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EPIGENETIC MECHANISMS IN CHRONIC PAIN: FROM MOLECULAR PLASTICITY TO THERAPEUTIC INNOVATION – A SYSTEMATIC REVIEW

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ABSTRACT

Background: Chronic pain is increasingly recognized as a complex neurobiological disorder driven by persistent alterations in neuronal signalling, gene expression, and central sensitization rather than sustained nociceptive input alone. Epigenetic mechanisms have emerged as key regulators of these long-term molecular changes, linking environmental exposures with sustained pain states.

Objective: To systematically synthesize current evidence on epigenetic mechanisms involved in chronic pain, including DNA methylation, histone modifications, and non-coding RNA regulation, and to evaluate their therapeutic implications.

Methods: A structured literature search was conducted across PubMed, Scopus, and Google Scholar for studies published between 2005 and 2024. Keywords included "chronic pain," "epigenetics," "DNA methylation," "histone modification," and "microRNA." Eligible studies included experimental, clinical, and review articles examining epigenetic regulation in pain pathways. Data were extracted systematically, and findings were synthesized qualitatively. Risk of bias was assessed based on study design and methodological clarity, and evidence quality was evaluated using a modified GRADE approach.

Results: Fifteen key studies were included. Evidence consistently demonstrates that epigenetic mechanisms modulate neuronal plasticity, inflammatory signalling, and synaptic transmission in chronic pain. DNA methylation and histone modifications regulate transcriptional activity in nociceptive pathways, while non-coding RNAs influence post-transcriptional gene expression. These mechanisms contribute to the transition from acute to chronic pain through central sensitization. Environmental factors such as stress and lifestyle further influence epigenetic profiles, contributing to variability in pain susceptibility and treatment response.

Conclusion: Epigenetic regulation represents a critical interface between environmental factors and chronic pain pathophysiology. Targeted epigenetic therapies, including HDAC inhibitors and RNA-based approaches, hold promise for precision pain management. Further translational and clinical studies are required to validate these emerging therapeutic strategies

KEYWORDS: Chronic pain; Epigenetics; DNA methylation; Histone modification; MicroRNA; Central sensitization; Precision analgesia

1. INTRODUCTION

Pain is defined by the International Association for the Study of Pain as *"an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."* While acute pain serves an adaptive role by signalling tissue injury, persistent pain beyond the expected healing period evolves into **chronic pain**, a condition associated with profound alterations in neural function.

Chronic pain affects approximately one-fifth of the global population and represents a major medical and socioeconomic challenge. Traditional models have largely attributed chronic pain to structural damage or persistent nociceptive input. However, recent research indicates that long-term changes in **gene expression and neuronal plasticity** are central to the maintenance of chronic pain states.

The concept of Epigenetics, originally introduced by Conrad Waddington, provides a framework for understanding how environmental and physiological factors influence gene expression without altering the DNA sequence. Epigenetic regulation allows external stimuli such as inflammation, nerve injury, or psychological stress to produce persistent molecular changes in neuronal circuits. These modifications may create a form of **molecular memory**, contributing to the persistence of pain long after the initial injury has resolved.

METHODOLOGY OF LITERATURE SEARCH

A structured literature search was conducted to identify relevant studies on epigenetic mechanisms in chronic pain. Electronic databases including **PubMed**, **Scopus**, and **Google Scholar** were systematically searched for peer-reviewed articles published between **2005 and 2024**. The search strategy used combinations of keywords such as *"chronic pain," "epigenetics," "DNA methylation," "histone modification," "microRNA," "central*

sensitization," and *"pain neuroplasticity."* Boolean operators (AND/OR) were applied to refine the search and improve retrieval of relevant literature.

Articles were included if they discussed epigenetic regulation in pain pathways, mechanisms linking epigenetics to chronic pain development, or potential epigenetic-based therapeutic strategies. Both experimental and clinical studies, as well as authoritative review articles, were considered. Studies not directly related to pain mechanisms or lacking sufficient methodological clarity were excluded. Reference lists of selected papers were also screened to identify additional relevant sources. The final references were chosen based on relevance, scientific quality, and contribution to the understanding of epigenetic regulation in chronic pain.

