

*Systematic Review*

# Glucagon-like Peptide-1 Receptor Agonists as Modulators of Pain-Related Mechanisms: A Systematic Review of Experimental and Translational Evidence

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## Abstract

**Background/Objectives:** Glucagon-like peptide-1 receptor agonists, widely used for diabetes and obesity, have recently attracted interest because of their potential effects on biological pathways involved in nociception and neuroinflammation. This systematic review synthesized experimental and translational evidence regarding the influence of GLP-1RAs on pain-related mechanisms, rather than on clinical pain outcomes. **Methods:** A systematic review was conducted according to PRISMA guidelines and registered in PROSPERO (CRD420261367538). Fourteen experimental studies were included, the majority of which were preclinical. Methodological quality was assessed using the CAMARADES checklist, and risk of bias was evaluated using the SYRCLE tool. **Results:** Most included studies were conducted in animal models or experimental systems. Across these studies, GLP-1 receptor activation was associated with reduced neuroinflammation, inhibition of microglial activation, decreased pro-inflammatory cytokine production, increased IL-10 levels, and modulation of TRPV1/TRPA1 channels. Additional effects included enhancement of endogenous opioid signaling, activation of PI3K/Akt pathways, and attenuation of central sensitization. Overall study quality was moderate, with an unclear-to-moderate risk of bias. **Conclusions:** Current experimental evidence suggests that GLP-1RAs modulate multiple biological pathways involved in nociception, neuroinflammation, and pain-related signaling. However, these findings primarily derive from mechanistic and preclinical studies and should not be interpreted as evidence of clinical efficacy for pain treatment.

**Keywords:** GLP-1 receptor agonists; nociception; neuroinflammation; central sensitization; microglial activation; pain-related mechanisms



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## 1. Introduction

Chronic pain is among the leading causes of long-term disability worldwide, affecting approximately 20% of adults and generating a substantial socioeconomic and healthcare burden [1,2]. Beyond its conventional definition as a persistent sensory and emotional experience, chronic pain is well-recognized as a complex and multifactorial disorder characterized by maladaptive neuroplastic changes within the peripheral (PNS) and central nervous systems (CNS) [3–5]. Increasing evidence suggests that the persistence of pain is

not merely a consequence of ongoing tissue injury but rather the result of dynamic interactions between neural, immune, and metabolic pathways that contribute to the maintenance and amplification of nociceptive signaling [6,7].

Several pathophysiological mechanisms have been implicated in the transition from acute nociception to chronic pain. Among these, central sensitization, neuroimmune activation, glial cell dysfunction, and persistent low-grade inflammation have raised as key drivers of pain chronification [8–11]. These processes promote a state of sustained neuronal hyperexcitability, impaired endogenous pain inhibition, and altered sensory processing, ultimately allowing pain to persist beyond its physiological protective role [12]. Consequently, chronic pain is increasingly understood as a disorder of aberrant neural regulation rather than a simple symptom of tissue damage.

Concurrently, growing attention has focused on the contribution of metabolic dysfunction to chronic pain pathogenesis. Metabolic disorders such as obesity, insulin resistance, and metabolic syndrome are consistently associated with increased pain prevalence, greater symptom severity, and poorer clinical outcomes [13–15]. These conditions are characterized by systemic inflammatory activation, altered adipokine signaling, oxidative stress, and immune dysregulation, all of which may facilitate nociceptive sensitization and neuroinflammation. This emerging perspective has led to metabolic–immune–neural crosstalk, whereby metabolic and inflammatory disturbances interact with neural pathways to influence pain perception and chronicity [16].

Within this context, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have attracted increasing scientific interest. Originally developed for the treatment of type 2 diabetes mellitus [17], GLP-1RAs have subsequently become established therapeutic agents for obesity and metabolic syndrome owing to their efficacy in improving glycemic control, promoting weight loss, and reducing cardiovascular risk [18,19]. As analogues of the endogenous incretin hormone glucagon-like peptide-1 (GLP-1), these agents enhance glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying, and increase satiety, thereby contributing to the metabolic homeostasis [20].

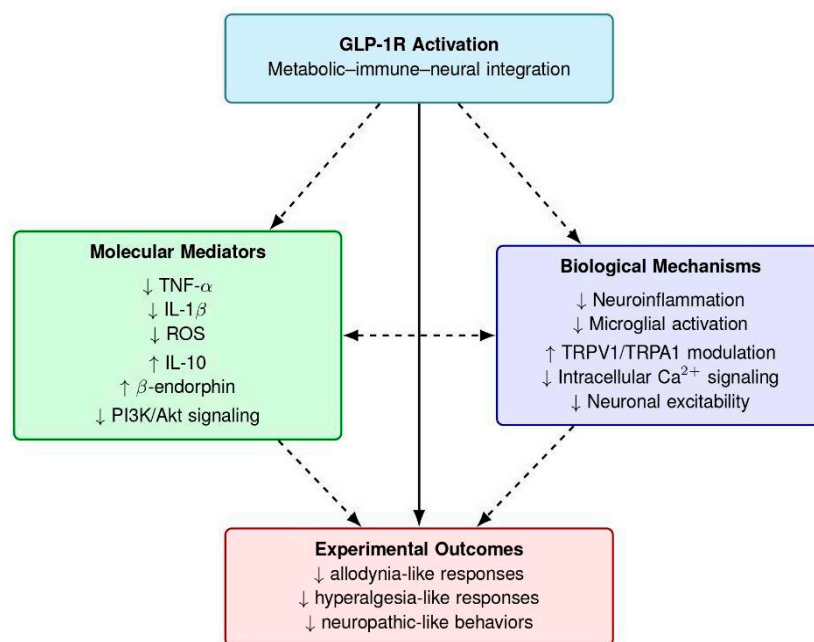
Notably, the biological effects of GLP-1RAs extend well beyond glycemic control. GLP-1 receptors are widely distributed throughout both the PNS and CNS, including regions critically involved in autonomic regulation, energy balance, cognition, emotion, and sensory processing, such as the brainstem, hypothalamus, hippocampus, and limbic structures [21–26]. Moreover, activation of GLP-1 receptors influences neuronal activity and systemic physiology through multiple interconnected mechanisms, including the regulation of appetite and energy balance, modulation of autonomic function, and enhancement of metabolic efficiency [27,28].

