Protective Effects of Imeglimin Against Oxaliplatin-Induced Peripheral Neurotoxicity: Evidence From In Vitro and In Vivo Studies

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出版情報：Journal of Applied Toxicology, 2026-06-05. Wiley
バージョン：

Journal of Applied Toxicology

WILEY

Journal of AppliedToxicology

RESEARCH ARTICLE OPEN ACCESS

Protective Effects of Imeglimin Against Oxaliplatin-Induced Peripheral Neurotoxicity: Evidence From In Vitro and In Vivo Studies

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Received: 27 March 2026 | **Revised:** 19 May 2026 | **Accepted:** 22 May 2026

Keywords: adverse effect | drug-repositioning | imeglimin | oxaliplatin | peripheral neuropathy

ABSTRACT

Oxaliplatin is a platinum-based anticancer agent widely used for gastrointestinal malignancies; however, it is known to cause dose-dependent peripheral neuropathy (OIPN), a characteristic adverse effect. OIPN results in a reduced quality of life and often necessitates dose reduction or discontinuation of oxaliplatin; however, effective preventive strategies for OIPN have yet to be established. Imeglimin, an oral antidiabetic agent belonging to the glimin class, has been suggested to influence key aspects of cellular energy metabolism. Because metformin, which shares structural and mechanistic features with imeglimin, prevents OIPN and exhibits unique pharmacological actions, we investigated whether imeglimin also prevents OIPN using both in vitro and in vivo models. In vitro, imeglimin attenuated oxaliplatin-induced cell death, axonal shortening, and oxidative stress in F11 neuronal cells. In vivo, imeglimin prevented reductions in withdrawal thresholds to mechanical stimulation and mitigated sciatic nerve axonal injury in a rat OIPN model. Importantly, imeglimin did not diminish the cytotoxicity of oxaliplatin in several cancer cell lines or its antitumor efficacy in tumor-bearing mice. These findings suggest that imeglimin may prevent OIPN without compromising the antitumor activity of oxaliplatin.

1 | Introduction and Background

Oxaliplatin is a third-generation platinum-based anticancer agent widely used for the treatment of colorectal, pancreatic and gastric cancers (de Gramont et al. 2023; G. Zhao et al. 2010; André et al. 2004; Conroy et al. 2018; Wang et al. 2019), and chemotherapy regimens containing oxaliplatin are positioned as the first-line therapy for several malignancies. However, oxaliplatin is known to cause oxaliplatin-induced peripheral neuropathy (OIPN), which is primarily characterized by numbness, hypersensitivity, and mechanical allodynia of the extremities (Cavaletti and Marmiroli 2020; Staff et al. 2017).

OIPN consists of two clinically distinct forms: acute and chronic neuropathy. Acute OIPN typically appears shortly after oxaliplatin infusion and is characterized by cold-induced paresthesia and dysesthesia. These symptoms generally resolve within several days to 1 week and rarely influence treatment continuation. Mechanistically, acute symptoms are attributed to oxalate-mediated alterations in the expression and function of temperature-sensitive ion channels (Kawashiri et al. 2012; M. Zhao et al. 2012). In contrast, chronic OIPN is caused by the platinum–DNA adduct–related cytotoxic effects of oxaliplatin. It develops in a cumulative dose-dependent manner and manifests as persistent pain, numbness, and sensory loss. Chronic OIPN can last for months to years and, when severe, leads to treatment discontinuation and a marked decline in patients' quality of life. Given that chronic OIPN represents the major dose-limiting toxicity of oxaliplatin-based chemotherapy, the development of therapeutic strategies to prevent

or attenuate chronic neuropathy is of critical clinical importance. Therefore, the present study focused on identifying agents capable of mitigating chronic OIPN.

Although the mechanisms underlying OIPN have not been fully elucidated, previous studies have reported that oxaliplatin uptake by neurons in the dorsal root ganglia (DRG) induces neuronal somatic damage through increased oxidative stress and mitochondrial dysfunction. This subsequently causes the degeneration of axons and myelin sheaths (Wei et al. 2021; Lehky et al. 2004; Shahsavani et al. 2025; Sorensen et al. 2016). A wide range of compounds has been investigated as potential preventive agents for OIPN, targeting various pathogenic mechanisms such as ion channel dysregulation, oxidative stress, and inflammation. However, none of these candidates has demonstrated clinical efficacy in randomized trials (Yang et al. 2021). Current clinical guidelines weakly recommend duloxetine as a therapeutic option for OIPN (Loprinzi et al. 2020; Jordan et al. 2020), and no effective preventive agents have been established. Because OIPN can persist for long periods once it develops, resolving symptoms is time-intensive (Sereno et al. 2014), and establishing preventive strategies is crucial. In addition, repurposing approved drugs represents a practical and efficient approach for identifying clinically applicable therapeutic candidates.

Imeglimin is an oral glimin-class antidiabetic agent that has been approved in Japan and is currently under development toward regulatory approval in the United States and Europe. It exerts pancreatic effects, promoting glucose-dependent insulin secretion and extrapancreatic effects, which improve glucose metabolism in the liver and skeletal muscles (Tajima et al. 2026; Hallakou-Bozec, Kergoat, Fouqueray, et al. 2021; Fujisawa et al. 2025). Metformin, another agent with glucose-lowering and metabolic regulatory actions, has been reported to prevent OIPN in rats (Martinez et al. 2020) and reduce the incidence of Grade 2–3 OIPN in a randomized controlled trial (El-Fatatry et al. 2018). Among its diverse pharmacological actions, activation of AMP-activated protein kinase (AMPK), a master regulator of cellular energy metabolism, contributes to the maintenance and protection of neurons and other cellular functions. Imeglimin shares partial structural similarity (Figure S1) and AMPK-activating properties with metformin (Hyodo et al. 2026); however, it has a more favorable safety profile, including a lower risk of lactic acidosis. Moreover, imeglimin has been reported to exert neuroprotective effects through its unique antioxidant properties and ability to improve mitochondrial function and Schwann cell activity (Kato et al. 2025; Ohguro, Higashide, et al. 2025).

