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Cisplatin's Silver Lining: The Potential of Curcumin as A Mitigating Agent

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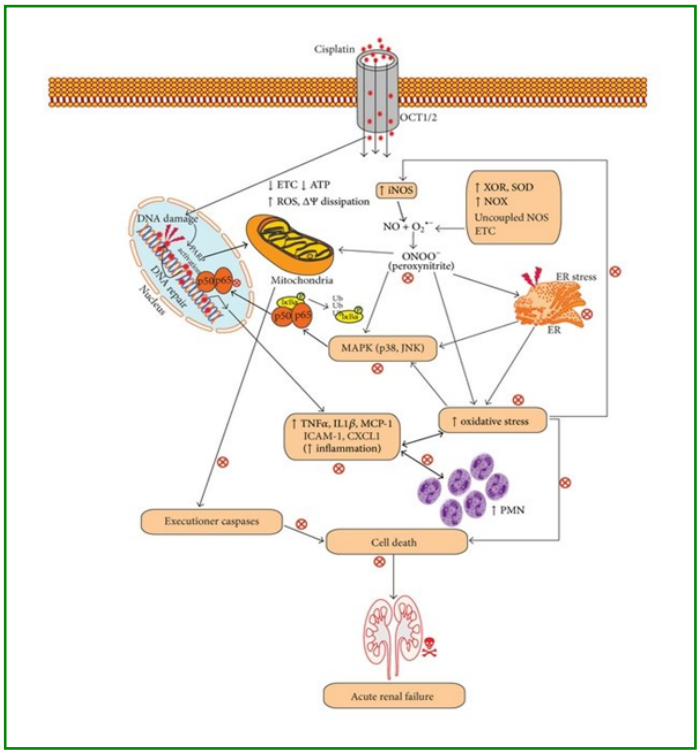
Graphical Abstract



Abstract

Cisplatin, a platinum-based chemotherapy drug, has been a cornerstone in treating various cancers, particularly testicular and ovarian tumours, for nearly four decades. It works by damaging DNA and forming bonds between DNA and proteins, leading to

cancer cell death. However, its effectiveness is often limited by severe side effects, including nephrotoxicity, and the development of drug resistance due to cancer cells' ability to repair DNA damage. Recent advancements have mapped cisplatin-induced DNA damage across the human genome, offering insights into cancer sensitivity and resistance mechanisms. One promising approach to enhancing cisplatin's efficacy and reducing its side effects is combining it with curcumin, a polyphenolic compound from turmeric known for its anticancer properties and minimal side effects. Curcumin has shown potential in sensitizing cancer cells to cisplatin, although its low bioavailability remains a challenge. More high-quality research is needed to fully understand the effectiveness of this combination therapy and to optimize its use in clinical settings. This review explores the side effects of cisplatin, the benefits of curcumin, and the potential of their combination delivered via nanocarriers as a novel cancer treatment strategy.

Keywords: Diaminodichloroplatinum; Chemotherapy; Nanocarriers; Cisplatin's; Nephrotoxicity

Abbreviations

FDA: Food And Drug Administration; NER: Nucleotide Excision Repair; HR: Homologous Recombination; NHEJ: Nonhomologous End Joining; ICLs: Interstrand Crosslinks; MOMP: Mitochondrial Outer Membrane Permeabilization; ROS: Reactive Oxygen Species; BUN: Blood Urea Nitrogen; GPX: Glutathione Peroxidase; OAT: Organic Anion Transporter; OCT: Organic Cation Transporter; ERCC1: Excision Repair Cross-Complementation Group 1.

