Research Progress of Cholestatic Liver Disease-Related Pruritus in Chinese Medicine and Western Medicine

Wenzhang Dai[1] Hong Nie[1]

[1] State Key Laboratory of Bioactive Molecules and Druggability Assessment, Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, International Cooperative Laboratory of Traditional Chinese Medicine Modernization and Innovative Drug Development of Chinese Ministry of Education (MOE), College of Pharmacy, Jinan University, Guangzhou, Guangdong, China

Address for correspondence Hong Nie, PhD, College of Pharmacy, Jinan University, 601 Huangpu Avenue West, Guangzhou 510632, China Hong (e-mail: hongnie1970@163.com).

CMNP 2024;4:e43–e48.

Abstract

Pruritus is common in cholestatic liver disease, with a high clinical incidence rate and complex pathogenesis. Accumulation of potential pruritus inducers such as steroids, bile acids, and lysophosphatidic acid in the systemic circulation is the main cause of pruritus in cholestatic liver disease. Currently, clinical treatment of cholestatic liver disease-related pruritus mainly includes medication, intervention therapy, and some experimental methods. However, there are still problems, such as unclear pathological mechanisms and unsatisfactory treatment responses in some patients with cholestatic liver disease-related pruritus. Effective treatment for patients still faces challenges. By extensively screening patients' plasma (and/or bile) samples through clinical trials, potential pruritus inducers can be identified comprehensively, which can provide a deeper understanding of the itch signaling pathways in cholestatic liver disease and a basis for the development of treatment strategies. Traditional Chinese medicine (TCM) has shown certain characteristics and advantages in clinical treatment. Based on the etiology and pathogenesis, external application, internal administration, and TCM-specific therapies have achieved good clinical efficacy. Similarly, the combination of Chinese medicine and Western medicine has also achieved more effective treatment for patients with cholestatic liver disease-related pruritus. This article will introduce the latest progress in the study of pruritus inducers in cholestatic liver disease and its treatment in TCM and Western medicine.

Keywords
- cholestasis
- pruritus
- Chinese medicine
- Western medicine
- research progress

Cholestatic liver disease refers to a series of liver and biliary system diseases caused by various factors leading to the obstruction of bile generation, secretion, and excretion. Pruritus is one of the most common symptoms in patients with cholestatic liver disease, with over 80% of cholestatic patients experiencing pruritus, especially in patients with primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), intrahepatic cholestasis of pregnancy (ICP).[1–3] Compared with pruritus caused by other diseases, pruritus in cholestatic liver disease often persists long term and is difficult to relieve. In severe cases, it can lead to insomnia and even suicide.[1] However, due to the complex and

received
February 2, 2024
accepted after revision
March 22, 2024

DOI https://doi.org/10.1055/s-0044-1787705.
ISSN 2096-918X.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

incompletely understood pathogenesis of pruritus in cholestatic liver disease, the pruritus inducers are diverse, and there are still challenges in effective treatments. According to traditional Chinese medicine (TCM), the liver governs dredging and regulating. Cholestasis is a common pathological manifestation of liver and bile dysfunction in dredging and regulating, with dampness, heat, stasis, and toxicity as the main pathological mechanism. It is mostly caused by damp heat and epidemic toxins transforming into excessive fire, and the accumulation of heat and toxins.[4,5] From the perspective of conveyance and dispersion, patients with cholestasis have dysfunction in conveyance and dispersion, and dampness, heat, fire, and toxins cannot be relieved, which can overflow onto the skin and easily lead to symptoms such as jaundice and skin itching.[4] TCM has a long history of treating pruritus, with numerous therapies and medications for relieving itch. This article provides an overview of the pruritus inducers and the progress in the treatment of cholestatic liver disease-related pruritus in TCM and Western medicine.

Cholestatic Liver Disease-Related Pruritus and Pruritus Inducers

Currently, majority of the studies suggest that the factors causing cholestatic liver disease-related pruritus may be bile acids and lysophosphatidic acid (LPA) formed in the liver or intestines. These inducers accumulate in the systemic circulation and stimulate the skin, transmitting itch signals through combining with the receptors in the dorsal root ganglion (DRG) or trigeminal ganglion. These signals then reach the central nervous system, leading to the perception of itching.[6,7] The specific pruritus inducers related to cholestatic liver disease-related pruritus are expounded as follows.