To enhance methodological rigor, this review followed key principles of systematic reviews, including predefined inclusion and exclusion criteria, structured database searching, and critical appraisal of study relevance. Although a formal PRISMA flow diagram was not constructed, study selection was performed in a stepwise manner involving identification, screening, eligibility assessment, and inclusion. Emphasis was placed on reproducibility and transparency in search strategy. Where possible, findings from multiple studies were compared to identify consistent patterns in epigenetic regulation across different chronic pain conditions, thereby improving the reliability and interpretability of the synthesized evidence.

Data extraction was performed by reviewing full-text articles and summarizing key variables including study design, population characteristics, type of epigenetic mechanism studied, and major outcomes related to pain modulation. Particular attention was given to distinguishing between preclinical and clinical evidence. Studies were grouped based on epigenetic mechanisms such as DNA methylation, histone modification, and non-coding RNA regulation to facilitate thematic synthesis. Any discrepancies in interpretation were resolved through consensus discussion, ensuring consistency in data interpretation and minimizing subjective bias in the review process.

Risk of bias was qualitatively assessed based on study design, methodological clarity, and reproducibility, and categorized as low, moderate, or high

2. EPIGENETIC MECHANISMS IN PAIN REGULATION

Epigenetic processes regulate gene transcription through chemical modifications that alter chromatin structure or RNA activity. Three major mechanisms have been implicated in pain modulation. Collectively, the evidence across these epigenetic mechanisms highlights a converging role in modulating neuronal plasticity and pain signaling. While individual mechanisms such as DNA methylation or histone modification have distinct regulatory functions, their interactions are increasingly recognized as critical in shaping transcriptional responses in chronic pain states. Cross-study comparisons suggest that these mechanisms do not operate in isolation but rather form an integrated regulatory network. This integrated perspective strengthens the understanding of chronic pain as a systems-level disorder and supports the need for multimodal therapeutic strategies targeting multiple epigenetic pathways simultaneously.

2.1 DNA Methylation

DNA methylation involves the addition of a methyl group to cytosine bases, typically within CpG islands located in gene promoter regions. This modification generally suppresses gene transcription by preventing transcription factor binding or by recruiting proteins that condense chromatin structure.

Alterations in DNA methylation patterns have been identified in several chronic pain conditions. Reduced methylation in certain neural regions has been associated with increased expression of genes involved in nociceptive signalling. Conversely, hypermethylation of genes such as *OPRM1*, which encodes the μ-opioid receptor, may reduce receptor expression and contribute to diminished opioid responsiveness in some chronic pain patients.

Importantly, DNA methylation is **potentially reversible**, making it an attractive therapeutic target for future pain management strategies.

2.2 Histone Modifications

DNA in the nucleus is wrapped around histone proteins, forming nucleosomes that organize chromatin. Chemical modifications of histone tails—including acetylation, methylation, and phosphorylation—regulate the accessibility of DNA to transcriptional machinery.

Histone acetylation is mediated by histone acetyltransferases (HATs), which facilitate gene transcription by loosening chromatin structure. In contrast, histone deacetylases (HDACs) remove acetyl groups and typically suppress gene expression.

Experimental studies have demonstrated that nerve injury can increase HDAC activity within the spinal cord and brain, resulting in reduced expression of genes that normally inhibit nociceptive signaling. Pharmacological inhibition of HDACs has been shown to reverse these effects and reduce pain hypersensitivity in animal models.

2.3 Non-coding RNAs

Non-coding RNAs regulate gene expression at the post-transcriptional level without encoding proteins. Among them, **microRNAs (miRNAs)** are particularly important in pain regulation.

MicroRNAs bind to complementary sequences on messenger RNA molecules, leading to mRNA degradation or inhibition of translation. Altered microRNA expression profiles have been reported in chronic pain disorders such

as Fibromyalgia and Complex Regional Pain Syndrome. These regulatory RNAs influence inflammatory pathways, neuronal excitability, and synaptic plasticity, thereby contributing to persistent pain signaling.

3. Epigenetic Basis of the Transition from Acute to Chronic Pain

The progression from acute to chronic pain involves complex molecular changes that stabilize nociceptive signalling within the nervous system.

