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Investigating the Role of the Gut Microbiota in Chronic Pain Development and its Potential in Pain Relief

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Abstract

Despite its extensive impact, chronic pain lacks an effective treatment due to its diverse origins, with existing options often causing unwanted side effects in the long term. However, emerging research suggests a promising solution: the gut microbiome. Continued stress induces dysbiosis of the gut microbiota, influencing an individual's hormone levels and perception of pain, altering serotonin (5HT) and short-chain fatty acids (SCFA) production through the gut-brain axis (a bidirectional communication network of the central nervous system). These alterations engender a cycle of stress and neuroinflammation, ultimately leading to the development of chronic pain. Compelling evidence suggests a correlation between gut microbiota dysbiosis and chronic pain — posing the element as a direct agent towards the development and persistence of long-standing pain — further strengthening the notion that targeting the gut microbiome could pave the way toward the creation of innovative approaches for pain management. This review focused on the relationship between gut microbiota dysbiosis and chronic pain, highlighting the possibilities of microbiome-based treatments for chronic pain.

Keywords: Gut microbiome, Serotonin(5HT), Gut-brain axis, Pain, Short-chain fat acids (SCFA), Stress, Target treatment

1. Introduction

Chronic pain, defined as pain persisting for more than three months, is a prevalent condition more than 20% of adults suffer from globally (Lucas and Sohi, 2024), with a 10% increase in patients each year (Goldberg and McGee, 2011). In the United States alone, over 50 million individuals have been reported to experience chronic pain, leading to considerable physical, financial, and economic burdens (Yong et al., 2021). In fact, the total annual cost associated with chronic pain is estimated to range between $560 to $635 billion in the nation, surpassing the combined costs of other notable health conditions such as cancer ($243 billion), heart disease ($309 billion), and diabetes ($188 billion) (Gaskin and Richard, 2012). Moreover, its close association with mental health disorders such as depression and anxiety (Aaron et al., 2025), further amplifies the urgency for an effective solution that is yet to be found.

Although chronic pain stems from diverse sources, recent studies indicate that two major factors significantly contribute to its overall development: acute pain and stress (Timmers et al., 2019; Basbaum et al., 2009).

Pain, by definition, is an unpleasant feeling associated with potential tissue damage (Raja et al., 2020). Within the field of pain, acute pain is the immediate, intense stress response activated by the body's stress response system for specific injuries or conditions that may require immediate action to prevent further consequences (Jungquist et al., 2017). Thus, while it is often the initial source of chronic pain, acute pain itself is not inherently harmful.

Typically, acute pain arises from tissue damage or injuries, caused by outside factors such as trauma (Johnson et al., 2013). This triggers the body's stress response system, leading to the release of stress hormones such as cortisol, which acts as an anti-inflammatory that mobilizes glucose reserves for the modulation of inflammation (Hannibal and Bishop, 2014).

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However, when acute pain persists without proper healing, patients experience detrimental effects. Lack of treatment can cause acute pain to evolve into long-term pain, and later, a chronic condition. Although short-term stress — caused by acute pain — can be adaptive, persistent stress associated with chronic pain can exert deleterious effects on the body (Timmers et al., 2019).

Recent research reveals a pivotal insight: the gut and the brain are connected by the gut-brain axis, a bidirectional communication pathway, with prolonged stress having the potential to induce gut microbiota dysbiosis (Appleton, 2018) — findings that may not only aid the explanation of the underlying cause of chronic pain but also provide critical insight into the development of a promising new treatment. This disruption can lead to changes in the production of serotonin (5HT) and the integrity of the gut barrier, increasing the permeability of the gut (Guo et al., 2019). Unessential immune responses can then be triggered by heightened chances of harmful substances passing through the gut, leading to neuroinflammation and exacerbated stress — both of which are central to the pathogenesis of chronic pain (Sun et al., 2020) — reducing the production of SCFAs, whose anti-inflammatory properties are essential for maintaining gut health (Vinolo et al., 2011). This establishes a self-perpetuating loop of stress and pain, wherein reduced SCFA production leads to an inflammatory response and sensitized pain receptors, thereby facilitating the development of chronic pain (NINDS, 2023).

As such, long-term stress serves as the harbinger of chronic pain, causing dysbiosis of the gut microbiota. This dysbiosis subsequently induces greater stress and inflammation, ultimately leading to the establishment of chronic pain.

This review examines the relationship between gut microbiome dysbiosis and chronic pain, while evaluating the therapeutic potential of gut microbiome-target treatments as novel solutions for effective pain alleviation.

2. Materials and Methods

This study adopted a structured qualitative review methodology to evaluate the role of gut microbiota dysbiosis in the development of chronic pain and the potential of microbiome-targeted treatments. The research used in the paper was designed to synthesize findings across various scientific fields such as neurobiology, psychoneuroimmunology, gastroenterology, and microbiology.

2.1 Search Engines and Databases

A comprehensive literature search was conducted on peer-reviewed databases, primarily PubMed. To ensure greater credibility and relevance, further verification was done through Google Scholar, ScienceDirect, and JSTOR.

