

Systematic Review

Immunomodulatory and Anti-Inflammatory Effects of Gabapentin: A Systematic Review and Risk of Bias Analysis of Preclinical Studies

Annette d'Arqom ^{1,2,*} , Kireina Azizah Rizky ³ , Nasya Malfa Aqilah ³ , Fathul Huda ^{4,5}, Ming Tatt Lee ^{6,7} , Belinda Anasthasya Tansy ⁸, Suzita Mohd Noor ⁹ , Rimbun ^{1,2}  and Ni Luh Ayu Megasari ¹⁰

- ¹ Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya 60131, Indonesia; rimbun@fk.unair.ac.id
- ² Molecular and Biomedical Science Research Group, Faculty of Medicine, Universitas Airlangga, Surabaya 60131, Indonesia
- ³ Faculty of Medicine, Universitas Airlangga, Surabaya 60131, Indonesia; kireina.azizah.rizky-2024@fk.unair.ac.id (K.A.R.); nasya.malfa.aqilah-2024@fk.unair.ac.id (N.M.A.)
- ⁴ Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Bandung 40161, Indonesia; fathul@unpad.ac.id
- ⁵ Neurology Clinic, Universitas Padjadjaran Hospital, Sumedang 45363, Indonesia
- ⁶ Office of Postgraduate Studies, UCSI University, Kuala Lumpur 56000, Malaysia; leemt@ucsiuniversity.edu.my
- ⁷ College of Health Sciences, Chang-Jung Christian University, Tainan 711301, Taiwan
- ⁸ Master Program in Biomedical Sciences, Faculty of Medicine, Universitas Airlangga, Surabaya 60131, Indonesia; belinda.anasthasya.tansy-2025@fk.unair.ac.id
- ⁹ Department of Biomedical Science, Faculty of Medicine, Universiti Malaysia, Kuala Lumpur 50603, Malaysia; suzita@um.edu.my
- ¹⁰ Postgraduate School, Universitas Airlangga, Surabaya 60132, Indonesia; ni.luh.ayu@pasca.unair.ac.id
- * Correspondence: annette-d-a@fk.unair.ac.id

Abstract

Gabapentin is widely used for epilepsy and neuropathic pain. Beyond neurological indications, preclinical evidence suggests that gabapentin may exert anti-inflammatory effects that have not been systematically reviewed. A systematic review (2015–2025) was performed, resulting in thirteen in vitro and in vivo studies evaluating gabapentin's impact on inflammatory signaling pathways, cytokine production, immune cell activity, and tissue inflammation. Outcomes included molecular pathways, inflammatory mediators, histopathological changes, and functional inflammatory measures. Risk of bias and study quality were assessed using the SYRCLE RoB tool for in vivo studies and the SciRAP approach for in vitro studies. Gabapentin demonstrated potential modulation of inflammatory responses in neuropathic pain, neuroinflammation, uveitis, and sepsis models through inhibition of MAPK and NF- κ B signaling, reduction in pro-inflammatory cytokines, modulation of PPAR signaling pathways, and activation of Nrf2/HO-1 pathway. Gabapentin's pharmacological actions extend beyond neuronal excitability to include modulation of inflammatory pathways, supporting a broader biological role for gabapentin. Although preclinical data support gabapentin's potential anti-inflammatory properties, further targeted experimental and clinical studies are warranted to confirm these findings.

Keywords: adjuvant analgesic; anti-inflammation; chronic diseases; GABA-analog; immunomodulator



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1. Introduction

Gabapentin, a structural analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) or 2-[1-(aminomethyl)cyclohexyl]acetic acid, has a molecular formula $C_9H_{17}NO_2$ (Figure 1A). In 1993, gabapentin was approved as adjunctive therapy for partial seizures in patients with epilepsy [1,2], and its therapeutic applications have expanded beyond seizure management. In 2004, the FDA approved gabapentin for the treatment of postherpetic neuralgia [3] and in 2007 it was approved for fibromyalgia [4]. Gabapentin is also used for neuropathic pain related to spinal cord injury, addressing a difficult-to-manage pain type resulting from nerve damage [5]. Even though gabapentin is not approved for the treatment of diabetic peripheral neuropathy, it is still used off-label for this indication [6].

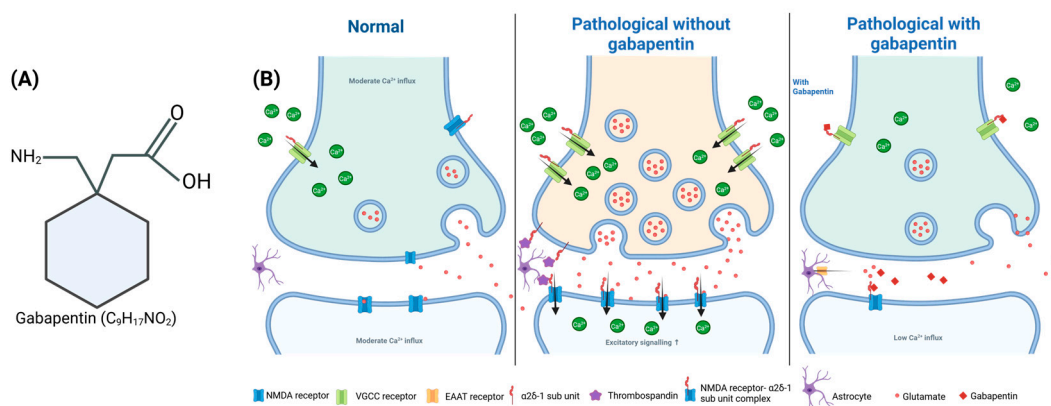


Figure 1. Chemical structure and mechanism of action of gabapentin. (A). Chemical structure of gabapentin; (B). Mechanism of action of gabapentin. Gabapentin binds to the $\alpha 2\delta-1$ subunit of voltage-gated calcium channels (VGCCs), resulting in reduced presynaptic Ca^{2+} influx and decreased excitatory neurotransmitter release. It also disrupts the interaction between the $\alpha 2\delta-1$ subunit and N-methyl-D-aspartate (NMDA) receptors, limiting NMDA receptor trafficking to the cell surface and attenuating excitatory neurotransmission. In addition, gabapentin has been reported to increase the expression of δ -subunit-containing GABA_A receptors [7], which may enhance tonic inhibitory signaling. Created using www.biorender.com, accessed on 15 April 2026.

It is also prescribed for the management of alcohol withdrawal syndrome, reducing anxiety, insomnia, and seizures commonly experienced during alcohol cessation. The dose starts at 1200 mg/day, with higher doses (≥ 1800 mg/day) used in severe cases, depending on clinical response [8]. The European Medicines Agency (EMA) and clinical guidelines recommend a maximum dose of 1800 mg, since increasing the dose does not provide significant additional benefit [9].

1.1. Pharmacokinetics of Gabapentin

Gabapentin acts intracellularly and requires active absorption. Its peak time is about 2–3 h with a half-life of 5–7 h. Its oral bioavailability ranges from 27 to 60% and follows zero-order kinetics. Consequently, gabapentin is recommended to be administered 3–4 times a day at a dose of 900–3600 mg/day, with a titration period of about 14 days to reach the effective dose [10]. Absorption in the small intestine relies on l-amino acid transporters (LAT), which are easily saturated at high doses. When the gabapentin dose increases, the area under the plasma concentration-time curve (AUC) does not increase proportionally. Gabapentin does not bind to plasma proteins and is actively transported across the blood–brain barrier by LAT-1 because its structure resembles the amino acid leucine. It is water-soluble, has a volume of distribution of 0.8 L/kg, and does not affect the spinal concentrations of the neurotransmitters glutamate and norepinephrine [11]. Gabapentin is not metabolized by the liver and does not affect cytochrome P450, although there have been

reports of hepatotoxicity [12]. Its primary elimination is via the kidneys, in an unchanged form. The elimination half-life is approximately 5–7 h and excessive accumulation can lead to kidney failure [10].