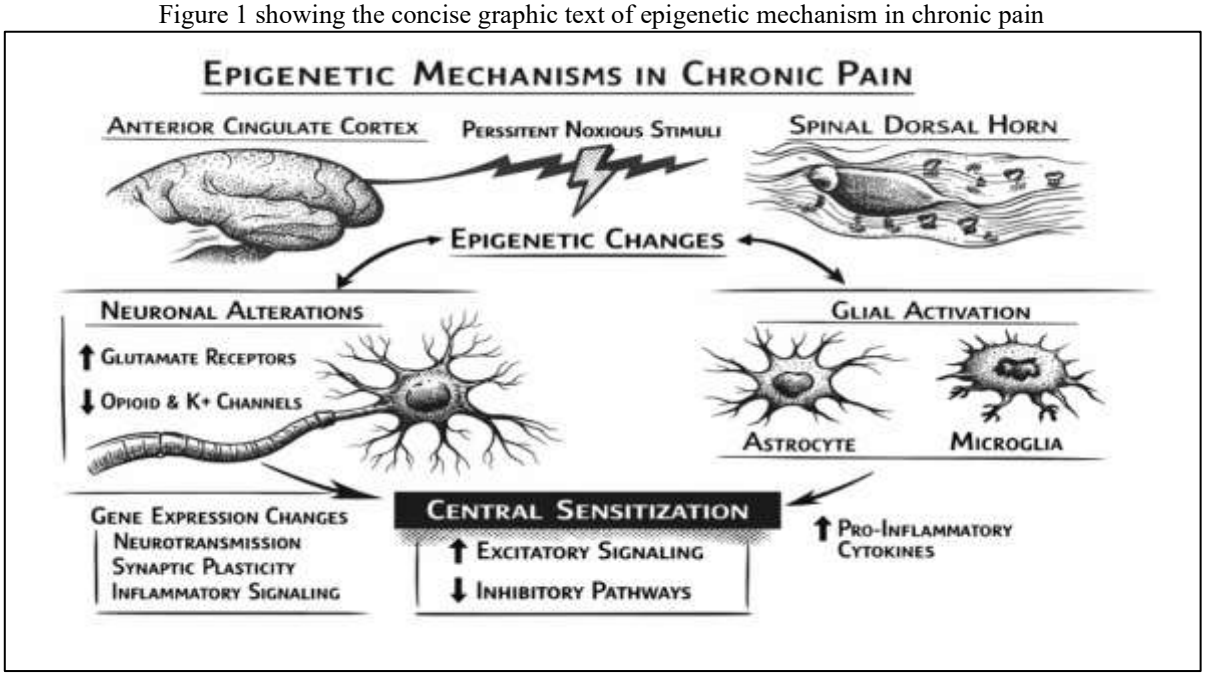
Persistent noxious stimuli can induce epigenetic remodelling in neurons of the spinal dorsal horn as well as higher cortical regions such as the anterior cingulate cortex. These changes alter the expression of genes involved in neurotransmission, synaptic plasticity, and inflammatory signalling.

Epigenetic modifications may enhance the expression of excitatory receptors, including glutamate receptors, while simultaneously suppressing inhibitory pathways such as potassium channel activity or opioid receptor signalling. This imbalance contributes to **central sensitization**, a condition in which the nervous system becomes hypersensitive to pain stimuli.

Glial cells, including astrocytes and microglia, also undergo epigenetic changes during chronic pain states. These alterations promote the release of pro-inflammatory cytokines that further amplify nociceptive transmission.

From a systematic perspective, multiple studies consistently demonstrate that epigenetic remodelling is a key driver in the transition from acute to chronic pain. Despite variability in experimental models and patient populations, common findings include enhanced excitatory signalling, reduced inhibitory control, and sustained inflammatory activation. These consistent patterns across studies support the hypothesis that epigenetic regulation serves as a unifying mechanism underlying chronic pain development. However, heterogeneity in methodologies and outcome measures across studies highlights the need for standardized research frameworks in future investigations. Figure 1

Figure 1 showing the concise graphic text of epigenetic mechanism in chronic pain



