

# A BRIEF REVIEW ON PRURITUS IN CHOLESTASIS

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**Abstract:** Pruritus is an enfeeble symptom in those patients having cholestatic liver disease, including primary sclerosing cholangitis, primary biliary cirrhosis, and intrahepatic cholestasis of pregnancy. Various factors are involved in the occurrence of pruritus, such as its appearance varies from patient to patient, it will be intermittent or persistent, generalized or localized to specific parts of the body like toes and palm. Based on the etiology of cholestasis, antihistamines show unresponsive effects in patients with Cholestasis pruritus and can lead to sleep deprivation, lack of attention, and prurigo nodularis due to scratching. In severe cases of cholestasis pruritus, suicidal ideations may develop, and pruritus becomes the primary indication for liver transplantation. Cholestasis-associated pruritus also shows a diurnal rhythm having a peak intensity at late evening and an early night. The peripheral and central neurological systems have been linked to the mechanism of pruritus, leading to the development of several treatment alternatives. Most of these treatments have little evidence of efficacy at this time, indicating that more research is needed. The following review scrutinizes the current literature on epidemiology, pathogenesis, and treatment of Pruritus in Cholestasis.

**Keywords:** Pruritus, Cholestasis, sclerosing cholangitis, prurigo nodularis

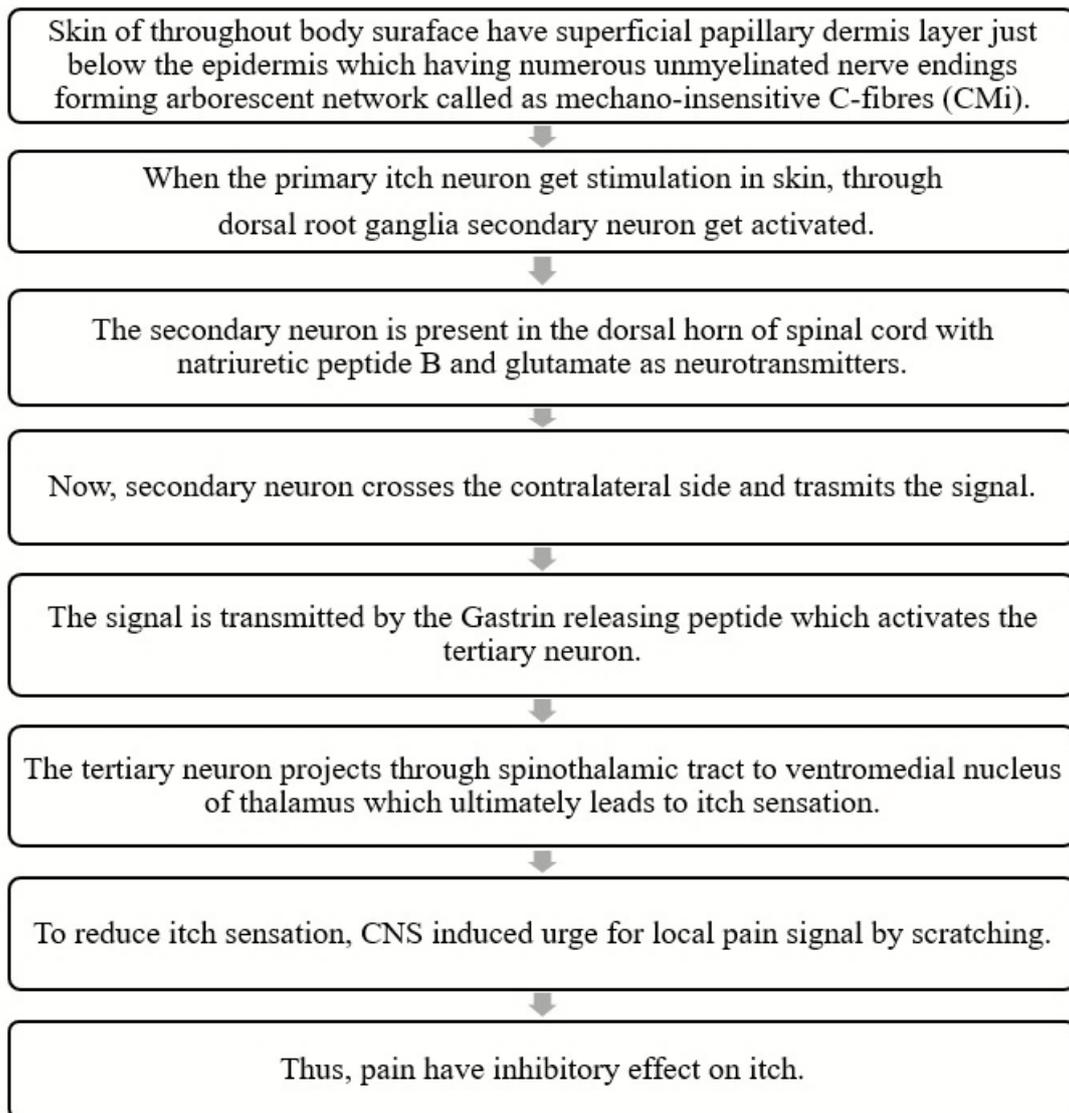
## I. INTRODUCTION:

