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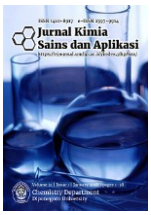

Mechanisms of Action, Resistance, Toxicity, and Recent Developments of Cisplatin as Anticancer Agent: A Comprehensive Review

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Abstract

Cisplatin is among the most potent chemotherapy agents used to treat a range of cancers, including those affecting the ovaries, testes, lungs, and bladder. Its primary mode of operation involves creating cross-links in DNA, which blocks cell division and gene expression, ultimately leading to programmed cell death. Unfortunately, its therapeutic benefits are frequently undermined by harmful side effects and the development of resistance in cancer cells. This research seeks to delve deeply into cisplatin's mechanisms, covering how it enters cells, gets activated internally, and interacts with DNA and key proteins. Additionally, it explores advancements in nanoparticle-based cisplatin delivery systems and platinum (Pt[IV]) compounds designed to enhance systemic absorption and reduce overall toxicity. Drawing on a review of 166 studies across five key databases, modifications to drug-delivery methods have shown notable improvements in cisplatin's performance across different cancer types. As a result, innovative formulations and tactics to tackle resistance could broaden cisplatin's role as a more targeted and safer cancer-fighting drug. This review was conducted using a structured literature search without a formal risk of bias assessment.

1. Introduction

Globally, cancer remains among the most significant contributors to mortality, claiming over 10 million lives each year according to GLOBOCAN 2020 statistics [1]. While therapeutic approaches have evolved considerably over recent decades, chemotherapy continues to serve as a cornerstone treatment across numerous malignancy types [2]. Within the chemotherapeutic arsenal, platinum-containing compounds, most notably cisplatin, have established themselves as fundamental components of oncological treatment regimens [3].

The compound cisplatin, chemically designated as cis-diamminedichloroplatinum(II), is a platinum(II) complex characterized by a square-planar geometry and two chloride ligands in a cis configuration [4]. Following regulatory approval from the FDA, this agent has found widespread application against multiple cancer types, encompassing testicular, ovarian, bladder, pulmonary, head and neck, cervical, and esophageal malignancies [5]. The therapeutic achievements with cisplatin have been particularly striking in testicular cancer management, where cure rates exceed 90% among individuals diagnosed at early stages [6].

Current estimates suggest that roughly half of all chemotherapy recipients are administered platinum-containing agents, underscoring the central role of cisplatin in contemporary oncological practice [7]. However, despite its demonstrated efficacy, cisplatin therapy encounters several substantial obstacles [8]. A considerable proportion of patients exhibit inadequate therapeutic responses, with many developing either inherent or acquired resistance mechanisms [9]. Additionally, the agent produces numerous severe adverse effects, including renal toxicity, neurological

damage, hearing impairment, and bone marrow suppression, which frequently necessitate dose reductions or treatment discontinuation [10].

Elucidating the molecular mechanisms of cisplatin has become essential for addressing these therapeutic limitations [11]. Scientific investigations conducted over the past ten years have demonstrated that cisplatin operates through remarkably complex pathways [12]. Beyond its primary action involving DNA-platinum adduct formation that disrupts replication and transcription processes, the compound activates multiple cellular signaling cascades culminating in programmed cell death [13]. Additional research has established that cisplatin induces oxidative stress, initiates DNA repair mechanisms, and influences immune system function [14].

The development of cisplatin resistance represents a critical clinical challenge, significantly compromising treatment outcomes [15]. This resistance arises through multifaceted mechanisms, including reduced intracellular drug concentration, enhanced detoxification, enhanced DNA repair, and impaired apoptotic signaling [16]. Recognition of these resistance pathways has created possibilities for novel therapeutic approaches, including combination regimens and inhibitors targeting resistance mechanisms [17].

Recent advances in research have enabled the discovery of biomarkers to predict therapeutic efficacy and toxicity, alongside the development of targeted delivery platforms, such as nanoparticle-based systems, to optimize therapeutic indices [18]. Second- and third-generation platinum analogs exhibit improved toxicity profiles, though their activity differs from that of the parent compound [19]. This review provides a comprehensive synthesis of cisplatin's mechanisms of action, clinical utility, resistance, and toxicity, while outlining future directions for platinum-based therapies based on literature from 2015–2025.

2. Methods

This review was developed through a structured examination of scientific publications addressing the mechanisms and therapeutic applications of cisplatin as an anticancer agent. Relevant studies were identified from PubMed, ScienceDirect, Scopus, Web of Science, and Google Scholar. The review primarily considered articles published between January 2015 and December 2025 to reflect recent developments in the field.

To obtain broad coverage of the topic, keywords were combined using Boolean operators (AND/OR). The primary search terms included "cisplatin," "mechanism of action," "DNA damage," "apoptosis," "drug resistance," "nephrotoxicity," "cancer therapy," and "platinum-based drugs." An example of the search strategy is as follows: ("cisplatin" OR "platinum-based drugs") AND ("mechanism of action" OR "DNA damage" OR "apoptosis") AND ("drug resistance" OR "chemoresistance") AND ("nephrotoxicity" OR "toxicity").

The review focused on peer-reviewed publications written in English, including original research articles, review papers, meta-analyses, and clinical studies. Articles were selected based on their relevance to cisplatin's mechanisms of action, resistance pathways, toxicity profiles, and clinical applications. Publications not directly related to these themes were not considered.

An initial pool of publications was identified, and studies were subsequently selected based on thematic relevance to the objectives of this review. The selected literature was organized into thematic categories, including the chemical characteristics of cisplatin, cellular uptake and DNA interaction, apoptosis signaling pathways, mechanisms of resistance, toxicity and its management, and recent clinical and formulation developments. The findings were synthesized descriptively to provide an integrated, up-to-date overview of cisplatin in cancer therapy.

This manuscript is presented as a structured narrative review. It does not involve prior protocol registration or formal quantitative risk of bias assessment. References follow the numerical citation format required by the Indonesian Journal of Chemistry.

3. Results and Discussion

To provide a clearer orientation before entering the detailed discussion, Table 1 presents a concise overview of the principal themes addressed in this review. The table summarizes the scope of each topic and key findings highlighted in the recent literature (2015–2025). This overview is intended to help readers follow the logical progression of the subsequent sections.

