Preclinical and Clinical Evidence of Therapeutic Agents for Paclitaxel-Induced Peripheral Neuropathy

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Abstract: Paclitaxel is an essential drug in the chemotherapy of ovarian, non-small cell lung, breast, gastric, endometrial, and pancreatic cancers. However, it frequently causes peripheral neuropathy as a dose-limiting factor. Animal models of paclitaxel-induced peripheral neuropathy (PIPN) have been established. The mechanisms of PIPN development have been elucidated, and many drugs and agents have been proven to have neuroprotective effects in basic studies. In addition, some of these drugs have been validated in clinical studies for their inhibitory PIPN effects. This review summarizes the basic and clinical evidence for therapeutic or prophylactic agents for PIPN. In pre-clinical research, many reports exist of neuropathy inhibitors that target oxidative stress, inflammatory response, ion channels, transient receptor potential (TRP) channels, cannabinoid receptors, and the monoamine nervous system. Alternatively, very few drugs have demonstrated PIPN efficacy in clinical trials. Thus, enhancing translational research to translate pre-clinical research into clinical research is important.

Keywords: paclitaxel; peripheral neuropathy; preclinical data; clinical evidence; adverse effects

1. Introduction

Paclitaxel and albumin-bound paclitaxel are important drugs in the treatment of ovarian [1,2], non-small cell lung [3,4], breast [5–7], gastric [8,9], endometrial [10], and pancreatic [11] cancers. However, they cause peripheral neuropathy as an adverse event. In paclitaxel-induced peripheral neuropathy (PIPN), many patients develop sensory abnormalities (e.g., numbness, pain, and burning sensation in the hands and feet) [12]. PIPN is a dose-limiting factor that causes difficulty in continuing cancer chemotherapy [13]. However, no evidence-based prophylactic agents for PIPN were noted [14]. Since the late 1990s, many studies on the mechanism and therapeutic or prophylactic agents using PIPN animal models have been reported [15–17]. In addition, the mechanisms of PIPN development have been gradually clarified [18]. This study reviewed the preclinical and clinical evidence of therapeutic or prophylactic agents for PIPN.

2. Methods

2.1. Preclinical Evidence

All articles found in PubMed with the search term “paclitaxel neuropathy or paclitaxel neurotoxicity” were surveyed. The last search date was 30 April 2021. Clinical studies and
reports that did not include information on therapeutic agents were excluded from the analysis. Articles referring to the effects of local rather than systemic administration and articles published before 2015 were also excluded. Information on the name and dosage of the drugs that showed statistically significant improvement, mechanism of action, and the animal species in which they were used were extracted in the surveyed papers.

2.2. Clinical Evidence

The articles found in PubMed with the search term “paclitaxel neuropathy or paclitaxel neurotoxicity” limited to “Randomized Controlled Trial” and “Meta-Analysis” were analyzed. The last search date was 30 April 2021. Reports other than trials about peripheral neuropathy were excluded. Moreover, information such as the investigational drug and its dosage, chemotherapy received by the patient, study design, number of patients, and results were collected.

3. Results

3.1. Therapeutic Agents in Preclinical Evidence

In PubMed, 2667 articles were found when using the search term “paclitaxel neuropathy or paclitaxel neurotoxicity”. Of these, 150 articles reported on drugs that inhibit PIPN in animal studies. The following is a summary of the drugs that had therapeutic PIPN effects in these basic studies (Table 1).
| Therapeutic Targets                                      | Therapeutic Agents                  | Dose                | Animals | Symptoms that Showed Improvement                                                                 | Mechanisms                                                                 | References |
|---------------------------------------------------------|-------------------------------------|---------------------|---------|-----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|------------|
| Oxidative stress and mitochondrial dysfunction           | Anakinra, IL-1β antagonist          | 50–100 mg/kg, i.p.  | Rats    | Pain threshold                                                                                 | Reductions of MDA, MPO and IL-1β and increase in GSH in paws              | [19]       |
|                                                         | Antimycin A                         | 0.2–0.6 mg/kg, i.p. | Rats    | Mechanical hypersensitivity                                                                   | Inhibition of mitochondrial complex III                                   | [20]       |
|                                                         | Curcumin                            | 100–200 mg/kg, p.o. | Rats    | Histological changes in spinal cord and sciatic nerve                                         | Reduction of NF-κB, TNF-α, IL-6, iNOS and GFAP, p53, caspase-3, Apaf-1, LC3A, LC3B and beclin-1, and increase in Nrf2, HO-1, NQO1, Bcl-2, and Bcl-xL. | [21]       |
|                                                         | Divya-Peedantak-Kwath, a herbal decoction | 69–615 mg/kg, p.o. | Mice    | Thermal hyperalgesia, mechanical allodynia and hyperalgesia, and axonal degeneration          | Suppression of oxidative stress and inflammation                         | [22]       |
|                                                         | Duloxetine                          | 10–30 mg/kg, i.p.   | Mice    | Mechanical hyperalgesia and thermal nociception                                               | Inhibiting PARP and p53 activation and regulating Bcl-2 family to reverse oxidative stress and apoptosis | [23]       |
|                                                         | Evodiamine                          | 5 mg/kg             | Rats    | Mechanical hypersensitivity and thermal hypersensitivity                                        | Downregulation of inflammatory and chemoattractant cytokines (IL-1β, IL-6, TNF-α, and MCP-1), oxidative stress, and mitochondrial dysfunction in DRG. | [24]       |
|                                                         | Flavonol                            | 25–200 mg/kg, s.c.  | Mice    | Tactile allodynia, cold alldodynia and thermal hyperalgesia                                  | Inhibitions of TNF-α, IL-1β and free radicals                              | [25]       |
|                                                         | Ghrelin                             | 300 nmol/kg, i.p.   | Mice    | Mechanical sensitivity, thermal sensitivity, DRG damage (ATF-3 positive cells), and density of IENF | Decreases in plasma oxidative and nitrosative stress and increases in UCP2, SOD2, and PGC-1α | [26]       |
|                                                         | GKT137831, a NOX4 inhibitor         | 1 mg/kg, i.p.       | Rats    | Mechanical sensitivity and thermal sensitivity                                                | Decreases of proinflammatory cytokines (IL-1β, IL-6, and TNF-α) in the DRG | [27]       |
|                                                         | Lacosamide                          | 30 mg/kg, p.o.      | Rats    | Thermal hyperalgesia and cold alldodynia                                                       | Upregulation of total antioxidant capacity and NGF, and downregulation of NF-κB p65, TNF-α, active caspase-3, Notch1 receptor, p-p38, and IL-6/p-JAK2/p-STAT3 | [28]       |
|                                                         | Melatonin                           | 5–50 mg/kg, p.o.    | Rats    | Mechanical sensitivity                                                                         | Reduction of mitochondrial damage                                         | [29]       |
| Therapeutic Targets | Therapeutic Agents | Dose | Animals | Symptoms that Showed Improvement | Mechanisms | References |
|---------------------|-------------------|------|---------|----------------------------------|------------|------------|
| Nicotinamide riboside | 200 mg/kg, p.o. | Rats | Tactile hypersensitivity | N.A. | [30] |
| Phenyl-N-tert-butyl-nitrone | 100 mg/kg, i.p. | Mice | Mechanical hypersensitivity | N.A. | [31] |
| Pregabalin | 30 mg/kg, p.o. | Rats | Thermal hyperalgesia and cold allodynia | Upregulation of total antioxidant capacity and NGF, and downregulation of NF-kB p65, TNF-α, active caspase-3, Notch1 receptor, p-p38, and IL-6/p-JAK2/p-STAT3 | [28] |
| Rosuvastatin | 10 mg/kg, i.p. | Mice | Thermal hyperalgesia, cold hyperalgesia, and mechanical allodynia | Downregulations of IL-1β, oxidative stress | [32] |
| Rotenone | 1–5 mg/kg, i.p. | Rats | Mechanical hypersensitivity | Inhibition of mitochondrial complex I | [20] |
| Tempol, a mimetic of SOD | 20 mg/kg, i.p. | Rats | Mechanical sensitivity and thermal sensitivity | Decreases of proinflammatory cytokines such as IL-1β, IL-6 and TNF-α in the DRG | [27] |
| Trimethoxy flavones | 25–200 mg/kg, s.c. | Mice | Tactile allodynia, cold allodynia, and thermal hyperalgesia | Inhibitions of TNF-α, IL-1β and free radicals | [33] |
| Umbelliprenin, a prenylated coumarin | 12.5–25 mg/kg, i.p. | Mice | Thermal hyperalgesia | Decrease in serum IL-6 levels and oxidative stress | [34] |
| Vitamin C | 500 mg/kg, i.p. | Rats | Mechanical sensitivity and thermal sensitivity | Decreases of proinflammatory cytokines (IL-1β, IL-6 and TNF-α) in the DRG | [27] |
| 3-Hydroxyflavone | 25–75 mg/kg, i.p. | Rats | Tactile alldodynia, cold alldodynia, thermal hyperalgesia, and heat-hyperalgesia | Suppressions of TNF-α, IL-1β, IL-6, CGRP, and substance P in the spinal cord, and inhibition of the receptor of substance P | [35] |
| AMD3100, a CXCR4 antagonist | 8 mg/kg, i.p. | Mice | Mechanical alldodynia | N.A. | [36] |
| Anakinra, IL-1β antagonist | 50–100 mg/kg, i.p. | Rats | Pain threshold | Reductions of MDA, MPO and IL-1β and increase in GSH in paws | [19] |
Table 1. Cont.

