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Review Article
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Schiff Bases and their Potential Role in Drug Resistance Cancer Therapy

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ABSTRACT

Schiff bases and their metal complexes are increasingly grasping focus as a promising cancer therapy, due to their ability to exhibit strong cytotoxic effects against various types of cancer cells and minimum effects on non-cancerous cells, therefore, effectively combating drug resistance. Schiff bases can easily be prepared and modified to form complexes with transition metals, which presents an exciting opportunity for scientists to develop innovative cancer therapies. Currently many scientific researchers are focusing on several Schiff bases, showing their promising applications as anticancer agents. This review will focus on the mechanisms of cancer drug resistance, the role of Cisplatin as a potent anticancer drug that is often limited by drug resistance, and the potential of using various Schiff bases in the inhibition of cancer cell proliferation consequently affecting cancer treatments.

Keywords- *Schiff base; Apoptosis; Cancer; Cisplatin; Drug resistance; Chemotherapy; DNA repair.*

INTRODUCTION

Schiff bases are a class of compounds first reported in 1864 by the German chemist Hugo Schiff, after whom they are named.[1] They are formed through the condensation of amines and carbonyl compounds, specifically aldehydes and ketones[2]. All Schiff bases contain the azomethine group, with the general formula RHC=N-R1. In this formula, R and R1 represent a variety of groups, including alkyl, aryl, cycloalkyl, or heterocyclic groups with various substitutions[3,4] (Figure 1).

Several studies have shown that the lone pair of electrons in the sp^2 hybridized orbital of the nitrogen atom in the azomethine group exhibits significant chemical reactivity.[5,6] This characteristic makes Schiff bases remarkable molecules with the ability to bind to transition metals. Because they possess at least one pair of unshared electrons, Schiff bases are classified as Lewis acids. The presence of an imine (a carbon-nitrogen double bond, -C=N-) in these compounds enhances their biological activities[6], particularly their potential as anticancer agents.[7]

Many studies indicated that Schiff bases and their metal complexes are cytotoxic to various types of cancer cells, including breast (MCF-7), liver (HepG2), and cervical cancers (HeLa).[8,9] Furthermore, several Schiff base complexes have been developed and studied for their potential use as antimicrobial, antifungal, and antimalarial agents.[10-12]

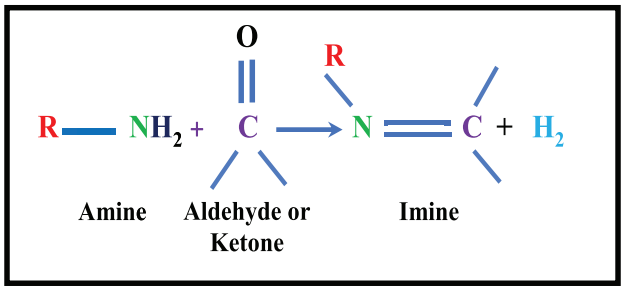

Figure 1: General scheme for the formation of Schiff bases.

Cancer

Cancer is a group of diseases characterized by uncontrolled cellular growth. Stage IV of cancer growth is known as metastasis. Metastasis occurs when cancerous cells spread from their original site to other parts of the body. The most common types of cancer are breast, lung, colorectal, and prostate cancers. Although they share a lot of similarities with each other, each cancer is characterized by a different resistance mechanism even within the same cancer type. Cancer cells often develop various mechanisms that enable them to resist treatment, making standard chemotherapy less effective. The emergence of drug resistance is substantially challenging to patient treatment. In 2020, cancer was responsible for nearly 10 million deaths worldwide.[13] Below are the key mechanisms that cause drug resistance.

1. Changes in Drug Targets: Cancer cells can undergo genetic mutations that alter drug target proteins, reducing the effectiveness of treatments. For instance, a reciprocal

