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Scratching the Surface: Exploring Gastrointestinal Serotonin's Impact on Chronic Pruritus in Irritable Bowel Syndrome and Dyspepsia

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Abstract

Background and Aims: Gastrointestinal-derived serotonin (5-HT) plays a crucial role in the enteric nervous system and has been identified as a key mediator in the pathogenesis of chronic pruritus associated with irritable bowel syndrome (IBS) and functional dyspepsia (FD). Dysregulated serotonin signaling, driven by altered enterochromaffin cell activity and abnormal serotonin reuptake, contributes to gut-brain axis dysfunction and sensitizes peripheral nerves, leading to increased pruritic sensations. This review explores the interplay between serotonin dysregulation, neurogenic inflammation, and chronic pruritus in IBS and FD, with an emphasis on potential therapeutic interventions. This review aims to address the gap in understanding the specific mechanisms by which serotonin dysregulation affects pruritus and gastrointestinal function, offering new insights into potential therapeutic approaches. **Methods:** A comprehensive literature review was conducted to examine the role of serotonin dysregulation in chronic pruritus associated with IBS and FD. Relevant studies were analyzed to assess serotonin's impact on visceral hypersensitivity, systemic inflammation, and neurogenic skin responses. Additionally, the effectiveness of serotonin receptor modulators, systemic agents such as gabapentinoids, and microbiota-targeted therapies in mitigating pruritic symptoms was evaluated. **Results:** Dysregulated serotonin

signaling in IBS and FD exacerbates visceral hypersensitivity and systemic inflammation, contributing to neurogenic inflammation in the skin and the release of pruritogenic mediators, including substance P and histamine. This persistent itch response significantly reduces patients' quality of life. Evidence suggests that serotonin receptor modulators, particularly 5-HT3 and 5-HT4 antagonists, can alleviate pruritic symptoms by addressing both gastrointestinal motility and pruritus-associated pathways. Additionally, systemic agents like gabapentinoids provide complementary neural desensitization. Emerging data indicate that gut microbiome imbalances in IBS and FD influence serotonin production, highlighting a potential role for microbiota-targeted therapies in reducing pruritus severity. **Conclusions:** Addressing the complex interaction between gastrointestinal serotonin dysregulation, neurogenic inflammation, and chronic pruritus is essential for advancing therapeutic strategies. A comprehensive approach targeting the gut-brain-skin axis has the potential to redefine pruritus management and improve patient outcomes in IBS and FD. Future research should focus on optimizing serotonin-targeted therapies and exploring microbiota-based interventions to enhance treatment efficacy. This review highlights the novel contributions of serotonin modulation and microbiome-targeted therapies in treating pruritus and gastrointestinal conditions, offering a framework for future research in this integrated therapeutic area.

Keywords

Serotonin Dysregulation, Chronic Pruritus, Gut-Brain Axis, Irritable Bowel Syndrome, Functional Dyspepsia, Neurogenic Inflammation, Serotonin Receptor Modulators, Microbiota-Targeted Therapies

1. Introduction

Chronic pruritus is a persistent and distressing sensation lasting for more than six weeks, significantly impairing quality of life. It is most commonly associated with inflammatory skin conditions and systemic disorders, often necessitating a multidisciplinary approach for effective management [1]. Psychiatric comorbidities, such as anxiety and depression, further compound the impact of chronic pruritus, underscoring the interconnected nature of its physical and systemic manifestations. In particular, gastrointestinal conditions like irritable bowel syndrome (IBS), characterized by chronic abdominal pain and visceral hypersensitivity, are frequently reported in patients with pruritus. This overlap complicates clinical presentations and contributes to significant distress, given the limited effective treatments for managing visceral pain, making IBS a particularly debilitating condition [2] [3]. Addressing these interconnected issues is crucial, as they highlight the systemic nature of pruritus and the need for novel therapeutic approaches. Parvizi *et al.* (2021) explored the relationship between functional dyspepsia (FD) and dermatological conditions, finding potential connections that warrant further

research to better understand the interplay between gastrointestinal and dermatologic health.

FD is a common gastrointestinal disorder associated with upper abdominal discomfort and bloating; research suggesting potential links to skin health [3]. Similarly, IBS affects approximately 11% of the global population, presenting with abdominal pain, bloating, and altered bowel habits driven by visceral hypersensitivity [4]. This hypersensitivity involves heightened nerve responsiveness in the gut without visible inflammation, paralleling mechanisms observed in sensory pathways of the skin. In both systems, dorsal root ganglion (DRG) neurons mediate sensations such as pain and itch, influenced by irritant mediators and specific receptors [5]. These shared pathways provide valuable insights for understanding the mechanisms underlying IBS and FD, emphasizing the need for innovative treatments targeting these sensory responses. Therapies aimed at these pathways could address the underlying causes of hypersensitivity, improving outcomes for patients experiencing IBS, FD, and associated systemic symptoms.