We aimed to determine whether imeglimin mitigates chronic OIPN by reducing oxidative stress and preserving axonal and neuronal integrity in both in vitro and in vivo models.

2 | Methods

2.1 | Animals

Male Sprague–Dawley rats (6 weeks old, body weight 200–250 g, Japan SLC Ltd., Shizuoka, Japan) were used as the peripheral neuropathy model, and male BALB/c mice (6 weeks old, body weight 15–25 g, Japan SLC) were used as the tumor model. Animals were housed under constant temperature and humidity conditions with a 12-h light–dark cycle (light period: 7:00 a.m.–7:00 p.m.) and had free access to solid food and water. All animal experiments were conducted in compliance with the 'Act on the Protection and Management of Animals' (Ministry of the Environment), the 'Kyushu University Animal Experimentation Regulations', the 'Kyushu University Animal Experimentation Rules', and domestic and international guidelines detailed in the 'Animal Experimentation: Guidelines for Reporting In Vivo Experiments'. The experiments were approved by the Kyushu University Animal Experimentation Committee (approval numbers: A25-140-0 and A25-426-2). All necessary precautions were taken to minimize the number of animals used and pain inflicted. All experiments were conducted in a manner that ensured the evaluator was blinded to the treatment conditions.

2.2 | Cell Culture

F11 cells (rat dorsal root ganglion neurons and mouse neuroblastoma hybrid cells, DS Pharma Biomedical Co. LLC., Osaka, Japan), human colorectal cancer cells (HCT116, RIKEN, Saitama, Japan), and mouse colorectal adenocarcinoma (CT26, Tohoku University Biomedical Research Cell Resource Centre, Miyagi, Japan) were cultured in Dulbecco's modified Eagle's medium (DMEM) (Sigma-Aldrich Co. LLC., St. Louis, Missouri, USA) supplemented with 2-mM L-glutamine, 100-U/mL penicillin, 100-μg/mL streptomycin, and 10% fetal bovine serum. Human gastric carcinoma (MKN45, RIKEN) and human pancreatic carcinoma (MIA PaCa-2, National Cancer Centre Hospital, Fukuoka, Japan) cells were cultured in the Roswell Park Memorial Institute (RPMI) medium (Sigma-Aldrich Co. LLC) supplemented with 2-mM L-glutamine, 100-U/mL penicillin, 100-μg/mL streptomycin, and 10% fetal bovine serum. All cells were cultured at 37°C in a 5% CO_2 environment.

2.3 | Drugs

Oxaliplatin (4 mg/kg, Yakult Honsha Co. Ltd., Tokyo, Japan) or a solvent (5% glucose solution) was administered intraperitoneally (i.p.) twice weekly for 4 weeks (on Days 1, 2, 8, 9, 15, 16, 22, and 23) to animals in the OIPN model. Imeglimin (100 mg/kg and 300 mg/kg; Ambeed Inc., Arlington Heights, Illinois, USA) or solvent (distilled water) was administered orally (p.o.) five times weekly for 4 weeks (Days 1–5, 8–12, 15–19, and 22–26). Each drug was administered at 1 mL/kg. Drug dosages were determined based on previous reports (Hallakou-Bozec, Kergoat, Moller, and Bolze 2021; Sakurai et al. 2009; Mine et al. 2022; Egashira et al. 2021).

2.4 | Evaluation of Cell Viability Using F11 Cells

The viability of F11 cells was assessed to evaluate the neurotoxicity of oxaliplatin. Cell viability was evaluated using the water-soluble tetrazolium salt-8 (WST-8) assay with the Cell Counting Kit-8 (DOJINDO Laboratories, Kumamoto, Japan). Cells were

treated with oxaliplatin (100 μM) for 24 h in the presence or absence of imeglimin (100, 200, 500, and 1000 μM). The concentration of each drug was determined according to previous reports (Li et al. 2022; Mori et al. 2025).

2.5 | Evaluation of Neurites Using F11 Cells

Axonal assessment was performed using F11 cells to evaluate oxaliplatin-induced neurotoxicity. Axial assessment was conducted as follows: Axonal outgrowth was induced with 100 ng/mL nerve growth factor (NGF) (Fujifilm Wako Pure Chemical Corporation; Osaka, Japan) 72 h before drug exposure. Cells were treated with oxaliplatin (30 μM) for 48 h in the presence or absence of imeglimin (100–1000 μM). Subsequently, the cells were stained with trypan blue (Thermo Fisher Scientific Inc., Waltham, MA, USA), and unstained viable cells were analyzed using a phase-contrast microscope (CKX41SF, Olympus Co., Tokyo, Japan). Axonal length was measured using the ImageJ 1.54 software (National Institutes of Health, Bethesda, MD, USA). The concentration of oxaliplatin used for neurite assessment (30 μM) was selected based on preliminary experiments demonstrating that neurite shortening occurs at lower concentrations than those required to induce overt cytotoxicity; these data are provided as Figure S2.

2.6 | Assessment of Oxidative Stress Using F11 Cells

To assess oxidative stress induced by oxaliplatin (a cellular reactive oxygen species [ROS] probe), DCFH-DA staining was performed using F11 cells. The evaluation was performed as follows. F11 cells were seeded in an 8-well plate and cultured for 72 h to allow the cells to proliferate in each well. The cells were then treated with oxaliplatin (100 μM) for 24 h, either in the presence or absence of imeglimin (500 μM). Subsequently, the cells were incubated with DCFH-DA (DOJINDO Laboratories) and Hoechst (DOJINDO Laboratories) for 30 min and evaluated using a fluorescence microscope (CKX41SF, Olympus Co.). The brightness of the images was measured using ImageJ 1.54 software.

2.7 | Evaluation of Mechanical Allodynia Using the von Frey Test

The von Frey test was performed to evaluate the effects of imeglimin on mechanical allodynia. The test was conducted on Day 0 (pretreatment) and on Days 4, 11, 18, and 25 between 9:00 a.m. and 12:00 p.m. in chronic OIPN model rats. Each rat was acclimated to a wire mesh cage for 30 min before testing. The von Frey test methodology has been previously described (Mine et al. 2022). The withdrawal thresholds for stimulation with von Frey filaments (Aesthesio; DanMic Global LLC, San Jose, CA, USA) were measured using the up-and-down method. Experiments were conducted with six to seven animals per group.