3.1. Chemical Structure and Properties of Cisplatin

The molecular formula of cisplatin is cis-$[Pt(NH_3)_2Cl_2]$, with a molecular mass of 300.05 g/mol. Structurally, it adopts a square-planar arrangement in which a central platinum(II) atom coordinates with two amine groups and two chloride atoms, with the latter in a cis configuration [20]. This particular geometric arrangement is essential for biological activity, as the corresponding trans isomer shows minimal anticancer activity [21]. This disparity in therapeutic activity stems from the cis isomer's ability to form severely distorted intrastrand DNA adducts, whereas the trans form produces adducts with limited efficacy in disrupting DNA replication [22]. The chemical architecture of cisplatin is illustrated in Figure 1.

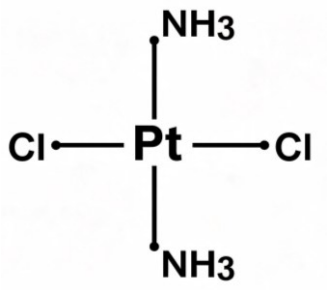

Figure 1. Chemical structure of cisplatin. This figure was created by the author using ChemDraw

Table 1. Overview of major themes and recent insights on cisplatin discussed in this review

Major Theme	Scope of Discussion	Key Points Highlighted in Recent Literature (2015–2025)
Chemical Characteristics and Activation	Structural configuration, physicochemical properties, and aquation process under physiological conditions.	Recent studies emphasize the importance of chloride concentration in regulating aquation kinetics and intracellular activation efficiency.
Cellular Uptake and Efflux Mechanisms	Transporter-mediated drug entry and export, including copper and organic cation transport systems.	Updated findings indicate that differential expression of CTR1, OCT2, and ATP7B correlates with therapeutic response variability and nephrotoxicity risk.
DNA Binding and Adduct Formation	Formation of intra- and interstrand crosslinks and subsequent DNA distortion.	Contemporary molecular analyses further clarify structural distortion patterns and their influence on transcriptional inhibition.
DNA Damage Response Pathways	Activation of checkpoint signaling cascades and cell cycle regulation following DNA injury.	Emerging data highlight the central roles of ATM/ATR signaling and p53 status in determining whether apoptosis or repair occurs.
Apoptotic Signaling Mechanisms	Intrinsic mitochondrial pathway and extrinsic death receptor pathway activation.	Recent investigations demonstrate cross-talk between mitochondrial dysfunction and caspase activation in enhancing cytotoxic efficacy.
Role of Oxidative Stress	Generation of reactive oxygen species and mitochondrial impairment.	Current literature supports oxidative stress as a dual contributor to tumor cell death and dose-limiting toxicities.
Mechanisms of Drug Resistance	Reduced accumulation, enhanced detoxification, DNA repair enhancement, and apoptosis evasion.	Studies from the last decade underline glutathione conjugation, ERCC1-mediated repair, and transporter regulation as dominant resistance drivers.
Toxicity and Clinical Management	Nephrotoxicity, neurotoxicity, ototoxicity, and associated preventive strategies.	Recent evidence links OCT2-mediated renal uptake and oxidative injury to nephrotoxicity, supporting hydration and protective interventions.
Clinical Applications	Use in solid tumors and combination chemotherapy regimens.	Continued clinical evaluations confirm its central role in testicular, ovarian, lung, and head and neck cancers.
Novel Formulation and Delivery Approaches	Liposomal systems, polymeric carriers, and nanoparticle-based strategies.	Advances in nanotechnology aim to enhance tumor selectivity through passive targeting mechanisms and improved pharmacokinetics.
Development of Platinum Derivatives	Structural modification of platinum compounds for improved safety and efficacy.	Newer platinum analogs and prodrug strategies are being explored to reduce toxicity and overcome resistance.
Future Directions	Personalized therapy, biomarker development, and targeted optimization.	Ongoing research focuses on integrating molecular profiling and combination strategies to enhance therapeutic precision.

In physiological environments, cisplatin participates in aquation reactions, in which chloride ligands are progressively substituted by water molecules, generating active species capable of binding to biological targets [23]. The velocity of aquation depends significantly on environmental chloride ion levels, with elevated blood chloride concentrations (roughly 100 mM) decelerating the aquation mechanism and preserving drug integrity throughout systemic distribution [24]. Upon cellular entry, where chloride levels diminish (approximately 4-20 mM), aquation accelerates dramatically, yielding mono-aqua $[Pt(NH_3)_2Cl(H_2O)]^+$ and di-aqua $[Pt(NH_3)_2(H_2O)_2]^{2+}$ species characterized by electrophilic properties and pronounced reactivity toward biological nucleophiles [25].

Contemporary investigations employing spectroscopic techniques and computational modeling have furnished more comprehensive insights into the kinetic and thermodynamic parameters governing cisplatin aquation [26]. These activated species mediate cytotoxic effects by binding to DNA and other target molecules, including proteins and membrane phospholipids [27]. Emerging evidence indicates that pH levels and medium composition influence cisplatin stability and reactivity, with implications for formulation enhancement and delivery optimization [28].

3.2. Cellular Penetration and Activation

The process by which cisplatin penetrates cellular membranes constitutes a critical preliminary step for anticancer efficacy. Current research emphasizes the substantial role of active transport in cisplatin cellular uptake [29]. Multiple transporter proteins have been implicated in facilitating cisplatin entry, notably copper transporter 1 (CTR1) and organic cation transporter 2 (OCT2), among others [30]. CTR1 functions as the predominant transporter mediating cisplatin cellular internalization [31]. Genetic and molecular investigations demonstrate that cellular systems exhibiting elevated CTR1 expression display enhanced cisplatin sensitivity, whereas diminished CTR1 expression associates with resistance development [32]. The transport process via CTR1 involves conformational changes in the protein structure that permit cisplatin to traverse plasma membranes [33]. Studies utilizing cryo-electron microscopy alongside crystallographic methods have elucidated CTR1's three-dimensional architecture and the molecular basis of platinum transport [34].

