



A Review on Cisplatin-Induced Peripheral Neuropathy: Pathophysiology, Molecular Mechanisms, Oxidative Stress, Biomarkers and Therapeutic Strategies

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ABSTRACT:

Cisplatin is an important anticancer drug used for the treatment of several types of cancer. However, its clinical use is limited by adverse effects, particularly cisplatin-induced peripheral neuropathy (CIPN). CIPN mainly affects sensory nerves and can cause numbness, tingling, pain, burning sensation and reduced sensation in the hands and feet. The development of CIPN involves several mechanisms, including DNA damage, mitochondrial dysfunction, oxidative stress, calcium imbalance, axonal damage and neuroinflammation. Increased production of reactive oxygen species can further damage nerve cells and reduce the activity of antioxidant defenses. Biomarkers such as malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) are useful for studying oxidative stress associated with cisplatin-induced nerve injury. Animal models have helped in understanding the mechanisms and evaluating potential treatments for CIPN. Current management mainly includes dose modification and symptomatic treatment, while drugs such as duloxetine have shown clinical benefit for painful chemotherapy-induced neuropathy. Antioxidants, anti-inflammatory agents and natural products are also being investigated as potential neuroprotective approaches. This review summarizes the pathophysiology, molecular mechanisms, oxidative stress, biomarkers, experimental models and therapeutic strategies associated with cisplatin-induced peripheral neuropathy and highlights potential areas for future research.

KEYWORDS: Cisplatin; Peripheral neuropathy; Chemotherapy-induced peripheral neuropathy; Oxidative stress; Reactive oxygen species; Mitochondrial dysfunction; Dorsal root ganglion; Biomarkers; Neuroinflammation; Natural products.

1. INTRODUCTION:

Cisplatin is an important anticancer drug used to treat many types of cancer. It kills cancer cells mainly by damaging their DNA. However, cisplatin can also cause side effects such as kidney damage, hearing problems, nausea, vomiting, and nerve damage. Cisplatin-induced peripheral neuropathy (CIPN) is a common side effect of

cisplatin treatment. It mainly affects the sensory nerves. Patients may experience numbness, tingling, burning, pain, and reduced sensation, especially in the hands and feet. Severe neuropathy can affect movement, balance, and daily activities. CIPN is caused by several factors.

Cisplatin can damage nerve DNA and mitochondria, increase reactive oxygen species (ROS), cause inflammation, disturb calcium balance, and lead to nerve-cell death. These changes can result in nerve damage and neuropathic pain. Oxidative stress is an important cause of cisplatin-induced nerve damage. Increased ROS can damage nerve cells. At the same time, natural antioxidant defenses such as SOD, CAT, and GSH may decrease. Therefore, these markers can be used to study oxidative damage in CIPN. There is currently no completely effective treatment to prevent CIPN. Treatment mainly focuses on reducing symptoms. Therefore, new and safer neuroprotective treatments are needed.

This review focuses on the causes, mechanisms, oxidative stress, biomarkers, and treatment approaches for cisplatin-induced peripheral neuropathy, with particular attention to natural products and their potential neuroprotective effects.

2. CISPLATIN: PHARMACOLOGICAL OVERVIEW

Cisplatin, chemically known as cis-diamminedichloroplatinum(II), is a platinum-based cytotoxic chemotherapeutic agent. It is a non-cell-cycle-specific anticancer drug and is widely used either alone or in combination with other chemotherapeutic agents and radiotherapy. Cisplatin remains

an important component of cancer treatment because of its broad antitumor activity; however, its clinical use is limited by significant dose-related and cumulative toxicities, particularly nephrotoxicity, ototoxicity, and peripheral neurotoxicity.

2.1 MECHANISM OF ANTITUMOR ACTION

The antitumor activity of cisplatin mainly results from its ability to damage cellular DNA. After entering the cell, cisplatin undergoes activation through aquation, in which its chloride ligands are replaced by water molecules. The activated platinum complex then becomes highly reactive and binds predominantly to the N7 position of purine bases, especially guanine and adenine, in DNA. Cisplatin produces mainly intrastrand DNA cross-links, along with smaller amounts of interstrand cross-links and DNA-protein cross-links. These DNA adducts distort the normal DNA structure and interfere with DNA replication and transcription. As a result, the cancer cell is unable to properly divide and repair its damaged DNA.

Persistent DNA damage activates several intracellular signaling pathways, including ATR, p53, MAPK, and mitochondrial apoptotic pathways. These events promote cell-cycle arrest and ultimately lead to programmed cell death. Cisplatin may also induce oxidative stress, mitochondrial dysfunction, and activation of caspases, which further contribute to apoptosis of tumor cells.