Introduction

Today, heart disease is the leading cause of death in developed countries and cancer is the second leading cause of death in developing countries. According to GLOBOCAN, there were 12.7 million cancer cases and 7.6 million cancer deaths in 2008; 64% of cancer deaths and 56% of cancer cases occurred in developing countries [1]. In addition, the incidence of cancer has been predicted to almost double between 2020 and 2030 [1]. Scientists and medical professionals around the world are interested in the use of platinum and other metals in cancer treatment, including the development of cisplatin analogues. Cisplatin analogues with antitumor efficacy comparable to cisplatin but with a lower toxicity profile are carboplatin and oxaliplatin [2]. The platinum coordination complex is cis-diaminodichloroplatinum (II) (NSC 119875), also known as cisplatin, is a planar shape. Two amine groups and two chloride ions are attached to platinum. Cisplatin is called the "penicillin of cancer" because it is often used in clinics and because it was the first effective chemotherapy agent used in cancer treatment when it was approved by the FDA in 1978 as the platinols [3-5]. Cisplatin, also known as CDDP or platinol, is an antitumor drug that is the basis of many different cancer regimens and has improved survival and led to cures [6,7]. Cisplatin is a platinum-based alkylating agent that interacts with DNA to form interstrand bifunctional N-7 DNA adducts d(GpG) and d(ApG) and interstrand crosslinks [8-11]. Despite side effects, particularly nephrotoxicity and ototoxicity at low doses, cisplatin remains the first-line treatment for many types of solid tumors [12]. When used, CDDP-based therapy often works to achieve initial therapeutic success, characterized by a partial or stabilization tumour response. However, a large proportion of patients develop intrinsic drug resistance or cisplatin resistance during treatment, leading to treatment failure [13,14]. Cisplatin is given to 10-20% of cancer patients because of its effectiveness in reducing cancer growth. Cisplatin is absorbed and excreted by the kidney via proximal tubule-specific transporters such as OCT2 and MATE1. As a result, cisplatin accumulates in renal proximal tubule cells, causing swelling, damage, and cell death [15]. However, persistent adverse effects of cisplatin, such as inhibition of transcription, cell cycle arrest, production of reactive oxygen species (ROS) and apoptosis, limit its therapeutic use [16]. Compared with a control group that received no treatment, the five-year absolute benefit of cisplatin chemotherapy was a 6.9% reduction in lung cancer-related deaths [17]. The precise antitumor effects of cisplatin are still poorly understood [18-21]. Gastrointestinal symptoms (such as nausea and vomiting), bone marrow suppression, ototoxicity, neurotoxicity (such as peripheral neuropathy), hepatotoxicity, genotoxicity, etc. some side effects are also seen at therapeutic levels [22]. Currently, there are no FDA-approved treatments to reduce or prevent permanent hearing loss caused by cisplatin [23]. Due to ineffective medication delivery to the tumors, many potent therapeutic medicines tested in vitro did not provide any effects in vivo. To get around this obstacle, researchers have had success employing protective substances like curcumin [24], berberine [25], resveratrol [26], and cinnamon [27], among others, to lessen side effects or boost the anticancer effectiveness of cisplatin. Additionally, platforms for drug delivery that incorporate micro- and nanocarriers can

improve the bioavailability of medications [28-30]. Typically, DNA is thought to be its main biological target [31]. About 65% of cis-(Pt (NH3)2d(GpG)) ("cis-GG") and about 25% of cis-(Pt (NH3)2d(ApG) ("cis-AG") are produced when the platinum atom of cisplatin forms covalent connections to the N7 sites of purine bases. 1,2-intrastrand adducts and 5–10% 1,3-intrastrand adducts (also known as "cis-GNG") are present [32].

The Discovery of Platinum Compounds as Anticancer Agents

Until the mid-1960s, cancer chemotherapy was exclusively based on organic chemical substances. A significant shift occurred when it was unexpectedly discovered that platinum-based inorganic compounds had anticancer properties. In 1965, Barnett Rosenberg observed that a platinum complex produced during electrolysis with platinum electrodes inhibited binary fission in Escherichia coli. Further research showed that Pt^{2+} species, generated through photoreactions, were effective in preventing cell division. Among the compounds examined, the platinum complexes cis-($PtCl_2(NH_3)_2$) with Pt^{2+} and cis-($PtCl_4(NH_3)_2$) with Pt^{4+} were particularly effective in stopping cell division [3]. Since Rosenberg and colleagues accidentally discovered cisplatin's antitumor properties in the 1960s, platinum (II) complexes have become a key component of cancer chemotherapy. These complexes primarily target DNA by binding to nitrogen atoms in nucleic acids, ultimately inhibiting tumour cell formation [34,35] (Figures 1 & 2).

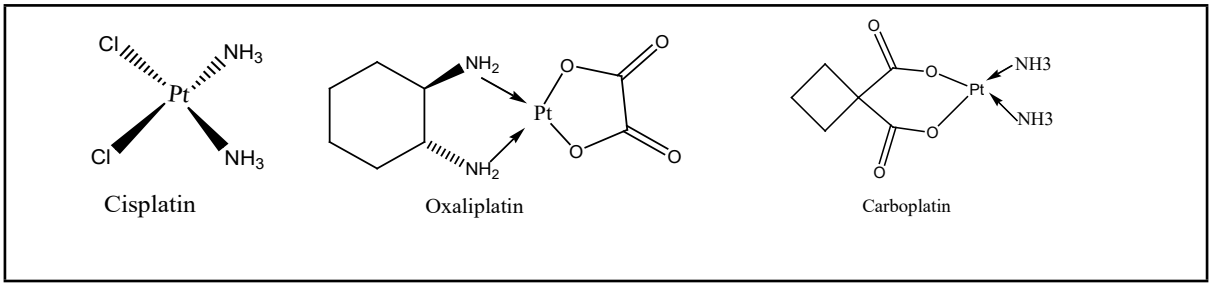


Figure 1: Examples of platinum complexes used in therapy.

