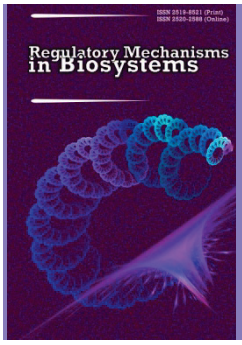

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Paclitaxel-induced neuropathy induces changes in oral cavity organs of rats

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The developmental mechanisms of pathological changes in the oral cavity organs, in particular, periodontal tissues and salivary glands, were elucidated in the model of paclitaxel-induced neuropathy. Experimental studies were performed on 41 white nonlinear rats of both sexes weighing 180–220 g. Toxic neuropathy was modeled by intraperitoneal injection of paclitaxel (Actavis Ltd; series 5GN5122) 2 mg/kg for 4 days (0, 2, 4 and 6). The presence of paclitaxel-induced peripheral neuropathy was confirmed by the Randall-Selitto tensoalgometric test to determine the threshold of pain sensitivity. The total proteolytic activity, total antitryptic activity, and the content of TBA-active products were determined in the homogenate of the rat submandibular and sublingual salivary glands and periodontal soft tissues, content of oxidatively modified proteins, content of average mass molecules and catalase activity; α-amylase activity was also determined in the salivary glands of animals, and the content of free fucose and glycosaminoglycans in periodontal tissues. Paclitaxel-induced neuropathy causes the development of pathological changes in the oral cavity, in particular in periodontal tissues and salivary glands of rats, as evidenced by impaired proteinase-inhibitory potential, intensification of carbonyl oxidative stress, inhibition of protein synthetic function in salivary glands and increased depolymerization of non-collagenous proteins in periodontal soft tissues.

Keywords: neuropathy; paclitaxel; neurotoxicity; periodontium; salivary glands.

Introduction

Chemotherapy-induced peripheral neurotoxicity is one of the most frequent and long-term side effects of cancer chemotherapy (Cavaletti et al., 2014; Gordon-Williams & Farquhar-Smith, 2020), leading to the development of peripheral neuropathy. Peripheral neuropathy is a negative consequence caused by several classes of commonly used anticancer therapeutic agents that leads to dose reduction or discontinuation of chemotherapy regimens, and its symptoms can persist long after the end of chemotherapy and significantly reduce the quality of life of patients. The differences in the clinical presentation of chemotherapy-induced peripheral neurotoxicity across a wide variety of classifications of anticancer drugs have given rise to numerous hypotheses that seek to explain its pathogenesis (Flatters et al., 2017; Fukuda & Segal, 2017). Despite its relevance, widespread occurrence, and extensive research, the pathophysiology of chemotherapy-induced peripheral neuropathy remains unclear. In addition, there is no unequivocal gold standard for the prevention and treatment of chemotherapy-induced peripheral neurotoxicity. In order to identify potential targets and approaches for prevention and treatment, it is crucial to clarify the underlying mechanisms of chemotherapy-induced peripheral neurotoxicity (Flatters et al., 2017), in particular in the oral cavity. There is no consensus on the molecular mechanisms that contribute to the development of chemotherapy-induced peripheral neurotoxicity.

Paclitaxel is a chemotherapeutic agent widely used for the treatment of breast, ovarian, small cell and non-small cell lung, stomach, esophageal, bladder, head and neck, pancreatic, Kaposi's sarcoma, and melanoma cancers (Duggett et al., 2017). The widespread clinical use of paclitaxel is hampered by the development of peripheral neuropathy, which remains the main side effect that limits its use (Eldridge et al., 2019), in particular, patients report numbness, tingling, spontaneous pain and pain caused by mechanical and cold stimuli in the hands and feet, facial lesions (Dougherty et al., 2004; Boyette-Davis et al., 2012; Pachman et al., 2016). A meta-analysis (Hershman et al., 2014) showed that paclitaxel-induced peripheral neuropathy affects 44% to 98% of patients and can contribute to the disabling pain syndrome resulting from cancer chemotherapy. In addition, neuropathy can persist for several months or years after the end of paclitaxel chemotherapy (van den Bent et al., 1997; Seretny et al., 2014). Thus, paclitaxel treatment is an important cause of sensory impairment and chronic pain, significantly affecting the quality of life of cancer patients (Tofthagen et al., 2013).

