Hindawi
Journal of Chemistry
Volume 2022, Article ID 9261683, 19 pages
https://doi.org/10.1155/2022/9261683

Review Article

Metal Complexes in Target-Specific Anticancer Therapy: Recent Trends and Challenges

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Received 11 January 2022; Revised 28 March 2022; Accepted 4 May 2022; Published 17 May 2022

Academic Editor: Wagdy Eldehna

Cancer is characterized by abnormal cell differentiation in or on the part of the body. The most commonly used chemotherapeutic drugs are developed to target rapidly dividing cells, such as cancer cells, but they also damage healthy epithelial cells. This has serious consequences for normal cells and become responsible for the development of various disorders. Several strategies for delivering the cytotoxic drugs to cancerous sites that limit systemic toxicity and other adverse effects have recently been evolved. Among them, biomolecule-conjugated metal complexes-based cancer targeting strategies have shown tremendous advantages in cancer therapy. This review focuses on several chemoselective biomolecules-bound metal complexes as prospective cancer therapy-targeted agents. In this review, we presented the details of the various extra- and intracellular targeting mechanisms in cancer therapy. We also addressed the current clinical issues and recent therapeutic strategies in targeted cancer therapy that may pave a way for the future direction of metal complexes-based targeted cancer therapy.

1. Introduction

1.1. Introduction to Cancer Therapy. Cancer is a more complicated and fatal disease that poses a threat to human health all over the world. It involves multiple genes and crosstalk between signaling networks, changes in DNA, and/or gene transcription and/or translation [1]. Cancer is caused by the malfunctioning of normal cell genes, which promotes uncontrolled proliferation, metastasis, and the rapid expansion of aberrant cells that grow beyond their normal limits. In the year 2020, the US was anticipated to witness 606,520 deaths and 1.8 million new cases [2]. About 4.5 million premature cancer-caused deaths were reported worldwide in 2016 [3]. Based on current data, the International Agency for Research on Cancer (IARC) forecasts that around 13 million cancer-related deaths would occur by 2030, prompting researchers to continue their hunt for an effective anticancer medicine [4, 5]. The most common clinical approaches for cancer treatment are chemotherapy, radiation therapy, surgery, hormone therapy, and targeted therapy with anticancer drugs [6]. All cancer therapies have the potential to harm normal cells while destroying cancer cells [7]. Targeted therapy, on the other hand, is a potential choice since normal cells can survive when cancer cell proliferation is reduced during targeted therapy [8]. The damaged proteins produced by these mutated genes could be treated with targeted therapy [9, 10].

1.2. Challenges in Recent Cancer Chemotherapy. The finding of the anticancer drug cisplatin is a noticeable breakthrough in cancer chemotherapy [11]. Cisplatin, also known as *cis-*

diamminedichloroplatinum(II), is an antitumor drug used in the treatment of a range of malignancies, including testicular, ovarian, bladder, cervix, lung, head and neck, and breast cancers [12]. However, cisplatin's clinical use is limited due to the appearance of hazardous side effects like nephrotoxicity, neurotoxicity, and cytotoxicity [13, 14]. The primary drawbacks of cancer therapy are mainly the lack of specificity of drugs and ineffective accumulation of drugs at tumor sites, as well as development of drug resistance [15, 16]. As a result, second-generation anticancer medicines, such as metal-based compounds with a tailored drug delivery mechanism, are being developed as potential alternatives [17, 18]. TDDS is a promising field of study that requires an interdisciplinary approach to deliver drugs to target sites while avoiding damage to healthy tissues and organs [19, 20].

Many research groups have demonstrated delivery systems based on target-specific groups, primarily peptide substrates, heterocyclics, oligonucleotides, and monoclonal antibodies [21, 22]. However, their unreducible mass makes it difficult to penetrate solid tumors, and the excretion of unbound reagent is a disadvantage for future use [23]. Only cancer cells would be affected by targeted therapeutic medications that inhibit the mutated form of the protein while maintaining activity of the normal version. Agents that do not contain metals as well as metal complexes are the active agents in medicinal inorganic chemistry. Since the nonemitting ligands are biomolecules (protein or peptide, lipids, vitamins, and nucleic acid), metal complex fragments that keep a part of the carrier ligands are essential because they can help with conjugation and provide selectivity or controlled release activity [24, 25]. There are seven different types of metal-based drugs: (i) one or more ligands are involved in biological activity [26], (ii) a fragment of the complex [27], (iii) the entire reactive complex [28], (iv) the metal is a radiation enhancer [29], (v) the metal ion or its biotransformation product is the active ingredient [30], (vi) the metal is radioactive [31], and (vii) the entire inert complex [32]. Understanding how metals interact with biomolecules raises the potential for modifying metal characteristics, speciation, reactivity, and, ultimately, biological function [33, 34].

Currently, researchers are focusing their efforts on ligand-targeted delivery of medicines. Franz and Metzler-Nolte [35] have reported many biomolecule ligands such as peptides, carbohydrates, lipids, and vitamins, which act as ligand-targeted delivery of drugs. This review attempts to investigate the anticancer metal complexes bound to folic acid, albumin, biotin, and hyaluronic acid, as well as folic acid-human serum albumin, erlotinib, suberoylanilide hydroxamic acid, and valproic acid. The capacity to serve as drug-carriers delivering drugs to receptors and their high selectivity and affinity are the two advantages of these biomolecules [35]. There is a pressing need to develop carriers (vectors) and delivery methods that can carry chemotherapeutic medicines only to the precise target site, thereby improving treatment efficiency and reducing undesirable systemic side effects [19, 20, 36]. The other approach makes use of the fact that malignant cells have more receptors on their surface than healthy cells, allowing cytotoxic drugs to be targeted more effectively at tumor cells. As a result, therapeutic efficacy enhances while side effects diminish [37].

The targeting ligands are biomolecules that include folic acid, biotin, albumin, and hyaluronic acid. Folic acid (FA) is a targeted molecule that has been studied extensively in the fields of imaging, diagnostics, and cancer treatment [35]. Because of their rapid development and cell division, several cancer cell lines overexpress FA receptors (FARs), including ovary, prostate, lung, nose, brain, and colon cancer. Normal cells, on the other hand, express very little folate receptors (FARs). Therefore, some of the anticancer drugs conjugated with biomolecules and metal complexes can selectively accumulate in tumor tissues. By utilizing specific or overexpressed receptors, anticancer drugs can be delivered to cancerous cells and tissues in a targeted manner. However, the use of biomolecules-conjugated metal complexes remains a challenge in the realm of cancer treatment [38, 39].