Beyond cellular uptake, cisplatin can undergo cellular efflux through multiple ATP-binding cassette (ABC) transporter proteins, including MRP2, ABCC1, ABCC2, and ATP7A/B, which participate in resistance mechanisms [35]. ATP7A and ATP7B, which ordinarily regulate copper homeostasis, possess the capability to recognize cisplatin and either expel it from cells or sequester it within intracellular vesicular compartments [36]. Elevated expression of these efflux systems has been documented across various cisplatin-resistant cancer types, presenting potential targets for combinatorial therapeutic strategies [37].

Investigations have also identified contributions from other transporters in cisplatin uptake, including OCT1, OCT2, and OCT3, which are predominantly expressed in renal and hepatic tissues [38]. The substantial OCT2 expression in renal tubular cells accounts for the preferential accumulation of cisplatin in the kidneys, contributing to nephrotoxic complications [39]. Understanding these transport dynamics creates opportunities to develop toxicity-reduction strategies through selective transporter modulation in non-malignant tissues [40]. Recent work has explored genetic variations in transporter-encoding genes that may influence cisplatin pharmacokinetic profiles and toxicity manifestations in individual patients [41].

3.3. DNA Interaction and Adduct Formation

The primary mechanism underlying cisplatin cytotoxicity involves covalent adduct formation with DNA (Figure 2) [42]. Aquated cisplatin species can attach to nitrogen bases within DNA, particularly at the N7 position of guanine and adenine residues, which function as potent nucleophiles [43]. DNA-platinum adduct generation proceeds through sequential stages: initially, a single chloride atom undergoes replacement by N7 guanine, establishing a monofunctional linkage; subsequently, the second chloride atom becomes substituted by N7 from a neighboring purine base, creating a bifunctional bond [44].

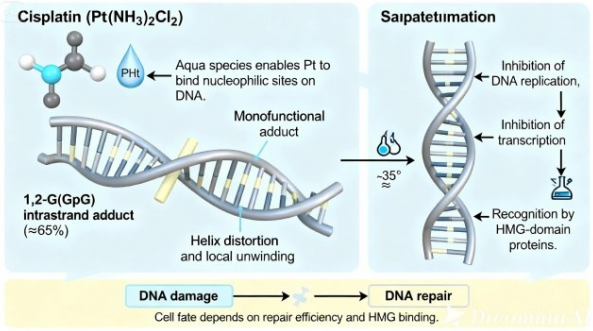

Figure 2. Mechanism of cisplatin interaction with DNA and DNA–Platinum adduct formation. *This figure was created by the author using Dreamina AI*

The spectrum of DNA-platinum adducts encompasses intrastrand 1,2-d(GpG) adducts representing the predominant lesion type (roughly 65% of total adducts), intrastrand 1,2-d(ApG) adducts (approximately 25%), intrastrand 1,3-d(GpXpG) adducts (around 6-10%), and interstrand adducts bridging two DNA strands (about 1–3%) [45]. Intrastrand 1,2-d(GpG) adducts induce the most pronounced structural deformation to the DNA helix, producing bending angles of approximately 32–35 degrees, accompanied by considerable kinking [46].

Structural alterations resulting from DNA-platinum adducts interfere with numerous DNA-dependent cellular processes [47]. Initially, platinum adducts impede DNA replication by obstructing DNA polymerase advancement, precipitating DNA synthesis arrest, and activating cell cycle checkpoints [48]. Additionally, platinum adducts obstruct gene transcription by inhibiting RNA polymerase II activity, potentially triggering diverse cellular stress signaling cascades [49]. Furthermore, platinum adducts are recognized by various DNA-binding proteins, including high-mobility group (HMG) proteins and the DNA repair machinery, which influence cellular outcomes following DNA damage [50].

Recent crystallographic X-ray analyses and NMR spectroscopic investigations have yielded detailed structural information regarding DNA-platinum adducts and their interactions with cellular proteins [51]. HMG-domain proteins, particularly HMGB1, can associate with cisplatin-DNA adducts and shield them from repair processes, consequently enhancing cytotoxicity [52]. Conversely, HMG protein overexpression may also promote resistance through protective mechanisms that restrict access of DNA repair proteins to lesion sites [21]. The intricate nature of these molecular interactions indicates that cellular responses to cisplatin reflect a delicate equilibrium among numerous interacting factors [53].

3.4. DNA Damage Response and Signal Pathways

When platinum-DNA adducts form, they set off an elaborate cellular alarm system known as the DNA damage response (DDR). This system involves molecular sensors that detect damage, signaling proteins that relay the signal, and effector proteins that ultimately determine whether the cell lives or dies [54]. Two key

protein kinases, ATM (Ataxia Telangiectasia Mutated) and ATR (ATM and Rad3-related), serve as primary sensors that kickstart protective responses, including cell cycle checkpoints and DNA repair mechanisms [55]. These two kinases respond to different types of damage: ATR springs into action when replication machinery stalls at platinum-damaged DNA sites, while ATM gets activated by double-strand breaks that can occur when cells attempt to replicate or repair platinum-damaged DNA [56].

Once ATM or ATR becomes active, they add phosphate groups to various downstream proteins, particularly the checkpoint kinases CHK1 and CHK2. These kinases then modify p53, a critical tumor suppressor protein, activating it [57]. Scientists often call p53 the "guardian of the genome" because it controls genes that halt cell division, repair DNA damage, and initiate programmed cell death [58]. After cisplatin damages DNA, p53 can stop the cell cycle at specific checkpoints (G1/S or G2/M transitions), giving the cell time to attempt repairs [59]. However, if the damage proves too extensive to repair, p53 activates genes such as BAX, PUMA, and NOXA that drive the cell toward death [60].

The loss or malfunction of p53, which occurs in more than 50% of human cancers, creates a major obstacle for cisplatin treatment [61]. Cancer cells with faulty or missing p53 struggle to execute proper cell death programs after DNA damage, allowing them to survive cisplatin exposure more effectively [62]. Fortunately, research has shown that cisplatin can activate alternative death pathways that do not require p53, which may help overcome this type of resistance [63].

