

GABAPENTIN IN ANIMAL MODELS OF NEUROPATHIC PAIN: A REVIEW ARTICLE
OF PHARMACOLOGICAL EFFECTS AND INTERACTIONS WITH PLANT –DERIVED
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ABSTRACT

Neuropathic pain arises from lesions or diseases of the somatosensory system that are insufficiently treated with existing drugs. Gabapentin, a ligand of $\alpha 2\delta$ receptor, is a frequently employed drug, although the underlying mechanism remain poorly understood. This paper critically evaluates 28 provided papers. Six general papers regarding neuropathic pain, pharmacology and animal models of gabapentin: 13 experimental papers on gabapentin in rodents; and 9 papers concerning phytochemicals and their extracts. In case of the papers on gabapentin, they demonstrate antiallodynic or antihyperalgesic properties in models of chronic constriction injury, Spinal nerve ligation, partial sciatic ligation, ischemia, trigeminal and diabetes. Proposed mechanism including inhibition of ectopic discharge, changes in spinal and supraspinal activity, inhibition of nav1.7 and p-ERK1/2 and CaMK II modification. No evidence for GABA receptor or opioid mechanisms was found. One study demonstrated pro inflammatory activity along with antinociceptive effects. Only a small fraction of plant compound studies that have investigated gabapentin combined with the respective plant compounds. Gabapentin- plant combination studies have indicated various interactions, such as synergism and additive effect, among others. Nonetheless, some studies conducted on gabapentin and plants involved the use of gabapentin as the sole positive control but not as an interaction with the plant constituents. This research is limited by model diversity, doses and routes, abstract level data and lack of clinical validation.

KEYWORDS: Gabapentin, neuropathic pain, animal models, mechanical allodynia, $\alpha 2\delta$ subunit, botanical compounds, drug- herb interaction.**1. INTRODUCTION**

The term refers to a condition arising from somatosensory system injury or disease of the A β , A δ , and C fibers or central neurons and effecting up to 7-10% of the general population.^[1] The frequency of neuropathic pain is expected to increase owing to population ageing prevalence of diabetes and better survival of cancer patients.^[1]

Pathogenesis: The suggested factors include an abnormal balance between somatosensory excitation and inhibition, changes in the function ion channels and variable regulation of pain signaling at the spinal level.^[1] The ectopic discharge from injury afferents appears to be

one of the major mechanism of induction and maintenance of neuropathic pain and therefore represents a rational target for pharmacotherapy.

Gabapentin: The medicine emerged as a preferred drug for the first-line therapy due to its efficacy and favorable adverse effects profile despite and unclear mechanism of action.^[2] A breakthrough event occurred with the discovery of specific binding of (3H) Gabapentin to the protein isolated from pig cerebral cortex and identified as the $\alpha 2\delta$ subunit of voltage- dependent calcium channel.^[3]

Animal models: Pharmacological and mechanistic studies require models which stimulate human

neuropathic pain. Among basic models of there are CCI model of sciatic nerve injury.^[4] Spinal nerve ligation^[5], SNI model.^[6] All these models result in a unique combination of injured and spared fibers: thus, none of the models covers the whole spectrum of mechanism.^[6]

Justification of plant compound usage. Gabapentin's inefficiency resulted in combination with natural compounds to improve its effectiveness or reduce the doses. In the provided literature there are combinations of sinomenine and gabapentin.^[7,8] Mangiferin.^[9] Sulforaphane^[10], Fraction of centella asiatica^[11], bacopa monnieri.^[12], Cannabis extract^[13] and ginsenosides.^[14] Clinical evaluation of cannabis drugs was performed, but the quality of evidence is low.^[15] Only some of these studies tested gabapentin in combination with plant compound (sinomenine, mangiferin, sulforaphane, centella asiatica); in the Bacopa monnieri, cannabis and ginsenoside studies gabapentin served only as benchmark.

2. Animal Model of Neuropathic Pain

Chronic constriction injury (CCI). Ligation of the common sciatic nerve results in thermal hyperalgesia starting from postoperative day2 for more than two months, implying allodynia and spontaneous pain- like symptoms.^[4] Studies on gabapentin involved chronic constriction of sciatic nerve in wistar rats^[16, 17], a CCI model investigating CaMKII^[18], and a bacopa monnieri CCI model^[12], in which allodynia was assessed both statically and dynamically heat and punctate hyperalgesia.