1.3. Methodology of the Review. Web-based literature searching tools, such as SciFinder, PubMed, and Google Scholar, were used to carefully select articles. The literature survey mainly covers the years from 2010 to 2021. However, some relevant literatures out of the interval were also highlighted. The review emphasized on reports on metal complexes in cytotoxic target-specific anticancer therapy, cellular targeting and mechanisms, metal complex-conjugated biomolecules, and folate-conjugated metal-nanoparticles for target drug delivery. By unbalancing the cellular redox state, the metal complex takes up the cell membrane through a receptor on the cell's surface and interacts with organelles, causing cellular death. This review also looks at how biomolecules like folic acid, biotin, and hyaluronic acid can be used to selectively interact with and accumulate metallodrugs in cells.

2. Mechanism of Cellular Targeting and Targeted Cancer Therapy

2.1. Intracellular Targets

2.1.1. Nucleic Acids. The nucleus, the cell's largest organelle, was initially found in the early 1800s. It functions as the cell's brain since it contains the most genetic components, such as chromosomes made up of lengthy DNA strands and nucleoproteins like histones that regulate gene expression [40–42]. Transcription from rDNA to rRNA that occurs in the nucleolus, which includes both nucleic acid and proteins, is one of the most important phases in the gene expression process [43].

Metal complexes are appealing candidates in cancer research, due to their enormous range of structures and activities, as well as the metals' various oxidation state and coordination geometry, among large range of organic ligands attached to the metal center [44]. They are modular systems with a great deal of adaptability. Functionalization of ligands can alter cellular absorption, accumulation, and

biomolecule targeting (Figure 1). With ligand alterations, the metal core can have photophysical, electrochemical, and spectroscopic properties that can be tuned. These features can be used to improve diagnosis and treatment of diseases. Metal complexes bind to nucleic acids in two ways: covalent bonds via direct coordination of metal ions (e.g., platinum agents) or noncovalent bonds via supermolecular interactions of organic ligands (for instance, numerous metal complexes used in bioimaging). As seen in platinum drugs, the metal center attaches directly to the nitrogen atoms of the nucleobases in the first case [45]. The organic ligands, on the other hand, determine the interaction that can be hydrophobic groove bonding, hydrogen bonding, electrostatic interaction, intercalation, insertion, or a mix of these. Due to these, metal complexes that interact with nucleic acids have been proposed for a variety of applications such as pharmaceuticals, fluorescent imaging probes, foot printing agents, and nanotechnology [23, 40, 46].

In addition, recent research has focused on the development of metal compounds capable of targeting DNA noncanonical configurations, even though DNA is generally found as a duplex structure. Target specific sequences using tailored compounds to target certain structural features allows metal complexes to attach to nucleic acids [47, 48]. Ruthenium(II) complexes that can bind to extended DNA; iron(II) that binds to DNA in three-way junctions; and various metal-containing polycyclic planar aromatic compounds that bind to G-quadruplex DNAs, such as metal-salphen and platinum(II) terpyridine complexes, were reported [49–51]. All of these noncanonical structures are found to be potential targets for structure- and shape-specific binders. Moreover, RNA has even more noncanonical structural components than DNA, but it has been less investigated as a metal complex target. RNA is an important molecule: in recent decades, messenger ribosomal and transfer RNA have been discovered, permitting the passage of genetic material from DNA to proteins in enormous quantities of noncoding RNAs [52, 53]. Examples include short microRNAs (miRNA) and ribo-switches, which both play a role in gene regulation, as do ribozymes, which are catalytically active RNAs that can catalyze reactions without the use of a protein. They target noncanonical elements, which is a difficult but effective technique to disrupt RNA function [54, 55]. Also, various small compounds that target RNAs have been developed [46].

2.1.2. Mitochondria. The mitochondrion is a semi-independent organelle with a double membrane that controls most the cell's metabolic functions. The electron transport chain is stored within the inner mitochondrial membrane, where electrons are moved from NADH to oxygen in redox processes and energy is used to pump H^+ out of the matrix, resulting in a negative charge within [56]. Mitochondria control cell metabolism, the production of reactive oxygen species (ROS), cell death, and calcium, the second universal messenger. Mitochondria, the cell's powerhouses and energy centers, are essential for cancer metabolism. The phrase "aerobic glycolysis," known as the Warburg effect, was used

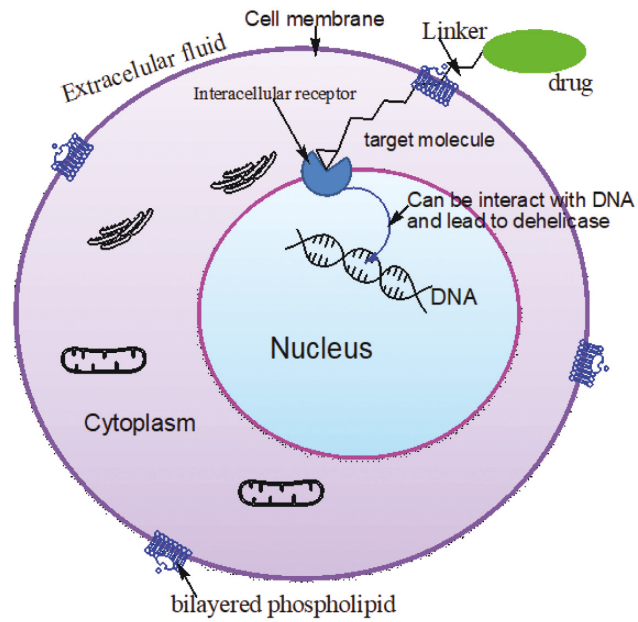


Figure 1: General model of intracellular targeting mechanism (adapted from Ref. [44]).

to explain mitochondria's role in carcinogenesis. This is because tumor cells create energy via glycolysis rather than the tricarboxylic acid (TCA) cycle. This phenomenon was linked by Warburg to tumor cell mitochondrial malfunction, and he suggested that tumor cells were forced to rely on glycolysis due to the loss of the mitochondrial respiratory chain [57, 58].