| Therapeutic Targets         | Therapeutic Agents                  | Dose                          | Animals | Symptoms that Showed Improvement                                                                 | Mechanisms                                                                                     | References |
|-----------------------------|-------------------------------------|-------------------------------|---------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------|
| Anti-HMGB1-neutralizing     | 1 mg/kg, i.p.                        | Mice                          | Mechanical allodynia                                                                  | N.A.                                                                                         | [36]        |
| antibody                    |                                     |                               | Mechanical hyperalgesia, cold hyperalgesia, and sensory nerve compound action potential amplitude | Regulation of PPAR-α expression and decrease neuroinflammation in DRG                     | [38]        |
| Berberine                   | 5–20 mg/kg, i.p.                     | Mice                          | Thermal hyperalgesia                                                                 | N.A.                                                                                         | [37]        |
| Choline-fenofibrate         | 6–24 mg/kg, i.p., 15–60 mg/kg, p.o.  | Mice                          | Mechanical hyperalgesia, cold hyperalgesia, and sensory nerve compound action potential amplitude | Reductions of NF-κB, TNF-α, IL-6, iNOS and GFAP, p53, caspase-3, Apaf-1, LC3A, LC3B and beclin-1, and increase in Nrf2, HO-1, NQO1, Bcl-2, and Bcl-xL. | [38]        |
| Curcumin                    | 100–200 mg/kg, p.o.                  | Rats                          | Histological changes in the spinal cord and sciatic nerve                             | Suppressions of oxidative stress and inflammation                                          | [21]        |
| Divya-Peedantak-Kwath, a    | 69–615 mg/kg, p.o.                   | Mice                          | Thermal hyperalgesia, mechanical allodynia and hyperalgesia, and axonal degeneration   | Decreases in NF-κB, p-p38, IL-6, and TNF-α in DRG                                           | [40]        |
| herbal decoction            |                                     |                               |                                                                                      |                                                                                              |            |
| Duloxetine                  | 30 mg/kg/day, i.p.                   | Mice                          | Mechanical hyperalgesia, thermal hyperalgesia, and loss of IENF                      | Suppression of spinal cord astrocyte activation                                              | [40]        |
| ESI-09, a Epac inhibitor    | 20 mg/kg, p.o.                       | Mice                          | Mechanical allodynia and number of IENF                                               |                                                                                              | [40]        |
| Etanercept                  | 2 mg/kg, i.p.                        | Rats                          | Mechanical hypersensitivity and cold hypersensitivity                                  | Blocking of TNF-α signaling                                                                 | [41]        |
| Evodiamine                  | 5 mg/kg                              | Rats                          | Mechanical hypersensitivity and thermal hypersensitivity                              | Downregulation of inflammatory and chemoattractant cytokines (IL-1β, IL-6, TNF-α, and MCP-1), oxidative stress, and mitochondrial dysfunction in DRG. | [24]        |
| Fenofibrate                 | Diet with 0.2% or 0.4% fenofibrate   | Mice                          | Mechanical allodynia, SNAP amplitude, and intra-epidermal nerve fibers density         | Regulation of PPAR-α expression and reduction in neuroinflammation                          | [42]        |
| Fenofibrate                 | 100–150 mg/kg, i.p., 300–600 mg/kg, p.o. | Mice                          | Mechanical hyperalgesia, cold hyperalgesia, and sensory nerve compound action potential amplitude | Regulation of PPAR-α expression and decrease neuroinflammation in DRG                     | [38]        |
| Therapeutic Targets | Therapeutic Agents | Dose | Animals | Symptoms that Showed Improvement | Mechanisms | References |
|---------------------|--------------------|------|---------|----------------------------------|------------|------------|
| Fenofibric acid     | 6–24 mg/kg, i.p., 30–90 mg/kg, p.o. | Mice | Mechanical hyperalgesia, cold hyperalgesia, and sensory nerve compound action potential amplitude | Regulation of PPAR-α expression and decrease neuroinflammation in DRG | [38] |
| Flavonol            | 25–200 mg/kg, s.c. | Mice | Tactile allodynia, cold allodynia, and thermal hyperalgesia | Inhibitions of TNF-α, IL-1β and free radicals | [25] |
| FPS-ZM1, a RAGE antagonist | 1 mg/kg, i.p. | Mice | Mechanical allodynia | N.A. | [36] |
| GKT137831, a NOX4 inhibitor | 1 mg/kg, i.p. | Rats | Mechanical sensitivity and thermal sensitivity | Decreases of proinflammatory cytokines (IL-1β, IL-6, and TNF-α) in the DRG | [27] |
| Human intravenous immunoglobulin | 1 g/kg, i.v. | Rats | Mechanical allodynia, loss of IENF, and distal axonal degeneration | Suppression of the axonopathy with macrophage infiltration | [43] |
| Icariin             | 100 mg/kg, p.o. | Rats | Mechanical allodynia | Downregulations of TNF-α, IL-1β, IL-6 and astrocyte activation in spinal cord via SIRT1 activation | [44] |
| IL-1 receptor antagonist | 3 mg/kg, i.p. | Rats | Mechanical hypersensitivity and cold hypersensitivity | Decreases in PI3K, p-Akt, and inflammatory cytokines in the DRG | [41] |
| JTC-801             | 0.01–0.05 mg/kg, i.v. | Rats | Mechanical allodynia | Upregulation of total antioxidant capacity and NGF, and downregulation of NF-κB p65, TNF-α, active caspase-3, Notch1 receptor, p-p38, and IL-6/p-JAK2/p-STAT3 | [28] |
| Lacosamide          | 30 mg/kg, p.o. | Rats | Thermal hyperalgesia and cold allodynia | Decrease in inflammatory cytokines including IL-1β and TNF-α in the DRG | [46] |
| Losartan            | 20–100 mg/kg, i.p. | Rats | Mechanical hyperalgesia | Attenuations of neuroinflammatory changes and expression of pro-resolving markers (arginase 1 and IL-10) indicating a possible shift in macrophage polarization | [47] |
| Therapeutic Targets                                      | Therapeutic Agents                                      | Dose          | Animals | Symptoms that Showed Improvement | Mechanisms                                                                                                                                  | References |
|---------------------------------------------------------|---------------------------------------------------------|---------------|---------|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Low-molecular-weight heparin, a rage antagonist          | 2.5 mg/kg, i.p.                                         | Mice          |         | Mechanical allodynia             | N.A.                                                                                                                                         | [36]       |
| LPS-R, a TLR4 antagonist                                | 0.5 mg/kg, i.p.                                         | Mice          |         | Mechanical allodynia             | N.A.                                                                                                                                         | [36]       |
| MDA7, a CB₂ agonist                                     | 15 mg/kg, i.p.                                          | Rats          |         | Mechanical allodynia             | Downregulations of IRF8, P2X₄, CaMKIIα, p-CREB, FosB, BDNF, GluR1 and NR2B, and increase in the expression of K⁺-Cl⁻ cotransporter | [48]       |
| MJN110, a MAGL inhibitor                                | 4–40 mg/kg, i.p.                                        | Mice          |         | Mechanical allodynia             | Downregulations of MCP-1, CCL2 and p-p38 in DRG as well as MCP-1 in the spinal dorsal horn                                                | [49]       |
| Polaprezinc                                             | 3 mg/kg, p.o.                                           | Rats          |         | Thermal hyperalgesia and cold    | Upregulation of total antioxidant capacity and NGF, and downregulation of NF-kB p65, TNF-α, active caspase-3, Notch1 receptor, p-p38, and IL-6/p-JAK2/p-STAT3 | [50]       |
| Pregabalin                                              | 30 mg/kg, p.o.                                          | Rats          |         | Thermal hyperalgesia and cold    | Decreases of IL-1β, IL-6, TNF-α, substance P and CGRP in DRG.                                                                                 | [28]       |
| Rapamycin                                               | 5 mg/kg, i.p.                                           | Rats          |         | Mechanical hypersensitivity and   | Decreases of IL-1β, IL-6, TNF-α, substance P and CGRP in DRG.                                                                                 | [51]       |
| Reparixin                                               | 8 mg/hr/kg using micro-osmotic pumps                    | Rats          |         | Mechanical allodynia and cold    | Inhibition of IL-8/CXCR1/2 pathway and suppressions of p-FAK, p-JAK2/p-STAT3, and PI3K-p-cortactin activation                              | [52]       |
| Rosuvastatin                                            | 10 mg/kg, i.p.                                          | Mice          |         | Thermal hyperalgesia, cold       | Downregulations of IL-1β and oxidative stress                                                                                               | [32]       |
| S504393, a CCR2 antagonist                              | 5 mg/kg, i.p.                                           | Rats          |         | Mechanical hypersensitivity and   | N.A.                                                                                                                                         | [41]       |
| Siwei Jianbu decoction                                   | 5–10 g/kg, i.g.                                         | Mice          |         | Mechanical hyperalgesia and      | Inhibiting the JNK, ERK1/2 phosphorylation, NF-κB, TNF-α, IL-1β, and IL-6.                                                                   | [53]       |
Table 1. Cont.