2.2 CLINICAL APPLICATIONS

Cisplatin has broad activity against several solid tumors and is commonly used as part of combination chemotherapy regimens. It plays an important role in the treatment of:

- Testicular cancer
- Ovarian cancer
- Bladder cancer
- Non-small cell and small cell lung cancers
- Head and neck cancers
- Cervical cancer
- Gastric and esophageal cancers
- Certain sarcomas and other solid tumors

Cisplatin is particularly important in highly curable malignancies such as testicular cancer and is also frequently combined with other anticancer drugs to improve therapeutic efficacy. In many treatment protocols, its use is carefully balanced against the risk of cumulative toxicity.

2.3 DOSE-DEPENDENT TOXICITY

Cisplatin is an effective anticancer drug, but it can cause several toxic effects. These effects may increase with higher doses and repeated treatment. The severity depends on the dose, treatment schedule, kidney function, age, and individual response.

- ✓ **Nephrotoxicity:** Kidney damage is one of the major side effects of cisplatin. Cisplatin can damage renal tubular cells by causing oxidative stress and inflammation. It may increase serum creatinine and cause electrolyte imbalance. Adequate hydration and kidney-function monitoring are important during treatment.
- ✓ **Peripheral Neurotoxicity:** Cisplatin mainly affects sensory nerves and can cause peripheral neuropathy. Symptoms include numbness, tingling, sensory loss, and neuropathic pain. The risk increases with higher cumulative doses.
- ✓ **Ototoxicity:** Cisplatin can damage the ear, causing tinnitus and hearing loss, especially at high doses and after repeated treatment. The hearing loss may sometimes be permanent.
- ✓ **Gastrointestinal Toxicity:** Cisplatin commonly causes nausea and vomiting. These effects can affect food intake, nutrition, and treatment compliance. Antiemetic drugs are often used to control these symptoms.
- ✓ **Myelosuppression:** Cisplatin can reduce the production of blood cells in the bone marrow. This may increase the risk of infection, anemia, and bleeding.

Overall, cisplatin has important anticancer effects, but its toxicities can limit its use and may require careful monitoring during treatment.

3. CISPLATIN- INDUCED PERIPHERAL NEUROPATHY

3.1 DEFINITION AND CLINICAL SIGNIFICANCE

Cisplatin-induced peripheral neuropathy (CIPN) is a common dose-related side effect of cisplatin treatment. It mainly damages sensory nerves, especially the dorsal root ganglion (DRG) and sensory nerve pathways. CIPN usually affects both sides of the body and mainly involves the hands and feet, producing a typical “stocking-and-glove” pattern.

Common symptoms include numbness, tingling, burning, abnormal sensation, reduced sensation, and neuropathic pain. In severe cases, patients may have problems with balance, walking, and coordination. Neuropathy may continue or become worse even after chemotherapy has stopped. This is known as “coasting.” CIPN can reduce the quality of life and interfere with daily activities.

Severe nerve damage may require a reduction or interruption of cisplatin treatment. Therefore, early detection and regular monitoring of neuropathy are important during cisplatin therapy.

3.2 INCIDENCE AND RISK FACTORS

The incidence of cisplatin-induced peripheral neuropathy varies considerably depending on the cumulative dose, treatment schedule, duration of therapy, and method used for assessment. Earlier clinical studies have reported peripheral nerve damage in approximately 60% of patients receiving cumulative cisplatin doses of about 225–500 mg/m², although severe grade 3–4 neurotoxicity occurs in a smaller proportion of patients.

Cumulative cisplatin exposure is considered one of the most important determinants of neurotoxicity. Early clinical evidence suggests that symptoms may become more apparent at cumulative doses around 250–350 mg/m², with increasing incidence and severity at higher cumulative exposure. However, substantial individual variability exists, and neuropathy may develop at lower doses in susceptible patients.

Important factors that may influence the development or severity of CIPN include:

- ❖ High cumulative cisplatin dose
- ❖ Prolonged duration of chemotherapy
- ❖ Previous exposure to neurotoxic chemotherapy
- ❖ Pre-existing peripheral neuropathy
- ❖ Combination with other neurotoxic anticancer drugs
- ❖ Renal dysfunction or altered drug handling
- ❖ Patient-related metabolic and lifestyle factors

However, not all proposed risk factors have shown consistent associations specifically with cisplatin neuropathy. Age, diabetes, alcohol consumption, and serum creatinine have been investigated, but their contribution to cisplatin-induced neurotoxicity remains variable between studies.

3.3 CLINICAL MANIFESTATIONS

Cisplatin-induced peripheral neuropathy is predominantly a sensory neuropathy. Symptoms are generally bilateral and symmetrical and initially occur in the distal extremities. Patients may experience both positive sensory symptoms, such as tingling and burning, and negative sensory symptoms, such as numbness and loss of sensation.

Common clinical manifestations include:

- ❖ Numbness of the hands and feet
- ❖ Tingling and pins-and-needles sensations
- ❖ Burning or shooting neuropathic pain
- ❖ Paresthesia and dysesthesia
- ❖ Reduced sensation to touch
- ❖ Reduced vibration and joint-position sensation
- ❖ Decreased or absent deep tendon reflexes
- ❖ Impaired proprioception
- ❖ Sensory ataxia and impaired balance in severe cases

Cisplatin neuropathy may initially be more noticeable in the hands and feet and can gradually extend proximally with continued exposure. Persistent symptoms may remain after completion of treatment, and in some patients neurological deterioration may continue temporarily after chemotherapy has stopped.