Anticancer drugs that directly target mitochondrial functionality have significant benefits over traditional chemotherapy drugs that cause mitochondrial dysfunction in an indirect manner by employing damaged DNAs to generate apoptosis-initiating signals. Many transition-metal complexes that accumulate within mitochondria are emissive, and the fluorescence of these complexes can be used to demonstrate both cellular uptake and organelle-specific distribution. The contribution of the Au(I) (phosphine) moiety to mitochondria has been described, with an emphasis on di- and tetrapeptides. The cause is an increase in reactive oxygen species (ROS) within the cells [59]. Hao and coworkers described three novel Ir metallic complexes containing cdppz (11-chlorodipyrido[3,2-a,2′,3′-c]phenazine) as mitochondrial-targeting anticancer agent: [Ir(ppy)2(cdppz)] (PF6) (ppy = 2-phenylpyridine), [Ir(bzq)2(cdppz)](PF6) (2) (bzq = benzo[h]quinolone), and [Ir(piq)2(cdppz)](PF6) (3) (piq = 1-phenylisoquinoline). These complexes increase intracellular ROS levels, diminish mitochondrial membrane capacity, and cause apoptosis by regulating the stages of apoptosis-related proteins, preventing colony formation, and slowing the cellular cycle at G0/G1 phase [60].

2.1.3. Lysosome. Lysosomes are dense granular structures with hydrolytic enzymes that are mainly responsible for intracellular and extracellular digestion. A hydrogen proton

pump is located on the lysosomal membrane and is responsible for maintaining the pH of the enzymes. The lysosomal enzymes' functionality is ensured by the acidic media maintained by the proton pump, which pumps H^+ into the lumen. Lysosomes, which are loaded with enzymes known as hydrolases, are responsible for the breakdown of extracellular and intracellular materials. It contains around 40 different enzymes that are divided into five categories: proteases, lipases, amylase, nucleases, and phosphoric acid monoesters. Hydrolases are a class of enzymes that use water molecules to cleave substrates. Most lysosomal enzymes work in an acidic environment [61].

Cancer growth, invasion, and metastasis all require lysosome migration toward the cell periphery. Lysosomes alter in number, shape, hydrolase concentration, luminal pH, and intracellular distribution during neoplastic transformation. The population of lysosomes has migrated from the center to the periphery of the cytoplasm, which is a particularly noticeable modification. Changes in the tumor microenvironment, such as acidity, or changes in the expression of genes that control lysosome location and motility, which occur during oncogenic transformation, could trigger this redistribution. Lysosome's exocytosis, extracellular matrix breakdown, cell adhesion, and migration are facilitated by centrifugal transport of lysosomes, all of which lead to cancer. Anticancer treatments should investigate targeting the regulation of lysosome placement and motility [58, 61].

Yang and coauthors [62] synthesized lysosome-targeted cyclometalated iridium(III) anticancer complexes containing imine-N-heterocyclic carbene ligands $[Ir(ppy)_2(CN)]PF_6^-$ (wherein CN are imine-N-heterocyclic carbene ligands with diverse substituents and ppy is 2-phenylpyridine). Iridium complexes cause cellular autolysis and cell death by destroying the lysosomal membrane in which lysosomal damage changes accountable for the cell apoptosis. Moreover, rhodamine-modified metalated Ir(III) complexes that target lysosomes exert effective anticancer outcomes through unique mechanisms, along with targeting subcellular organelles and inhibiting protein activities [63]. Ru-1@TPP-PEG-biotin has also been used in targeting lysosomes as a brand new anticancer therapeutic strategy, and it was also stated that it contributed to the instability of the lysosomal membrane through the reduced expression of ceramide [64].

2.2. Extracellular Targeted Therapy

2.2.1. Cell Membrane. The cell membrane is vital for its receptors, signal transmission, enzymatic activity, fusion-fission, endocytosis, and transport, in addition to its structural function. It is responsible for cell-environment interaction. Specific bilayer activities are linked to high lipid compositional diversity, flexibility, interactions, and dispersion, impacting membrane or cell characteristics. Lipid research has shown to be critical in better understanding the intricacies of biological systems and disorders. Lipids feature a lengthy hydrophobic tail and a polar head. Due to thermodynamic factors, hydrophobic tails are covered by a layer of hydrophilic heads, forming micelles or bilayered sheets that are thought to be the origin of cell membranes and spontaneously associate in aqueous conditions. These components facilitate noncovalent interactions with other biomolecules including proteins and lipids, which help to shape cellular and organelle membranes. Membranes' lipid composition and distribution are not uniform. Lipid asymmetry between the inner and outer membrane leaflets is caused by phospholipid enrichment with amine or serine moieties in the inner leaflet, whereas choline and sphingomyelins (SMs) predominate on the exterior. For millennia, people have used lipids in their meals and supplements to improve their health and avoid illness [65]. Mono- and polyunsaturated fatty acids, together with oleic acid, linoleic acid, and fish oils, are thought to prevent colon cancer. The cellular membrane may be used alone or in combination with current chemotherapeutics and small compounds to deal with cancer. The cellular membrane and its components ought to be considered in cancer treatment, and clean therapeutic techniques need to be advanced [66, 67].

2.2.2. Cellular Receptors. A cell receptor structure (CRS) is a structure on a cell's surface that permits it to admit outside molecules like nutrients and hormones, as depicted in Figure 2. There are many different types of receptors, but they can be categorized into two groups: intracellular receptors (found in the cytoplasm or nucleus) and extracellular or cell surface receptors (found in the plasma membrane) [68]. The CRS plays a role in a wide range of physiological and pathological processes, such as the extracellular matrix, growth factor signaling, and cell activation in response to microbial invasion. The progression of degenerative diseases such as cancer, atherosclerosis, and neurological disorders is dependent on cell surface receptors [69].

The main goal of cancer detection and/or treatment is to develop drugs that can target the tumor microenvironment. Some overexpressed receptors, such as $\alpha V\beta 3$ integrin, folate receptor (FAR-α), epidermal growth factor receptor (EGFR), vascular endothelial cell growth factor receptor 2 (VEGFR2), and neuropilin-1 (NRP1), are commonly exploited as targets for cancer applications [69]. Overexpression of the human epidermal receptor 2 (*HER2*) proteins is frequently seen in a variety of primary tumors and contributes to carcinogenesis, particularly in breast cancer [71, 72].