More recently, accumulating preclinical evidence has revealed that GLP-1 receptor activation exerts potent anti-inflammatory, antioxidant, and neuroprotective effects [29,30]. These actions appear to be mediated through the modulation of microglial activation, suppression of pro-inflammatory cytokine release, attenuation of oxidative stress, and regulation of intracellular signaling pathways such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) and AMP-activated protein kinase (AMPK) [31–34]. Through these mechanisms, GLP-1 signaling promotes cellular survival, preserves mitochondrial function, enhances synaptic plasticity, and supports neuronal resilience under conditions of metabolic and inflammatory stress [35–38].

The convergence of these metabolic, immunological, and neurobiological effects has generated increasing interest in the potential role of GLP-1RAs as modulators of pain-related pathways. Experimental studies suggest that GLP-1 receptor activation may influence nociceptive transmission, neuroinflammatory responses, synaptic remodeling, and central sensitization, thereby providing a plausible biological rationale for their potential

analgesic effects [39]. Such findings have positioned GLP-1RAs as promising candidates within an emerging therapeutic paradigm that targets the interconnected mechanisms linking metabolism, inflammation, and pain.

Despite these advances, the evidence remains fragmented, and several important questions remain unresolved [40]. In particular, it is unclear whether the beneficial effects observed in pain-related outcomes from direct modulation of neuroimmune and nociceptive pathways or occur indirectly through improvements in body weight, metabolic function, and systemic inflammatory status. Furthermore, the translational relevance of findings derived from cellular and animal models remains to be fully established in clinical populations. More details are depicted in Figure 1.



**Figure 1.** Conceptual framework of GLP-1 receptor signaling and pain-related mechanisms. Experimental evidence suggests that GLP-1R activation modulates inflammatory mediators, intracellular signaling, and neuroimmune processes involved in nociception. These effects reduce neuroinflammation, neuronal excitability, and sensitization, contributing to decreased allodynia-like, hyperalgesia-like, and neuropathic-like responses in preclinical models. The bidirectional dashed arrow denotes reciprocal crosstalk between molecular mediators and biological mechanisms. Colored boxes group related concepts: blue = GLP-1R activation/biological mechanisms, green = molecular mediators, and red = experimental outcomes. Upward (↑) and downward (↓) arrows indicate increased and decreased activity or expression, respectively. Source: Own work.

Therefore, the aim of this systematic review is to synthesize and critically evaluate the available experimental and translational evidence regarding the effects of GLP-1 receptor agonists on pain-related mechanisms, with particular emphasis on their role in modulating neuroinflammatory processes implicated in pain pathophysiology. By integrating findings from in vitro, preclinical, and clinical studies, this review aims to provide a comprehensive overview of the biological rationale and therapeutic potential of GLP-1RAs as emerging modulators of pain.

## 2. Materials and Methods

### 2.1. Research Questions

The review question was formulated using the PICOS framework. Specifically, it assessed the effects of GLP-1 receptor agonists (intervention) on neuroinflammatory mechanisms and pain-related outcomes (outcomes) in experimental cellular systems, animal

models of chronic pain, and human populations (population), compared with placebo, vehicle-treated controls, untreated groups, or standard care when available (comparison), across in vitro, preclinical, observational, and clinical studies (study design). Consequently, the resulting research question was as follows: What evidence supports the role of GLP-1 receptor agonists in modulating neuroinflammatory pathways and attenuating pain-related outcomes in experimental, preclinical, and clinical settings?

## 2.2. Study Design

The present review was rigorously carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [41]. The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews within PROSPERO database (registration number CRD420261367538; <https://www.crd.york.ac.uk/PROSPERO/view/CRD420261367538>, accessed on 12 April 2026), thereby enhancing the reliability, traceability and scientific rigor of the review process. More details have been provided in Table S1.

A comprehensive literature search was performed to identify all relevant studies exploring the role of GLP-1 receptor agonists in neuroinflammatory mechanisms associated with chronic pain. The search was conducted between 12 April 2026 to 3 May 2026, without initial restrictions on study design, given the exploratory and mechanistic focus of the review. The following electronic databases were systematically searched: MEDLINE (*PubMed*), Web of Science (*WoS*), Scopus, Cochrane Library, and Embase. Additional sources included reference lists of included articles and relevant reviews to ensure comprehensive coverage of the literature.

In MEDLINE (*PubMed*), the search strategy combined Medical Subject Headings (*MeSH*) and free-text terms using Boolean operators. The primary search equation was as follows: ("Glucagon-Like Peptide-1 Receptor Agonists"[*MeSH Terms*] OR "GLP-1"[*tiab*] OR "GLP-1 receptor agonist"[*tiab*] OR "liraglutide"[*tiab*] OR "semaglutide"[*tiab*]) AND ("chronic pain"[*MeSH Terms*] OR "pain"[*tiab*] OR "nociception"[*tiab*] OR "central sensitization"[*tiab*]) AND ("neuroinflammation"[*tiab*] OR "microglia"[*tiab*] OR "cytokines"[*tiab*] OR "inflammation"[*tiab*]).

In Web of Science and Scopus, searches were performed using title, abstract, and keyword fields, applying combinations such as: ("GLP-1" OR "GLP-1 receptor agonist" OR "liraglutide" OR "semaglutide") AND ("chronic pain" OR "nociception" OR "central sensitization") AND ("neuroinflammation" OR "microglia" OR "inflammatory pathways"). In the Cochrane Library, the search focused on identifying clinical and experimental studies using simplified booleans of GLP-1-related terms and pain/inflammation-related outcomes. Similarly, in Embase, controlled vocabulary (*Emtree terms*) and free-text keywords were combined to maximize sensitivity.

Given database-specific constraints, adapted search strategies were applied where necessary, maintaining consistency in the core conceptual domains: GLP-1 signaling, pain mechanisms, and neuroinflammation. The literature search and study selection process were conducted independently by two reviewers (I.M.M.P. and S.E.M.P.), who screened titles and abstracts for relevance, followed by full-text assessment of potentially eligible studies. Discrepancies were resolved through discussion and consensus between the two reviewers. The search strategy for each database is provided in Supplementary Table S2.

## 2.3. Eligibility Criteria

Studies were considered eligible if they met the following criteria: (1) published within the last 15 years; (2) in vitro or ex vivo experimental studies investigating GLP-1 receptor signaling in neural, glial, immune, or sensory tissues relevant to nociception; (3) in vivo

preclinical studies evaluating the effects of GLP-1 receptor agonists in experimental models of inflammatory, neuropathic, neuroinflammatory, or centrally mediated pain; (4) translational studies—including electrophysiological, molecular, genetic, or biomarker-based investigations—providing mechanistic insights into GLP-1-mediated modulation of pain-related pathways; and (5) clinical studies only when they contributed mechanistic or translational evidence relevant to nociceptive or neuroinflammatory processes rather than solely reporting symptomatic or analgesic outcomes.