Paclitaxel is known to interact with β-tubulin of microtubules in the cell cytoskeleton, inhibiting dynamic polymerization and depolymerization, which leads to their stabilization and cell cycle arrest and death. Stabilization of microtubules is the main mechanism of action of taxanes and is responsible for their antitumour activity (Gornstein & Schwarz, 2017). Although it has been proposed that this mechanism causes neurotoxicity through impaired axonal transport, a growing body of evidence suggests a number of additional mechanisms, including impaired neuronal and glial cell metabolism, mitochondrial dysfunction, oxidative stress, and neuroinflammation, underlie the development of paclitaxel-induced neuropathy (Chua et al., 2021).

The aim of the study was to investigate the effect of paclitaxel-induced peripheral neuropathy on the development of pathological changes in the organs and tissues of the oral cavity of animals.

Materials and methods

Experimental studies were performed on 41 white nonlinear rats of both sexes weighing 180–220 g. The research was conducted at the scientific laboratory of the Department of Bioorganic and Biological Chemistry

of PSMU and the research laboratory of the Institute of Biology and Medicine of Taras Shevchenko National University of Kyiv. The experiments were conducted in accordance with the standards of the 1997 Council of Europe Convention on Bioethics, the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, and the general ethical principles of animal experimentation approved by the First National Congress of Ukraine on Bioethics. Toxic neuropathy was modeled by intraperitoneal injection of paclitaxel (Actavis Ltd; 5GN5122 series) 2 mg/kg for 4 days (0, 2, 4 and 6) (Pachman et al., 2016). The presence of paclitaxel-induced peripheral neuropathy was confirmed by the Randall-Selitto method (Randall & Selitto, 1957; Santos-Nogueira et al., 2012) by examining the pain sensitivity threshold (PST), the average value of which, determined before the start of neuropathy modeling, was taken as 100%. The PST in experimental animals was measured before paclitaxel administration (day zero), on days 16 and 25 after the first injection of the drug. Throughout the experiment, the animals were kept on a standard vivarium diet. The objects of the study were the submandibular, sublingual salivary glands of rats and periodontal soft tissues, in the homogenate of which the total proteolytic activity (Ugolev, 1969) and total antitryptic activity (Veremeenko, 1988) were determined. The pro- and antioxidant balance of the studied tissues and organs was assessed by determining the content of TBA-active products (Stalnaya, 1977), the content of oxidatively modified proteins (Dubinina et al., 1995), the content of medium molecular weight molecules (Kaidashev, 2003) and catalase activity (Korolyuk et al., 1988). The activity of α-amylase was determined in the salivary glands of animals (Caraway, 1959), and the content of free fucose (Sharaev et al., 1997) and glycosaminoglycans (Sharaev et al., 1987) in periodontal soft tissues. The animals were withdrawn from the experiment by bleeding under thiopental anesthesia. The obtained results of the experimental studies were analyzed using the methods of variation statistics. To test the distribution for normality, the Shapiro-Wilk test was used. If the data corresponded to a normal distribution, the reliability of their difference when comparing arithmetic means was determined using Student's t-test for independent samples; reliable data were considered to be those corresponding to $P < 0.05$. In the case when the data series were not subject to normal distribution, statistical processing was performed using the nonparametric method – the Mann-Whitney test.

Results

We found that in experimental animals on day 16 after paclitaxel injection, the PST increased by 39.0% ($P < 0.01$) compared with the initial value; on day 25 after the first paclitaxel injection, the PST increased by 69.1% ($P < 0.001$) compared with day zero (Fig. 1). Thus, the results confirm the literature data that paclitaxel causes toxic polyneuropathy, in which the speed of impulses along the nerve fiber decreases.

