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Review

Vincristine Sulfate Induced Neurotoxicity: Pathophysiological and Molecular Approach.

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ABSTRACT

Vincristine sulfate (VCR), a vinca alkaloid derived from Catharanthus roseus, has been a cornerstone in cancer therapy since its FDA approval in the 1960s. Despite its efficacy in treating hematologic malignancies and solid tumors, VCR is recognized for inducing peripheral neuropathy and significantly affecting patient quality of life. The present review explores the current literature on the pathophysiological and molecular mechanisms underlying VCR-induced neurotoxicity. Mainly explore the effects of VCR on microtubule dynamics, axonal transport, calcium homeostasis, mitochondrial function, and neuroinflammatory pathways. Moreover, examine the pharmacogenetic factors and genetic polymorphisms such as CYP3A5 and ABCB1 that may influence individual susceptibility to VCR-induced peripheral neuropathy (VIPN). Also, the present review highlights critical insights into how VCR disrupts microtubule assembly, leading to axonal degeneration and neuronal dysfunction. Furthermore, neuroinflammation and mitochondrial dysfunction were found to exacerbate neuronal damage, underscoring the complex interplay of factors contributing to VIPN. So, understanding the molecular basis of VCR dysfunction is essential for developing strategies to mitigate VIPN while preserving the drug's antineoplastic efficacy and improving patient management in cancer treatment.

1. INTRODUCTION

Vincristine sulfate (VCR), derived from the Catharanthus roseus plant, is a potent vinca alkaloid that has been widely used in cancer treatment since its approval by the FDA in the 1960s [1]. The primary mode of action includes the inhibition of microtubule assembly, which affects the development of the mitotic spindle, leading to the arrest of cell division at the metaphase[2]. VCR exhibits potent antimitotic activity, specifically targeting rapidly dividing cells, which are a hallmark of cancerous tissues. This makes VCR an indispensable element in combination chemotherapy protocols for hematologic malignancies as well as solid tumors like Wilms' tumor and rhabdomyosarcoma.

Although VCR is effective in therapy, its clinical usefulness is greatly limited by its neurotoxicity, primarily shown as peripheral neuropathy [3]. This side effect, which limits the dosage, causes a range of neurological impairments which can range from slight tingling sensations to severe malfunctions in movement, sensation, and autonomic functions [4]. VCR-induced peripheral neuropathy (VIPN) is a condition characterized by complex and diverse changes in the functioning of the nervous system. It includes direct damage to nerve cells, disturbances in their metabolic processes, and the activation of neuroinflammatory responses [5].

Pharmacogenetics has emerged as a tool to forecast an individual's reaction to a particular treatment, with the aim of tailoring therapeutic management to their specific needs. Recently, numerous researchers have recognized the pharmacogenomic approach as a potent and efficient tool for identifying genetic differences that can help identify individuals who are at either a low or high risk of developing chemotherapy-induced peripheral neuropathy (CIPN) [6, 7].

The purpose of this review is to investigate the pathophysiological and molecular bases of VIPN to understand the specific molecular pathways that are affected and identify any genetic factors that may contribute to an individual's susceptibility to VIPN. Furthermore, investigate the potential biomarkers which can be used for early detection and to assess the risk level of developing VIPN. Through a comprehensive study of the literature, we will highlight the progress made in understanding VIPN, the problems that remain, and the future paths for research in this essential part of cancer treatment.

1.1. Vincristine mechanism of action

The VCR's major method of action includes binding tubulin, the protein subunit of microtubules. Tubulin is a heterodimer comprised of α- and β-tubulin. VCR selectively binds to the β-tubulin subunit, preventing its polymerization into microtubules. This binding prevents the formation of microtubules, which are critical for several cellular activities, including cell shape maintenance, intracellular transport, and, most critically, mitosis [8, 9].

Microtubules are dynamic structures that go through continual polymerization and depolymerization cycles, a phenomenon known as “dynamic instability”. VCR disrupts this process by attaching to tubulin subunits in the microtubule lattice, preventing

microtubule polymerization. This disturbance destabilizes microtubules, which is critical for their function during cell division. During cell division, microtubules create the mitotic spindle, a dynamic structure that segregates chromosomes into daughter cells. VCR inhibits microtubule polymerization, which inhibits the development of the mitotic spindle and disrupts chromosomal alignment and segregation and cell cycle arrest. This arrest is a vital stage in VCR's anticancer effect, as it limits the proliferation of rapidly proliferating cancer cells [10].