Spinal nerve ligation (SNL). Ligation of L5 and L6, or only L5 nerves, resulted in thermal hyperalgesia (minimum duration of five weeks) and allodynia (minimum duration of ten weeks) as well as behaviour indicative of spontaneous pain: separation of the injured and unaffected segments is considered an advantage.^[5] Provided studies included the following: L5 – L6 ligation or nerve root ligation in rats^[19, 21], and L5 SNL in mice.^[22]

Partial sciatic ligation. Pan et al. utilized partial sciatic ligation and determined mechanical allodynia with von Frey filaments and single- fibre recordings proximally to the ligation.^[23]

Spared nerve injury: It lesions the tibial and common peroneal nerves but spares the sural nerve; it causes early (<24 hours), long-lasting (> 6 months) and pronounced changes; testing of adjacent normal skin is possible.^[6] SNI is not employed in the gabapentin experiments provided- that's another model to be compared to others.

Models of painful diabetic neuropathy. Mechanical allodynia and thermal hyperalgesia were demonstrated in diabetic rats.^[24] Also, diabetic rats have been shown to exhibit abnormal behaviour during the formalin test,

manifested as enhanced flinching during the phase when it usually doesn't occur.^[25]

Other models included. The model set of comprises photochemical induced ischemia of the mouse sciatic nerve with erythrosin B and laser irradiation^[26], vincristine induced neuropathy in rats.^[13] Tail nerve injury and contusive spinal cord injury in rats.^[14] Formalin – induced secondary allodynia and hyperalgesia^[9], fibromyalgia like pain model.^[10], transgenic mice over expressing human wild type and mutant torsin A in SNL^[22] and acute nociceptive tests [hotplate, tail clip, tail flick, writhing].^[27] The Centella asiatica experiment utilizes the pentylene tetrazole seizure model, not the pain one.^[11]

3. Pharmacological actions of gabapentin

3.1 Antiallodynic and antihyperalgesic actions

Most models experienced reduction in evoked hypersensitivity using gabapentin; however, dosages, route, and timing differ greatly among studies. In rats subjected to CCI, 100mg/kg i.p. 15 minutes prior to surgery followed by 12hours treatment every day for days 1 through 4, gabapentin reducing mechanical allodynia and thermal hyperalgesia, achieving the highest effect postoperatively on day 8.^[18] In Wistar rats having sciatic constriction, oral gabapentin (30, 60 and 120 mg/kg) administered at 60mg/kg orally, reduced scratching and biting, along with mechanical allodynia on days 5&15^[16]; heat hyperalgesia at 60 and 120mg/kg at day 5.^[17] Intravenous administration of 30- 90 mg/kg of gabapentin reduced mechanical allodynia in partially ligated sciatic nerves^[23], while subarachnoid gabapentin (10- 1000µg) reduced allodynia in Chung model.^[19] In mice with photochemical sciatic ischemia, repeated subcutaneous administration of 30-51 mg/kg doses increased the withdrawal threshold from 0.55g to 1.85g in comparison with 2.4g in intact animals and did not have any effect in intact mice.^[26] In L5 SNL mice, 100mg/kg attenuated allodynia at its peak (postoperative days 7-10) but not during recovery.^[22] In trigeminal models, repeated (30 and 50 mg/kg) but no single (30-100mg/kg) doses partially attenuated allodynia, while lamotrigine did not have any effect.^[28] In diabetic rats, gabapentin decreased mechanical allodynia and thermal hyperalgesia^[24] and attenuated formalin- induced flinching.^[25]

In acute studies in mice and rats (n=7 per group), gabapentin demonstrated peripheral antinociceptive at all doses and central antinociceptive at 30mg/kg.^[27] This dose not refer to neuropathic pain models, so they may provide information about the mechanism but not the neuropathic efficacy of gabapentin.