4. Environmental and Lifestyle Influences on Pain Epigenetics

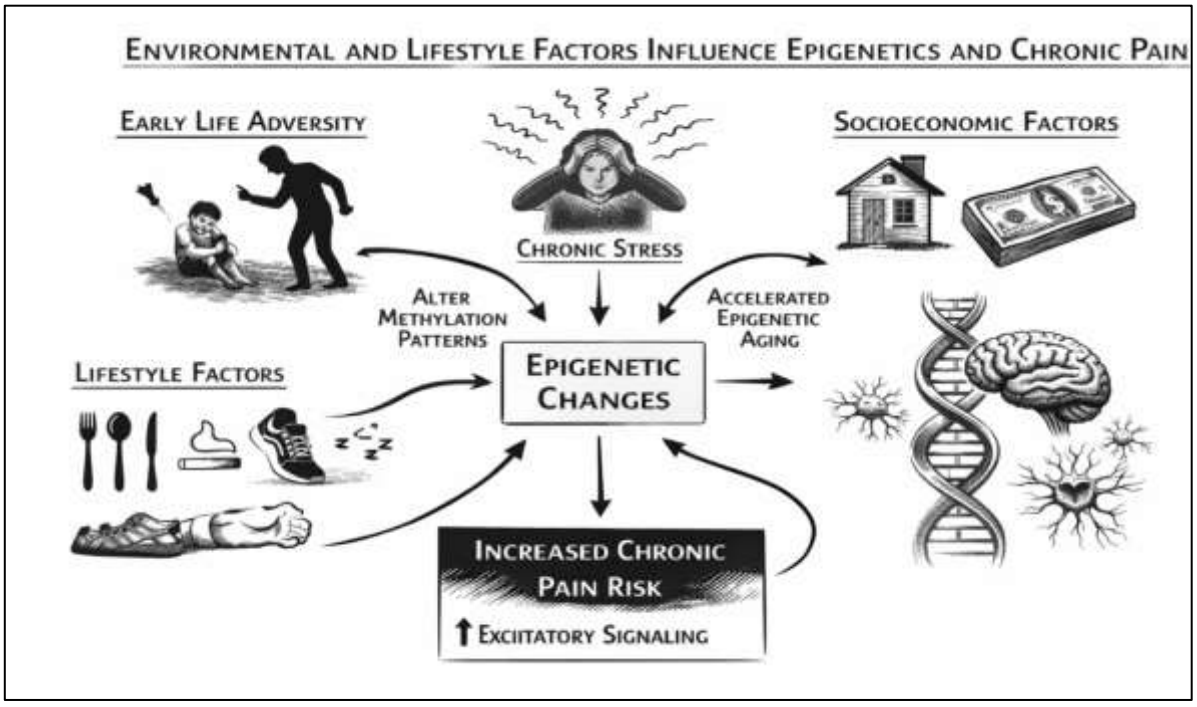
The epigenome is highly dynamic and can respond to environmental and lifestyle factors throughout life. Unlike genetic mutations, epigenetic modifications—such as DNA methylation and histone modification—are reversible and influenced by external exposures. This adaptability helps explain why individuals with similar genetic backgrounds can experience very different susceptibility to chronic pain. Environmental factors can shape the regulation of genes involved in inflammation, neuronal plasticity, and stress responses, thereby influencing pain perception and long-term pain outcomes.

One of the most important environmental influences on epigenetic regulation is early life stress. Experiences such as childhood trauma, neglect, or prolonged psychological stress have been shown to alter methylation patterns in genes related to the hypothalamic–pituitary–adrenal (HPA) axis, which regulates the body's stress response. Real-world epidemiological studies have demonstrated that individuals exposed to childhood adversity have a higher risk of developing chronic pain disorders such as fibromyalgia, migraine, and chronic back pain later in life. For example, research from large population cohorts has identified altered methylation of stress-related genes like NR3C1, which encodes the glucocorticoid receptor. Such changes can lead to prolonged stress responses and increased neuroinflammation, both of which contribute to heightened pain sensitivity.