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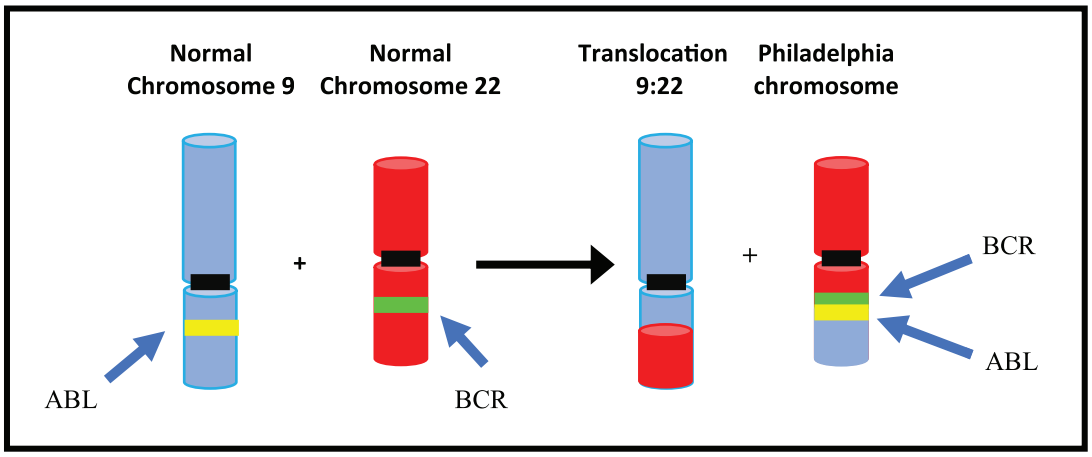
translocation between chromosomes 9 and 22 resulted in the formation of the Philadelphia chromosome t (9:22) (Figure 2a). This occurs when the BCR-ABL1 gene has resulted from the abnormal fusion of the ABL1 gene from chromosome 9 with the BCR gene from chromosome 22.[14] Mutations in the BCR-ABL gene especially in the kinase domain, such as those identified as T315I, E255K, and Y253F enable chronic myeloid leukemia (CML) cells to develop resistance to imatinib, a tyrosine kinase inhibitor that is used in the treatment of CML. The T315I mutation is of particular concern because it confers resistance to all currently approved tyrosine kinase inhibitors (TKIs).[15]

Acute Promyelocytic Leukemia (APL) is identified by a disruption in the differentiation process, causing leukemic cells to stop at the promyelocyte stage. Most cells have the PML-RARα fusion oncoprotein due to a t (15;17) chromosomal translocation (Figure 2b). Studies revealed that chromosomes 15 and 17 are close in lymphoid cells, which could account for the frequent t (15;17) abnormality seen in hematopoietic cells. The introduction of retinoic acid (RA) and arsenic trioxide (ATO) resulted in impressive cure rates. Nonetheless, recurrence of APL, especially among high-risk patients showed growing resistance. Furthermore, despite the successful outcomes of ATRA and ATO, new research using laboratory models has indicated that mutation in the B2 domain of the PML protein is responsible for arsenic resistance.[16] Because of these clinical outcomes, there is a high demand for alternative agents and approaches to tackle ATO resistance. Additionally, mutations in the Epidermal Growth Factor Receptor (EGFR) gene, which encodes for the transmembrane protein receptor Epidermal Growth Factor (EGF), are significant. This receptor is crucial for cell signaling pathways, particularly in growth and proliferation. Drug-resistant EGFR mutations alter the formation of ligand-free, active oligomers, enhancing and maintaining the formation of dimer sub-units that require oligomerization. These mutations lead to acquired resistance to targeted therapies in non-small cell lung cancer and other cancers, resulting in uncontrolled cellular growth.[17]

2. Drug efflux: Drug efflux is characterized by the up regulation of adenosine triphosphate (ATP) binding cassette (ABC) genes, which are a family of integral membrane proteins that are often overexpressed in cancer cells. This family consists of 49 transporter proteins that utilize ATP energy to facilitate the removal of drugs from cells, leading to decreased intracellular



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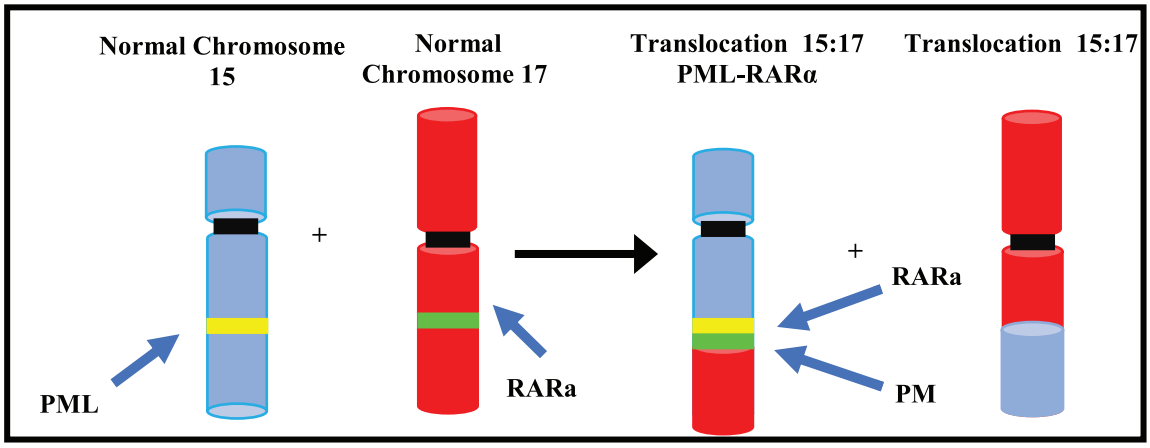


2b

Figures 2a and 2b: A schematic representation of chromosomal translocations t (9;22), which results in the Philadelphia chromosome, and t (15;17), which leads to Acute Promyelocytic Leukemia.