Cisplatin does not just work through the ATM/ATR-p53 route; it also activates several other important signaling networks that contribute to killing cancer cells [64]. The MAPK (Mitogen-Activated Protein Kinase) family, which includes ERK, JNK, and p38 MAPK, is activated by cisplatin and plays complex, sometimes contradictory roles in the cell's response [65]. Activation of JNK and p38 MAPK typically pushes cells toward death, supporting cisplatin's cancer-killing effects. In contrast, ERK activation often helps cells survive and can contribute to drug resistance [66]. The final outcome, whether a cell dies or survives, depends on the balance between these competing death-promoting and survival-promoting signals [67].

3.5. Cisplatin-Induced Apoptosis Mechanism

Programmed cell death, or apoptosis, is the primary mechanism by which cisplatin kills cancer cells [68]. This drug can initiate cell death via two distinct pathways: the intrinsic pathway (which centers on mitochondria) and the extrinsic pathway (which involves cell-surface receptors) [69]. The intrinsic route is triggered when DNA damage and cellular stress cause the mitochondrial outer membrane to become leaky, a process called mitochondrial outer membrane permeabilization (MOMP) [70]. Whether MOMP occurs depends on a tug-of-war between two groups within the Bcl-2 protein family: death-promoting proteins (such as BAX, BAK, BID, BIM, PUMA, and NOXA) and survival-promoting proteins (like Bcl-2, Bcl-XL, and MCL-1) [71].

When cisplatin damages DNA, it activates p53, which then ramps up production of specific death-promoting proteins called BH3-only proteins, particularly PUMA and NOXA [60]. These proteins essentially neutralize the survival-promoting Bcl-2 family members, freeing up BAX and BAK to do their work. BAX and BAK then cluster together, punching holes in the mitochondrial outer membrane [72]. Through these holes, cytochrome c and other death-promoting molecules escape from the space between the mitochondrial membranes into the cell's cytoplasm [73].

After cytochrome c gets released, it binds to a protein called APAF-1 (Apoptotic Protease Activating Factor-1). Together, they assemble into a wheel-like structure called the apoptosome, which activates caspase-9, the enzyme that initiates the intrinsic death cascade [74]. Caspase-9 then cuts and activates executioner caspases (specifically caspase-3, -6, and -7). These enzymes carry out cell dismantling by degrading numerous cellular components, from structural supports to DNA repair machinery and regulatory proteins [75]. As these caspases do their work, they create the telltale signs of apoptosis: the cell's DNA becomes tightly packed, the nucleus breaks apart, small membrane-bound fragments called apoptotic bodies form, and a lipid molecule called phosphatidylserine flips from the inner to the outer surface of the cell membrane [76].

The alternative route to cell death, the extrinsic pathway, initiates at the cell surface when death-signaling molecules (such as FasL, TRAIL, or TNF-α) bind their respective receptors (Fas, DR4/DR5, or TNFR1) [77]. Interestingly, cisplatin can increase the number of these death receptors on cells and make cells more responsive to death signals [78]. Upon activation, these receptors recruit the adaptor protein FADD and procaspase-8, leading to the formation of the death-inducing signaling complex (DISC), which subsequently activates caspase-8 [79]. Active caspase-8 can activate the executioner caspases directly or cleave a protein called BID into its active form (tBID), which then engages the mitochondrial pathway to amplify the death signal [80]. Figure 3 illustrates how cisplatin triggers these apoptotic mechanisms.

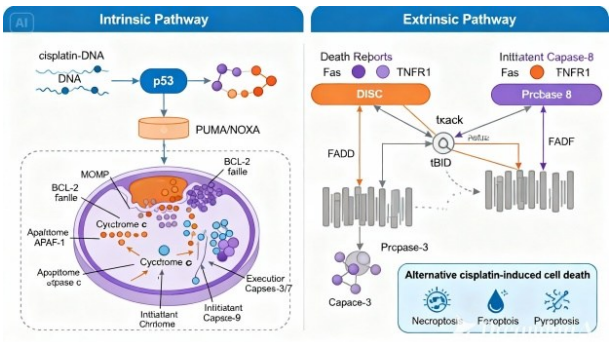

Figure 3. Schematic representation of cisplatin-induced apoptosis through intrinsic (mitochondrial) and extrinsic (death receptor) pathways. *This figure was created by the author using Dreamina AI*

Recent studies have revealed that cisplatin does not just kill cancer cells through the classical apoptosis pathway; it can actually trigger several other types of cell death, including necroptosis, ferroptosis, pyroptosis, and autophagy-dependent death [81]. Necroptosis is a form of programmed cell death regulated by three kinases: RIPK1, RIPK3, and MLKL. Unlike apoptosis, which quietly dismantles cells, necroptosis causes cells to burst open and spill their contents, which can spark inflammatory reactions in surrounding tissues [82]. Ferroptosis is another distinct death mechanism in which cells accumulate damaged lipids in their membranes due to iron-catalyzed oxidation, ultimately leading to cell death [83]. The fact that cisplatin can activate all these different death pathways helps explain its effectiveness against cancer, and scientists believe we might be able to harness these mechanisms to make the drug work even better [84].

3.6. Role of Oxidative Stress in Cisplatin Cytotoxicity

While oxidative stress plays a significant role in how cisplatin kills cancer cells, it is not the primary mechanism by which the drug works [85]. Cisplatin can trigger the production of harmful molecules called reactive oxygen species (ROS), including superoxide anion, hydrogen peroxide, and hydroxyl radicals, through several different cellular mechanisms [86]. Initially, cisplatin can interact with mitochondrial enzymes and disrupt electron transport chains, causing electron leakage and ROS generation [87]. Additionally, cisplatin can activate NADPH oxidase, which catalyzes the production of superoxide [88]. Furthermore, cisplatin can inactivate antioxidant enzymes, including glutathione peroxidase and catalase, diminishing cellular capacity for ROS detoxification [89].

Excessive ROS production can inflict oxidative damage upon various cellular macromolecules, including DNA, proteins, and lipids [90]. Oxidative damage to DNA, in combination with cisplatin's direct toxic effects on genetic material, strengthens the signal for cells to undergo apoptosis [91]. Membrane lipid peroxidation can compromise membrane integrity and cellular function [92]. Protein oxidation can cause enzyme inactivation and disruption of signaling pathways [93]. The cumulative impact of oxidative stress contributes to cisplatin cytotoxicity in malignant cells [94].