3.4 SENSORY, MOTOR AND AUTONOMIC INVOLVEMENT

- ✓ **Sensory Involvement:** Sensory nerve damage is the main feature of cisplatin-induced peripheral neuropathy. Cisplatin mainly affects the dorsal root ganglion (DRG) and sensory nerves. Common symptoms include numbness, tingling, burning pain, abnormal sensations, and increased pain sensitivity. Loss of vibration and joint-position sensation may also occur.
- ✓ **Motor Involvement:** Motor nerve damage is less common than sensory damage. Most patients have normal muscle strength during the early stages. In severe cases, patients may develop muscle weakness, poor coordination, and difficulty with fine movements.
- ✓ **Autonomic Involvement:** Autonomic nerve involvement is uncommon in cisplatin-induced peripheral neuropathy. In severe cases, some autonomic nerve functions may be affected, but these changes are much less common than sensory symptoms.

Thus, the clinical pattern of cisplatin-induced peripheral neuropathy can be summarized as:

Sensory involvement > Motor involvement > Autonomic involvement

This predominantly sensory pattern distinguishes cisplatin neurotoxicity from some other chemotherapy-induced neuropathies in which motor or autonomic abnormalities may be more prominent.

4. PATHOPHYSIOLOGY OF CISPLATIN- INDUCED PERIPHERAL NEUROPATHY:

DORSAL ROOT GANGLION INVOLVEMENT: The dorsal root ganglia are important targets of cisplatin neurotoxicity. DRG neurons are particularly vulnerable because their cell bodies lie outside the blood–brain barrier, allowing greater exposure to circulating cisplatin. Cisplatin can accumulate within these sensory neurons and form DNA adducts, resulting in cellular stress and impaired neuronal function. Damage to DRG neurons can interfere with the transmission of sensory information from peripheral tissues to the central nervous system. Cisplatin-induced injury to DRG neurons is therefore considered an important early event in the development of sensory neuropathy. Persistent neuronal damage can subsequently promote abnormal sensory signaling, pain, numbness, and other sensory disturbances.

AXONAL DEGENERATION: Axonal degeneration is an important structural consequence of cisplatin-induced neuronal injury. Damage to sensory neuron cell bodies and their axons can impair axonal transport and disrupt the maintenance of peripheral nerve fibers. Cisplatin-associated oxidative damage and mitochondrial impairment can further reduce the energy available for axonal maintenance. As axonal injury progresses, sensory nerve conduction becomes impaired, resulting in reduced sensory function. Degeneration of peripheral axons contributes to clinical manifestations such as paresthesia, numbness, reduced sensation, and neuropathic pain.

MITOCHONDRIAL DYSFUNCTION: Mitochondrial dysfunction is an important component of cisplatin-induced neuronal injury. Cisplatin can interfere with mitochondrial function and increase the generation of reactive oxygen species (ROS). Excessive ROS can damage mitochondrial membranes, proteins, lipids, and mitochondrial DNA. This creates a vicious cycle in which mitochondrial impairment promotes further oxidative stress. Damaged mitochondria produce less ATP, resulting in an inadequate energy supply for neuronal and axonal functions. Mitochondrial dysfunction can also promote membrane depolarization and release of pro-apoptotic factors, thereby contributing to neuronal death. These changes are particularly important in long peripheral axons, which have high energy requirements.

CALCIUM DYSREGULATION: Cisplatin-induced cellular stress can disturb intracellular calcium (Ca^{2+}) homeostasis in sensory neurons. Mitochondrial dysfunction and oxidative stress can interfere with normal calcium storage and regulation. Excessive intracellular calcium activates calcium-dependent enzymes and signaling pathways that can damage cellular proteins, membranes, and cytoskeletal components. Persistent calcium elevation can also increase mitochondrial injury and promote the activation of apoptotic pathways. Thus, calcium dysregulation can act as an important link between mitochondrial dysfunction, oxidative stress, and neuronal apoptosis.

5. MOLECULAR MECHANISMS OF CISPLATIN-INDUCED PERIPHERAL NEUROPATHY

Cisplatin-induced peripheral neuropathy is associated with multiple interconnected molecular pathways. Cisplatin enters sensory neurons and produces DNA damage, mitochondrial dysfunction, oxidative stress, inflammatory signaling, and changes in neuronal excitability. These processes activate signaling pathways such as MAPK and NF- κ B, alter the protective Nrf2/ARE antioxidant pathway, increase pro-inflammatory cytokines, and disturb ion-channel function. Together, these molecular changes contribute to neuronal injury, axonal degeneration, and neuropathic pain.