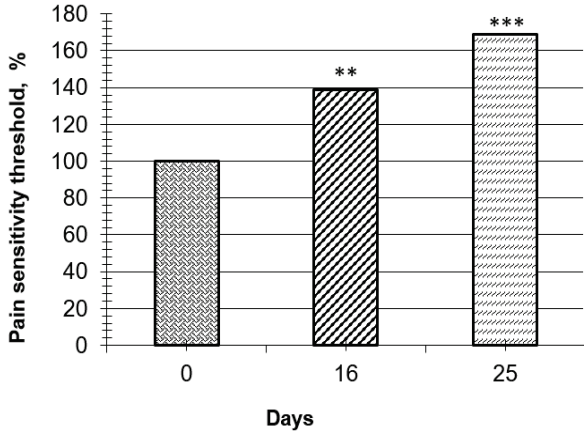

Fig. 1. Pain sensitivity threshold of (%) measured by the Randall-Selitto test in rats with paclitaxel modeling of toxic neuropathy: ** – $P < 0.01$, *** – $P < 0.001$ compared to day 0 (before paclitaxel administration)

In the conditions of paclitaxel-induced neuropathy, we found an imbalance of proteinase-inhibitory potential in periodontal tissues and salivary glands of rats, as evidenced by a decrease in total proteolytic activity against the background of a probable increase in proteinase inhibitors (Tables 1 and 2).

Table 1
Changes in biochemical parameters of salivary glands of rats after administration of 2 mg/kg paclitaxel for 4 days (0, 2, 4 and 6) and development of toxic neuropathy

Biochemical parameters	Control (n = 10)	Paclitaxel-induced neuropathy (n = 21)
Total proteolytic activity, μg/g-min	3.33 ± 0.06	2.79 ± 0.19
Total antitryptic activity, g/kg	32.64 ± 1.74	55.94 ± 6.53*
α-amylase activity, mg/sL	38.8 ± 4.67	23.75 ± 1.61*
Content of TBA-reactants, μmol/g	4.25 ± 0.72	9.62 ± 1.14*
Content of molecules of average mass, units	0.294±0.001	0.414 ± 0.002*
Content of oxidatively modified proteins, unit	0.34 ± 0.002	0.46 ± 0.003*
Catalase activity, μcat/g-min	0.74 ± 0.003	0.35 ± 0.005*

Note: * – $P < 0.05$ compared with animals of the control group.

Under the conditions of paclitaxel-induced neuropathy modeling, the activity of α-amylase in the salivary glands of rats significantly decreased by 1.60 times compared with control animals (Table 1), indicating inhibition of protein synthetic activity of the salivary glands.

Analyzing the development of carbonyl-oxidative stress in the salivary glands of rats under these conditions, we found a 1.40-times increase in the content of oxidatively modified proteins, 1.41-times increase in the content of medium-molecular weight molecules, and 2.32-times increase in the content of TBA-reactive substances compared to these indicators in control animals (Table 1). The activity of catalase in the submandibular and hyoid salivary glands of rats under conditions of toxic neuropathy was significantly reduced by 2.11 times compared to the control (Table 1). The content of oxidatively modified proteins in the soft tissues of the rat periodontium increased by 1.40 times and the content of TBA-reactants by 1.33 times compared with these values in the control group. The activity of catalase in periodontal tissues of animals modeled with toxic neuropathy significantly increased compared to the control (Table 2).

Thus, the modeling of paclitaxel-induced neuropathy is accompanied by the development of carbonyl-oxidative stress in the salivary glands and periodontal tissues of rats.