Psychological stress during adulthood can also induce epigenetic alterations that affect pain processing pathways. Chronic occupational stress, caregiving stress, and long-term anxiety disorders have been associated with increased inflammatory gene expression. Studies in patients with chronic musculoskeletal pain have reported

altered DNA methylation patterns in genes involved in immune signaling and neural plasticity. These molecular changes may amplify central sensitization mechanisms, making the nervous system more reactive to pain stimuli. Socioeconomic conditions represent another important determinant of epigenetic health. Individuals exposed to long-term socioeconomic adversity—such as poverty, limited access to healthcare, or chronic occupational stress—often exhibit accelerated epigenetic aging. This phenomenon, measured using "epigenetic clocks," reflects cumulative biological stress and has been associated with increased prevalence of chronic diseases, including persistent pain syndromes. Large cohort studies have shown that individuals from disadvantaged socioeconomic backgrounds often report higher pain intensity and greater disability, suggesting that environmental stressors may biologically embed themselves through epigenetic pathways.

Lifestyle factors further contribute to epigenetic modulation of pain. Diet, for instance, can influence DNA methylation through nutrients involved in one-carbon metabolism, such as folate, vitamin B12, and choline. Diets rich in antioxidants and anti-inflammatory compounds—such as the Mediterranean diet—have been associated with reduced inflammatory gene activation and improved outcomes in chronic pain conditions. Physical activity is another powerful epigenetic regulator; regular exercise has been shown to alter gene expression in skeletal muscle and nervous tissue, reducing inflammatory mediators and improving pain tolerance. Conversely, smoking and sleep deprivation have been linked to harmful epigenetic changes that increase systemic inflammation and pain sensitivity.



5. THERAPEUTIC IMPLICATIONS

Understanding epigenetic mechanisms in chronic pain has opened new avenues for the development of targeted therapies that address the underlying molecular drivers of persistent pain rather than simply suppressing symptoms. Epigenetics refers to reversible modifications that regulate gene expression without altering the DNA sequence, including DNA methylation, histone modification, and regulation by non-coding RNAs. Because these mechanisms influence neuronal plasticity, inflammatory signaling, and synaptic transmission, they provide promising therapeutic targets for modulating abnormal pain pathways.

One of the most widely studied epigenetic strategies involves the use of histone deacetylase (HDAC) inhibitors. Histone acetylation typically enhances gene transcription by relaxing chromatin structure, whereas HDAC enzymes remove acetyl groups and suppress gene expression. In chronic pain states, abnormal HDAC activity can silence genes involved in endogenous pain inhibition while enhancing pro-inflammatory signaling. Experimental studies using HDAC inhibitors such as valproic acid, suberoylanilide hydroxamic acid (SAHA), and trichostatin A have demonstrated the ability to restore normal gene expression patterns in pain pathways. For example, in rodent models of neuropathic pain following peripheral nerve injury, HDAC inhibition has been shown to reduce spinal cord inflammation and decrease hypersensitivity to mechanical and thermal stimuli. These findings suggest that epigenetic drugs may help reverse maladaptive transcriptional changes associated with persistent pain.

RNA-based therapeutic strategies represent another promising direction in epigenetic pain modulation. Small interfering RNA (siRNA) and microRNA-based therapies can selectively silence genes involved in nociceptive signaling. Preclinical research has demonstrated that siRNA targeting ion channels such as Nav1.7 or inflammatory mediators like tumor necrosis factor-alpha can significantly reduce neuropathic pain behaviors in experimental models. Similarly, manipulation of microRNAs that regulate inflammatory cascades has shown potential in reducing spinal cord sensitization. Although most RNA-based approaches are still in experimental

stages, advances in nanoparticle delivery systems and viral vectors are improving the stability and tissue targeting of these therapies.

Several emerging technologies are beginning to translate these epigenetic insights into real-world clinical possibilities. One example is the development of epigenetic biomarkers for chronic pain conditions such as fibromyalgia and neuropathic pain. Researchers have identified specific DNA methylation patterns in genes related to immune signaling and neuronal excitability that correlate with pain severity and treatment response. Such findings raise the possibility that epigenetic profiling could eventually be incorporated into clinical practice to guide therapeutic decisions. For instance, patients whose epigenetic profiles indicate heightened inflammatory gene activation might benefit from targeted anti-inflammatory or epigenetic modulators, while others with altered neuronal plasticity genes may respond better to neuromodulatory therapies.