2.8 | Evaluation of Axonal Injury of the Sciatic Nerve

Sciatic nerves were harvested from three to six rats in the vehicle, oxaliplatin, and 300 mg/kg imeglimin groups and anesthetized with sevoflurane (Fujifilm Wako Pure Chemical Co.) on Day 30. The sciatic nerves were fixed in glutaraldehyde (2%), replaced with sucrose (8%), and embedded in epoxy resin. The sections were stained with toluidine blue. Each section was evaluated under an optical microscope (CKX41SF; Olympus Co.). As a quantitative indicator of axonal injury, axonal circularity was calculated from 5708 to 20,797 nerve fibers in each group. Circularity was computed using the standard formula: $4\pi \times (\text{area}/\text{perimeter}^2)$, with values approaching 1.0 indicating a more regular circular profile. In injured axons, circularity decreases because axonal swelling, myelin disruption, fragmentation, and vacuolization increase perimeter irregularity without a proportional increase in cross-sectional area. Therefore, reduced circularity has been widely used as a quantitative indicator of axonal injury in models of chemotherapy-induced peripheral neuropathy (Coleman and Höke 2020; Kawashiri et al. 2025; Shigematsu et al. 2020).

2.9 | Evaluation of the Effects on Antitumor Activity Using Cancer Cells

The viability of CT26, HCT116, MKN45, and MIA PaCa-2 cells was assessed to evaluate the effects of imeglimin on the antitumor efficacy of oxaliplatin. Cell viability was assessed using a WST-8 assay. The cancer cell lines were treated with oxaliplatin or imeglimin for 72 h. Cell viability was subsequently evaluated using Cell Counting Kit-8 (DOJINDO Laboratories). The oxaliplatin concentration used for each cell line was determined based on preliminary experiments identifying the dose that resulted in approximately 30%–60% cell viability, allowing evaluation under comparable levels of cellular stress; these data are provided in Figure S3.

2.10 | Evaluation of the Effects on Antitumor Efficacy Using Mice Implanted With Cancer Cells

CT26 cells (1.5×10^6 cells) were subcutaneously implanted into the right hind paw of BALB/c mice. The CT26 tumor-bearing mouse model was selected because it has been used in previous studies and does not require nude mice. In this study, tumor cells were implanted into the right hind paw because this site allows easy and reliable measurement of tumor size, avoids direct involvement of thoracic or abdominal organs, and minimizes the risk of severe distress such as respiratory or feeding difficulties, thereby aligning with animal welfare considerations. The drug was administered on the day of tumor cell implantation. Mice were treated with oxaliplatin (6 mg/kg, i.p. on Days 4, 5, 11, 12, 18, and 19) and imeglimin (100 and 300 mg/kg, p.o. on Days 1–5, 8–12, and 15–19). The oxaliplatin dose was determined based on previous reports (Shigematsu et al. 2020; Kawashiri et al. 2020;

Yamamoto et al. 2017). Tumor volume was measured on Days 8, 15, and 22 and calculated as follows: Volume (mm^3) = $\pi/6 \times$ thickness (mm) × length (mm) × width (mm). Each experiment was conducted with six to eight animals per group.

2.11 | Statistical Analyses

Results are presented as mean ± standard error of the mean. All statistical analyses were performed using the JMP student Edition 18 software (JMP Statistical Discovery LLC., Cary, NC, USA) to conduct one-way analysis of variance (ANOVA), followed by Tukey–Kramer tests for intergroup comparisons. Statistical significance was set at $p < 0.05$.

3 | Results

3.1 | Effects of Imeglimin on OIPN in In Vitro Models

The efficacy of imeglimin against oxaliplatin-induced cellular damage was evaluated. The assessment was based on cell viability, which was measured using the WST-8 assay. When F11 cells were treated with oxaliplatin (100 μM) and imeglimin (100, 200, 500, and 1000 μM), the group treated with oxaliplatin alone displayed a significant decrease in cell viability compared with the control group ($p < 0.01$). The group treated with imeglimin (1000 μM) significantly suppressed the oxaliplatin-induced reduction in cell viability ($p < 0.05$) (Figure 1A).

The effect of imeglimin on oxaliplatin-induced neuroaxonal damage was evaluated. When F11 cells were treated with oxaliplatin (30 μM) and imeglimin (100, 200, 500, and 1000 μM), the group treated with oxaliplatin alone exhibited significantly shorter neurites compared with the control group ($p < 0.01$). The group treated with imeglimin (1000 μM) significantly suppressed oxaliplatin-induced neurite shortening ($p < 0.01$) (Figure 1B).

We evaluated the effects of imeglimin on oxaliplatin-induced oxidative stress using DCFH-DA, with fluorescence intensity used as an index of ROS production. Oxaliplatin significantly increased oxidative stress compared with the control group ($p < 0.01$), whereas imeglimin significantly suppressed oxaliplatin-induced ROS generation ($p < 0.05$) (Figure 1C,D).

3.2 | Effects of Imeglimin on OIPN in In Vivo Models

Repeated administration of oxaliplatin (4 mg/kg, i.p.) significantly reduced the withdrawal thresholds in a time-dependent manner compared with the vehicle group on Day 25 ($p < 0.01$; Figure 2A). Imeglimin co-administration (100 mg/kg or 300 mg/kg, p.o.) significantly attenuated the oxaliplatin-induced decrease in withdrawal thresholds on Day 25 in a dose-dependent manner (100 mg/kg, $p < 0.05$; 300 mg/kg, $p < 0.01$) (Figure 2A).

Oxaliplatin (4 mg/kg, i.p.) induced axonal injury in rat sciatic nerves, which was prevented by the repeated administration of imeglimin (300 mg/kg, p.o.) (Figure 2B). Compared with the vehicle group, the oxaliplatin group demonstrated a significant reduction in axonal circularity ($p < 0.01$) (Figure 2C). The imeglimin (300 mg/kg, p.o.) group showed a significant suppression of oxaliplatin-induced reduction in axonal circularity ($p < 0.01$) (Figure 2C).