2.2 Keywords and Filters

Keywords were selected to maximize relevant sources. The primary search terms were “chronic pain,” “gut microbiota,” “microbiome inflammation,” “gut dysbiosis,” “gut-brain axis,” “serotonin dysregulation,” “short-chain fatty acids (SCFA),” “stress and dysbiosis,” “gut permeability,” and “stress and chronic pain.”

To ensure relevance and accuracy, filters were applied to select sources that were written in English and published in peer-reviewed journals from 2001 onward.

2.3 Inclusion and Exclusion Criteria

Inclusion criteria: Systematic reviews and research articles that presented empirical data (that were peer-reviewed), including animal studies, molecular analyses, and focused on the relationship between the gut microbiome and chronic pain, associated pathways such as the gut microbiome, serotonin production, and inflammation were included.

Exclusion criteria: Studies that lacked primary data (such as ones that revolved around unreferenced opinions or inferences rather than data), were not peer-reviewed, focused exclusively on acute pain, and did not investigate neuroinflammation, gut microbiota, or relevant pathways were excluded.

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2.4 Study Categorization

To enhance depth and clarity in analysis, selected studies were organized into three main categories that addressed their primary focuses: Neurotransmitters and Serotonin Pathways, Stress-Induced Gut Dysbiosis, and Microbiome-Targeted Therapeutics.

Neurotransmitters and Serotonin Pathways: Research on gut microbiota's influence on the production, regulation, signaling of neurotransmitters (especially serotonin), and their effects on nociceptive processing and psychological well-being.

Stress-Induced Gut Dysbiosis: Studies on chronic stress and its impact on microbial imbalance, increasing gut permeability, heightened pain perception due to pain sensitization, and increased serotonin production due to gut dysbiosis.

Microbiome-Targeted Therapeutics: Research and clinical studies evaluating the effects of probiotic treatments on mice suffering from gut dysbiosis, dietary interventions, and the role of microbial transplants used to restore gut health and alleviate chronic pain symptoms.

The employment of this classification allowed for a better examination of the underlying mechanisms of chronic pain and the multifaceted pathway linking gut health and pain perception, providing a foundation for the analysis of chronic pain and its potential treatments.

3. Cited Evidence on the Relationship between the Gut Microbiota and Chronic Pain

3.1 The Transition from Acute to Chronic Pain: Stress as a Central Mediator

As previously defined, pain can be categorized into acute or chronic. Often, chronic pain arises from unresolved acute episodes that persist beyond the expected period of healing, typically lasting 3~6 months (Dydyk and Conermann, 2023). Unlike acute pain, which signals immediate harm (Woolf, 2010), chronic pain lacks a clear ongoing injury, marking a shift in the body's perception of pain (and pain mechanisms in general), with the customary pain-signaling pathways becoming greatly altered due to redundant sensitization (Mifflin and Kerr, 2013).

Stress, particularly cortisol, plays a central role in this process. First, prolonged stress caused by intensified cortisol — a primary stress hormone that mobilizes glucose reserves for energy and inflammatory modulation (Hannibal and Bishop, 2014) — production due to maladaptive responses to pain or other stressors (Hannibal and Bishop, 2014), can significantly harm the body. Over time, persistent stress can lead to overall dysfunction of cortisol regulation (Hannibal and Bishop, 2014), further amplifying pain perception and causing widespread inflammation.

When acute stress persists and develops into long-standing stress, elevated levels of these hormones remain longer than necessary, disrupting the normal function of the brain by modifying its structure (Hannibal and Bishop, 2014). Stress hormones activate microglia, the brain's immune cells, leading to a prolonged pro-inflammatory state, increasing inflammatory cytokines production and neurodegenerative processes (Frank et al., 2011). Furthermore, chronic stress also impairs the integrity of the blood-brain barrier, allowing peripheral inflammatory mediators to enter and amplify inflammation (Roszkowski and Bohacek, 2016). Dysregulation of the hypothalamic-pituitary- adrenal axis due to chronic stress leads to continual cortisol elevation, promoting neurodegenerative changes and exacerbating inflammatory responses in the brain (Ménard et al., 2016).

3.2 Gut Microbiota Dysbiosis as a Driver of Inflammation

The gut microbiome, composed of numerous microorganisms such as bacteria, plays a critical role in maintaining gastrointestinal and systemic homeostasis (Rinninella et al., 2019). These microorganisms, collectively known as the gut microbiota, each perform diverse functions, including the regulation of immune responses and metabolic pathways (Richards et al., 2019). Under normal conditions, these microbes produce signaling molecules such as SCFAs and neurotransmitters, which, when balanced, allow better facilitation of immune responses and metabolic processes, protecting the body from harm. Specifically, SCFAs such as butyrate, propionate, and acetate — produced by gut

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bacteria — have been revealed to alleviate inflammation, highlighting their function as anti- inflammatory properties (Pinilla et al., 2020)

Yet not all microorganisms are favorable, as the gut microbiota can be broadly categorized into two categories: beneficial or harmful. In the gut, these microorganisms form a hierarchy. Normally, a balanced gut at equilibrium maintains homeostasis by allowing beneficial microorganisms — such as butyrate-producing species with anti-inflammatory properties (Chen and Vitetta, 2020; Pereg and McMillan, 2015) — to predominate, while the harmful bacteria remain subordinate (Zhang et al., 2015).

