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REVIEW ARTICLE

Taxane-induced neurotoxicity: Pathophysiology and therapeutic perspectives

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Taxane-derived drugs are antineoplastic agents used for the treatment of highly common malignancies. Paclitaxel and docetaxel are the most commonly used taxanes; however, other drugs and formulations have been used, such as cabazitaxel and nab-paclitaxel. Taxane treatment is associated with neurotoxicity, a well-known and relevant side effect, very prevalent amongst patients undergoing chemotherapy. Painful peripheral neuropathy is the most dose-limiting side effect of taxanes, affecting up to 97% of paclitaxel-treated patients. Central neurotoxicity is an emerging side effect of taxanes and it is characterized by cognitive impairment and encephalopathy. Besides impairing compliance to chemotherapy treatment, taxane-induced neurotoxicity (TIN) can adversely affect the patient's life quality on a long-term basis. Despite the clinical relevance, not many reviews have comprehensively addressed taxane-induced neurotoxicity when they are used therapeutically. This article provides an up-to-date review on the pathophysiology of TIN and the novel potential therapies to prevent or treat this side effect.

Abbreviations: Ca_v, voltage-gated calcium; CB_1, cannabinoid receptor 1; CB_2, cannabinoid receptor 2; CCL2, chemokine (C-C motif) ligand 2; CCR2, C-C motif chemokine receptor 2; CIPN, chemotherapy-induced peripheral neuropathy; CREB, cAMP response element-binding; CX3CL1, C-X3-C motif chemokine ligand 1; CXCL1, C-X3-C motif chemokine ligand 1; CXCL12, C-X-C motif chemokine ligand 12; CXCR1, C-X-C motif chemokine receptor 1; CXCR2, C-X-C motif chemokine receptor 2; DRG, dorsal root ganglion; GHS-R, growth hormone secretagogue receptor; IENFs, intra-epidermal nerve fibres; K_{ATP}, ATP-sensitive potassium channel; K_v, voltage-gated potassium channel; mPTP, mitochondrial permeability transition pore; Na_v, voltage-gated sodium channel; Nrf2, nuclear factor-2 erythroid-related factor-2; PIPN, paclitaxel-induced peripheral neuropathy; TICN, taxane-induced central neurotoxicity; TIN, taxane-induced neurotoxicity; TIPN, taxane-induced peripheral neuropathy; TLR4, toll-like receptor-4; TRPA1, transient receptor potential cation channel subfamily A member 1; TRPV1, transient receptor potential cation channel subfamily V member 1; TRPV4, transient receptor potential cation channel subfamily V member 4.

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1 | INTRODUCTION

Taxane-derived drugs are antineoplastic agents originally isolated from plants of the *Taxus* genus. Paclitaxel, commercially known as Taxol®, is the prototype of taxanes and was firstly isolated in 1971 from *Taxus brevifolia* (Pacific yew). **Docetaxel** (Taxotere®) was semi-synthetically obtained from *Taxus baccata* (European yew) in the 1980s. Paclitaxel and docetaxel are the most commonly used taxanes. However, other drugs and formulations have been developed, such as **cabazitaxel** (Jevtana®) and nab-paclitaxel (Abraxane®). Taxanes are used for the treatment of highly prevalent malignancies, including lung, breast, prostate, stomach, oesophageal, bladder, pancreas, melanoma, Kaposi's sarcoma, ovarian and head and neck cancers.

Their mechanism of action consists in interrupting the G_2 phase of the cell cycle by binding to polymerized tubulins (α and β), stabilizing microtubules. Taxanes also bind to mitochondrial β-tubulin, causing mitochondrial damage by opening the mitochondrial permeability transition pore (mPTP) and increasing calcium efflux. These events trigger cancer cell apoptosis and necrosis (Weaver, 2014). However, taxanes have limited selectivity against cancer cells. Their use is associated with neurotoxicity, a well-known and important side effect. The neurotoxic effects of taxanes can affect both the peripheral and the central (CNS) nervous systems.

Peripheral neurotoxicity, known as peripheral neuropathy, is the most dose-limiting side effect of taxanes, including paclitaxel and docetaxel. Although less frequent, taxane-induced peripheral neuropathy (TIPN) can also occur in patients treated with cabazitaxel or nab-paclitaxel (Velasco & Bruna, 2015). Taxane-induced peripheral neuropathy affects up to 97% of paclitaxel-treated patients and becomes chronic in over 60% of the cases (Tanabe et al., 2013). It causes patient discomfort and often leads to dose reduction or even termination of chemotherapy, limiting therapeutic success. Importantly, chronic neuropathy significantly impairs patient's life quality on a long-term basis.

Taxane-induced central neurotoxicity (TICN) is an emerging side effect which manifests as acute encephalopathy (Ziske et al., 2002), ataxia (Hofstra, van der Graaf, de Vries, Haaxma-Reiche, & Willemse, 1997), emotional distress (Thornton, Carson, Shapiro, Farrar, & Andersen, 2008) and cognitive impairment (Lange et al., 2016; Wefel, Saleeba, Buzdar, & Meyers, 2010). Chemotherapy-related cognitive impairment, also known as 'chemofog' or 'chemobrain', has been described in the domains of working memory, executive function, processing speed and verbal/visual memory (Vardy & Tannock, 2007). The prevalence of acute chemotherapy-related cognitive impairment ranges from 17% to 75% and may last for up to 2 years following treatment, although some patients (17%–34%) exhibit persistent deficits for decades after treatment (de Ruiter et al., 2012; Schagen, Das, & Vermeulen, 2012). Taxane-associated cognitive impairments have been increasingly recognized as an important side effect, with long-term and detrimental impacts on life quality.

Due to the increased survival rates of cancer patients, taxane-induced neurotoxicity (TIN) has become a growing epidemiological problem. Its management has proven to be difficult due to the complexity of mechanisms. Herein, we revise the risk factors, pathophysiological mechanisms and current therapeutic perspectives for TIN, as well as the animal models employed to study this side effect, in order to shed light into novel and effective therapies.

2 | ANIMAL MODELS OF TAXANE-INDUCED NEUROTOXICITY

Animal models have been useful tools to investigate the pathophysiological mechanisms of TIN and find potential therapies (Hopkins, Duggett, & Flatters, 2016). The main protocols employed to study TIN are presented in Table 1. The available protocols differ regarding animal strains, taxane type and doses, treatment schemes (single or multiple doses) and routes of administration. C57BL/6 mice and variants are commonly used, whilst rat models have been performed in Sprague Dawley and Wistar strains. Paclitaxel is the most used taxane in the existing models.

3 | TAXANE-INDUCED PERIPHERAL NEUROPATHY

Taxane-induced peripheral neuropathy generally manifests as paraesthesia and, to a lesser extent, painful extremities. However, in the most severe cases, it can progress to loss of sensory perception, motor deficits and autonomic dysfunction. Patients commonly present with a 'stocking and glove' distribution of the sensory symptoms, affecting both the upper and lower limbs and gravitating to the proximal regions of the body. Typical sensations include paraesthesia, dysesthesia, numbness, burning and shooting or electric shock sensations. Hyperalgesia and allodynia induced by mechanical and/or thermal stimuli may also occur (Grisold, Cavaletti, & Windebank, 2012; Velasco & Bruna, 2015).

One hallmark of the peripheral effect of paclitaxel is the acute pain syndrome which rapidly occurs after the first treatment (usually within 24 h). Acute pain syndrome is also observed in docetaxel-treated patients. Although acute symptoms subside between treatment cycles, it seems to be causally connected to a later occurring chronic neuropathy. Chronic neuropathy can persist for months or years after treatment cessation (Loprinzi et al., 2011; Velasco & Bruna, 2015). The incidence of acute neuropathy in patients treated with paclitaxel or docetaxel can reach 97% and 47%, respectively,