The gut-brain-skin axis offers a comprehensive framework for understanding the links between gut microbiota, emotional states, and systemic and skin inflammation. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and gut microbiota contributes to inflammatory and immune processes observed in conditions like psoriasis and depression, paralleling mechanisms in IBS and FD [6]. Dysregulated serotonin signaling exacerbates visceral hypersensitivity and systemic inflammation, amplifying neurogenic skin inflammation through mediators such as substance P and histamine [6] [7]. Disruptions in gut microbiota and increased gut permeability further activate toll-like receptors (TLRs), driving systemic inflammation. Emerging therapies—including serotonin receptor modulators (5-HT3 and 5-HT4 antagonists), probiotics, and agents targeting Th17 cells and IL-17—highlight the potential of these pathways in reducing inflammation and pruritus [8] [9]. By addressing gut-brain-skin axis dysfunction, these treatments offer hope for managing overlapping disorders and improving patient outcomes.

Pruritogenic receptors in the gut may act similarly to those in the skin, serving as protective mechanisms for detecting and responding to irritants. However, dysfunctional serotonin signaling in conditions like IBS and FD amplifies pruritic sensations by driving neurogenic inflammation and abnormal sensory responses [5]. The serotonin 5-HT7 receptor (5-HT7R) has emerged as a key mediator in acute and chronic itch, presenting a promising target for therapeutic intervention in both gastrointestinal and dermatological inflammatory conditions [10]. Complementary approaches, such as acupuncture, have demonstrated anti-inflammatory and anti-itch effects by modulating serotonergic pathways, as evidenced in chronic itch models [11]. Probiotic therapies further show potential for restoring microbiome balance and reducing systemic inflammation, offering safe and cost-effective strategies for managing conditions like psoriasis and IBS [12]. These findings underscore the interconnectedness of serotonin-mediated pathways and

the gut-brain-skin axis, paving the way for integrated therapeutic strategies to address pruritic and systemic conditions.

2. Serotonin and Its Role in the Gut-Brain-Skin Axis

2.1. Overview of Serotonin's Functions in the CNS, Gut, and Skin

5-Hydroxytryptamine (5-HT, serotonin) is found in both the central nervous system and peripheral tissues, where it also acts as a hormone in platelets. Although over 95% of the body's serotonin is concentrated in the gut, serotonin is primarily recognized for its role in mental health disorders. Serotonin regulates CNS neurons and influences pain transmission, as well as platelet aggregation.

2.2. Serotonin in the Gut, Microbiome, and Peripheral Tissues

In the gut, 5-HT directly affects muscle motility, influencing digestive processes, and acts through neurons in other peripheral tissues such as the bronchi, uterus, and blood vessels [10] [13]. Serotonin synthesis begins with the hydroxylation of tryptophan, followed by decarboxylation, enabling its action through multiple receptor types. It acts through various receptors and plays a significant role in conditions such as migraines, carcinoid syndrome, and gastrointestinal disorders. Additionally, 5-HT functions as a paracrine hormone and growth factor. Serotonin receptors in the brain and gut are targets for drugs that alter serotonin signaling. The role of 5-HT receptors in the gastrointestinal (GI) tract has shed light on serotonin's impact on GI physiology, pathology, and its therapeutic potential in GI-related diseases [13]. Understanding the diverse roles of serotonin receptors in the GI tract provides insight into its physiological and pathological mechanisms, paving the way for novel treatments for GI disorders.

5-HT receptors, including 5-HT3 and 5-HT4, play a crucial role in the pathophysiology of functional dyspepsia and irritable bowel syndrome, specifically their effects on visceral hypersensitivity and gastrointestinal motility. Notably, 5-HT3 receptors are involved in modulating visceral afferent activity and are targeted by various antagonists like alosetron, ondansetron, and granisetron, which have shown effectiveness in treating diarrhea-predominant IBS. These specific antagonists work by decreasing the release of excitatory neurotransmitters in the enteric nervous system, helping to alleviate pain and discomfort. In contrast, 5-HT4 receptors stimulate neurotransmitter release and enhance colonic motility, with agonists, for example, tegaserod and prucalopride, implemented for constipation-predominant IBS. These agonists promote prokinetic effects by increasing intestinal movement [14].

As discussed, serotonin is known to play a role in sensory processing and neurogenic inflammation, which are mechanisms involved in pruritus. Since 5-HT3 receptors modulate afferent nerve signaling and contribute to visceral pain hypersensitivity, they may also influence pruritus by affecting similar sensory pathways. Additionally, serotonin's involvement in central and peripheral sensitization mechanisms may connect gastrointestinal disorders to systemic sensory disturb-

ances like chronic pruritus. By targeting different 5-HT receptor subtypes, therapeutic strategies for functional gastrointestinal disorders can regulate motility and reduce hypersensitivity, which may indirectly impact symptoms—like chronic pruritus—that share overlapping mechanisms [14].