Additionally, (6) narrative reviews were consulted exclusively for contextualization and cross-referencing but were not considered primary sources of evidence; and (7) studies focusing exclusively on glycemic control were excluded unless they provided mechanistic evidence related to pain modulation, neuroinflammation, or metabolic-immune interactions involved in chronic pain.

#### 2.4. Data Extraction and Thematic Synthesis

Relevant data were extracted and synthesized qualitatively to identify recurring mechanistic patterns across studies. Extracted information included: (1) study design and experimental model; (2) GLP-1 receptor agonist, dosage, and duration; (3) biological targets and signaling pathways investigated; and (4) outcomes related to nociception, neuroinflammation, metabolic regulation, and neural signaling.

Due to substantial heterogeneity in experimental models, interventions, and outcome measures, a quantitative synthesis was not feasible. Therefore, findings were narratively synthesized to identify recurring mechanisms and areas of convergence across the available evidence. Methodological quality and risk of bias were formally assessed using the CAMARADES checklist [42,43] and the SYRCLE Risk of Bias tool [44], respectively.

#### 2.5. Methodological Quality Assessment (CAMARADES Checklist)

The quality of the included preclinical animal studies was evaluated using the CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) checklist [42,43]. This tool assesses methodological domains relevant to experimental validity and reproducibility, including: (1) peer-reviewed publication; (2) statement of temperature control; (3) random allocation to experimental groups; (4) blinded induction of the model; (5) blinded assessment of outcome; (6) use of appropriate animal models (e.g., comorbidities or age relevance); (7) sample size calculation; (8) compliance with animal welfare regulations; and (9) statement of potential conflicts of interest. Each study was qualitatively assessed based on the presence or absence of these criteria, allowing for an overall appraisal of methodological robustness across the preclinical evidence base.

#### 2.6. Risk of Bias (SYRCLE's Risk of Bias Tool)

The risk of bias in the included animal studies was assessed using the SYRCLE's Risk of Bias (RoB) tool [44], specifically designed for preclinical research. This instrument is adapted from the Cochrane RoB tool and evaluates potential biases across several domains, including: (1) selection bias (sequence generation and baseline characteristics); (2) performance bias (random housing and blinding of caregivers/investigators); (3) detection bias (blinding of outcome assessment); (4) attrition bias (incomplete outcome data); (5) reporting bias (selective outcome reporting); and (6) other sources of bias.

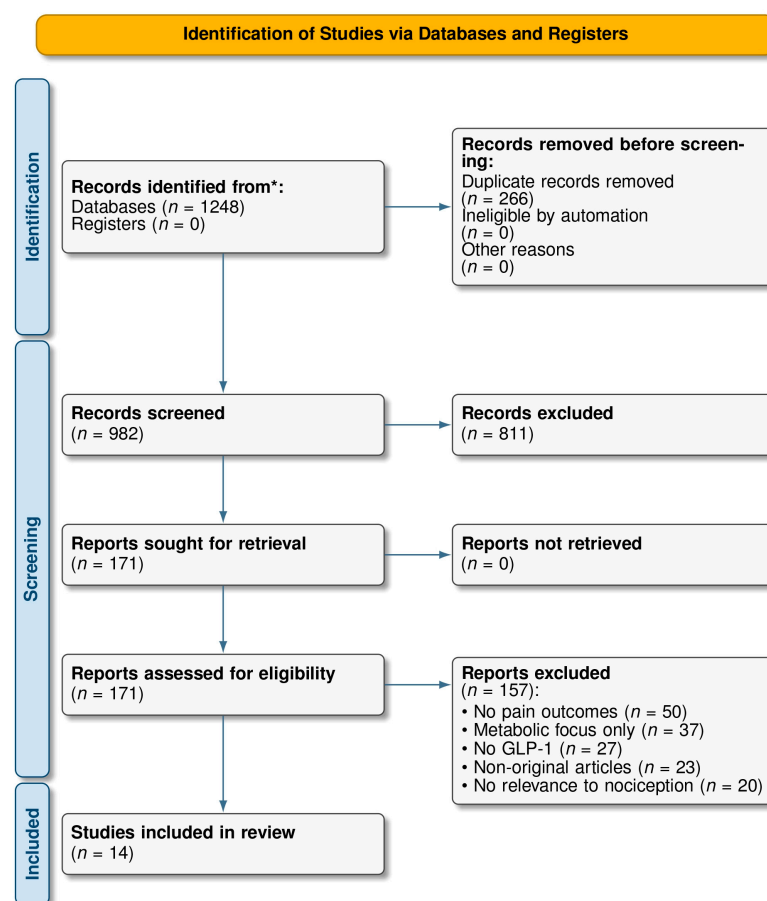
Each domain was assessed as low risk, high risk, or unclear risk of bias, based on the information reported in the primary studies. Given the exploratory and mechanistic nature of this review, the results of the risk-of-bias assessment were not used as exclusion criteria but were considered in the interpretation of findings, particularly when evaluating the strength and reliability of the preclinical evidence.

### 3. Results

#### 3.1. Study Selection

A literature search was carried out across the selected databases, yielding a total of 1248 records. After the removal of duplicates ( $n = 266$ ), 982 studies remained for title and abstract screening. Following this initial screening phase, 811 records were excluded due to lack of relevance to the research question, resulting in 171 reports being sought for retrieval. Moreover, all reports were successfully retrieved and subsequently assessed in full text for eligibility.

Full-text evaluation led to the exclusion of 157 studies based on predefined criteria. The main reasons for exclusion included: (i) absence of pain-related outcomes ( $n = 50$ ); (ii) exclusive focus on metabolic or glycemic endpoints without mechanistic relevance to nociception ( $n = 37$ ); (iii) lack of GLP-1 receptor agonist intervention ( $n = 27$ ); (iv) non-original articles, including reviews, editorials, and conference abstracts ( $n = 23$ ); and (v) lack of relevance to nociceptive processes ( $n = 20$ ). The study selection process is summarized in a PRISMA flow diagram (Figure 2).



**Figure 2.** PRISMA 2020 flow diagram illustrating the study selection process. The systematic search identified 1248 records from databases. After the removal of 266 duplicates, 982 records were screened by title and abstract, of which 811 were excluded. A total of 171 full-text reports were assessed for eligibility, and 157 were excluded based on predefined criteria. Ultimately, 14 studies met the inclusion criteria and were included in the qualitative synthesis. Source: Own work.