Table 2
Changes in biochemical parameters of periodontal soft tissues of rats after administration of 2 mg/kg paclitaxel for 4 days (0, 2, 4 and 6) and development of toxic neuropathy

Biochemical parameters	Control (n = 10)	Paclitaxel-induced neuropathy (n = 21)
Total proteolytic activity, μg/g-min	3.45 ± 0.04	3.16 ± 0.06*
Total antitryptic activity, g/kg	33.19 ± 1.65	41.65 ± 1.07*
Content of TBA-reactants, μmol/g	2.38 ± 0.11	3.17 ± 0.18*
The content of molecules of average mass, units	0.29 ± 0.01	0.33 ± 0.02*
The content of oxidatively modified proteins, units	1.35 ± 0.09	1.89 ± 0.03*
Catalase activity, μcat/g-min	0.27 ± 0.04	0.38 ± 0.03*
Glycosaminoglycans content, μmol/g	0.61 ± 0.005	2.32 ± 0.067*
Fucose content, μmol/g	7.93 ± 0.19	10.61 ± 0.38*

Note: see Table 1.

Analyzing the non-collagenous proteins of the extracellular matrix of the periodontal connective tissue of animals with toxic neuropathy, we found a significant increase in the content of glycosaminoglycans by 3.81 times and in the content of free fucose by 1.32 times compared with these indicators in control rats (Table 2).

Discussion

Paclitaxel-induced neuropathy promotes the development of carbonyl-oxidative stress in the salivary glands and periodontal tissues of rats. Stabilization of microtubules has been proposed as a potential cause of axonal degeneration, but most studies suggest other mechanisms involved in the development of paclitaxel neurotoxicity. *In vitro* and *in vivo* observations indicate the development of mitochondrial dysfunction, which re-

sults in the development of oxidative stress, which also contributes to nerve damage and is the main cause of axonal degeneration due to the formation of reactive oxygen species. Numerous experimental studies have shown that chemotherapy causes oxidative stress in patients (Gordon-Williams & Farquhar-Smith, 2020), treatment of rat dorsal root ganglia neural stem cells with taxane increased ROS production and oxidative stress, while reducing mitochondrial metabolic activity, membrane potential and antioxidant bioavailability (McCormick et al., 2016; Shim et al., 2019). Duggett et al. (2016) and Duggett et al. (2017) substantiated the development of mitochondrial dysfunction and paclitaxel-induced increased production of reactive oxygen species and nitrogen, which, in their opinion, are important factors in neuropathic pain and neurotoxicity.

Oxidative stress-mediated neurodegeneration can occur through hypoergosis, depletion of antioxidant defenses, stabilization of cytoskeletal microtubules, ion channel activation, demyelination, neuroinflammation, and neuronal apoptosis (Areti et al., 2014; Staff et al., 2020; Klein & Lehmann, 2021).

In the context of paclitaxel-induced neuropathy, we found an imbalance of proteinase-inhibitory potential in rat periodontal tissues and salivary glands, as evidenced by a decrease in total proteolytic activity against the background of a probable increase in proteinase inhibitors. Lisse et al. (2016) proved that MMP-13 mediates axonal degeneration in the experiment, as its activity increases during paclitaxel administration, and its selective inhibition prevents axonal degeneration. Pharmacological inhibition of MMP-13 by intraperitoneal injection or topical application to the paw pad of rats prevented paclitaxel-induced neuropathy based on mechanical and cold hypersensitivity studies (Lisse et al., 2016). MMP-13 is a major inducer of axonal degeneration (Cirrincione et al., 2020).

By studying informative biochemical markers of the integrity of fucoproteins and proteoglycans of the extracellular matrix of periodontal connective tissue in rats modeling paclitaxel-induced neuropathy, we found a significant increase in the content of free fucose and glycosaminoglycans compared to these indicators in the control. Thus, under the conditions of toxic neuropathy, there is an increased catabolism of polymers of the periodontal connective tissue of rats. In our opinion, the increased degradation of non-collagenous proteins of periodontal tissues under conditions of paclitaxel-induced neuropathy is caused by oxidative stress and inflammation. The results of studies by Al-Mazidi et al. (2017) indicate that cytokines/chemokines, the level of which increased in blood plasma in paclitaxel-treated rats, are involved in the pathophysiology of neurotoxicity and the development of neuropathic pain. The authors argue that the release of cytokines, rather than nerve damage, may be the cause of neuropathy in this model. Nevertheless, their results suggest that strategies aimed specifically at inhibiting cytokines or using antagonists of their receptors may be effective in treating paclitaxel-induced neurotoxicity. Paclitaxel induces inflammation through the release of cytokines and chemokines, in particular interleukin-1β, interleukin-8 and tumour necrosis factor α (Ji et al., 2013) and infiltration by non-resident macrophages, and this inflammatory response leads to neuropathic pain (Zhang et al., 2016). The same applies to interleukin-8 and its receptors, the inhibition of which reduces nociception, as well as mechanical and cold hypersensitivity caused by paclitaxel (Laura et al., 2017).