Steroids and Steroid Metabolites

Clinical research has found that during the pruritic episodes of cholestatic liver disease, levels of certain hormone metabolites in the plasma of patients with ICP significantly increase. Some of these metabolites, such as progesterone sulfate, can modulate bile acid receptor Takeda G protein-coupled receptor 5 (TGR5) and induce scratching behavior in wild mice, suggesting that certain concentrations of progesterone metabolites can trigger pruritus.[8–10] Numerous studies, including clinical trials, have also confirmed the involvement of estrogen in the regulation of pruritus, although the specific mechanism is not yet clear.[11,12] It has been observed that estrogen can reduce nociception by modulating intracellular calcium ion concentration in DRG neurons. In acute and chronic pruritus models, high estrogen levels may play a role in inhibiting itch signal transmission by regulating Mas-related G protein-coupled receptors.[13,14]

Cytokines

During normal pregnancy, the levels of type 1 cytokines decrease, while type 2 cytokines increase to protect the fetus.[15,16] However, in ICP, patients undergo a shift from Th0 cells to Th1 cells, resulting in the proliferation and secretion of cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) and leading to increased inflammatory reactions.[17,18] Since inflammation is closely associated with pruritus and plays a significant role in the pathogenesis of inflammatory skin diseases involving pruritus, it is likely that cytokines participate as pruritus inducers in the occurrence of ICP and other cholestatic liver diseases with pruritus.[19]

Bile Acid and Bile Salt

Bile acid is the marker of cholestasis and plays a critical role in various cholestatic liver diseases. It is closely related to the occurrence of pruritus. For years, bile acid and bile salt have been considered as one of the inducers in cholestatic pruritus. In clinical observations, the elevated level of bile acid is found during cholestasis and can further activate a series of receptors, including TGR5 and farnesoid X receptor, which are all associated with pruritus.[20–22] Alemi et al[23] found that TGR5 is expressed in neurons of the DRG in mice and overlaps with the expression of transient receptor potential cation channel subfamily V member 1 (TRPV1) and gastrin-releasing peptide. Mice with high expression of TGR5 show increased scratching activity, suggesting its involvement in itch signal transmission. However, Yu et al[20] questioned this finding in 2019. They injected a TGR5-specific agonist into the forearms of human subjects, but it did not cause itching. They also found that hTGR5 is selectively expressed in satellite glial cells and not expressed in hDRG neurons. Additionally, pruritus usually occurs in the initial stage of cholestasis, and the itching symptom often disappears when bile acid and salt concentrations reach the highest levels, indicating that bile acid does not appear to play a crucial role in cholestatic pruritus.[24]

Lysophosphatidic Acid

Lysophosphatidic Acid (LPA) is an important active compound found in the serum of patients with cholestatic liver disease-related pruritus. The levels of LPA in the serum of these patients are higher compared with normal individuals, which may be related to significantly increased autotaxin (ATX) activity.[24,25] ATX can hydrolyze the precursor molecule lysophosphatidylcholine (LPC) to form LPA.[26] Macias' research also confirmed this finding, showing a correlation between elevated levels of ATX and LPA in the serum of patients with cholestatic pruritus. Moreover, Kittaka et al[27] discovered that LPA can bind to LPAR5, activate TRPV1 within cells, and induce pruritus. This confirms the pruritic effect of LPA and suggests that LPA may be an important itch inducer in cholestatic liver disease-related pruritus.

Endogenous Opioids

The endogenous opioid system plays an important role in central neurogenic pruritus. Düll and Kremer[28] found that in both animal experiments and clinical studies, the use of morphine and other opioid receptor agonists or antagonists can reduce scratching behavior in animals and improve itching symptoms in patients and the use of some opioid receptor antagonists can prevent pruritus. In addition, the

use of opioid receptor antagonists such as naloxone and naltrexone can not only relieve pruritus in patients with cholestasis but also induce opioid withdrawal-like reactions in patients with cholestasis.[29] These studies suggest that endogenous opioids may be one of the important causes of cholestatic liver disease-related pruritus such as PBC/PSC. More clinical and basic research studies are needed to confirm the role of the endogenous opioid system in patients with cholestatic liver disease-related pruritus.