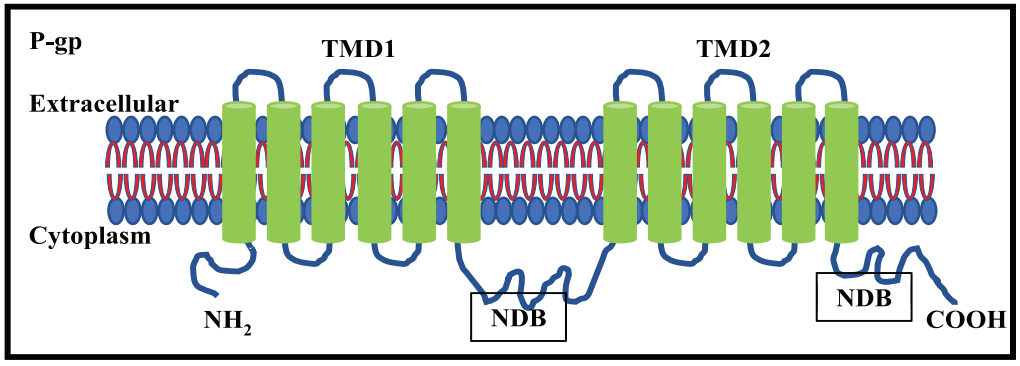
drug levels and, consequently, drug resistance.

Notable examples of ABC transporters are P-glycoprotein (P-gp)[17] (Figure 3a) and Multidrug Resistance Associated Protein (MRP)[18] (Figure 3b). MRP has a subfamily of nine members.[19-21]. P-gp and MRP1 share only 15% of their amino acid sequence similarity, and they exhibit some unique characteristics. In terms of structure, MRP1 has a distinctive feature compared to P-gp: it contains an additional membrane-spanning domain, known as MSD0, which consists of five transmembrane (TM) helices. Additionally, MRP1 as P-gp has two other MSDs (MDS1 and MDS2), each containing six TM helices, with two nucleotide-binding domains (NBDs) positioned between them. These transporters play a critical role in the survival of multidrug-resistant (MDR) cancer cells. They act as ATP-dependent efflux pumps that expel various anticancer drugs, thereby reducing the drugs' effectiveness.

Efforts to inhibit P-gp and enhance drug efficacy have led to the discovery of Verapamil[22], a calcium channel blocker that specifically inhibits the efflux of chemotherapeutic agents like cisplatin from the cells. Verapamil competes with antitumor agents at binding sites on P-gp, blocking their efflux. Studies suggest that Verapamil can enhance the effectiveness of cisplatin in cancer treatment, such as gallbladder cancer and pancreatic carcinoma. Thus, the co-administration of verapamil and cisplatin may enhance therapeutic efficacy in malignancies.

MRP1 confers resistance to multiple anti-cancer drugs such as anthracyclines, vinca alkaloids (Vincristine), epipodophyllotoxins, camptothecins, methotrexate (MTX), saquinavir, and mitoxantrone (MX). Vincristine was used as an additional palliative care drug in the treatment of recurrent Glioblastoma multiforme (GBM) because Vincristine is encountering MRP1 resistance. It is important to evaluate its effectiveness in both primary and recurrent GBM cell line treatments, MK571 was used as a chemosensitizer to inhibit MRP1, and the ability of vincristine to induce cell death is greatly improved, meaning that MK571 is inhibiting drug resistance, which will eventually increase the effectiveness of overall cancer treatment.[22] Pre-treatment with Reversan, an inhibitor of MRP1 and P-glycoprotein (P-gp), significantly enhanced the cell death when combined with temozolomide, vincristine, and etoposide in both primary and recurrent glioblastoma (GBM) cells. Notably, when MK571 used in the experiment substantially increased the effectiveness of vincristine and etoposide across all three cell lines studied, while not affecting the efficacy of temozolomide. This suggests that P-gp plays a role in the resistance to temozolomide and MRP1 is the transporter involved in the resistance to vincristine and etoposide.[22,23]

3. Mechanisms of DNA Repair: DNA is the essential building block of inheritance, crucial for maintaining the structure and function of human cells and tissues.



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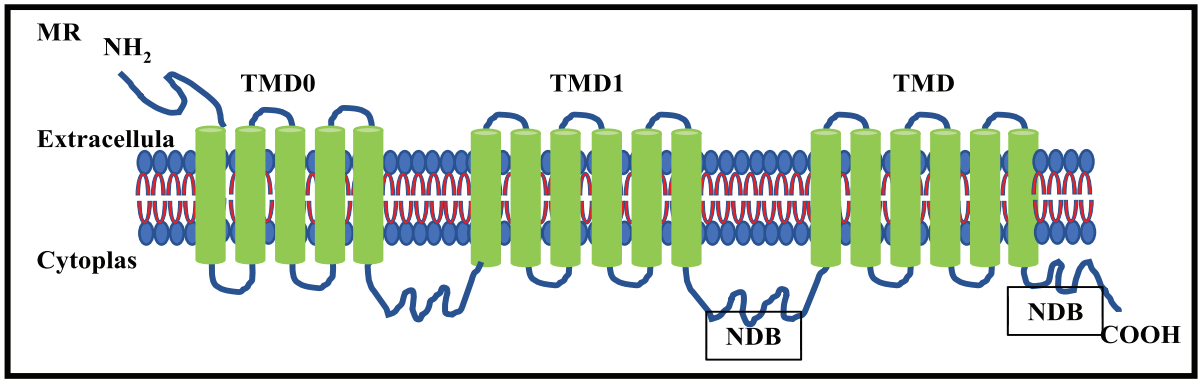