3.3 | Effects of Imeglimin on Oxaliplatin-Induced Toxicity in Cultured Cancer Cell Line

Treatment of CT26, HCT116, MKN45, and MIA PaCa-2 cells with oxaliplatin (3, 1, 3, and 10 μM) significantly reduced the cell survival rate of each cancer cell line ($p < 0.01$) (Figure 3). Imeglimin potentiated the cytotoxic effect of oxaliplatin in CT26, HCT116, and MKN45 cells, with significant enhancements observed at 1000 μM in CT26 ($p < 0.05$), 1000 μM in HCT116 ($p < 0.01$), and 500–1000 μM in MKN45 cells ($p < 0.01$) (Figure 3A–C). The treatment of MIA PaCa-2 cells with imeglimin did not affect the cytotoxicity of oxaliplatin (Figure 3D).

3.4 | Effects of Imeglimin on the Antitumor Activity of Oxaliplatin in Tumor-Bearing Mice

Oxaliplatin (6 mg/kg, i.p.) significantly suppressed the increase in tumor volume compared with the vehicle group ($p < 0.05$). Imeglimin administration (100 and 300 mg/kg, p.o.) did not alter the antitumor effect of oxaliplatin (Figure 4).

4 | Discussion

This is the first study to demonstrate that imeglimin suppresses OIPN while preserving the antitumor efficacy of oxaliplatin. Although oxaliplatin is a key chemotherapeutic agent for several gastrointestinal cancers, chronic OIPN, which develops in a cumulative dose-dependent manner, represents major dose-limiting toxicity. OIPN is a serious adverse effect that leads to treatment interruption and reduced quality of life. However, no effective preventive strategies have been established. In this study, we focused on imeglimin, an antidiabetic agent for type 2 diabetes, as a potential preventive drug for chronic OIPN, and evaluated its efficacy in both in vitro and in vivo models.

OIPN is thought to originate from neuronal soma damage caused by oxaliplatin uptake into DRG neurons. Because axonal degeneration accompanies neuronal soma injury, suppressing these pathological changes is essential for preventing OIPN. In vitro, imeglimin significantly attenuated oxaliplatin-induced reductions in cell viability, neurite shortening, and oxidative stress in F11 cells. Consistently, in vivo administration of imeglimin to OIPN model rats significantly prevented decreases in withdrawal thresholds to mechanical stimulation and mitigated sciatic nerve axonal injury. These findings indicate that the neuroprotective effects observed in vitro—such as inhibition of axonal shortening and suppression of oxidative stress—are consistent with the protective effects seen in vivo. Although oxidative stress was not directly assessed in the animal model, the in vitro results suggest that suppression of