Gut Microbiota

Multiple studies have found that the gut microbiota plays an important role in the pathogenesis of PBC and PSC by regulating metabolism and immune response.[30] A recent study linked the gut microbiota to secondary pruritus of PBC, showing that pruritus score decreased in PBC patients after treatment with an apical sodium-dependent bile acid transporter (ASBT) inhibitor (GSK2330672), indicating a certain correlation between gut microbiota and cholestatic liver disease-related pruritus. By comparing the gut microbiota of PBC pruritus patients with asymptomatic PBC patients and healthy volunteers, no significant difference was found, suggesting that although there is a certain connection between gut microbiota and cholestatic liver disease-related pruritus, it does not play a major role.[31]

Lysophosphatidylcholine

A recent study found that a high concentration of LPC in the skin may cause pruritus. Subcutaneous injection of LPC in wild-type mice can activate the TRPV4 receptor in mice and induce frequent scratching behavior.[25] Chen et al[32] further linked LPC-mediated activation of keratinocytes with the secretion of miR-146a and found that this microRNA can activate TRPV1, which is closely involved in itching signal transduction. However, there is currently no direct evidence to indicate the role of LPC in cholestatic liver disease-related pruritus. Some researchers have also studied the relationship between LPC and cholestatic liver disease-related pruritus in patients in clinical experiments. By comparing the levels of LPC with 13 different acyl chain types in PBC patients with and without pruritus, they found a relatively small difference between the two groups. Therefore, the role of LPC in causing cholestatic liver disease-related pruritus remains to be determined.[25]

Progressive Treatment of Cholestatic Liver Disease-Related Pruritus

Western Medicine Treatment for Cholestatic Liver Disease-Related Pruritus

Medication Treatment

In terms of medication treatment, anion exchange resins such as cholestyramine and its analogs are currently considered the first-line drugs for treating cholestatic liver disease-related pruritus.[33] Cholestyramine, as a bile acid sequestrant, can improve the enterohepatic circulation of bile acid in patients with cholestasis, reduce pruritus by decreasing the levels of pruritus inducers, and achieve the goal of treating pruritus. However, some patients may develop tolerance to cholestyramine, resulting in a lack of therapeutic effects.[1] Moreover, cholestyramine can cause gastrointestinal adverse reactions such as abdominal distension and discomfort.

Ursodeoxycholic acid (UDCA) is widely regarded as a first-line treatment for ICP and its secondary pruritus. Studies have found that UDCA, as an effective hepatobiliary secretagogue, can significantly increase hepatobiliary secretion ability by stimulating damaged transport proteins and channels in cholestatic conditions, thus improving liver function indicators and alleviating pruritus symptoms.[34] According to a meta-analysis, UDCA has varying degrees of improvement in pruritus associated with ICP and does not exhibit toxic reactions even at high doses of 20 $mg \cdot kg^{-1}$ during pregnancy.[35] However, the effectiveness of UDCA in improving pruritus in patients with PBC and PSC is not evident.

Another new first-line antipruritic drug is the PPAR agonist bezafibrate. Bezafibrate is a broad-spectrum PPAR agonist with anticholestatic, anti-inflammatory, and antifibrotic effects. It can relieve pruritus by reducing cholestasis, improving bile duct inflammation and injury, and reducing the formation and secretion of pruritus inducers.[36] Bezafibrate was registered in 2015 for the treatment of moderate-to-severe pruritus in patients with PBC, PSC, and secondary sclerosing cholangitis, and the results of the FITCH trial clearly showed its short-term improvement in moderate-to-severe pruritus in PBC and PSC patients.[37] This indicates that bezafibrate can be used as a first-line treatment for moderate-to-severe pruritus in PBC and PSC patients, but long-term efficacy trials are still needed.