Other behaviors. Gabapentin increased climbing and rearing^[16] and walking scores^[17], which were considered as motor activity increase by authors rather than sedation. Contrarily, repeated 50 mg/kg (but not 30 mg/kg) induced motor deficit in trigeminal models.^[28]

3.2 Effects on neuronal excitability

Dose- dependent effect of gabapentin (30- 90 mg/kg) decreased ectopic activity in 15 neuropathic sciatic afferent fibers, but did not affect conduction velocity and mechanosensitivity in 12 normal fibers.^[23] Gabapentin (10- 100 mg/kg), administered subcutaneously to SNL rats, attenuated spontaneous neuronal activity in the spinal cord, unlike carbamazepine, gabapentin also attenuated evoked activity in sham- operated rats, without difference between SNL and sham.^[20] Thus, the effect of gabapentin is unlikely to be specific for neuropathy. In diabetic rats, gabapentin decreased the neuronal hyperexcitability of DRG neurons associated with diabetes, together with Nav1.7 and p- ERK1/2 expression.^[24] PhMRI in SNL rats revealed the significant effects of gabapentin in the hippocampal formation and other limbic and sensorimotor brain areas, minor responses in sham- operated rats, and greater decrease in functional connectivity in SNL rats.^[21]

3.3 Molecular Mechanism

The most confirmed molecular mechanism is binding to the $\alpha 2\delta$ subunit of voltage-gated calcium channels, demonstrated by purification and characterization of a [3H]gabapentin-binding protein.^[3] Additionally, the supplied studies postulate the following mechanisms, one for each study.

- GABA receptors: Antagonists of GABA –A (bicuculline 0.3 μ g) and GABA- B (CGP 35348, 30 μ g) failed to counter spinal antiallodynic effect, hence alternative mechanisms were involved.^[19]
- CaMKII: gabapentin inhibited CaMKII expression and phosphorylation in CCI rats.^[18]
- Nav1.7 and ERK signaling: downregulation of Nav1.7 and p- ERK1/2 in diabetic DRG neurons.^[24]
- Arachidonic acid, nitergic and serotonergic systems'- NAME and cyproheptadine affected gabapentin's effects, naloxone didn't affect it, PGE2 decreased and nNOS increased and authors interpreted it as an adaptive phenomenon, there wasn't any support for opiodergic pathway.^[27]
- Supraspinal modulation: Changes in limbic and connective response.^[21]

3.4 Inflammation and nerve morphology

Gabapentin 60mg/kg increased myelin basic protein (by about three folds by western blotting on day 15) and improved axon, fiber and myelin morphology on electron microscopy in CCI rats.^[16] In another parallel study carried out at day 5, both 60 mg/kg elevated myeloperoxidase in nerve tissue, TNF – α , IL-1 β and 120 mg/kg lowered IL-10 and gabapentin enhanced carrageenan paw edema and macrophage peritoneal migration.^[17] It was resolved that gabapentin enhance inflammation responses but keep the analgesic action probably through a CNS pathway.^[17] In these two studies, the same species and model were used but the results are not conflicting due to differences in measured parameters and time points (5 and 15 days).

4. Gabapentin and Plant-Derived Compounds

Nine publications regarding plants can be classified according to evidence type: combination tested: sinomenine^[7,8], mangiferin^[9], sulforaphane^[10], *Centella asiatica*.^[11]

Only gabapentin used as a compactor: *Bacopa monnieri*^[12], and *Cannabis sativa* extracts^[13] ginsenosides.^[14] A review of cannabis - based drugs in clinical medicines^[15] is provided. Isobolographic analysis in mangiferin and centella studies only.^[9,11]

4.1 Sinomenine

Gao et al. studied the ability of sinomenine to potentiate either gabapentin or ligustrazine hydrochloride in animal models of neuropathic pain.^[7] Since the full text is not available, results of a quantitative nature are not included here. A Data in Brief paper describes an open field test in mice (n=6 per group) for detecting sedative effects, body temperature, oedema, and itching with combination treatments, as well as microdialysis experiments to assess whether there is accumulation of sinomenine in blood and CNS tissue upon repeated administration.^[8] Additionally, a previous finding that repeated administration of sinomenine and gabapentin increased baseline pain thresholds is mentioned.^[8] A doctoral thesis by the same group mentions strong synergy in rat and mouse models of neuropathic pain without tolerance upon repeated administrations, however, it is out of the provided set, synergy.^[7]