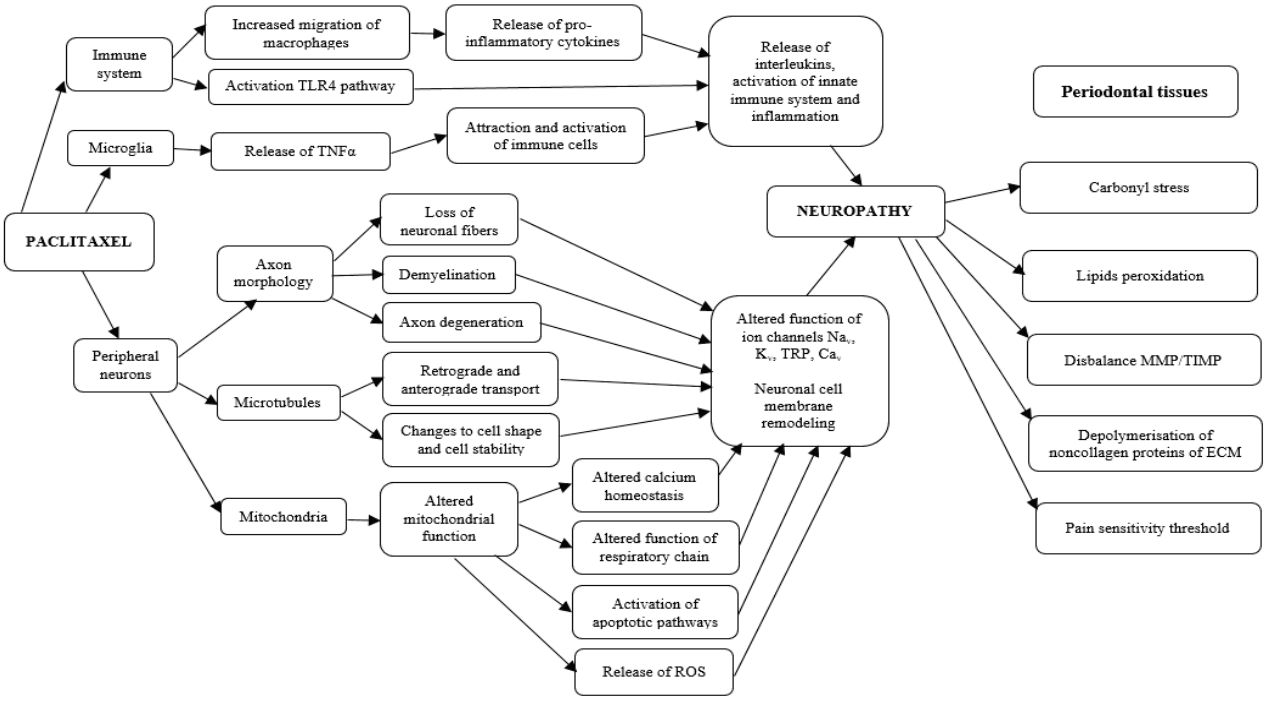

Fig. 2. Scheme of paclitaxel-induced neuropathy development, according to our own and literature sources

The pathophysiological processes caused by paclitaxel include inflammation, oxidative stress, loss of mainly epidermal nerve fibers, as well as changes in mitochondrial function and excitability of peripheral neurons. Paclitaxel has been shown to affect various cell types in the peripheral and central nervous system, including dorsal root ganglion neurons, Schwann cells, satellite glial cells, microglia, epidermis, and spinal astrocytes (Staff et al., 2020).