The cell membrane, which separates the interior of cells from the outside environment, is engaged in a number of cellular functions, including selectively identifying and transporting specific molecules, as well as cell signaling transmission. Deng and coauthors [73] discovered that Ru complexes containing phenylterpyridine derivatives had anticancer properties and identified their cell membrane target receptors. The coupling of ruthenium polypyridyl subunits and EGFR-inhibiting 4-anilinoquinazoline ligands results in a class of extremely active dual-targeting anticancer drugs. The anticancer potency of the most active Ru(II) polypyridyl complexes is similar to that of cisplatin and higher than that of gefitinib, according to an *in vitro* antiproliferation experiment

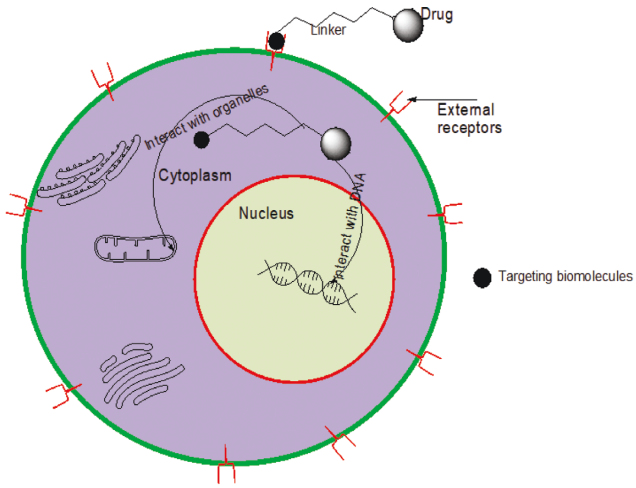


Figure 2: Model of extracellular/surface cell target mechanism (adapted from Ref. [70]).

against a range of EGRF-overexpressing cancer cell lines [73].

3. Metal Complexes-Biomolecule Conjugation in Targeted Cancer Therapy and Their Challenges

The production of metal complexes as medications or diagnostic agents has piqued the interest of medicinal chemistry. A metal complex, also known as a coordination compound, is made up of a core metal atom and an array of molecules or anions known as ligands. Metal compounds provide therapeutic action mechanisms that organic agents cannot achieve due to their vast range of coordination numbers, geometries, and their kinetic properties (Figure 3) [74]. Preclinical studies *in vitro* and *in vivo* have investigated various metal compounds as antitumor medicines. Complexes with ionic organic ligands, classical inorganic agents, and increasingly organometallic species are all present in the various agents examined. Main group metals (such as bismuth, tin, antimony), transition metals (such as rhodium, vanadium, iron, cobalt, and gold), and cerium are among the metals studied. In contrast to organic molecules, metals provide accessible redox states, a wide range of coordination numbers, and ligand substitution kinetics for the design of anticancer medicines [75, 76].

Metallocomplexes have created new challenges in terms of pharmacological limitations including low water solubility and reduced bioavailability. In order to attain a greater therapeutic index, breakthrough metal complexes must boost the selectivity of tumor cells over healthy cells, in addition to improving solubility. Targeting ligands, which are coupled to metal and carry the medicine to the interesting cells, can provide precise delivery. A targeted delivery system is defined as the ability of a molecule (ligands or metal complexes) to be recognized by membrane receptors on tumor cells, resulting in efficient accumulation into tumor tissue. This build-up can also be caused by tumor cells' high need for a substance that is not or lesser required by normal cells, like vitamins and sugars [77, 78].

Metals have distinct properties such as various coordination modes, redox activity, and reactivity and are required for a variety of metabolic activities in cells. Their concentration is tightly regulated inside the cells due to their reactivity. These metals all could produce reactive oxygen species (ROS), which are important in cell metabolism, signaling for proliferation, differentiation, and cell death, and are a part of the cellular redox balance. Furthermore, ligand substitution and modification of existing chemical structures resulted in the synthesis of a wide spectrum of metal-based compounds, some of which have a better cytotoxic and pharmacokinetic profile than others. Figure 4 depicts the mechanism and specific function of metal complexation in increased drug-metal complex efficacy or potency [79].

Many anticancer drug applications had been designed to apply as cancer cell reductase enzymes for target-specific activation. Some may also comprise metal complexes as prodrugs for bioreductive activation [80]. For instance, cobalt complexes are reported to be bioreductive prodrugs, having a completely inert oxidized cobalt(III) state and really labile reduced cobalt(II) state [81]. The Pt(IV) metal complex is an inert prodrug, and its reduction yields an active Pt(II) complex and equivalents of active ligands. Metal complex-drug conjugation can grow the potency and the performance of the drug. Besides these, curcumin is a bioactive ligand; however, it has poor stability and bioavailability [82]. The coordination of curcumin to an oxovanadium(IV) dipyridophenazine (dppz) complex was found to prevent the hydrolytic cleavage of curcumin under physiological conditions and increases the efficiency of curcumin to target DNA cleavage [83]. The metal complex can itself be biologically active. With the active metal complex and active organic molecules from a single prodrug, more than one way of acting upon a target can be realized. Synergy action drugs can be more potent than the parent organic drug and be able to avoid drug resistance mechanisms [84].

Conjugation of a drug to a positively charged metal complex has been shown to greatly enhance the aqueous solubility of the drug because of its hydrophilicity. Alternatively, conjugation of metal to negatively charged groups can reduce the negative charge of a drug, enhancing passive cellular uptake and absorption [79]. Those are effective approaches to enhancing both the pharmacokinetic and pharmacodynamic properties of the parental drug and metal-conjugated drugs to enter the cell. Reducing side effects and booming of the bioavailability of the metal-drug complexes can mainly depend on changes in environmental situations, which include the redox status of the metals and the pH conditions [85–87].

3.1. Folic Acid-Conjugated Metal Complexes. Folic acid belongs to a category of water-soluble vitamins that function as a coenzyme in the production of DNA, RNA, and protein constituents, as well as numerous single carbon transfer processes [88]. Hamed and coauthor [89] investigated the