5.1 DNA DAMAGE AND DNA ADDUCT FORMATION

DNA damage is one of the primary molecular effects of cisplatin. After entering cells, cisplatin undergoes aquation and forms reactive platinum species that bind to DNA, particularly to the N7 position of guanine. This results mainly in intrastrand DNA cross-links, with smaller amounts of interstrand cross-links and DNA-protein cross-links. These adducts distort the DNA structure and interfere with DNA replication and transcription.

In peripheral sensory neurons, particularly dorsal root ganglion neurons, accumulation of cisplatin and formation of DNA adducts can activate DNA-damage response pathways. Persistent DNA damage promotes cellular stress, mitochondrial dysfunction, and activation of apoptotic signaling. Therefore, DNA adduct formation provides an important initial molecular trigger for cisplatin-induced neuronal injury.

5.2 MAPK SIGNALING

The mitogen-activated protein kinase (MAPK) family regulates cellular responses to stress, inflammation, survival, and apoptosis. Cisplatin-induced cellular stress and ROS production can activate MAPK pathways, particularly p38 MAPK, JNK, and ERK.

Activation of p38 and JNK is particularly associated with stress and inflammatory responses. Increased MAPK signaling can enhance the production of inflammatory mediators and promote neuronal apoptosis. In sensory neurons and pain pathways, abnormal activation of MAPK signaling may also increase neuronal excitability and contribute to the development and persistence of neuropathic pain.

5.3 NF- κ B PATHWAY

The nuclear factor-kappa B (NF- κ B) pathway is an important regulator of inflammatory and cellular stress responses. Cisplatin-induced oxidative stress and cellular injury can activate NF- κ B signaling. Activated NF- κ B translocates into the nucleus and promotes the transcription of several inflammatory genes.

Activation of NF- κ B can increase the production of inflammatory mediators, including TNF- α , IL-1 β , and IL-6. These mediators can enhance neuronal sensitization and contribute to peripheral nerve inflammation and neuropathic pain. Thus, NF- κ B provides an important molecular link between oxidative stress, inflammation, and neuronal dysfunction.

5.4 Nrf2/ARE PATHWAY

The nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway represents one of the major endogenous defense mechanisms against oxidative stress. Under normal conditions, Nrf2 is maintained at relatively low levels through continuous degradation. When oxidative stress increases, Nrf2 becomes stabilized and translocates into the nucleus, where it binds to ARE sequences and stimulates the expression of antioxidant and cytoprotective genes.

Cisplatin-induced excessive ROS can disturb the balance of this antioxidant defense system. Impairment or insufficient activation of Nrf2/ARE signaling may reduce the expression of antioxidant enzymes and increase neuronal susceptibility to oxidative injury. Important Nrf2-regulated defenses include glutathione-related enzymes, heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), and other antioxidant proteins.

5.5 PRO-INFLAMMATORY CYTOKINES

Cisplatin-induced neuronal injury can stimulate inflammatory signaling in peripheral and central nervous tissues. Activation of inflammatory pathways results in increased production of cytokines and chemokines such as TNF- α , IL-1 β , and IL-6.

These cytokines can increase neuronal excitability, alter ion-channel function, and enhance pain transmission. They may also promote further oxidative stress and mitochondrial dysfunction, creating a positive feedback cycle that maintains neuronal injury and neuropathic pain. Therefore, increased pro-inflammatory cytokine signaling is an important molecular component of CIPN.

5.6 ION-CHANNEL ALTERATIONS

Normal sensory nerve function depends on the regulated activity of voltage-gated sodium, potassium, calcium, and transient receptor potential (TRP) channels. Cisplatin-induced oxidative stress and inflammatory signaling can alter the expression or activity of these ion channels, resulting in abnormal neuronal excitability.

Alterations in voltage-gated sodium channels can promote abnormal action-potential generation, while changes in potassium and calcium channel activity can disturb neuronal membrane excitability and neurotransmitter release. TRP channels, including TRPV1 and TRPA1, are also involved in nociceptive signaling and may contribute to abnormal pain sensitivity following chemotherapy. These changes can manifest as hyperalgesia, allodynia, burning pain, and other sensory abnormalities.

5.7 MITOCHONDRIAL SIGNALING

Mitochondria are important targets of cisplatin-induced neurotoxicity. Cisplatin can accumulate in mitochondria and interfere with mitochondrial DNA and mitochondrial proteins, resulting in impaired electron transport and reduced ATP production. Mitochondrial dysfunction also increases the generation of ROS, thereby intensifying oxidative stress.

Persistent mitochondrial damage can cause loss of mitochondrial membrane potential and facilitate the release of cytochrome c, which activates downstream caspases and promotes apoptosis. Mitochondrial dysfunction also contributes to calcium imbalance and impaired axonal energy supply. Thus, mitochondrial signaling connects oxidative stress, calcium dysregulation, energy failure, and neuronal apoptosis.