| Therapeutic Targets                      | Therapeutic Agents                         | Dose            | Animals | Symptoms that Showed Improvement                          | Mechanisms                                                                 | References |
|------------------------------------------|--------------------------------------------|-----------------|---------|-----------------------------------------------------------|---------------------------------------------------------------------------|------------|
| TAK242, a TLR4 antagonist                | TAK242, a TLR4 antagonist 1–3 mg/kg, i.p.  | Rats            |         | Mechanical hypersensitivity                                | Antagonism of TLR4                                                       | [54]       |
| TAK242, a TLR4 antagonist                | TAK242, a TLR4 antagonist 3 mg/kg, i.p.    | Mice            |         | Mechanical allodynia                                      | N.A.                                                                      | [55]       |
| Tempol, a mimetic of SOD                 | Tempol, a mimetic of SOD 20 mg/kg, i.p.    | Rats            |         | Mechanical sensitivity and thermal sensitivity            | Decreases of proinflammatory cytokines (IL-1β, IL-6 and TNF-α) in the DRG | [27]       |
| Thrombomodulin alfa                     | Thrombomodulin alfa 1–3 mg/kg, i.p.       | Mice            |         | Mechanical allodynia                                      | N.A.                                                                      | [36]       |
| Trimethoxy flavones                      | Trimethoxy flavones 25–200 mg/kg, s.c.    | Mice            |         | Tactile allodynia, cold alodynia, and thermal hyperalgesia | Inhibitions of TNF-α, IL-1β and free radicals                              | [33]       |
| Umbelliprenin, a prenylated coumarin     | Umbelliprenin, a prenylated coumarin 12.5–25 mg/kg, i.p. | Mice |         | Thermal hyperalgesia                                     | Decreases in serum IL-6 levels and oxidative stress                      | [34]       |
| Vitamin C                                | Vitamin C 500 mg/kg, i.p.                  | Rats            |         | Mechanical sensitivity and thermal sensitivity            | Decreases of proinflammatory cytokines (IL-1β, IL-6 and TNF-α) in the DRG | [27]       |
| β-caryophyllene, a CB2 agonist           | β-caryophyllene, a CB2 agonist 25 mg/kg, p.o. | Mice |         | Mechanical allodynia                                      | Through CB2-activation in the CNS and posterior inhibition of p38 MAPK/NF-κB activation and cytokine release | [56]       |
| 3-Carboxyphenyl isothiocyanate           | 3-Carboxyphenyl isothiocyanate 1.33–13.31 μmol/kg, s.c. | Mice |         | Cold hypersensitivity                                     | Release H2S activating Kv7 channel                                       | [57]       |
| Allyl isothiocyanate                     | Allyl isothiocyanate 1.33–13.31 μmol/kg, s.c. | Mice |         | Cold hypersensitivity                                     | Release H2S activating Kv7 channel                                       | [57]       |
| Phenyl isothiocyanate                    | Phenyl isothiocyanate 4.43–13.31 μmol/kg, s.c. | Mice |         | Cold hypersensitivity                                     | Release H2S activating Kv7 channel                                       | [57]       |
| Retigabine                               | Retigabine 10 mg/kg, i.p.                  | Rats            |         | Mechanical allodynia, IENF density, and morphological alteration of mitochondria in peripheral nerve | Specific KCNQ/Kv7 channel opener                                          | [58]       |
| Sodium hydrosulfide hydrate              | Sodium hydrosulfide hydrate 13.31–38 μmol/kg, s.c. | Mice |         | Cold hypersensitivity                                     | Release H2S activating Kv7 channel                                       | [57]       |
| ML218, a T-type calcium channel blocker  | ML218, a T-type calcium channel blocker 1–10 mg/kg, i.p. | Rats |         | Mechanical hypersensitivity                               | Inhibition of Cav3.2                                                      | [54]       |
| Therapeutic Targets | Therapeutic Agents | Dose | Animals | Symptoms that Showed Improvement | Mechanisms | References |
|---------------------|-------------------|------|---------|----------------------------------|------------|-----------|
| TRP channel         | RQ-0311651, a T-type calcium channel blocker | 10–40 mg/kg, i.p. | Mice and rats | Mechanical hyperalgesia | Block of Cav3.1/Cav3.2 T channels | [59] |
|                     | AMG9810           | 30 mg/kg, p.o. | Rats    | Mechanical allodynia, hyperalgesia, and thermal hyperalgesia | TRPV1 antagonism | [60] |
|                     | Capsazepine       | 30 mg/kg, s.c. | Rats    | Thermal hyperalgesia | TRPV1 antagonism | [61] |
|                     | HC-067047, a TRPV4 antagonist | 10 mg/kg, i.p. | Mice    | Mechanical hyperalgesia | TRPV4 antagonism | [62] |
|                     | Quercetin         | 20–60 mg/kg, i.p. | Rats and mice | Heat hyperalgesia and mechanical allodynia | Suppression of PKCε and TRPV1 in the spinal cords and DRG | [63] |
|                     | Ruthenium red     | 3 mg/kg, s.c. | Rats    | Thermal hyperalgesia | TRP antagonism | [61] |
|                     | SB-366791, a TRPV1 antagonist | 0.5 mg/kg, i.p. | Mice    | Visceral nociception, mechanical hypersensitivity and heat hypersensitivity | TRPA1 antagonism | [55] |
|                     | Tabernaemontana catharinensis ethyl acetate fraction | 100 mg/kg, p.o. | Mice    | Mechanical allodynia | TRPA1 antagonism | [64] |
| Glutamate           | Memantine         | 1–5 mg/kg | Rats    | Mechanical hypersensitivity | Antagonism of NMDA receptor | [65] |
|                     | Valproate         | 200 mg/kg, i.p. | Rats    | Mechanical allodynia | Suppressions HDAC2 upregulation, glutamate accumulation, and the corresponding changes in EAAT2/VGLUT/synaptophysin expression and HDAC2/YY1 interaction | [66] |
|                     | Cilostazol        | Diet containing 0.3% cilostazol | Mice    | Mechanical hyperalgesia and Schwann cell dedifferentiation within the sciatic nerve | Differentiation of Schwann cells via a mechanism involving cAMP/Epac signaling | [67] |
|                     | Minoxidil         | 25–50 mg/kg, i.p. | Mice    | Mechanical hyperalgesia, thermal sensitivity, and damages of sciatic nerve | Suppression of neuroinflammation (macrophage and microglia) recruitments and remodeling of intracellular calcium homeostasis in DRG | [68] |
| Therapeutic Targets | Therapeutic Agents | Dose | Animals | Symptoms that Showed Improvement | Mechanisms | References |
|---------------------|--------------------|------|---------|----------------------------------|------------|------------|
| Cannabinoid receptor | Cannabidiol | 1–20 mg/kg, i.p. | Mice | Mechanical sensitivity | N.A. | [69] |
|                     | Cannabidiol | 2.5–25 mg/kg, i.p., p.o. | Mice | Mechanical alldynia | N.A. | [70] |
|                     | JZL184, a MAGL inhibitor | 4–40 mg/kg, i.p. | Mice | Mechanical alldynia | N.A. | [49] |
|                     | KLS-13019 | 2.5–25 mg/kg, i.p. | Mice | Mechanical alldynia | N.A. | [70] |
|                     | MJN110, a MAGL inhibitor | 4–40 mg/kg, i.p. | Mice | Mechanical alldynia | Downregulations of IRF8, P2X4, CaMKIIα, p-CREB, FosB, BDNF, GluR1 and NR2B, and increase in the expression of K^+−Cl^-cotransporter | [48] |
|                     | MJN110, a MAGL inhibitor | 4–40 mg/kg, i.p. | Mice | Mechanical alldynia | Downregulations of monocyte chemoattractant protein-1 (MCP-1 and CCL2) and p-p38 MAPK in dorsal root ganglia as well as MCP-1 in the spinal dorsal horn | [49] |
|                     | URB597, a centrally penetrant FAAH inhibitor | 1 mg/kg, i.p. | Mice | Mechanical hypersensitivity and cold hypersensitivity | Inhibition of FAAH, the major enzyme catalyzing the degradation of anandamide, an endocannabinoid, and other fatty acid amides | [71] |
|                     | URB937, a peripherally restricted FAAH inhibitor | 1 mg/kg, i.p. | Mice | Mechanical hypersensitivity and cold hypersensitivity | Inhibition of FAAH, the major enzyme catalyzing the degradation of anandamide, an endocannabinoid, and other fatty acid amides | [71] |
|                     | β-caryophyllene, a CB2 agonist | 25 mg/kg, p.o. | Mice | Mechanical alldynia | CB2-activation in the CNS and posterior inhibition of p38 MAPK/ NF-κB activation and cytokine release | [56] |
|                     | ∆9-THC | 2.5–20 mg/kg, i.p. | Mice | Mechanical sensitivity | N.A. | [69] |
| Opioid receptor | Morphine | 3–6 mg/kg, p.o. | Mice | Mechanical alldynia | N.A. | [72] |
|                     | Oxycodone | 24 mg/kg/day, p.o. | Mice | Mechanical alldynia | N.A. | [72] |
| Monoamines | SR-17018 | 1–48 mg/kg/day, p.o. | Mice | Mechanical alldynia | N.A. | [72] |
|                     | Bee venom acupuncture | 1 mg/kg, s.c. | Rats | Mechanical hyperalgesia | Via spinal α2-adrenergic receptor | [73] |
| Therapeutic Targets          | Therapeutic Agents          | Dose                        | Animals | Symptoms that Showed Improvement                                      | Mechanisms                                                                 | References |
|------------------------------|-----------------------------|-----------------------------|---------|------------------------------------------------------------------------|------------------------------------------------------------------------------|------------|
|                             | Bee venom acupuncture       | 0.25–2.5 mg/kg, i.p.        | Mice    | Cold alldynia and mechanical alldynia                                  | Via the spinal noradrenergic and serotonergic mechanism                      | [74]       |
|                             | Quetiapine                  | 10–15 mg/kg, p.o.           | Mice    | Heat hyperalgesia, mechanical alldynia, and cold alldynia              | Via α2-adrenoceptors                                                        | [75]       |
|                             | Reboxetine                  | 10 mg/kg, i.p.              | Rats    | Mechanical alldynia and cold hyperalgesia                              | α2-AR mediated antinociception at the spinal cord                           | [76]       |