Bristol-Myers (now Bristol-Myers Squibb), which conducted extensive research on anticancer medications, conducted additional studies later in 1979 to provide details regarding the safety and effectiveness of the Food and Drug Administration (FDA). The FDA granted cisplatin approval in 1978 for use in chemotherapy for cancer. It became acceptable for inorganic chemists to send their compounds to cancer institutes for testing for antitumor activity all of a sudden [36].

Pharmacokinetics of Platinum Drugs

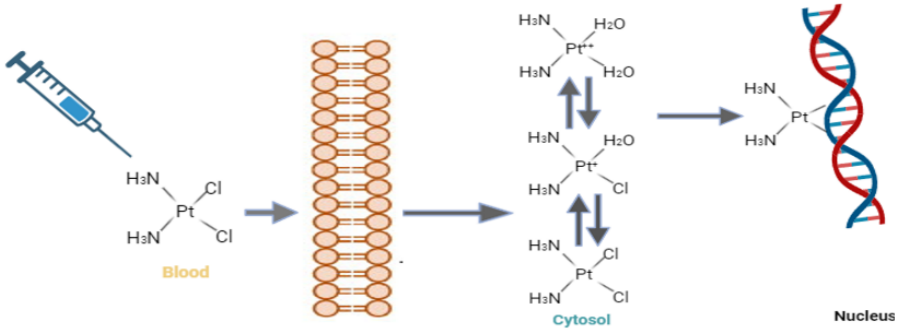


Figure 2: Platinum prescription drug's pharmacology.

Cancer patients receive intravenous (i.v.) injections of cisplatin. The injection solutions are newly made just before use due to the drug's inadequate stability in aqueous media. Because of the blood's relatively high (100 mM) chloride concentration, free cisplatin is present in this medium in its complete form. However, due to the decreased chloride content (4 mM) inside cells, the water is eventually replaced by the chloride ligands following cellular absorption, leading

to the production of positively charged aqua species. These cations subsequently move to the nucleus, where they interact with the DNA's nucleobases [37-41].

Cytotoxicity of Cisplatin

Inter-strand lesions are significantly less common than inter-strand crosslinks. Because it creates DNA crosslinks that can severely hinder replicative DNA polymerases and trigger apoptosis, cisplatin selectively kills cancer cells that are dividing quickly [42]. In addition, cisplatin adducts hinder gene transcription and elongate RNA polymerases [43], which both contribute to cisplatin-induced cell death Figure 3.

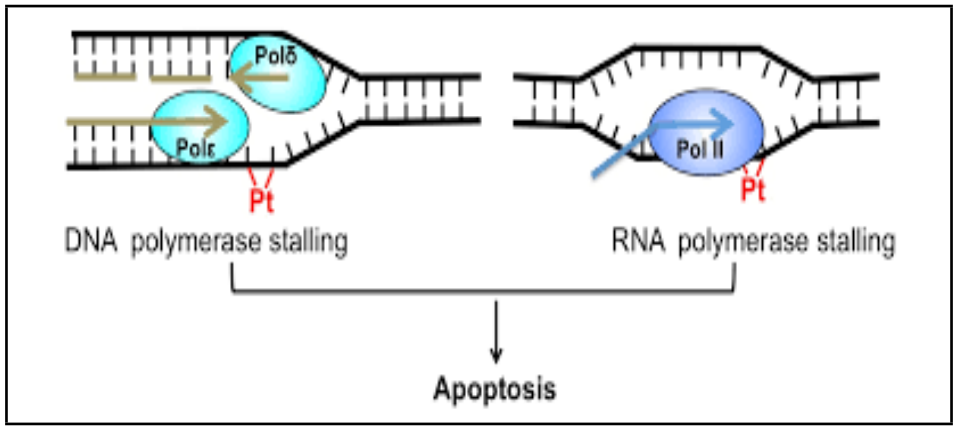


Figure 3: Cytotoxicity of cisplatin. Cisplatin-induced DNA adduct (red) blocks replicative DNA polymerase (left) and RNA polymerase (right). Both replication and transcription stalling can trigger apoptosis.