5.8 NEURONAL APOPTOSIS

Severe and persistent cellular damage caused by cisplatin can activate programmed cell death (apoptosis) in sensory neurons. DNA damage, oxidative stress, mitochondrial dysfunction, and calcium imbalance can activate pro-apoptotic signaling pathways. Mitochondrial injury may result in the release of cytochrome c and subsequent activation of caspases, particularly caspase-9 and caspase-3, ultimately leading to neuronal apoptosis. Loss of sensory neurons reduces the functional capacity of peripheral nerves and contributes to the persistence and progression of neuropathic symptoms. Therefore, neuronal apoptosis represents a downstream consequence of several earlier pathological events.

5.9 NEUROINFLAMMATION

Neuroinflammation also contributes to the development and persistence of cisplatin-induced peripheral neuropathy. Neuronal injury can activate immune and glial cells and promote the release of inflammatory mediators. Cytokines and chemokines such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) can enhance neuronal excitability and contribute to pain signaling.

Inflammatory signaling can interact with oxidative stress and mitochondrial dysfunction, producing a self-amplifying cycle of neuronal injury. Activation of spinal glial cells may further increase the release of inflammatory mediators and contribute to the maintenance of neuropathic pain.

6. ROLE OF OXIDATIVE STRESS IN CISPLATIN-INDUCED PERIPHERAL NEUROPATHY

6.1 ROS GENERATION

Cisplatin treatment increases the production of reactive oxygen species (ROS) in peripheral sensory neurons. Important ROS include superoxide anion, hydrogen peroxide, and hydroxyl radicals. Cisplatin-induced mitochondrial dysfunction can impair the electron transport chain and promote electron leakage, resulting in increased ROS generation. In addition, cisplatin can disturb cellular antioxidant systems, further increasing oxidative stress.

Excessive ROS can oxidize cellular macromolecules and interfere with normal neuronal function. ROS can also activate stress-responsive pathways such as MAPK and NF- κ B, thereby linking oxidative stress with inflammation and apoptosis. Persistent ROS production therefore contributes to the progression of peripheral nerve damage.

6.2 LIPID PEROXIDATION

Neuronal membranes contain a high proportion of polyunsaturated fatty acids, making them particularly susceptible to oxidative damage. Excess ROS can attack membrane lipids and initiate lipid peroxidation. This process produces unstable lipid radicals and secondary reactive products that can further damage cellular membranes.

Lipid peroxidation can alter membrane integrity, mitochondrial function, ion-channel activity, and neuronal signaling. Consequently, increased lipid peroxidation may contribute to axonal dysfunction and abnormal sensory processing associated with CIPN.

6.3 MALONDIALDEHYDE (MDA)

Malondialdehyde (MDA) is one of the major secondary products generated during lipid peroxidation and is widely used as an indicator of oxidative damage. Increased MDA levels indicate enhanced lipid peroxidation and oxidative injury to cellular membranes.

In cisplatin-induced neurotoxicity, increased ROS production can enhance lipid peroxidation, resulting in elevated MDA levels in nervous tissues. Therefore, MDA can serve as a useful biochemical marker of oxidative stress and may help evaluate the extent of lipid oxidative damage during CIPN.

6.4 GLUTATHIONE (GSH) DEPLETION

Reduced glutathione (GSH) is an important intracellular antioxidant that protects cells against oxidative damage. It directly participates in the detoxification of reactive oxygen species and serves as a substrate for glutathione-dependent antioxidant enzymes, including glutathione peroxidase.

Cisplatin-induced oxidative stress can increase the utilization of GSH and disturb cellular glutathione homeostasis. Depletion of GSH reduces the ability of neurons to neutralize ROS and increases their susceptibility to oxidative damage. Thus, decreased GSH levels can contribute to mitochondrial injury, lipid peroxidation, and neuronal dysfunction.

6.5 SOD AND CAT ALTERATIONS

Superoxide dismutase (SOD) and catalase (CAT) are important enzymatic antioxidants involved in the removal of ROS. SOD converts superoxide anions into hydrogen peroxide, while CAT converts hydrogen peroxide into water and molecular oxygen.

During cisplatin-induced oxidative stress, excessive ROS generation can overwhelm endogenous antioxidant defenses and alter the activities or levels of these enzymes. A reduction in SOD and CAT activity can result in the accumulation of reactive oxygen species and intensification of oxidative damage. Therefore, changes in SOD and CAT are commonly investigated as indicators of the antioxidant status of neural tissue.

6.6 MITOCHONDRIAL ROS

Mitochondria are both an important source and target of ROS during cisplatin-induced neurotoxicity. Cisplatin can interfere with mitochondrial function and mitochondrial DNA, resulting in impaired respiratory-chain activity and increased production of mitochondrial ROS. Excess mitochondrial ROS can damage mitochondrial proteins, lipids, and DNA and reduce mitochondrial membrane potential and ATP production. This further compromises neuronal energy metabolism and can promote calcium dysregulation and activation of apoptotic pathways. Importantly, mitochondrial dysfunction and ROS generation can form a self-amplifying cycle, in which mitochondrial damage increases ROS production and ROS further damages mitochondria.