5-HT is a highly versatile molecule with conserved production across both prokaryotes and eukaryotes. In the gastrointestinal tract, enterochromaffin (EC) cells are the primary producers of 5-HT, though certain intestinal bacteria also contribute to its synthesis [13]. This highlights the complex interplay between the microbiome and serotonin regulation. In addition to its role as a neurotransmitter, 5-HT influences immune cells by regulating their activation. Altered 5-HT signaling in the gut has been implicated in individuals with inflammatory bowel disease (IBD). Koopman *et al.* (2021) explored the production, secretion, and signaling pathways of 5-HT within the gut, highlighting its effects on intestinal immune and epithelial cells and its influence on maintaining intestinal homeostasis. Disruptions in these pathways may contribute to the progression of IBD. Thus, it is paramount to understand the therapeutic potential of targeting intestinal 5-HT signaling [15]. A deeper understanding of 5-HT's role in gut physiology may lead to innovative strategies for managing inflammatory bowel diseases.

2.3. Serotonin's Role in Immune Modulation and Inflammation

Beyond its central and peripheral functions in the neuroendocrine system, serotonin regulates behaviors and physiological states such as pain, appetite, mood, and sleep [16]. There is growing evidence that serotonin also plays a significant role in immune signaling. Derived from L-tryptophan, serotonin interacts with a variety of receptors, including the 5-HT1R to 5-HT7R families, and its release and reuptake are controlled by the serotonin transporter (5-HTT or SERT), which is highly expressed in platelets [17]. These interactions highlight serotonin's multifaceted role within the gut and beyond [7]. 5-HT plays a key role in vasodilation, inflammation, immunomodulation, and itch-inducing effects in the skin. Immune and non-immune skin cells can produce or metabolize serotonin, express serotonin receptors, and utilize the serotonin transporter (SERT), underscoring its importance in maintaining skin homeostasis. Additionally, serotonin, along with stress mediators, contributes to the impact of psychological stress on skin function. Stress worsens psoriasis and atopic dermatitis, delays wound healing, and increases susceptibility to recurring viral infections [7]. Thus, serotonin's effects are particularly significant in conditions such as pruritus, where it directly stimulates sensory neurons in the skin, contributing to the sensation of itching. This action further highlights serotonin's role in disrupting normal skin homeostasis, particularly under stressful conditions. Serotonin's impact on the skin can also influence the progression of various dermatological conditions, further emphasizing its importance in maintaining overall health [18]. IBS is a chronic gastrointestinal disorder closely tied to dysregulation of the brain-gut-microbiome (BGM) axis. Dysregulation in serotonin signaling plays a critical role in the devel-

opment and exacerbation of IBS symptoms.

2.4. Serotonin Dysregulation in Irritable Bowel Syndrome (IBS)

Serotonin (5-HT) plays a crucial role in IBS, affecting motility, pain, inflammation, immune responses, and brain function. Genetic variations linked to serotonergic pathways and overactive enterochromaffin (EC) cells, which produce serotonin in the gut, contribute to the disorder [19]. Dysregulated serotonin signaling in IBS results from both overactive EC cells and abnormal serotonin reuptake. Changes in gut microbiota (dysbiosis) further exacerbate serotonin imbalances, disrupting the brain-gut-microbiome (BGM) axis. Targeting serotonin signaling and modulating the microbiota are potential treatment strategies, though the exact mechanisms remain unclear. In the gastrointestinal tract, serotonin is released by EC cells in response to stimuli, with its regulation influenced by tryptophan hydroxylase enzymes and the serotonin transporter (SERT). Increased serotonin levels in colonic tissue and elevated serotonin in the blood and urine of IBS patients indicate disrupted serotonin signaling. These imbalances are linked to hypersensitivity and altered 5-HT metabolite levels, with notable gender and subtype differences. Understanding the interactions between serotonin signaling and gastrointestinal dysfunction is critical for developing targeted treatments for IBS and FD [20]. Further research into these pathways could lead to effective therapies for these complex conditions.

2.5. Pathophysiology of Functional Gastrointestinal Disorders (FGIDs) and Serotonin

Functional gastrointestinal disorders (FGIDs), including IBS and functional dyspepsia (FD), are now classified as DGBIs to emphasize the critical role of the gut in these conditions. DGBIs manifest through disturbed motility, visceral hypersensitivity, immune dysregulation, altered gut microbiota, and disrupted gut-brain communication. Dysregulated serotonin signaling, particularly from overactive enterochromaffin (EC) cells, plays a central role in the pathophysiology of DGBIs [21]. These cells, which produce most of the body's serotonin, are involved in sensing mechanical and chemical stimuli in the gut and transmitting signals to the enteric nervous system (ENS) and central nervous system (CNS). Abnormal serotonin release and reuptake contribute to disturbed motility, altered gut sensation, and inflammation in DGBIs like IBS and FD. Despite serotonin's crucial role, the precise mechanisms linking serotonin dysregulation, EC cell function, and DGBIs are not fully understood. Ongoing research into these pathways is vital for improving diagnostic methods and developing targeted therapies to manage these complex disorders [22]. Research into serotonin's involvement in these conditions is essential for advancing treatment options, as better-targeted therapies could reduce the impact of DGBIs on patients' daily lives. A deeper understanding of serotonin's role in gastrointestinal disorders offers a promising avenue for advancing diagnostic approaches and refining treatments that address the underlying causes

of these challenging conditions.

