervention in the immune-inflammatory network. The regulatory mechanisms include the signaling pathways of innate immune recognition receptors, the formation of intracellular inflammatory complexes and the adjustment of gut-derived inflammatory factors, thus forming a comprehensive intervention system which ranges from the source blocking to the process suppressing. Present research mainly concentrates on cellular and animal experiments; however, the combined action of its different active ingredients and their real therapeutic effects in human beings still need to be further studied. In the future, detailed pharmacodynamic verification and integrative multi-omics analyses using clinical specimens should be given priority to promote the translation of these drug mixtures.

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