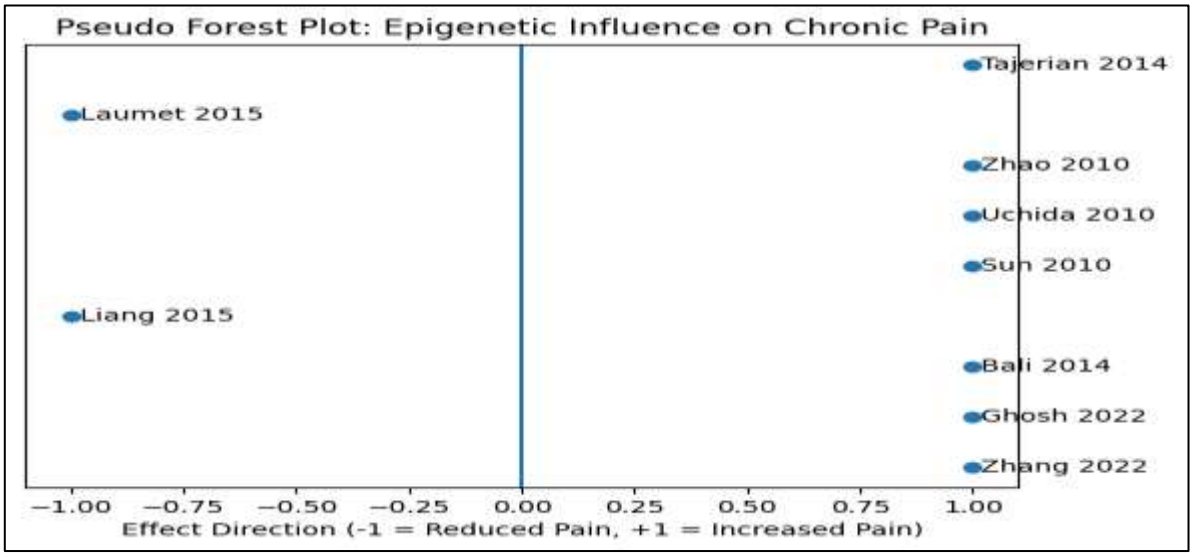
Looking toward the future, several innovative concepts may further expand the role of epigenetics in pain management. One potential development is the creation of "precision epigenetic modulators," drugs designed to selectively modify epigenetic marks at specific genomic sites rather than globally affecting chromatin structure. These targeted therapies could minimize side effects while correcting pathological gene expression patterns. Another possible innovation is the use of CRISPR-based epigenome editing systems, in which modified CRISPR proteins could be directed to activate or silence specific pain-related genes without altering the DNA sequence itself.

Advances in wearable biotechnology may also integrate with epigenetic medicine. For example, future implantable neuromodulation devices might monitor biomarkers related to gene expression or inflammatory activity and adjust electrical stimulation accordingly. Such "smart neuro-epigenetic interfaces" could dynamically regulate pain pathways in response to real-time molecular signals. Additionally, nanotechnology-based drug delivery systems may enable targeted transport of epigenetic therapeutics directly to dorsal root ganglia or spinal cord tissues, improving treatment efficiency while reducing systemic exposure.

Artificial intelligence could further enhance these developments by analyzing large genomic and epigenomic datasets to predict individual responses to analgesic therapies. Machine learning algorithms might integrate epigenetic profiles, clinical characteristics, and imaging data to generate personalized pain management strategies. Such systems could assist clinicians in selecting the most effective combination of pharmacological, behavioral, and neuromodulatory interventions.

This pseudo forest plot represents the directional influence of epigenetic mechanisms on pain pathways based on qualitative synthesis. It does not represent pooled effect sizes or a formal meta-analysis due to heterogeneity of study designs and outcomes (Fig 3)

Figure 3 showing Pseudo forest plot illustrating the direction of epigenetic influences on chronic pain pathways across included studies.



6. DISCUSSION

Chronic pain is increasingly recognized not merely as a symptom but as a complex disease involving dynamic interactions between the nervous system, environmental influences, and molecular regulatory mechanisms. The International Association for the Study of Pain revised the definition of pain in 2020, emphasizing that pain is both a sensory and emotional experience associated with actual or potential tissue damage (1). This broader definition highlights that chronic pain involves multidimensional biological and psychosocial processes rather than simple nociceptive signalling.