4.2 Mangiferin

Godinez- Chaparro et al. used peripheral injection of gabapentin, mangiferin or a fixed ratio combination to study their activity secondary allodynia and hyperalgesia in formalin- induced inflammation in rats.^[9] Experimental ED50s of the combination (29.45 and 37.73 μ g) were smaller than additive values, suggesting synergy in this case. Synergy was shown to be inhibited by L- NAME, the guanyl cyclase inhibitor ODQ and glibenclamide depend on NO- cGMP- ATP sensitive potassium channel mechanism.^[9] It is a combination study with isobolographic demonstration of synergy, but done on an inflammatory (formalin) model of secondary sensitivity, not a neuropathic one.

4.3 Sulforaphane

Zamora –Diaz et al. evaluated the interaction of gabapentin and sulforaphane in fibromyalgia like pain, with electrocorticography and docking assay in mice.^[10] Both agents had a dose- dependent antiallodynic and antihyperalgesic effect individually, and the authors concluded that sulforaphane and its combination with gabapentin can be used to treat fibromyalgia – type pain, depending on the dosage.^[10] The abstract provided does not specify the type of interaction, synergistic, additive, or antagonistic, therefore, no interaction is assumed. The title mentions murine, while the abstract describes rats for the pain model and mice for ECoG. This needs to be verified in the full- text version.

4.4 *Centella asiatica*

In their research, Vattanaian et al. tested the combination of an oral ethyl acetate fraction (EACA) with intraperitoneally injected phenytoin, valproate, or gabapentin phenylenetetrazole test on mice and tested rotarod for possible neurotoxicity.^[11] Median effective doses alone were 13, 104 and 310 mg/kg for phenytoin, valproate, and gabapentin, and 5, 29 and 79 mg/kg with EACA. Analysis showed that all combinations had additive, but not synergistic properties and the combination of gabapentin and EACA had a wider difference between effective and neurotoxic doses.^[11] Since the model is anticonvulsant, the results cannot be extrapolated to neuropathic pain.

4.5 *Bacopa monnieri* (gabapentin as comparator)

Shahid et al. Studied a standardized methanolic extract (BM-40 and BM- 80) along with gabapentin (GBP-75) in CCI rats (n=6 per group) using the extract orally in one group at 40 mg/kg/day.^[12] The CCI rats exhibited static (day 3-21), dynamic (day 14- 21) and cold allodynia as well as heat and mechano- hyperalgesia which was reduced by the extracts treatment. Authors proposed to use of extracts as an adjuvant therapy.^[12] Gabapentin worked as the reference arm. No combination was used. Hence no interaction is implied. No mechanistic study was described in the abstract.

4.6 *Cannabis sativa* extracts (gabapentin as comparator)

Two cannabis extracts (D and B) were compared with gabapentin (60 mg/kg) in male Wistar rats (n=130) in vincristine-induced neuropathy model (0.1 mg/kg).^[13] Vincristine down-regulated the levels of CB1R protein and CB2R mRNA in the cortex; gabapentin was effective in pain reduction and increased the levels of CB1R protein in the hippocampus; extracts affected the CB1R and CB2R in region and dose-dependent manner.

The authors found that alterations in receptor expression are not entirely responsible for the observed behaviour, providing antinociceptive effects equivalent to those of gabapentin.^[13] Gabapentin acted alone in the control group, rather than in combination with any other drug.

4.7 Ginsenosides and total saponin extract (gabapentin as comparator)

The literature mentions one study on the use of total saponin extract, ginsenoside Rb1 and compound K in the treatment of peripheral and central neuropathic pain, involving the participation of estrogen receptor.^[14] As described by the published abstract, male Sprague – Dawley rats with injured tail- nerve or constusive spinal cord were given orally saponin extract (50 mg/kg), Rb1(12.5 mg/kg) or compound K (7mg/kg), experiencing alleviation of allodynia/hyperalgesia, unchanged locomotor function, decreased levels of IL-1b,IL-6, INOS,COX-2, reduced microglia and astrocyte activation. Lee et al.^[14] also involved a gabapentin arm (60mg/kg, orally) as a positive correlative, and antinociceptive effects of the saponin extract and RB1 were counteracted by the estrogen receptor antagonist ICI182780. Gabapentin was failed to combined with the plant compounds, so no interaction is implied.