Conclusions

The administration of paclitaxel to rats promotes the development of neurotoxicity and peripheral neuropathy, as evidenced by a significant increase in the threshold of pain sensitivity. Paclitaxel-induced neuropathy causes the development of pathological changes in the organs of the oral cavity, in particular, in the periodontal tissues and salivary glands of rats, as evidenced by impaired proteinase-inhibitory potential, intensification of carbonyl-oxidative stress, inhibition of protein synthetic function in the salivary glands and increased depolymerization of non-collagenous proteins in the periodontal soft tissues.

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References

Al-Mazidi, S., Alotaibi, M., Nedjadi, T., Chaudhary, A., Alzoghaibi, M., & Djouhri, L. (2017). Blocking of cytokines signalling attenuates evoked and spontaneous neuropathic pain behaviours in the paclitaxel rat model of chemotherapy-induced neuropathy. European Journal of Pain, 22(4), 810–821.

Areti, A., Yerra, V. G., Naidu, V., & Kumar, A. (2014). Oxidative stress and nerve damage: Role in chemotherapy induced peripheral neuropathy. Redox Biology, 2, 289–295.

Boyette-Davis, J. A., Cata, J. P., Driver, L. C., Novy, D. M., Bruel, B. M., Mooring, D. L., Wendelschafer-Crabb, G., Kennedy, W. R., & Dougherty, P. M. (2012). Persistent chemoneuropathy in patients receiving the plant alkaloids paclitaxel and vincristine. Cancer Chemotherapy and Pharmacology, 71(3), 619–626.

Caraway, W. T. (1959). A stable starch substrate for the determination of amylase in serum and other body fluids. American Journal of Clinical Pathology, 32(1), 97–99.

Cavaletti, G. (2014). Chemotherapy-induced peripheral neurotoxicity (CIPN): What we need and what we know. Journal of the Peripheral Nervous System, 19(2), 66–76.

Chua, K. C., El-Haj, N., Priotti, J., & Kroetz, D. L. (2021). Mechanistic insights into the pathogenesis of microtubule-targeting agent-induced peripheral neuropathy from pharmacogenetic and functional studies. Basic and Clinical Pharmacology and Toxicology, 130(S1), 60–74.

Cirrincione, A. M., Pellegrini, A. D., Dominy, J. R., Benjamin, M. E., Utkina-Sosunova, I., Lotti, F., Jergova, S., Sagen, J., & Rieger, S. (2020). Paclitaxel-induced peripheral neuropathy is caused by epidermal ROS and mitochondrial damage through conserved MMP-13 activation. Scientific Reports, 10, 3970.

Dougherty, P. M., Cata, J. P., Cordella, J. V., Burton, A., & Weng, H.-R. (2004). Taxol-induced sensory disturbance is characterized by preferential impairment of myelinated fiber function in cancer patients. Pain, 109(1), 132–142.

Dubinina, E. E., Burmistrov, S. O., Khodov, D. A., & Porotov, I. G. (1995). Okislitel'naja modifikatsija belkov syvorotki krovi cheloveka, metod ee opredelenija [Oxidative modification of human serum proteins. A method of determining it]. Voprosy Meditsinskoj Khimii, 41(1), 24–26 (in Russian).

Duggett, N. A., Griffiths, L. A., & Flatters, S. J. L. (2017). Paclitaxel-induced painful neuropathy is associated with changes in mitochondrial bioenergetics, glycolysis, and an energy deficit in dorsal root ganglia neurons. Pain, 158(8), 1499–1508.

Duggett, N. A., Griffiths, L. A., McKenna, O. E., de Santis, V., Yongsanguanchai, N., Mokori, E. B., & Flatters, S. J. L. (2016). Oxidative stress in the development, maintenance and resolution of paclitaxel-induced painful neuropathy. Neuroscience, 333, 13–26.