The word 'cholestasis' is derived from the Greek words 'chole' and 'stasis' meaning bile and standing still respectively, which commonly referred to as impairment of bile formation or bile flow whereas the word 'Pruritus' is derived from the Latin verb prurire, meaning to itch<sup>[1,2]</sup>. Pruritus is an enfeeble symptom in those patients having cholestatic liver disease, including primary sclerosing cholangitis, primary biliary cirrhosis, and intrahepatic cholestasis of pregnancy. Patients with cholestatic itch frequently develop secondary lesions as a result of scratching to relieve pruritus and they are characterized by reduction of hepatocellular and/or cholangiocellular bile production and flow<sup>[3]</sup>. Various factors are involved in the occurrence of pruritus, such as its appearance varies from patient to patient, it will be intermittent or persistent, generalized or localized to specific parts of the body like toes and palm. It will be more complicated while wearing tight clothes, in the hot humid environment and other factors like premenstrual condition in females, psychological factors like excitation, and various cutaneous complications such as lichenification, folliculitis, excoriation, prurigo nodularis, result from long-lasting vigorous scratching activity<sup>[1, 4]</sup>. Based on the etiology of cholestasis, antihistamines show unresponsive effects in patients with Cholestasis pruritus and can lead to sleep deprivation, lack of attention, and prurigo nodularis due to scratching. In severe cases of cholestasis pruritus, suicidal ideations may develop, and pruritus becomes the primary indication for liver transplantation. Cholestasis-related pruritus has a diurnal cycle, with peak intensity in the late evening and early night<sup>[5]</sup>. Peripheral pruritus and central pruritus are the two types of itching mechanisms. Histamine released by mast cells triggers the itch receptor at the epidermal-dermal junction, resulting in peripheral pruritus and in central pruritus, Met-enkephalin-like substances which are known as endogenous opioids stimulate the  $\mu$  receptors in nerve tissue and it causes itching<sup>[6]</sup>. The following review scrutinizes the current literature on epidemiology, pathogenesis, and treatment of Cholestatic Pruritus<sup>[3]</sup>.

## II. PATHOGENESIS:

### Pain and Itch Signaling Pathway in Cholestasis Pruritus:

Itch perception depends upon the intricate relation of pruritogens, their receptors, peripheral nerve fibres, and intraspinal and cerebral neural pathways. Itch signaling gets provoked with histamine, chloroquine, or cowhage that activate histamine 1 or 4 receptor. Antihistamines cannot relieve Cholestasis Pruritus when itch sensation occurs through cowhage so pruritus is called a non-histaminergic itch and it signals through mechanoheat-sensitive C-fibres<sup>[1, 5]</sup>. The following Figure 1 represents the itch signaling pathway in Cholestatic pruritus.