7. BIOMARKERS OF CISPLATIN-INDUCED PERIPHERAL NEUROPATHY

Biomarkers are measurable biological indicators that can provide information about neuronal injury, oxidative stress, inflammation, disease progression, or response to treatment. In CIPN research, biomarkers are particularly useful for understanding underlying mechanisms and identifying early changes that may occur before severe clinical symptoms become apparent. However, many proposed biomarkers remain investigational and require further clinical validation before routine use.

7.1 MALONDIALDEHYDE (MDA):

Malondialdehyde (MDA) is a major product of lipid peroxidation and is commonly used as an indicator of oxidative damage. Excessive ROS generated during cisplatin treatment can attack polyunsaturated fatty acids present in neuronal and mitochondrial membranes, leading to lipid peroxidation and increased MDA formation. Elevated MDA levels therefore indicate increased oxidative injury and membrane damage. In experimental CIPN studies, MDA is frequently measured in nervous tissue to evaluate the degree of oxidative stress and the protective effects of potential neuroprotective agents.

7.2 REDUCED GLUTATHIONE (GSH):

Reduced glutathione (GSH) is one of the major endogenous non-enzymatic antioxidants. It helps maintain cellular redox balance and participates in the removal of hydrogen peroxide and other reactive species through glutathione-dependent antioxidant systems. Cisplatin-induced oxidative stress can increase the utilization of GSH and disturb glutathione homeostasis. Depletion of GSH weakens the antioxidant defense of sensory neurons and makes them more susceptible to oxidative damage.

7.3 SUPEROXIDE DISMUTASE (SOD):

Superoxide dismutase (SOD) is an important antioxidant enzyme that converts the superoxide anion into hydrogen peroxide and oxygen. It represents one of the first enzymatic defenses against ROS. Cisplatin-induced oxidative stress may alter SOD activity or expression. Reduced SOD activity can result in greater accumulation of superoxide radicals and contribute to oxidative damage in peripheral nerves.

7.4 CATALASE (CAT):

Catalase (CAT) protects cells by converting hydrogen peroxide into water and oxygen. It works together with SOD and other antioxidant systems to control intracellular ROS levels. During cisplatin-induced oxidative stress, excessive ROS production may overwhelm antioxidant defenses and alter CAT activity. Reduced CAT activity can contribute to hydrogen peroxide accumulation and further oxidative damage.

7.5 INFLAMMATORY BIOMARKERS:

Inflammatory biomarkers provide information about the inflammatory component of CIPN. Cisplatin-induced neuronal injury can activate inflammatory signaling and increase the production of cytokines and chemokines.

- **Tumor Necrosis Factor- α (TNF- α):** TNF- α is a major pro-inflammatory cytokine involved in neuronal sensitization and inflammatory signaling. Increased TNF- α can activate NF- κ B and MAPK pathways and promote further oxidative stress and neuronal dysfunction.
- **Interleukin-1 β (IL-1 β):** IL-1 β contributes to neuroinflammation and can increase neuronal excitability and pain signaling. Increased IL-1 β has been associated with inflammatory processes involved in chemotherapy-induced neuropathic pain.
- **Interleukin-6 (IL-6):** IL-6 is another important inflammatory mediator that can participate in neuronal sensitization and neuroinflammatory responses. Altered IL-6 signaling may contribute to the persistence of neuropathic symptoms.

Other inflammatory mediators under investigation include IL-8, CCL2/MCP-1, and high-mobility group box 1 (HMGB1).

7.6 NEURONAL INJURY BIOMARKERS:

Biomarkers that reflect neuronal or axonal damage may provide additional information about the severity of peripheral nerve injury.

- **Neurofilament Light Chain (NfL):** Neurofilament light chain (NfL) is a structural component of neuronal axons. When axonal damage occurs, neurofilament proteins can be released into biological fluids. Consequently, circulating NfL has emerged as a potential marker of axonal injury and is being investigated in chemotherapy-induced neurotoxicity.
- **Neuron-Specific Enolase (NSE):** Neuron-specific enolase (NSE) is a neuronal enzyme that can be released following neuronal injury. Changes in NSE have been investigated as an indicator of neuronal damage, although its specificity for CIPN is limited.
- **Protein Gene Product 9.5 (PGP9.5):** PGP9.5 is a neuronal protein commonly used as a marker of peripheral nerve fibers, particularly in experimental studies evaluating intraepidermal nerve fiber density. A reduction in intraepidermal nerve fibers can indicate small-fiber damage.

Thus, neuronal injury biomarkers can complement clinical and electrophysiological assessments by providing information about structural nerve damage.

7.7 EMERGING MOLECULAR BIOMARKERS

Recent research has focused on molecular biomarkers that may provide earlier or more specific information about the development of CIPN. These include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), extracellular vesicles, metabolomic signatures, oxidative stress-related molecules, and inflammatory mediators.