TABLE 1 Taxane-induced neurotoxicity experimental models

Animal	Drug	Dose	Protocol	Behavioural effects	Reference
Mouse					
	Paclitaxel	2 mg·kg^{-1} (i.p.)	5 consecutive days	Heat hyperalgesia (plantar test) and mechanical (von Frey test) and cold (acetone test) allodynia	Nieto et al., 2008
	Paclitaxel	4 mg·kg^{-1} (i.v.) 4 mg·kg^{-1} (i.p.) 60, 70 or 80 mg·kg^{-1} (i.p.)	Single dose Single dose or 4 alternated days 1× week/4 weeks	Mechanical (paw pressure test) and heat (plantar test) hyperalgesia	Matsumoto et al., 2006
	Paclitaxel	2 mg·kg^{-1} (i.p.)	4 alternated days	Mechanical allodynia (von Frey test)	Segat et al., 2017
	Paclitaxel	2, 4 or 8 mg·kg^{-1} (i.p.)	4 alternated days	Mechanical (von Frey test) and cold (acetone test) allodynia; anxiety- and depression-like behaviours	Toma et al., 2017
	Paclitaxel	20 mg·kg^{-1} (i.p.)	12 injections on alternating weekdays for 4 weeks	Spatial learning and memory impairment	Huehnchen et al., 2017
	Paclitaxel	1, 3 or 6 mg·kg^{-1} (i.p.)	Single dose	Dose-dependent spatial learning and memory impairment	Atarod et al., 2015
	Docetaxel	33 mg·kg^{-1} (i.p.)	Single dose	Spatial memory impairment	Seigers et al., 2015
	Docetaxel	8 mg·kg^{-1} (i.p.)	Continuously delivered for a total dose of 32 mg·kg^{-1} over 4 weeks or 1× week/4 weeks	Novel object recognition memory impairment; spatial memory impairment	Fardell et al., 2014
Rat					
	Paclitaxel	0.5, 1 or 2 mg·kg^{-1} (i.p.)	4 alternated days	Mechanical (von Frey) and thermal hyperalgesia and allodynia	Polomano et al., 2001
	Paclitaxel	2 mg·kg^{-1} (i.p.)	4 alternated days	Spatial learning and memory impairment; reversal learning impairment	Li, Zhao, et al., 2018; Panoz-Brown et al., 2017
	Docetaxel	1 mg·kg^{-1} (i.v.)	1× week/4 weeks	Spatial memory impairment; depression-like behaviour	Callaghan & O'Mara, 2015
	Docetaxel	10 mg·kg^{-1} (i.p.) 6 or 10 mg·kg^{-1} (i.p.)	Single dose Once a week for 3 weeks	Novel object recognition memory impairment	Fardell, Vardy, & Johnston, 2013

whilst chronic neuropathy is present in 64% of paclitaxel- and 45% of docetaxel-treated patients (Tanabe et al., 2013).

3.1 | Risk factors and pathophysiology of taxane-induced peripheral neuropathy

3.1.1 | Risk factors

The occurrence of taxane-induced peripheral neuropathy has been associated with different risk factors including the number of cycles and duration of therapy, patient age, use of other neurotoxic agents and existence of predisposing conditions such as alcoholism, diabetes or prior neuropathy (Molassiotis et al., 2019). Additionally, polymorphisms in genes such as *KCNN3* (potassium calcium-activated channel subfamily N member 3), *CYP2C8* (cytochrome P450 family 2 subfamily C member 8), *CYP3A4* (cytochrome P450 family 3 subfamily A member 4), *ABCB1* (ATP binding cassette subfamily B member 1), *EPHA4* and *EPHA5* (ephrin receptors A4 and A5), *FGD4* (FYVE, RhoGEF and PH domain containing 4), *FZD3* (frizzled class receptor 3), *ARHGEF10* (Rho guanine nucleotide exchange factor 10), *SLCO1B1* (solute carrier organic anion transporter family member 1B1) and *TUBB2A* (tubulin β 2A class IIa) may influence the susceptibility to taxane-induced peripheral neuropathy (Cliff et al., 2017; Sisignano, Lötsch, Parnham, & Geisslinger, 2019).

3.1.2 | Mechanisms of neuronal injury

Taxane-induced toxicity affects the somatosensory nerves leading to the development of neuropathic pain. Paclitaxel-treated mice present with increased levels of the activating transcription factor-3, a marker of neuronal injury, in large and medium dorsal root ganglion (DRG) neurons (Jimenez-Andrade et al., 2006). Axonal degeneration and loss of intra-epidermal nerve fibres (IENFs) have also been described in paclitaxel-induced peripheral neuropathy (PIPN) (Liu et al., 2010), suggesting that DRG injury drives taxane-induced nerve damage. Different pathophysiological mechanisms were described for taxane-induced peripheral neuropathy, including microtubule dysfunction, mitochondrial damage and oxidative stress (Figure 1) (Staff et al., 2020). These will now be discussed.

Altered microtubule dynamics

Taxanes act as microtubule-stabilizing agents and prevent mitosis, such actions are responsible for their anti-cancer activities. However, altered microtubule dynamics can lead to impaired neuronal transport of organelles, nutrients and neurotransmitters through the axons. Therefore, loss of microtubule function results in axonal degeneration or axonopathy, leading to peripheral neuropathy (Fukuda, Li, & Segal, 2017).

Mitochondrial dysfunction and oxidative stress

Mitochondrial alterations, including morphology, electrolyte balance and generation of ROS, have been described as key elements of taxane-induced peripheral neuropathy. In rats, paclitaxel-induced peripheral neuropathy was positively correlated with the development of pain-like behaviours and mitochondrial damage in myelinated and C-fibres, without any evidence of a mitotoxic effect in motor neuron axons (Xiao & Bennett, 2012). In addition to morphological alterations, including swelling and vacuolization, mitochondrial damage was characterized by changes in the calcium efflux mediated by mitochondrial permeability transition pore opening (Flatters & Bennett, 2006).

Deficiencies in the mitochondrial respiratory chain were also observed in rodent models of paclitaxel-induced peripheral neuropathy, even after treatment cessation and in the absence of any detectable drug levels in the DRG. These findings indicate that persistent DRG mitochondrial dysfunctions are important mechanisms of taxane-induced peripheral neuropathy. Mitochondrial respiratory dysfunctions and ATP deficits are early events of paclitaxel neurotoxicity as they occur in DRGs prior to the development of pain. Although mitochondrial respiration was restored at the peak of pain severity, ATP deficits persisted and were accompanied by increased glycolytic function (Duggett, Griffiths, & Flatters, 2017). These data demonstrated that changes in the bioenergetics of DRG neurons are

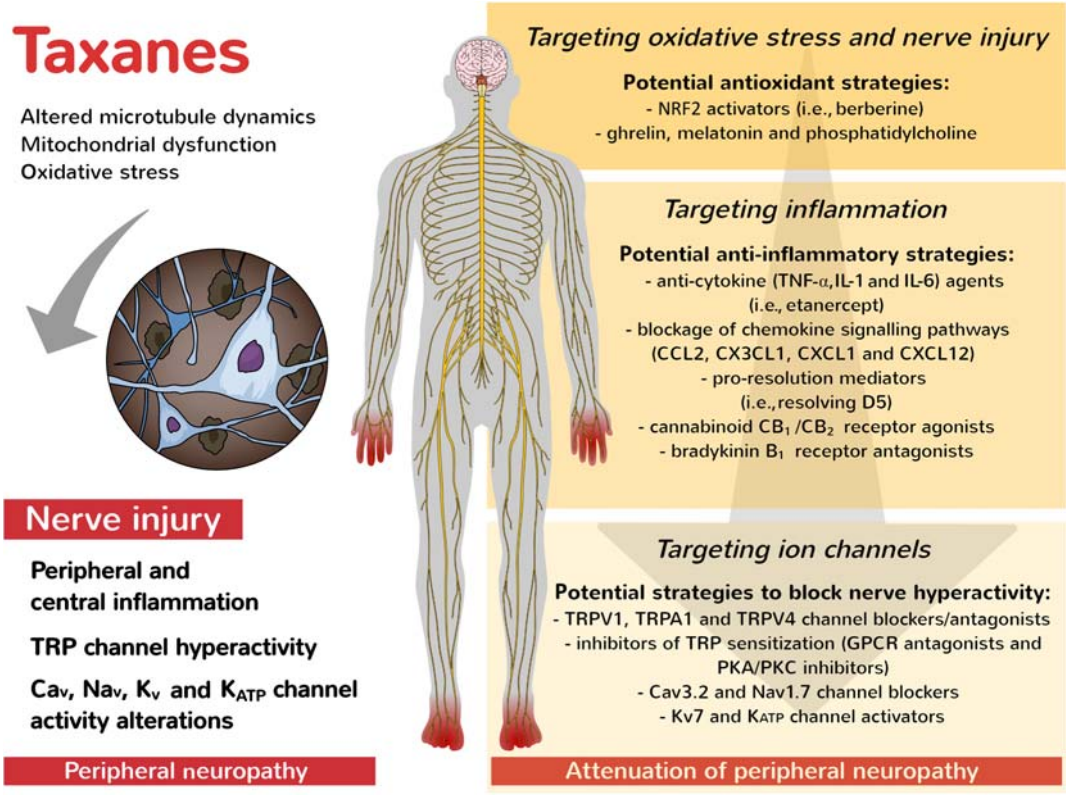

FIGURE 1 Taxane-induced peripheral neuropathy (TIPN)—pathophysiology and potential therapeutic strategies. Taxanes induce nerve injury by three main mechanisms: alteration of microtubule dynamics, mitochondrial dysfunction and oxidative stress in peripheral nerves. Nerve injury is followed by peripheral and central inflammation and changes in the activity of ion channels (TRP, Ca_v, Na_v, K_v and K_{ATP}), leading to peripheral neuropathy. Targeting of oxidative stress and nerve injury, inflammation and ion channel activity represent potential therapeutic strategies to treat TIPN

fundamental for the development and maintenance of taxane-induced peripheral neuropathy.