When metaphase arrest is prolonged, a biological response occurs, causing the cell to die by apoptosis. The failure of cells to continue through mitosis triggers numerous signaling pathways that result in apoptosis. This mechanism is particularly effective against quickly dividing cancer cells, which are more likely to be in the mitotic phase. VCR induces apoptosis by activating both intrinsic and extrinsic apoptotic mechanisms. An intrinsic pathway, sometimes referred to as the mitochondrial pathway, is initiated when pro-apoptotic substances, such as cytochrome C, are released from damaged mitochondria, activating caspase-9 that then activates downstream effector caspases like caspase-3, resulting in cell death [11].

1.2. Side Effects of Vincristine

The most severe and prevalent adverse effect is neurotoxicity, which presents as peripheral neuropathy and includes symptoms like numbness, tingling, and pain in the extremities [12, 13]. Additionally, VCR can produce hematologic toxicity, such as neutropenia and thrombocytopenia, which is very commonly encountered. Ovarian toxicity, resulting in lower fertility, has been found in preclinical research. Immunotoxicity, which impairs dendritic cell activity, can impede the immune response. Other adverse effects include alopecia (hair loss), tiredness, and ototoxicity. In pediatric patients, VIPN is a prominent concern, and the concomitant use of fluconazole has been evaluated for its potential to aggravate these adverse effects, but no significant association was observed [14]. These side effects underline the necessity for careful treatment and monitoring during VCR therapy to prevent its unfavorable effects on patients' quality of life.

1.3. Mechanisms of Vincristine-Induced Neurotoxicity

1.3.1. Microtubule Disruption and Axonal Transport Impairment

Microtubules are important for axonal transport, a process critical for neuron maintenance and function. Studies have shown that VCR causes widespread axonal injury, characterized by the presence of axonal spheroids, congested white matter, focal perivascular hemorrhages, and disruption of axonal transport, as evidenced by immunohistochemical studies for amyloid precursor protein (APP) presented in proximal axon segments of anterior horn neurons and anterior spinal nerve roots [15]. As a result of reduced axonal transport, peripheral neuropathy develops [16, 17]. Moreover, VCR binds β-tubulins, causing microtubule changes and neurotoxicity in the axon. Occasionally, genes coding for microtubule-associated proteins and/or tubulin have polymorphisms, with difficulties stabilizing them. Researchers Martin-Guerrero and

colleagues investigated the genetic variants in tubulin genes (TUBB1, TUBB2A, TUBB2B, TUBB3, TUBB4) and microtubule-associated proteins (MAPT), but found that VIPN was not associated with any of the aforementioned genetic variants [18]. Additionally, Skiles and colleagues looked for any possible link between MAP genotypes and VIPNs [19]. Additional variants of the MAP4 gene other than TUBB1 were also studied by Ceppi and associates, but they did not discover these variations as a possible danger [20, 21, 22].

1.3.2. Calcium Homeostasis Disruption

The VCR also impacts calcium homeostasis, which is crucial for neuronal function. Calcium ions serve as a key part of several cellular functions, including neurotransmitter release, signal transduction, and cell survival. VCR changes calcium channels and modifies calcium transport via neuronal membranes, affecting calcium signaling. This disturbance leads to aberrant neuronal excitability and contributes to neurotoxicity. Studies have indicated that VCR can affect calcium homeostasis in dorsal root ganglia, resulting in elevated intracellular calcium levels and eventual neuronal damage [23, 24]. The disruption of calcium signaling pathways is a crucial component of VIPN [21]. Variants in genes involved in calcium signaling (e.g., CACNA1G, CACNA1H) may be related to VIPN risk [25]. CACNA1G encodes the voltage-gated calcium channels (T-type) (Cav3.1 channel), whereas CACNA1H encodes the Cav3.2 channel. Studies in knockout mice have indicated that Cav3.1 is related to peripheral pain and trigeminal neuropathic pain. Cav3.2 channels, encoded by CACNA1H, have been identified to have a function in sensory signal processing in the dorsal horn of the spinal cord and have been implicated in chronic pain causes [26]. The function of these genes in neuropathic pain pathways suggests they could potentially be involved in VIPN.