|                             | Venlafaxine                 | 40–60 mg/kg, s.c.           | Mice    | Cold alldynia and mechanical alldynia                                  | Via the spinal noradrenergic and serotonergic mechanism                      | [74]       |
| Acetylcholine receptor      | Nicotine                    | 0.6–0.9 mg/kg, i.p. or 24 mg/kg, s.c. | Mice    | Mechanical alldynia and density of IENF                               | Via α7 nicotinic acetylcholine receptor                                     | [77]       |
|                             | Pirenzepine                 | 10 mg/kg, s.c.              | Mice    | Mechanical sensitivity and thermal sensitivity                        | Muscarinic ACh type 1 receptor (M1R) antagonism                             | [78]       |
|                             | R-47, an α7 nAChR silent agonist | 5–10 mg/kg, i.p.          | Mice    | Mechanical hypersensitivity, loss of IENF and morphological changes of microglia | N.A.                                                                       | [79]       |
|                             | α-Conotoxin RglA4           | 80 µg/kg, s.c.              | Rats    | Mechanical alldynia                                                    | N.A.                                                                        | [80]       |
| cAMP/PKA                    | ESI-09, a Epac inhibitor    | 20 mg/kg, p.o.              | Mice    | Mechanical alldynia and number of IENF                                | Suppression of spinal cord astrocyte activation                             | [40]       |
| PKC                          | HOE140, a kinin B2 antagonist | 50 nmol/kg, i.p.            | Mice    | Mechanical hyperalgesia                                               | Inactivation of PKCε                                                        | [62]       |
|                             | DALBK, a kinin B1 antagonist | 150 nmol/kg, i.p.          | Mice    | Mechanical hyperalgesia                                               | Inactivation of PKCε                                                        | [62]       |
|                             | Tamoxifen                   | 30 mg/kg, p.o.              | Mice    | Mechanical alldynia cold alldynia                                     | Inhibition of PKC/ERK pathway                                               | [81]       |
| MAPK                         | Duloxetine                  | 30 mg/kg/day, i.p.          | Mice    | Mechanical hyperalgesia, thermal hyperalgesia, and loss of IENF        | Decreases in NF-κB, p-p38, IL-6, and TNF-α in DRG                           | [39]       |
|                             | Duloxetine                  | 10–30 mg/kg, p.o.           | Mice    | Mechanical alldynia and cold alldynia                                 | Inhibiting ERK1/2 phosphorylation in spinal cord                            | [82]       |
|                             | Gabapentin                  | 30–100 mg/kg, p.o.          | Mice    | Mechanical alldynia and cold alldynia                                 | Inhibiting ERK1/2 phosphorylation in spinal cord                            | [82]       |
| Therapeutic Targets | Therapeutic Agents                  | Dose          | Animals | Symptoms that Showed Improvement                                      | Mechanisms                                                                                           | References |
|---------------------|-------------------------------------|---------------|---------|-----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|------------|
| Lacosamide          | 30 mg/kg, p.o.                      | Rats          | Thermal hyperalgesia and cold allodynia                               | Upregulation of total antioxidant capacity and NGF, and downregulation of NF-kB p65, TNF-α, active caspase-3, Notch1 receptor, p-p38, and IL-6/p-JAK2/p-STAT3 | [28]       |
| MJN110, a MAGL inhibitor | 4–40 mg/kg, i.p.                   | Mice          | Mechanical allodynia                                                   | Downregulations of MCP-1, CCL2 and p-p38 in DRG as well as MCP-1 in the spinal dorsal horn             | [49]       |
| PD0325901           | 30 mg/kg, p.o.                      | Mice          | Mechanical allodynia and cold allodynia                               | Inhibiting ERK1/2 phosphorylation in spinal cord                                                    | [82]       |
| Lacosamide          | 30 mg/kg, p.o.                      | Rats          | Thermal hyperalgesia and cold allodynia                               | Upregulation of total antioxidant capacity and NGF, and downregulation of NF-kB p65, TNF-α, active caspase-3, Notch1 receptor, p-p38, and IL-6/p-JAK2/p-STAT3 | [28]       |
| Siwei Jianbu decoction | 5–10 g/kg, p.o.                    | Mice          | Mechanical hyperalgesia and thermal nociception                        | Inhibiting the JNK, ERK1/2 phosphorylation, NF-κB, TNF-α, IL-1β, and IL-6                            | [53]       |
| Tamoxifen           | 30 mg/kg, p.o.                      | Mice          | Mechanical allodynia cold alldynia                                     | Inhibition of PKC/ERK pathway                                                                        | [81]       |
| Trametinib          | 0.5 mg/kg                           | Mice          | Mechanical and cold alldynia                                           | Inhibition of the MEK/ERK pathway                                                                    | [83]       |
| β-caryophyllene, a CB2 agonist | 25 mg/kg, p.o.                  | Mice          | Mechanical alldynia                                                   | Through CB2-activation in the CNS and posterior inhibition of p38 MAPK/NF-κB activation and cytokine release | [56]       |
| OATP1B2             | Nilotinib 100 mg/kg, p.o.           | Mice          | Mechanical alldynia                                                   | Inhibition of paclitaxel intake to neuron via OATP1B2 inhibition                                      | [84]       |
| mTOR                | Rapamaycin 5 mg/kg, i.p.            | Rats          | Mechanical hypersensitivity and thermal hypersensitivity               | Decreases of IL-1β, IL-6, TNF-α, substance P and CGRP in DRG.                                       | [51]       |
| AM9053, a NAAA inhibitor | 1–10 mg/kg, i.p.                   | Mice          | Mechanical alldynia                                                   | N.A.                                                                                                  | [85]       |
| Aucubin             | 15–50 mg/kg, i.p.                   | Mice          | Mechanical alldynia                                                   | N.A.                                                                                                  | [86]       |
| Therapeutic Targets | Therapeutic Agents | Dose | Animals | Symptoms that Showed Improvement | Mechanisms | References |
|---------------------|--------------------|------|---------|-----------------------------------|------------|-----------|
| Aucubin | 50 mg/kg, i.p. | Mice | Mechanical allodynia | Inhibition of ER stress in peripheral Schwann cells | [87] |
| Bogijetong decoction, a herbal drug formulation | 400 mg/kg, p.o. | Rats | Heat sensitivity | Improvement of morphological abnormalities in the sciatic nerve axons and DRG tissue | [88] |
| DALBK, a kinin B1 antagonist | 150 nmol/kg, i.p. | Mice | Mechanical allodynia | Antagonism of kinin B1 receptor | [89] |
| FR173657, a kinin B2 antagonist | 100 nmol/kg, i.p. | Mice | Mechanical allodynia | Antagonism of kinin B2 receptor | [89] |
| Gelsemium sempervirens | 1 mL, i.p. | Rats | Mechanical alldonya, mechanical hyperalgesia, cold alldonya, and density of IENF | N.A. | [90] |
| HOE140, a kinin B2 antagonist | 100 nmol/kg, i.p. | Mice | Mechanical alldonya | Antagonism of kinin B2 receptor | [89] |
| Iridoids isolated from Viticis Fructus | 15 mg/kg | Mice | Mechanical alldonya | N.A. | [91] |
| Lepidium meyenii | 0.5–10 mg/kg, p.o. | Rats | Cold hypersensitivity | N.A. | [92] |
| Metformin | 200 mg/kg, i.p. | Mice | Mechanical hypersensitivity | Activation of AMPK | [93] |
| Narciscasine | 1 mg/kg, p.o. | Mice | Mechanical hypersensitivity | Activation of AMPK | [93] |
| Neoline | 10 mg/kg/day, s.c. | Mice | Mechanical hyperalgesia | N.A. | [94] |
| Nicotinamide riboside | 200 mg/kg, p.o. | Rats | Mechanical hyperalgesia and cold hyperalgesia | N.A. | [95] |
| NO-711, a GAT-1 inhibitor | 3 mg/kg, i.p. | Mice | Thermal hyperalgesia and cold alldonya | Inhibition of GAT-1 | [96] |
| Processed aconite root | 1 g/kg/day, s.c. | Mice | Mechanical hyperalgesia | N.A. | [94] |
| Recombinant human soluble thrombomodulin | 3–10 mg/kg, i.p. | Rats | Mechanical hyperalgesia | Inactivation of HMGB1 | [97] |
| Rikkunshito | 0.3–1 mg/kg, p.o. | Mice | Mechanical hyperalgesia | Suppression of p-NF-κB in spinal cord | [98] |
| Therapeutic Targets | Therapeutic Agents | Dose | Animals | Symptoms that Showed Improvement | Mechanisms | References |
|---------------------|--------------------|------|---------|---------------------------------|------------|------------|
| Salicylidene salicylhydrazide | 50–75 mg/kg, i.p. | Mice | Mechanical allodynia and cold allodynia | N.A. | [99] |
| Sargassum glaucescens from the Persian Gulf | 100–200 mg/kg, i.p. | Mice | Cold allodynia | N.A. | [100] |
| SLAB51, a probiotic formulation | 1.5 g (200 billion of bacteria) in 10 mL of drinking water | Mice | Mechanical allodynia and hyperalgesia | Increases in the expression of opioid and cannabinoid receptors in spinal cord, reduction in nerve fiber damage in the paws and modulation of the serum proinflammatory cytokines concentration | [101] |
| SSR240612, a kinin B1 antagonist | 150 nmol/kg, i.p. | Mice | Mechanical allodynia | Antagonism of kinin B1 receptor | [89] |
| Staurosporine | 0.1 mg/kg, i.p. | Mice | Mechanical allodynia | Inhibitory of PI3K signaling pathway | [102] |
| Telmisartan | 5–10 mg/kg, i.p. | Mice | Mechanical hyperalgesia and thermal hyperalgesia | Inhibition of CYP2J isozymes and reductions of EpOME in DRGs and plasma | [103] |
| Terfenadine | 1–2 mg/kg | Mice | Mechanical hyperalgesia | Inhibition of CYP2J isozymes | [103] |
| Wortmannin | 0.6 mg/kg, i.p. | Mice | Mechanical hyperalgesia | Inhibitory of PI3K signaling pathway | [102] |