Pregabalin, a derivative of gabapentin, shares the same mechanism of binding to the $\alpha 2\delta$ -1 subunit of voltage-gated calcium channels and offers a better pharmacokinetic profile, notably higher bioavailability (60% vs. 90%) and more predictable absorption. Although these pharmacokinetic advantages make pregabalin theoretically more potent, comparative trials consistently show that its long-term outcomes are not clearly superior to gabapentin [13], even though another systematic review reported greater effectiveness of pregabalin for neuropathic pain [14]. Pregabalin is also reported to reduce opioid consumption and milder side effects such as dizziness and somnolence [14], even though one study reported that pregabalin is associated with the development of heart failure compared with gabapentin. Table 1 summarizes the pharmacokinetic and pharmacodynamic properties of gabapentin.

Table 1. Pharmacokinetics and pharmacodynamics aspects of Gabapentin [10,11,15].

Pharmacokinetics/ Pharmacodynamics	Details
Absorption	Active absorption via l-amino acid transporters in small intestine; saturable at high doses
Bioavailability	27–60% (decreases with higher doses)
Half-life	5–7 h
Administration	3–4 times/day; titrated over ~14 days
Metabolism	Not metabolized; no CYP450 interaction
Elimination	Renally excreted unchanged
Mechanism of Action	Binds to $\alpha 2\delta$ -1 subunit of VGCC thereby reducing Ca^{2+} influx and excitatory neurotransmission
Common Side Effects	Dizziness (19%), somnolence (14%), gait disturbance (14%), blurred vision (7%)
CNS Effects	Confusion, memory loss, speech issues, vertigo
Misuse Risk	15–22% misuse rate; concerns in substance abuse populations
Contraindications	Renal impairment, hypersensitivity

1.2. Pharmacodynamics of Gabapentin

Despite structurally resembling GABA, gabapentin does not bind to GABA receptors. The drug has a high affinity for the $\alpha 2\delta$ -1 subunit of VGCC (Voltage-Gated Ca^{2+} Channels). VGCCs are composed of several subunits: $\alpha 1$, β , γ , and $\alpha 2\delta$. The $\alpha 1$ subunit allows calcium entry, and the extracellular $\alpha 2\delta$ is bound to γ . The $\alpha 2\delta$ subunit plays a role in nociception as its levels increase after injury and take several months to return to baseline [16]. Gabapentin was initially thought to act by inhibiting calcium current through $\alpha 2\delta$ subunit binding, which weakens postsynaptic excitability. However, research suggests that its analgesic effect is more related to the inhibition of neurotransmitter release mediated by $\alpha 2\delta$ -1 when calcium influx is reduced [17]. Gabapentin also reduces the response to painful stimuli by inhibiting the accumulation of $\alpha 2\delta$ in the presynaptic terminals of the dorsal horn [18]. It also inhibits the trafficking of NMDA receptor- $\alpha 2\delta$ -1 complex, leading to inhibition of excitatory neurotransmitters, such as glutamate, release (Figure 1B) [7]. Interestingly, while it is well established that gabapentin does not bind to GABA receptors, even though it is the chemical analogue of GABA, recent studies suggested that repeated treatment with gabapentin increased the expression of the δ -subunit of GABA_A receptor [19], leading to increased tonic inhibition evoked by GABA at the synapse. Furthermore, a recent study

reported that blockade of $\alpha 6$ -subunit-containing GABA_A receptors in the cerebellum significantly reversed gabapentin's anti-tremor effect, further suggesting a potential modulatory effect of gabapentin in the GABA_A system, possibly on tonic inhibition [20].

Additionally, gabapentin exerts multiple effects on nociception and neuropathic pain. It inhibits the binding of thrombospondin from astrocytes to $\alpha 2\delta$ -1, thereby reducing the formation of new excitatory synapses [21], and enhances glutamate uptake via excitatory amino acid transporters (EAATs) [22]. It may indirectly influence inflammatory responses associated with pain processing [23]. Furthermore, gabapentin modulates the limbic system and cortical pathways involved in pain perception, partly through alterations in noradrenergic and serotonergic signaling [24–26]. These effects are primarily mediated through modulation of calcium-dependent neurotransmitter release at the synaptic level. Additional effects include reduced excitatory synapse formation, enhanced glutamate uptake, and modulation of descending inhibitory pathways, which collectively contribute to its analgesic and neuromodulatory properties [27].

1.3. Side Effects and Possible Misuse of Gabapentin

Gabapentin has pharmacodynamic interactions that can lead to side effects, causing about 11% of patients to discontinue treatment. The most common side effects include dizziness (19%), somnolence (14%), gait disturbance (14%), and blurred vision (7%) [15,28]. Other CNS side effects involve impaired concentration, confusion, memory loss, mood changes, movement disorders, sleep disturbances, speech disorders, and vertigo [10]. The risk of these side effects increases at higher doses [29].

A Cochrane review found that 38% of people with moderate to severe diabetic peripheral neuropathy receiving gabapentin at a dose of ≥ 1200 mg/day for a minimum of 8 weeks experienced a 50% reduction in pain. However, 63% experienced at least one side effect, 3.2% experienced serious side effects, and 1.1% misused gabapentin [15]. Although gabapentin is widely regarded as a well-tolerated medication, recent epidemiological reports indicate increasing patterns of misuse, particularly among individuals concurrently using opioids or sedative medications. Data from 2004 to 2015 showed 11,940 reports of gabapentin misuse and dependence, with a misuse rate 15–22% higher than opioids [30]. Co-administration of gabapentin and opioids exhibited dependence-like responses in a murine study [31] and increased the risk of opioid-related deaths in a clinical setting [32]. Moreover, it potentiates central nervous system depression and respiratory distress when used with other depressants [32]. High-dose or prolonged use has also been associated with dependence, withdrawal symptoms, and cognitive slowing, especially in vulnerable populations [33]. Thus, careful prescribing, routine monitoring, and patient education regarding potential risks are needed during gabapentin prescription.

Despite these issues, gabapentin still serves as first-line therapy for neuropathic pain in Australia, the United Kingdom, and Canada. Gabapentin is contraindicated in patients with hypersensitivity to the drug and in individuals with impaired renal function. The recommended dose involves titration over 3–7 days in divided doses until pain relief is achieved, with a maximum of 3600 mg/day [33]. These safety considerations are important when interpreting the potential anti-inflammatory use of gabapentin, particularly in relation to dose and long-term use.

1.4. Therapeutic Indications and Off-Label Applications of Gabapentin

Clinically, gabapentin is established as an adjunctive antiepileptic drug and as a first-line pharmacological option for several neuropathic pain conditions. In epilepsy, gabapentin is primarily used as add-on therapy for partial seizures, where systematic reviews have shown a significantly higher likelihood of achieving $\geq 50\%$ seizure reduc-

tion compared with placebo [34]. In pain management, gabapentin is FDA-approved for postherpetic neuralgia and fibromyalgia, and it is widely recommended in international guidelines as a first-line agent for neuropathic pain, including diabetic peripheral neuropathy and pain associated with spinal cord injury, despite some indications remaining off-label [15,35]. Across these indications, its clinical efficacy is largely attributed to attenuation of neuronal hyperexcitability and reduced excitatory neurotransmitter release via modulation of the $\alpha 2\delta$ -1 subunit of voltage-gated calcium channels.