Oxidative stress is also critical to the pathophysiology of taxane-induced peripheral neuropathy. Indeed, additional mitochondrial insults with mitotoxic compounds increased oxidative stress and the severity of paclitaxel-induced peripheral neuropathy (Xiao & Bennett, 2012). Conversely, the global inhibition of ROS by the non-specific ROS scavenger N-tert-butyl-α-phenylnitrone prevented the development of paclitaxel-induced peripheral neuropathy and reversed the established hypersensitivities, suggesting that ROS play an active role in the development and maintenance of paclitaxel-induced peripheral neuropathy (Fidanboylu, Griffiths, & Flatters, 2011). An enhanced ROS production via the mitochondrial complexes I and III is believed to mediate taxane-induced peripheral neuropathy as complex inhibition reversed the established paclitaxel-induced peripheral neuropathy in rats; inhibition of complex III also prevented the development of paclitaxel-induced peripheral neuropathy (Griffiths & Flatters, 2015). Direct evidence demonstrating that paclitaxel treatment increases ROS production in the rat DRG and spinal cord were recently provided. Additionally, paclitaxel increased the activity of manganese and copper zinc SOD and **GSH** peroxidase antioxidant enzymes, indicating a need to control elevated ROS levels (Duggett et al., 2016).

3.2 | Therapeutic perspectives for taxane-induced peripheral neuropathy

3.2.1 | Targeting oxidative stress and nerve injury

The efficacy of antioxidant molecules as neuroprotective strategies to preventing the development of peripheral neuropathy has been investigated in preclinical and clinical studies. Vitamin E and GSH have been explored as adjuvant therapies to preventing taxane-induced peripheral neuropathy; however, there is minimal evidence of their efficacy. Other tested neuroprotective treatments with limited success include amifostine, **glutamine** and acetyl L-carnitine (Schloss, Colosimo, Airey, Masci, & Linnane, 2013). Surprisingly, a recent randomized, double-blinded and multicentre trial using acetyl L-carnitine as an adjuvant therapy showed that this agent aggravates taxane-induced peripheral neuropathy (Hershman et al., 2018). Despite the disappointing results, novel therapies targeting oxidative stress and mitochondrial dysfunction continue to be investigated in animal models of taxane-induced peripheral neuropathy.

Nuclear factor-2 erythroid-related factor-2 (**NRF2**), a transcription factor activated by oxidative stress, promotes the expression of cytoprotective enzymes. Importantly, restoring the levels of the NRF2-antioxidant response element in the rat DRG inhibits the neuropathic pain, oxidative stress and inflammation induced by paclitaxel (Zhao et al., 2019). NRF2 can be activated by berberine, a quaternary benzylisoquinoline alkaloid obtained from *Berberis* spp. and used in Ayurveda and Chinese medicine. Recently, berberine was found to attenuate thermal hypersensitivity and oxidative stress responses in paclitaxel-injected rats. These effects were associated with reduced lipid peroxidation and GSH levels and increased SOD activity in the sciatic nerve (Singh et al., 2019). Berberine presented similar antinociceptive effects in paclitaxel-injected mice (Rezaee, Monemi, SadeghiBonjar, & Hashemzaei, 2019). In addition, **α-lipoic acid** attenuated nab-paclitaxel-induced nociceptive responses by increasing the levels of NRF2 and *NRF2*-responsive genes (Sun et al., 2019). This evidence indicates that NRF2 activators may represent interesting approaches to treating taxane-induced peripheral neuropathy via modulation of oxidative stress.

Ghrelin is an endogenous ligand for the growth hormone secretagogue receptor (**GHS-R**) recently investigated in models of diabetes- and chemotherapy-induced peripheral neuropathy (CIPN). Ghrelin was found to improve paclitaxel-induced peripheral neuropathy, whilst reducing the loss of intra-epidermal nerve fibres in mice; such effects were due to ghrelin's ability to reduce mitochondrial dysfunction, oxidative and nitrosative stresses in the mouse DRG. Interestingly, both ghrelin and GHS-R knockout mice developed more severe neuropathy in comparison with their wild-type counterparts, suggesting that ghrelin is neuroprotective in taxane-induced peripheral neuropathy (Ishii et al., 2018). Likewise, **melatonin**, a hormone well-known for regulating the sleep–wake cycle, prevented the reduction of C-fibre activity-dependent slowing and mechanical hypersensitivity induced by paclitaxel in rats, through the inhibition of oxidative stress (8-isoprostane F2α levels) in the peripheral nerves (Galley et al., 2017).

Phosphatidylcholine is a polyunsaturated fatty acid, with a choline head group in its structure, which is present in the mitochondria membranes. Its antioxidant activity has been demonstrated in different animal models, including in neuropathic pain models induced by cisplatin or docetaxel. Phosphatidylcholine antinociceptive actions were due to its ability to increase the antioxidant defence, thus decreasing neuronal damage in the sciatic nerve and modulating microglia activity in the spinal cord (Kim et al., 2018).

3.2.2 | Targeting inflammation

The interaction between glial and neuronal cells accounts for various types of chronic pain. Additionally, compelling evidence suggests that chronic pain largely relies on the release of a series of inflammatory mediators such as cytokines and chemokines (Ji, Berta, & Nedergaard, 2013). Therefore, the combination of anti-inflammatory agents might prevent or diminish the painful symptoms elicited by taxanes. This section will discuss the relevance of inflammation for taxane-induced peripheral neuropathy.

Most data linking inflammation and taxane-induced peripheral neuropathy come from preclinical studies. A recent study analysed a panel of cytokines and chemokines in the serum of rats treated with paclitaxel. The results showed an elevation of several inflammatory proteins, such as **IL-1β**, **IL-6**, **TNF-α** and chemokine (C-C motif) ligand 2 (**CCL2**) in paclitaxel-treated animals. Additionally, the treatment with the anti-TNF-α agent **etanercept**, the **IL-1 receptor antagonist** or the

C-C motif chemokine receptor 2 (CCR2) antagonist S504393 fully prevented painful alterations in paclitaxel-treated rats (Al-Mazidi et al., 2018). Supporting the relevance of chemokines for taxane-induced peripheral neuropathy, the selective CCR2 receptor antagonist RS-504393 was able to inhibit the cold hypersensitivity in paclitaxel-treated mice. Moreover, cold hypersensitivity and microglia activation secondary to paclitaxel administration were lessened by an anti-CCL2 antibody, in this mouse model of peripheral neuropathy there is an associated elevation of CCL2 levels in the spinal cord (Pevida, Lastra, Hidalgo, Baamonde, & Menendez, 2013). The chemokine C-X3-C motif chemokine ligand 1 (CX3CL1) was also up-regulated in the spinal neurons of rats pretreated with paclitaxel, possibly via the activation of the transcriptional factor NF-κB and histone acetylation. In addition, either the inhibition of CX3CL1 or NF-κB reversed the mechanical allodynia caused by paclitaxel (Li et al., 2015). Paclitaxel-induced neuropathic pain in rats was accompanied by infiltration of non-resident macrophages into the DRGs. The same study also demonstrated that macrophage depletion by clodronate fully prevents the increases of TNF-α and CCL2 in DRG samples and reduces "painful" symptoms in paclitaxel-treated rats by mechanisms involving Toll-like receptor-4 (TLR4) (Zhang et al., 2016). In another study, the intravenous administration of paclitaxel induced macrophage accumulation into DRGs and peripheral nerves of rats, a response that was accompanied by the activation of astrocytes and DRG satellite cells. These events were possibly secondary to paclitaxel-induced cell injury, as revealed by up-regulation of activating transcription factor 3 (ATF3) in sensory neurons, DRG satellite and Schwann cells (Peters et al., 2007).

It has been proposed that CX3CL1 receptor inhibition might be beneficial in taxane-induced peripheral neuropathy, by blocking peripheral macrophage–neuron interactions (Montague & Malcangio, 2017). *In vitro*, paclitaxel increased the excitatory postsynaptic currents in spinal dorsal horn neurons, an event that paralleled with a raise of C-X-C motif chemokine ligand 12 (CXCL12) expression, via STAT3-histone acetylation. *In vivo*, the inhibition of CXCL12 signalling pathways alleviated the mechanical allodynia induced by paclitaxel (Xu et al., 2017). Further evidence demonstrated the ability of reparixin, a blocker of the IL-8–C-X-C motif chemokine receptor 1 (CXCR1)/2 (CXCR2) pathways, to inhibit the mechanical and cold allodynia induced by paclitaxel in rats (Brandolini et al., 2017). Additionally, C-X3-C motif chemokine ligand 1 (CXCL1) levels were increased in the spinal cords of paclitaxel-treated mice and the blockage of CXCL1 and its receptor CXCR2 greatly improved paclitaxel-induced peripheral neuropathy (Manjavachi et al., 2019). It is tempting to propose that taxane-induced peripheral neuropathy likely relies on the interaction of neuronal and non-neuronal cells, with a relevant role for cytokines and chemokines in this context. Thus, anti-cytokine tools and chemokine inhibitors represent potential choices to treating neuropathic pain after taxane-based chemotherapy.