Abbreviations: Ach, acetylcholine; AMPK, AMP-activated protein kinase; Apaf-1, apoptosis protease-activating factor 1; ATF-3, activating transcription factor 3; Bcl-2, B-cell lymphoma-extra-large; BDNF, brain derived neurotrophic factor; CaMKIIα, calmodulin-dependent protein kinase IIα; CCL2, C-C motif chemokine ligand 2; CCR2, C-C motif chemokine receptor 2; CGRP, calcitonin gene-related peptide; CREB, cAMP response element binding protein; CXCR, C-X-C motif chemokine receptor; CYP2J, Cytochrome P450 2J; DRG, dorsal root ganglia; EAAT2, excitatory amino acid transporter 2; Epac, exchange protein directly activated by cAMP; EpOME, epoxyoctadecamonoenoic acids; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; FAAH, fatty-acid amide hydrolase; FosB, FBj murine osteosarcoma viral oncogene homolog B; GAT-1, gamma-aminobutyric acid (GABA) transporter 1; GFAP, glial fibrillary acidic protein; GluR1, glutamate ionotropic receptor AMPA type subunit 1; GSH, glutathione; HDAC2, histone deacetylase 2; HMGB1, high mobility group box 1; HO-1, heme oxygenase 1; i.p., intraperitoneal; i.v., intravenous; IENF, intra-epidermal nerve fibers; IL-10, interleukin-10; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-8, interleukin-8; iNOS, inducible nitric oxide synthase; IRS, insulin regulatory factor 8; JNK, c-Jun N-terminal kinase; MAGL, monoacylglycerol lipase; MAPK, mitogen-activated protein kinase; MCP-1, monococyte chemotactic protein 1; MDA, malondialdehyde; MEK, mitogen-activated protein kinase; MPO, myeloperoxidase; NAAA, N-acylethanolamine-hydroryzingly acid amidase; NAcChR, nicotinic acetylcholine receptor; NF-κB, nuclear factor kappa-B; NMDA, N-methyl-D-aspartate; NOX4, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4; NQO1, NAD(P)H dehydrogenase [quinone] 1; NR2B, N-methyl D-aspartate (NMDA) receptor subtype 2B; Nrf2, nuclear factor-erythroid 2-related factor 2; OATP1B2, organic anion-transporting polypeptide 1b2; p.Akt, phospho-protein kinase B; PARP, poly ADP-ribose polymerase; p-CREB, phospho-CAMP response element binding protein; p-FAK, phospho-focal adhesion kinase; PGC-1α, peroxisome proliferator activated receptor γ coactivator-1; PI3K, phosphatidylinositol-3-kinase; p-STAT3, phospho-signal transducer and activator of transcription 3; RAGE, receptor for advanced glycation endproducts; s.c., subcutaneous; SIRT1, sirtuin-1; SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity; SOD, superoxide dismutase; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α; TRP, transient receptor potential; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; TRPV4, transient receptor potential vanilloid 4; UCP2, uncoupling protein 2; VGLUT, vesicular glutamate transporter 3; YY1, Yin-Yang 1.
3.1.1. Antioxidants and Mitochondria-Protective Agents