Beyond its core indications, gabapentin is frequently prescribed off-label for conditions characterized by central sensitization or dysregulated neuronal signaling. These include generalized anxiety disorder and other anxiety states (particularly in patients intolerant to SSRIs/SNRIs), alcohol withdrawal syndrome, restless legs syndrome, migraine prophylaxis, essential tremor, and pain or spasticity associated with multiple sclerosis [36–38]. In alcohol withdrawal, gabapentin has demonstrated efficacy comparable to benzodiazepines in mild-to-moderate cases, with additional benefits in reducing relapse and alcohol craving, although results remain heterogeneous across studies [39,40]. For restless legs syndrome, gabapentin enacarbil (the prodrug gabapentin) has gained regulatory approval, underscoring the clinical relevance of this drug class in movement and sleep-related disorders [41].

However, evidence supporting gabapentin use in some off-label indications, including migraine prevention, essential tremor, and behavioral symptoms in dementia, remains mixed. Meta-analyses have reported limited or non-significant overall benefits compared with placebo, particularly for migraine and essential tremor [42,43]. Nevertheless, several individual studies have demonstrated potential benefits: randomized and open-label trials reported reductions in migraine frequency and pain intensity with gabapentin at doses of 900–2400 mg/day [44–46]. Several clinical and preclinical studies showed tremor suppression and improved patient-reported outcomes in essential tremor [20,47,48]. In addition, small case series suggested that low-dose gabapentin may reduce agitation and aggressive behavior in patients with vascular dementia [49]. However, growing concerns regarding adverse effects, misuse potential, and cognitive impairment in vulnerable populations necessitate careful patient selection and monitoring. Table 2 provides a comprehensive summary of the FDA-approved indications as well as the most common off-label uses of gabapentin.

Table 2. Therapeutic Indications and Off-label Uses of Gabapentin.

Condition	Approved Use	Typical Dose	Evidence Level
Partial Seizures (Epilepsy) [1,10]	FDA approved	900–3600 mg/day in 3 doses	Moderate-High
Postherpetic Neuralgia (PHN) [50]	FDA approved	≥ 1200 mg/day	High
Fibromyalgia [4,51]	Pregabalin: FDA approved	1200–2400 mg/day	Moderate
Neuropathic Pain (e.g., DPN) [3,35]	Off-label Pregabalin: FDA approved	≥ 1200 mg/day	High
Alcohol Withdrawal Syndrome (AWS) [37]	Off-label	900–1800 mg/day (can exceed in severe cases)	Moderate
Restless Legs Syndrome (RLS) [38]	Gabapentin Enacarbil	600–1200 mg/day	Moderate
Generalized Anxiety Disorder (GAD) [52]	Off-label	900–3200 mg/day	Moderate
Hot Flashes (Menopause) [53]	Off-label	300–900 mg/day	Low-moderate
Migraine Prevention [42,46]	Off-label	300–2400 mg/day	Low-moderate

Table 2. *Cont.*

Condition	Approved Use	Typical Dose	Evidence Level
Essential tremor [20]	Off-label	900–1800 mg/day	Moderate-High
Pain and spasm in Multiple sclerosis [54–56]	Off-label	300–2700 mg/day	Moderate-High
Pain and agitation in vascular dementia [49]	Rarely	100–200 mg/day	Low-moderate

Preclinical evidence suggests that gabapentin may modulate inflammatory processes beyond its effects on neuronal excitability. Experimental studies demonstrate that gabapentin inhibits MAPK and NF- κ B activation and reduces the production of pro-inflammatory cytokines, including IL-6 and TNF- α [57]. In addition, gabapentin interferes with thrombospondin- α 2 δ -1-mediated synaptogenesis [48], and modulates peroxisome proliferator-activated receptor (PPAR) signaling pathways [58], collectively contributing to the attenuation of neuroinflammation and peripheral inflammatory responses. However, these potential anti-inflammatory effects remain preliminary and context-dependent, and have not been systematically evaluated across different experimental models. Accordingly, this systematic review aims to comprehensively summarize and critically evaluate the available preclinical evidence, including both *in vitro* and *in vivo* studies, on the anti-inflammatory effects of gabapentin, and to discuss its potential direction.

2. Materials and Methods

2.1. Search Strategy and Eligibility Criteria

Literature searching was obtained from electronic databases, including PubMed and SCOPUS, using the keywords “Gabapentin AND Anti-inflamat*” from October to November 2025. The search was restricted to the English language during 2015–2025. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [59]. The screening process and data collection were performed by two independent reviewers. Titles and abstracts were screened prior to full-text assessment, and relevant cross-references were manually searched to identify additional eligible studies. Eligible studies included English-language publications involving human participants, animal models, or cell culture systems that investigated the anti-inflammatory properties of gabapentin. Studies conducted in veterinary settings, those using gabapentin in combination therapies, or those employing gabapentin as a control while investigating other agents were excluded. In addition, the following publication types were excluded: letters to the editor, short communications, conference abstracts, case reports, systematic reviews, and meta-analyses.

2.2. Risk of Bias and Quality Assessment

The methodological and reporting quality of *in vitro* studies was evaluated using the SciRAP (Science in Risk Assessment and Policy) approach, following the criteria provided in the SciRAP assessment template. Only the *in vitro* components of eligible studies were assessed. Each item was scored as yes (2), partly/unclear (1), or no (0), and non-applicable items were excluded from the final calculation. Scores were summed and expressed as percentages, and study quality was classified as high ($\geq 75\%$), moderate (50–74%), or low ($< 50\%$). The assessment focused on key aspects, including test compound description, experimental design, exposure conditions, outcome measurement, statistical analysis, and reporting transparency.

Risk of bias for in vivo animal studies was assessed using the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) Risk of Bias tool. Ten domains were evaluated, including sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers, random outcome assessment, blinding of outcome assessors, incomplete outcome data, selective reporting, and other potential sources of bias. Each domain was judged as low risk or with some concerns based on information reported in the Sections 2 and 3 of the articles. For studies that included both in vitro and in vivo experiments, only the in vivo components were assessed using the SYRCLE tool [60].

3. Results

An electronic comprehensive search yielded 1233 articles on the subject of gabapentin as an anti-inflammatory. After an initial screening of titles and abstracts, 59 studies were chosen for full-text screening. Finally, thirteen studies were included in this systematic review (Figure 2).