Figures 3a and 3b: Predicted molecular structure of ABC transporters P-glycoprotein and MRP1.

Mutations in genes are a fundamental aspect of cancer development. Cancer patients may experience DNA damage, that can arise from inherited germline mutations or acquired somatic mutations, factors that may induce mutations which are; exposure to carcinogenic chemicals, radiation, environmental agents, and chemotherapies. These mutations increase the pressure on cancer cells, activating DNA repair mechanisms and cell cycle checkpoints. These mechanisms work together to repair or tolerate DNA injury, ultimately causing cell survival and the evolution of drug resistance. Understanding how DNA damage occurs and how the DNA repair pathway functions is essential for grasping the impact of DNA damage on cell functions and disease progression. Specific types of DNA damage are repaired by specific mechanisms, these mechanisms include mismatch repair, base excision repair, transcription-coupled/global genome repair, and homologous recombination (HR)/ non-homologous end-joining (NHEJ)[24-27] (Figure 4). If these mechanisms were able to repair DNA damage, cells would be protected from apoptosis, consequently allowing cancer cells to grow and form tumors.

4. Epithelial-mesenchymal transition (EMT). The epithelial-mesenchymal transition (EMT) describes the process by which tumor cells alter their shape and structure from an epithelial to a mesenchymal morphology. This transition is characterized by a loss of cell polarity and the disruption of tight, gap, and adherent junctions in epithelial cells, enabling cancer cells to acquire migratory and invasive properties, this process contributes to drug resistance. Tumor heterogeneity refers to the presence of various cell populations within tumors, some of which are inherently resistant to treatment, making effective targeting challenging. A comprehensive understanding of the underlying mechanisms is essential for developing new strategies to combat drug resistance and improve patient therapy outcomes[28,29] (Figure 5).

The emergence of drug-resistant and the increasing incidence of side effects associated with nearly all cancer drugs have prompted researchers to seek more effective and safer agents. To address this issue extensive studies have investigated the causes and mechanisms of drug resistance, providing scientists with tools to understand the modes of action and effectiveness of newly discovered agents. Collaborative efforts across various fields aimed at identifying effective treatments for cancer patients are emerging. One of the best anticancer agents studied is Cisplatin.