#### 3.2. Characteristics of Included Studies

A total of 14 studies met the inclusion criteria and were included in the qualitative synthesis [45–58]. The studies were conducted across multiple countries, predominantly in Asia, particularly China and South Korea [48–54], with additional contributions from

the United Kingdom [45], Brazil [47], Hungary [46], Iran [56], Turkey [57], and North America [55,58].

Considerable methodological heterogeneity was identified, reflecting the translational nature of the available evidence. The included studies comprised both preclinical animal investigations and mechanistic in vitro and ex vivo experiments. Most studies employed animal models [46,48–50,53,54,57,58], whereas others used cellular or tissue-based systems, including dorsal root ganglia (DRG) neurons, human nerve fibers, microglial cells, and engineered cellular models [45,47,51,52,55,56]. Animal studies primarily utilized rats and mice [48,50,53,54], while in vitro and ex vivo studies enabled detailed characterization of nociceptive and neuroinflammatory signaling pathways.

The included studies were not restricted to diabetic pain models. Instead, they encompassed a broad spectrum of experimental pain paradigms. Neuropathic and neuropathy-related models were the most frequently investigated, including diabetic neuropathy [53], chemotherapy-induced peripheral neuropathy (CIPN) [52,57], spinal nerve ligation [54], and other nerve injury-related models [49]. Inflammatory pain models, including Complete Freund's Adjuvant (CFA), carrageenan, and formalin-induced nociception, were also employed [46,48,50]. Additional experimental paradigms included migraine-related central sensitization [51], systemic inflammatory conditions [58], neuroinflammatory models without direct behavioral nociceptive outcomes [47,56], and in vitro human sensory neuron models [55].

Importantly, studies examined GLP-1R-related effects at different anatomical levels of nociceptive processing. Several research focused on peripheral mechanisms involving sensory neurons, DRG, peripheral nerve fibers, TRPV1/TRPA1 channel activity, and neuropeptide release [45,49,55]. These studies investigated mechanisms associated with both peripheral and central sensitization, ranging from sensory neurons, dorsal root ganglia, peripheral nerve fibers, and TRPV1/TRPA1 channel activity to spinal dorsal horn signaling, microglial activation, and supraspinal pathways [45,48–51,54,55].

All included studies investigated GLP-1R agonists or modulators of GLP-1 signaling, including exendin-4, exenatide, semaglutide, liraglutide, native GLP-1, and related compounds [48–50,53,57]. Administration routes varied according to the experimental paradigm and included intrathecal delivery in studies targeting central mechanisms [48,50], systemic administration via subcutaneous or intraperitoneal routes [53,57], and direct exposure in cellular systems [45,55]. Doses ranged from nanomolar concentrations in vitro [45] to microgram- or milligram-per-kilogram ranges in vivo [48,53]. Both acute and chronic treatment paradigms were represented [50,58].

Primary outcomes focused on behavioral, physiological, and molecular measures related to nociception and sensory processing. In animal studies, behavioral assessments included mechanical allodynia (von Frey testing) [53,54], thermal hyperalgesia [48], formalin-induced nociceptive behaviors [50], and mechanical sensitivity thresholds in migraine models [51]. In vitro and ex vivo studies assessed neuronal excitability using calcium imaging and electrophysiological recordings, with particular emphasis on ion channel function and sensory neuron activity [45,55].

Beyond behavioral outcomes, all studies explored underlying mechanistic pathways. At the peripheral level, recurrent findings included modulation of TRPV1 and TRPA1 channels, regulation of calcium-dependent signaling, and reductions in sensory neuron excitability [45,49,55]. At the central level, several studies reported decreased microglial activation, attenuation of pro-inflammatory mediators such as TNF- $\alpha$  and IL-1 $\beta$ , and modulation of the spinal dorsal horn and related structures [48,50,54]. Additional mechanisms included activation of endogenous opioid-related pathways, reflected by increased  $\beta$ -endorphin levels and opioid receptor-mediated signaling [48,50,52]. One study added

transcriptomic analyses, revealing large-scale gene expression changes in neuropathic models [54], whereas others identified key intracellular signaling pathways, including PI3K/Akt and calcium-dependent mechanisms [49,51]. Additional study characteristics, including experimental model, anatomical site, proposed mechanisms, and principal outcomes, are summarized in Table 1.

### 3.3. Methodological Quality Assessment

Overall, the methodological quality assessment using the CAMARADES checklist suggests that, while preclinical research in this field shows acceptable foundational quality, significant improvements in study design, reporting transparency, and bias control are necessary to enhance the reliability and translational value of the evidence. All studies were published in peer-reviewed journals, supporting a baseline level of scientific rigor [45–58].

However, a systematic lack of temperature control and randomization procedures was observed, as these criteria were consistently not reported across most studies [45,46,48,50,53]. Similarly, allocation concealment and blinded outcome assessment were either absent or not reported, representing critical sources of potential bias and limiting internal validity. Conversely, most studies showed appropriate implementation of experimental models and anesthesia protocols, indicating adequate technical execution [47,51,54]. Nevertheless, the absence of sample size calculations across nearly all studies constitutes a major methodological weakness, potentially affecting statistical power and the reliability of conclusions.

Only a limited number of studies exhibited more robust methodological practices, particularly in terms of randomization and compliance with animal welfare regulations, with Navabi et al. (2021) [56] and Ozatik et al. (2025) [57] standing out as the most methodologically rigorous within the dataset. Additionally, Wong et al. (2024) [58] demonstrated partial adherence to welfare compliance, although other key criteria remained unmet. Finally, conflict of interest statements was largely not reported, introducing uncertainty regarding potential funding-related or interpretative biases. More details are shown in Table S3. Methodological Quality Analysis (CAMARADES Checklist).

### 3.4. Risk of Bias Assessment

The risk of bias assessment using the SYRCLE's Risk of Bias tool revealed an overall pattern of moderate risk of bias across the included preclinical studies, largely driven by insufficient reporting across multiple methodological domains. Most studies exhibited an unclear risk of bias (U) in key aspects related to internal validity, particularly sequence generation, allocation concealment, and blinding procedures [45–51,53,54,58].

Regarding selection bias, baseline characteristics were consistently rated as low risk across the majority of studies, indicating adequate group comparability [45–51,53,54,58]. However, sequence generation remained unclear in most cases [45,46,48,50,53], and allocation concealment was also insufficiently reported [47,51,54], raising concerns about potential allocation bias.