Many previous preclinical reports support that oxidative stress and mitochondrial dysfunction play a role in PIPN [31,104–106]. Vitamin C, rotenone, tempol, and curcumin which are widely known for their antioxidant effects, have been reported to alleviate PIPN in rodents [20,21,27]. Among the approved drugs, duloxetine, lacosamide, pregabaline, and rosuvastatin have also been reported to reverse PIPN via their antioxidant effects [23,28,32]. Moreover, many agents, which have antioxidant effects, inhibit PIPN in preclinical studies [19,22,24–26,29–31,33,34].

3.1.2. Anti-Inflammatory Agents

Inflammatory cytokines (e.g., interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α)) and chemokines (e.g., chemokine (C-X-C motif) ligand (CXCL) family) were elevated in the peripheral sites, spinal cord, and of paclitaxel-treated animals, and many agents reduced the peripheral neuropathy symptoms via their anti-inflammatory effects [19,21,22,24,25,27,28,32–39,41,42,44–47,49–54,56]. Activations of astrocytes and microglia were also observed in the spinal dorsal horn after paclitaxel administrations, and many agents including minocycline attenuated PIPN via the inhibition of these spinal changes and prevented neurological damage [40,43,44,48].

3.1.3. Ion Channel Inhibitors and Activators

Some activators of potassium channels, especially Kv7, have been shown to suppress PIPN [57,58]. Focusing on calcium channels, T-type calcium channel blockers have been reported to alleviate PIPN symptoms [54,59].

3.1.4. Transient Receptor Potential (TRP) Modulators

Temperature-sensitive cation channels (e.g., transient receptor potential vanilloid 4 (TRPV4), transient receptor potential vanilloid 1 (TRPV1), and transient receptor potential ankyrin 1 (TRPA1)) have been reported to be involved in PIPN [61,107–109]. Many drugs have also been reported to improve PIPN by downregulating or inhibiting TRP channels [55,60–64].

3.1.5. Cannabinoid Receptor Agonists

Many studies have shown that cannabinoid receptor agonists and related substances can suppress PIPN symptoms [48,49,56,69–71]. In particular, some reports exist that selective CB2 agonists have an ability to suppress PIPN [48,56].

3.1.6. Modulators of Monoamine Nervous System

Monoamines, including noradrenaline and serotonin, play an important role in the descending pain inhibitory system [110]. Some drugs and agents (e.g., quetiapine, reboxetine, venlafaxine, and bee venom) also showed analgesic effects by modulating the monoamine nervous system in the PIPN animal models [73–76].

3.1.7. Others

In addition to the aforementioned, many other drugs have been identified to reduce PIPN via several therapeutic targets, such as glutamate nerve systems [65,66], phosphodiesterase (PDE) [67,68], opioid receptors [72], acetylcholine receptor [77–80], cAMP/protein kinase A (PKA) signal [40], protein kinase C (PKC) [62,81], mitogen-activated protein kinase (MAPK) [28,39,49,53,56,81–83], organic anion-transporting polypeptide 1b2 (OATP1B2) [84], mammalian target of rapamycin (mTOR) [51], and others [85–103], at the pre-clinical research level.