4.8 Cannabis- based medicines (clinical context)

Petzke et al. reviewed cannabis- based medicines and medical cannabis for chronic neuropathic pain, monitoring poor quality of evidence, inconsistency in conclusions between systematic reviews and conflicting guidelines.^[15] It further explains that less than half of the patients receive any meaningful relief from the existing medications recommended like gabapentin. This paper is a review on clinical studies and not on animal studies.

5. Gabapentin and Herbal medicines

Herbal medicine/ Plant (ref)	Animal/model	Gabapentin dosage	Study design	Interaction observed	Proposed mechanism
Sinomenine (alkaloid from sinomenium Actum) plus gabapentin or ligustrazine ^[7, 8]	Rodents rat/mouse used in neuropathic pain models; open field and microdialysis(in mouse; n=6 per group) ^[8]	n/a in literature	combination	Title suggests sinomenine increases efficacy of gabapentin; baseline pain threshold was increased following administration of multiple doses of sinomenine and gabapentin ^[8] . Not verified by reading entire article.	Not mentioned in the available abstracts; PK studies show sinomenine uptake in blood and CNS tissue ^[8]
Mangiferin ^[9]	Rat; Formalin-induced secondary mechanical allodynia and hyperalgesia	n/a for drug monotherapy; combination ED50= 29.45µg/paw (allodynia) and 37.73µg/paw	Combination (fixed ratio isobolography)	Synergistic: experimental ED50 smaller than theoretical addition effects	No- cGMP-ATP-sensitive K ⁺ channel pathway activation (inhibition by L-NAME, ODQ, glibenclamide)

		(hyperalgesia) via peripheral injection			
Sulforaphane (circumferuous vegetables) ^[10]	Fibromyalgia paint (rat according to abstract: murine according to title); ECoG in mouse	n/a	combination	Both drugs individually demonstrated dose-dependent antiallodynic and antihyperalgesic effects; combination could prove useful at some dosages. Type of interaction not mentioned	Neuroprotective antioxidant, anti-inflammatory properties of sulforaphane indicated; ECoG and docking studies but no exact mechanism found in abstract
Centella asiatica ethyl acetate fraction (EACA) ^[11]	Mouse; pentylene tetrazole- induced seizures (no pain model)	ED50 310mg/kg solo (i.p.) and 79 mg/kg with EACA	Combination (isobolography; rotarod)	Additive, not synergic; increased therapeutic dose and reduced neurotoxic dose of gabapentin + EACA	Not determined abstracts only indicates possibility of adjunct therapy
Bacopa monnieri methanolic extract (bacosides) ^[12]	Rat; Chronic constriction injury (n=6)	Positive control GBP-75 (75 mg/kg, i.p.)	Gabapentin as comparator only (no combination)	None identified; extracts (at 40 and 80mg/kg) suppressed allodynia and hyperalgesia	Not evaluated in abstract
Cannabis sativa L extracts D&B ^[13]	Male wistar rat (n=130); vincristine-induced neuropathy	60mg/kg	Gabapentin as positive control (no combination)	None identified; extracts displayed antinociceptive effect equivalent to that of gabapentin	Changes in CB1R and CB2R levels (cortex, hippocampus); according to authors, these changes do not completely explain behavior, increased CB1R in hippocampus
Ginsenosides: Saponin extract, Rb 1, compound K (ponax ginseng) ^[14]	Male speauge-Dawley rat; tail-nerve and spinal cord injury	60mg/kg p.o. (positive control)	Gabapentin as positive control (no combination)	None identified (no combination tested)	Estrogen receptors; lowered IL- β , IL-6 iNOS, COX- 2, and gliosis (from secondary review)

6. DISCUSSION

Similarities and difference. All thirteen gabapentin experiments^[16-28] concur that gabapentin decreases evoked hypersensitivity or aberrant neuronal firing in the nerve injury, ischemic, trigeminal and diabetic models, but the animal species (rat, mouse) administration (oral, intraperitoneal, subcutaneous, intravenous, subarachnoid), dose (approximately 10 to 100mg/kg systematically) and outcome (behavior, electrophysiology, imaging or biochemical analysis of brain tissue) differ, precluding any comparative evaluation of their potency. Several experiments used only one dose^[18, 24,25], and little information is provided about sex and sample size in the abstracts.