1.3.3. Mitochondrial Dysfunction

The dysfunction of mitochondria is another important mechanism of neurotoxicity caused by VCR. Mitochondria are critical for energy production, calcium homeostasis, and the regulation of apoptotic pathways. VCR disrupts mitochondrial function by altering calcium homeostasis inside the mitochondria, resulting in mitochondrial enlargement, membrane potential loss, and production of reactive oxygen species (ROS). These alterations result in oxidative stress and neuronal cell death. Studies have demonstrated that VCR-induced mitochondrial dysfunction leads to higher ROS levels and axonal damage, which can be reduced by antioxidants such as glutathione [27].

The MRPL47 gene encodes a mitochondrial ribosomal protein that is part of the mitochondrial ribosome's large 39S subunit. Mutations in the MRPs family of genes may be related to neurological ailments, muscular diseases, and developmental problems due to their capacity to limit ATP synthesis [28]. A common variation in the MRPL47 gene was found to be strongly related to an elevated risk of Grade III/IV VIPN. While the specific mechanism by which MRPL47 variations influence VIPN risk is not fully understood, the association suggests that genetic changes in this gene may impair mitochondrial function or other cellular processes that contribute to the development of neuropathy when exposed to VCR [25].

1.3.4. Neuroinflammation

Neuroinflammatory pathways also play a substantial role in VCR-induced neurotoxicity. Microglia and astrocytes are involved in neuroinflammation, as well as the production of cytokines that promote inflammation. VCR-induced neuroinflammation adds to neuronal damage and exacerbates neuropathic pain. There is evidence that VCR activates glial cells and increases production of inflammatory cytokines in the nervous system, including interleukin-1 beta (IL-1) and tumor necrosis factor-alpha (TNF) [29]. This inflammatory reaction further amplifies neuronal injury and contributes to the development of peripheral neuropathy. The involvement of neuroinflammatory pathways in VIPN emphasizes the potential for anti-inflammatory therapy to attenuate VCR-induced neurotoxicity [30].

The TNF-α has been implicated in several neuropathic pain disorders, including chemotherapy-induced peripheral neuropathy [31, 32]. Inhibition of TNF-α signaling has shown positive effects in animal models of diabetic peripheral neuropathy [33]. Bromo Adjacent Homology Domain Containing 1 (BAHD1) is involved in gene silencing and heterochromatin production that has been related to sensory and autonomic neuropathy. A single nucleotide polymorphism (SNP) variant rs3803357 in the BAHD1 gene was found to be related to a decreased incidence of VIPN toxicity, suggesting a potential protective function [25]. Importantly, the mechanisms by which TNF-α and BAHD1 may contribute to VIPN are not fully understood, despite these promising findings. Further work is needed to clarify their precise roles and examine their potential as therapeutic targets or biomarkers for VIPN risk assessment.

1.3.5. Pharmacokinetic genes

The CYP3A5 is a member of the cytochrome P450 family of enzymes that are involved in the metabolism of many medicines, including VCR. VCR is processed by the cytochrome P450 3A subfamily of enzymes, including CYP3A5. Studies have demonstrated that CYP3A5 is more efficient in catalyzing the synthesis of VCR metabolites compared to CYP3A4, another enzyme in the same family. The main oxidative metabolite of VCR, designated as M1, is produced more efficiently by CYP3A5 than by CYP3A4, with a 9- to 14-fold higher intrinsic clearance [34, 35]. Genetic polymorphisms in CYP3A5, such as the CYP3A5*3 variation, can lead to changes in enzyme expression and activity. Individuals with specific SNPs may have altered VCR metabolism, decreased drug clearance, and potentially raised the incidence of VIPN. High CYP3A5 expressers are projected to have a much higher hepatic clearance of VCR compared to low expressers, which may alter the drug's neurotoxic effects [35]. In children with acute lymphoblastic leukemia (ALL), a low CYP3A5 expression genotype has been linked to an increased risk of VCR neurotoxicity. CYP3A5 expressers experienced reduced VCR neuropathy compared to non-expressers (16% vs. 27% of treatment months with neurotoxicity) [36].