Cisplatin Binds with DNA

For cisplatin to exhibit anticancer action, DNA is the primary target [44,45]. The mono- or dehydrated platin that has entered the nucleus is sufficiently susceptible to DNA base reactions. Fig. 4 lists the probable binding sites for each DNA nucleotide. (Figure 4. Schematic illustration of several DNA base binding locations when cisplatin moiety is present) (article 4)**.** In vitro, studies have shown that the N7 position of guanine's imidazole ring is more amenable to attack than adenine or any other bases found in DNA, such as cytosine and thymine [46-48]. Cells that respond with cisplatin on DNA must either repair the lesions or accept them in order to endure the effects of the treatment; otherwise, cisplatin-induced DNA damage, including apoptosis, would cause massive cell death. Once cisplatin has generated a range of DNA lesions, the majority of the major DNA repair systems get involved in mending the DNA damage that drug exposure has caused. Actually, nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and nonhomologous end joining (NHEJ) are used to repair DNA damage brought on by cisplatin [49]. During the aquation process, cisplatin is made highly reactive and quickly binds to a number of biomolecules inside the cell [50]. When cisplatin binds to DNA bases covalently in its reactive form, it produces DNA adducts. Cisplatin is very reactive with the nucleophilic N7-sites of purine bases, and a two-step reaction could covalently link purines. In contrast to purines on the same strand, which form interstrand adducts, purines on the opposite strand generate interstrand crosslinks (ICLs) [51] (Figure 1B).

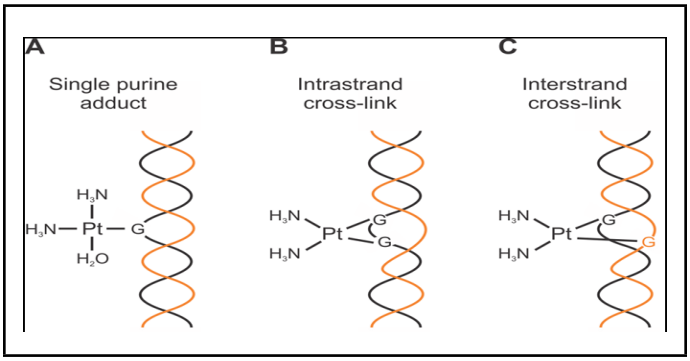


Figure 4: Cisplatin-induced DNA adducts. The predominant DNA adducts caused by cisplatin include (A) bulky cisplatin adducts on singular purines, (B) inter-strand crosslinks between bases on the same strand, and (C) inter-strand cross-links between bases on opposing strands.

Resistance after Cisplatin-DNA Binding

NER [52] is the most effective technique for eradicating DNA lesions that result in cisplatin resistance. The NER system excises damaged nucleotides on both strands and then synthesizes DNA to restore the integrity of the gene [53] L.C. Gillet and O.D. Scharer published Molecular Mechanics of mammalian global genome nucleotide excision repair in Chem. Rev. 106 (2006) 253-276. NER overexpression

decreases cisplatin sensitivity in cells [54] MMR, a highly critical protein, is involved in the normal repair of DNA damage caused by cisplatin. If it is unable to repair itself, apoptosis occurs [55].

Cytochrome P450 Enzymes

Monooxygenases are a class of more than 50 enzyme isoforms collectively referred to as CYP450. Studies have shown that CYP450 enzymes are mostly found in the human liver's endoplasmic reticulum membranes as well as in cells beyond the liver, including those in the lung, kidney, small intestine, brain, bone marrow, and blood cells [56-58].

An extensive range of endogenous or exogenous lipophilic substances are metabolized by CYP450 enzymes. Two main proteins make up CYP450 enzymes: an iron-containing haemoprotein and a flavoprotein part that transfers electrons from NADPH to the CYP450 substrate complex. The heme iron is situated near the drug-binding site on the CYP450 molecule. The iron atom is first in its ferric form (Fe^{+3}), then with the transfer of one electron from NADP via NADPH reductase, it is subsequently reduced to its ferrous form (Fe^{+2}). The heme iron is subsequently reduced to its ferrous state (Fe^{+2}) by the transfer of one electron from NADP via NADPH reductase after being oxidized back to Fe^{+3}. The subsequent oxidation of the heme iron to Fe^{+3} results in the simultaneous introduction of an oxygen atom into the substrate. H_2O is then created by adding another oxygen molecule [59].