Though various factors contribute to dysbiosis, stress has been shown to greatly alter the composition and diversity of the gut microbiota, potentially diminishing the population of beneficial microorganisms (Foster et al., 2017). Given the microbiota's crucial role in immune regulation, such imbalances can impair the body's immune function and promote the proliferation of harmful microorganisms (Wu and Wu, 2012). The resulting shift intensifies inflammation, exacerbated by the disruption of the integrity of the gut barrier created by the decrease in SCFA production, allowing unfavorable substances to penetrate the gut with greater ease (Bidell et al., 2022).

3.3 Serotonin Production in Stress-Related Pain Sensitization

Tryptophan is an essential amino acid metabolized by the gut-inhabiting microorganisms to produce neuroactive compounds (Kaur et al., 2019). Serotonin, a type of chemical synthesized from tryptophan (Terry and Margolis, 2017), is used to transport messages through the gut-brain axis from the nerve cells in the brain to the body (Ustianowska et al., 2022), functioning as a regulate of mood and pain (Bosi et al., 2020).

In terms of pain perception, by interacting with numerous serotonin receptors, the chemical modulates nociceptive pathways that lie within the nervous system. These receptors mediate differing effects, with some alleviating pain while others intensifying it (Martin et al., 2017). For example, when 5-HT3 receptors are triggered, excitatory neurotransmitters that promote pain are elicited, rendering heightened pain sensitivity and stimuli (Zeitz et al., 2002). On the other hand, the initiation of 5-HT1A receptors inhibits the release of such transmitters, minimizing pain perception (Haleem, 2018).

When pain persists, it elevates chronic stress levels, disrupting serotonergic signaling by altering serotonin synthesis and heightening receptor sensitivity (Hao et al., 2023). In parallel, chronic stress can cause neuroinflammation (Calcia et al., 2016) which can activate the immune system, causing increased production of stress-induced cytokines, signaling molecules that activate inflammatory responses (Zhang and An, 2007). As pro-inflammatory cytokines directly stimulate pain-sensing neurons — called nociceptors — these inflammatory responses increase pain perception, rendering the body more vulnerable to stressors (Shubayev et al., 2010).

3.4 Experimental Evidence for the Gut-Brain Axis: Gut Microbiota Dysbiosis and Its Impact on Mood Disorders

Serotonin dysregulation also connects to mood disorders such as depression and anxiety. Under conventional physiological conditions, serotonin helps regulate mood and emotions via the gut-brain axis (Karayol et al., 2021), with the blood-brain barrier playing a critical role in serotonin transportation to the central nervous system. Consequently, serotonin availability in the brain is limited due to alterations caused by inflammation of the blood-brain barrier, thereby impacting an individual's mood (Appleton, 2018). Although the relationship between mental disorders and serotonin has not yet been fully understood, recent research highlights serotonin's role in such illnesses, portraying a strong association between serotonin dysregulation, depression, and inflammation (Marazziti, 2017).

The first study, "Changes in Gut Microbiota by Chronic Stress Impair the Efficacy of Fluoxetine" (Siopi et al., 2020), focused on researching the relationship between chronic stress — the product of unresolved overwhelming stressors (Mariotti, 2015) — gut microbiota (GM), and the effectiveness of antidepressant medications on mice exhibiting symptoms of depression. The study aimed to better explore the potential of microbiota-targeted treatments for major depressive disorders (MDDs).

To establish depressive-like behaviors in mice, researchers exposed the animals to unpredictable chronic mild stress (UCMS). To isolate the impact of stress-altered gut microbiota (GM), microbiota from stressed mice were

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transplanted into healthy mice that were not subjected to UCMS.

The researchers discovered that the recipient mice — which had not been exposed to direct stress-inducing factors — began to exhibit depression-like behaviors mirroring those of the donor mice. The recipient mice suffered from decreased neurogenesis in the hippocampus, a pivotal region of the brain in charge of mood regulation, and deficits in serotonin (5HT) bioavailability.

However, once the mice were treated with 5-hydroxytryptophan (5-HTP), such symptoms were alleviated. The researchers concluded that the transferred gut microbiome hindered serotonin production and transportation.

The second study investigated the effects of serotonin (mainly produced in the gut) on the cognitive functions of mice that were subjected to chronic unforeseeable mild stress stimulation (CUMS) (Ma et al., 2023). Chronic stress is often associated with weakened cognitive function, causing issues in areas such as memory maintenance, learning, and emotional control. The researchers of the following experiment sought to mitigate these detrimental effects by focusing on the role of the gut-brain axis in the development of depression. To do so, the researchers probing the experience used CUMS to induce stress-related behaviors in TPH2 knockout mice — which lacked enzymes vital for serotonin synthesis, causing the mice to suffer from inadequate serotonin production. Behavioral tests were then conducted on the mice to assess their cognitive function, along with anxiety and depressive-like behaviors.