PRISMA flow diagram

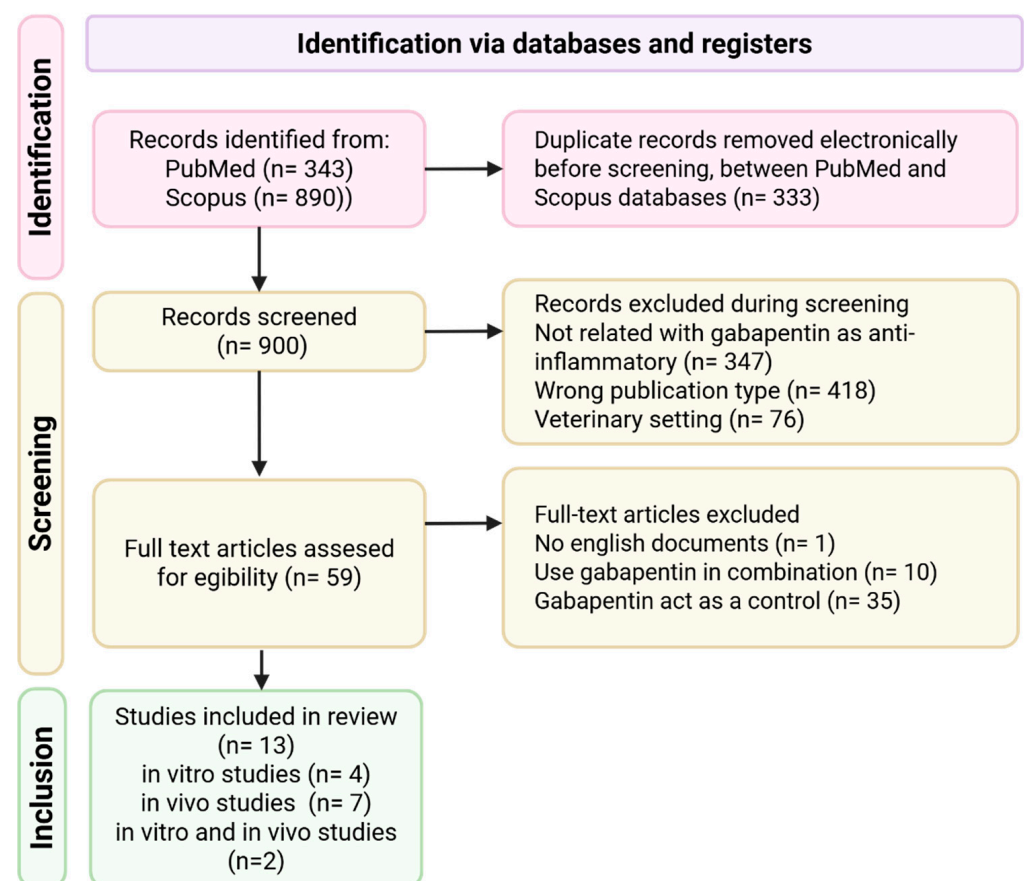


Figure 2. PRISMA results. Created using www.biorender.com, accessed on 4 February 2026.

The included studies were published between 2015 and 2025, including four in vitro studies [57,61–63], seven in vivo studies [56,58,64–69], and two studies combining in vitro and in vivo approaches [70,71]. The preclinical evidence is presented according to study design. Table 3 summarizes the included study types, inflammation induction methods, gabapentin dose, and the outcome.

Table 3. Gabapentin in anti-inflammatory studies.

Study	Types	Induction	GBP	Outcomes	Conclusion
In vitro					
Yamaguchi, 2017 [57]	U373 MG human glioblastoma astrocytoma cells (1×10^5 cells/well)	Substance P (100 nM) for 10–15 min or 24 h	Gabapentin 1 mM for 60 min	GBP (1 mM) substantially suppressed SP-induced phosphorylation of p38 MAPK (but not ERK1/2). GBP significantly abolished SP-induced phosphorylation of NF- κ B and suppressed IL-6 and IL-8 production	GBP likely prevents SP-induced IL-6 and IL-8 production in U373 MG cells via inhibition of p38 MAPK and NF- κ B, exhibiting anti-neuroinflammatory effects
Palmieri, 2024 [63]	Human monocytes (THP-1 cells) differentiated to M0-naïve macrophages	Drug-induced gingival overgrowth model, including gabapentin	Gabapentin 100 μ M	Gabapentin induced M0 macrophages to polarize toward pro-inflammatory M1 phenotype. Increased expression of M1-associated genes: <i>CCL5</i> , <i>CXCL10</i> , and <i>IDO1</i> expression.	Gabapentin drives pro-inflammatory polarization of macrophages in vitro, contributing to drug-induced gingival overgrowth pathogenesis
Nürnberg, 2022 [61]	Primary cell cultures of rat spinal dorsal horn	Lipopolysaccharide (LPS) stimulation for 4 h	Gabapentin 100 μ M or Pregabalin 100 μ M	Gabapentinoids suppressed LPS-induced IL-6 production in primary spinal dorsal horn cultures	Gabapentinoids exhibit anti-inflammatory effects by suppressing cytokine production in spinal cord cells
Leisengang, 2020 [62]	Primary cultures from rat dorsal root ganglia (DRG)	Inflammatory stimuli (LPS) for 120 min and capsaicin	Gabapentin 100 μ M or Pregabalin 100 μ M or capsaicin 1 μ M	Gabapentinoids modulated inflammatory responses in DRG cultures. Reduced cytokine release in response to inflammatory stimuli	Gabapentinoids suppress inflammatory responses in peripheral sensory neurons.
Li, 2024 [70]	THP-1-derived macrophages	Lipopolysaccharide (LPS) stimulation for 6 h	Gabapentin 100 μ M, 2 h prior LPS stimulation	GBP reduced NGF, iNOS, TNF- α , and IL-1 β expression in LPS-stimulated macrophages. Effects attenuated by PPAR- γ antagonist GW9662. Reduced α 2 δ 1 expression and calcium content	Gabapentin inhibits M1 macrophage polarization via PPAR- γ activation and calcium channel modulation.

Table 3. Cont.

Study	Types	Induction	GBP	Outcomes	Conclusion
Anfuso, 2017 [71]	ARPE-19 cells Human retinal endothelial cells	TNF- α (10 ng/mL) stimulation for various time points	Gabapentin (0.1–10 μ M) pre-treatment for 30 min before TNF- α	Highest dose GBP significantly inhibited TNF- α -induced IL-1 β production. GBP reduced TNF- α -induced cPLA2 (cytosolic phospholipase A2) phosphorylation and activation. GBP suppressed COX-2 expression and PGE2 production in dose-dependent manner.	GBP attenuates ocular inflammation by inhibiting the cPLA2–COX-2–PGE2 pathway and proinflammatory cytokines.
In vivo					
Samra, 2021 [64]	Male Wistar rats (n = 48), 10 weeks old	Doxorubicin-induced myocardial toxicity	10–30 mg/kg, p.o., once daily	GBP reduced myocardial MDA content by 34–41.5%, increased TAC by 200–212%, reduced TRAIL by 27.8–32.5%, and caspase-8 by 34–39.6%	Gabapentin confers cardioprotective effects against DOX-induced myocardial injury by modulating inflammatory/apoptotic signaling pathway
Motavallian, 2021 [65]	Male Wistar rats, 6 groups (n = 6–8/group)	Acetic acid-induced colitis (2 mL of 3% acetic acid intracolonic)	25, 50, and 100 mg/kg, i.p., daily	GBP (50 and 100 mg/kg) significantly reduced macroscopic and microscopic colonic lesions, MPO activity, and colonic IL-6, IL-1 β , and TNF- α concentrations	Gabapentin exerts beneficial anti-inflammatory effects in experimental colitis, potential therapeutic agent for IBD
Yosri, 2018 [66]	Swiss Albino mice (n = 30), male, 8 weeks old, 20–25 g	Ovalbumin-induced allergic asthma (10 mg OVA with Al(OH) ₃ , days 0 and 7; nebulized 1% OVA days 14–16)	50 mg/kg, p.o., once daily	GBP significantly reduced lung inflammatory cell counts, serum LDH and catalase activities, lung/body weight index. Increased lung GSH and SOD activity. Reduced TNF- α , IL-4, and IL-13. Improved lung histopathology	Gabapentin's modulatory effect on IL-4, IL-13, and TNF- α accounts for anti-inflammatory and anti-allergic properties in asthma

Table 3. Cont.