Wang, Li, Zhao, and Zhang (2018) demonstrated that oestrogen levels influence TNF-α production in the DRG and are correlated with the neuroinflammation caused by paclitaxel, as both mechanical and thermal hypersensitivities are attenuated by bilateral ovariectomy in rats (Wang et al., 2018). This is an important observation as taxanes are used in the chemotherapy schemes for the treatment of breast cancer in women at pre- or post-menopausal phases (Willson et al., 2019). The influence of sexual hormones in taxane-induced peripheral neuropathy has been supported by another study, which showed that the intrathecal administration of the pro-resolution mediator resolvin D5 reduces paclitaxel-induced mechanical allodynia in male but not female mice (Luo, Gu, Tao, Serhan, & Ji, 2019).

The induction of peripheral neuropathy by paclitaxel led to the activation of spinal astrocytes in rats, without any evidence for microglia participation, an effect that was sensitive to the treatment with the microglia inhibitor minocycline (Zhang, Yoon, Zhang, & Dougherty, 2012). The modulation of paclitaxel-induced peripheral neuropathy by the synthetic cannabinoid receptor 1 (CB_1) and 2 (CB_2) agonist WIN 55,212-2 was fully associated with an inhibition of spinal inflammation in rats. Accordingly, the repeated administration of WIN 55,212-2 prevented glial activation, besides blocking IL-1β, IL-6 and TNF-α up-regulation. Cannabinoid receptor agonism resulted in similar decline of paclitaxel-induced peripheral neuropathy and neuroinflammation, as it was observed for minocycline (Burgos et al., 2012). Thus, taxane-induced peripheral neuropathy depends on microglia activation, which in turn triggers pro-inflammatory cytokine up-regulation at the spinal level, a mechanism that is sensitive to the activation of the cannabinoid system. Supporting this finding, the co-treatment with the non-steroidal anti-inflammatory drug indomethacin and minocycline synergistically reduced paclitaxel-induced thermal hyperalgesia in mice of both sexes, an effect that was reversed by CB_1 receptor antagonism (Parvathy & Masocha, 2015). Moreover, paclitaxel-related cold and mechanical allodynia were prevented by both CB_1 Δ(9)-tetrahydrocannabinol and CB_2 AM1710 agonists in mice. Of interest, AM1710 inhibited TNF-α and CCL2 mRNA expressions in the spinal cord of paclitaxel-treated mice without evoking tolerance (Deng et al., 2015). Thus, CB agonists might well represent a strategy to manage the neuroinflammation underlying taxane-induced peripheral neuropathy. In this regard, the dietary CB_2 receptor agonist β-caryophyllene exhibited marked analgesic effects in mice injected with paclitaxel, by modulating spinal cord p38 MAPK and NF-κB activation. The same mice presented with reduced spinal microglia activation and attenuated levels of IL-1β and CCL2 (Segat et al., 2017).

Clinical studies also indicate a relationship between inflammation and the neuropathy induced by taxanes. A retrospective study enrolling 67 patients with breast cancer, who had been treated with docetaxel, showed that peripheral neuropathy was present in 51 subjects. This adverse condition was proportional to the number of chemotherapy cycles and it was directly correlated with the neutrophil-to-lymphocyte and monocyte-to-lymphocyte ratios (Yamanouchi et al., 2017). The authors suggested that systemic inflammation contributes for the development of peripheral neuropathy in cancer patients undergoing treatment with docetaxel. An elegant study investigated the differential gene expression in breast cancer survivors, with and without neuropathy symptoms. Several neuroinflammatory pathways were found to be significantly perturbed in patients with neuropathic pain, including cytokines and their

receptors, besides NF-κB-related signalling pathways (Miaskowski et al., 2019). Conversely, in a proteomic study carried out to identify potential biomarkers from serum exosomes, individuals with a low inflammatory response preceding the chemotherapy with taxanes presented a higher susceptibility to develop peripheral neuropathy. These data contrast with the hypothesis that taxane-induced peripheral neuropathy is related to a higher inflammatory response. It is possible though that different degrees of inflammation affect taxane-induced peripheral neuropathy, depending on the period of evaluation, that is, prior or after chemotherapy onset (Chen et al., 2015).

3.2.3 | Targeting TRP channels

Transient receptor potential channels (**TRPs**) are non-selective calcium channels distributed in different subfamilies: (i) ankyrin (transient receptor potential cation channel subfamily A member 1 [TRPA1]), (ii) canonical (TRPC1–7), vanilloid (transient receptor potential cation channel subfamily V members 1–6 [TRPV1–6]), melastatin (TRPM1–8), mucolipin (TRPML1–3) and polycystin (TRPP1–3). TRPs participate in a range of cellular responses, from cell survival to death, and therefore are involved in different pathophysiological states. They are best known for participating in pain transduction, but also influence inflammation, tissue remodelling and neuronal plasticity, and are known to sense and modulate oxidative stress. All of these characteristics make TRP receptors interesting targets for the treatment of several illnesses, including taxane-induced peripheral neuropathy. In this context, the greatest deal of evidence has been gathered from studies on **TRPV1**, **TRPA1** and transient receptor potential cation channel subfamily V member 4 (**TRPV4**). These will be discussed below.

Transient receptor potential cation channel subfamily V member 1 (TRPV1)

The mechanosensor and thermal sensor TRPV1 is the most well-studied channel of the TRP family. Indeed, its role in painful conditions has been widely investigated in a range of disease models and in translational researches in humans. Not surprisingly, TRPV1 has been implicated in neuropathies including those associated with diabetes and chemotherapy. An initial report demonstrated a time-dependent increase in TRPV1 mRNA and protein expression on small- and medium-sized DRG neurons of rats with paclitaxel-induced peripheral neuropathy (Hara et al., 2013). An increased expression of TRPV1 in paclitaxel rat DRGs was also observed in later reports (Gao, Zan, Wang, Hu, & Huang, 2016). Accordingly, paclitaxel induces c-fos expression—a marker of neuronal activation—in a TRPV1-dependent manner (Kalynovska, Adamek, & Palecek, 2017). Also, TRPV1 protein overexpression was observed in rat peripheral tissues such as the paw skin (Hara et al., 2013). In the same study, treatment with the non-selective TRPV1 antagonist **capsazepine** attenuated the neuropathic pain caused by the taxane.

Studies in mice indicate conflicting results for capsazepine in paclitaxel-induced peripheral neuropathy. Both capsazepine and the selective TRPV1 antagonist **SB366791** attenuated heat but not mechanical hyperalgesia induced by paclitaxel (Chen, Yang, & Wang, 2011). Conversely, it was recently showed that capsazepine does not present anti-hyperalgesic activity, but instead it exacerbates the painful response to heat caused by chemotherapy (Salat & Filipek, 2015). The discrepancies between these studies may be due to the different treatment schemes of paclitaxel (single vs. cumulative doses). Similarly, studies with TRPV1 knockout (TRPV1 KO) mice have provided different results. Although previous studies have shown that TRPV1 KOs exhibit reduced mechanical nociception and heat sensitivity, a recent study showed that TRPV1 ablation does not affect the neuropathic responses caused by the taxane (Luo et al., 2019).

Different TRPV1 pathways are implicated in taxane-induced peripheral neuropathy. The enhanced neuronal excitability observed following paclitaxel treatment was associated with an impaired glutamate clearance (Cata, Weng, Chen, & Dougherty, 2006), a neurotransmitter known to induce TRPV1 expression on DRG neurons via **mGluR1** activation (Masuoka et al., 2016). The repeated *in vitro* incubation of paclitaxel with DRG small diameter sensory neurons from adult rats resulted in no additional release of **CGRP**, however it presented a dual effect on **capsaicin**-stimulated neurons (Pittman, Gracias, Vasko, & Fehrenbacher, 2014). The study showed that low concentrations of paclitaxel enhance **CGRP** release triggered by capsaicin in these cells, whilst high concentrations of the taxane have the opposite effect (Pittman et al., 2014). Such responses were not associated with neuronal death but were dependent on the time of exposure to paclitaxel. Interestingly, the effects of the low concentrations of this compound on CGRP levels are related to increased expression of TRPV1, whilst those of higher concentrations were secondary to channel desensitization (Pittman et al., 2014). This evidence is supported by *in vivo* data demonstrating that the administration of high doses of paclitaxel reduces thermal nociceptive responses in rats (Authier, Gillet, Fialip, Eschalier, & Coudore, 2000; Campana et al., 1998). Conversely, lower doses of the compound induce both mechanical and thermal nociception (Polomano, Mannes, Clark, & Bennett, 2001). It was demonstrated that the *in vivo* nociception triggered by low doses of paclitaxel is attenuated by the intrathecal administration of the selective TRPV1 antagonist **AMG9810**. This response was found to be associated with a direct stimulatory effect of paclitaxel on TRPV1. It was also suggested that this compound drives TLR4 activation and a subsequent sensitization of TRPV1 (Li et al., 2015).