The findings of the study revealed the following: (1) TPH2 knockout CUMS mice showed reduced serotonin levels along with intensified cognitive dysfunction. (2) the mice exhibited decreased levels of neurotransmission but increased records of neuroinflammatory responses and hippocampal autophagy.

In response, the researchers implemented a probiotic treatment (Lactococcus lactis E001-B-8 fungus powder), which improved the cognitive behavior, modulation of gut microbiome composition, and serotonin metabolism of CUMS mice — the probiotic treatment even outperformed fluoxetine, an antidepressant commonly used for alleviation of depressive and anxiety-like symptoms induced by CUMS.

4. Discussion

Chronic pain, long considered a condition without clearly defined fundamental origins, is now increasingly understood to be shaped by gut microbiota dysbiosis. Specifically, disruption in the gut-brain axis, particularly through dysbiosis, has been implicated in the development and persistence of chronic pain.

A foundational starting point of chronic pain (as mentioned above) is unresolved acute pain. A central mediator in this transitional process is stress, which, when prolonged, triggers hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis (Ménard et al., 2016). Persistent release of cortisol leads to inadequate neuroplastic changes that amplify pain perception, with cortisol contributing to neuroinflammation, while its degradation of the blood-brain barrier permits peripheral cytokines to enter the central nervous system, further intensifying inflammation (Frank et al., 2011; Roszkowski and Bohacek, 2016). This intrusion of peripheral inflammatory mediators of the central nervous system intensifies inflammation within the brain, promoting a self-sustaining loop between stress and inflammation. The persistent state of neuroinflammation heightens pain stimuli, contributing to the remodeling in pain processing, illustrating how stress can initiate chronic pain even in the absence of ongoing damage.

Integral to this process is the role of the gut microbiota. As explained, under normal conditions, these microbes maintain equilibrium by promoting the production of beneficial metabolites such as SCFAs, which are crucial in regulating immune responses, reducing inflammation, and sustaining the gut epithelial barrier (Vinolo et al., 2011). Thus, it can be interpreted that a balanced gut microbiome is essential for controlling inflammatory responses and preventing overactivation of immune cells.

However, chronic stress disrupts this balance, reducing microbial diversity through the depletion of beneficial bacteria and the domination of harmful populations (Foster et al., 2017). This dysbiosis of the gut leads to a decline in SCFA production, impairing the gut barrier by increasing intestinal permeability — a phenomenon referred to as “leaky gut” (Camilleri, 2021). This increased permeability of the gut barrier allows harmful bacterial products to transport into the bloodstream at higher rates, triggering immune activation and inflammation. The inflammatory cytokines released in response travel to the brain, enhancing neuroinflammation, a significant factor in the development and continuation of chronic pain (Sun et al., 2020). Such relationships not only suggest the existence of

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the gut-brain axis but also underscore the connection between microbiota dysbiosis and chronic pain.

Additionally, beyond its influence on inflammatory processes, gut dysbiosis disrupts the synthesis and signaling of key neuroactive compounds. Notably, approximately 90% of serotonin is synthesized in the gastrointestinal tract (Bektas et al., 2020), positioning the gut as a central regulator of serotonin production and function. Consequently, gut dysbiosis can be interpreted as a significant contributor to altered pain perception, mood regulation, and overall neuroimmune communication.

Under conditions of chronic stress, serotonergic signaling becomes disrupted as stress reduces the synthesis of serotonin by altering tryptophan metabolism (Hao et al., 2023). These changes result in heightened pain sensitivity, paving the way towards chronic pain. Moreover, dysregulation of serotonin levels contributes to the development of mood disorders such as depression and anxiety, which frequently coexist with chronic pain. Such mood disorders not only intensify stress but also the perception of pain as well, further embedding individuals in the cycle of chronic pain.

Experimental evidence supports this cycle as well. In the study by Siopi et al. The mice who received gut microbiota from chronically stressed mice exhibited depression-like behaviors. These mice also exhibited reduced neurogenesis and serotonin bioavailability, highlighting the gut microbiota's capacity to modulate stress and serotonin through the gut-brain axis (2020). Further insights were provided by the study conducted by Ma et al., which examined the cognitive effects of chronic stress in mice (2023). These mice showed a significant elevation in neuroinflammation. However, after probiotic treatment with Lactococcus lactis the mice restored serotonin metabolism along with its composition of the gut microbiome. The study underscores the role of the gut microbiota, supporting the notion of the gut-brain axis. However, its results can be applied to other aspects, especially chronic pain. The research supports the gut microbiota's relationship with chronic pain, as it signifies that chronic stress — which is often associated with chronic pain — leads to notable changes in the gut microbiota. Such alterations were closely related to cognitive impairments and neuroinflammation, both of which are widely occurring features of chronic pain.

This cycle is represented in Figure 1, which illustrates the progression of stress-induced dysbiosis to neuroinflammation and heightened pain sensitivity. The figure demonstrates the role of gut dysbiosis in the development of chronic pain, emphasizing mechanisms such as serotonergic disruption, immune activation, and SCFA deficiency. Through visual synthesis, Figure 1 reinforces the relevance of microbiome-targeted solutions for future chronic pain interventions.