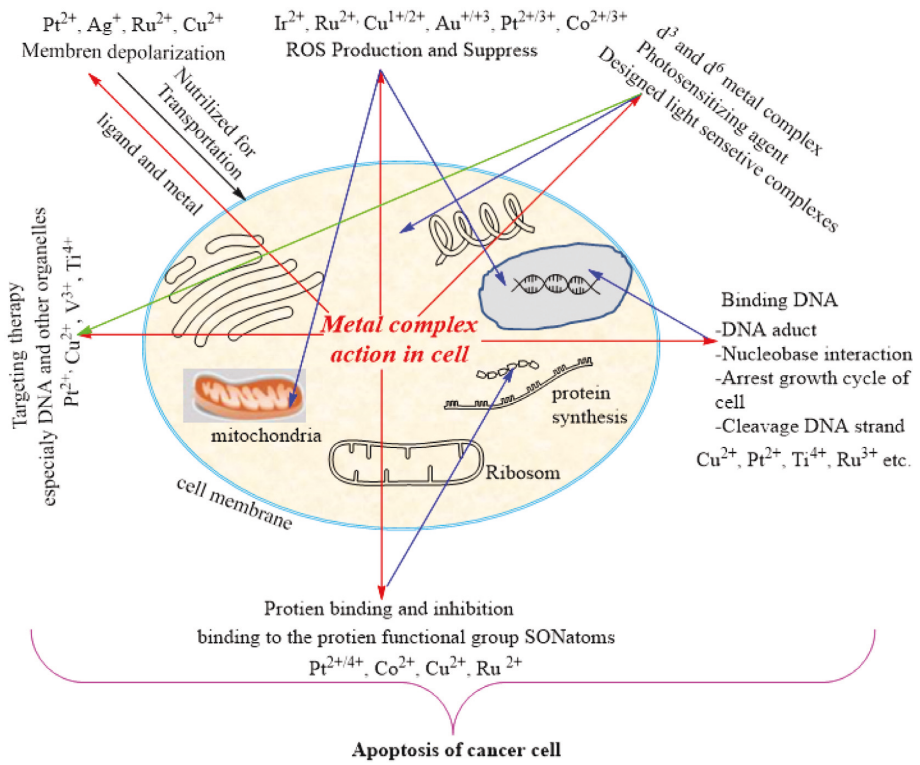


Figure 3: Mechanism of metal complex targeting cellular structure. Adapted from Ref. [74].

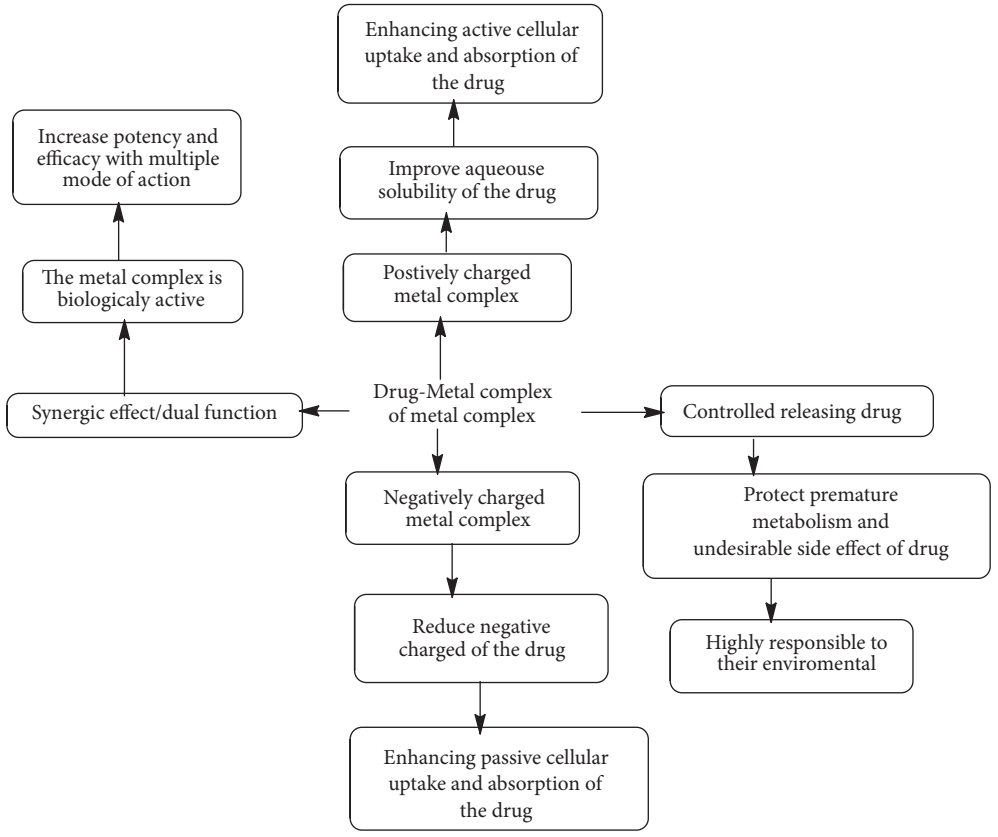


Figure 4: Illustration the mechanism and potency of drug-metal complex.

absorption efficiencies of folic acid alone and in complexes with metals like Fe(III) and Cu(I), finding that the metal complexes were substantially more absorbed in the blood than folic acid. Therefore, they have concluded that folic acid-transition metal complexes are preferential over folic acid alone because of their higher absorption efficiency than folic acid. On the other hand, folic acid serves as a bidentate ligand, allowing it to extract or withdraw important metals from the blood serum [89].

Yang and coauthors [39] reported the platinum porphyrin complex (PPC) coupled with folic acid can selectively accumulate in tumor tissue. PPC is an efficient photosensitizer for tumor-targeted photodynamic treatment (PDT) [90]. The folic acid used as a targeting biomolecule is bonded to PPC to improve the photosensitizer's tumor-targeting competency via folate receptor mediated. Through the heavy atom impact, platinum is coordinated with the porphyrin conjugate to boost the photodynamic therapeutic efficacy of the drug [91]. As a result, the folate-conjugated PPC demonstrated remarkable therapeutic efficacy in a dose-dependent manner against HeLa cells, with an IC_{50} of roughly 5.78 μM after irradiation. The surviving rate of HeLa cells (positive folate receptor) was only $22.25 \pm 4.75\%$; when the concentration of sample was increased to 20 μM, the survival rate of A549 cells (negative folate receptor) was $75.25 \pm 4.75\%$, indicating that PPC accumulates selectively in cancerous cells with high folate receptor expression. As PPC is one of the photo sensors, even if it accumulated in the cell due to folic acid, it is not active in the absence of radiation. These findings showed that the synthesized platinum-porphyrin with folate might be employed as an effective photosensitizing agent for cancer treatment.