Study	Types	Induction	GBP	Outcomes	Conclusion
de Brito, 2020 [58]	Male Wistar rats (150–200 g)	TNBS-induced colitis (trinitrobenzene-sulfonic acid)	0.6, 3.0, and 15 mg/kg, i.p.	High dose of GBP decreased macroscopic lesion scores, wet weight, mast cell count, MPO, MDA, nitrate/nitrite, IL-1 β , TNF- α , COX-2, iNOS, and NF κ B. Restored GSH levels. Effects blocked by PPAR- γ inhibitor	Gabapentin inhibits bowel inflammation by activating PPAR- γ receptor, which inhibits NF κ B activation and reduces inflammatory gene expression
Li, 2024 [70]	Male rats (MI model); Sham (n = 12), MI (n = 20), MI + GBP (n = 16)	Myocardial infarction by left coronary artery ligation	100 mg/kg p.o for 28 consecutive days with 24 h interval	At 1 week: reduced iNOS (M1 marker), TNF- α , IL-1 β ; increased Arginase-1, CD163 (M2 markers), IL-10, TGF- β . At 4 weeks: improved cardiac function, reduced infarct size and fibrosis. Reduced sympathetic nerve activity, TH, GAP43, and NGF	Gabapentin attenuates cardiac remodeling after MI by inhibiting M1 macrophage polarization through PPAR- γ pathway and preventing calcium overload
Broto, 2025 [67]	Rattus norvegicus Sprague-Dawley (n = 23); Normal, PSL, PSL + GBP groups	Partial sciatic nerve ligation (PSL)-peripheral neuropathic lesion model	50 mg/kgBW/day p.o	Significant reduction in CGRP expression in PSL + GBP group vs. PSL group ($p = 0.002$). No significant difference in IL-10 expression between groups ($p = 0.85$)	Gabapentin reduces CGRP expression in dorsal horn of spinal cord after neuropathic lesions but does not increase IL-10 expression
Abdelnaser, 2024 [68]	Male Wistar rats (n = 120, 200–250 g) Sepsis-induced acute kidney injury model	Cecal ligation and puncture (CLP) to induce polymicrobial sepsis and acute renal damage	Gabapentin (50 and 100 mg/kg i.p for 4 days. administered after CLP induction for evaluation period	GBP improved renal function, reduced inflammation and oxidative stress, modulated Nrf2/HO-1 and NF- κ B signaling, and alleviated renal histopathological damage.	GBP mitigated CLP-induced septic AKI by activating Nrf2/HO-1 signaling, suppressing inflammation and oxidative stress, and inhibiting apoptosis, demonstrating renoprotective effects.

Table 3. *Cont.*

Study	Types	Induction	GBP	Outcomes	Conclusion
Li et al., 2022 [69]	Male Sprague-Dawley rats (n = 70, 8–10 weeks old, 220–260 g)	Intermittent access to 20% ethanol in 2-bottle choice (IA2BC) procedure for 4 weeks to establish high voluntary ethanol consumption (>5.5 g/kg/day)	GBP (30, 60, and 120 mg/kg) once daily for 20 days. GBP (60 mg/kg) and co-administration GBP 60 mg/kg + BADGE (PPAR- γ inhibitor) 30 mg/kg	GBP dose-dependently reduced ethanol intake, suppressed IL-1 β /TNF- α and hippocampal NF- κ B, and increased PPAR- γ expression without motor impairment; these effects were completely abolished by the PPAR- γ inhibitor BADGE.	GBP reduces alcohol intake and neuroinflammation by activating PPAR- γ , suppressing NF- κ B signaling and proinflammatory cytokines; reversal by BADGE confirms PPAR- γ as the causal target.
Anfuso, 2017 [71]	New Zealand White rabbits (endotoxin-induced uveitis model)	Intravitreal injection of LPS (100 ng/0.1 mL) to induce endotoxin-induced uveitis (EIU)	Topical GBP eye drops (0.1%, 0.3%, 1.0% solutions) applied 2 h before and 1, 4, 8, 12, 16, 20 h after LPS injection	Topical GBP (1.0%) dose-dependently reduced uveitis severity, suppressed TNF- α /IL-1 β , and inhibited the cPLA2-COX-2-PGE2 pathway, with maximal efficacy at 1.0%.	Topical GBP attenuates ocular inflammation by inhibiting the cPLA2-COX-2-PGE2 pathway and proinflammatory cytokines, demonstrating therapeutic potential for uveitis.

Note: GBP: Gabapentin, SP: Substance P, CLP: Cecal ligation and puncture, LPS: Lipopolysaccharide, EIU: Endotoxin-induced uveitis, IA2BC: Intermittent access 2-bottle choice, BADGE: Bisphenol A diglycidyl ether (PPAR- γ antagonist), cPLA2: Cytosolic phospholipase A2, COX-2: Cyclooxygenase-2, PGE2: Prostaglandin E2, MDA: Malondialdehyde, GSH: Glutathione, SOD: Superoxide dismutase.

3.1. In Vitro Studies and Study Quality

In vitro studies utilized a range of experimental models, including THP-1-derived macrophages [63,70], primary cultures of rat spinal dorsal horn and dorsal root ganglion [61,62], human glioblastoma astrocyte cell line [57], and ARPE-19 cells, human retinal endothelial cells [71]. Based on the SciRAP evaluation, four of the six included in vitro studies were classified as high quality, while two studies were rated as moderate quality. High-quality studies showed clear descriptions of the test systems, exposure conditions, appropriate controls, adequate replication, and reliable outcome measurements. Moderate-quality studies mainly lacked detailed reporting on compound purity, vehicle controls, or cytotoxicity testing. Overall, the in vitro evidence demonstrated acceptable methodological quality and provided supportive data for the interpretation of gabapentin's anti-inflammatory effects, while acknowledging some limitations in reporting consistency across studies (Figure 3A).

These studies demonstrated that gabapentin modulates inflammatory responses through effects on cytokine production and intracellular signaling pathways. Several studies reported suppression of pro-inflammatory cytokines such as IL-6, IL-8, TNF- α , and IL-1 β [57,61,62,71] primarily through inhibition of MAPK and NF- κ B signaling pathways [57]. In addition, gabapentin has been shown to influence macrophage polarization and calcium-dependent signaling mechanisms [70]. However, inconsistent findings were

observed, as one study reported pro-inflammatory M1 polarization in macrophages, highlighting the context-dependent effects of gabapentin [63].