Together, these studies illustrate a cyclical relationship in which chronic stress (developed initially from acute pain) initiates gut dysbiosis, leading to impaired immune function and serotonin regulation. These disruptions heighten pain sensitivity and contribute to the development of mood disorders, which in turn heighten stress levels, reinforcing the cycle of inflammation, which ultimately progresses into chronic pain.

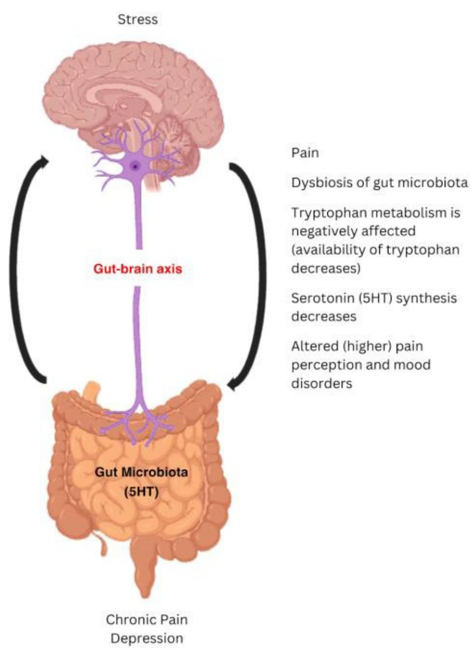

Figure 1. Visual representation of the gut microbiome-chronic pain cycle

4.1 The Therapeutic Potential of Gut Microbiota in Chronic Pain Management

Understanding this dynamic has important implications for future treatments. Traditional chronic pain treatments, particularly opioids (Ballantyne, 2006), often fail to provide long-term relief and may result in addiction or other health issues, as they focus more on symptom management (which often leads to higher doses) rather than addressing the root cause (DuPen et al., 2007).

However, unlike conventional methods of pain relief, probiotic treatment (noted in the second study), specifically with Lactococcus lactis E001-B, shows to be effective in reducing depression, anxiety-like symptoms,

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neuroinflammation, and restoring serotonin production. These findings underscore the potential of microbiota-targeted interventions to address not only the symptoms but the underlying sources of chronic pain.

5. Limitations

While emerging evidence suggests a relationship between gut dysbiosis and chronic pain, several limitations and alternative perspectives warrant consideration, as noted in "Gut dysbiosis in patients with chronic pain: a systematic review and meta-analysis" (Goudman et al., 2024).

The systematic review synthesizes data from 21 studies to examine the relationship between gut microbiota dysbiosis and chronic pain, reporting reduced alpha diversity and taxonomic shifts (such as decreased Faecalibacterium and increased Eggerthella) in patients compared to controls. However, the article also highlights important limitations worth consideration. Notably, results for beta-diversity, which reflect overall microbial community structure, were incoherent, undermining the notion of gut dysbiosis as a universal feature of chronic pain. Goudman et al. also acknowledge that most included studies were cross-sectional, raising the possibility that microbiota alterations may be consequential, rather than causational for chronic pain (2024).

Additionally, methodological heterogeneity across cited studies (such as varieties in sequencing technologies, patient populations, and analytic approaches) used in the research limits direct comparability and generalizability — with factors such as diet, medication, and comorbidities being inconsistently controlled as well — further challenging the notion of the gut-brain axis and its role in chronic pain.

While rodent models offer experimental control, the validity of these findings is limited, due to differences in immune system complexity, microbiota diversity, and neurocognitive functions between mice and humans. Moreover, inconsistency in microbial profiling methods across cited studies and short study durations introduce variability that complicates direct comparison of the relationship between gut dysbiosis and chronic pain — as chronic pain, by definition, develops and persists over months or years, raising reasonable doubt towards the reliability of conclusions about causality, long-term efficacy, and safely. Consequently, greater methodological rigor and mechanistic research are needed to clarify and justify the clinical relevance of gut microbiota changes in chronic pain.

6. Ethical Concerns and Future Directions

While microbiome-targeted treatments hold therapeutic potential worth consideration, certain ethical considerations remain unresolved. As Ma et al. emphasize, microbiome-manipulating interventions may inadvertently affect not only immunity and mental health, but also broader issues such as individual identity and social dynamics, including stigma, privacy, and ownership of biological data (2018). As long-term immunological disruptions, psychological impacts from incidental findings, and misinterpretation of microbial "fingerprints" also pose concerns regarding personal consent, microbiome-targeted treatments continue to be a topic of ethical debate (Ma et al., 2018). Additionally, Olesen and Alm caution against the widespread but vague usage of diagnostic terms such as "dysbiosis" without mechanistic clarity, explaining that such labels could lead to unjustified and premature interventions (2016).

To address these concerns, future research should prioritize mechanistic validation by minimizing risk through controlled trials involving robust donor screening and sample processing protocols and enforce strong data protections aligned with standards such as the Health Insurance Portability and Accountability Act (HIPAA).