However, the role of oxidative stress in cisplatin's anticancer activity remains debated, as some studies show that antioxidants fail to significantly diminish cisplatin cytotoxicity in vitro, suggesting that ROS may not serve as primary mediators of cell death [95]. Conversely, cisplatin-induced oxidative stress plays a crucial role in normal tissue toxicity, particularly nephrotoxicity, ototoxicity, and neurotoxicity [10]. Understanding the differential role of oxidative stress in malignant versus normal cells proves essential for developing selective toxicity protection strategies [96].

3.7. Resistance Mechanisms to Cisplatin

Cisplatin resistance constitutes a major clinical challenge limiting therapeutic success [97]. Resistance may be intrinsic (pre-existing) or acquired following drug exposure [98]. Cisplatin resistance mechanisms are multifactorial and can be categorized into several principal groups: (1) diminished intracellular drug accumulation; (2) enhanced drug detoxification; (3) augmented DNA repair capacity; (4) tolerance to DNA damage; and (5) disruption of apoptotic pathways [16].

Reduced intracellular cisplatin accumulation can occur through decreased drug uptake or enhanced drug efflux [32]. CTR1 downregulation or mutation has been documented in resistant cancer cells and correlates with diminished cisplatin sensitivity [99]. Conversely, efflux transporter overexpression, including ATP7A, ATP7B, and MRP2, can increase cisplatin export from cells or sequester it in intracellular vesicles, reducing the drug concentration reaching nuclear DNA [35, 36].

Enhanced cisplatin detoxification primarily operates through the glutathione (GSH) and metallothionein (MT) systems [98]. GSH, a tripeptide containing thiol groups, can react with cisplatin to form platinum-glutathione conjugates exhibiting reduced reactivity and enhanced cellular export [100]. Resistant cancer cells frequently display elevated expression of GSH biosynthesis enzymes, including γ-glutamylcysteine synthetase and glutathione synthetase, as well as glutathione S-transferase (GST), which catalyzes cisplatin conjugation to GSH [101]. Metallothionein, a cysteine-rich protein, can bind platinum and inactivate cisplatin [102]. MT overexpression has been documented in various cisplatin-resistant cancers and correlates with an unfavorable prognosis [103].

Augmented DNA repair capacity represents an important resistance mechanism by removing DNA-platinum adducts before inducing cell death [104]. The principal repair pathway involved is nucleotide excision repair (NER), which can recognize and excise platinum-DNA adducts [105]. Cells exhibiting high expression of NER proteins, including ERCC1, XPA, XPC, and XPF, demonstrate elevated cisplatin resistance [106]. ERCC1 has been identified as a predictive biomarker for response to platinum-based therapy in non-small cell lung cancer [107]. Additional repair pathways, including mismatch repair (MMR) and base excision repair (BER), can also contribute to resistance [108].

3.8. Cisplatin Toxicity and Its Management

The clinical use of cisplatin faces substantial limitations due to its side effects, some of which can be severe enough to force dose reductions or treatment discontinuation [10]. The drug's most troubling toxicities, including kidney damage, nerve damage, hearing loss, bone marrow suppression, and severe nausea with vomiting, can dramatically reduce patients' quality of life [109]. Among these, kidney toxicity stands out as the most concerning problem, affecting roughly one in four to one in three patients [110]. This kidney damage occurs because cisplatin is concentrated in the kidney's proximal tubular cells via the OCT2 transporter. Once inside these cells, the drug triggers a cascade of harmful events: excessive oxidative stress, mitochondrial breakdown, inflammatory responses, and ultimately cell

death [39]. The flood of reactive oxygen species in these tubular cells wreaks havoc by degrading membrane lipids, damaging DNA, and activating death pathways [111]. Patients with kidney toxicity typically show declining kidney filtration capacity, rising creatinine levels in their blood, loss of essential electrolytes (especially magnesium and potassium), and, in the worst scenarios, sudden kidney failure [112].

To minimize kidney damage, doctors employ several protective measures: aggressive intravenous fluid administration with saline to increase urine production and flush cisplatin from the kidney tubules, replacement of depleted electrolytes, and sometimes kidney-protective medications [113]. Researchers have tested various protective drugs, including amifostine (which neutralizes toxic cisplatin breakdown products), antioxidants like N-acetylcysteine and vitamin E, and medications that block the OCT2 transporter [114]. The challenge with these protective agents is finding the right balance; they must shield healthy kidney tissue without interfering with cisplatin's ability to kill cancer cells [115].

Nerve damage from cisplatin depends on both the dose per treatment and the total amount received over time, affecting 30–40% of patients who receive high cumulative doses [116]. This nerve toxicity typically presents as peripheral sensory neuropathy, starting in the fingers and toes, with abnormal sensations such as tingling, increased pain sensitivity, and numbness [117]. The underlying problem involves platinum buildup in the dorsal root ganglia (nerve cell clusters near the spine), oxidative injury to sensory nerve cells, mitochondrial malfunction, and deterioration of nerve fibers [118]. Unfortunately, this nerve damage can become permanent and seriously diminish patients' quality of life [119]. Despite testing numerous potential treatments from antioxidants to nerve-protecting compounds to anti-inflammatory drugs, doctors still lack a proven effective way to prevent or reverse cisplatin-related nerve damage [120].

Hearing damage occurs in anywhere from 20% to 60% of adults taking cisplatin, with children experiencing even higher rates [121]. The drug destroys the delicate hair cells in the cochlea (inner ear) by generating oxidative stress and triggering their death, resulting in permanent hearing loss that particularly affects high-frequency sounds [122]. The likelihood of hearing damage increases with higher total doses, simultaneous head radiation, and certain genetic predispositions [123]. To protect hearing, doctors may use antioxidants such as sodium thiosulfate, which the FDA has approved specifically for preventing hearing loss in children with neuroblastoma, and may also administer cisplatin more slowly through prolonged infusions [124]. The various toxic effects discussed above, including nephrotoxicity, neurotoxicity, and ototoxicity, along with their underlying mechanisms and corresponding protective strategies, are summarized in Figure 4.