In terms of performance bias, both random housing and blinding of caregivers were consistently rated as unclear due to lack of reporting [45,46,48,49,53,58], suggesting limited control over environmental and procedural confounders. Similarly, detection bias domains—including random outcome assessment and blinding of outcome assessment—were uniformly classified as unclear across nearly all studies [50,51,53,54], indicating a potential risk of observer bias. With respect to attrition bias, incomplete outcome data were generally handled adequately, resulting in a low-risk classification across studies [45–51,53,54,58]. However, selective reporting bias remained unclear in all cases due to the absence of accessible study protocols or pre-registered outcomes [56,57].

Table 1. Characteristics of included studies.

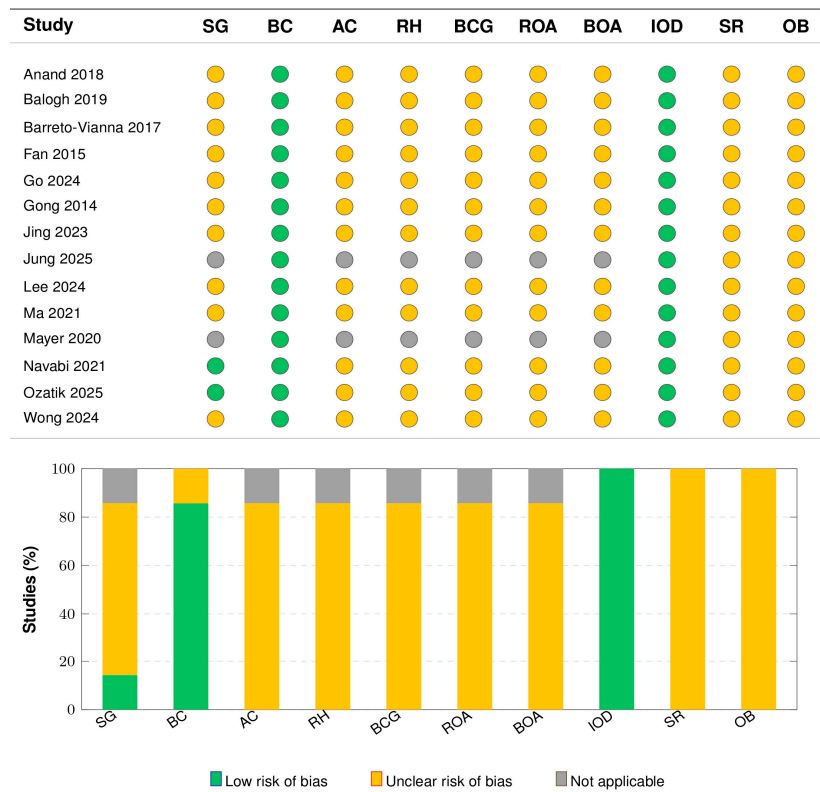
| Study (Year)                    | Country     | Design                          | Population               | Pain Model                 | Intervention (Dose/Route)          | Measures                             | Outcomes                                                                                                                   | Mechanisms              | Key Findings                   |
|---------------------------------|-------------|---------------------------------|--------------------------|----------------------------|------------------------------------|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------------------------|
| Anand et al. 2018 [45]          | UK          | In vitro + ex vivo              | Human DRG + nerve fibers | Nociceptive signaling      | GLP-1/exendin-4                    | Ca <sup>2+</sup> imaging, TRPV1, ATP | <ul style="list-style-type: none"><li>• ↓ TRPV1 activation</li><li>• ↓ ATP signaling</li></ul>                             | TRPV1, purinergic       | Reduced excitability           |
| Balogh et al. 2019 [46]         | Hungary     | Preclinical                     | Rats                     | CFA, formalin              | DPP-4 inhibitors (intrathecal)     | Hyperalgesia                         | <ul style="list-style-type: none"><li>• ↓ hyperalgesia (dose-dependent)</li></ul>                                          | Opioid receptors        | GLP-1-related modulation       |
| Barreto-Vianna et al. 2017 [47] | Brazil      | Experimental                    | Mice                     | Neuroinflammation          | Liraglutide (ICV + SC)             | Cytokines                            | <ul style="list-style-type: none"><li>• ↓ TNF-α</li><li>• ↓ IL-6 (<i>p</i> &lt; 0.05)</li></ul>                            | Microglia               | Reduced neuroinflammation      |
| Fan et al. 2015 [48]            | China       | Preclinical                     | Rats                     | Formalin, CFA, carrageenan | WB4-24 (0.3–100 µg IT)             | Licking time, cytokines              | <ul style="list-style-type: none"><li>• ↓ hypersensitivity (~60–80%)</li></ul>                                             | Microglia, β-endorphin  | Opioid-mediated analgesia      |
| Go et al. 2024 [49]             | South Korea | Preclinical + electrophysiology | Mice + neurons           | CFA, SNI                   | GLP-1 peptides                     | TRPV1 current, Ca <sup>2+</sup>      | <ul style="list-style-type: none"><li>• ↓ TRPV1 current</li><li>• ↓ heat sensitivity</li></ul>                             | Direct TRPV1 inhibition | Noncompetitive TRPV1 blockade  |
| Gong et al. 2014 [50]           | China       | Preclinical                     | Rodents                  | Neuropathic + inflammatory | Exenatide/GLP-1                    | Allodynia tests                      | <ul style="list-style-type: none"><li>• ↓ hypersensitivity (~60–90%)</li></ul>                                             | Microglia, β-endorphin  | Strong antihyperalgesia        |
| Jing et al. 2023 [51]           | China       | Preclinical                     | Mice                     | Migraine (NTG model)       | Liraglutide                        | von Frey, cytokines                  | <ul style="list-style-type: none"><li>• ↓ IL-1β, TNF-α</li><li>• ↓ allodynia (<i>p</i> &lt; 0.05)</li></ul>                | PI3K/Akt, microglia     | Reduced central sensitization  |
| Jung et al. 2025 [52]           | South Korea | In vitro                        | DRG neurons              | CIPN (paclitaxel)          | GLP-1RA                            | ROS, cytokines, neurites             | <ul style="list-style-type: none"><li>• ↓ oxidative stress</li><li>• ↑ neurite length</li><li>• ↓ TRP expression</li></ul> | TRP channels, IL-10     | Neuroprotection + regeneration |
| Lee et al. 2024 [53]            | Taiwan      | Preclinical                     | Diabetic rats            | Neuropathic pain           | Semaglutide (1.44–2.88 mg/kg oral) | Allodynia, cytokines                 | <ul style="list-style-type: none"><li>• ↓ IL-1β, IL-6</li><li>• ↓ hyperalgesia (<i>p</i> &lt; 0.05)</li></ul>              | Microglia, astrocytes   | Anti-inflammatory analgesia    |
| Ma et al. 2021 [54]             | China       | Preclinical + RNA-seq           | Rats                     | SNL neuropathy             | Exenatide                          | PWL, gene expression                 | <ul style="list-style-type: none"><li>• ↑ IL-10 (~2–3×) 591 genes normalized</li></ul>                                     | Microglia, opioids      | Transcriptomic modulation      |