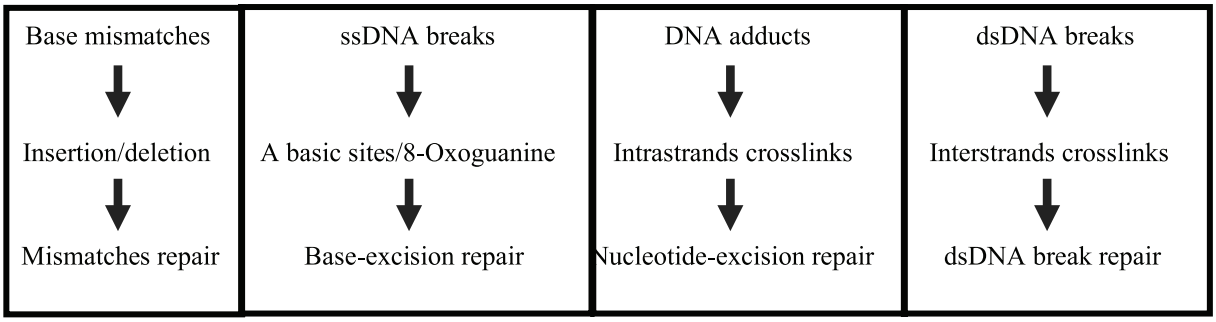

Figure 4: DNA and repair mechanisms

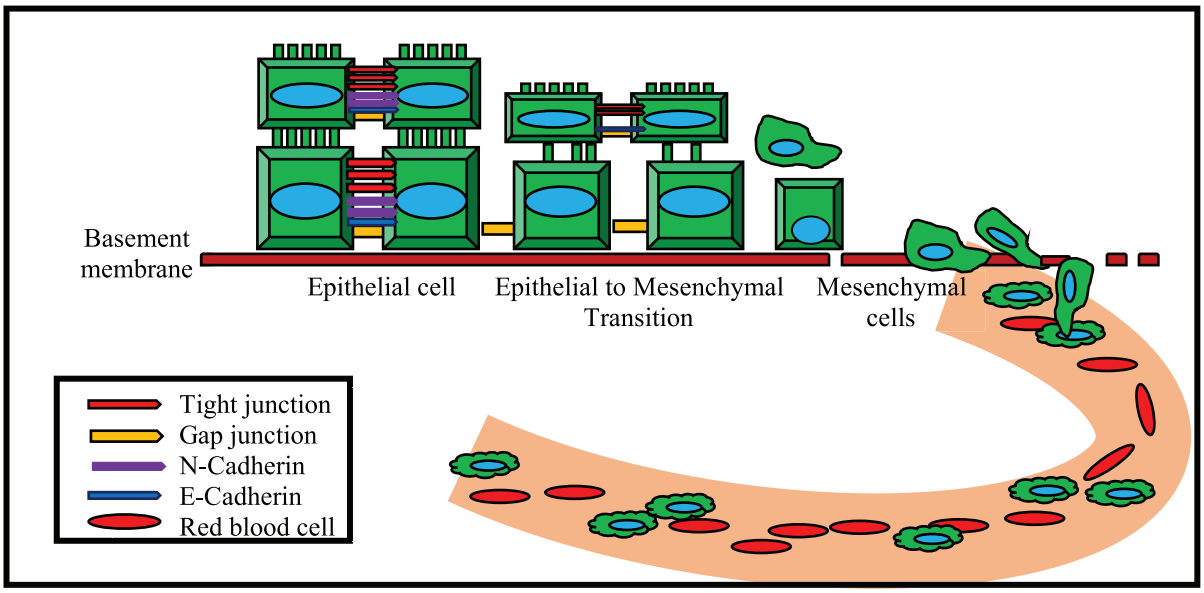

Figure 5: Schematic diagram of the Epithelial-mesenchymal transition (EMT) process.

Cisplatin

Cisplatin (cis-diammine-dichloro-platinum II) is a platinum-based consisting of a platinum ion coordinated with two amine and two chloride ligands, forming a square planar geometry. Although Michele Peyrone first reported it in 1845, it became more widely recognized after Barnett Rosenberg discovered its biological properties in 1965, observing that the platinum complex inhibited the growth of Escherichia coli.[30] In 1978, Cisplatin was approved in the U.S. for treating testicular and ovarian cancers, significantly improving survival rates.[31] It has also exhibited cytotoxic effects against various malignancies, including leukemia, lymphomas, breast, head and neck, cervical cancers, and sarcomas. Despite concerns regarding toxicity and resistance, it is now recognized as a first-line chemotherapy option for multiple cancers.

Cisplatin›s mode of action involves forming covalent bonds with DNA, specifically targeting purine bases. The resulting adducts predominantly target the N7 position of guanine and adenine, leading to the formation of monofunctional and bifunctional adducts that account for approximately 65% GPG, 25% APG 1,2-intrastrand crosslinks, and around 5-10% GPNPG 1,3-intra-strand crosslinks.[32] Intra-strand adducts formed when cisplatin crosslinks two bases on the same strand, while inter-strand adducts form when it crosslinks bases from different strands.[33] Adduct formation disrupts DNA replication and RNA transcription, critical processes for cell division, growth and tissue formation. This disruption can lead to genomic instability and inhibit protein production, triggering a process known as programmed cell death (apoptosis).[34]

Cells in a multicellular organism undergo proliferation and division to form organized tissues, with biological activities tightly regulated by both cell division and apoptosis. Cells will undergo apoptosis in response to abnormalities such as DNA damage or shortened telomere repeats. During apoptosis, the cell shrinks and becomes denser, resulting in the collapse of the cytoskeleton, disintegration of the nuclear envelope, and fragmentation of DNA. DNA fragmentation is a well-known marker of apoptosis, often appearing as a DNA ladder pattern on agarose gel electrophoresis. Nearby cells then phagocytize the remains of the apoptotic cells, facilitating controlled cell death while preserving the surrounding cells. In contrast, cells exposed to injury or infection trigger an inflammatory response that leads to necrosis, impacting nearby cells. Agarose gel electrophoresis of necrotic cells shows a smear pattern, unlike the distinct DNA laddering pattern observed in apoptosis (Figure 6).