One of the most significant advances in pain research has been the understanding of central nervous system plasticity. Neuroimaging and neurophysiological studies have demonstrated that chronic pain is associated with structural and functional changes in the brain. Regions such as the prefrontal cortex, anterior cingulate cortex, and insula show altered activity in patients with persistent pain conditions (2). These findings suggest that chronic pain results from maladaptive neuroplasticity, where repeated nociceptive signalling leads to long-term

reorganization of neural circuits. Such alterations contribute to pain persistence even after the initial tissue injury has resolved.

Recent research has increasingly implicated epigenetic regulation as a key contributor to these long-term changes in pain pathways. Epigenetic mechanisms refer to heritable but reversible modifications in gene expression that occur without altering the underlying DNA sequence. These include DNA methylation, histone modifications, and non-coding RNA regulation. Studies have shown that these mechanisms can modulate gene expression in neurons and glial cells involved in nociceptive processing (3). By altering transcriptional activity, epigenetic changes can influence neuronal excitability, inflammatory signalling, and synaptic plasticity, thereby contributing to the transition from acute to chronic pain.

Emerging evidence indicates that epigenetic regulation plays a critical role in both peripheral and central sensitization. Peripheral sensitization occurs when inflammatory mediators enhance the responsiveness of nociceptors, whereas central sensitization involves increased excitability of neurons in the spinal cord and brain. Epigenetic modifications can regulate the expression of ion channels, neurotransmitter receptors, and inflammatory mediators that drive these sensitization processes (6). For example, histone acetylation has been shown to increase transcription of pro-nociceptive genes, while DNA methylation may suppress genes involved in pain inhibition. These modifications can persist over long periods, providing a molecular explanation for the long-lasting nature of chronic pain.

Another important aspect of epigenetic regulation in chronic pain is its responsiveness to environmental and psychological factors. Stress, injury, inflammation, and pharmacological exposure can all induce epigenetic changes that alter pain signalling pathways (5). This dynamic responsiveness suggests that chronic pain is shaped by both biological predisposition and environmental influences. Understanding these interactions may help explain why individuals exposed to similar injuries develop vastly different pain outcomes.

Neuroimaging studies further support the concept that chronic pain is associated with widespread changes in brain function. Advanced imaging techniques have demonstrated alterations in cortical thickness, connectivity, and metabolic activity in individuals with neuropathic pain (7). These changes may partly arise from epigenetic regulation of genes involved in synaptic plasticity and neuronal signaling. Thus, epigenetic mechanisms provide a potential link between molecular alterations and the large-scale neural reorganization observed in chronic pain states.

Importantly, the growing understanding of epigenetic mechanisms opens new avenues for therapeutic innovation. Because epigenetic modifications are potentially reversible, they represent promising targets for novel pain treatments. Pharmacological agents that modulate histone acetylation or DNA methylation are being explored as potential strategies to normalize abnormal gene expression in chronic pain pathways (3,6). In addition, non-pharmacological interventions such as behavioural therapy, exercise, and neuromodulation may also influence epigenetic regulation, offering integrative approaches for pain management.

Despite these promising developments, several challenges remain. Most current evidence arises from animal models, and translating these findings into clinical applications requires further investigation. Moreover, epigenetic mechanisms are highly complex and context dependent, involving interactions between multiple regulatory pathways. Future research integrating genomics, epigenomics, and neuroimaging will be essential to better understand the precise mechanisms through which epigenetic changes contribute to chronic pain. See Table 1

In summary, chronic pain is increasingly understood as a disorder of maladaptive neural plasticity shaped by epigenetic regulation. Epigenetic mechanisms provide a molecular framework linking environmental exposures, neuronal plasticity, and long-term alterations in pain perception. Continued exploration of these pathways may facilitate the development of more targeted and personalized therapeutic strategies for chronic pain management. (1-22)