Table 1. Cont.

| Study (Year)            | Country    | Design                | Population    | Pain Model            | Intervention (Dose/Route)  | Measures                         | Outcomes                                                                                                                                    | Mechanisms                     | Key Findings                         |
|-------------------------|------------|-----------------------|---------------|-----------------------|----------------------------|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|--------------------------------------|
| Mayer et al. 2020 [55]  | USA        | In vitro + ex vivo    | DRG neurons   | Neuroimmune           | Exendin-4 (50 nM)          | Ca <sup>2+</sup> , Substance P   | <ul style="list-style-type: none"><li>• ↑ Ca<sup>2+</sup> (~2-fold)</li><li>• ↑ SP release</li></ul>                                        | TRPV1/TRPA1                    | Context-dependent nociception ↑      |
| Navabi et al. 2021 [56] | Iran       | Preclinical           | Primates      | Diabetic inflammation | Liraglutide + MSC          | Cytokines                        | <ul style="list-style-type: none"><li>• ↑ IL-10</li><li>• ↓ IL-6, IL-1β</li></ul>                                                           | Immunomodulation               | Synergistic anti-inflammatory effect |
| Ozatik et al. 2025 [57] | Turkey     | In vivo               | Rats (n = 32) | Cisplatin neuropathy  | Liraglutide 0.8 mg/kg (sc) | von Frey, tail flick, biomarkers | <ul style="list-style-type: none"><li>• ↓ allodynia (p &lt; 0.001)</li><li>• ↓ NO (p &lt; 0.001)</li><li>• ↑ IL-10 (p &lt; 0.001)</li></ul> | Oxidative stress, inflammation | Weekly dosing superior               |
| Wong et al. 2024 [58]   | Canada/USA | Preclinical + genetic | Mice          | Systemic inflammation | Exendin-4/semaglutide      | Cytokines                        | <ul style="list-style-type: none"><li>• ↓ TNF-α</li><li>• ↓ IL-1β, IL-6</li></ul>                                                           | CNS GLP-1R, opioids            | Brain-immune anti-inflammatory axis  |

Abbreviations: GLP-1 glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; GLP-1R, glucagon-like peptide-1 receptor; DRG, dorsal root ganglion; TRPV1, transient receptor potential vanilloid 1; TRPA1, transient receptor potential ankyrin 1; CFA, complete Freund’s adjuvant; SNI, spared nerve injury; SNL, spinal nerve ligation; CIPN, chemotherapy-induced peripheral neuropathy; PWL, paw withdrawal latency; ROS, reactive oxygen species; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor alpha; IL-10, interleukin-10; CNS, central nervous system; RNA-seq, RNA sequencing; Ca<sup>2+</sup>, intracellular calcium; ATP, adenosine triphosphate; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; n, sample size. Symbols: ↑, increase; ↓, decrease; =, no significant change; ~, approximately.

A subset of studies, particularly those based on in vitro or ex vivo models, were classified as not applicable (NA) in several domains, reflecting the limited applicability of SYRCLE criteria in these experimental contexts [52,55]. Among the included studies, Navabi et al. (2021) [56] and Ozatik et al. (2025) [57] showed comparatively stronger methodological profiles, with low-risk ratings in sequence generation and baseline characteristics, although other domains remained unclear. Additional information is reported in Table S4. The methodological quality and risk of bias of the included preclinical studies, assessed using the SYRCLE Risk of Bias tool, are summarized in Figure 3.



**Figure 3.** SYRCLE risk-of-bias summary across included studies. Stacked bar plot showing the proportion of studies classified as low, unclear, or not applicable risk of bias across SYRCLE domains for the included studies [45–58]. Green indicates low risk of bias, yellow indicates unclear risk of bias, and gray indicates not applicable. Most domains were rated as unclear risk due to insufficient reporting of allocation concealment, random housing, and blinding procedures, whereas incomplete outcome data was consistently judged as low risk. Abbreviations: SG, sequence generation; BC, baseline characteristics; AC, allocation concealment; RH, random housing; BCG, blinding of care-givers/investigators; ROA, random outcome assessment; BOA, blinding of outcome assessment; IOD, incomplete outcome data; SR, selective reporting; OB, other bias. Source: Own work.

3.5. Synthesis of Included Studies

3.5.1. Modulation of Nociceptive Excitability and TRP Channels

A consistent body of evidence indicates that GLP-1R signaling reduces nociceptive excitability, particularly through modulation of TRP channels. In an in vitro and ex vivo using human DRG tissue and nerve fibers, Anand et al. (2018) [45] showed that GLP-1/exendin-4 attenuated TRPV1 activation and ATP-mediated signaling, suggesting a direct reduction in peripheral nociceptive responsiveness. Similarly, in a preclinical electrophysiological study combining mouse models and isolated neurons, Go et al. (2024) [49] showed that GLP-1 peptides decreased TRPV1 currents and heat sensitivity, proposing a noncompetitive inhibitory mechanism at the channel level.

Additionally, in an in vitro model of chemotherapy-induced peripheral neuropathy (CIPN), Jung et al. (2025) [52] further reported that GLP-1R agonists reduced oxidative stress, downregulated TRP channel expression, and enhanced neurite outgrowth in DRG neurons, indicating both functional suppression of nociceptive signaling and structural neuro-regeneration. However, this inhibitory profile is not universal. In this regard, Mayer et al. (2020) [55] reported, using in vitro and ex vivo sensory neuron models, that exendin-4 enhanced intracellular  $\text{Ca}^{2+}$  influx and stimulated substance P release via TRPV1/TRPA1-mediated pathways, suggesting that GLP-1R activation may produce context-dependent responses under certain experimental conditions.

### 3.5.2. Anti-Inflammatory and Neuroimmune Mechanisms

A major and highly consistent finding across studies is the anti-inflammatory action of GLP-1R modulation. In a preclinical murine model, Barreto-Vianna et al. (2017) [47] showed that liraglutide significantly reduced  $\text{TNF-}\alpha$  and IL-6 levels, linked to decreased microglial activation. Likewise, in a preclinical nitroglycerin-induced migraine model, Jing et al. (2021) [51] reported that liraglutide reduced IL-1 $\beta$  and  $\text{TNF-}\alpha$  expression alongside mechanical allodynia, implicating the PI3K/Akt signaling pathway in the attenuation of central sensitization.