Cisplatin-induced DNA damage activates nucleotide excision repair pathways (NER), specifically transcription-coupled repair (TCR) and global genome repair (GGR), which are responsible for eliminating cisplatin-induced DNA adducts.[33] TCR specifically binds to transcribed gene strands currently being expressed. The process begins when RNA polymerase encounters the damaged DNA and induces CSA and CSB to bind to the damaged site. Conversely, the GGR molecule binds to non-transcribed regions of transcribed genes and the non-transcribed regions of the genome. The XPE protein and the XPC-HR23B complex play a crucial role in recognizing DNA damage. Once DNA damage is detected, XP-B and XP-D helicases unwind the surrounding region, accompanied by XP-A, XP-G, and replication protein A (RPA). Following this, the XPF-ERCC1 nuclease complex and XP-G endonuclease remove the damaged DNA, and the resulting gap is replaced by de novo DNA synthesis.[35,36]

Additionally, cisplatin-induced DNA damage activates the ataxia telangiectasia mutated (ATM) pathway. The ATM protein is vital for the cellular response to DNA double-strand breaks (DSBs). It primarily functions as a serine/threonine kinase, phosphorylating proteins involved in regulating cell cycle checkpoints and DNA repair mechanisms. Upon detecting DNA damage,

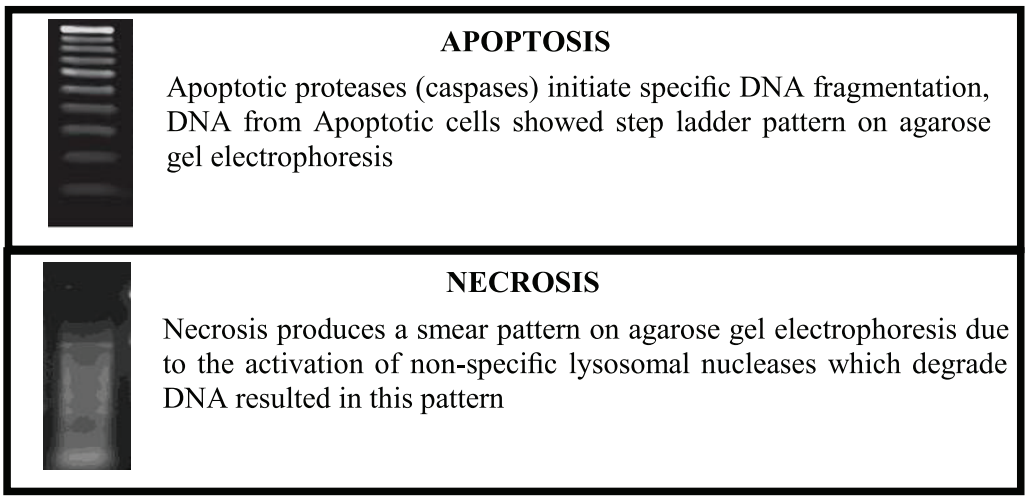

Figure 6: DNA ladder pattern in Apoptosis vs DNA smear in necrosis.

ATM transitions from an inactive dimer to an active monomer, a critical step for its functional activity.[36] This activation of cellular response pathways ultimately inhibits apoptosis, leading to drug resistance and relapse in some patients. While cisplatin remains a primary choice for chemotherapy, its limitations have inspired the development of new metal-based anticancer drugs. Numerous studies have identified Schiff base compounds as highly promising anticancer agents. Schiff bases are typically categorized as bidentate, tridentate, tetradentate, pentadentate, or hexadentate. These compounds can form highly stable complexes with transition metal ions based on their coordination numbers due to the presence of functional groups such as amine ($-NH_2$), thiol (–SH), or hydroxyl (OH). Schiff base ligands can act as a donor in bi-, tri-, or tetra- coordination states with transition metals. Extensive research has explored the effects of combining Schiff base with anticancer drugs across various cancer cell types. One important study focused on mouth Squamous cell carcinoma (SCC), a common type of cancer for which current treatments are often ineffective. In a study conducted by Rasha H Al-Serw and her team, the toxic effects of a Cu (II)–Mn (II) tetradentate Schiff base complex on SCC cells were evaluated in vitro using the 3-(4,5-dimethylthazolk-2-yl)-2,5-diphenyl tetrazolium bromide assay (MTT) assay. This rapid colorimetric test estimates viable cell numbers based on the cleavage of the MTT tetrazolium ring by dehydrogenases in active mitochondria of living cells. The Cu (II)–Mn (II) Schiff base and cisplatin were tested individually and in combination on SCC and oral-derived gingival mesenchymal stem cells (GMSCs), with GMSCs serving as controls. Significant differences were observed in the IC_{50} values of the Schiff base and cisplatin in the two cell lines.[37] The Cu (II)-Mn (II) Schiff base complex exhibited IC_{50} values of approximately 600 µM in SCC cells and 450 µM in GMSCs, whereas, cisplatin demonstrated an IC_{50} of 1µg/mL (approximately 2.5 µM) for both cell lines.[37] These results indicate that cisplatin has a stronger effect than the Schiff base complex in these specific cell lines.[37] However, the Schiff base complex exhibited lower toxicity towards normal cells compared to cisplatin alone. While cisplatin forms DNA adducts, Schiff bases enhance these adducts by binding to DNA, hindering repair processes and promoting apoptosis.