Targeted therapy medications are gaining popularity because most cancer-killing drugs lack specificity for tumor cells, causing significant toxic effects in healthy organs during treatment. Ru-NO@FA@CDs is a NO-delivery nanoplatform in which a folic acid (FA), a Ru-NO donor, and ruthenium nitrosyl molecules are covalently bound to the surface of carbon dots (CDs) was described as a targeted medication (Scheme 1). Confocal laser scanning microscopy was used to confirm the specific binding of Ru NO@FA@CDs to the folate receptor (FAR) human cervical cancer cell. The Ru-NO@FA@CDs nanoplatform exhibited targeted NO delivery to several cell lines, which was monitored using fluorescence under complete control of visible light irradiation [92].

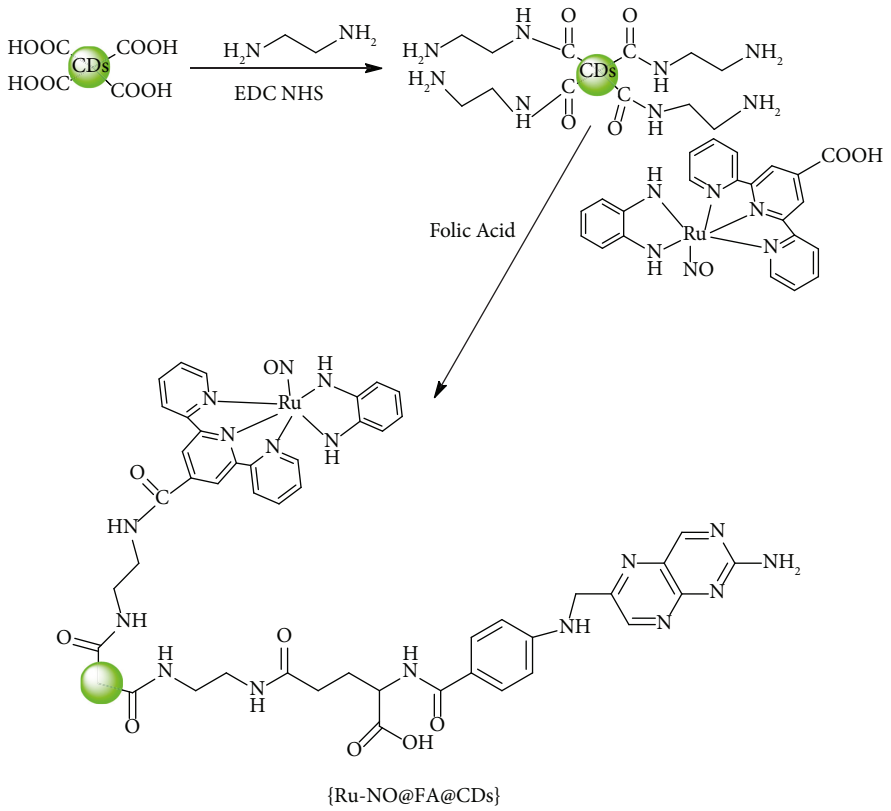
To create a multifunctional NO-delivery nanoplatform, ruthenium nitrosyls were covalently linked onto the surface of a CD carrier, together with cancer-cell-guiding FA molecules. The RF-overexpressed cancer cell lines are preferentially targeted by the Ru-NO@FA@CDs nanoplatform, which allows for intracellular delivery of NO under the control of light to kill cancer cells. The Ru-NO@FA@CDs nanoplatform could be monitored by fluorescence as it was utilized and absorbed by cells since CDs have inherent fluorescence. Furthermore, the amount of NO released from the Ru-NO@FA@CDs nanoplatform may be regulated by altering the exposure of the nanoplatform to visible light, allowing for spatiotemporal delivery of NO at concentrations ranging from nM to M. This opened the possibility of using it to treat disorders caused by a lack of NO, as well as cancer therapy mediated by NO [39].

Folates (also known as vitamin B9) play a crucial role in metabolic activities like RNA and DNA synthesis, making them vital for the human genome and cell health. The decreased tetrahydrofolate form of folate, which plays a critical role in rapid cell division and growth, has been associated with the pivotal role of folates in DNA synthesis, repair, and methylation. Reduced folate levels have been linked to the development of cancers like colorectal, lung, and breast cancers, possibly due to higher DNA damage and mutation rates. The reduced folate carrier (RFC) is an anion exchanger that primarily carries reduced folate; the proton-coupled folate transporter (PCFT) can carry folate in an acidic environment; and the folate receptors (FARs), which have a high affinity for folic acid (FA), can transport it into cells via endocytosis [93].

Kidney, lung, breast, ovarian, colorectal, cervical, brain, and nasopharyngeal carcinomas all show elevated expression of the FARs, and this enhanced expression has been associated with tumor growth. The FA, which is stable across a wide pH and temperature range, can be employed as a nonimmunogenic and biocompatible targeting motif to covalently conjugate with an optical imaging or therapeutic agent, making the FAR a possible target for cancer diagnostics and treatment [38].

Eu-FA, Eu-MTX, Tb-FA, and Tb-MTX are the visual probes (lanthanide(III)) developed by Du and coauthors [94] to make it possible to image folate receptors in cancer cells. Each complex consists of a high-intensity antenna complex covalently coupled to FA or methotrexate (MTX) (Figure 5). A crucial enzyme in the conversion of folate to its tetrahydrofolate form is dihydrofolate reductase; it is inhibited by MTX, causing cell death by reducing DNA and RNA synthesis. Folates and antifolates have also been utilized as targeting agents in a range of imaging applications. The scientists were able to effectively create four luminous lanthanide complexes that are extremely stable in a wide range of environments. Nonmalignant cells do not readily absorb the folate- and MTX-tethered complexes. FAR-positive cancer cell lines, on the other hand, internalized all four complexes, showing that both FA and MTX can be employed as folate receptor-targeting groups (Table 1). As expected, the complex bound to MTX turned out to be more dangerous than FA, even though the MTX complexes allowed for imaging of the therapeutic activity location. Significantly, Eu(III) complexes were discovered to be considerably more hazardous than Tb(III) complexes. By incubating cells with both Eu-MTX and Tb-FA, cell biologists can investigate MTX toxicity coupled with FA action. This is due to the fact that the emission from these compounds is solved easily. The fact that FA- and MTX-labeled complexes differ in the oral adenosquamous cell line (CAL-27) indicates that folate and antifolate imaging can be utilized to evaluate changes in folate receptors [94].