- **MicroRNAs:** MicroRNAs are small non-coding RNAs that regulate gene expression at the post-transcriptional level. Altered miRNA expression may influence inflammation, oxidative stress, neuronal survival, and pain signaling. Therefore, specific miRNA profiles are being investigated as potential biomarkers of chemotherapy-induced neurotoxicity.
- **Long Non-Coding RNAs:** Long non-coding RNAs can regulate gene expression and cellular signaling. Changes in their expression may influence neuroinflammation, oxidative stress, and neuronal apoptosis. Their potential value as biomarkers in CIPN is an emerging area of research.
- **Extracellular Vesicles:** Extracellular vesicles can transport proteins, lipids, and nucleic acids between cells. Because their molecular contents can reflect pathological changes, they may provide a minimally invasive source of biomarkers for chemotherapy-induced neuronal injury.
- **Metabolomic Biomarkers:** Changes in metabolites associated with energy metabolism, oxidative stress, lipid metabolism, and mitochondrial function may provide additional information about the development of CIPN. Metabolomics-based approaches may help identify patients at increased risk and improve understanding of the biochemical changes associated with neuropathy.

However, these emerging biomarkers are still largely at the research and validation stage. Their clinical usefulness requires confirmation through larger, well-designed prospective studies.

8. COMPARISON OF EXPERIMENTAL MODELS

MODEL	MAIN USE	MAJOR ADVANTAGE	MAJOR LIMITATION
<i>In vivo</i>	Whole-body CIPN evaluation	Reproduces integrated biological responses	Animal-to-human differences
<i>In vitro</i>	Cellular toxicity	Highly controlled conditions	Limited physiological complexity
<i>Ex vivo</i>	Tissue/DRG studies	Preserves some native tissue characteristics	No complete systemic response
<i>In silico</i>	Target/pathway prediction	Rapid and cost-effective screening	Requires experimental validation

MODEL	MAIN USE	MAJOR ADVANTAGE	MAJOR LIMITATION
Translational	Connecting preclinical and clinical findings	Clinically relevant outcomes	Human symptoms are difficult to model completely
Cellular	Specific cellular mechanisms	Detailed molecular investigation	Limited cell–cell interactions
Animal	Behavioral, biochemical and structural studies	Comprehensive evaluation	Ethical and resource requirements
Alternative	Human-specific and advanced modeling	May reduce animal use	Still requires validation

Table 01: Comparison of experimental models

10. CURRENT THERAPEUTIC APPROACHES

Approach	Main mechanism/aim	Current status
Dose modification	Reduces further cisplatin exposure	Established clinical strategy when toxicity is significant
Duloxetine	Enhances descending pain inhibition	Best-supported pharmacological option for painful CIPN
Gabapentin/Pregabalin	Modulates calcium-channel activity	Used for neuropathic pain; CIPN evidence is less consistent
Antioxidants	Reduce oxidative stress and ROS	Mainly investigational for CIPN prevention/treatment
Anti-inflammatory approaches	Reduce cytokine and inflammatory signaling	Mainly experimental
Natural products	Antioxidant, anti-inflammatory, mitochondrial protection	Promising but requires stronger clinical evidence
Mitochondrial therapies	Protect mitochondrial function	Emerging
Ion-channel modulators	Reduce abnormal neuronal excitability	Emerging
Nrf2/ARE activation	Enhances endogenous antioxidant defense	Emerging/preclinical
Non-pharmacological approaches	Symptom control and functional improvement	Supportive/emerging

Table 02: Current therapeutic approaches

11. ROLE OF NATURAL PRODUCTS IN CISPLATIN-INDUCED NEUROPATHY

Natural products are being studied as possible treatments for cisplatin-induced peripheral neuropathy (CIPN). Cisplatin can damage nerves through oxidative stress, mitochondrial damage, inflammation, DNA damage, calcium imbalance, and apoptosis. Many plant compounds have antioxidant, anti-inflammatory, and neuroprotective properties. Therefore, they may protect nerves through different mechanisms.

- ❖ **Antioxidant Effects:** Oxidative stress is an important cause of cisplatin-induced nerve damage. Cisplatin increases reactive oxygen species (ROS), which can damage lipids, mitochondria, DNA, and nerve cells. Natural products containing flavonoids, polyphenols, and terpenoids can reduce oxidative stress and improve the body's antioxidant defense. They may increase GSH, SOD, and CAT and reduce oxidative damage.
- ❖ **Anti-inflammatory Effects:** Inflammation also contributes to CIPN. Cisplatin can increase inflammatory mediators such as TNF- α , IL-1 β , and IL-6. Natural products may reduce inflammation by controlling pathways such as NF- κ B and MAPK. This may help reduce nerve sensitivity and neuropathic pain.