2.6. Serotonin's Role in Itch and Skin Disorders

Serotonin (5-HT) plays a key role in both central and peripheral itch sensation, contributing to neurogenic inflammation in the skin. Released by mast cells, melanocytes, and platelets, serotonin acts as an inflammatory mediator in conditions like atopic dermatitis (AD) [23]. Elevated serotonin levels in the skin and spinal cord induce itching by activating specific receptors, including HTR7 and TRPA1. Additional receptors, such as TRPV4 and 5-HT2, also mediate serotonin-induced itching [23] [24]. In the CNS, serotonin amplifies itch via the 5-HT1A receptor and GRP-GRPR pathways. While targeting serotonin receptors has shown promise in animal studies for treating conditions like AD and psoriasis, no serotonin-based therapies are yet available.

Pruritus, a key symptom of cholestatic liver diseases, is linked to serotonin, bile acids, histamine, and opioids [24]. Serotonin, released by mast cells and other cells, contributes to itch by activating receptors like TRPV1, TRPA1, and 5-HT. Bile acids and lysophosphatidic acid (LPA) also play a role in cholestatic pruritus. Elevated bile salts activate the ATX-LPA pathway, stimulating LPA receptors and sensory neurons, while LPA enhances responses through TRPV1 and TRPA1 [25]. Lysophosphatidylcholine (LPC) activates TRPV4 receptors, releasing microRNA-146a, which sensitizes pruriceptive neurons. Elevated LPC and miR-146a levels correlate with increased itch severity [25] [26]. Additionally, the TGR5 receptor is involved in bile acid-induced pruritus, though recent studies suggest the MRGPRX4 receptor may be a more important target for cholestatic itch. Current treatments focus on reducing pruritogen levels or modulating serotonin signaling.

3. Neurogenic Inflammation and Pruritic Mediators

Dysregulated serotonin plays a critical role in sensitizing peripheral nerves to pain and itch through neurogenic inflammation, underscoring its importance in the modulation of sensory perception. Normally, serotonin functions as a neuromodulator in the peripheral nervous system, fine-tuning responses to stimuli, including pain and itch. During tissue inflammation, however, serotonin is released as part of the immune response, contributing significantly to the cutaneous perception of pruritus [27]. This process occurs through a combination of direct effects on peripheral nerves and indirect amplification of inflammatory signals. Evidence supports a strong link between serotonin and pruritus, with serotonin dysregulation implicated in several chronic dermatologic conditions such as atopic dermatitis, psoriasis, and urticaria [10]. These findings suggest that serotonin dysregulation not only amplifies itching but also interacts with immune and neural mechanisms to enhance inflammation and sensory hypersensitivity.

3.1. Mechanisms of Serotonin in Pruritus

The mechanisms by which serotonin influences pruritus involve multiple path-

ways, particularly those that activate or amplify pruritogenic mediators such as histamine and cytokines. Pruritus arises from the dynamic interplay between mast cells, sensory neurons, and immune signaling. Mast cells, key effectors in inflammatory responses, release mediators such as histamines, prostaglandins, and cytokines, which directly induce itch sensations [24]. Simultaneously, sensory nerves release substances like substance P and vasoactive inflammatory peptide, which can indirectly activate mast cells, creating a feedback loop that perpetuates inflammation and itch. Additionally, cytokines, such as IL-31, have been shown to exacerbate pruritus by sensitizing peripheral nerves and promoting inflammatory responses [28]-[30]. These interactions highlight the bidirectional communication between immune cells and sensory nerves, forming a complex network that underlies the sensation of chronic itching.

In addition to the localized interactions between mast cells and sensory neurons, systemic factors, particularly gut-derived serotonin, contribute to pruritus. Approximately 95% of the body's serotonin is produced in the gut by enterochromaffin cells [30]. This gut-derived serotonin is not confined to local gastrointestinal effects. Instead, it enters the circulation, where it can influence systemic inflammatory and neural pathways. These systemic effects can indirectly modulate sensory neurons in the skin, contributing to cutaneous inflammation and pruritus [31] [32]. This connection forms part of the gut-brain-skin axis, a framework describing how gastrointestinal health and function influence dermatological and neural outcomes. For example, dysregulated serotonin signaling in the gut has been associated with increased pruritus in conditions such as IBS and FD [31] [33]. Thus, serotonergic dysregulation within the gut-brain-skin axis exerts widespread effects, sensitizing neural pathways and ultimately contributing to conditions such as pruritus.