Although promising, TRPV1 blockers have failed to attenuate pain and have caused major adverse effects in humans such as hyperthermia and loss of noxious heat perception. A more recently developed TRPV1 blocker—NEO6860—did not cause these adverse responses but promoted other reactions (feel hot, headache, nausea, dizziness, fatigue, hypoesthesia and increased BP), whilst conferring little analgesia in patients with knee pain (Arsenault et al., 2018). In this context, modulators of TRPV1 sensitization such as GPCR antagonists and **PKA** or **PKC** inhibitors may be interesting approaches to the clinical management of taxane-induced peripheral neuropathy.

Transient receptor potential cation channel subfamily A member 1 (TRPA1)

TRPA1 was initially described as a mechanosensor and it is recognized as an important transducer of noxious cold. Its expression on neuronal and non-neuronal cells involved in pain transduction has unveiled a detrimental role for TRPA1 in painful conditions such as rheumatoid arthritis and neuropathy. TRPA1 contribution to taxane-induced peripheral neuropathy is relatively novel and not as well understood as the one attributed to TRPV1. Of note, paclitaxel antineoplastic actions are associated with its capacity of inducing oxidative stress. Indeed, paclitaxel treatment triggers the accumulation of atypical mitochondria, increasing the production of mitochondrial ROS and the formation of DNA oxidative adducts (Barriere et al., 2012). Interestingly, TRPA1 can sense oxidative stress. These evidences point towards a significant role for TRPA1 in taxane-induced peripheral neuropathy.

Studies in rodents have indicated that TRPA1 is important for both thermal and mechanical nociceptive responses to paclitaxel. It was found that the treatment of mice with a single dose of the selective TRPA1 antagonist **HC030031** abrogates the mechanical and thermal (cold and heat) hypersensitivities induced by paclitaxel (Chen et al., 2011). A later report by Materazzi et al. (2012) demonstrated a similar effect for HC030031 in the mechanical and cold-induced hypersensitivities caused by this taxane in mice. TRPA1 KO mice phenotype resembled that of mice treated with the TRPA1 antagonist (Materazzi et al., 2012). The same study showed that TRPA1 role in paclitaxel-induced peripheral neuropathy depends on CGRP release from primary DRG neurons and ROS production.

Interestingly, TRPA1 seems to participate only in the repeated but not the acute effects of paclitaxel, as no differences were noted in mechanical nociceptive thresholds to cold stimulation following the single administration of the taxane (Zhao et al., 2012). Conversely, in a report by Luo et al. (2019), TRPA1 ablation did not affect the neuropathy caused by the repeated administration of paclitaxel (Luo et al., 2019). This evidence suggests that pathways other than TRPA1 and TRPV1 may influence taxane neuropathy. As observed for TRPV1, TRPA1 role in paclitaxel-induced peripheral neuropathy may depend on the amount of taxane used to stimulate small diameter sensory neurons (Pittman et al., 2014). Indeed, Pittman et al. (2014) showed that neurons incubated with the TRPA1 agonist **allyl isothiocyanate** release less CGRP following higher concentrations of paclitaxel.

Transient receptor potential cation channel subfamily V member 4 (TRPV4)

TRPV4 channel was first described as an osmosensor activated by hypo-osmotic stress and has been implicated in mechano-transduction. TRPV4 expressed in DRG and trigeminal ganglion sensory neurons and keratinocytes seems to play an important role in pain signalling (Alessandri-Haber et al., 2003). Indeed, inflammatory mediators have been shown to sensitize DRG neurons to hypotonicity leading to increase of intracellular calcium concentration (Alessandri-Haber et al., 2003; Alessandri-Haber, Dina, Joseph, Reichling, & Levine, 2006). Inflammation can also sensitize rodents to the nociceptive effects of hypotonicity, causing overt nociception and mechanical hyperalgesia that are absent in response to TRPV4 selective antagonists or in TRPV4-deficent mice (Alessandri-Haber et al., 2006; Alessandri-Haber et al., 2003; Costa et al., 2018).

A role for TRPV4 channel in different neuropathic pain states has also been proposed (Alessandri-Haber, Dina, Joseph, Reichling, & Levine, 2008; Alessandri-Haber et al., 2004; Dias et al., 2019). Indeed, paclitaxel-induced peripheral neuropathy is accompanied by increased nociception after intraplantar injection of a hypotonic solution, which is prevented by genetic deletion of TRPV4 (Alessandri-Haber et al., 2004). Similarly, mechanical hypersensitivity induced by paclitaxel was reduced in TRPV4-deficient mice and in rats treated with TRPV4 antisense oligodeoxynucleotides (Alessandri-Haber et al., 2008; Alessandri-Haber et al., 2004). Different mechanisms have been proposed to increase TRPV4 channel activity in paclitaxel-induced peripheral neuropathy, including its sensitization by integrin/Src TK and PKA and PKCε pathways (Alessandri-Haber et al., 2008; Alessandri-Haber et al., 2004; Chen et al., 2011; Costa et al., 2018). GPCRs, such as **protease-activated receptor 2** and **bradykinin B_1** and **B_2** receptors, seem to trigger TRPV4 sensitization via PKA and PKCε signalling (Chen et al., 2011; Costa et al., 2018; Costa et al., 2011).

Drugs that act on TRPV4 may have therapeutic applications in the management of taxane-induced peripheral neuropathy. **HC067047**, a potent and selective TRPV4 antagonist, displayed antinociceptive effects in different models of pain, including diabetic painful neuropathy and inflammatory, orofacial and visceral pain (Dias et al., 2019). Importantly, HC067047 was also effective in inhibiting the established mechanical hypersensitivity induced by paclitaxel in mice (Costa et al., 2018). **RN1734** is a selective TRPV4 antagonist that has also shown efficacy in reversing paclitaxel-induced peripheral neuropathy in mice (Chen et al., 2011). Despite the effectiveness on established peripheral neuropathy, the preventive effect of TRPV4 antagonists in taxane-induced peripheral neuropathy has yet to be assessed.

3.2.4 | Targeting other ion channels

Calcium channels

Gabapentin and **pregabalin** have been widely used in the treatment of post-herpetic neuralgia and diabetic peripheral neuropathy, as they reduce the excitability of nerve cells by binding to the α2δ-1 subunit of voltage-gated calcium (**Ca_V**) channels. Both drugs have shown efficacy on paclitaxel-induced peripheral neuropathy in rodents, by acting on up-regulated α2δ-1 subunits in DRG neurons (Mangaiarkkarasi, Rameshkannan, & Ali, 2015; Matsumoto, Inoue, Hald, Xie, & Ueda, 2006). Although few clinical studies proved their efficacy on taxane-induced peripheral neuropathy, gabapentin and pregabalin have been used to treat neuropathic pain caused by taxanes. The administration of gabapentin or pregabalin improved the neuropathic pain symptoms in patients undergoing treatment with paclitaxel and **carboplatin**. Of note, gabapentin did not affect patient's quality of life

(Avan et al., 2018). Due to gabapentin and pregabalin side effects and limited efficacy, novel Ca_v channel modulators have been investigated as therapeutic approaches to treating taxane-induced peripheral neuropathy.

Experimental findings suggest that T-type **$Ca_v3.2$** channel isoform blockers may be effective in taxane-induced peripheral neuropathy. Enhanced activity and expression of $Ca_v3.2$ channel were detected in DRG and spinal cord samples of paclitaxel-treated rats. Two main mechanisms were attributed to the hyperactivity of this channel: a direct activation by hydrogen sulfide and an indirect activation by TLR4 (Li et al., 2017; Okubo et al., 2011). Importantly, silencing of $Ca_v3.2$ channels by intrathecally injected antisense oligodeoxynucleotides suppressed paclitaxel-induced peripheral neuropathy (Li, Tatsui, et al., 2017). In addition, T-type Ca_v channel blockers (**ethosuximide**, **mibefradil**, **NNC 55-0396**, **ML218** and RQ-00311651) reversed paclitaxel-induced neuropathy in rodents (Li, Tatsui, et al., 2017; Okubo et al., 2011). These results indicate that blockage of selective calcium channels may be an interesting approach to treating taxane-induced peripheral neuropathy.

Sodium channels

Altered expression and activity of voltage-gated sodium (**Na_v**) channels in sensory neurons contribute to neuropathic and inflammatory pain. Previous studies suggested a role for Na_v channels in taxane-induced peripheral neuropathy, as their blockers attenuate the mechanical and thermal hypersensitivities induced by paclitaxel in rats (Nieto et al., 2008; Xiao, Naso, & Bennett, 2008). Of note, low doses of **tetrodotoxin** which block Nav1.1–1.4 and Nav1.6–1.7 subtypes were able to reverse and prevent paclitaxel-induced peripheral neuropathy (Nieto et al., 2008).