Tocopherol transfer protein alpha (TTPA) is related to hereditary neuropathies and has been implicated in VIPN. The body's vitamin E levels are controlled by TTPA. Mutations in TTPA can cause ataxia with isolated vitamin E insufficiency, a disease linked to peripheral neuropathy [37]. A variation in TTPA (rs10504361) has been related to VIPN

risk. This variant is connected to variable expression of TTPA in the peripheral nervous system, which may influence the absorption of alpha-tocopherol and lead to neuropathy. Increased expression of TTPA has been anticipated in VIPN cases compared to controls, suggesting that greater levels of TTPA expression may be related to an increased risk of VIPN [38].

VCR substrates include P-glycoprotein (P-gp), encoded by ABCB1, and multidrug resistance-associated proteins (MRPs, encoded by ABCC genes) [20]. ABCB1 is implicated in the transport and resistance to VCR. Genetic variants in ABCB1 have been observed to be related to VIPN in pharmacogenomic investigations [39, 40]. ABCC1 encodes multidrug resistance protein 1, which is implicated in both the transport of and resistance to VCR. The ADME variation rs3784867 in ABCC1's intron exhibited the strongest evidence for a connection with VIPN [38]. While less widely investigated compared to ABCB1 and ABCC1, ABCC2 has also been involved in VIPN risk. Genetic variations in ABCC2 have been identified to be related to VIPN in pharmacogenomic studies [39]. These findings imply that genetic differences in drug transporters, including ABCB1, ABCC1, and ABCC2, can influence VCR pharmacokinetics and potentially affect an individual's likelihood of developing VIPN.

1.3.6. Inherited neuropathy genes:

Patients with pre-existing inherited neuropathies may be more sensitive to VIPN. Variants in genes associated with Charcot-Marie-Tooth disease (e.g., SLC5A7, TRPV4) may be connected to VIPN. A study by Wright et al. (2019) identified a relationship between a mutation in SLC5A7 (rs1013940) and greater susceptibility to VIPN [38]. SLC5A7 encodes the choline transporter and is related to inherited neuropathies. Mutations in this gene can lead to distal hereditary motor neuropathy type VII (dHMN-VII) [39]. The TRPV4 is an ion channel that, when altered, can contribute to increased calcium influx and neurotoxicity. Studies have revealed that TRPV4 suppression can reduce paclitaxel-induced neurotoxicity in preclinical mice [41]. TRPV4's significance in VIPN is less explicitly proven, but its participation in other forms of CIPN and neuropathic pain implies it could potentially play a role in VIPN as well. Future research is needed to completely explain the particular roles of these genes in VIPN and to evaluate their potential use as predictive biomarkers or therapeutic targets in clinical practice.

1.3.7. Centrosomal and cytoskeletal genes:

During cellular functions such as microtubule organization, cell division, and cilium formation, the CEP72 gene encodes a centrosomal protein. CEP72 is involved in the recruitment of essential centrosomal proteins to the centrosome, providing centrosomal microtubule-nucleation action on the γ-tubulin ring complex. It serves a key role in effective bipolar spindle formation during cell division, ensuring precise chromosomal segregation. CEP72 is also implicated in the creation of cilia, which are critical for cell signaling and motility. Data analysis of 1095 cancer patients indicated a substantial increase in VIPN risk for patients having the CEP72 rs924607 TT genotype [42]. Moreover, inherited genetic variation in the CEP72 promoter predisposes to VIPN in

adults with ALL [43]. Also, a significant link between CEP72 rs924607 and higher VIPN susceptibility in pediatric patients was observed [38]. In addition to encoding a centrosomal protein, the CEP72 gene variants have been linked with VIPN through the fact that the T allele at rs924607 suppresses transcription in the promoter region of the gene, resulting in lower expression of CEP72 mRNA and protein in leukemia cells and nerve cells, as well as increased sensitivity to VCR [39, 44]. According to a meta-analysis of the Spanish subgroup, patients with childhood ALL bearing the rs924607 TT genotype have a significantly elevated risk of VIPN [45, 46].

The SYNE2 encodes nesprin-2, is a component of the nuclear envelope and plays a role in maintaining nuclear structure and placement. ACTG1 encodes a cytoplasmic actin protein involved in several biological functions, including cell motility and maintenance of the cytoskeleton. rs1135989 is a synonymous G-to-A mutation at the Ala310 position in the ACTG1 gene. There was an increased risk of high-grade neurotoxicity in those carrying the A allele for this variant. Adding rs1135989/ACTG1 to a genetic risk model significantly increased its efficacy in predicting VIPN risk. These cytoskeletal genes are involved in VIPN risk, indicating that changes in proteins critical for cellular structure and function may alter susceptibility to VCR-induced neurotoxicity [22, 25].