3.2. Cross-Organ Sensitization

One phenomenon illustrating the systemic influence of serotonin is cross-organ sensitization, where dysfunction in one organ system, such as the gastrointestinal tract, leads to heightened sensitivity in another, such as the skin. This occurs through shared neural pathways, particularly those processed by the dorsal root ganglia, which integrate sensory inputs from multiple organs [34] [35]. In conditions like IBS and FD, visceral hypersensitivity, characterized by an exaggerated response to normal stimuli, can extend to the skin, resulting in cutaneous hypersensitivity and chronic pruritus. Verne *et al.* demonstrated that hypersensitivity in both visceral and cutaneous tissues originates from peripheral afferent signaling rather than the central nervous system, underscoring the role of sensory pathways in cross-organ interactions. These findings provide a mechanistic explanation for how gastrointestinal disorders can exacerbate dermatologic symptoms and emphasize the interconnected nature of bodily systems [36]. Recognizing the systemic influences of serotonin, including its role in cross-organ sensitization, provides a broader perspective on the origins of chronic pruritus and paves the

way for innovative treatment strategies.

4. Therapeutic Strategies Targeting Serotonin and Skin Symptoms

Serotonin receptor antagonists, particularly those targeting 5-HT3 and 5-HT4 receptors, have garnered significant attention for their dual role in modulating pruritic symptoms and intestinal motility. This makes them promising candidates for the treatment of various related conditions. Among these receptors, 5-HT3 antagonists, such as alosetron, cilansetron, and ramosetron, have shown substantial efficacy in managing both male and female IBS-D patients, as evidenced by numerous large-scale clinical trials [35] [36]. In contrast, studies focusing on 5-HT4 antagonists remain limited, leaving their therapeutic potential less well-defined. 5-HT3 antagonists like granisetron and ondansetron, although less impactful for the lower gastrointestinal tract, are widely used as antiemetics, effectively controlling nausea and vomiting in patients undergoing chemotherapy, radiation therapy, or postoperative recovery. The widespread distribution of 5-HT3 receptors across physiological systems underscores their therapeutic relevance. These receptors are present in neurons of the autonomic and enteric nervous systems, sensory neurons, the central nervous system, and the chemoreceptor trigger zone [37]. Serotonin's role in inducing and amplifying pain is mediated via the activation of 5-HT3 receptors on sensory nerve endings, an effect that is effectively neutralized by 5-HT3 receptor antagonists. By influencing serotonin signaling in both gastrointestinal and sensory pathways, 5-HT3 and 5-HT4 antagonists represent a unique approach to managing not only gastrointestinal symptoms but also pruritus. Their dual functionality highlights their potential as key therapeutic agents in addressing complex conditions where serotonin plays a central role.

4.1. Gabapentinoids in Pruritus Treatment

Due to the debilitating role of pruritus in a patient's quality of life, multimodal treatment methods are recommended. This includes the use of gabapentinoids in the treatment of pruritus, particularly gabapentin and pregabalin [38]. Often recommended as first-line, gabapentinoids desensitize neural pathways linked to pruritus. The efficacy of gabapentin and pregabalin in modulating itch may be because the voltage-gated calcium channels they affect regulate the release of substance P (SP) and calcitonin gene-related peptide (CGRP) [39] [40]. Gabapentin has also been shown to significantly improve pruritus secondary to interleukin-2 (IL-2), theoretically by blocking pruritic stimulation at afferent nerves [40]. While beneficial in alleviating pruritic symptoms, gabapentinoids require patient screening for potential side effects, including mood changes, increased depression or anxiety, suicidal ideation, dizziness, fatigue, blurred vision, balance or coordination difficulties, and extremity edema. Given the complex nature of chronic pruritus, addressing it often requires a combination of therapies targeting multiple pathways, highlighting the importance of complementary treatments like gabapen-

tinoids to provide comprehensive symptom relief and improve patients' quality of life.

4.2. Serotonin Receptor-Targeted Treatments for Pruritus

Cutaneous manifestations of serotonin dysfunction significantly impact patients' quality of life and necessitate treatment approaches that directly target the underlying physiological mechanisms. In rat models, specifically, 5-HT-induced pruritus was suppressed by repeated administration of capsaicin and the opioid antagonist naloxone [41]. Capsaicin has been widely used in the treatment of pruritus, as its local, topical application inhibits C-fiber conduction and reduces neuropeptide release from peripheral nerve endings [42]. Systemically, ondansetron has shown positive results, with oral administration leading to rapid absorption and a large volume of distribution, including the central nervous system [43]. While there are increasing case reports of serotonin receptor-targeted treatments, further research is necessary to establish their effectiveness across different administration methods. Given the overlapping mechanisms underlying gut dysfunction and pruritus, the concept of combined therapies targeting both conditions simultaneously represents a promising avenue for achieving more comprehensive symptom relief.