(Fig.1 Itch signaling pathway of Pruritus in Cholestasis <sup>[1, 5]</sup>)

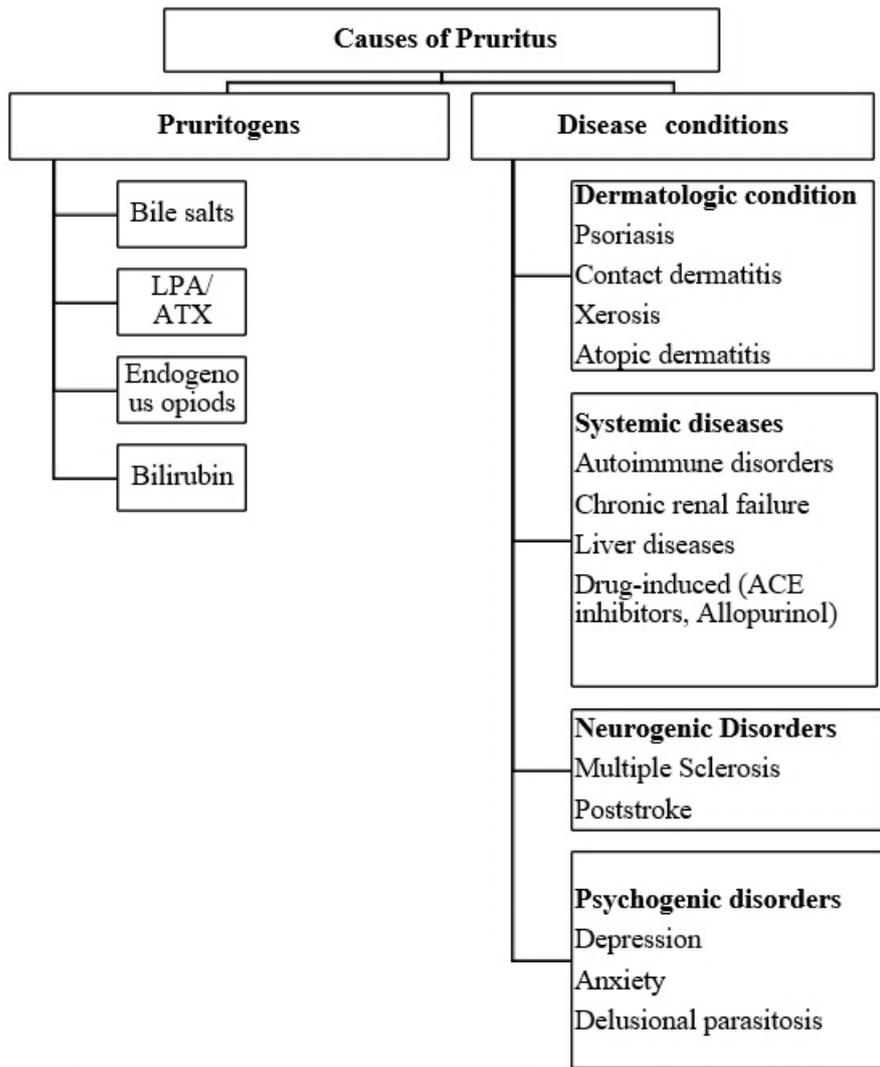
The contrast mechanism of itch sensation includes inhibitory neurons present in the dorsal horn of the spinal cord which creates constant tonus of inhibition by nociceptive to pruriceptive neurons. GPCRs are involved in the pruritus and on activation, which leads to an increase in intracellular  $Ca^{2+}$  release that activates PLC and PKC which are coupled with TRP channels. TRP channel will now amplify the intracellular cation wave along with the  $Na_v$  channel and will generate the action potential which ultimately leads to itch sensation <sup>[1, 5]</sup>.