Molecular Mechanisms of Cisplatin

Cisplatin's structure is simple, consisting only of one platinum, two chlorine ions, and two ammonia groups. Cisplatin produces intra- and/or inter-strand crosslinks and mono adducts when it reacts with the DNA's purine bases. The aquated platinum molecule has the potential to interact with DNA early on and produce mono adducts. The majority of these mono adducts will then form DNA crosslinks, about 90%. The majority of the crosslinks created by cisplatin are intra-strand, connecting adjacent guanines (65%) and adjacent guanines and adenines (approximately 25%) on the same DNA strand. It has also been shown that cisplatin can create a modest number of intra-strand crosslinks connecting any nucleoside; however, these crosslinks form gradually. Inter-strand crosslinks caused by cisplatin can form between two guanine residues on opposing strands at a very low rate (1%) [60]. Cisplatin interacts with DNA (including mitochondrial DNA), RNA, and proteins as a result of its positively charged nature because it prefers the nucleophilic N7 atoms of the imidazole rings of guanosine and adenosine [61]. DNA crosslinks created by cisplatin prevent RNA transcription and DNA replication Cisplatin's modes of action as shown in Figure 6 [62].

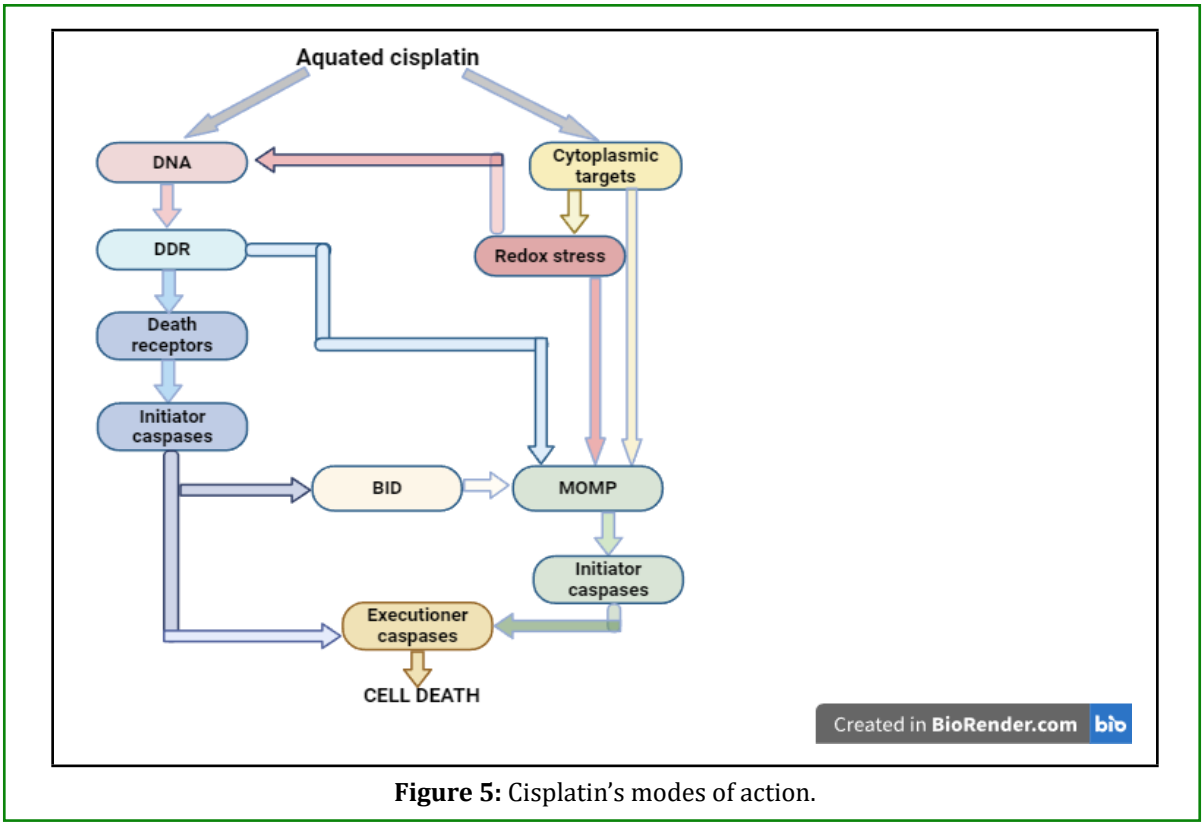


Figure 5: Cisplatin's modes of action.