5. The Gut Microbiome and Its Influence on Skin and Pruritus

The gut microbiome modulates serotonin production through complex interactions, significantly influencing both gut and systemic inflammation. Gut bacteria directly modulate serotonin levels through several mechanisms, including the metabolism of tryptophan, the precursor for serotonin synthesis, and the production of short-chain fatty acids (SCFAs) like butyrate, which stimulate enterochromaffin cell activity [44]. Certain skin-resident bacteria and probiotic gut strains, such as *Escherichia coli* Nissle 1917, influence serotonin pathways by modulating immune activity, serotonin synthesis, and clearance. Additionally, microbiota can regulate serotonin signaling through receptor and transporter modulation [45] [46]. Dysbiosis, or an imbalance in gut microbiota, can lead to aberrant serotonin signaling, contributing to an inflammatory environment via altered immune responses, including increased pro-inflammatory cytokines like IL-6 and TNF-α [47] [48]. This insight connects microbiota health with inflammation management, suggesting that restoring microbial balance could alleviate serotonin-mediated inflammatory conditions. Understanding these dynamics implies that modulating the gut microbiota through prebiotics or probiotics could offer novel strategies for managing neuropsychiatric conditions involving serotonin dysregulation.

The Role of Microbiota in Skin Disorders

The intricate connection between microbiota imbalances (dysbiosis) and skin symptoms is mediated, in part, by serotonin-driven pathways. Dysbiosis disrupts

the balance of the skin microbiome, a diverse ecosystem of microorganisms essential for maintaining skin immune and barrier functions. This disruption often leads to conditions such as eczema, acne, and rosacea, which are associated with inflammation, pruritus, and discomfort [49]. These findings highlight how microbial diversity is critical for preventing inflammatory skin disorders, suggesting that restoring balance may improve symptom management.

The microbiota influences serotonin production and regulation through multiple mechanisms, which research is beginning to elucidate. Gut bacteria, for instance, metabolize tryptophan, the precursor for serotonin synthesis, and produce short-chain fatty acids (SCFAs) like butyrate, which regulate serotonin levels by activating enterochromaffin cells [44]. These SCFAs also influence serotonin transporter (SERT) expression and function, thereby controlling serotonin reuptake and extracellular availability [47]. By modulating serotonin levels, SCFAs impact not just gut motility and secretion but also systemic immune responses, highlighting their broader physiological significance. Dysbiosis, or microbial imbalance, disrupts these processes, altering SCFA production and serotonin signaling, which can worsen inflammation and delay skin healing [50]. Furthermore, specific skin-resident bacteria, including indigenous spore-forming species, interact with the serotonin pathway by modulating immune cell activity [51]. This interaction promotes the release of pro-inflammatory cytokines, and increases oxidative stress, ultimately compromising skin integrity and barrier function. Meanwhile, probiotic gut strains like *Escherichia coli* Nissle 1917 affect serotonin synthesis and clearance [45]. These relationships reveal opportunities to target microbiota-serotonin interactions through innovative interventions like prebiotics, probiotics, or advanced skincare solutions to restore microbiome balance and alleviate skin symptoms effectively.

Microbiome-targeted interventions such as probiotics and prebiotics have shown promise in reducing pruritus severity by improving gut health and mitigating inflammation. Probiotics, live beneficial bacteria, can restore microbial balance in the gut, influencing systemic immune responses. For instance, a study on dogs with pruritic dermatitis demonstrated that a probiotic and nutraceutical blend not only improved skin symptoms but also reduced pathogenic gut bacteria, suggesting a link between gut health and inflammation resolution [52]. This indicates that altering the gut microbiome can directly alleviate pruritus by reducing inflammatory triggers.

However, it is essential to note that this study acknowledges several significant limitations that may affect the significance of its findings. One limitation is the lack of follow-up assessments, which may prevent understanding whether the observed benefits were retained over time. Prior research has shown that alterations to the gastrointestinal microbiome in healthy canines returned to baseline levels within two weeks after discontinuing synbiotic supplementation. Additionally, the absence of mid-trial gastrointestinal microbiome samples hinders the ability to assess the various dynamics of microbiome changes and their potential associ-

ation with clinically relevant outcomes [52].

Furthermore, the study recommends incorporating more comprehensive measures of impact, including biological and functional biomarkers and evaluation of barrier function, to provide a more holistic assessment of the intervention's effects. Due to these multiple limitations, future studies would improve the quality of the study by using a more controlled experimental design conducted explicitly under the supervision of a single physician. Thus reducing potential confounding factors that could be easily avoided. Also, including skin microbiome samples is recommended, as maintaining skin biodiversity is crucial, given that pruritic diseases are often linked to dysbiosis and reduced species richness and diversity [52].