Interestingly, several Na_v channel subunits (α and β) are up-regulated in the mouse anterior cingulate cortex (ACC) following paclitaxel injection, suggesting a role for anterior cingulate cortex Na_v channels in this response (Masocha, 2016). **$Na_v1.7$** mRNA and protein levels were also increased in rat DRGs after paclitaxel injection (Xia, Xiao, Wu, & Zhao, 2016). More recently, $Na_v1.7$ was found to be up-regulated in small-diameter DRG neurons and their central terminals in the spinal cord after paclitaxel treatment in rats. Importantly, $Na_v1.7$ immunostaining and neurophysiological activity were detected in DRG neurons isolated from health and neuropathic pain patients (Chang et al., 2018; Li et al., 2018). Treatment of isolated human DRG neurons with paclitaxel increased $Na_v1.7$ expression, transient sodium currents and action potential firing frequency in small-diameter neurons (Chang et al., 2018).

Thus, the blockage of Na_v channels, particularly the $Na_v1.7$ subtype, may have a positive impact in the treatment of taxane-induced peripheral neuropathy. In fact, intraganglionic or intrathecal injection of anti-$Na_v1.7$ antibodies reversed and prevented paclitaxel-induced mechanical allodynia in rodents (Bang et al., 2018; Xia et al., 2016). Additionally, paclitaxel-induced peripheral neuropathy was attenuated by the selective $Na_v1.7$ and non-selective $Na_v1.7$–1.8 channel blockers **ProTx II** and ralfinamide, respectively (Li, North, et al., 2018; Liang, Yu, & Su, 2018).

Potassium channels

Voltage-gated (**Kv**) and ATP-sensitive (K_{ATP}) potassium channels were proposed to mediate the antinociceptive effects of different compounds in taxane-induced peripheral neuropathy. For instance, H_2S donors presented anti-allodynic activities in paclitaxel-induced cold hypersensitivity in mice, a response that was attenuated by the Kv7 channel blocker **XE991** (Di Cesare Mannelli et al., 2017). Additionally, the K_{ATP} channel inhibitor **glibenclamide** reversed the antinociceptive actions of different compounds in paclitaxel-induced peripheral neuropathy in mice (Braga et al., 2019; Brito et al., 2018). These findings suggest that activators of Kv and K_{ATP} channels might be effective alternatives to relief taxane-induced peripheral neuropathy.

Natural compounds

Natural compounds can be valuable adjuvant strategies for patients receiving chemotherapy, in order to minimize their cytotoxic effects. Most of the literature indicates that a series of animal- and plant-derived agents can lessen the development of taxane-induced peripheral neuropathy. This part of the article highlights the beneficial effects of natural compounds in painful symptoms secondary to taxane administration.

The product named cinobufacini, an aqueous extract derived from the skin and parotids of the toad *Bufo bufo gargarizans* Cantor, is used in traditional Chinese medicine as an anti-cancer and analgesic agent. Of note, a single parenteral administration of cinobufacini prevented the painful-like alterations in paclitaxel-treated rats, probably via modulation of spinal TRPV1 expression and astrocyte activation. This animal-derived compound also reduced IL-1β and TNF-α levels in the spinal cord of rats injected with paclitaxel, accounting for its analgesic effects (Ba et al., 2018). TsTxP, a non-toxic protein obtained from the South American scorpion *Tityus serrulatus*, also attenuated the mechanical and cold allodynia caused by paclitaxel in mice. These effects were noted when the compound was intrathecally administered and were related to the modulation of glutamate release in the spinal cord (Rigo et al., 2019). The spinal administration of either **ω-conotoxin MVIIA** (from the marine snail *Conus magus*) or Phα1β (derived from the Brazilian spider *Phoneutria nigriventer*) inhibited the acute and the chronic mechanical hypersensitivities secondary to paclitaxel in rats. Noteworthy, both animal-derived toxin fractions are inhibitors of calcium influx via N-type Ca_v channels (Rigo et al., 2013).

Plant-derived compounds also display favourable effects in taxane-induced neuropathy. For instance, the tetracyclic triterpene euphol, obtained from *Euphorbia tirucalli* L., widely prevented paclitaxel-induced peripheral neuropathy in mice, when given in either acute or chronic treatment schemes. Its analgesic actions primarily involved the inhibition of PKCε activation, with a sequential modulation of NF-κB and cAMP response element-binding (**CREB**) protein, thus preventing the up-regulation of **COX-2** (Dutra et al., 2015). The alkaloid verticinone, obtained from the bulbs of the Chinese plant *Bulbus fritillaria*, was able to prevent neuropathy in paclitaxel-treated rats. Despite some sedative effects, verticinone did not elicit tolerance, presenting advantage in comparison with opioid analgesics such as **morphine** (Xu et al., 2011). A study investigating a library of plant-

TABLE 2 Clinical trials for taxane neurotoxicity around the world

Study	Taxane	Trial # or reference	Country	Subjects	Start (year)	Status	Remarks
Antidepressants							
Duloxetin	PTX/DTX	NCT00489411	USA	231	2008	Completed	Phase III—pain reduction
	PTX/DTX	NCT00489411	USA	106	2008	Completed	Phase III—pain reduction
Amitriptyline	PTX/DTX	Kautio et al., 2009	Finland	114	2003	Completed	Preventive protocol; use not supported
Topical amitriptyline/ketamine	Taxanes	NCT00471445	USA	462	2007	Completed	Use not supported
Anticonvulsant							
Gabapentin	PTX/DTX	NCT00027963	USA	100	2002	Completed	Phase III—use not supported
Pregabalin	PTX/DTX	NCT02394951	USA	26	2015	Completed	Results not mentioned
Lamotrigine	PTX/DTX	Rao et al., 2008	USA	131	2004	Completed	Use not supported
Chemoprotective agent							
Dimesna (BNP7787)	PTX	NCT00003569	USA	2	2003	Completed	Phase I—results not mentioned
	PTX	NCT00039780	USA	764	2001	Completed	Phase III—results not mentioned
Amifostine trihydrate	PTX	NCT00003072	USA	80	2004	Completed	Phase II—results not mentioned
Amifostine	PTX	NCT00078845	USA	24	2004	Completed	Phase II—results not mentioned
Olesoxime (TRO19622)	PTX/DTX	NCT00876538	France	17	2009	Completed	Phase II—results not mentioned
Antioxidant agent							
GSH	PTX	NCT02311907	USA	195	2014	Completed	Phase III—results not mentioned
Antibiotic							
Minocycline hydrochloride	PTX	NCT02297412	USA	47	2014	Completed	Phase II—results not mentioned
Nutraceutic							
Nicotinamide riboside	PTX	NCT03642990	USA	39	2018	Recruiting	Phase II
Vitamins B6 and B12	PTX/DTX	NCT00659269	USA	319	2008	Completed	Phase III—results not mentioned
Calcium gluconate and magnesium sulfate	PTX	NCT01682499	USA	50	2012	Completed	Phase I—results not mentioned
L-Carnitine L-Tartrate	PTX/DTX	NCT00754767	USA	2	2007	Terminated	Phase IV—insufficient participants
Acetyl-L-carnitine hydrochloride	PTX/DTX	NCT00775645	USA	437	2008	Completed	Phase III—unsupported use
	PTX/DTX	NCT01526564	China	239	2012	Completed	Phase III—results not mentioned
Omega-3/Vitamin D3	PTX/DTX	NCT02294149	Canada	600	2014	Unknown	Phase III
Vitamin E	PTX/DTX	NCT00363129	USA	207	2006	Completed	Phase III—use not supported
TRP agonist							
Menthol	PTX/DTX	NCT01855607	USA	60	2013	Unknown	Phase II
Cannabinoid agonist							
Cannabinoids	PTX/DTX	NCT03782402	USA	100	2019	Recruiting	Phase II
Nabiximol	PTX	NCT00872144	Canada	16	2009	Completed	Phase III—reduced pain
Toxin							

TABLE 2 (Continued)

Study	Taxane	Trial # or reference	Country	Subjects	Start (year)	Status	Remarks
IncobotulinumtoxinA (Xeomin®, Merz)	PTX/DTX	NCT03571334	USA	40	2018	Not yet recruiting	Phase II
Tetrodotoxin	PTX/DTX	NCT01655823	USA	125	2012	Terminated	Phase II—preceded to phase III trial
Association							
Memantine XR–pregabalin combination	PTX/DTX	NCT03272919	USA	20	2017	Recruiting	Observational study
Baclofen-amitriptyline hydrochloride-ketamine gel (BAK)	PTX/DTX	NCT00516503	USA	208	2007	Completed	Phase III—reduced pain
Other							
Monosialoganglioside	PTX	NCT02500810	China	106	2015	Recruiting	Phase II
Ganglioside-monosialic acid	PTX/DTX	NCT02468739	China	206	2015	Completed	Phase III—results not mentioned
Nano formulation							
Nab-PTX	PTX	NCT01763710	Spain	60	2012	Completed	Phase II—results not mentioned

[a]Source: PubMed and www.clinicaltrial.org, accessed on November 22, 2019.
Abbreviations: DTX, docetaxel; PTX, paclitaxel.

derived compounds identified the pentacyclic triterpenoid **betulinic acid** from the native North American lavender *Hyptis emoryi*, as a potential strategy to treat the neuropathic pain induced by taxanes. *In vivo*, betulinic acid inhibited the mechanical allodynia caused by paclitaxel in rats, lacking opioid-like effects. Thus, betulinic acid may represent a promising alternative to treat taxane-related peripheral neuropathy, without causing tolerance (Bellampalli et al., 2019). In a continuous effort to identify new analgesic drugs lacking abuse potential, Shan et al. (2019) demonstrated that the small molecule physalin F, isolated from *Physalis acutifolia*, prevents paclitaxel-induced tactile allodynia in rats when dosed intrathecally. The same study indicated that physalin F promotes analgesia by blocking R- and N-type Ca_v channels and excitatory postsynaptic currents, without any interaction with opioid receptors (Shan et al., 2019). Evodiamine, isolated from the Chinese plant *Evodia rutaecarpa*, improved the anticancer effects of paclitaxel and prevented paclitaxel-induced peripheral neuropathy in rats by reducing IL-1β, IL-6, TNF-α and CCL2 levels in the DRG (Wu & Chen, 2019).