Intracellular cisplatin quickly equates and turns extremely reactive due to the comparatively low concentration of chloride ions (in comparison to the extracellular surroundings). Indeed, a wide variety of nucleophilic molecules, such as cysteine and methionine residues on proteins and DNA bases, can be bound by aqueous cisplatin. This causes the formation of inter- and intra-strand adducts in the nucleus, which are detected by the DNA damage-sensing. machinery. Cisplatin adducts activate a DNA damage response (DDR) [63], which frequently involves the ATR kinase, CHEK1 and CHEK2, and the tumour suppressor protein TP53 if the degree of damage is too great to be repaired. Then, TP53 transactivates numerous genes that code for elements of the extrinsic apoptotic cascade as well as genes that promote mitochondrial outer membrane permeabilization (MOMP), which results in the onset of intrinsic apoptosis. The caspase cascade and numerous caspase-independent processes are activated by MOMP (alone or in conjunction with the contribution of death receptor-ignited BID-transduced signals), which ultimately seals the cell fate. MOMP and cell death are linked to cisplatin-induced DNA damage via a number of other signalling pathways (details are provided in the main text; not displayed). When cisplatin interacts with GSH, metallothionein's, or mitochondrial proteins like VDAC in the cytoplasm, reducing equivalents are depleted, and/or reactive oxygen species (ROS) are directly sustained. ROS can worsen cisplatin-induced MOMP or directly cause.

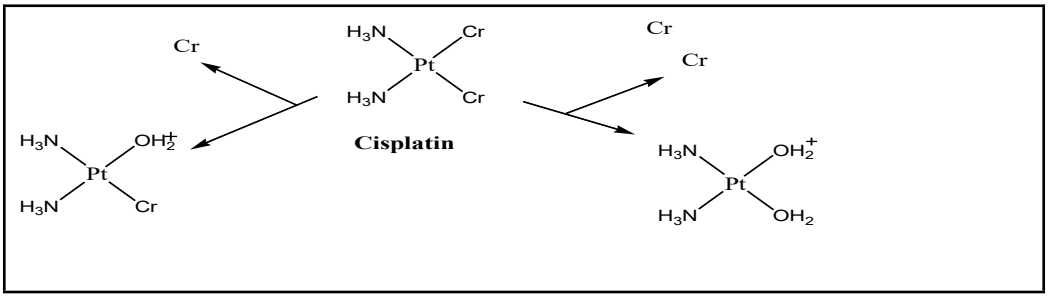


Figure 6: Cisplatin.

Factor	Mode of action	Relevance	References
CTR1	Plasma membrane copper transporter.	Downregulated in cancer cell lines resistant to CDDP.	[63-66]
		CDDP resistance is heightened by CTR1 depletion. In vitro and in vivo absorption and effectiveness of CDDP are improved by copper chelators.	
ATP7A/ATP7B	Copper-extruding P-type ATPases involved in the regulation of ion homeostasis	Increased cancer cell lines that are resistant to CDDP. The effectiveness of CDDP treatment in ovarian cancer patients may be predicted by ATP7B expression levels.	[67-70]
MRP2	Member of the ABC family of plasma membrane transporters. Mediates the ATP-dependent cellular efflux of CDDP.	overexpressed in cancer cell lines that are CDDP-resistant. CDDP sensitivity is increased by antisense cDNA modification. The effectiveness of CDDP regimens in patients with ESCC and HCC depends on expression levels.	[71-75]
GSH/g-GCS/GST	GSH scavenges electrophiles and ROS. g-GCS catalyses GSH synthesis. GST conjugates GSH to CDDP, thus facilitating its extrusion.	CDDP-resistant cells often exhibit elevated levels of GSH, g-GCS, and GST. No conclusive clinical evidence.	[76,77]
Metallothionein's	Intracellular thiol-containing proteins are involved in the detoxification of metal ions.	May bind and inactivate CDDP. No conclusive clinical evidence.	[78,79]

Table 1: Mechanisms of pre-target resistance (article – molecular 1).

Curcumin: Structure, Chemistry and Pharmacokinetics

Diferuloylmethane, often known as curcumin, is an active substance that was extracted from the herb Curcuma longa, which grows in south and southeast tropical Asia and has long been used in traditional Chinese medicine [80]. Curcumin is a potential polyphenolic phytonutrient that is obtained from the turmeric plant (Curcuma longa) and is used to treat various malignancies by chemoprevention [81]. Curcumin has the ability to fight cancer, but it also triggers a variety of other powerful reactions [82]. Its structure (Figure 7) consists of two identical aromatic rings connected by a single linear carbon, each of which contains o methoxy phenolic groups and a b-unsaturated moiety of b-diketone [83].