#### Pruritogens:

The pathogenesis of cholestatic pruritus is not delineated as it is complex but according to the recent study, several pruritogens are proposed which mediate itch (pruritus) <sup>[3, 7]</sup>. Various pruritogens which induce itching include bile salts, LPA/ATX, histamine, endogenous opioid, serotonin, bilirubin, and steroid metabolites <sup>[5]</sup>. There are various assumptions about the pruritogens based on the clinical observations of the present day:

1. It is supposed that the endogenous opioid and serotonergic system is affected by pruritogens as study shows that opioid receptor antagonists,  $\kappa$ -opioid receptor agonists, and 5-HT reuptake inhibitors will assist to treat cholestatic pruritus.
2. Pruritogens are secreted through bile in the intestinal lumen where intestinal anion exchange resin, cholestyramine, and colestipol bind with many hydrophobic substances which relieves cholestatic pruritus.
3. Because of nasobiliary drainage and external biliary diversion direct or indirect pruritogens undergo hepatic circulation which improves pruritus in cholestatic patients.
4. Cholestatic patients are improved by hepatic and intestinal enzyme inducers like rifampicin and phenobarbital as biotransformation of pruritogens takes place in the liver and intestine <sup>[7]</sup>.

The pruritogens and disease conditions that are responsible for the pruritus in Cholestasis are mentioned in Figure 2.



(Fig.2 Etiology of Cholestatic Pruritus<sup>[3, 5, 7-10]</sup>)

**Bile salts:** Bile salts are the most abundant components of bile which bind intracellularly with the nuclear receptor farnesoid x-receptor (FXR) regulates transmembrane GPCR and stimulate cAMP production. A subset of bile salts can bind to the pregnane X receptor, causing an increase in bile salt synthesis and as a result, cholestasis progression. Bile is mainly eliminated by nasobiliary drainage or removal of the albumin-bound substance by albumin dialysis which ultimately causes a diminution in itch perception and it lasts only for a few weeks to months<sup>[5]</sup>. During cholestasis, bile acid diffuses in both systemic circulation and activate TGR5 expressed on itch encoding sensory neuron. Serum bile acid is not always get elevated in every case of cholestatic Pruritus. So, pruritus does not correlate with the bile salt concentration<sup>[3]</sup>.

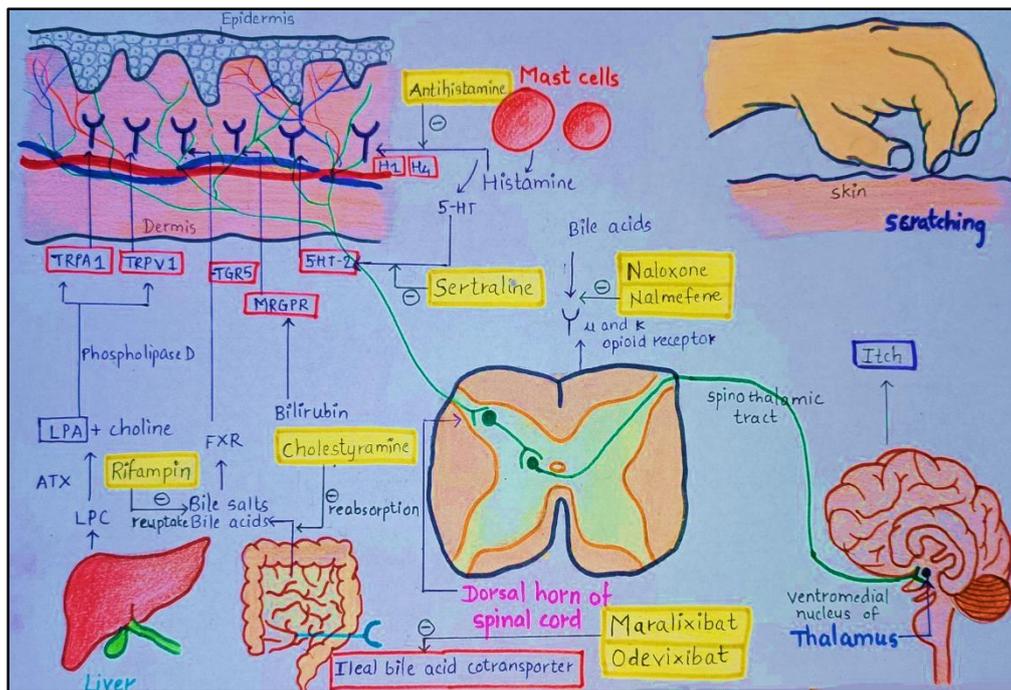
**LPA/ ATX:** Lysophosphatidic acid (LPA) is reported to be the potential pruritogen in cholestasis based on earlier studies. LPA is produced from the Lysophosphatidylcholine (LPC) on catalyzation in LPA and choline by phospholipase D Autotaxin (ATX), which is ectonucleotide pyrophosphatases/ phosphodiesterases. In humans, a high amount of ATX mRNA expression has been described in the brain, lungs, ovary, and kidney. Whereas it has been found that enzymatic activity of ATX is seen in blood, cerebrospinal and seminal fluid, urine, and saline. To date, which organ contributes to circulating ATX in human plasma and cerebrospinal fluid is unclear. LPA activates the neuronal and satellite glial cells through six different LPA specific receptors (LPAR 1-6), which further activates phospholipase D intracellularly that is responsible for activation of transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential vanilloid 1 (TRPV1) and thereby, it induces itch sensation (pruritus)<sup>[5]</sup>.