3.3 | Clinical studies on taxane-induced peripheral neuropathy

Clinical strategies to minimize or prevent taxane neurotoxicity are limited. According to the American Society of Cancer and American Society of Clinical Oncology recommendations, the only Food and Drug Administration (FDA)-approved drug for the treatment of chemotherapy-induced peripheral neuropathy is duloxetine. Drugs usually effective for neuropathic pain of other aetiologies have failed to reduce or prevent chemotherapy-induced peripheral neuropathy and taxane-induced peripheral neuropathy, including gabapentin, pregabalin and **amitriptyline** (Quintao et al., 2019).

Ongoing clinical trials have investigated novel pharmacological strategies to prevent or treat taxane-induced peripheral neuropathy (Table 2). These include nutraceuticals and chemoprotective agents with antioxidant activity. Also, modulators of TRP channels, cannabinoid agonists, gangliosides, toxins and new taxane formulations (e.g. nab-paclitaxel) are being evaluated in an attempt to increase the number of effective therapies to deal with taxane neurotoxicity (Table 2). Unfortunately, most of the clinical trials, even when completed, do not publish their results limiting the general access to promising therapeutic tools.

4 | TAXANE-INDUCED CENTRAL NEUROTOXICITY

In addition to taxane-induced peripheral neuropathy, taxanes can also induce short- and long-term toxic effects in the CNS. Acute encephalopathy (Ziske et al., 2002), emotional distress and ataxia (Thornton et al., 2008) have been described in patients who have undergone paclitaxel therapy, despite its poor blood brain barrier penetration (Fellner et al., 2002). Importantly, a large proportion of patients display cognitive deficits after 1 year of treatment (Lange et al., 2016; Wefel et al., 2010).

Acute and persistent cognitive dysfunctions were reported for paclitaxel (Mandilaras et al., 2013; Tchen et al., 2003) and docetaxel (Aotani et al., 2016; Lange et al., 2016). Noteworthy, short- and long-term memory impairments were reported in rats (Callaghan & O'Mara, 2015) and mice treated with docetaxel (Fardell et al., 2014;

Seigers et al., 2015). Additionally, depressive- and anxiety-like behaviours were observed in some studies using rodent models (Callaghan & O'Mara, 2015; Toma et al., 2017), whilst others found no relevant alterations of affective behaviours in paclitaxel-treated mice (Huehnchen, Boehmerle, Springer, Freyer, & Endres, 2017).

4.1 | Risk factors and pathophysiology of taxane-induced central neurotoxicity

4.1.1 | Risk factors

Aging is not only an important risk factor for cancer, but it is also a major predisposing factor to cognitive decline. Age-related cognitive decline is associated with increased neuroinflammation, impaired synaptic plasticity and reduced neurogenesis (Elmore et al., 2018); these factors may contribute to an enhanced susceptibility to the neurotoxic effects of chemotherapy. Indeed, elderly patients are more prone to cognitive decline when submitted to combined chemotherapy regimens that include docetaxel (Lange et al., 2016). Similar findings were observed in a cohort of older breast cancer patients receiving paclitaxel (Hurria et al., 2006). However, further prospective studies are needed to provide additional understanding of the impact of aging on the susceptibility to taxane-induced central neurotoxicity. Nevertheless, factors other than aging are potential contributors. Depression, anxiety and stress are commonly associated to cancer and these factors, as well as the cancer itself, might influence cognition (Ahles & Saykin, 2007).

Taxane-induced central neurotoxicity susceptibility is also related to variability in genes that regulate neuronal repair, plasticity and neurotransmission. Apolipoprotein E (APOE) effects are genotype dependent and have been implicated in neuroinflammation, synaptic integrity and plasticity, with ApoEε4 allele being the strongest genetic risk factor for Alzheimer's disease (Yamazaki, Zhao, Caulfield, Liu, & Bu, 2019). In accordance, ApoEε4 allele carriers with lymphoma or breast cancer, undergoing chemotherapy, present increased processing speed, visual memory and spatial ability impairments in comparison with non-carriers (Ahles et al., 2014). Similar findings were reported prostate cancer patients (Amidi et al., 2017). This evidence indicates that the development of taxane-induced central neurotoxicity may be affected by individual factors including age, mental disorders and genetic factors, in addition to the chemotherapy dosage adopted. In fact, high doses of chemotherapy favour the development of cognitive impairments (Collins, MacKenzie, Tasca, Scherling, & Smith, 2013).

4.1.2 | Mechanisms of neuronal dysfunction

Although taxane-induced central neurotoxicity is described from a clinical perspective, its underlying mechanisms are poorly understood (Figure 2). The first generation taxanes have limited ability to cross the blood brain barrier (Kemper, Boogerd, Thuis, Beijnen, & van Tellingen, 2004). However, studies using radiolabelled taxanes demonstrated that small amounts of these drugs are capable of entering the brain (Gangloff et al., 2005; van der Veldt et al., 2010). Regional differences in the brain distribution of paclitaxel were found in mice, with the highest levels of the compound detected in the hippocampus (Huehnchen et al., 2017). These data suggest that the hippocampus, a brain region crucial for cognition, may be particularly susceptible to paclitaxel-induced neurotoxicity. Of interest, cabazitaxel can also cross the blood brain barrier and penetrate the brain, causing dose-dependent neurotoxicity and apoptosis in rat neurons (Karavelioglu et al., 2016).

Microtubule dynamicity, neuronal apoptosis and neurogenesis

Taxanes negatively affect microtubule dynamics. As microtubule dynamicity is known to directly affect synaptic plasticity and memory formation, its reduction in neuronal cells may contribute to paclitaxel-induced cognitive impairments (Atarod et al., 2015; You et al., 2018). Neuronal apoptosis following paclitaxel involves a distinct mechanism from that of non-neuronal cells (Figueroa-Masot, Hetman, Higgins, Kokot, & Xia, 2001), including endoplasmic reticulum stress responses (Tanimukai, Kanayama, Omi, Takeda, & Kudo, 2013). Furthermore, neuronal progenitor cells are more vulnerable to paclitaxel-induced toxicity compared with mature post-mitotic hippocampal neurons and malignant cells (Huehnchen et al., 2017). Visuo-spatial memory impairments were seen in paclitaxel-treated mice, which correlated with decreased hippocampal cell proliferation. Similar findings were described in rats, with decreased hippocampal neurogenesis associated with impaired reversal learning (Panoz-Brown et al., 2017). Interestingly, the decrease in hippocampal neuronal cell proliferation caused by paclitaxel in mice was found to be similar to that observed for cyclophosphamide and fluorouracil, two chemotherapeutic agents that readily cross the blood brain barrier (Janelsins et al., 2010), reinforcing the hypothesis that small amounts of paclitaxel may reach the CNS, impairing cognition.

Neuroinflammation

Due to the limited CNS penetration of paclitaxel, its central neurotoxic effect is proposed to be mediated by indirect mechanisms, including neuroinflammation. Clinical studies have demonstrated increased circulating levels of **IL-6**, **IL-8**, GM-CSF and **IFN-γ** in patients treated with paclitaxel and docetaxel (Pusztai et al., 2004; Tsavaris, Kosmas, Vadiaka, Kanelopoulos, & Boulamatsis, 2002). Of note, peripheral circulating cytokines can cross the blood brain barrier, potentiating chemotherapeutic drugs to trigger microglial release of pro-inflammatory cytokines (Wang et al., 2015). Increased IL-1β and IL-6 levels are associated with impaired induction and maintenance of hippocampal LTP, and therefore, memory (Murray & Lynch, 1998; Tancredi et al., 2000). Accordingly, overexpression of pro-inflammatory cytokines in mice resulted in learning and memory disturbances (Fiore et al., 1996; Hein et al., 2010). Additionally, TNF-α activates NF-κB signalling pathways in the brain, triggering neuroinflammation and apoptosis (Li et al., 2017).