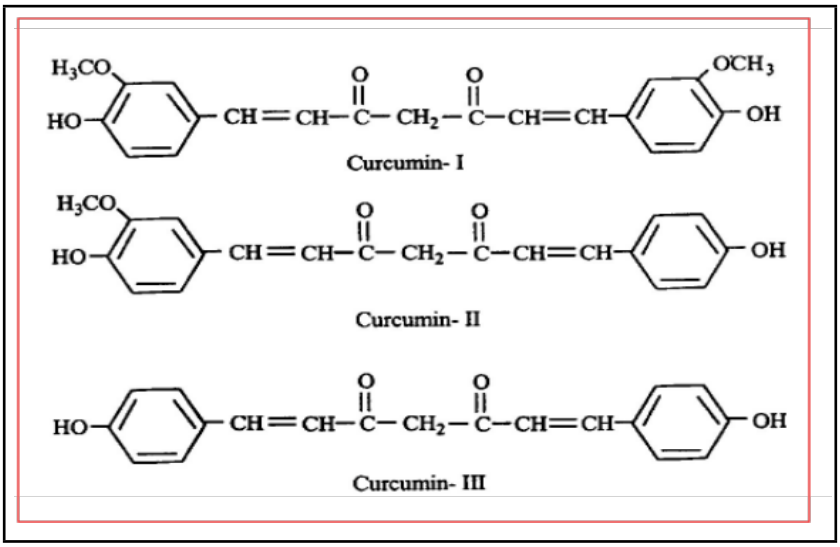


Figure 7: Chemical structure of curcumin.

Curcumin has limited bioavailability and a restricted distribution due to its hydrophobic nature [84]. Before and after absorption, curcumin either undergoes transformation or degradation [85]. The reactive structure of ingested curcumin is primarily responsible for its metabolism. The heptad enedione system's conjugation decrease is mostly caused by phase I metabolism, primarily through interaction with alcohol dehydrogenase [86]. Phase II metabolic activities successfully conjugate curcumin and its reduced metabolites. The most typical conjugates are glucuronides and sulphates. Glutathione and curcumin frequently interact without the use of enzymes, most likely through a Michael-type addition [87]. Some of the formulations being researched to increase the oral bioavailability of curcumin are meant to slow down the rapid metabolic rate. Even at doses as high as 12 g/day, curcumin is recognized as a safe substance, and when given orally to patients with advanced pancreatic cancer for three months, it was well tolerated [88].

Anti-Cancer and Chemo Sensitizing Effects of Curcumin

People from Southeast Asian nations were said to have a lower risk of developing colon, gastrointestinal, prostate, breast, ovarian, and other cancers than Western ones [89].

Protective Effects of Curcumin against Cisplatin Toxicity

Given that peripheral neuropathy affects about one-third of CP participants and causes one-fifth of them to stop receiving therapy, neurotoxicity (affecting dorsal root ganglia) is one of the main adverse effects [90]. Curcumin treatment before and in conjunction with CP administration was reported to restore plasma neurotensin and greatly improve the histopathology of the sciatic nerve in rats [91]. As one of the most often documented adverse effects of CP, auditory disorders such as tinnitus, a permanent, bilateral, and progressive hearing loss, are also common [92-94]. According to a paper, dexamethasone and nano-encapsulated curcumin treatment dramatically but only partially protected guinea pigs from CP-induced ototoxicity. This may be because curcumin has antioxidant capabilities. This is because a 10-day course of curcumin (100 mg/kg, orally) treatment recovered serum urea, creatinine, and MDA levels in CP-treated rats, leading to the suggestion that co-administration of curcumin broadens the therapeutic window for CP.

Nephroprotective Effects

Signs of nephrotoxicity, such as a decline in glomerular filtration rate and an increase in blood urea nitrogen (BUN)

and creatinine levels, have reportedly been seen shortly after the commencement of CP treatment [95]. CP-induced nephrotoxicity has been linked to an increase in ROS levels, which in turn led to an increase in the oxidation of lipids, proteins, and nucleic acids, as well as a decrease in SOD, glutathione peroxidase (GPX), and catalase, all of which are known to be crucial components of the antioxidant defence. Similarly to this, it was stated that CP-induced nephrotoxicity is eliminated when antioxidant medicines are also administered. The prevention of mitochondrial malfunction and the inflammatory response, the restoration of antioxidant enzymes, and the decrease of oxidative stress are all ways that curcumin protects the kidneys, according to numerous studies. Furthermore, protein transporters, including the organic anion transporter (OAT) and organic cation transporter (OCT), are crucial for renal secretion, the process of delivering medications, poisons, etc. into the lumen of nephrons. OAT and OCT expressions that were reduced after CP therapy have been shown to be able to be restored by curcumin [96].