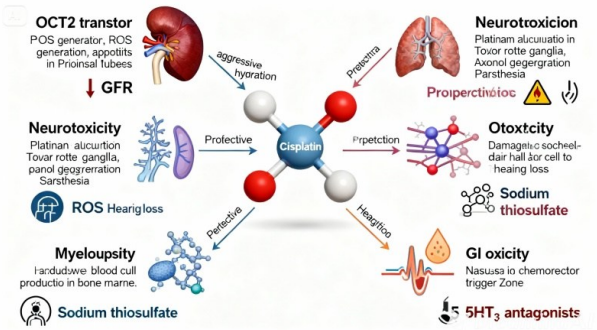

Figure 4. Schematic overview of cisplatin-induced toxicities, mechanisms, and protective strategies. *This figure was created by the author using Dreamina AI*

3.9. Clinical Applications of Cisplatin

Cisplatin has established itself as a fundamental component in chemotherapy protocols across diverse cancer types, with variable success rates [5]. In testicular malignancies, cisplatin is part of the BEP regimen (bleomycin, etoposide, cisplatin), which has cure rates exceeding 90% in patients presenting with early-stage disease [6]. This extraordinary achievement positions testicular cancer as a paradigm for curative chemotherapy in solid tumor management [125].

For ovarian malignancies, the combination of cisplatin or carboplatin with paclitaxel constitutes standard first-line therapy [126]. Clinical investigations demonstrate that this combination yields response rates spanning 60–80% with median survival durations of 3–4 years in advanced-stage presentations [127]. Nevertheless, platinum resistance persists as a substantial obstacle, with the majority of patients experiencing disease recurrence [128].

For patients with advanced non-small cell lung cancer (NSCLC), doctors typically use platinum-containing treatment regimens that pair either cisplatin or carboplatin with other drugs like paclitaxel, gemcitabine, or pemetrexed as the established treatment approach [129]. When researchers have pooled data from multiple studies, the evidence clearly shows that patients receiving platinum-based chemotherapy live longer than those getting only supportive care [130]. In small-cell lung cancer, combining cisplatin with etoposide produces impressive initial tumor responses, though unfortunately, most patients eventually experience disease recurrence [131].

Head and neck malignancies are frequently managed with combined cisplatin and radiation therapy (chemoradiotherapy), which has demonstrated improved local control and survival compared to radiation monotherapy [132]. Cisplatin functions as a radiosensitizer, amplifying the effectiveness of radiation by inhibiting the repair of radiation-induced DNA damage [133]. Alternatively, cisplatin can be paired with other chemotherapeutic agents, including 5-fluorouracil, in neoadjuvant or adjuvant regimens [134].

3.10. Strategies to Overcome Resistance and Improve Effectiveness

Given the resistance challenges that constrain the success of cisplatin therapy, numerous strategies have emerged to overcome resistance and enhance therapeutic effectiveness [17]. Combination therapy is a principal approach in which cisplatin is paired with other chemotherapeutic agents with complementary mechanisms of action [7]. This combination can enhance effectiveness through synergistic effects and reduce the possibility of resistance by targeting multiple cellular pathways [135]. Combining cisplatin with inhibitors of signaling pathways that facilitate resistance represents a promising strategy [136]. For instance, combining with PI3K/AKT/mTOR pathway inhibitors, which are frequently activated in platinum-resistant cancers, has yielded encouraging results in preclinical investigations [137]. Drugs that block PARP (poly ADP-ribose polymerase), an enzyme involved in fixing damaged DNA, have gained regulatory approval for treating ovarian cancers that have defects in homologous recombination repair. These PARP inhibitors work particularly well when combined with platinum drugs, producing effects greater than either treatment alone [138].

Transporter modulation to enhance cisplatin accumulation or reduce efflux represents another approach under exploration [139]. ATP7A/B and MRP2 inhibitors have been investigated to enhance intracellular cisplatin retention [140]. Conversely, OCT2 inhibitors can be used to reduce cisplatin uptake in the kidneys and thereby reduce nephrotoxicity without compromising anticancer efficacy [40].

The development of nanotechnology-based drug delivery systems is a highly active research domain aimed at improving selectivity and reducing cisplatin toxicity [141]. Nanoparticles can enhance cisplatin accumulation in tumors through the enhanced permeability and retention effect and reduce distribution to normal tissues [18]. Various nanocarrier platforms have been developed, encompassing liposomes, polymeric micelles, polymer nanoparticles, and inorganic nanoparticles [142].

Table 2. Comparison of various cisplatin formulation systems to improve therapeutic effectiveness

Objective	Method (formulation system & test model)	Results	Conclusion	Remarks (nanoparticle type/technical notes)	Ref
Develop Pt(IV) prodrug in PLGA-PEG nanoparticle with aptamer for targeted delivery of cisplatin to prostate cancer cells.	Pt(IV) prodrug synthesis → encapsulation in PLGA-PEG nanoparticles → surface conjugated with targeting aptamer; tested in vitro on cancer cells and preclinical models.	Increased cellular uptake and antitumor effectiveness compared to free cisplatin.	Pt(IV)-PLGA-PEG + aptamer formulation increases selectivity and efficacy while reducing systemic toxicity.	Nanocarrier: PLGA-PEG nanoparticle with aptamer targeting, significant results in preclinical studies.	[141]
Use gold nanoparticles (AuNPs) to polyvalently carry Pt(IV) prodrugs via oligonucleotides.	Conjugation of Pt(IV) warheads to gold-oligonucleotide nanoparticle; tested in vitro on various cancer cells.	Increased uptake and cytotoxic activity compared to free Pt(IV) prodrug.	AuNP-oligo increases the delivery efficiency and therapeutic potential of platinum.	Gold nanoparticle + oligonucleotide scaffold increases payload and targeting ability.	[18]
Develop mesoporous silica nanoparticles (MSNs) with pH-sensitive nanovalves for autonomous drug release.	MSNs formulation with nanovalves → drug loading → in vitro release and anticancer activity testing.	Controlled drug release responsive to tumor microenvironment pH; increased drug delivery.	MSNs with nanovalves enable controlled and selective drug release in the tumor area.	Mesoporous silica nanoparticle (MSN) with a pH-responsive nanovalve system.	[142]
Assess the effectiveness of liposomal cisplatin (Lipoplatin) compared to conventional cisplatin in combination with paclitaxel in lung cancer (NSCLC).	Randomized phase III clinical trial; comparing liposomal cisplatin + paclitaxel vs cisplatin + paclitaxel.	Better pharmacokinetic profile and lower toxicity with Lipoplatin, with similar clinical effectiveness.	Liposomal cisplatin reduces systemic toxicity without decreasing efficacy.	Liposomal formulation (Lipoplatin) --- phase III clinical trial.	[143]
Characterize phenanthriplatin, a monofunctional Pt(II) candidate with new anticancer potential.	Compound synthesis → in vitro testing of cytotoxic activity, DNA binding, and cellular mechanisms.	Stronger cytotoxic activity and a different mechanism of action from cisplatin.	Phenanthriplatin offers an alternative Pt(II) design with high efficacy and reduced toxicity.	Platinum derivative (not nanoparticle), important for new drug design direction.	[27]