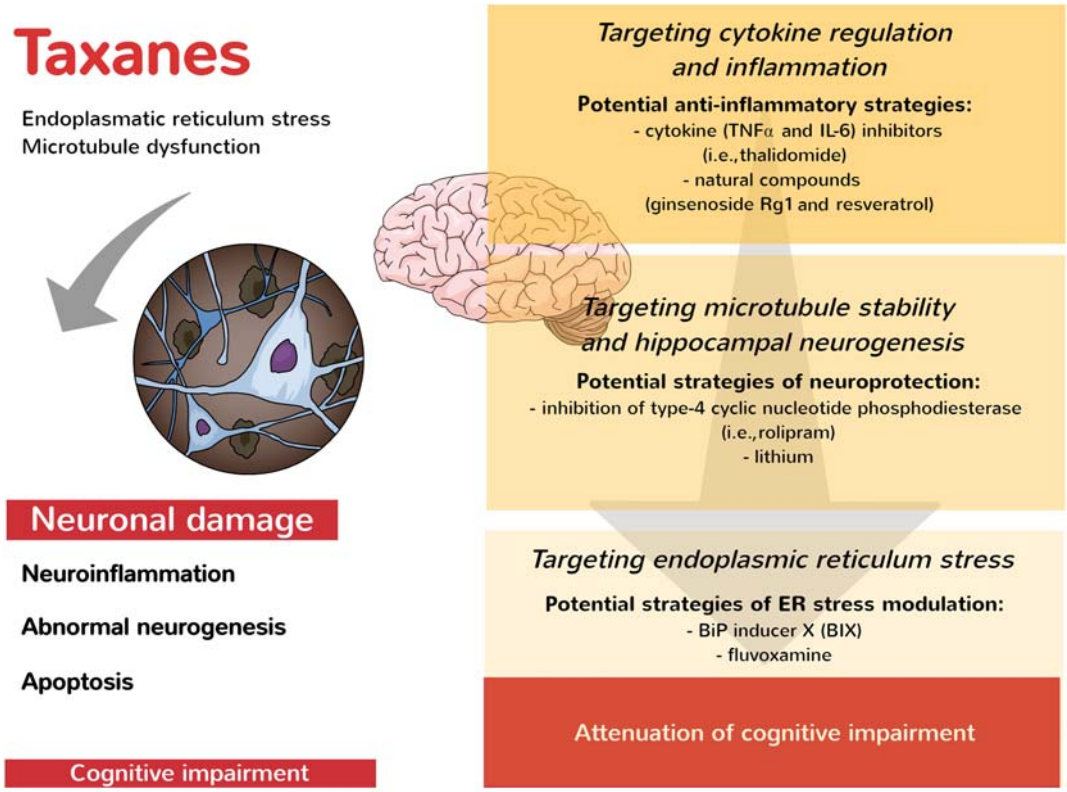

FIGURE 2 Taxane-induced central neurotoxicity (TICN)—pathophysiology and potential therapeutic strategies. Neuronal damage caused by taxanes is induced by two main mechanisms: alteration of microtubule dynamics and endoplasmic reticulum stress. Neuronal damage is accompanied by neuroinflammation, impaired neurogenesis and apoptosis resulting in cognitive impairment. Putative therapeutic strategies to treat TICN include targeting of cytokine regulation and inflammation, microtubule stability and hippocampal neurogenesis, or targeting of endoplasmic reticulum stress

Therefore, hippocampal cell apoptosis and the resulting learning and memory impairments in paclitaxel-treated rats likely depend on TNF-α synthesis (Li et al., 2018).

Endoplasmic reticulum stress

Endoplasmic reticulum stress pathways are involved in taxane-induced apoptosis (Liao, Tan, Lieu, & Jung, 2008; Mhaidat, Thorne, Zhang, & Hersey, 2008). Importantly, Tanimukai et al. (2013) suggested that neuronal cells are more vulnerable to paclitaxel-induced endoplasmic reticulum stress than other cell types and that this response contributes to paclitaxel-induced neurotoxicity (Tanimukai et al., 2013).

4.2 | Therapeutic perspectives for taxane-induced central neurotoxicity

As no therapy regimen for taxane-induced central neurotoxicity has been established, and preclinical data on potential therapies are still scarce, the identification of novel therapeutic strategies is an urgent need. Thus, the importance of potential targets for treating taxane-induced central neurotoxicity will be now discussed.

4.2.1 | Targeting cytokine regulation and inflammation

Despite the evidence correlating the up-regulation of pro-inflammatory cytokines with the development of chemotherapy-related cognitive impairment, only few studies evaluated the effects of cytokine inhibitors in preventing and/or treating this condition. Recently, the oral co-administration of the TNF-α inhibitor **thalidomide** with paclitaxel to rats hindered chemotherapy-induced cell apoptosis in the hippocampus and restored learning and memory impairments (Li, Zhao, et al., 2018). Thalidomide readily crosses the blood brain barrier and blocks TNF-α expression by different mechanisms, including down-regulation of NF-κB and increased TNF-α mRNA degradation (Majumder, Sreedhara, Banerjee, & Chatterjee, 2012). These data reinforce the hypothesis that TNF-α is critically involved in taxane-induced central neurotoxicity and suggest that anti-TNF-α therapies are candidates for its management.

Another study indicating inflammation as a target for the development of taxane-induced central neurotoxicity therapies was recently published (Shi et al., 2019). The authors demonstrated that ginsenoside Rg1, a natural compound derived from ginseng, significantly inhibits chemobrain-like behaviour induced by a combination of

docetaxel, adriamycin (doxorubicin) and cyclophosphamide in mice (Mohanan, Subramaniyam, Mathiyalagan, & Yang, 2018). Its effects in cognition were associated with reduced expression of TNF-α and IL-6 and increased expression of neuroplasticity markers (Shi et al., 2019). A similar effect was observed for the polyphenol resveratrol, indicating the importance of plant-derived compounds as immunomodulatory and neuroprotective agents (Shi et al., 2018).

4.2.2 | Targeting endoplasmic reticulum stress

The recent knowledge of a role for endoplasmic reticulum stress in cerebral dysfunction prompted the search for molecules capable of modulating this pathway. BIX, an inducer of endoplasmic reticulum chaperone immunoglobulin heavy-chain binding protein, protected neurons from endoplasmic reticulum stress (Kudo et al., 2008). Treatment with BIX was effective against paclitaxel-induced neuronal apoptosis *in vitro* (Tanimukai et al., 2013). Interestingly, the antidepressant fluvoxamine diminished the neurotoxicity caused by paclitaxel in human neuroblastoma cell line (SK-N-SH) through endoplasmic reticulum stress modulation (Tanimukai & Kudo, 2015). However, *in vivo* studies are needed to evaluate the effects of endoplasmic reticulum stress modulators in taxane-induced central neurotoxicity.

4.2.3 | Targeting microtubule stability and hippocampal neurogenesis

Microtubule dynamicity, an important player in synaptic plasticity, is dependent on the cAMP signalling cascade and was proposed as a target for the treatment of cognitive and mood disorders (Bianchi, Hagan, & Heidbreder, 2005). Rolipram, an inducer of cAMP through inhibition of type-4 cyclic nucleotide PDE, impacts neuroplasticity, improves cognition and produces anxiolytic- and antidepressant-like behaviours in animals with cerebral ischaemia and Alzheimer's disease (Soares et al., 2016). Its chronic administration attenuated long-term docetaxel-induced spatial memory impairment and depressive-like behaviours in rats (Callaghan & O'Mara, 2015). Mechanisms other than microtubule stability may account for these effects, including increased CREB activation and hippocampal neurogenesis (Sasaki et al., 2007).

Another pharmacological strategy capable of preventing cognitive impairment and abnormal adult hippocampal neurogenesis in paclitaxel-treated mice is the administration of lithium. *In vitro* data suggest that the neuroprotective effect of lithium is mediated by the inhibition of calcium-dependent apoptosis of neural stem cells (Huehnchen et al., 2017). Additionally, lithium presents anti-inflammatory actions, inhibiting microglia activation and reducing the production of cytokines (Khan et al., 2017); these actions can also contribute to lithium-conferred protection in taxane-induced central neurotoxicity.

5 | CONCLUSIONS

Peripheral and central neurotoxicity induced by taxanes has huge effects on treatment and post-treatment outcomes of cancer patients. During the last years, *in vitro* and *in vivo* studies permitted to gain insights into the mechanisms underlying the neurotoxic effects of taxanes (Figures 1 and 2). Additionally, validated animal models of taxane-induced neurotoxicity allowed the identification of potential alternatives for restoring the neural injuries evoked by taxanes. In spite of that, the level of translation of this knowledge to clinics is still very modest, especially when considering the central effects. Indeed, the current therapeutic options rely on the prescription of unspecific drugs originally developed to treat distinct neurological diseases. As a result, the life quality of the individuals during or after taxane-based chemotherapy is widely compromised, with great social and economic impacts. Considering the rapid aging of the population and the increasing numbers of cancer diagnosis, the approval of innovative options to manage taxane-related neurotoxicity is an urgent need, what requires efforts of researchers in both basic and clinical pharmacology.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander, Christopoulos et al., 2019; Alexander, Mathie et al., 2019).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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