Effect on Chemotherapy Resistance

A lot of patients do not react to chemotherapy that uses cisplatin. Only 20% of individuals respond to immunotherapy, and due to genomic sub-typing of tumors, there may be significant overlap between those who respond to cisplatin and those who respond to immunotherapy. Curcumin is a natural bioactive substance that may provide ingredients for treating cisplatin-related problems. These substances have the power to activate a variety of pathways, all of which have the potential to positively or negatively affect cisplatin sensitivity. Through the downregulation of Bcl_2 and survivin, curcumin and cisplatin can work together to inhibit the development of chemoresistance to cisplatin [97]. Cancer stem cells make up a very small portion of the tumor population. Due to the stem cell-like characteristics of these cells, cytotoxic agent resistance develops, which causes cancer to return. These stem cells become sensitive to cytotoxic substances like cisplatin because of the chemosensitivity actions of polyphenols, particularly curcumin. The osteosarcoma (MG63) cell line was used to study the co-delivery of curcumin and cisplatin. The findings demonstrated that curcumin-cisplatin combination therapy decreases the expression of BMIL-1 as well as E-cadherin and Notch-1 signaling pathways. It was determined that co-delivering curcumin and cisplatin can be a better method for increasing chemotherapy effectiveness in osteosarcoma patients. The effects of curcumin and cisplatin on invasion, metastasis, and apoptosis in nasopharyngeal cancer cells were examined. The study's findings demonstrated that the combination of curcumin and cisplatin therapy increased the expression of the transforming growth factor (TGF)-1/Smad's signalling pathway, inducing apoptosis [98]. In this context, a study was conducted to determine whether cisplatin exposure causes the release of NOX5, which, in turn, activates the Akt pathway to produce resistance to cisplatin in cancer cells. Delivering curcumin reduces NOX5 expression, preventing cisplatin resistance. Thus, curcumin and cisplatin combined therapy decrease cisplatin resistance in epithelial cancer cells, increasing the effectiveness of chemotherapy for the target cancer. The adverse effects of cisplatin are also controlled [99].

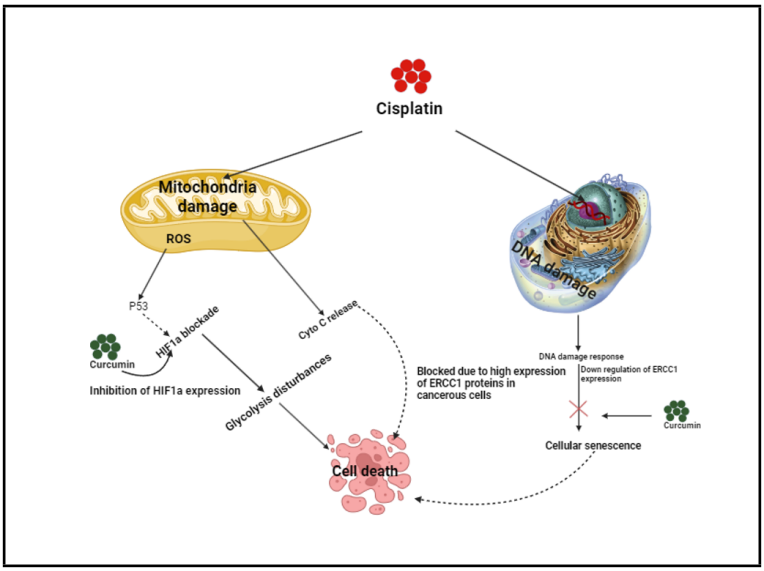


Figure 8: Molecular models of curcumin enhance cisplatin's therapeutic effectiveness. The schematic illustration shows how curcumin boosts cisplatin's anticancer effects by inhibiting the expression of excision repair cross-complementation group 1 (ERCC1) and hypoxia-inducible factor 1-alpha (HIF-1α) proteins.

Conclusion

This review summarizes the protective effects of curcumin against cisplatin (CP)-induced neurotoxicity, ototoxicity, and nephrotoxicity, as well as its role in enhancing CP's therapeutic efficacy. Plant-derived natural substances, such as curcumin, have been systematically used in cancer treatment due to their ability to target multiple cellular and molecular aspects of cancer cells with minimal harm. Curcumin has been shown to modify key molecular targets, potentially reducing the antitumor effectiveness of CP, a widely used chemotherapy drug that induces DNA damage in cancer cells. However, curcumin's chemo preventive properties affect various tumour-related pathways, targeting transcription factors, growth factors, and receptors involved in cell proliferation and apoptosis.

Research suggests that combining natural anticancer compounds like curcumin with chemotherapy enhances therapeutic efficacy while reducing side effects. Despite evidence supporting curcumin's benefits in treating various diseases, including cancer, uncertainties remain due to the limitations of initial studies. More rigorous research is needed to confirm curcumin's clinical effectiveness. In summary, curcumin appears to reduce chemoresistance and mitigate CP's side effects without compromising its antitumor properties. Further clinical trials are necessary to explore the benefits of new curcumin formulations with improved bioavailability and structural analogues.

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