**Serotonin:** Serotonin (5-HT) is a neurotransmitter in the central nervous system that excites the nociceptive nerve fibres. In the skin, serotonin is released from the mast cells and might act as pruritogen that enhanced scratching behavior was noted in mice after the intradermal administration of serotonin<sup>[5, 10]</sup>. Among several 5-HT receptors, 5-HT<sub>2</sub> which are a metabotropic GPCR is supposed to induce pruritus through signaling via Gq/11 which activates phospholipase C. Pruritogens binds on primary sensory neurons through metabotropic receptors that are coupled with ionotropic channels and allow sufficient current influx for generation of action potential and thereby, itch sensations are produced<sup>[5]</sup>. Various clinical studies show that 5-HT<sub>3</sub> receptor antagonists, 5-HT reuptake inhibitors improve the condition of patients with Cholestatic Pruritus. Thus, serotonin is involved in itch perception in Cholestatic patients<sup>[7]</sup>.

**Endogenous Opioids:** Cholestatic Pruritus is mediated by the endogenous opioid peptides because it has been found in the study that opiate antagonist Nalmefene, triggers opiate- withdrawal, and elevated levels of Methionine-enkephalin in plasma are observed in cholestatic patients.  $\mu$ -opioid receptor agonist and  $\kappa$ -opioid receptor agonist evokes scratching and decreases itching sensation, respectively in animal models. Thus, endogenous opioids are considered as pruritogens for the Cholestatic Pruritus, although the mechanism by opioid peptides that evokes itch is not clearly understood they may influence the sensation of itch by modulating other pruritogens. For example, a decrease in the level of bile acid is observed with opioid antagonist Naloxone [3].

**Bilirubin:** The bilirubin (heme metabolite) acts as potential pruritogens in Cholestatic Pruritus. In addition to bile acid and LPA, bilirubin is an underlying cause of jaundice and pruritus in cholestasis as it binds and activates 2 members of the Mas-related GPCR (MRGPR) family of receptors which are expressed on itch sensitive neurons and for non-histaminergic pruritus, MRGPR is major mediators. As plasma bilirubin does not correlate with itching so, whether skin bilirubin itself acts as pruritogen is still unclear [3].

The diagrammatic representation of the Itch signaling pathway in Cholestatic pruritus with their pruritogens is mentioned in Figure 3.



(Fig.3 Diagrammatic representation of Itch signaling pathway<sup>[1, 11-15]</sup>)

### III. SIGNS AND SYMPTOMS:

Cholestasis is a destruction in the regular bile flow and it is associated with various symptoms like digestion, detoxification, and signaling excretion.

1. Pruritus is the primary symptom of cholestasis due to the accumulation of bile in the skin.
2. Pale stool - post hepatic obstruction - No bile to the duodenum
3. Jaundice due to the increase conjugated Bilinogen.
4. Dark urine - due to the very much urobilinogen into the urine.
5. Xanthoma and xanthelasma due to hyperlipidemia.
6. Fatigue - persistent sense of tiredness, inability to the regular work and slow the activity of mental and physical work.
7. Steatorrhea - excretion of an unusual amount of fat in the stool. Faeces may contain a higher amount of fat due to bile has not entered the intestine to digest the lipid content of food.
8. Rashes may occur due to itching.
9. Abdomen pain
10. Nausea
11. Pregnant women feel unwell and tired and lose their appetite. Liver enlargement and abdominal distension (an outward belly extension that's noticeably beyond your normal baby bump), discomfort, and itching on the palms and soles of the feet tend to be especially noticeable at night<sup>[10]</sup>.