Moreover, ethical review boards must also be involved in study design, particularly in research involving vulnerable populations or novel microbiome-targeted therapies. Only by addressing these issues can microbiome-targeted treatments be responsibly and safely applied in clinical practices.

7. Conclusion

The intricate relationship between chronic pain and the gut microbiome is an area of growing interest, though concrete empirical evidence is still in finding, with several studies indicate that the gut microbiome is highly likely to play a significant role in the development and persistence of chronic pain. The process often starts with acute pain that, over time, triggers sustained inflammation. Though, under normal circumstances, the gut-brain axis maintains at equilibrium, stress disrupts the hierarchy of the gut microbiota, leading to dysbiosis, reducing production of serotonin. As the gut and brain communicate through the gut-brain axis, this imbalance may also render the body to be more susceptible to mental health issues, further exacerbating stress and pain.

Chronic stress can also lead to neuroinflammation, which promotes the release of pro-inflammatory cytokines, prolonging inflammation, and increasing pain sensitivity and stress levels. These molecules contribute to a feedback loop where inflammation and stress perpetuate each other, ultimately resulting in chronic pain, highlighting the complex relationship between stress, gut microbiota, and chronic pain.

On a personal level, individuals can alleviate chronic pain to a certain extent by prioritizing gut health. Taking on a diet composed of various nutrients, particularly those high in fiber, can promote healthy gut activity. Consuming varieties of fruits, vegetables, and whole grains will provide essential nutrients that support the development of beneficial gut bacteria, while reducing the intake of processed goods and refined sugars could stabilize the balance of the gut environment. Beyond diet, regular exercise exerts effects on chronic pain management, as exercise is strongly correlated with stress management. However, individual efforts alone are not sufficient, as medical treatment remains a dominant source for comprehensive pain management.

Given the potential role of the gut microbiome in chronic pain, more research is needed to explore how modulating the microbiome might offer a novel approach to pain management. Targeting the gut microbiome could allow for more direct intervention at the root of chronic pain, potentially offering relief with fewer side effects than traditional pain management strategies. Although such treatments may require greater time to take effect, their potential benefits, such as more sustainable pain relief and improved overall well-being, could outweigh these drawbacks.

References

Aaron, R. V., et al. (2025). Prevalence of Depression and Anxiety Among Adults With Chronic Pain: A Systematic Review and Meta-Analysis. *JAMA Network Open*, 8(3), e250268. https://doi.org/10.1001/jamanetworkopen.2025.0268

Appleton, J. (2018). The Gut-Brain Axis: Influence of Microbiota on Mood and Mental Health. *Integrative Medicine: A Clinician's Journal*, 17(4), 28–32. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6469458/

Ballantyne, J. C. (2006). Opioids for Chronic Nonterminal Pain. *Southern Medical Journal*, 99(11), 1245–1255. https://doi.org/10.1097/01.smj.0000223946.19256.17

Bamalan, O. A., & Al Khalili, Y. (2023, July 30). Physiology, Serotonin. *PubMed; StatPearls Publishing*. https://www.ncbi.nlm.nih.gov/books/NBK545168/

Basbaum, A. I., et al. (2009). Cellular and Molecular Mechanisms of Pain. *Cell*, 139(2), 267–284. https://doi.org/10.1016/j.cell.2009.09.028

Bektas, A., et al. (2020). Does Seratonin in the intestines make you happy? The Turkish Journal of Gastroenterology, 31(10), 721–723. https://doi.org/10.5152/tjg.2020.19554

Bidell, M. R., Hobbs, A. L. V., & Lodise, T. P. (2022). Gut microbiome health and dysbiosis: A clinical primer. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 42(11), 849–857. https://doi.org/10.1002/phar.2731

Bosi, A., et al. (2020). Tryptophan Metabolites Along the Microbiota-Gut-Brain Axis: An Interkingdom Communication System Influencing the Gut in Health and Disease. *International Journal of Tryptophan Research*, 13, 117864692092898. https://doi.org/10.1177/1178646920928984

Calcia, M. A., et al. (2016). Stress and neuroinflammation: a systematic review of the effects of stress on microglia and the implications for mental illness. *Psychopharmacology*, 233(9), 1637–1650. https://doi.org/10.1007/s00213-016-4218-9

Camilleri, M. (2021). What is the leaky gut? Clinical considerations in humans. Current Opinion in Clinical Nutrition & Metabolic Care, Publish Ahead of Print. https://doi.org/10.1097/mco.0000000000000778

Chen, J., & Vitetta, L. (2020). The Role of Butyrate in Attenuating Pathobiont-Induced Hyperinflammation. *Immune Network*, 20(2). https://doi.org/10.4110/in.2020.20.e15

Chou, R., et al. (2020). Treatments for Acute Pain: A Systematic Review [Internet]. In www.ncbi.nlm.nih.gov. *Agency for Healthcare Research and Quality (US)*. https://www.ncbi.nlm.nih.gov/books/NBK566500/

DuPen, A., Shen, D., & Ersek, M. (2007). Mechanisms of Opioid-Induced Tolerance and Hyperalgesia. *Pain Management Nursing*, 8(3), 113–121. https://doi.org/10.1016/j.pmn.2007.02.004