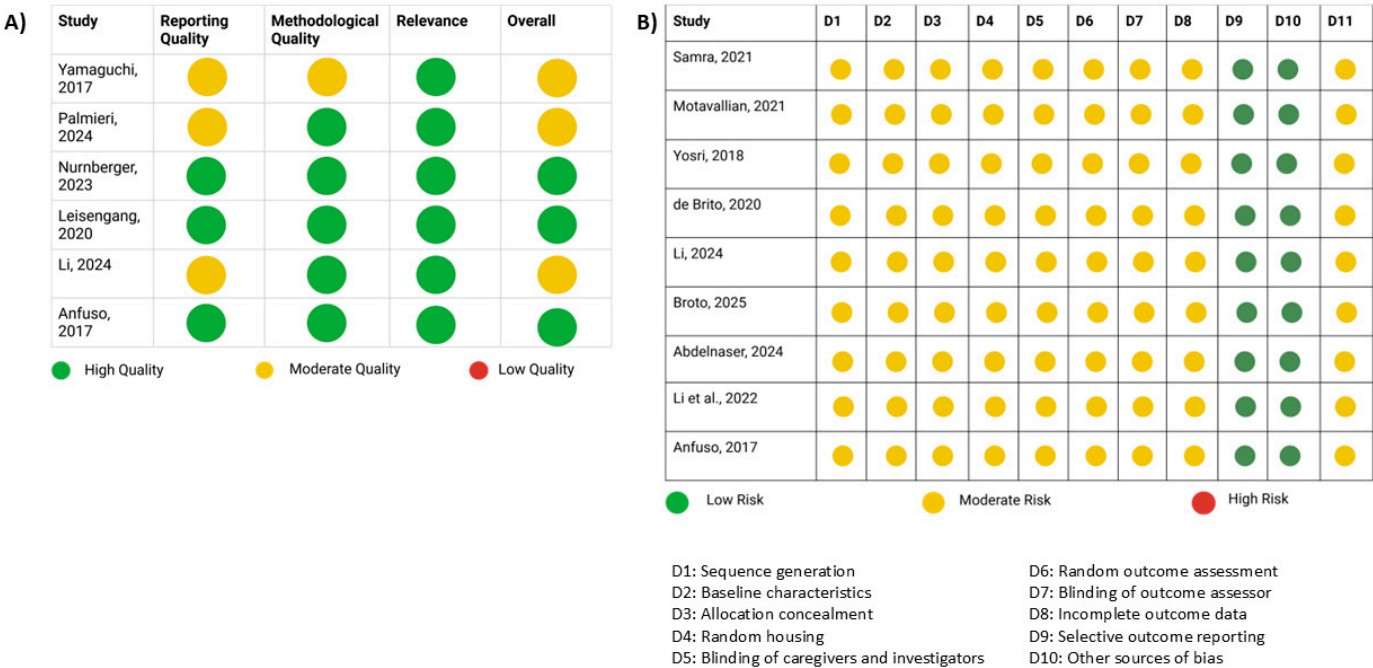


Figure 3. Study quality and risk of bias assessment of preclinical studies on gabapentin. (A) Study quality of in vitro studies assessed using the SciRAP tool. (B) Risk of bias of in vivo studies assessed using the SYRCLE tool [57,58,61–71]. Created using www.biorender.com, accessed on 17 April 2026.

3.2. In Vivo Studies and Risk of Bias

Seven of nine in vivo studies were conducted in rats, with five studies in Wistar rats [58,64,65,68,69], one in Sprague Dawley [67], and one in a myocardium infarction model [70]. One study was conducted in Swiss Albino mice [66], and the last study was conducted in New Zealand White rabbits [71]. These studies employed various disease models, including myocardial injuries [64], cardiac remodeling [70], colitis [58,65], asthma [66], neuropathic pain [67], sepsis and kidney injury [68], alcohol withdrawal syndrome [69], and uveitis [71].

Based on the SYRCLE assessment, most in vivo studies showed some concerns in domains related to sequence generation, allocation concealment, and blinding, mainly due to insufficient reporting of randomization procedures and blinding of caregivers or outcome assessors. In contrast, incomplete outcome data and selective reporting were consistently assessed as low risk, as all animals were accounted for and prespecified outcomes were reported. Overall, the risk of bias across in vivo studies was considered moderate (Figure 3B).

Gabapentin treatment reduced inflammatory cytokines (TNF-α, IL-1β, IL-6), oxidative stress markers, and histopathological damage, while improving functional outcomes [58,65,66,71]. Mechanistically, these effects were associated with modulation of MAPK/NF-κB signaling [69], activation of PPAR-γ [58,69,70], and engagement of the Nrf2/HO-1 pathway [68]. Overall, the in vivo evidence suggests a broader systemic anti-inflammatory effect compared to in vitro findings.

4. Discussion

This systematic review suggests that gabapentin may exert anti-inflammatory and immunomodulatory effects beyond its established neuromodulatory role. However, these

effects should be interpreted cautiously, as they are preliminary, context-dependent, and largely based on specific experimental models. Preclinical studies, both in vivo and in vitro, support potential anti-inflammatory effects of gabapentin through modulation of inflammatory signaling pathways, immune cell activity, and neuroimmune interaction [57,58,61–71] which contribute to neuroinflammation in both central and peripheral tissues.

This extended pharmacological profile is particularly relevant considering the interplay between inflammation and neuronal excitability; for example, chronic inflammation might enhance neuronal sensitization, while sustained neuronal activity can promote inflammatory responses through glial activation and cytokine release [72]. Gabapentin's capacity to influence both domains may explain its wide-ranging effects on various neurological and non-neurological disorders.

Although structurally related to γ -aminobutyric acid (GABA), gabapentin does not directly activate GABA_A or GABA_B receptors. However, some experimental studies have reported an upregulation of δ -subunit-containing GABA_A receptors in the presence of gabapentin [19]. Its primary molecular target is the $\alpha 2\delta$ -1 subunit of voltage-gated calcium channels [16]; its binding to this subunit is associated with reduced presynaptic calcium influx, thereby limiting neurotransmitter release and neuronal excitability [18,19]. Reduction of calcium influx may contribute to decreased immune cell activation, cytokine secretion, and transcription factor signaling, which may underlie the anti-inflammatory effects of gabapentin. An in vitro study in THP-1-derived macrophages demonstrated a reduction of calcium influx during gabapentin treatment [70]; however, other in vitro studies using primary cultures of spinal dorsal horn demonstrate that gabapentin and pregabalin did not modulate calcium influx in the presence of LPS, substance-P, or glutamate [61]. Preclinical studies showed gabapentin might inhibit pro-inflammatory cytokines through inhibition of NF- κ B and MAPK, as well as promote anti-inflammatory cytokines, IL-10, and anti-oxidant enzymes. Figure 4 summarizes the proposed mechanism of gabapentin's anti-inflammatory effects.

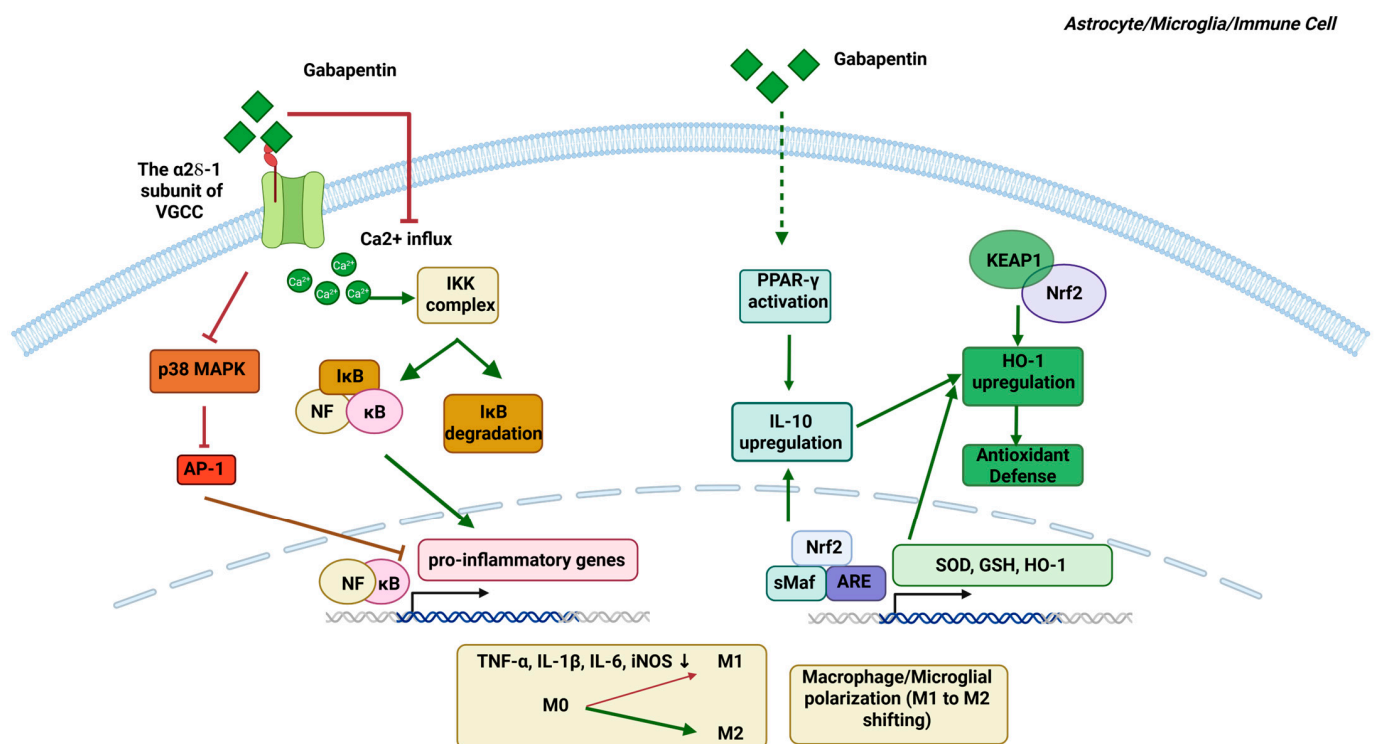


Figure 4. Proposed Molecular Mechanisms of Gabapentin's Anti-inflammatory and Immunomodulatory Effects. Gabapentin binds to the $\alpha 2\delta$ -1 subunit of voltage-gated calcium channels (VGCC), leading to reduced