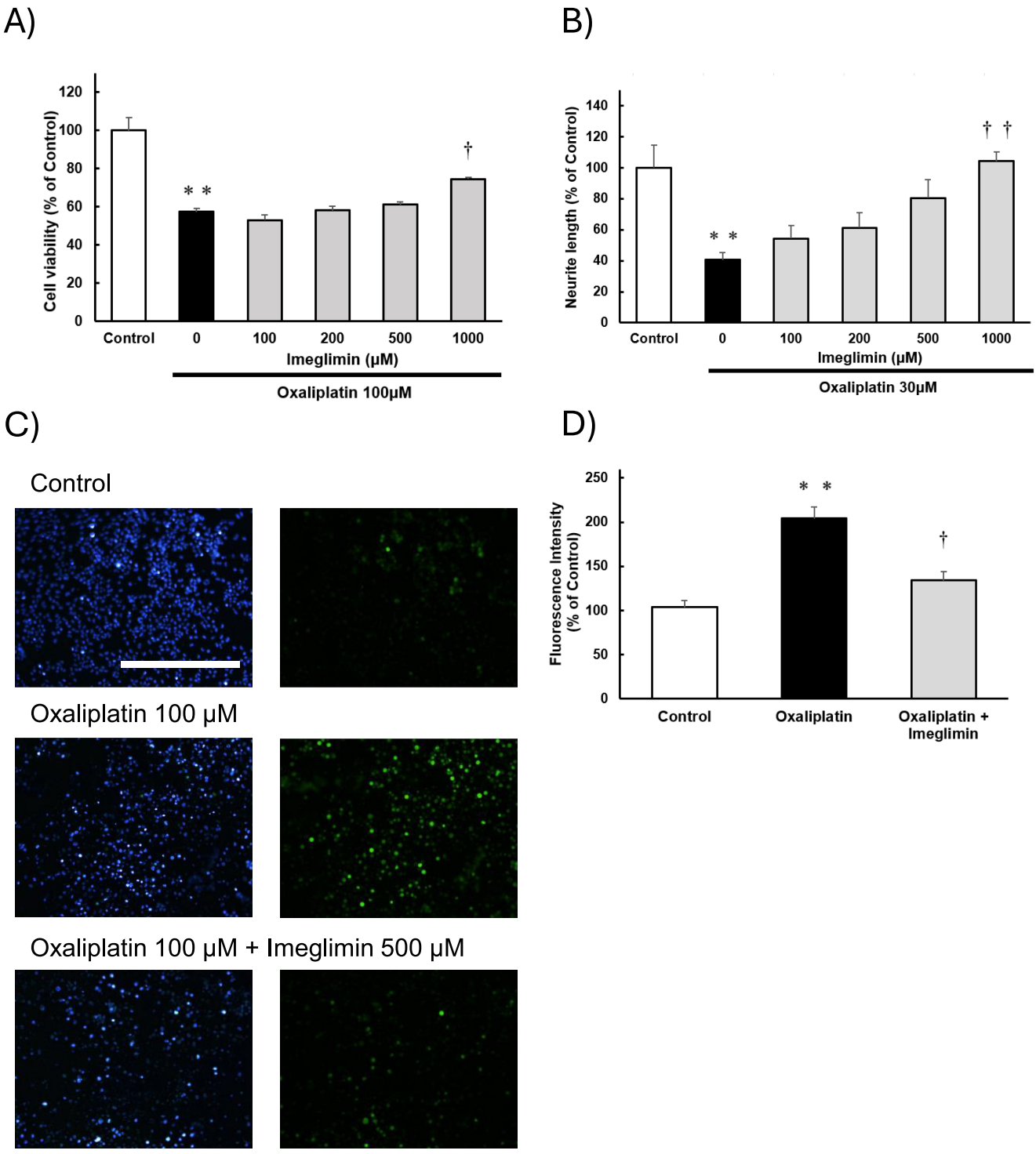

FIGURE 1 | Effect of imeglimin on oxaliplatin-induced cytotoxicity in F11 neuronal cells. (A) Cells were treated with imeglimin (100, 200, 500, and 1000 μM) plus 100 μM oxaliplatin. (B) Neurite injury induced by 30-μM oxaliplatin with imeglimin (100–1000 μM). (C) Cells were stained with a cellular reactive oxygen species probe (DCFH-DA), hoechst, and examined using a fluorescence microscope. (10×; scale bar = 1000 μm) (D) Oxidative stress induced by 100-μM oxaliplatin with 500-μM imeglimin. Data are mean ± SEM ($n = 4–8$). *$p < 0.05$, **$p < 0.01$ vs. control; †$p < 0.05$, ††$p < 0.01$ vs. monotherapy (one-way ANOVA with Tukey–Kramer test). ANOVA, analysis of variance; SEM, standard error of the mean.

oxidative stress may at least partially contribute to the preventive effects of imeglimin against OIPN. In the present in vivo study, chronic OIPN was evaluated over a 4-week observation period. However, because clinical OIPN often persists for months to years, the findings of this study cannot be directly extrapolated to clinical efficacy. Nevertheless, considering the results obtained in this animal model, suppression of OIPN onset may contribute to long-term maintenance of quality of life and treatment intensity. In addition, because this study evaluated only preventive administration, further studies are needed to determine whether imeglimin also exerts therapeutic effects once OIPN has developed.

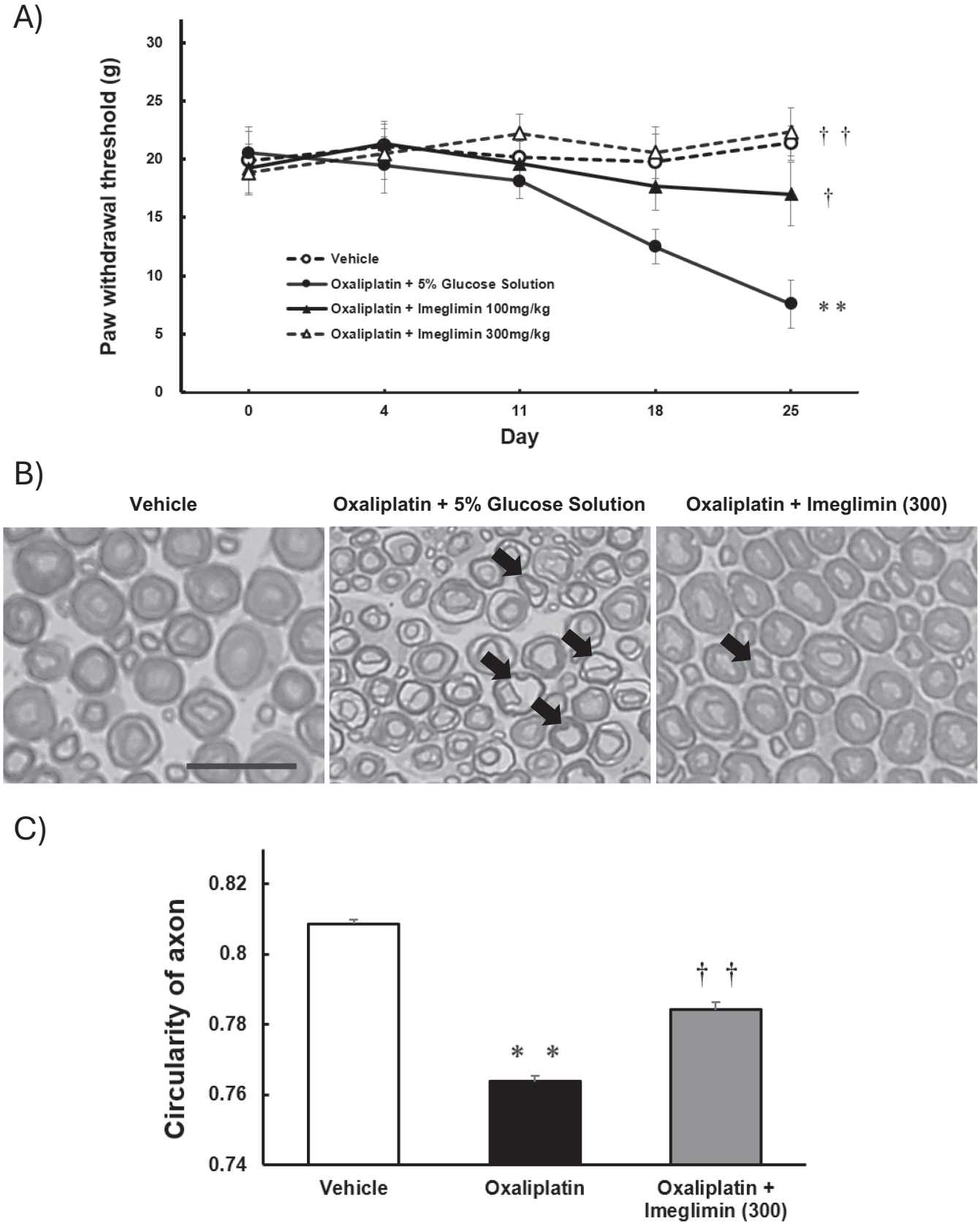

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FIGURE 2 | Oxaliplatin (4 mg/kg, i.p.) was administered twice weekly for 4 weeks, and imeglimin (100 or 300 mg/kg, p.o.) was administered five times weekly. (A) Mechanical allodynia assessed by the von Frey test at baseline and Days 0, 4, 11, 18, and 25. Data are mean ± SEM ($n = 6–7$). (B) Toluidine blue-stained rat sciatic nerve sections on Day 30 (40×; scale bar = 500 μm). Arrows indicate axons exhibiting prominent degenerative changes. (C) Axonal circularity quantified using ImageJ 1.54. Data are mean ± SEM ($n = 3–6$). **$p < 0.01$ vs. vehicle; †$p < 0.05$, ††$p < 0.01$ vs. monotherapy (one-way ANOVA with Tukey–Kramer test). ANOVA, analysis of variance; SEM, standard error of the mean.