Similarly, in a diabetic rat model, Lee et al. (2024) [53] showed that oral semaglutide reduced IL-1 $\beta$  and IL-6 levels and improved behavioral pain responses, effects linked to reduced activation of both microglia and astrocytes. Expanding this framework, Wong et al. (2024) [58], using a preclinical genetic mouse model, identified a brain-immune regulatory axis, showing that exendin-4 and semaglutide decreased systemic and central proinflammatory cytokines (e.g.,  $\text{TNF-}\alpha$ , IL-1 $\beta$ , IL-6) through central GLP-1R signaling and opioid-dependent mechanisms. In a preclinical primate study, Navabi et al. (2021) [56] further showed that liraglutide combined with mesenchymal stem cells enhanced IL-10 release while reducing IL-6 and IL-1 $\beta$ , indicating a synergistic immunomodulatory effect.

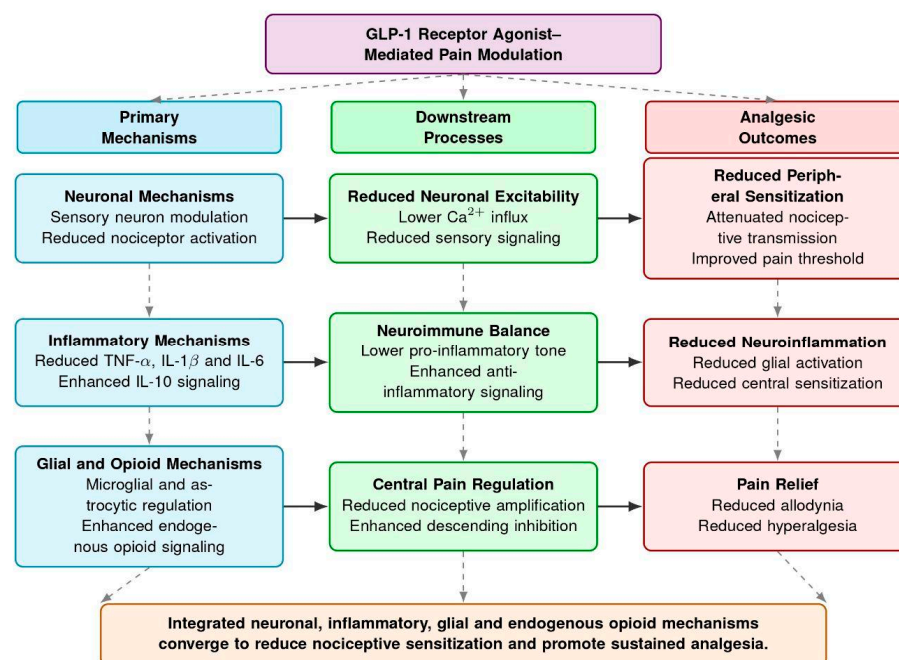
### 3.5.3. Opioid System Involvement and Endogenous Analgesia

Several experimental studies suggest a potential interaction between GLP-1 receptor signaling and the endogenous opioid system. In rat models of inflammatory nociception, Fan et al. (2015) [48] reported that intrathecal administration of the GLP-1 analogue WB4-24 was linked with reduced nociceptive hypersensitivity, an effect associated with microglial activation and  $\beta$ -endorphin release. Similarly, Gong et al. [50] observed reductions in nociceptive responses following administration of exenatide and GLP-1 in rodent models, with findings suggesting the involvement of  $\beta$ -endorphin-mediated pathways.

Additional evidence was provided by Balogh et al. (2019) [46] in a preclinical rat study that showed that intrathecal DPP-4 inhibitors reduced the enhanced nociceptive hypersensitivity in CFA and formalin models. These effects appeared to involve opioid receptor-mediated signaling, supporting a potential link between GLP-1 receptor activation and endogenous opioid pathways. More details are summarized in Figure 4.

### 3.5.4. Effects in Neuropathic Pain and Transcriptomic Regulation

The analgesic effects of GLP-1R activation extend robustly to neuropathic pain models. In a preclinical spinal nerve ligation (SNL) rats analysis, Ma et al. (2021) [54] showed that exenatide increased IL-10 levels by approximately 2–3-fold and normalized the expression of a total of 591 genes, indicating profound transcriptomic reprogramming associated with microglial modulation and opioid pathways. In a diabetic neuropathy model, Lee et al. (2024) [53] confirmed reductions in hyperalgesia and inflammatory cytokines following semaglutide administration.



**Figure 4.** Analgesic mechanisms of GLP-1-based therapies. GLP-1 receptor agonists reduce neuronal excitability, neuroinflammation, and peripheral and central sensitization through modulation of TRPV1/TRPA1, inflammatory cytokines, glial activity, and endogenous opioid pathways. Blue, green, red, and orange boxes represent primary mechanisms, downstream processes, analgesic outcomes, and the integrated mechanism, respectively. Solid arrows indicate direct relationships, whereas dashed arrows indicate indirect or conceptual interactions. Source: Own work.

In CIPN, Ozatik et al. (2025) [57] showed that subcutaneous liraglutide significantly reduced allodynia, decreased nitric oxide levels, and increased IL-10, with weekly dosing showing superior efficacy. These findings are complemented by the *in vitro* observations of Jung et al. (2025) [52], who highlighted additional neuroprotective and regenerative effects, including reduced oxidative stress and enhanced neurite growth.

### 3.5.5. Anti-Hyperalgesic Effects Across Inflammatory Pain Models

Across inflammatory pain paradigms, GLP-1R agonists consistently demonstrated strong anti-hyperalgesic effects. Gong et al. (2014) [50] and Fan et al. (2015) [48] reported reductions in pain hypersensitivity ranging from 60% to 90% in formalin, CFA, and carrageenan models. These effects were corroborated by Balogh et al. (2019) [46], who showed dose-dependent attenuation of hyperalgesia via DPP-4 inhibition, reinforcing the role of GLP-1 signaling in inflammatory pain modulation.

## 4. Discussion

The synthesized evidence delineates a coherent and biologically plausible framework in which GLP-1R signaling acts as a multimodal regulator of pain through complementary mechanisms with potential translational relevance [59]. Notably, these mechanisms were consistently observed across a broad spectrum of experimental pain models—including inflammatory, neuropathic, neuroimmune, and central sensitization paradigms—rather than being confined to diabetic neuropathy, suggesting that GLP-1 receptor signaling may represent a common modulatory pathway across diverse nociceptive conditions.