Ca²⁺ influx. This inhibition suppresses downstream pro-inflammatory signaling pathways, including the IKK/NF-κB and p38 MAPK/AP-1 cascades, thereby reducing the transcription of pro-inflammatory genes (TNF-α, IL-1β, IL-6). Simultaneously, gabapentin promotes anti-inflammatory and antioxidant defenses by activating the PPAR-γ and Nrf2/HO-1 pathways, which upregulate IL-10 and antioxidant enzymes (SOD and GSH). These combined actions facilitate a phenotypic shift in macrophages and microglia from a pro-inflammatory (M1) to a resolving (M2) state. Solid arrows indicate activation or signaling flow, blunt-ended lines indicate inhibition, and dashed arrows represent indirect or modulatory effects. Green elements denote anti-inflammatory/antioxidant pathways, whereas orange/red elements indicate pro-inflammatory signaling. Created using www.biorender.com; accessed on 16 April 2026.

4.1. Gabapentin Inhibits Pro-Inflammatory Pathway

Among the most consistently reported findings across preclinical studies is gabapentin's inhibitory effect on MAPK and NF-κB signaling pathways. These pathways are master regulators of inflammatory gene expression and play pivotal roles in both innate and adaptive immune responses [73]. Several studies demonstrate that gabapentin suppresses key inflammatory signaling pathways downstream of calcium influx, including p38 MAPK and NF-κB activation. An in vitro study provided direct experimental evidence showing that gabapentin and pregabalin suppressed substance P-induced IL-6 and IL-8 production in U373 MG astrocytoma cells by inhibiting phosphorylation of p38 MAPK and blocking activation and nuclear translocation of NF-κB [57]. Notably, these effects have been observed in experimental models of neuropathic pain, neuroinflammation, and peripheral inflammatory injury, suggesting a conserved mechanism across tissues. In many of these studies, however, gabapentin was primarily employed as a comparator or reference drug when evaluating the anti-inflammatory efficacy of other agents, rather than as the primary investigational compound [74–76]. From a translational perspective, modulation of MAPK–NF-κB signaling is highly relevant, as dysregulation of these pathways is implicated in a wide range of chronic inflammatory conditions, including autoimmune diseases, metabolic disorders, and neurodegenerative processes [77].

In parallel, increasing evidence indicates that gabapentin activates PPAR-γ signaling, a nuclear receptor that plays a pivotal role in resolving inflammation, regulating lipid metabolism, and suppressing NF-κB-dependent transcription. A murine study demonstrated that gabapentin reduced hippocampal and serum IL-1β and TNF-α levels and decreased NF-κB expression in the hippocampus in an alcohol consumption model, and crucially, these effects were abolished by the PPAR-γ inhibitor BADGE, supporting a causal role for PPAR-γ activation in mediating gabapentin's anti-inflammatory effects [69]. Similarly, one study showed that gabapentin reduced macroscopic and microscopic colonic inflammation and oxidative stress markers in an intestinal inflammation model, with evidence implicating PPAR-γ receptor involvement in these protective effects [58]. Modulation of PPAR signaling by gabapentin introduces an important immunometabolic dimension to its pharmacological profile. This mechanism is especially relevant in metabolic and systemic inflammatory disorders such as alcoholic liver disease and non-alcoholic fatty liver disease, where inflammation and lipid dysregulation are tightly linked [78]. Although evidence in this area remains limited, the available data suggest that gabapentin may influence inflammatory processes through pathways traditionally targeted by metabolic anti-inflammatory agents.

Consistent with its effects on inflammatory signaling cascades, gabapentin has been shown to reduce the production of key pro-inflammatory cytokines, particularly IL-6, IL-1β, and TNF-α [65,68,71]. These cytokines play critical roles in amplifying inflammatory responses, mediating tissue damage, and sustaining chronic inflammation [79]. Reduction

in these mediators suggests that gabapentin may exert immunomodulatory effects that extend beyond symptomatic relief.

Cytokine suppression by gabapentin has been reported in both central nervous system-derived cells (e.g., microglia and astrocytes) [56] and peripheral immune cells [63,71]. This dual activity supports the hypothesis that gabapentin's anti-inflammatory effects are not restricted to neuroinflammatory contexts but may also influence systemic immune responses. Such properties are particularly relevant to diseases characterized by low-grade chronic inflammation, where modest but sustained cytokine modulation may have meaningful therapeutic implications.

4.2. Gabapentin Induces Anti-Inflammatory Cytokines and Anti-Oxidant Enzymes

Beyond MAPK and PPAR- γ pathways, recent work has identified engagement of the Nrf2/HO-1 antioxidant pathway as another mechanism contributing to gabapentin's anti-inflammatory actions. A study found that gabapentin attenuated sepsis-induced acute kidney injury by reducing TNF- α , IL-1 β , IL-6, and NF- κ B expression while upregulating Nrf2 and HO-1 protein expression, linking activation of antioxidant defense mechanisms to reduced inflammatory signaling [68]. Furthermore, gabapentin was reported to enhance morphine effect in increasing IL-10 and HO-1 expression while decreasing proinflammatory cytokines in the spinal cord during neuropathic pain, and blockade of IL-10 or HO-1 partially reversed gabapentin's analgesic effects, indicating that engagement of anti-inflammatory cytokines contributes functionally to its therapeutic actions [80]. Gabapentin also reported to induce expression and production of anti-oxidant enzymes, including GSH and SOD in the lung and gut [58,66].

4.3. Gabapentin Effects on Glia and Tissue Inflammation

In the central nervous system, neuroinflammation is increasingly recognized as a critical contributor to chronic pain and neurodegenerative processes [81]. Gabapentin has been shown to suppress inflammatory mediator release from astrocytes [57] and spinal cord cells [60], suggesting that its analgesic effects may partially arise from modulation of glial activation. In vitro studies demonstrated that gabapentin and pregabalin suppressed substance P-induced IL-6 and IL-8 production and blocked p38 MAPK and NF- κ B activation in human astrocytoma cells, providing direct evidence for astrocyte-directed inhibition of proinflammatory signaling cascades [57]. Complementing these findings, a murine study reported that gabapentin and pregabalin attenuated lipopolysaccharide-induced IL-6 expression and release in rat superficial dorsal horn neuro-glial primary cultures, supporting a direct reduction in glial-derived proinflammatory mediators in the spinal cord [61].

Emerging evidence suggests that gabapentin may also influence microglial polarization. An integrative transcriptomic analyses and drug-signature predictions study proposed that gabapentin may modulate a CX3CR1-TLR4-NF- κ B axis and influence microglial polarization toward less proinflammatory states, providing a mechanistic rationale for microglial immunomodulation [82]. While this evidence is predictive and translational rather than a direct in vivo demonstration of polarization, it offers important mechanistic hypotheses for future investigation.