Similarly, prebiotics, which stimulates the growth of beneficial gut bacteria, have been shown to reduce intestinal inflammation markers like fecal calprotectin, thereby decreasing systemic inflammatory responses associated with pruritic conditions [53]. These findings highlight the potential of prebiotics as a dietary intervention to combat pruritus while improving overall skin health. Furthermore, the use of such interventions aligns with evidence from human inflammatory diseases, where targeted microbiota therapies have effectively reduced pro-inflammatory cytokine levels, emphasizing their broader therapeutic implications [54]. Together, these approaches underscore the significance of microbiome modulation as a novel strategy for managing pruritus and related inflammatory conditions.

Personalized microbiome therapies hold immense potential for managing gut-brain-skin axis dysfunction by addressing individual microbiota compositions. The gut-brain axis facilitates bidirectional communication via microbial metabolites like short-chain fatty acids (SCFAs) and neurotransmitters such as serotonin, influencing systemic inflammation and stress-related conditions [55]. This connection underscores how dysbiosis can exacerbate systemic inflammation and its downstream effects on skin health, emphasizing the importance of microbial balance for optimal therapeutic outcomes. Psychobiotics, a subset of probiotics with demonstrated efficacy in modulating brain function, offer a targeted approach to reducing stress-induced physiological changes by influencing immune and neural pathways [56]. This is particularly significant as chronic stress is a common exacerbating factor in both inflammatory and psychological conditions, suggesting that psychobiotics could alleviate skin symptoms indirectly by addressing stress-related mechanisms. Furthermore, next-generation sequencing (NGS) technologies enable precise mapping of an individual's microbiome, allowing for the development of highly specific interventions [57]. By tailoring treatments to the unique microbial profiles of individuals, these interventions have the potential to improve outcomes in complex, multifactorial disorders, such as those involving the gut-brain-skin axis. Collectively, these advancements reinforce the transformative potential of microbiome-based therapies in addressing interconnected physiological and psychological conditions.

A deeper understanding of serotonin-driven mechanisms in pruritus is crucial

to exploring therapeutic strategies. Table 1 outlines the key pathways by which serotonin influences pruritus, highlighting mechanisms such as neurogenic inflammation, mast cell activation, cytokine amplification, and microbiome influence. By dissecting these interactions, researchers can develop targeted microbiome-based interventions to mitigate pruritic conditions more effectively.

Table 1. Key mechanisms involved in serotonin-driven pruritus.

Mechanism	Description	Key Players	Outcome
Neurogenic Inflammation	Serotonin sensitizes peripheral nerves to pain and itch through immune response	Serotonin, immune cells (mast cells), sensory neurons	Amplifies sensation of pruritus
Mast Cell Activation	Release of mediators like histamines, prostaglandins, cytokines from mast cells	Mast cells, histamines, cytokines, sensory neurons	Induces itching and inflammatory responses
Cytokine Amplification	Cytokines like IL-31 sensitize peripheral nerves and promote inflammation	IL-31, sensory neurons, cytokines	Enhances itching and inflammatory feedback loop
Gut-Derived Serotonin	Serotonin produced in the gut influences systemic inflammation and skin pruritus	Enterochromaffin cells, serotonin, systemic circulation	Contributes to gut-brain-skin axis and pruritus
Cross-Organ Sensitization	Dysfunction in one organ system (gut) leads to heightened sensitivity in another (skin)	Dorsal root ganglia, sensory neurons, gut-derived serotonin	Results in cutaneous hypersensitivity and pruritus
Microbiome Influence	Dysbiosis impacts serotonin levels, exacerbating inflammation and pruritus	Gut microbiota, short-chain fatty acids (SCFAs)	Alters immune responses, increasing pruritus

6. Integration and Future Directions: The Gut-Brain-Skin Axis in Chronic Pruritus

Dysregulation of serotonin signaling can worsen pruritus, especially when there is hyperactivation of serotoninergic pathways or imbalances in serotonin receptor subtypes [58]. Receptors like 5-HT2 and 5-HT7 are particularly involved in mediating pruritus via sensory neuronal pathways, intensifying pruriceptive signaling. Neurogenic inflammation further contributes to this process, as neuropeptides such as substance P and CGRP are released from sensory nerve endings, amplifying local inflammation and sustaining the itch cycle [59] [60]. Pruritogenic signaling also involves histaminergic and non-histaminergic pathways, such as those activated by interleukin-31 (IL-31) and thymic stromal lymphopoietin (TSLP), which interact with JAK-STAT signaling pathways to sensitize pruriceptive neurons [60]. Together, these mechanisms illustrate the multifaceted nature of pruritus and highlight the importance of targeting various pathways in treatment strategies.