3.2. FA-HSA-Conjugated Metallodrugs. When 9–10 FA groups for each HSA molecule were introduced, it was possible to preferentially target tumor cells and tissues while



{Ru-NO@FA@CDs}

Scheme 1: Synthesis of {Ru-NO@FA@CDs} nanoplatform.

reducing nonspecific damage to normal cells. Molecular or biomaterial FA-conjugated drug delivery techniques include copolymer nanoparticles, albumin, and liposomes [95]. Drug delivery systems based on human serum albumin (HSA) may be the most effective of them due to their unique properties. HSA is a biopolymer with several desirable characteristics, including water solubility, biocompatibility, biodegradability, and high safety. More importantly, HSA possesses a large number of surface functional groups that are easily conjugated to FA. At the stage, the target carriers were FA-functionalized human serum albumin (FA-HSA) conjugates [96–98]. Human serum albumin (HAS) carriers for Cu(II) complexes (Figure 6) were produced by conjugating folic acid (FA) with HAS, as reported by Gou *et al.* [99]. C3 and C4 have a significant cytotoxic effect against both cancerous and noncancerous cells.

On the other hand, in cancer cells, the cytotoxic activity of the FA-HAS metallodrug complexes is three times higher, whereas no such effects are detected in normal cells (Table 2). In comparison to Cu(II) complexes alone, FA-HSA metallodrugs complex have the potential to target FAR-positive tumor cells preferentially while causing minimal cytotoxicity in normal cells. The intrinsic ROS-mediated mitochondrial pathway may play a role in cancer cell death caused by FA-HSA-Cu(II) complexes. In addition, targeting FA-HSA carriers enhances anticancer activity, arrests the cell cycle during the G2/M phase of cancer cells (HeLa), and downregulates cyclin-dependent kinase 1 (CDK1) and cyclin B1. Furthermore, HeLa cells are killed by the FA-HSA metallodrug combination through an endogenous ROS-mediated mitochondrial pathway, which is aided by Bcl-2 family gene regulation [99, 100].

3.3. Albumin-Conjugated Metal Complexes. Cancer cells' redox metabolism differs from that of normal cells in that they have higher intracellular ROS concentrations. In addition to intercalation, metal-based drugs seem to increase ROS levels in cancer cells and/or block ROS-detoxifying enzymes (e.g., glutathione) as an anticancer mechanism [101]. Certainly, metal-based drugs' redox cycling is suggested to be a vital factor for enhanced ROS generation, which can damage DNA and contribute to cancer cell death. In blood plasma, human serum albumin (HSA) is the most abundant protein in millimolar quantities [102, 103]. HSA transports fatty acids, drugs, metal ions, and metal complexes and includes amino acid tryptophan at the position 214, which fluoresces intensely at 347 nm when excited at 295 nm. In the presence of the complex, the quenching of HSA fluorescence was evaluated [104]. When the complex binds to the tryptophan residue of HSA, fluorescence quenching occurs, resulting in albumin conformational change, subunit interactions, denaturation, and substrate binding [105, 106].

Simunkova and collaborators investigated the anticancer properties of copper(II) complexes containing flufenamic acid, mefenamic acid, tolfenamic acid, and 1,10-phenathroline (Figure 7). The complexes interact with albumin as targeting biomolecules, and the targeted drug delivery vehicles for Cu(II) complexes have a high affinity binding constant ($K = 106$). Once the albumin-bound complexes

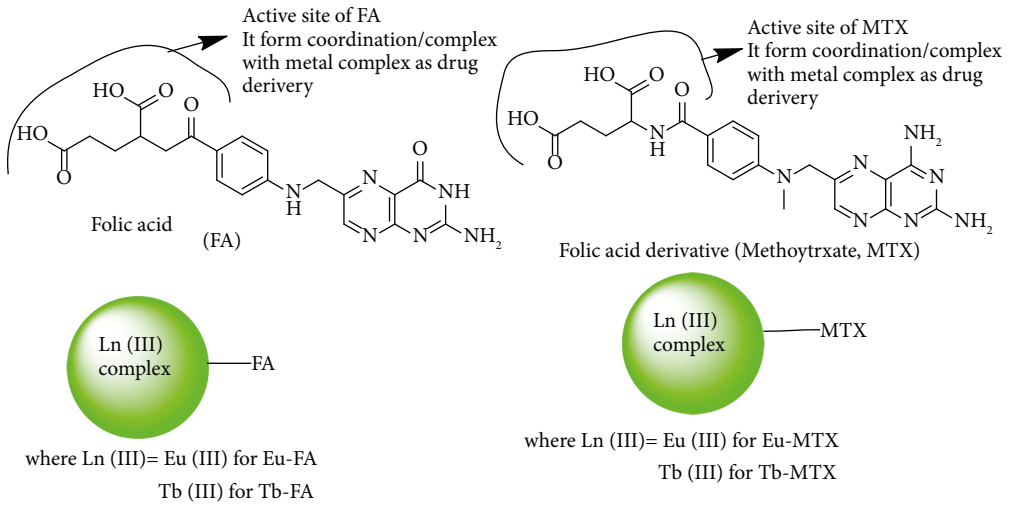


Figure 5: The chemical structures of folic acid (FA), methotrexate (MTX), and the four lanthanide complexes Eu-FA, Tb-FA, Eu-MTX, and Tb-MTX.

Table 1: The cytotoxic effects of Ln-tethered complexes.

As synthesis agents	MDA-MB-231 (IC_{50}, mM)	HeLa (IC_{50}, mM)	MLO-Y4 (IC_{50}, mM)
Eu-FA	3.59 ± 1.33	1.67 ± 0.52	12.86 ± 4.61
Tb-FA	5.24 ± 1.27	2.25 ± 0.86	12.79 ± 3.56
Eu-MTX	0.26 ± 0.06	0.58 ± 0.79	9.07 ± 3.25
Tb-MTX	1.90 ± 0.32	1.64 ± 0.79	9.22 ± 4.17
MTX	1.60 ± 0.22	1.91 ± 0.17	2.91 ± 0.25

(adapted from [94]).