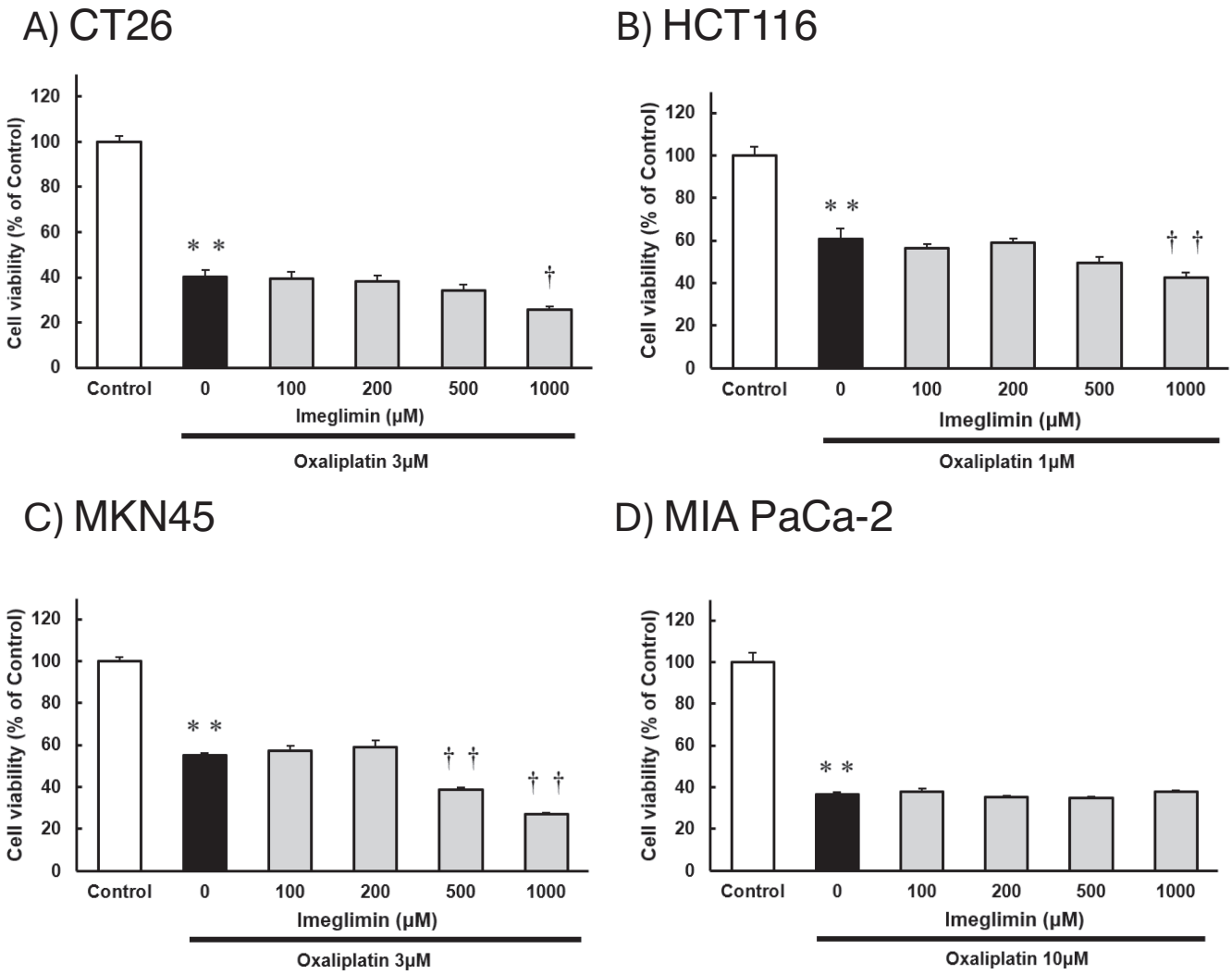

FIGURE 3 | Effects of imeglimin on the antitumor activity of oxaliplatin. (A) CT26, (B) HCT116, (C) MKN45, and (D) MIA PaCa-2 cells were treated with oxaliplatin (3, 1, 3, and 10 μM, respectively) with or without imeglimin (100–1000 μM) for 72 h. Cell viability was measured using the WST-8 assay and expressed as mean ± SEM ($n = 4$). **$p < 0.01$ vs. control; †$p < 0.05$, ††$p < 0.01$ vs. monotherapy (one-way ANOVA with Tukey–Kramer test). ANOVA, analysis of variance; SEM, standard error of the mean; WST-8, water-soluble tetrazolium salt-8.

Given the neuroprotective effects of imeglimin, we examined whether it interferes with the antitumor activity of oxaliplatin. The following cancer cell lines corresponding to the tumor types, for which oxaliplatin is clinically indicated, were used: CT26 and HCT116 for colorectal cancer, MKN45 for gastric cancer, and MIA Paca-2 for pancreatic cancer. Oxaliplatin reduced cell viability in all cell lines, and co-treatment with imeglimin did not attenuate this cytotoxicity. Furthermore, oxaliplatin reduced tumor volume in tumor-bearing mice; however, tumor growth was not enhanced in the group receiving the combined oxaliplatin and imeglimin treatment. These results indicated that imeglimin did not diminish the antitumor efficacy of oxaliplatin.