Dydyk, A. M., & Conermann, T. (2023). Chronic Pain. *PubMed; StatPearls Publishing.* https://www.ncbi.nlm.nih.gov/books/NBK553030/

Foster, J. A., Rinaman, L., & Cryan, J. F. (2017). Stress & the gut-brain axis: Regulation by the microbiome. *Neurobiology of Stress*, 7(7), 124–136. https://doi.org/10.1016/j.ynstr.2017.03.001

Frank, M. G., Watkins, L. R., & Maier, S. F. (2011). Stress- and glucocorticoid-induced priming of neuroinflammatory responses: Potential mechanisms of stress-induced vulnerability to drugs of abuse. *Brain, Behavior, and Immunity*, 25, S21–S28. https://doi.org/10.1016/j.bbi.2011.01.005

Gaskin, D. J., & Richard, P. (2012). The Economic Costs of Pain in the United States. *The Journal of Pain*, 13(8), 715–724. https://doi.org/10.1016/j.jpain.2012.03.009

Goldberg, D. S., & McGee, S. J. (2011). Pain as a Global Public Health Priority. *BMC Public Health*, 11(1). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3201926/

Goudman, L., et al. (2024). Gut dysbiosis in patients with chronic pain: a systematic review and meta-analysis. *Frontiers in Immunology*, 15. https://doi.org/10.3389/fimmu.2024.1342833

Guo, R., et al. (2019). Pain regulation by gut microbiota: molecular mechanisms and therapeutic potential. *British Journal of Anaesthesia*, 123(5), 637–654. https://doi.org/10.1016/j.bja.2019.07.026

Haleem, D. J. (2018). Serotonin-1A receptor dependent modulation of pain and reward for improving therapy of chronic pain. *Pharmacological Research*, 134, 212–219. https://doi.org/10.1016/j.phrs.2018.06.030

Hannibal, K. E., & Bishop, M. D. (2014). Chronic Stress, Cortisol Dysfunction, and Pain: A Psychoneuroendocrine Rationale for Stress Management in Pain Rehabilitation. *Physical Therapy*, 94(12), 1816–1825. https://doi.org/10.2522/ptj.20130597

Hao, S., et al. (2023). Multiple modulatory roles of serotonin in chronic pain and injury-related anxiety. *Frontiers in Synaptic Neuroscience*, 15. https://doi.org/10.3389/fnsyn.2023.1122381

Johnson, Q., Borsheski, R. R., & Reeves-Viets, J. L. (2013). A Review of Management of Acute Pain. *Missouri Medicine*, 110(1), 74–79. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6179627/

Jungquist, C. R., et al. (2017). Assessing and Managing Acute Pain. *AJN, American Journal of Nursing*, 117(3), S4–S11. https://doi.org/10.1097/01.naj.0000513526.33816.0e

Karayol, R., et al. (2021). Serotonin receptor 4 in the hippocampus modulates mood and anxiety. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-020-00994-y

Kaur, H., Bose, C., & Mande, S. S. (2019). Tryptophan Metabolism by Gut Microbiome and Gut-Brain-Axis: An in silico Analysis. *Frontiers in Neuroscience*, 13. https://doi.org/10.3389/fnins.2019.01365

Vol. 2025 (10) 806 – 816
ISSN 2688-3651 [online]

Lucas, J. W., & Sohi, I. (2024). Chronic pain and high-impact chronic pain in U.S. adults, 2023 (NCHS Data Brief No. 518). *National Center for Health Statistics*. https://doi.org/10.15620/cdc/169630

Ma, J., et al. (2023). 5-HT attenuates chronic stress-induced cognitive impairment in mice through intestinal flora disruption. *Journal of Neuroinflammation*, 20(1). https://doi.org/10.1186/s12974-023-02693-1

Ma, Y., Chen, H., Lan, C., & Ren, J. (2018). Help, hope and hype: ethical considerations of human microbiome research and applications. *Protein & Cell*, 9(5), 404–415. https://doi.org/10.1007/s13238-018-0537-4

Marazziti, D. (2017). Understanding the role of serotonin in psychiatric diseases. *F1000Research*, 6. https://doi.org/10.12688/f1000research.10094.1

Mariotti, A. (2015). The effects of chronic stress on health: new insights into the molecular mechanisms of brain–body communication. *Future Science OA*, 1(3). https://doi.org/10.4155/fso.15.21

Martin, S. L., et al. (2017). 5-HT modulation of pain perception in humans. *Psychopharmacology*, 234(19), 2929–2939. https://doi.org/10.1007/s00213-017-4686-6

Ménard, C., et al. (2016). Immune and Neuroendocrine Mechanisms of Stress Vulnerability and Resilience. *Neuropsychopharmacology*, 42(1), 62–80. https://doi.org/10.1038/npp.2016.90

Mifflin, K. A., & Kerr, B. J. (2013). The transition from acute to chronic pain: understanding how different biological systems interact. *Canadian Journal of Anesthesia/Journal Canadien D'anesthésie*, 61(2), 112–122. https://doi.org/10.1007/s12630-013-0087-4