Lipoplatin, a liposomal cisplatin formulation, has advanced to clinical trials and demonstrates superior pharmacokinetics with reduced toxicity [143]. Active targeting utilizing nanoparticles conjugated with antibodies, peptides, or aptamers that recognize specific receptors on cancer cells can further enhance selectivity and effectiveness [18]. Recent investigations also explore stimuli-responsive nanoparticles that are sensitive to pH, enzymes, or light for improved control of drug release [142].

3.11. New Generation Platinum Derivatives

To address cisplatin's limitations, various new-generation platinum derivatives have been developed to improve effectiveness and reduce toxicity [19]. Carboplatin, a second-generation platinum analog, exhibits a superior toxicity profile compared to cisplatin with diminished nephrotoxicity, neurotoxicity, and ototoxicity, though it induces more severe myelosuppression [143]. Carboplatin has emerged as an alternative to cisplatin across various indications, particularly ovarian cancer [19].

Oxaliplatin, a third-generation platinum derivative, possesses a distinct activity spectrum from cisplatin and carboplatin [4]. Oxaliplatin demonstrates effectiveness against colorectal cancer, which typically resists cisplatin, and has become standard care for advanced-stage colorectal cancer when combined with 5-fluorouracil and leucovorin (FOLFOX regimen) [7]. Nedaplatin, a platinum analog developed in Japan, shows activity comparable to cisplatin with reduced toxicity in certain cancer types [14].

Newer platinum derivatives are at various stages of clinical development, with diverse structural modifications designed to increase cellular uptake, overcome resistance, or reduce toxicity [8]. Satraplatin represents the first oral platinum compound to reach phase III clinical trials for castration-resistant prostate cancer [9]. Picoplatin was designed to overcome resistance mediated by thiol detoxification systems and has entered clinical trials for various cancer types [10].

Platinum(IV) complexes are also being developed as prodrugs that can be reduced to active platinum(II) within cancer cells, aiming to increase stability and reduce systemic toxicity [11]. Several platinum(IV) complexes have advanced to preclinical studies and display promising pharmacokinetic and pharmacological profiles [12]. The dual-action platinum complexes approach, combining platinum with other bioactive molecules, is also under exploration to enhance effectiveness [13].

3.12. Future Perspectives and Research Directions

Cisplatin maintains its position as the cornerstone of platinum-based cancer therapy, yet its clinical application and effectiveness remain constrained by numerous significant challenges. Future perspectives in platinum-based therapy development must integrate deeper mechanistic comprehension with innovative strategies capable of overcoming current limitations. Research directions warranting prioritization include, first, the development of precise predictive biomarkers to forecast tumor sensitivity and potential toxicity in individual patients, thereby enabling the implementation of personalized medicine [144]. Second, elucidation of multifactorial resistance mechanisms involving dynamic interactions among cancer cells, tumor microenvironment, and epigenetic factors to identify novel targetable pathways [16]. Third, optimization of nanoparticle-based delivery systems with active targeting capabilities that can selectively enhance cisplatin accumulation in tumors while diminishing toxicity in normal tissues [145].

Fourth, exploration of cisplatin combinations with immunotherapy and targeted therapy targeting specific resistance pathways through rigorously designed clinical studies to identify optimal strategies that yield synergistic benefits [146]. Fifth, development of protective strategies capable of preventing or mitigating long-term toxicities, including neurotoxicity and ototoxicity, through mechanistic, pharmacological, and regenerative medicine approaches [147]. Finally, the development of new generation platinum derivatives with enhanced pharmacological profiles and broader activity spectra against tumors resistant to conventional cisplatin will expand the platinum-based therapy armamentarium [13].

3.13. Strategies to Enhance Therapeutic Effects and Minimize Side Effects

Efforts to augment cisplatin's therapeutic effects while minimizing adverse effects have become the focal point of intensive research. Various approaches have been developed by leveraging an in-depth understanding of cisplatin's mechanism of action and previously described toxicity. One strategy demonstrating promising outcomes involves modifying the cisplatin administration schedule and route. Cisplatin administration via slow infusion has been shown to reduce the incidence of nephrotoxicity compared to bolus injection, as it provides temporal windows for the kidneys to engage endogenous protective mechanisms [113]. Combination with aggressive saline hydration before and after cisplatin administration remains the standard of care to maintain renal function [109]. Electrolyte supplementation, particularly magnesium and potassium, is essential, as cisplatin can cause substantial electrolyte depletion through renal tubular damage [112].

The utilization of selective protective agents represents another approach under continuous development. Amifostine, as a cytoprotective agent, has found application in clinical practice to reduce nephrotoxicity, although its use requires balancing against the potential anticancer effectiveness reduction [114]. Sodium thiosulfate has received FDA approval specifically for preventing ototoxicity in pediatric neuroblastoma patients, providing clinical evidence that selective normal tissue protection can be achieved without sacrificing antitumor efficacy [124].