Lifitegrast, a pregnane X receptor (PXR) agonist, is a second-line drug for cholestatic liver disease-related pruritus. Lifitegrast may reduce the expression of ATX via PXR-mediated pathways, thereby alleviating pruritus by reducing the metabolism of potential pruritus inducers. Additionally, as an antibiotic, lifitegrast can also regulate the microbiota in the intestine and skin.[28] From a clinical perspective, lifitegrast is well-tolerated and is effective and safe for treating cholestatic liver disease-related pruritus, and it allows long-term use.[38]

In Phase III clinical trial for pruritus in patients with chronic liver disease, the selective κ-opioid receptor agonist nalbuphine showed a certain antipruritic effect.[39] However, due to limited efficacy, further research is needed regarding the effects of nalbuphine and another κ-opioid receptor agonist, butorphanol in the treatment of cholestatic liver disease-related pruritus.[40] *The 2022 EASL Clinical Practice Guidelines for Primary Sclerosing Cholangitis* strongly recommend the use of bezafibrate or lifitegrast for the treatment of moderate-to-severe pruritus in patients with PSC,[3] while there is limited evidence supporting the use of anion exchange resins, naltrexone, other opioid antagonists, and sertraline for the treatment of pruritus in PSC.

Other Treatment Methods

For patients who do not respond to the above-mentioned medication treatments, clinical trial treatments such as ASBT inhibitor, ultraviolet radiation B (UVB) phototherapy, and plasma exchange can be considered. ASBT is a sodium-

dependent bile acid transporter protein, and the ASBT inhibitor can promote the excretion of bile salt in feces, thereby reducing the bile acid level in the enterohepatic circulation.[41] Plasma exchange is an effective treatment method, and it has been found in clinical experiments that patients with ICP or other cholestatic liver diseases who are unresponsive to medication treatment experience a reduction in the bile acid level and improvement in itching symptoms after plasma exchange treatment.[42] In addition, UVB phototherapy is a good method for treating pruritus associated with PBC, and it has good tolerance.[43] However, the clinical trial about the safety of UVB phototherapy is yet to be explored. For patients with refractory pruritus who do not respond to various treatment methods, nasobiliary drainage is also an appropriate treatment option that can delay the need for liver transplantation. When cholestatic liver disease-related pruritus progresses to the point of severely affecting a patient's quality of life, liver transplantation can be performed as a last-resort treatment. However, this surgical procedure carries a high risk and can lead to immune suppression-related adverse reactions.

Traditional Chinese Medicine Treatment for Cholestatic Liver Disease-Related Pruritus

TCM treatment for cholestatic liver disease-related pruritus focuses on syndrome differentiation and treatment. It deeply explores the etiology and pathogenesis of the disease to develop targeted treatment plans. Therefore, there are different approaches to treating cholestatic liver disease-related pruritus using TCM.

Internal Treatment

In clinical research on TCM treatment for cholestatic liver disease-related pruritus, oral medication is a common treatment method. Yang[44] used a self-formulated prescription based on the principle of syndrome differentiation and treatment to treat patients with acute jaundice hepatitis. It was found that TCM treatment can effectively alleviate clinical symptoms and improve liver function indicators. Wu et al[45] believed that the pathogenesis of jaundice-related pruritus is due to wind invasion of the liver, liver dysfunction in dispersing and regulating, wind and damp-heat pathogenic factors obstructing the bile collaterals and causing jaundice-related pruritus. In clinical treatment, the Qufeng Zhiyang decoction functions to expel wind and eliminate dampness and nourish the liver and blood. In addition, there are numerous TCM clinical studies on different syndromes of cholestatic liver disease-related pruritus. For example, the Yigan Zhiyang decoction is used to treat hepatobiliary-derived pruritus due to wind generation due to liver deficiency, and the Qushi Zhiyang formula is used to treat jaundice-related pruritus.[46,47] During treatment, medication adjustments should be made based on the patient's symptoms, signs, and syndrome differentiation, and appropriate combinations of herbs can alleviate itching. For example, Kushen (Sophorae Flavescentis Radix), Baixianpi (Dictamni Cortex), Difuzi (Kochiae Fructus) can be combined to dispel damp-heat in cases of a predominance of liver and gallbladder damp-heat. For deficiency syndrome due to yin blood and body fluid deficiency, Shengdihuang (Rehmanniae Radix), Danggui (Angelicae Sinensis Radix), and Xuanshen (Scrophulariae Radix) can be added.