Eldridge, S., Guo, L., & Hamre, J. (2019). A comparative review of chemotherapy-induced peripheral neuropathy in *in vivo* and *in vitro* models. Toxicologic Pathology, 48(1), 190–201.

Flatters, S. J. L., Dougherty, P. M., & Colvin, L. A. (2017). Clinical and preclinical perspectives on chemotherapy-induced peripheral neuropathy (CIPN): A narrative review. British Journal of Anaesthesia, 119(4), 737–749.

Fukuda, Y., Li, Y., & Segal, R. A. (2017). A mechanistic understanding of axon degeneration in chemotherapy-induced peripheral neuropathy. Frontiers in Neuroscience, 11, 481.

Gordon-Williams, R., & Farquhar-Smith, P. (2020). Recent advances in understanding chemotherapy-induced peripheral neuropathy. F1000Research, 9, 177.

Gornstein, E. L., & Schwarz, T. L. (2017). Neurotoxic mechanisms of paclitaxel are local to the distal axon and independent of transport defects. Experimental Neurology, 288, 153–166.

Hershman, D. L., Lacchetti, C., Dworkin, R. H., Lavoie Smith, E. M., Bleeker, J., Cavaletti, G., Chauhan, C., Gavin, P., Lavino, A., Lustberg, M. B., Paice, J., Schneider, B., Smith, M. L., Smith, T., Terstriep, S., Wagner-Johnston, N., Bak, K., & Loprinzi, C. L. (2014). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. Journal of Clinical Oncology, 32(18), 1941–1967.

Ji, R.-R., Berta, T., & Nedergaard, M. (2013). Glia and pain: Is chronic pain a gliopathy? Pain, 154, S10–S28.

Kaidashev, I. P., (2003). Metody klinichnykh ta eksperymentalnykh doslidzhen' v medytsyni [Methods of clinical and experimental research in medicine]. Polimet, Poltava (in Ukrainian).

Kapitein, L. C., & Hoogenraad, C. C. (2015). Building the neuronal microtubule cytoskeleton. Neuron, 87(3), 492–506.

Klein, I., & Lehmann, H. C. (2021). Pathomechanisms of paclitaxel-induced peripheral neuropathy. Toxics, 9(10), 229.

Koroliuk, M. A., Ivanova, L. I., Maĭorova, I. G., & Tokarev, V. E. (1988). Metod opredelenija aktivnosti katalazy [A method of determining catalase activity]. Laboratornoe Delo, 1, 16–19 (in Russian).

Brandolini, L., Benedetti, E., Ruffini, P. A., Russo, R., Cristiano, L., Antonosante, A., d'Angelo, M., Castelli, V., Giordano, A., Allegretti, M., & Cimini, A. C. (2017). CXCR1/2 pathways in paclitaxel-induced neuropathic pain. Oncotarget, 8(14), 23188–23201.

Lisse, T. S., Middleton, L. J., Pellegrini, A. D., Martin, P. B., Spaulding, E. L., Lopes, O., Brochu, E. A., Carter, E. V., Waldron, A., & Rieger, S. (2016). Paclitaxel-induced epithelial damage and ectopic MMP-13 expression promotes neurotoxicity in zebrafish. Proceedings of the National Academy of Sciences, 113(15), E2189–E2198.

McCormick, B., Lowes, D. A., Colvin, L., Torsney, C., & Galley, H. F. (2016). MitoVitE, a mitochondria-targeted antioxidant, limits paclitaxel-induced oxidative stress and mitochondrial damage *in vitro*, and paclitaxel-induced mechanical hypersensitivity in a rat pain model. British Journal of Anaesthesia, 117(5), 659–666.