Using nanotechnology to deliver cisplatin opens exciting possibilities to improve the drug's tumor-killing effects while causing fewer side effects. Liposomal

formulations such as Lipoplatin have shown promising results in clinical studies. These tiny fat-based bubbles carrying cisplatin tend to accumulate preferentially in tumors due to their leaky blood vessels (a phenomenon called the enhanced permeability and retention effect), while largely avoiding healthy organs like the kidneys [143]. Scientists have taken this a step further by attaching tumor-seeking molecules, either aptamers or antibodies, to nanoparticles, essentially giving them a homing mechanism that guides them specifically to cancer cells [141]. Some researchers have designed even smarter nanoparticles that respond to the acidic environment surrounding tumors, releasing their cisplatin payload only when they reach the right location. This targeted approach ensures maximum drug exposure where it is needed while sparing the rest of the body [142].

Another promising direction involves carefully choosing drug combinations. When cisplatin gets paired with medications that block DNA repair enzymes like PARP, the results can be particularly impressive, especially in cancers that already have trouble repairing certain types of DNA damage through homologous recombination [138]. Adding drugs that alter how cells transport cisplatin can help the drug penetrate resistant tumor cells more effectively [139]. There is also potential in using selective inhibitors of the OCT2 transporter in kidney tissue, which could protect against kidney damage without interfering with cisplatin's ability to reach and kill cancer cells that do not rely on this particular transporter [40].

Scientists are also working to block the specific mechanisms tumors use to resist cisplatin. For instance, drugs that inhibit glutathione S-transferase, an enzyme that helps cancer cells detoxify cisplatin, can make resistant tumors vulnerable again [101]. Similarly, targeting survival pathways like PI3K/AKT/mTOR, which resistant tumors often activate to stay alive, can restore their sensitivity to cisplatin [137]. Researchers are even exploring combinations with immunotherapy, based on evidence that cisplatin can alter immune responses, making tumor cells more visible to the immune system [146].

Finding the right biomarkers to predict treatment outcomes has become crucial for personalizing therapy. Testing for ERCC1 protein levels, which reflects a tumor's DNA repair capacity, can help doctors determine which patients are most likely to respond to platinum drugs [107]. Genetic variations in the SLC22A2 gene, which encodes the OCT2 transporter, can help doctors identify patients at higher risk of kidney damage, allowing them to adjust doses accordingly [41]. Similarly, knowing whether a patient's tumor has mutated p53, a key protein in the cell death response to DNA damage, can provide valuable prognostic clues [61].

Development of platinum derivatives with improved toxicity profiles represents an important alternative. Carboplatin, with substantially lower nephrotoxicity, has become a choice for patients with a high risk of kidney disorders [143]. Platinum(IV) complexes, which can be reduced to active forms in tumor cells, offer enhanced stability during circulation and the potential for reduced systemic toxicity [11]. The design of platinum complexes with ligands that can modulate pharmacokinetics and biodistribution continues under development to achieve optimal therapeutic profiles [8].

Proactive side effect management also contributes significantly to therapeutic success. Use of new-generation antiemetics, including NK1 receptor antagonists, has greatly improved control of cisplatin-induced nausea and vomiting, thereby improving patient quality of life and treatment compliance [109]. Close monitoring of renal function, auditory function, and neurological status enables early detection of toxicity and timely intervention [112, 119, 121]. Patient education on the importance of adequate hydration and early reporting of toxicity symptoms is an integral part of comprehensive management.

Multidisciplinary approaches integrating these strategies offer hope of maximizing the benefits of cisplatin therapy while minimizing its negative impacts. Ongoing research to understand the molecular mechanisms underlying response and toxicity, combined with pharmaceutical innovation and biomarker identification, will continue to open new opportunities to optimize cisplatin use as an effective and safe anticancer agent.

4. Limitations

This review has several limitations. As a narrative review, it does not include formal protocol registration or a quantitative risk of bias assessment of the included studies. The selected publications were screened based on relevance and scientific contribution to the topic. Although efforts were made to include high-quality, peer-reviewed articles from reputable databases, the absence of a formal bias assessment may affect the interpretation of the findings.

5. Conclusion

Cisplatin maintains its position as one of the most significant and widely utilized chemotherapy drugs in cancer management. Cisplatin's action mechanism is remarkably complex and encompasses multiple molecular pathways culminating in cancer cell death. DNA-platinum adduct formation constitutes the principal cytotoxic mechanism that disrupts DNA replication and transcription, activates DNA damage responses, and triggers apoptosis through intrinsic and extrinsic pathways. Oxidative stress, activation of the MAPK pathway, and induction of various cell death modalities also contribute to cisplatin's anticancer activity. Cisplatin resistance represents a major clinical obstacle limiting therapeutic success. Resistance mechanisms are multifactorial, encompassing decreased drug accumulation, enhanced detoxification, increased DNA repair, DNA damage tolerance, and disruption of apoptotic pathways. An in-depth understanding of resistance mechanisms has enabled the development of strategies to overcome resistance, including combination therapy, transporter modulation, targeting resistance signaling pathways, and nanotechnology-based drug

delivery systems. Cisplatin toxicity, particularly nephrotoxicity, neurotoxicity, and ototoxicity, remains a major challenge constraining clinical use. Toxicity management strategies, including aggressive hydration, electrolyte supplementation, nephroprotective and ototoxicity agents, and dose adjustment, continue to be under development. The development of predictive biomarkers for therapeutic response and toxicity can facilitate personalized medicine approaches that optimize the use of cisplatin. Clinical applications of cisplatin span a wide range of cancer types, with variable success rates. The remarkable success in testicular cancer demonstrates the curative potential of platinum-based chemotherapy in solid tumor management. The development of new-generation platinum derivatives with improved toxicity profiles and distinct activity spectra has expanded the platinum-based therapy armamentarium. Future research should focus on identifying more precise biomarkers for response and toxicity prediction, developing effective strategies to overcome resistance, optimizing drug delivery systems to improve tumor selectivity, and exploring combinations with targeted therapy and immunotherapy. With a deeper understanding of cisplatin mechanisms and the development of more rational therapeutic strategies informed by research from 2015 to 2025, improvements in the effectiveness of platinum-based therapy are expected while minimizing toxicity, thereby improving outcomes and quality of life for cancer patients.

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