Although the underlying mechanisms are not fully understood, mitochondrial dysfunction and increased production of ROS in DRG neurons have been implicated in neuronal soma injury, axonal degeneration and demyelination, ultimately leading to chronic OIPN (Wei et al. 2021; Lehky et al. 2004; Shahsavani et al. 2025; Sorensen et al. 2016). In contrast, imeglimin has been reported to exert antioxidant effects and improve mitochondrial function (Kato et al. 2025; Ohguro,

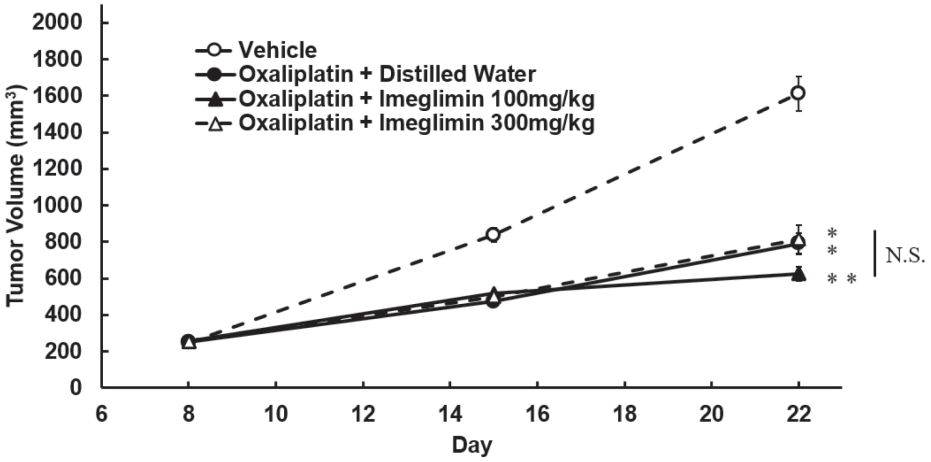

FIGURE 4 | CT26 tumor-bearing mice were treated with oxaliplatin (6 mg/kg, i.p.) twice weekly and imeglimin (100 or 300 mg/kg, p.o.) five times weekly for 3 weeks. Tumor volume was calculated as $\pi/6 \times$ thickness $\times$ length $\times$ width and expressed as mean ±SEM ($n = 6$–8). *$p < 0.05$, **$p < 0.01$ vs. vehicle (one-way ANOVA with Tukey–Kramer test). ANOVA, analysis of variance; SEM, standard error of the mean.

Higashide, et al. 2025; Ohguro, Watanabe, et al. 2025; Hallakou-Bozec, Vial, Kergoat, et al. 2021). Imeglimin competitively inhibits mitochondrial respiratory chain complex I and activates complex III, thereby reducing mitochondrial ROS production without impairing ATP synthesis (Kato et al. 2025). Given these findings, imeglimin may reduce ROS production through its mitochondrial actions, which could at least partially contribute to the suppression of oxaliplatin-induced oxidative stress and the prevention of OIPN. However, this study did not clarify how oxaliplatin affects mitochondrial membrane potential, ATP production, or oxygen consumption rate (OCR), nor how imeglimin modulates these parameters. Further investigation of these mitochondrial indices will be essential for elucidating the detailed mechanisms by which imeglimin mitigates oxaliplatin-induced neurotoxicity.

Axonal extension is an energy-demanding process that requires an intact mitochondrial function. Growth cones and branching points depend on local ATP supply from the mitochondria, and reductions in ATP or excessive ROS production can cause axonal degeneration and cytoskeletal collapse (Rumpf et al. 2023; Wang et al. 2021). Therefore, the effects of imeglimin on mitochondria may contribute to its ability to prevent the oxaliplatin-induced shortening of neurites. In addition, imeglimin protected Schwann cells from both hyperglycemia- and hypoglycemia-induced cell death by reducing oxidative stress, restoring mitochondrial membrane potential, inhibiting excessive complex I activation, recovering ATP production, and suppressing apoptotic signaling (Kato et al. 2025). In OIPN, neuronal damage originates in the DRG and subsequently leads to degeneration of peripheral sensory axons. In this study, we evaluated the sciatic nerve as a representative tissue reflecting this pathological cascade; however, we did not assess the DRG itself or distal nerve fibers within the paw skin. Given the diverse neuroprotective actions of imeglimin, evaluating additional neural tissues beyond the sciatic nerve may help clarify its broader effects on the peripheral nervous system.

Furthermore, metformin, which shares a similar structure and mechanism of action with imeglimin, has been reported to prevent OIPN in rats (Martinez et al. 2020). Metformin is known to activate AMPK, which is considered a master regulator of energy metabolism and has been reported to reduce ROS production in immune cells (Hartwig et al. 2021). Moreover, activating AMPK and inhibiting mechanistic target of rapamycin (mTOR) can alleviate neuropathic pain (Cao et al. 2021), suggesting that AMPK-mediated signaling pathways may also play a crucial role. Considering these reports, imeglimin may suppress OIPN expression by reducing oxidative stress in the DRG and inhibiting neuronal cell body damage and axonal injury through its effects on mitochondria and AMPK activation. However, further detailed investigations are required to clarify the oxaliplatin-induced changes in mitochondrial function within nerve cells and the effects of imeglimin.

Because imeglimin attenuates oxaliplatin-induced cytotoxicity in neuronal cells in vitro, we investigated its effects on cancer cell lines for which oxaliplatin is clinically indicated. Imeglimin did not reduce oxaliplatin cytotoxicity in colorectal, gastric and pancreatic cancer cell lines, and decreased cell viability in some lines. Compared with neurons, cancer cells proliferate rapidly and require substantial energy (Hu et al. 2024). Metformin also modulates cellular metabolism and enhances antitumor effects by reducing oxygen consumption in cancer cells (Song et al. 2022; Zhu et al. 2022). Imeglimin may exert similar metabolic effects, and our findings indicate that imeglimin does not weaken the antitumor activity of oxaliplatin. Consistent with this finding, tumor-bearing mice treated with oxaliplatin plus imeglimin did not exhibit increased tumor growth compared with those treated with oxaliplatin alone. However, no previous studies have examined the effects of imeglimin on cancer cells, and our findings alone cannot predict its effects in humans. Further basic and clinical research is required to elucidate the detailed impact of imeglimin on tumors and its underlying mechanisms.