NINDS. (2023). Pain | *National Institute of Neurological Disorders and Stroke*. Www.ninds.nih.gov. https://www.ninds.nih.gov/health-information/disorders/pain

Olesen, S. W., & Alm, E. J. (2016). Dysbiosis is not an answer. *Nature Microbiology*, 1(12). https://doi.org/10.1038/nmicrobiol.2016.228

Pereg, L., & McMillan, M. (2015). Scoping the potential uses of beneficial microorganisms for increasing productivity in cotton cropping systems. *Soil Biology and Biochemistry*, 80, 349–358. https://doi.org/10.1016/j.soilbio.2014.10.020

Pinilla, A., Tamayo, R. M., & Neira, J. (2020). How Do Induced Affective States Bias Emotional Contagion to Faces? A Three-Dimensional Model. *Frontiers in Psychology*, 11. https://doi.org/10.3389/fpsyg.2020.00097

Raja, S. N., et al. (2020). The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*, 161(9). PubMed. https://doi.org/10.1097/j.pain.0000000000001939

Richards, A. L., et al. (2019). Gut Microbiota Has a Widespread and Modifiable Effect on Host Gene Regulation. *MSystems*, 4(5). https://doi.org/10.1128/msystems.00323-18

Rinninella, E., et al. (2019). What is the Healthy Gut Microbiota composition? A Changing Ecosystem across age, environment, diet, and Diseases. *Microorganisms*, 7(1), 14. https://doi.org/10.3390/microorganisms7010014

Roszkowski, M., & Bohacek, J. (2016). Stress does not increase blood–brain barrier permeability in mice. *Journal of Cerebral Blood Flow & Metabolism*, 36(7), 1304–1315. https://doi.org/10.1177/0271678x16647739

Shubayev, V. I., Kinshi Kato, & Myers, R. R. (2010). Cytokines in Pain. *Nih.gov; CRC Press/Taylor & Francis*. https://www.ncbi.nlm.nih.gov/books/NBK57275/

Siopi, E., et al. (2020). Changes in Gut Microbiota by Chronic Stress Impair the Efficacy of Fluoxetine. *Cell Reports*, 30(11), 3682-3690.e6. https://doi.org/10.1016/j.celrep.2020.02.099

Vol. 2025 (10) 806 – 816
ISSN 2688-3651 [online]

Sun, L.-J., Li, J.-N., & Nie, Y.-Z. (2020). Gut hormones in microbiota-gut-brain cross-talk. *Chinese Medical Journal*, 133(7), 826–833. https://doi.org/10.1097/cm9.0000000000000706

Terry, N., & Margolis, K. G. (2017). Serotonergic Mechanisms Regulating the GI Tract: Experimental Evidence and Therapeutic Relevance. *Handbook of Experimental Pharmacology*, 239, 319–342. https://doi.org/10.1007/164_2016_103

Timmers, I., et al. (2019). The interaction between stress and chronic pain through the lens of threat learning. *Neuroscience & Biobehavioral Reviews*, 107, 641–655. https://doi.org/10.1016/j.neubiorev.2019.10.007

Ustianowska, K., et al. (2022). The Role of the Human Microbiome in the Pathogenesis of Pain. *International Journal of Molecular Sciences*, 23(21), 13267. https://doi.org/10.3390/ijms232113267

Vinolo, M. A. R., et al. (2011). Regulation of Inflammation by Short Chain Fatty Acids. *Nutrient*s, 3(10), 858–876. https://doi.org/10.3390/nu3100858

Wachsmuth, H. R., Weninger, S. N., & Duca, F. A. (2022). Role of the gut–brain axis in energy and glucose metabolism*. Experimental and Molecular Medicine*, 54(4), 377–392. https://doi.org/10.1038/s12276-021-00677-w

Woolf, C. J. (2010). What is this thing called pain? *Journal of Clinical Investigation*, 120(11), 3742–3744.

Wu, H.-J., & Wu, E. (2012). The role of gut microbiota in immune homeostasis and autoimmunity*. Gut Microbes*, 3(1), 4–14. https://doi.org/10.4161/gmic.19320

Yong, R. J., et al. (2021). The prevalence of chronic pain among adults in the United States. *Pain*, 163(2), e328–e332. https://doi.org/10.1097/j.pain.0000000000002291

Zeitz, K. P., et al. (2002). The 5-HT3Subtype of Serotonin Receptor Contributes to Nociceptive Processing via a Novel Subset of Myelinated and Unmyelinated Nociceptors. *The Journal of Neuroscience*, 22(3), 1010–1019. https://doi.org/10.1523/jneurosci.22-03-01010.2002

Zhang, J.-M., & An, J. (2007). Cytokines, Inflammation, and Pain. *International Anesthesiology Clinics*, 45(2), 27–37. https://doi.org/10.1097/AIA.0b013e318034194e

Zhang, Y.-J., et al. (2015). Impacts of Gut Bacteria on Human Health and Diseases. *International Journal of Molecular Sciences*, 16(12), 7493–7519. https://doi.org/10.3390/ijms16047493