1.3.8. Neurotrophic Factors

BDNF (brain-derived neurotrophic factor) is an essential neuronal growth factor that contributes to neurological maintenance. Val66Met is a frequent SNP in the gene that produces BDNF [47]. As a result, the BDNF protein is substituted with methionine (Met) at codon 66 [48]. This polymorphism alters the activity-dependent release of BDNF. The Met allele has been associated with impaired hippocampus function and altered intracellular trafficking of BDNF [49]. Polymorphisms of this gene have been linked with structural and functional changes in the brain, which may influence neurotoxicity susceptibility [48]. Further research explicitly exploring the relationship between this polymorphism and VIPN would be needed to validate and describe any potential association.

1.4. Histopathological Changes

The VCR-induced neurotoxicity and peripheral neuropathy are characterized by a spectrum of histopathological and immunohistochemical alterations. These changes provide insights into the causes of neurotoxicity and help identify potential treatment targets.

1.4.1. Neuronal Degeneration

Histopathological investigation of the brain and peripheral nerves in animal models has indicated severe neuronal degeneration, defined by the presence of degenerated neurons and satellitosis (aggregation of glial cells surrounding degenerated neurons). This deterioration is commonly accompanied by congestion of blood vessels and extensive demyelination in the white matter of the cerebrum [50, 51].

1.4.2. Axonal Injury

The VCR causes axonal damage, as evidenced by the fragmentation and abolishment of axons. VCR treatment led to axonal breakage and elevated expression of neuronal injury markers such as activating transcription factor 3 (ATF3) [52]. In a study on VCR-induced neuropathy in rats, histological examination indicated axonal degeneration, which was correlated with decreased calcitonin gene-related peptide (CGRP) expression and increased N-methyl-D-aspartate (NMDA) receptor expression [53, 54]. Another study using bioengineered sensory nerve tissue found that VCR caused length-dependent nerve conduction and histopathological changes, including axonal degeneration; CIPN is associated with clinical electrophysiological changes and neuropathological biopsy findings in animals and humans [55, 56].

1.4.3. Demyelination

Demyelination is another prominent histological change reported in VCR-induced neurotoxicity. Studies have indicated extensive demyelination in the white matter of the cerebrum and peripheral nerves following VCR treatment. This demyelination contributes to poor nerve impulse conduction and the development of neuropathic symptoms [50, 54]. VCR-induced alterations in the biochemical composition of the myelin sheath were identified in the brain, spinal cord, and sciatic nerve of mice, indicating demyelination [57].

1.5. Immunohistochemical Changes

1.5.1. Upregulation of Inflammatory Markers

The VCR treatment raises a number of inflammatory markers. An immunohistochemical study has indicated increased expression of inducible nitric oxide synthase (iNOS), ionized calcium-binding adapter molecule 1 (Iba1), and nestin in the brain and peripheral nerves of VCR-treated mice. These indicators are suggestive of neuroinflammation and glial cell activation, which play a significant role in the pathogenesis of VIPN [50, 58].

1.5.2. Substance P

Substance P, a neuropeptide implicated in pain transmission, is dramatically elevated in the spinal cord following VCR treatment. Immunohistochemical investigations have indicated that VCR treatment enhances substance P expression in the superficial layers of the spinal dorsal horn, contributing to mechanical allodynia and hyperalgesia [59- 62]. The use of neurokinin 1 receptor antagonists, such as aprepitant, has been demonstrated to reduce these symptoms by decreasing substance P signaling [60, 61].

1.5.3. Apoptotic Markers

The VCR-induced neurotoxicity is associated with increased apoptosis in neuronal cells. An immunohistochemical study has demonstrated elevation of apoptotic markers such as caspase 3 and poly (ADP-ribose) polymerase (PARP) in the brain and peripheral nerves of VCR-treated mice. PARP is a nuclear enzyme that plays a role in DNA repair and

apoptosis regulation. During apoptosis, PARP is cleaved by caspases, which inactivates its DNA repair activity and promotes the apoptotic process. Increased expression and cleavage of PARP have been found in the brain and peripheral nerves of VCR-treated mice. These indicators indicate the activation of apoptotic pathways, leading to neuronal cell death and contributing to neurotoxicity [58].