Altered serotonin signaling, through changes in enterochromaffin cell activity and serotonin reuptake dysfunction, exacerbates gastrointestinal dysfunction and peripheral nerve sensitization, leading to increased pruritic sensations and inflammation [26]. This dysfunction triggers visceral hypersensitivity, further amplifying neurogenic inflammation in the skin, which sustains the pruritus cycle [6]. The chronic nature of pruritus in IBS and FD patients significantly impacts quality of life, highlighting the need for effective, comprehensive treatments. Recent re-

search has explored serotonin receptor modulators, such as 5-HT3 and 5-HT4 antagonists, as potential therapeutic options for both gastrointestinal and pruritic symptoms [61]. These agents may help regulate gastrointestinal motility while simultaneously reducing pruritic signaling, providing a dual benefit for patients. Future research could investigate the combined effects of serotonin receptor modulators and gut motility agents to optimize the therapeutic outcomes for pruritus associated with functional gastrointestinal disorders. Targeting serotonin pathways could offer a promising approach to managing pruritus in these conditions, addressing both the gut and skin components of the disease.

Further studies are implicating gut microbiome imbalances in serotonin dysregulation and pruritus severity, particularly in IBS and FD. Changes in microbial populations in the gut can influence serotonin biosynthesis, which in turn affects both gut function and systemic inflammatory responses [26] [62]. These imbalances provide a novel opportunity for therapeutic intervention, as targeting the microbiome may help restore serotonin balance and alleviate pruritus. Future investigations should focus on the gut microbiome's specific role in modulating serotonin biosynthesis and its subsequent impact on pruritic symptoms. Research has shown that serotonin receptor modulators can reduce neurogenic inflammation and improve gastrointestinal motility, making them a promising option for managing both symptoms of IBS and pruritus. Additionally, systemic treatments such as gabapentinoids provide neural desensitization, decreasing the intensity of the itch response [39]. Combining microbiome-targeted therapies with serotonin modulators and neural desensitization agents could lead to a more comprehensive approach to treating chronic pruritus. As the research into the gut-brain-skin axis continues to unfold, these insights may lead to more effective treatments that target the underlying causes of pruritus rather than just the symptoms.

The Need for an Interdisciplinary Approach in Treating Chronic Pruritus

An interdisciplinary approach is essential to optimize treatment strategies and improve patient outcomes. Chronic pruritus is a complex condition that involves multiple systems, including the gastrointestinal, dermatological, and neurological systems [63]. Collaboration between gastroenterologists, dermatologists, and neurologists will provide a more holistic understanding of the condition and allow for the development of personalized treatment plans. Future research should investigate the clinical efficacy of collaborative, multi-specialty approaches in improving patient management of chronic pruritus. An integrated approach that recognizes the interconnectedness of the gut, skin, and nervous systems can help tailor interventions to each patient's specific needs. By fostering collaboration across these disciplines, clinicians can address the root causes of chronic pruritus while also managing its symptoms. This multidisciplinary approach will enable more effective, patient-centered care and lead to the development of innovative therapies that can provide lasting relief for patients. Ultimately, the goal is to improve the

quality of life for those suffering from chronic pruritus by offering targeted, comprehensive treatment options.

7. Conclusions

The dysregulation of serotonin plays a critical role in various conditions, particularly functional gastrointestinal disorders (FGIDs) and pruritic dermatologic conditions. In FGIDs like IBS and FD, disturbed serotonin signaling contributes to abnormal gut motility, altered sensations, and inflammation, underscoring its significance in the pathophysiology of these disorders. The role of serotonin extends beyond the gut, influencing the skin's response to pruritus through neurogenic inflammation and immune signaling. Elevated serotonin levels in the skin contribute to conditions like atopic dermatitis, psoriasis, and cholestatic pruritus, activating receptors that mediate itching.

Recent findings emphasize the gut-brain-skin axis, where serotonin dysfunction in the gastrointestinal system affects both systemic inflammation and cutaneous sensitivity, leading to the exacerbation of skin-related symptoms such as pruritus. Targeting serotonin through receptor antagonists, gabapentinoids, and other therapies offers a promising approach to treating conditions influenced by serotonin dysregulation. Additionally, the gut microbiome plays a crucial role in serotonin production and systemic inflammation, providing further insight into potential treatments. Microbiome-targeted interventions such as prebiotics and probiotics could offer novel strategies to restore balance, improve gut health, and alleviate serotonin-mediated skin symptoms.

As research continues to explore the complex interactions between serotonin, the gut, and the skin, there is significant potential for developing more targeted and effective treatments for patients suffering from conditions driven by serotonin dysregulation. Longitudinal studies examining the effects of serotonin modulation on pruritus severity and patient quality of life will be crucial for informing future clinical practice.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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