Pachman, D. R., Qin, R., Seisler, D., Smith, E. M. L., Kaggal, S., Novotny, P., Ruddy, K. J., Lafky, J. M., Ta, L. E., Beutler, A. S., Wagner-Johnston, N. D., Staff, N. P., Grothey, A., Dougherty, P. M., Cavaletti, G., & Loprinzi, C. L. (2016). Comparison of oxaliplatin and paclitaxel-induced neuropathy (Alliance A151505). Supportive Care in Cancer, 24(12), 5059–5068.

Randall, L. O., & Selitto, J. J. (1957). A method for measurement of analgesic activity on inflammed tissue. Archives Internationales de Pharmacodynamie et de Therapie, 111, 409–419.

Santos-Nogueira, E., Redondo Castro, E., Mancuso, R., & Navarro, X. (2012). Randall-Selitto test: A new approach for the detection of neuropathic pain after spinal cord injury. Journal of Neurotrauma, 29(5), 898–904.

Seretny, M., Currie, G., Sena, E., Ramnarine, S., Grant, R., Macleod, M., Colvin, L., & Fallon, M. (2014). CN-16 incidence, prevalence and predictors of chemotherapy induced peripheral neuropathy: A systematic review and meta-analysis. Neuro-Oncology, 16(Suppl. 5), v49.

Sharaev, P. N., Pishkov, V. N., Soloveva, N. I., Shirokova, T. I., & Soloveva, T. V. (1987). Metod opredeleniia glikozaminoglikanov v biologicheskikh zhidkostiakh [Method of determining glycosaminoglycans in biological fluids]. Laboratornoe Delo, 5, 330–332.

Sharaev, P. N., Strelkov, R. R., & Kyldyiarova, A. A. (1997). Metod opredelenija fukozy, nesviazannoji z belkamy [Method for the determination of fucose not bound to proteins]. Klynycheskaja Laboratornaja Diahnostyka, 4, 17–18.

Shim, H. S., Bae, C., Wang, J., Lee, K.-H., Hankerd, K. M., Kim, H. K., Chung, J. M., & La, J.-H. (2019). Peripheral and central oxidative stress in chemotherapy-induced neuropathic pain. Molecular Pain, 15, 174480691984009.

Staff, N. P., Fehrenbacher, J. C., Caillaud, M., Damaj, M. I., Segal, R. A., & Rieger, S. (2020). Pathogenesis of paclitaxel-induced peripheral neuropathy: A current review of *in vitro* and *in vivo* findings using rodent and human model systems. Experimental Neurology, 324, 113121.

Stalnaya, I. D., & Garishvili, T. G. (1977). Metod opredelenija malonovogo dial'degida s pomoshchyu tiobarbiturovoj kisloty [Method for the determination of malondialdehyde using thiobarbituric acid]. Sovremennye Metody v Biokhimii, 1977, 66–68 (in Russian).

Tofthagen, C., McAllister, R. D., & Visovsky, C. (2013). Peripheral neuropathy caused by paclitaxel and docetaxel: An evaluation and comparison of symptoms. Journal of the Advanced Practitioner in Oncology, 4, 204–215.

Ugolev, A. M., Iezuitova, N. N., & Masevich, U. G. (1969). Issledovanie pishchevaritel'nogo apparata u cheloveka [Study of the human digestive system]. Nauka, Leningrad (in Russian).

Van den Bent, M. J., van Raaij-van den Aarssen, V. J. M., Verweij, J., Doorn, P. A. V., & Sillevis Smitt, P. A. E. (1997). Progression of paclitaxel-induced neuropathy following discontinuation of treatment. Muscle and Nerve, 20(6), 750–752.

Veremeenko, K. N., Goloborodko, O. P., & Kizim, A. I. (1988). Proteoliz v norme i pri patologii [Proteolysis in norm and pathology]. Zdorovya, Kiev (in Russian).

Zhang, H., Li, Y., de Carvalho-Barbosa, M., Kavelaars, A., Heijnen, C. J., Albrecht, P. J., & Dougherty, P. M. (2016). Dorsal root ganglion infiltration by macrophages contributes to paclitaxel chemotherapy-induced peripheral neuropathy. The Journal of Pain, 17(7), 775–786.