The anti-inflammatory effects in the central nervous system extend to the modulation of central sensitization processes. The ability of gabapentin in increased IL-10 and HO-1 while reducing spinal proinflammatory cytokines in a neuropathic pain model, and these changes contributed to reduced morphine tolerance and pain signaling [80]. This aligns with broader evidence that targeting glial-derived cytokines and chemokines can attenuate central sensitization and chronic pain states [83]. Additionally, gabapentin effect on decreas-

ing hippocampal NF- κ B and IL-1 β /TNF- α in an alcohol consumption model, consistent with central anti-inflammatory effects that could influence neuroimmune contributions to behavior and sensitization [69].

Despite predominantly anti-inflammatory findings, gabapentin's effects are not uniform across experimental conditions. One in vitro study reported polarization of naïve macrophages (M0) to pro-inflammatory macrophage (M1) marked by increasing of CCL5, CXCL10, related to gingival overgrowth [63], whereas multiple other studies demonstrated inhibition of M1 macrophage markers and promotion of M2-associated phenotypes [70]. Such discrepancies highlight the importance of cellular context, differentiation status, and baseline inflammatory condition. This reflects the complexity of immune regulation [84].

Gabapentin's anti-inflammatory effects have been studied in multiple organ systems. In the gastrointestinal tract, gabapentin (50–100 mg/kg) reduced macroscopic and histological colonic lesions, decreased myeloperoxidase (MPO) activity, and lowered colonic IL-6, IL-1 β , and TNF- α levels in an acetic acid-induced colitis model, with effects comparable to dexamethasone [64]. In ocular inflammation, it showed that topical gabapentin reduced lipopolysaccharide-induced TNF- α , IL-1 β , cytosolic phospholipase A2 (cPLA2) activation, cyclooxygenase-2 (COX-2) expression, and prostaglandin E2 (PGE2) levels in rabbit endotoxin-induced uveitis, demonstrating efficacy in reducing clinical signs of ocular inflammation [70]. These studies collectively show anti-inflammatory effects across colon, eye, kidney, and central nervous system tissues, with common endpoints being reductions in TNF- α , IL-1 β , IL-6, MPO, or COX-2/PGE2, and engagement of PPAR- γ or Nrf2/HO-1 pathways as context-dependent mediators [58,65,68–70].

Gabapentin's anti-inflammatory actions have been observed in models of colitis, asthma, myocardial injury, and liver-associated inflammation, suggesting relevance beyond neuroinflammatory disorders [64–66,70]. These findings raise the possibility that gabapentin may modulate systemic inflammation through neuroimmune and immunometabolic mechanisms, including attenuation of oxidative stress, reduction in cytokine burden, and preservation of tissue integrity. Given its widespread clinical use, these effects may have implications for patients with comorbid inflammatory conditions.

4.4. Translational Relevance and Therapeutic Implications

The convergence of multiple molecular pathways, calcium channel modulation, MAPK/NF- κ B inhibition [57], PPAR- γ activation [58,69], and Nrf2/HO-1 upregulation [68], suggests that gabapentin acts as a multi-targeted immunomodulator rather than through a single anti-inflammatory mechanism. Unlike conventional anti-inflammatory drugs that directly inhibit cyclooxygenases or cytokine receptors, gabapentin exerts indirect and modulatory effects on intracellular signaling pathways. Even though an in vitro study showed the ability of gabapentin to suppress COX-2 and PGE2 [71], it may be more appropriate to position gabapentin as an adjunctive rather than a primary anti-inflammatory therapy. Its ability to modify immune responses rather than induce broad immunosuppression may represent a therapeutic advantage in chronic inflammatory states.

Comparative studies have shown that gabapentin and pregabalin share similar anti-inflammatory properties. Both agents suppressed substance P-induced IL-6/IL-8 production and inhibited p38 MAPK and NF- κ B activation in astrocyte cells [57], and both attenuated lipopolysaccharide-induced IL-6 release in spinal dorsal horn cultures [61]. In the colitis model, Motavallian et al. (2021) included dexamethasone as a comparator and reported that gabapentin significantly reduced macroscopic and microscopic colitis lesions and inflammatory markers, demonstrating efficacy comparable to the corticosteroid in that experimental system [65].

However, direct head-to-head comparisons with nonsteroidal anti-inflammatory drugs (NSAIDs), biologics, or other targeted anti-inflammatory agents across equivalent models remain limited. Experimental findings suggest that gabapentin may exhibit anti-inflammatory effects comparable to established agents such as corticosteroids, including reductions in hepatic steatosis, immune cell infiltration, and goblet cell hyperplasia. However, this evidence remains limited and requires further validation [85]. Furthermore, the current literature does not include randomized clinical trials or human biomarker studies explicitly demonstrating gabapentin's anti-inflammatory effects in clinical populations. This represents a critical gap in translating preclinical findings to clinical practice.

4.5. Limitations and Future Directions

This study reviewed the preclinical evidence of gabapentin's anti-inflammatory effects. While mechanistic studies provide compelling evidence for multiple anti-inflammatory pathways, these findings have not yet been supported by human data. Variability in dosing regimens, disease models, and experimental endpoints further limits direct comparison across studies. In addition, the literature search was restricted to PubMed and Scopus, which may have resulted in the omission of relevant studies.

Future research should prioritize clinical translation through well-designed randomized controlled trials evaluating the anti-inflammatory effects of gabapentin in selected inflammatory conditions, with appropriate biomarker assessment. In addition, dose–response relationships need to be clarified to determine whether clinically relevant anti-inflammatory effects occur at standard therapeutic doses or require higher exposure. Further studies should also elucidate underlying mechanisms, identify predictive biomarkers, and evaluate effects on immune cell function. Finally, long-term safety, potential impacts on immune function and disease progression, and comparative effectiveness with established anti-inflammatory agents should be assessed to support safe therapeutic repurposing. Therefore, the anti-inflammatory role of gabapentin remains to be validated in clinical settings.

5. Conclusions

The body of preclinical evidence suggests that gabapentin may possess anti-inflammatory and immunomodulatory properties mediated through multiple molecular pathways, including calcium channel modulation, MAPK and NF- κ B inhibition, PPAR- γ activation, and engagement of antioxidant defense mechanisms. These effects extend across neural and peripheral tissues, with documented efficacy in models of colitis, uveitis, acute kidney injury, and neuroinflammation. The mechanistic diversity and favorable safety profile position gabapentin as a potentially valuable adjunctive agent in inflammatory conditions. However, the absence of clinical validation represents a critical limitation, and future translational research is essential to determine whether these preclinical findings translate to clinically meaningful anti-inflammatory effects in human populations. Clarifying dose–response relationships, identifying responsive patient populations, and establishing safety in long-term immunomodulatory use will be essential for evidence-based therapeutic repurposing of gabapentin beyond its current neurological indications.

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Data Availability Statement: No new data were generated in this study.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AWS	Alcohol Withdrawal Syndrome
DRG	Dorsal Root Ganglion
EIU	Endotoxin-Induced Uveitis
HO-1	Heme Oxygenase-1
LPS	Lipopolysaccharide
MDA	Malondialdehyde
MPO	Myeloperoxidase
Nrf2	Nuclear Factor Erythroid 2-Related Factor 2
PPAR	Peroxisome Proliferator-Activated Receptor
SciRAP	Science in Risk Assessment and Policy
SYRCLE	Systematic Review Centre for Laboratory Animal Experimentation
VGCC	Voltage-Gated Calcium Channel

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