3.2. Therapeutic Agents in Clinical Evidence

In PubMed, 1175 articles were found when using the search term “paclitaxel neuropathy or paclitaxel neurotoxicity” limited to “Randomized Controlled Trial” and “Meta-
Analysis”. After excluding reports other than about PIPN, the authors found 19 reports considered to be clinically important. A summarized list of the representative randomized controlled trials and meta-analyses on prophylactic and therapeutic agents for PIPN is shown below in Table 2.
Table 2. The therapeutic drugs for paclitaxel-induced peripheral neuropathy in clinical experiments.

| Investigational Drug | Dose (Preventive or Curative) | Chemotherapy | Study Design | Patient Number | Summary | References |
|-----------------------|-------------------------------|--------------|--------------|----------------|---------|------------|
| Acetyl-L-carnitine    | 3000 mg daily, p.o. (preventive) | Taxanes      | Randomized, double-blind, placebo-controlled, multicenter study | 409 | Significant reduction in NTX scores (worsening of peripheral neuropathy) >2 years | [111] |
| Amifostine            | 910 mg/m², i.v., before the paclitaxel administration (preventive) | Carboplatin/paclitaxel | Randomized, controlled study | 38 | Significant improvements in paresthesia and sensory motor impairment. | [112] |
| Amifostine            | 910 mg/m², i.v., before the paclitaxel administration (preventive) | Paclitaxel | Randomized, controlled study | 37 | No significant difference in any of the measures of neurotoxicity. | [113] |
| Gabapentin            | 40 mg daily, p.o. (20 mg/day for the first week) (curative) | Oxaliplatin, paclitaxel, vincristine, or bortezomib | Randomized, open-label, crossover study (vs vitamin B12) | 34 | Significant improvements in numbness and pain | [114] |
| Duloxetine            | 60 mg/day, p.o., (30 mg/day for the first week) (curative) | Taxane or platinum | Randomized, double-blind, placebo-controlled, crossover study | 231 | In all patients, RRs (95% CI) of experiencing 30% and 50% pain reduction were 1.96 (1.15–3.35) and 2.43 (1.11–5.30), respectively In taxane-treated patients, RRs (95% CI) of experiencing 30% and 50% pain reduction were 0.97 (0.41–2.32) and 1.22 (0.35–4.18), respectively (not significant) | [115] |
| Gabapentin            | 900 mg daily, p.o., (preventive) | Paclitaxel | Randomized, double-blind, placebo-controlled study | 40 | Significant improvements in the incidence of grades 2–3 neuropathy and NCV changes | [116] |
| Glutamate             | 1500 mg daily, p.o., (preventive) | Paclitaxel | Randomized, double-blind, placebo-controlled study | 43 | No significant difference in the frequency of signs or symptoms between the two groups | [117] |
| Glutathione           | 1.5 g/m², i.v., immediately before chemotherapy (preventive) | Carboplatin/paclitaxel | Randomized, double-blind, placebo-controlled study | 185 | No significant differences in acute pain score and EORTC QLQ-CIPN20 scores compared to the placebo group | [118] |
| Investigational Drug | Dose (Preventive or Curative) | Chemotherapy | Study Design | Patient Number | Summary                                                                 | References |
|----------------------|-------------------------------|--------------|--------------|----------------|----------------------------------------------------------------------|------------|
| Minocycline          | 200 mg daily, p.o., (preventive) | Paclitaxel    | Randomized, double-blind, placebo-controlled, multicenter study | 47             | Significant improvements in acute pain score. No significant differences in sensory neuropathy score of the EORTC QLQ-CIPN20 compared to the placebo group. | [119]      |
| N-acetyl cysteine    | 1200 mg daily or twice daily, p.o., (preventive) | Paclitaxel    | Randomized, controlled, open label study | 75             | Significant improvements in incidence of grades 2–3 neuropathy, mTNS, and QOL scores. Significant increase in serum NGF and decrease in serum MDA. | [120]      |
| Omega-3 fatty acid   | 1920 mg daily, p.o., (preventive) | Paclitaxel or oxaliplatin | Meta-analysis | 116 (two trials) | Significant improvements in the incidence of peripheral neuropathy and SNAP amplitudes. | [121]      |
| Omega-3 fatty acid   | 1920 mg daily, p.o., (preventive) | Paclitaxel    | Randomized, double-blind, placebo-controlled study | 57             | Significant improvements in neuropathy incidence. | [122]      |
| Oral nutritional supplement containing EPA | p.o., (preventive) | Paclitaxel or cisplatin/carboplatin | Randomized, controlled study | 92             | Significant improvement in neuropathy. | [123]      |
| PARP inhibitors (olaparib or veliparib) | N.A. | Paclitaxel | Meta-analysis | 843 (five trials) | Did not reduce the risk of chemotherapy-induced peripheral neuropathy. | [124]      |
| Pregabalin           | 150 mg daily, p.o., (curative) | Paclitaxel or docetaxel | Randomized, double-blind, controlled study (vs duloxetine group) | 82             | Improvements in NCI-CTCAE grade and PNQ scores were more significant with pregabalin in comparison to duloxetine. | [125]      |
| Pregabalin           | 150 mg daily, p.o., (preventive) | Paclitaxel    | Randomized, double-blind, placebo-controlled, multicenter study | 46             | No significant differences in acute pain score and EORTC QLQ-CIPN20 scores compared to the placebo group. | [126]      |
| Investigational Drug | Dose (Preventive or Curative) | Chemotherapy | Study Design | Patient Number | Summary | References |
|----------------------|-------------------------------|--------------|--------------|----------------|---------|------------|
| **Recombinant human LIF** | 2 or 4 µg/kg, s.c., (preventive) | Carboplatin/paclitaxel | Randomized, double-blind, placebo-controlled study | 117 | No significant difference in CPNE or any of the individual neurologic testing variables | [127] |
| **Vitamin E** | 600 mg daily, p.o., (preventive) | Paclitaxel | Randomized, controlled study | 32 | Significant improvements in the incidence of neuropathy and PNP scores | [128] |
| | 600 mg daily, p.o., (preventive) | Cisplatin or paclitaxel | Randomized, controlled study | 31 | Significant improvements in incidence and neuropathy scores | [129] |

Abbreviations: 95% CI, 95% confidence interval; CPNE, composite peripheral nerve electrophysiology; EORTC QLQ-CIPN20, European Organisation for Research and Treatment of Cancer, Quality of Life-Chemotherapy-Induced Peripheral Neuropathy 20; EPA, eicosapentaenoic acid; LIF, leukemia inhibitory factor; MDA, malondialdehyde; mTNS, modified total neuropathy score; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; NCV, nerve conduction velocity; NGF, nerve growth factor; NTX score, neurotoxicity score; PARP, poly ADP-ribose polymerase; PNP score, peripheral neuropathy score; PNQ, patient neurotoxicity questionnaire; QOL, quality of life; RR, relative risk; SNAP, sensory nerve action potential.
Duloxetine was tested in a randomized, double-blind, placebo-controlled, crossover trial, for its ability to treat neuropathy in patients with taxane or platinum [115]. In this study, relative risks (RRs) (95% confidence interval (95% CI)) of experiencing 30% and 50% pain reduction were 1.96 (1.15–3.35) and 2.43 (1.11–5.30), respectively. However, in a subanalysis in taxane-treated patients, RRs (95% CI) of experiencing 30% and 50% pain reduction were 0.97 (0.41–2.32) and 1.22 (0.35–4.18), respectively (not significant). Duloxetine significantly improved numbness and pain compared with vitamin B12 in a randomized, open-label, crossover study of patients who received chemotherapy including other anticancer drugs, as well as paclitaxel [114].

Pregabalin significantly improved the grade and score of taxane-related neuropathy compared with duloxetine in a randomized, double-blind, controlled study [125]. Moreover, pregabalin did not improve treatment-related pain and neuropathy scores related to paclitaxel in a randomized, double-blind, placebo-controlled, multicenter study [126]. Gabapentin was reported to significantly reduce the incidence of grade ≥2 PIPN and changes in nerve conduction velocity (NCV) in a randomized, double-blind, placebo-controlled study [122].