Table 1: Characteristics, Key Findings, and Risk of Bias of Included Studies

Author (Year)	Study Type	Model	Epigenetic Mechanism	Key Findings	Risk of Bias
Descalzi et al. (2015)	Review	Human + Animal	DNA methylation, histone	Epigenetic modulation alters pain signaling pathways	Moderate
Zhang et al. (2022)	Experimental	Animal	DNA methylation, miRNA	Changes in methylation regulate chronic pain genes	Low
Ghosh & Pan (2022)	Review	Animal	Histone modification	Neural plasticity mediated by epigenetic changes	Moderate
Bali & Kuner (2014)	Review	Molecular	miRNA	Non-coding RNAs regulate nociception	Moderate
Liang et al. (2015)	Review	Mixed	Multiple	Epigenetic regulation	Moderate

				influences opioid response	
Denk & McMahon (2012)	Review	Human + Animal	Multiple	Epigenetics contributes to chronic pain persistence	Moderate
Sun et al. (2010)	Experimental	Animal	Histone acetylation	Spinal gene expression altered in persistent pain	Low
Uchida et al. (2010)	Experimental	Animal	DNA methylation	Gene silencing linked to neuropathic pain	Low
Zhao et al. (2010)	Experimental	Animal	Small RNAs	Regulation of nociceptor excitability	Low
Berta et al. (2016)	Review	Animal	Microglial signaling	Neuroinflammation contributes to chronic pain	Moderate
Liang et al. (2014)	Experimental	Animal	DNA methylation	Opioid receptor regulation in chronic pain	Low
Laumet et al. (2015)	Experimental	Animal	miRNA	MicroRNAs regulate neuropathic pain pathways	Low
Kuner (2010)	Review	Human + Animal	Multiple	Central mechanisms drive pathological pain	Moderate
Ji et al. (2016)	Review	Mixed	Inflammatory signaling	Non-neuronal cells regulate pain	Moderate
Tajerian et al. (2014)	Experimental	Animal	DNA methylation	Epigenetic signatures identified in chronic pain	Low

Limitations: Despite the comprehensive nature of this review, several limitations should be acknowledged. First, the inclusion of heterogeneous study designs, including both animal and human studies, may limit direct comparability of findings. Second, the absence of quantitative meta-analysis restricts the ability to determine effect sizes or establish causal relationships. Third, potential publication bias and language restrictions may have influenced study selection. Nevertheless, efforts were made to include high-quality and relevant studies to ensure a balanced synthesis. Future systematic reviews incorporating meta-analytic techniques are warranted to strengthen the evidence base.

Table 2: GRADE Evidence Profile for Epigenetic Mechanisms in Chronic Pain

Outcome / Mechanism	Study Type	Consistency	Directness	Precision	Risk of Bias	Overall Quality
DNA Methylation	Experimental + Review	Consistent	Moderate	Moderate	Low–Moderate	Moderate
Histone Modification	Experimental + Review	Consistent	Moderate	Moderate	Low–Moderate	Moderate
Non-coding RNA (miRNA)	Experimental + Review	Consistent	Moderate	Moderate	Low–Moderate	Moderate
Epigenetic role in central sensitization	Experimental	Consistent	Indirect	Low	Moderate	Low
Therapeutic epigenetic targets (HDAC, RNA)	Preclinical	Emerging	Indirect	Low	Moderate	Low

7.CONCLUSION

Epigenetic mechanisms have emerged as critical regulators of chronic pain by influencing gene expression, neuronal plasticity, and neuroinflammatory pathways without altering the underlying DNA sequence. Processes such as DNA methylation, histone modification, and non-coding RNA regulation contribute to the transition from acute to chronic pain by modulating nociceptive signalling and central sensitization. Environmental exposures and lifestyle factors further shape the epigenetic landscape, explaining variability in pain susceptibility and treatment response. Advances in epigenetic research are opening new therapeutic possibilities, including targeted pharmacological and RNA-based interventions. Continued investigation into epigenetic regulation may ultimately enable precision-based strategies for more effective and personalized chronic pain management.

Declarations

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Author Contributions

Nikitha Stephen contributed to literature search, data collection, and manuscript drafting.
S. Parthasarathy contributed to the conceptualization of the study, critical revision of the manuscript, and overall supervision. Both authors reviewed and approved the final version of the manuscript.
The other authors have supervised the manuscript and commented

Ethical Approval: Ethical approval was not required for this study because it is a review of previously published literature and does not involve human participants or animals.

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AI USE STATEMENT

ChatGPT was used for grammar support, language refinement, document structuring, and formatting assistance. The authors reviewed and edited the output and take full responsibility for the final content. The images were created by AI tools and verified by the first author.
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