In this in vivo study, male rats were used to evaluate OIPN. This decision was based on the fact that male rodents have been extensively characterized in previous preclinical OIPN studies, providing high reproducibility. In addition, sex-dependent differences in the incidence and severity of OIPN have been suggested (Warncke et al. 2021). Because the present study was designed as a proof-of-concept investigation to assess the neuroprotective effects of imeglimin, male animals—whose responses are most consistently documented—were selected to minimize variability associated with sex differences. Male BALB/c mice were also used in the tumor model, as sex differences in tumor growth rate and drug responsiveness are known, and restricting the study to males helped reduce variability in tumor volume measurements. Because only male rats were included, potential sex-specific differences in oxaliplatin-induced neuropathy and imeglimin responses could not be addressed and should be investigated in future studies.

The imeglimin concentrations used in this study were determined based on previous reports and preclinical toxicology data. In vitro, we used concentrations up to the level at which imeglimin has been reported to activate AMPK and improve mitochondrial function in HepG2 cells (Hozumi et al. 2023). Although these concentrations exceed the plasma levels achieved clinically, they are comparable with those used in other cell-based studies and are considered appropriate for evaluating the pharmacological actions of imeglimin under in vitro conditions. In the present in vivo experiments, imeglimin was administered at 300 mg/kg, a dose selected based on preclinical toxicology findings indicating that repeated administration at this level does not produce toxicologically meaningful adverse effects (Sumitomo Pharma Co. Ltd. 2021). Consistent with these data, no marked body-weight loss associated with imeglimin treatment was observed in this study (Figure S4). This dose is close to the upper limit at which imeglimin can be safely administered in rodents, and it exerted clear neuroprotective effects in vivo without enhancing the antitumor activity of oxaliplatin.

Although imeglimin showed dose-dependent enhancement of oxaliplatin cytotoxicity in cancer cell lines in vitro, previous toxicology studies have reported pathological alterations at doses $\geq$ 500 mg/kg, suggesting that substantially higher systemic exposures may induce toxicity that could also affect peripheral nerves. Therefore, within the range of doses that can be ethically and safely administered in vivo, imeglimin is unlikely to potentiate oxaliplatin-induced neurotoxicity, at least in rats.

Although imeglimin appeared to suppress OIPN, its clinical application requires careful consideration. Hypoglycemia is a major concern with antidiabetic drugs; however, the risk of hypoglycemia is low because its primary mechanisms involve glucose-dependent insulin secretion and improved glucose metabolism in peripheral tissues (Hagi et al. 2023). Moreover, unlike metformin, imeglimin carries a low risk of lactic acidosis, which contributes to its favorable safety profile (Theurey et al. 2022). These characteristics support the potential clinical use of imeglimin for the prevention of OIPN, particularly in patients with diabetes. However, evidence regarding the efficacy and safety of imeglimin in non-diabetic patients is limited, and unexpected adverse events may occur in both the short and long term. In this study, body weight was monitored as a representative indicator of systemic toxicity, and no marked weight loss associated with imeglimin treatment was observed (Figure S4). However, potential organ toxicities such as hepatic or renal injury resulting from the combination of imeglimin and oxaliplatin could not be fully assessed. The use of imeglimin alone for its neuroprotective effects, without a clear indication for diabetes treatment, raises ethical concerns, and careful evaluation is required. Large-scale studies are needed to identify patient populations for whom the use of imeglimin would be acceptable, including those with preserved activity, good tolerability, low risk of hypoglycemia, and high risk of developing OIPN.

5 | Conclusion

Imeglimin suppressed oxaliplatin-induced reduction in cell survival, shortening of nerve axons, and oxidative stress in F11 cells in vitro. In vivo administration of imeglimin attenuated the reduction in withdrawal thresholds to mechanical stimulation and axonal injury of the sciatic nerve in OIPN model rats. Conversely, imeglimin did not inhibit the cytotoxicity of oxaliplatin against multiple cancer cell lines or affect the antitumor efficacy of oxaliplatin in tumor-bearing mice. Altogether, these findings identify imeglimin as a promising preventive strategy for OIPN, warranting further mechanistic and clinical investigations.

Author Contributions

Yusuke Koura: conceptualization, formal analysis, methodology, investigation, visualization, writing – original draft. **Kano Kinjo:** investigation, writing – review and editing. **Keisuke Mine:** methodology, investigation, writing – review and editing. **Yusuke Mori:** investigation, writing – review and editing. **Mami Ueda:** writing – review and editing. **Risa Kaneko:** investigation, writing – review and editing. **Yuna Kamiya:** writing – review and editing. **Taiga Sonoda:** investigation, writing – review and editing. **Haruka Mimata:** investigation, writing – review and editing. **Shunsuke Fujita:** conceptualization, funding acquisition, methodology, project administration, supervision, writing – review and editing. **Takehiro Kawashiri:** conceptualization, funding acquisition, methodology, writing – review and editing. **Daisuke Kobayashi:** supervision, writing – review and editing.

Acknowledgments

The authors thank Editage (www.editage.jp) for English language review.

Funding

This work was supported by the Japan Society for the Promotion of Science (grant numbers JP25K18681 and JP24K09940).

Conflicts of Interest

The authors declared no conflicts of interest.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Chemical structures of (A) Oxaliplatin, (B) Metformin, and (C) Imeglimin. **Figure S2:** Oxaliplatin dose-dependent neurite injury in F11 cell (3–30 μM).Data are mean ± SEM ($n = 4$). $^{**}p < 0.01$ vs. Control (one-way ANOVA with Tukey–Kramer test). ANOVA, analysis of variance; SEM, standard error of the mean. **Figure S3:** Oxaliplatin dose-dependent cytotoxicity in cancer cell lines. (A) CT26, (B) HCT116, (C) MKN45, and (D) MIA PaCa-2 cells were treated with oxaliplatin for 72 h at concentration ranges optimized for each cell line. Cell viability was measured using the WST-8 assay and expressed as mean ± SEM ($n = 4$). $^{**}p < 0.01$ vs. control (one-way ANOVA with Tukey–Kramer test). ANOVA, analysis of variance; SEM, standard error of the mean; WST-8, water-soluble tetrazolium salt-8. **Figure S4:** Oxaliplatin dose-dependent neurite injury in F11 cell (3–30 μM). Data are mean ± SEM ($n = 4$). $^{**}p < 0.01$ vs. Control (one-way ANOVA with Tukey–Kramer test). ANOVA, analysis of variance; SEM, standard error of the mean.