1.5.4. Synaptophysin

Synaptophysin, a measure of synaptic integrity, is diminished following VCR treatment. Immunohistochemical investigations have shown diminished synaptophysin expression in the brain, indicating synaptic loss and poor neural connectivity. This drop in synaptophysin is related to the neurotoxic effects of VCR [58].

1.5.5. Pain Receptors

The VCR administration has been demonstrated to increase the expression of pain receptors such as transient receptor potential vanilloid 1 (TRPV1), resulting in heightened pain sensitivity reported in VIPN. Immunohistochemical investigation of iPSC-SNs and DRG neurons has shown enhanced mRNA and protein expression of TRPV1 following VCR exposure. This increase is related to higher TRPV1 current density and membrane insertion, leading to mechanical allodynia and thermal hyperalgesia. The increased TRPV1 expression is part of a broader neuroinflammatory response, comprising the activation of glial cells and the production of pro-inflammatory cytokines like TNF-α, which further sensitize TRPV1 receptors. Targeting TRPV1 with antagonists like capsazepine or regulating TNF-α signaling has demonstrated potential for decreasing VCR-induced pain in preclinical mice, providing new therapeutic methods for controlling VIPN [63, 64].

1.6. Strategies for prevention and treatment of VCR-induced neurotoxicity:

As therapy with VCR related to the occurrence of neurotoxicity, many trials were adopted as treatments for prevention or lowering VCR associated neurotoxicity. Of them, gabapentin was frequently utilized as an analgesic to decrease pain associated with VCR-induced neuropathy in children [65].

Pyridoxine (vitamin B6) was also employed as a neuroprotector in a mouse model with VCR-induced neurotoxicity. This trial was related to the use of pyridostigmine (an acetylcholine esterase inhibitor) to promote intestinal motility in patients with impaired gastrointestinal motility [66, 67]. This treatment was published by Müller et al. [68], who recorded a complete recovery of bilateral ptosis in a 2-year-old boy affected by synovial sarcoma and treated with VCR, pyridoxine, and pyridostigmine. Similarly, Akbayram et al. [69] documented four cases of VCR-induced neurotoxicity in children suffering from acute lymphoblastic leukemia. The neurotoxicity symptoms were entirely healed after 2 weeks of treatment with 150 mg/sqm/day of pyridoxine and 3 mg/kg/day of pyridostigmine without any adverse effects. As potential protective measures against VCR-induced neurotoxicity, pyridoxine 150 mg/sqm/day and pyridostigmine 3

mg/kg/day were administered orally to children with acute lymphoblastic leukemia for 3 months [70].

Glutamic acid was also used as an excitatory neurotransmitter with a protective action against VCR-induced neurotoxicity [71]. For instance, Mokhtar et al. [72] found that glutamic acid was beneficial in lowering VCR-induced neurotoxicity in pediatric patients with acute lymphoblastic leukemia, non-Hodgkin's lymphoma patients, and Wilms' tumors without any harmful side effects. Besides, Bradfield et al. [73] studied the prospective use of glutamic acid in 250 juvenile patients with Wilm's tumor, rhabdomyosarcoma, and non-Hodgkin's lymphoma and developed VCR-induced neurotoxicity. Likely, glutamine was particularly helpful in the prevention of VCR-induced neurotoxicity in pediatric patients with non-Hodgkin's lymphoma, Ewing's sarcoma, Wilm's tumor, and rhabdomyosarcoma [74]. Among the proposed reasons for glutamine protective benefits is the elevation of circulating nerve growth factor (NGF) mRNA, as established in animal models. NGF was drastically reduced in patients who received chemotherapy with neurotoxic chemicals [75]. In addition, human research suggests that glutamine may increase microtubule formation and stability [76].

Bergapten, a furanocoumarin derivative found in a range of medicinal plants, was discovered to attenuate VCR-induced peripheral neuropathy by blocking inflammatory cytokines and NFκB signaling [77]. Furthermore, quercetin was reported to have protective effects against VCR-induced cytotoxicity, oxidative damage, apoptosis, and neurotoxicity in male Sprague-Dawley rats via activation of the antioxidant enzymes and reduction of the inflammatory cytokines increased by VCR [78].

1.7. Ethics approval

The animal procedures were approved by MBRSI- Research Ethics Committee number IORG0010947-MB-21-6-A.

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