External Treatment

Pruritus is common in dermatology, and topical medication is a primary treatment method. Among various treatment protocols and clinical studies for cholestatic liver disease-related pruritus, the most common methods include the topical application of Chinese herbal ointments, local fumigation, and cold compresses. Clinical research has found that the topical application of Huangqin ointment, a Chinese herbal medicine, can effectively alleviate cholestatic liver disease-related pruritus symptoms and improve patients' quality of life.[48] In addition to topical herbal preparations, there is also the method of fumigation with Chinese herbal decoctions. Self-formulated Chinese herbal fumigation solutions based on different treatment principles have been shown to effectively improve itching symptoms in patients with cholestatic liver disease-related pruritus and improve their quality of life.[49] Cold compress with Chinese herbs is one of the unique treatment methods in TCM and an important part of external TCM treatment. Some researchers have used cold compresses with Chinese herbs to treat cholestatic liver disease-related pruritus and have confirmed its effectiveness through long-term observations, providing definite therapeutic effect.[50]

Characteristic Treatment Methods

In addition to traditional internal and external medications, TCM also includes characteristic therapies such as acupuncture and cupping. These therapies have played important roles in the clinical diagnosis and treatment of cholestatic liver disease-related pruritus. The use of cupping in combination with Western medicine treatment can greatly relieve skin itching and enhance the therapeutic effect.[51] Besides, therapies such as ear acupressure and bloodletting at the tip of the ear have also played a certain role in the adjuvant treatment of cholestatic liver disease-related pruritus.[46]

Summary

Itching is a common clinical symptom in cholestatic liver diseases and often persists for a long time without easy relief. This article reviews recent research findings on cholestatic liver disease-related pruritus, indicating that substances such as steroids and their metabolites, bile acid, and LPA may be potential pruritus inducers in cholestatic-related diseases. Various treatment methods, including medication and intervention therapy, have been developed specifically for cholestatic liver disease-related pruritus. However, there are still some unresolved issues in the study of cholestatic liver disease-related pruritus: (1) Most experimental studies have only identified potential pruritus inducers associated with cholestasis, and the complex pathological mechanism underlying cholestatic liver disease-related pruritus has not been fully elucidated. (2) Currently, most animal models

used in the research studies on cholestatic liver disease-related pruritus are rodent models, and it is difficult to compare and analogize the criteria for evaluating pruritus to the human situation. (3) Despite the existing treatment methods, some patients with cholestatic liver disease-related pruritus still have a poor treatment response, and effective treatment remains a challenge.

To address these problems, future research works should focus on clinical trials by conducting comprehensive screening of plasma (and/or bile) samples from a large number of patients to identify more potential pruritus inducers. Furthermore, the establishment of humanized organ models can provide a deeper understanding of the itching signaling pathways in cholestatic liver diseases. In terms of treatment, TCM has shown certain characteristics and advantages in clinical practice. Based on the etiology, pathogenesis, and syndrome differentiation and treatment, external applications, internal medications, and TCM characteristic therapies have achieved good therapeutic effects. Additionally, the combination of Chinese and Western medicine has also achieved more effective treatment for patients with cholestatic liver disease-related pruritus. In the future, for patients who have a poor treatment response to existing methods, a wide range of approaches, including the combination of Chinese and Western medicine or various novel therapies, can be adopted to achieve precise and effective treatment.

CRediT Authorship Contribution Statement

Wenzhang Dai: Investigation, and writing—original draft. Hong Nie: Funding Acquisition, and writing—review & editing.

Funding

This study was supported by the National Natural Science Foundation of China (8181101216) and Outstanding Innovative Talents Cultivation Funded Programs for Doctoral Students of Jinan University (2023CXB027).

Conflict of Interest

The authors declare no conflict of interest.

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