### IV. TREATMENT:

The following are the drugs involved in the treatment of Cholestatic pruritus:

1. **Cholestyramine:** Cholestyramine is the anion exchange resin that binds with the bile acids inside the intestine and prevents reabsorption of bile acids from the terminal segment of the ileum through the enterohepatic circulation (EHC). The complex of bile acid and cholestyramine is eliminated in the stool<sup>[1]</sup>.

2. **Rifampin:** It inhibits the uptake of bile acid into the hepatocyte and it induces mixed-function like oxidases in the liver eventually this will alter bile acid metabolism. It is also responsible for the hydroxylation of bile acid <sup>[11, 12]</sup>.
3. **Opioid antagonist:** Nalmefene, elevates the Methionine-enkephalin level in plasma by acting on  $\mu$ -opioid receptor and  $\kappa$ -opioid receptor which leads to scratching and helps to relieve cholestatic pruritus <sup>[13]</sup>.
4. **Sertraline:** It is a selective serotonin reuptake inhibitor, by inhibiting the 5-HT, it gives relief from itching <sup>[14]</sup>.
5. **Odevixibat:** It is a reversible inhibitor of the ileal sodium or bile acid cotransporter. If the Odevixibat was taken for a week it will show a 56% of reduction in bile acid in an area under the curve with 3mg daily dose; decrease into reabsorption of bile acid leads to reduced stimulation of FXR which reduce expression of FGF19 eventually this all leads to decrease into bile acid synthesis <sup>[15]</sup>.
6. **Maralixibat:** Generally, Maralixibat inhibits IBAT (ileal bile acid transporter who reabsorb 95% of bile acid in distal ileum); this inhibition decreases reabsorption of bile acid in ileum it leads to decrease resorption of bile acid, which will cause increased elimination of bile acid in the faeces and decreases serum bile acid level (this is the major cause of the increasing rate of diarrhoea in patients) <sup>[16]</sup>.
7. **Other therapies:** Other therapy like Phototherapy, Fibrate therapy, albumin dialysis, plasmapheresis therapy.
  - a. Albumin dialysis: Using a molecular adsorbent recirculating system (MARS) can be mediate uncontrollable cholestatic pruritus.
  - b. Plasmapheresis: MARS shows its antipruritic effect by removing pruritogen from the systemic circulation <sup>[17]</sup>.
8. **Ursodeoxycholic acid:**
  1. It protects the epithelial cells of the bile duct against the cytotoxicity of hydrophobic bile salts such as Glycolic acid (GCA), Lithocholic acid (LCA), chenodeoxycholic acid (CDCA), Cholic acid (CA), Deoxycholic acid (DCA), so it reduces the concentration of hydrophobic bile acids in the epithelial cells of the bile duct called cholangiocytes.
  2. UDCA also protects the hepatocytes from the apoptosis induced by the bile acids. This mechanism involves the obstruction of mitochondrial membrane permeability transition (MMPT) and the excitement of survival pathways <sup>[18]</sup>.

The step-by-step treatment of Cholestatic pruritus is represented in Figure 4.



(Fig.4 Step by step treatment of Cholestatic Pruritus <sup>[1, 11-18]</sup>)

**V. CONCLUSION:** To summarise, the pathophysiology of cholestasis pruritus is likely complex, and the patient's genetic composition may alter the perception of pruritus. The peripheral and central neurological systems have been linked to the mechanism of pruritus, leading to the development of several treatment alternatives. Most of these treatments have little evidence of efficacy at this time, indicating that more research is needed. This provides a platform for researchers to consider thrust area in future.

**VI. ACKNOWLEDGMENT:** Authors would like to express their sincere thanks to all the researchers whose work help in preparing this review work.

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