This combination activates caspase 3 (Cysteine-aspartic protease encoded by the CASP3 gene) to trigger apoptosis through both intrinsic (induced by DNA damage and oxidative stress) and extrinsic (induced by tumor necrosis factor (TNF) superfamily) pathways. Schiff bases regulate proteins that promote apoptosis, such as Bax, while down-regulating anti-apoptotic proteins like Bcl-2, thereby shifting the balance towards apoptosis.[38-40] Additionally, Schiff bases induce mechanisms that initiate apoptosis in response to cellular stress, increasing the susceptibility of cancer cells to therapy. Combining cisplatin with Schiff base offers a promising strategy for cancer treatment due to their synergistic effect, enhancing the drug's cancer-killing efficacy while minimizing its impact on healthy cells.

Gastric cancer is complex and challenging to treat due to its diverse nature. It is considered one of the most common and deadly gastrointestinal cancers.[40,41] Cisplatin is commonly used for treatment, despite its toxic side effects and potential for drug resistance. Yan Xia and his team developed a new compound called Schiff base copper coordinated compound (SBCCC) and studied its effects on two gastric cancer cell lines (SGC-7901 and BGC-823), as well as in a gastric cancer mouse model.[42] SBCCC effectively inhibited the growth of gastric cancer cells in a dosage and time-dependent manner.[42] The IC_{50} of SBCCC in SGC-7901 and BGC-823 cells was 1µM, which is lower than the IC_{50} of cisplatin (ranging from 2.5 to 50 μM in various tested cancer cell lines). SBCCC induces cell death and arrests cell cycle progression at the G1 stage by suppressing NF-ϰB.[40]This suppression disrupts the phosphorylation and degradation of IϰBα, preventing NF-ϰB translocation to the nucleus, and inhibiting its transcriptional activity, which is involved in cell survival and proliferation. Increased levels of ROS typically promote apoptosis, but cancer cells adapt by enhancing antioxidant defenses, resulting in drug resistance. SBCCC counteracts this by reducing ROS production, destabilizing the cancer cell›s protective mechanisms. Consequently, this reduction in ROS facilitates the activation of pro-apoptotic pathways, including the downregulation of anti-apoptotic proteins like Bcl-2, thereby promoting apoptosis and enhancing the therapeutic efficacy of SBCCC against tumors. SBCCC has the potential to provide a more effective treatment with fewer side effects because of its lower IC_{50} compared to cisplatin.[42]

Ming Jiang and his group synthesized two new Schiff base Cu (II) complexes (Cu1 and Cu2) designed to exhibit a greater cytotoxic effect against HL-7402 cells compared to cisplatin. The Cu (II) complexes (Cu1 and Cu2) demonstrated significant cytotoxic effects against HL-7402 cells, with cytotoxicity being 5.79-fold and 3.82-fold greater than that of cisplatin, respectively. Moreover, these complexes inhibited hepatic cancer growth in a xenograft model.[43] Their study of the mechanisms of resistance revealed that the Cu (II) complexes decreased the mitochondrial membrane potential. Mitochondria play a crucial role in cancer cell growth, including energy production, cytoplasmic biosynthetic precursor generation, and regulation of cell death.[44] The reduction in mitochondrial membrane potential prompted an overproduction of ROS, leading to mitochondrial DNA (mtDNA) damage and, ultimately, promoting apoptosis.[44] Additionally, mtDNA is more susceptible to drug action due to a lack of histone protection, emerging as an efficient target for cancer therapy. Therefore, designing a metal complex capable of acting on mitochondria and their DNA may represent a promising approach to anticancer treatment.

Dithiocarbazate ligands form complexes with Cu (II), Ni (II), and Zn (II) that display potent cytotoxic effects on cancer cells, specifically MCF-7 and MDA-MB-231. More precisely, complex 2 displayed positive outcomes due to its efficient interaction with DNA, enhanced by

both hydrogen bonding and van der Waals interactions.[44]

Results from molecular docking experiments revealed a binding energy of -7.39 kcal/mol, indicating robust interactions with DNA. The affinity and interaction modes of Cu (II), Ni (II), and Zn (II) complexes differ in their DNA binding mechanisms. Cu (II) Complexes usually interact with DNA in the minor groove and can produce ROS, leading to DNA cleavage via oxidative mechanisms. Ni (II) complexes display an increased ability to bind to DNA by typically intercalating themselves within the DNA base pairs, leading to stronger interactions compared to Cu (II). Zinc (II) complexes typically show lesser interactions with DNA, frequently binding through coordination instead of substantial intercalation or groove binding.[44]