Strengths and weakness of the evidence. The strengths are the convergence of experiments carried out by independent laboratories using different models^[18,19,23,24,25,26,28], as well as the application of reflex and neurophysiological outcomes^[20,23] Weakness matter

too. Most of the evidence comes from single studies; mechanisms remain correlative (e.g., reduced CaMKII, Nav1.7, or p- ERK1/2 with analgesia^[18,24]; nociceptive and inflammatory tests (formalin, hot plate, writhing) were used in addition to neuropathic models.^[25-27]

Four require comments: (i) Gabapentin normalized myelin and nerve morphology on day 15^[16] but increased pro- inflammatory markers on day 5^[17]; be seen. (ii) single doses (30- 100mg/kg) did not work in trigeminal model but repeated doses did^[28], whereas acute actions were found elsewhere^[23,26], suggesting a possible model- or site - specific response (iii) in SNL mice, gabapentin was effective administered during peak allodynia but not during the recovery period^[22], indicating that the effect is dependent on disease phase. (iv) Gabapentin blocked evoked spinal response in both SNL and sham rats^[20], this is difficult to reconcile with an injury - specific mechanism, through it decreased ectopic activity in injured neurons only.^[23]

Established findings vs proposed mechanisms. Findings established by the literature supplied: binding to the $\alpha 2\delta$ subunit^[3]; reduction of evoked pain behavior in several rodent models; and no reversal of the spinal antiallodynic effect by GABA- A and GABA- B antagonist^[19]. Proposed (based on single study correlation): inhibition of ectopic discharge^[23], CaMKII^[18], Nav 1.7/p-ERK1/2^[24], network effects.^[21] It is unresolved how binding to $\alpha 2\delta$ causes these downstream effects, based on the provide research.

Interactions between plants and gabapentin. Only the study of mangiferin^[9] includes evidence of synergy in animal model that involves pain. However, this model is inflammation- induced rather than nerve injury- induced. The centella study demonstrates additivity in a seizure animal model.^[11] For sinomenine^[7,8] and sulforaphane^[10], benefits is reported but the nature of interaction cannot be determined from the provided literature. The Bacopa, ginsenoside and cannabis studies^[12, 14] used gabapentin only as a positive control; they show antinociceptive effects of the plant preparation but do not support interaction. The ginsenoside study^[14] seems to be unrelated to gabapentin based on the provided information. To interpret these studies in such a way evidence of synergy would be inappropriate.

Relevance to humans. All the provided experimental results are preclinical. Rodent doses in mg/kg do not provide direct guidance for human dosing and many models either acute or subacute. Clinically, less than half of the patient experience the substantial pain relief from the first- line treatment medications, including gabapentin^[15]. Adjunctive use is supported by these results; however, there is not one single study among these provided that offers any clinical proof of efficacy. Safety issues have been documented with pro-inflammatory^[17] and motor effects^[28] in rats at higher doses.

7. CONCLUSION

The provided literature indicates that gabapentin has significant antiallodynic and antihyperalgesic properties in a number of rat and mice models of neuropathic pain, with the binding to $\alpha 2\delta$ receptors being the most well-documented mechanism at a molecular level and other mechanism being proposed mainly correlatively. The data on plant- derived substances is diverse. Not all the studies involved the use of gabapentin along with substance under examination; isobolography proved synergism for mangiferin only and additive effects were shown in one studies indicate the beneficial effect of extracts and/ or reference substances without proving the interaction. As this information is based mostly on isolated preclinical studies and abstracts from those studies, it can be considered hypothesis- generating only.

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