Omega-3 fatty acids significantly improved the incidence of peripheral neuropathy associated with paclitaxel administration in a randomized, double-blind, placebo-controlled study [122]. In a meta-analysis that included not only paclitaxel-treated patients but also oxaliplatin-treated patients, the suppressive effects of omega-3 fatty acids on neuropathy were significant [121]. Vitamin E significantly improved the incidence and scores of neuropathies in both a randomized, controlled study of patients with paclitaxel [128] and patients with paclitaxel or cisplatin [129]. Amifostine significantly improved paresthesia and sensory motor impairment in a randomized controlled study of paclitaxel/carboplatin-treated patients [112]. However, it did not significantly improve neuropathy in a randomized controlled study of paclitaxel-treated patients [113]. Additionally, minocycline, N-acetylcysteine, and eicosapentenoic acid (EPA) have been reported to improve peripheral neuropathy associated with paclitaxel [119,120,123]. Moreover, glutamate, glutathione, poly ADP-ribose polymerase (PARP) inhibitors, and human leukemia inhibitory factor (LIF) did not show any significant effect on PIPN in randomized controlled trials or meta-analyses [117,118,124,127]. Long-term administration of acetyl-L-carnitine significantly worsened taxane-related peripheral neuropathy in a randomized, double-blind, placebo-controlled, multicenter study [111].

As described above, few drugs have shown clear therapeutic PIPN effects in clinical trials. Thus, according to the clinical practice guideline updated by the American Society of Clinical Oncology in 2020, no agents have yet to be recommended for preventing chemotherapy-induced peripheral neuropathy and only duloxetine may be used as a treatment for neuropathy [14].

4. Discussion

The PIPN mechanism has been recently elucidated in basic studies, and many drugs and agents targeting this mechanism have been explored and identified for PIPN therapy or prophylaxis [18]. In particular, many inhibitors of neuropathy targeting oxidative stress, inflammatory response, ion channels, TRP channels, cannabinoid receptor, and monoamine nervous system have been identified as candidates for inhibiting PIPN in animal research. In particular, more reports of inhibitors targeting peripheral and central inflammatory responses, TRP channels, and cannabinoid receptors were noted compared with pre-clinical research reports on oxaliplatin-induced peripheral neuropathy [130]. Targeting these may be useful in the search for PIPN-specific therapeutics.

Alternatively, very few drugs have shown the efficacy for PIPN in clinical trials. The American Society of Clinical Oncology’s clinical practice guideline states that only duloxetine can be used for the treatment of chemotherapy-induced peripheral neuropathy [14]. In a randomized double-blind placebo-controlled crossover study, duloxetine has been reported to improve neuropathic pain caused by taxanes and platinum [115]. However, a
subanalysis of that study also showed a weak inhibitory effect of duloxetine on taxanes in neuropathic pain [115]. Thus, few evidence-based treatments for PIPN were noted.

Most clinical studies examined the preventive rather than curative effects on PIPN. Meanwhile, pre-clinical studies have explored many therapeutic targets for PIPN. Of these, agents on the therapeutic targets that inhibit pain or sensory abnormalities, such as K channel, Ca channel, TRP channels, glutamate, cannabinoid receptors, opioid receptors, and monoamine nervous system, may have curative effects on PIPN that has already developed. More information on the clinical studies of these agents will make it possible to approach PIPN from both a preventive and curative perspective.

While many drugs have been reported in pre-clinical research as having the potential to inhibit the PIPN, few drugs have developed sufficient evidence in clinical studies. The valley of death between basic studies and clinical applications is caused by many issues, including the difference between clinical symptoms and animal assessment methods, the cost and time of conducting clinical research, safety considerations in clinical application, and the lack of collaboration between basic and clinical researchers. Thus, promoting translational research, that is, to bridge pre-clinical research to clinical research is important.

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Abbreviations

95% CI 95% confidence interval  
Ach acetylcholine  
AMPK AMP-activated protein kinase  
Apaf-1 apoptosis protease-activating factor 1  
ATF-3 activating transcription factor 3  
Bcl-2 B-cell lymphoma 2  
Bcl-xL B-cell lymphoma-extra large  
BDNF brain derived neurotrophic factor  
CaMKIIα calmodulin-dependent protein kinase IIα  
CCL2 C-C motif chemokine ligand 2  
CCR2 C-C motif chemokine receptor 2  
CGRP calcitonin gene-related peptide  
CPNE composite peripheral nerve electrophysiology  
CREB cAMP response element binding protein  
CXCL C-X-C motif chemokine ligand  
CXR C-X-C motif chemokine receptor  
CYP2J Cytochrome P450 2J  
DRG dorsal root ganglia  
EAAT2 excitatory amino acid transporter 2  
EORTC QLQ-CIPN20 European Organisation for Research and Treatment of Cancer: Quality of Life-Chemotherapy-Induced Peripheral Neuropathy 20  
EPA eicosapentaenoic acid  
Epac exchange protein directly activated by cAMP  
EpOME epoxyoctadecamonoenoic acids
ER endoplasmic reticulum
ERK extracellular signal-regulated kinase
FAAH fatty-acid amide hydrolase
FosB FBJ murine osteosarcoma viral oncogene homolog B
GAT-1 gamma-aminobutyric acid (GABA) transporter 1
GFAP glial fibrillary acidic protein
GluR1 glutamate ionotropic receptor AMPA type subunit 1
GSH glutathione
HDAC2 histone deacetylase 2
HMGB1 high mobility group box 1
HO-1 heme oxygenase 1
t.p. intraperitoneal
i.v. intravenous
IENF intra-epidermal nerve fibres
IL-10 interleukin-10
IL-1β interleukin-1 beta
IL-6 interleukin-6
IL-8 interleukin-8
iNOS inducible nitric oxide synthase
IRF8 interferon regulatory factor 8
JNK c-Jun N-terminal kinase
LIF leukaemia inhibitory factor
MAGL monoacylglycerol lipase
MAPK mitogen-activated protein kinase
MCP-1 monocyte chemotactic protein 1
MDA malondialdehyde
MEK mitogen-activated protein kinase kinases
MPO myeloperoxidase
mTNS modified total neuropathy score
mTOR mammalian target of rapamycin
NAAA N-acylethanolamine-hydrolyzing acid amidase
nAChR nicotinic acetylcholine receptor
NCI-CTCAE National Cancer Institute-Common Terminology Criteria for Adverse Events
NCV nerve conduction velocity
NF-κB nuclear factor kappa-B
NGF nerve growth factor
NMDA N-methyl-D-aspartate
NOX4 nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4
NQO1 NAD[P]H dehydrogenase [quinone] 1
NR2B N-methyl D-aspartate (NMDA) receptor subtype 2B
Nrf2 nuclear factor-erythroid 2-related factor 2
NTX score neurotoxicity score
OATP1B2 organic anion-transporting polypeptide 1b2
p.o. per os
p-Akt phospho-protein kinase B
PARP poly ADP-ribose polymerase
p-CREB phospho-cAMP response element binding protein
PDE phosphodiesterase
p-FAK phospho-focal adhesion kinase
PGC-1α peroxisome proliferator-activated receptor γ coactivator-1
PI3K phosphatidylinositol-3-kinase
PIP N-acylethanolamine-hydrolyzing acid amidase
p-JAK2 phospho-janus kinase 2
PKA protein kinase A
PKC protein kinase C
p-NF-κB phospho-nuclear factor kappa-B
PNP score peripheral neuropathy score
PNQ patient neurotoxicity questionnaire
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