The Cu (II) complex, which includes a dithiocarbazate ligand, exhibits effective cytotoxicity against MCF-7 and MDA-MB-213 cancer cell lines, similar to well-known drugs such as cisplatin. Despite its effectiveness, cisplatin frequently results in significant toxicity and resistance issues. In contrast, the Cu (II) complex has a reduced effect on healthy cells and an increased ability to bind to DNA, which can improve its effectiveness in battling cancer. Unlike typical agents, it showed diverse strategies that may help overcome resistance commonly encountered in traditional treatments.[44] In a study conducted by our team, copper (II) complexes with tetrahedrally distorted square planar structures show distinct geometries as a result of interactions with ligands. Characterization by X-ray diffraction (XRD) validates the coordination of the cis-isomer using bidentate N (azomethine) and S (thiol) ligands, showing bond lengths in agreement with density functional theory (DFT) calculations. Moreover, EPR spectroscopy shows considerable distortion, with tetrahedral characteristics indicated by the gz values. The distortion from ideal geometries in these copper (II) systems is influenced by the interaction between steric effects and ligand size, highlighting their complexity.[45]

Tetrahedrally distorted square planar copper (II) compounds exhibit significant anti-cancer properties through various mechanisms. These structures trigger cell death and self-degradation in cancer cells by generating ROS and influencing the cell cycle, particularly the G0/G1 and S phases.[46-47] Research shows that copper (II) complexes can specifically target cancer cells without harming healthy cells, enhancing their therapeutic effectiveness.[48] Their mechanisms include causing DNA damage, triggering mitochondrial-mediated cell death, and modulating proteins involved in the cell cycle, suggesting their potential as effective cancer treatments).[49,50]

In another study, the anticancer effects of binuclear copper (II) complex-1 and mononuclear copper (II) complex-2 were investigated. Several tests were conducted, including viability assays, flow cytometry for apoptosis and cell cycle assessment, migration assays, and gene expression analysis. The findings showed that complex-1 exhibited greater toxicity than complex-2 after 24 and 48 hours. Both compounds induced cell death at their respective IC_{50} concentrations and inhibited cell division at the G1-S phase boundary. Notably, complex-1 caused a more significant cell cycle arrest in the sub-G0/G1 phase compared to complex-2. Additionally, gene expression analysis showed that only complex-1 activated the p53 pathway. Both complexes led to an upregulation of Bcl-2 expression and effectively inhibited cell migration through various mechanisms, including amoeboid and collective movement, by activating protease-independent pathways. This research confirmed that the activity of the complexes was enhanced by incorporating multiple metal cores and co-ligands. Furthermore, copper-containing complexes inhibited cancer cell migration through protease-independent pathways, indicating potential for novel therapeutic applications.[51]

CONCLUSION

Health facilities and cancer patients are facing significant challenges due to rising cancer cases, which include high treatment costs, a lack of highly effective drugs, and the suffering caused by chemotherapy. While chemotherapy has improved survival rates for cancer patients in oncology departments, the high incidence of drug resistance presents substantial obstacles in addressing these issues.

Two main types of drug resistance exist: intrinsic and acquired. Intrinsic resistance occurs before treatment when the cancer is naturally unresponsive to existing drugs, while acquired resistance develops during treatment due to the biological pressures on cancer cells. Factors such as genetic mutations, changes in drug targets, alterations in the tumor microenvironment, and increased drug efflux can all negatively impact treatment outcomes. Drug efflux is a significant concern, often resulting from the overexpression of multidrug resistance (MDR) genes, particularly P-gp, which reduces drug levels within cancer cells. Another mechanism of resistance involves the inhibition of apoptosis, driven by nucleotide repair processes that promote tumor growth.

Addressing these challenges requires innovative strategies, such as developing new, safer drugs that are easy to manipulate and produce, targeting the root causes of resistance. One promising approach is the use of Schiff bases in combination with specific drugs like cisplatin. This methodology has the potential to effectively combat drug resistance and improve patient treatment outcomes. Numerous studies have shown that metal complexes of Schiff bases exhibit potent anti-cancer activity and can be chemically modified to target specific cancer types and overcome drug resistance.

Some mechanisms by which Schiff bases can address resistance include:

1 - *Regulating ABC transporters by blocking ATP-binding cassettes, leads to higher accumulation of chemotherapeutic drugs*.

2 - *Reducing lysosomal activity by directly targeting increased ABCB1 activity to prevent drug sequestration, trapping, or degradation, thus circumventing typical drug resistance.*

3 - *Stimulating cell death by restoring defective p53, triggering necrosis or paraptosis, and facilitating apoptosis, ultimately leading to the death of resilient cancer cells.*

4 - *Enhancing sensitivity to DNA-damaging agents and improving the efficacy of existing therapies.*

5 - *Modulating the immune system to overcome drug resistance.*

These mechanisms suggest that Schiff bases could be effective candidates for enhancing chemotherapy outcomes. Currently, there are no specific clinical trials focused on Schiff base compounds; however, ongoing preclinical research highlights the promising anticancer effects of various Schiff base metal complexes. Our team has recently synthesized new Schiff base complexes, with many more in preparation. These newly synthesized Schiff bases will undergo chemical characterization and evaluations of their antimicrobial and anticancer biological activities.

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