- ❖ **Mitochondrial Protection:** Cisplatin can damage mitochondria and increase ROS production. This can reduce energy production and lead to nerve-cell damage.
- ❖ Some natural compounds may protect mitochondria by reducing oxidative damage, maintaining mitochondrial function, and preventing apoptosis.
- ❖ **Anti-apoptotic Effects:** Cisplatin-induced oxidative stress, DNA damage, and mitochondrial dysfunction can cause neuronal apoptosis. Natural products may protect nerve cells by reducing apoptosis and regulating proteins involved in cell survival and cell death.

11.1 IMPORTANT NATURAL PRODUCTS STUDIED IN CIPN

- ❖ **Curcumin:** Curcumin, obtained from *Curcuma longa*, has antioxidant and anti-inflammatory effects. Studies suggest that it may reduce cisplatin-induced nerve damage by reducing oxidative stress and inflammation.
- ❖ **Ginkgo biloba:** Ginkgo biloba extract (EGb761) has shown protective effects against cisplatin-induced nerve damage in experimental studies. Its antioxidant activity may help protect sensory nerves.
- ❖ **Quercetin:** Quercetin is a flavonoid with antioxidant and anti-inflammatory properties. It may reduce oxidative stress and inflammation associated with chemotherapy-induced neuropathy. However, evidence specifically for cisplatin-induced neuropathy is mainly from experimental studies.
- ❖ **Resveratrol:** Resveratrol is a natural polyphenol with antioxidant and anti-inflammatory effects. It may protect mitochondria and nerve cells. However, more studies are needed to confirm its effectiveness against cisplatin-induced neuropathy.
- ❖ **Other Natural Compounds:** Other compounds studied for chemotherapy-related nerve damage include rutin, cyanidin, thymoquinone, caffeic acid phenethyl ester, salicylic acid, and 6-methoxyflavone. These compounds may reduce oxidative stress, inflammation, and nerve damage. However, the available evidence varies between compounds.

11.2 CLINICAL PERSPECTIVE AND LIMITATIONS

Natural products show promising neuroprotective effects in experimental studies, but they are not yet established treatments for CIPN. Most available evidence is from animal and laboratory studies. Clinical studies are still limited, and differences in plant preparations, doses, and study methods make comparison difficult. Another important concern is the possible interaction between natural products and cisplatin. A useful neuroprotective agent should protect nerves without reducing the anticancer effect of cisplatin. Therefore, more studies are needed to confirm the safety, effective dose, clinical benefits, and possible interactions of natural products before their routine use in CIPN.

12. RESEARCH GAPS AND FUTURE PERSPECTIVES

Although many studies have been conducted on cisplatin-induced peripheral neuropathy (CIPN), some important problems still remain.

- ✓ **Limited Treatment Options:** There is no completely effective treatment for CIPN. Duloxetine can reduce neuropathic pain, but it does not fully repair nerve damage. Therefore, better treatments are needed.
- ✓ **Lack of Reliable Biomarkers:** There is no single biomarker that can accurately predict CIPN. MDA, GSH, SOD, CAT, inflammatory cytokines, and NfL are being studied as possible biomarkers.
- ✓ **Need for Better Experimental Models:** Different studies use different animals, cisplatin doses, and testing methods. Standardized experimental methods are needed to obtain more reliable and comparable results.
- ✓ **Gap Between Animal and Human Studies:** Many treatments show good results in animals but do not always show the same effect in humans. More human-based models and clinical studies are required.
- ✓ **Natural Products:** Natural products and phytochemicals show promising antioxidant and anti-inflammatory effects against CIPN. However, more studies are needed to confirm their safety, effective dose, and clinical benefits.
- ✓ **Combination Therapy:** Since CIPN involves several mechanisms, combining treatments that target oxidative stress, inflammation, mitochondrial damage, and pain may provide better results.
- ✓ **Personalized Treatment:** Patients respond differently to cisplatin. Future studies should identify patients who are more likely to develop severe neuropathy and provide individualized treatment.

FUTURE PERSPECTIVE

Future research should focus on early detection, prevention, and treatment of nerve damage. More research on biomarkers, natural products, molecular targets, and new therapeutic approaches may help develop safer and more effective treatments for CIPN.

13. CONCLUSION

Cisplatin is an important anticancer drug, but it can cause peripheral neuropathy, leading to pain, numbness, tingling, and increased sensitivity. CIPN develops through several mechanisms, mainly oxidative stress, mitochondrial dysfunction, DNA damage, inflammation, calcium imbalance, and neuronal damage. Oxidative stress plays an important role in CIPN by increasing ROS and lipid peroxidation and reducing antioxidant protection such as GSH, SOD, and CAT. Biomarkers such as MDA, GSH, SOD, CAT, inflammatory markers, and neuronal injury markers may help in studying CIPN. Current treatment options are limited. Duloxetine can help reduce neuropathic pain, but it does not completely prevent nerve damage. Natural products and phytochemicals are promising because of their antioxidant and anti-inflammatory effects. Overall, more research is needed to develop safe and effective treatments that can protect nerves without reducing the anticancer effect of cisplatin.

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