Collectively, the available evidence supports the mechanistic plausibility of GLP-1R signaling as a regulator of pain-related pathways. Rather than acting through a single mechanism, GLP-1 receptor agonists appear to modulate an interconnected network involving nociceptive processing, neuroinflammation, endogenous analgesia, oxidative stress, and

neuronal plasticity [60,61]. Although these findings provide a strong biological rationale for further investigation, they are derived predominantly from experimental and preclinical studies. Consequently, robust clinical evidence demonstrating meaningful improvements in patient-centered pain outcomes remains limited.

First, the modulation of nociceptive excitability via TRP channels emerges as a key mechanism with direct clinical implications. The inhibition of channels such as TRPV1 contributes to reduced peripheral sensitization [62], potentially translating into diminished thermal and mechanical hyperalgesia in patients with neuropathic or inflammatory pain conditions [63,64]. This effect is reinforced by reductions in oxidative stress and downregulation of TRP channel expression, which suggest both functional and structural adaptations [45,49,55]. However, the presence of context-dependent pronociceptive responses—such as increased  $\text{Ca}^{2+}$  influx and substance P release—may show that clinical outcomes may vary [65]. Consequently, these findings should be interpreted as mechanistic observations that require validation in clinical populations before therapeutic implications can be established.

Second, the anti-inflammatory effects of GLP-1R activation represent one of the most robust and clinically translatable findings. The consistent reduction in proinflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6), along with decreased microglial and astrocytic activation, directly targets central sensitization mechanisms [66]. This positions GLP-1R agonists as promising candidates for conditions driven by neuroinflammation, such as fibromyalgia, osteoarthritis, and chronic migraine. Furthermore, the involvement of intracellular pathways like PI3K/Akt and the upregulation of IL-10 further support a shift toward resolution of inflammation [67,68]. Although these mechanisms may be relevant to disorders in which neuroinflammation contributes to symptom generation, the current evidence does not allow firm conclusions regarding clinical efficacy in specific pain conditions such as fibromyalgia, osteoarthritis, or migraine.

A third important component of the findings is the modulation of the endogenous opioid system. GLP-1R activation has been shown to promote  $\beta$ -endorphin release and enhance opioid receptor signaling in experimental studies [69,70], thereby amplifying intrinsic analgesic pathways. These observations suggest a potential interaction between GLP-1R signaling and endogenous pain-modulating systems; however, whether such effects translate into clinically opioid-sparing benefits remains to be determined in adequately powered clinical trials [71].

Particularly, in neuropathic pain models, GLP-1R-mediated effects appear especially pronounced at the molecular and cellular levels. Transcriptomic normalization of genes involved in inflammation, neuronal signaling, and synaptic plasticity, together with reductions in oxidative stress, suggests a neuroprotective environment conducive to repair [72–74]. These findings may support a role for GLP-1R activation in modulating biological processes associated with neuropathic injury. The additional observation of enhanced neurite outgrowth further supports the possibility of regenerative effects in experimental settings. Nevertheless, extrapolation from animal models to human neuropathic disorders should be approached with caution, and clinical confirmation is currently lacking.

Finally, anti-hyperalgesic effects were consistently reported in several experimental inflammatory pain models, including formalin, CFA, and carrageenan paradigms [75,76]. These observations suggest that GLP-1R signaling may influence biological pathways shared across different forms of induced nociception. Moreover, the convergence of findings obtained with both direct GLP-1R agonists and DPP-4 inhibitors strengthens the rationale for investigating the GLP-1 axis as a therapeutic target [77]. However, because most of the available evidence originates from preclinical studies, the translational relevance of these findings remains uncertain.

#### 4.1. Limitations

Several limitations should be considered when interpreting the findings of this review. First, the available evidence is predominantly derived from experimental and animal studies, with only limited human data available. Therefore, the findings should be interpreted primarily as mechanistic and translational evidence rather than as proof of clinical efficacy.

Second, considerable heterogeneity was observed across studies with respect to animal species and strains, experimental models, dosing regimens, treatment duration, routes of administration, outcome measures, and the specific GLP-1 receptor agonists evaluated. Such variability limits direct comparisons between studies and may draw discrepancies in reported findings.

Third, caution is warranted when extrapolating experimental findings to human populations. Although animal models provide insights into biological processes related to nociception and neuroinflammation, they do not fully capture the complexity, heterogeneity, and multidimensional nature of human pain conditions.

#### 4.2. Clinical Recommendations and Future Perspectives

Given that the available evidence is predominantly derived from experimental and preclinical studies, future research should focus on well-designed translational and clinical investigations to determine whether the mechanistic effects observed in vitro and in animal models translate into meaningful outcomes in human populations. Particular attention should be directed toward the identification of biomarkers associated with neuroinflammatory, neuroimmune, and metabolic pathways, which may help to clarify the biological contexts in which GLP-1 receptor signaling is most relevant.

Furthermore, studies incorporating stratification according to inflammatory status, neuroimmune characteristics, and metabolic profiles may improve our understanding of potential sources of heterogeneity and facilitate translational research strategies.

### 5. Conclusions

Current evidence suggests that GLP-1 receptor agonists modulate multiple biological pathways involved in nociception and neuroinflammation. However, the available literature is predominantly preclinical, and the clinical relevance of these findings remains uncertain. Therefore, the observed effects should be interpreted as mechanistic and translational evidence that generates hypotheses for future research. Well-designed clinical studies are needed to determine whether these experimental findings translate into meaningful benefits in human pain conditions.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/rheumato6030016/s1>, Table S1. PRISMA 2020 Checklist; Table S2. Search strategy; Table S3. Methodological Quality Analysis (CAMARADES Checklist), Table S4. Risk of Bias Analysis (SYRCLE's Risk of Bias tool).

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## Abbreviations

The following abbreviations are used in this manuscript:

|               |                                          |
|---------------|------------------------------------------|
| AMPK          | AMP-activated protein kinase             |
| ABCA1         | ATP-binding cassette transporter A1      |
| CNS           | Central nervous system                   |
| DRG           | Dorsal root ganglion                     |
| GLP-1         | Glucagon-like peptide-1                  |
| GLP-1R        | Glucagon-like peptide-1 receptor         |
| IL            | Interleukin                              |
| TNF- $\alpha$ | Tumor necrosis factor alpha              |
| TRPV1         | Transient receptor potential vanilloid 1 |
| TRPA1         | Transient receptor potential ankyrin 1   |

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