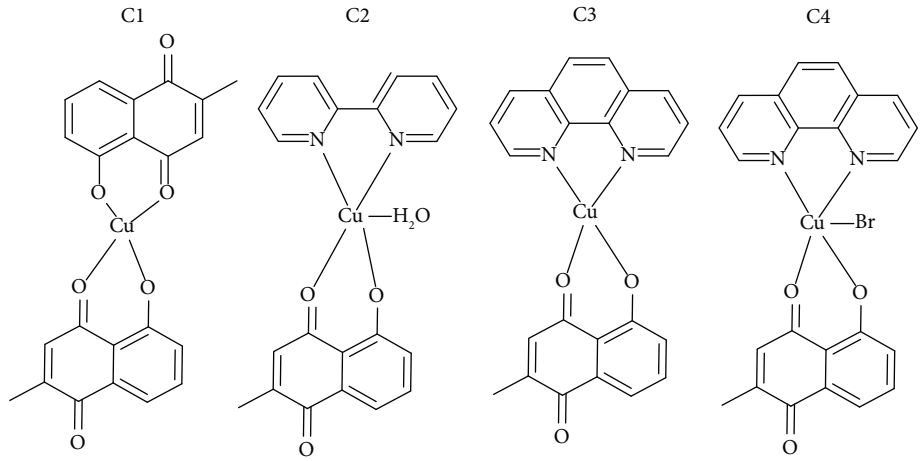


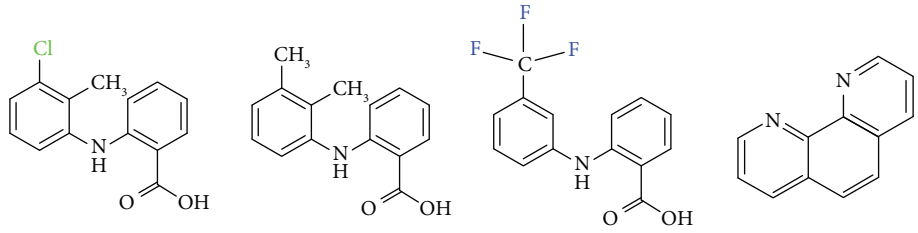
Figure 6: Chemical structure of Cu (II) complexes.

arrive at their destination, then the metal complex is freed from the carrier and binds to DNA. Cu(II) complexes are thus good superoxide dismutase (SOD) mimics as well as effective DNA intercalating agents. Furthermore, their ability to promote DNA damage is due to a redox cycling mechanism that produces hydroxyl radicals, singlet oxygen, and superoxide radical anions [107, 108].

3.4. Erlotinib-Conjugated Metal Complexes. In some malignancies, epidermal growth factor and its receptor (EGFR) overexpression is viewed as a prospective chemotherapeutic target. EGFR signaling activation has been linked to enhanced proliferation and reduced apoptosis, angiogenesis, and metastasis in tumor cells. Therefore, the EGFR gene is a promising target for the development of anticancer drugs. An EGFR-targeting drug, erlotinib, has shown promise in cancer therapy in clinical studies. It is a suitable organic pharmacophore and has good inhibitory capability. Erlotinib works by inhibiting the activity of the EGFR tyrosine kinase by binding to the kinase domain in an ATP-competitive manner. Erlotinib conjugates are made by

Table 2: Inhibition of human cancer cell lines growth (IC_{50} μM) for C1–C4 and their HSA-FA complexes.

Compound	Cell growth inhibition, $IC_{50} \pm SD$ (mM)	
	MCF-7	HeLa
PLN	14.15 ± 0.59	18.36 ± 1.75
PLN-HSA_FA	6.75 ± 1.27	8.25 ± 0.86
C1	6.62 ± 0.72	7.58 ± 0.95
C1-HSA_FA	3.57 ± 0.21	3.67 ± 0.34
C2	13.86 ± 0.35	4.68 ± 0.47
C2-HSA_FA	1.39 ± 0.16	1.45 ± 0.15
C3	3.32 ± 0.31	3.71 ± 0.27
C3-HSA_FA	1.24 ± 0.13	0.98 ± 0.11
C4	3.22 ± 0.29	3.68 ± 0.15
C4-HSA_FA	1.21 ± 0.16	1.01 ± 0.03
Cisplantin	20.15 ± 1.91	10.62 ± 1.12
Cisplantin-HSA_FA	45.64 ± 4.62	38.29 ± 2.47
HSA_FA	>50	>50



Tolfenamic acid Mefenamic acid Flufenamic acid 1, 10-phenanthroline

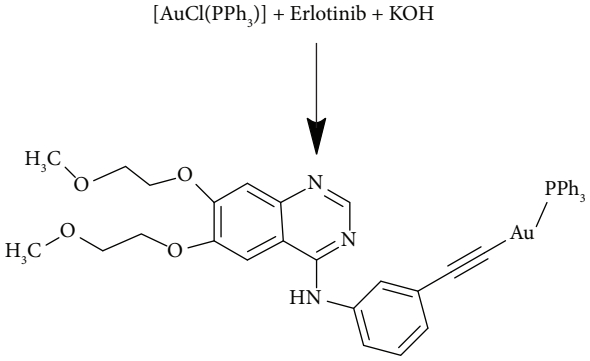
Figure 7: Structure of active anticancer fenamic acid derivatives and phenathroline.

combining erlotinib with a metal center that binds to a known biological target EGFR or a reactive gold complex that promotes erlotinib transfer. Indeed, Erlotinib-targeted zinc(II) phthalocyanine had show selective photodynamic activity in EGFR + HepG2 cancer cells [109–111].

Ortega and coauthor [110] used X-ray diffraction to characterize erlotinib triphenylphosphane gold(I) conjugate (Scheme 2), which is designed to bind to the well-known biological target EGFR with high affinity. In the tumorigenic and triple-negative MDA-MB-231 cell line, the gold compound showed 68-fold higher cytotoxicity than erlotinib. Studies using contrast phase inverted microscopy revealed that the conjugate caused significant alterations in cellular morphology. The compound can raise intracellular ROS levels, according to flow cytometry and cell-based fluorescence tests. The conjugate caused mitochondrial malfunction and DNA damage after producing ROS in cancer cells, resulting in S and G2/M arrest as well as apoptotic activation. While erlotinib is known to suppress EGFR tyrosine kinase efficacy and cause the arrest of G1-phase, this study discovered that adding a phosphane gold(I) substrate to the erlotinib pharmacophore modified the bioactivity of the resultant molecule substantially. When employing new erlotinib-gold(I) conjugates, it was studied whether changing the property of the co-ligand (i.e., phosphane and N-heterocyclic carbene-type ligands with varying electronic characteristics and/or lipophilicity) could increase selectivity for cancer than noncancer cells. Consequently, the complexes easily enter the cancer cell and generate ROS, which leads to apoptosis of cancer cells as well as decrease the side effect of the drug on normal cells [110].

To and coauthors [112] reported *in vitro* and *in vivo* effects of the gold(III)-porphyrin complex [Au(III)(TPP)]Cl in inhibiting proliferation of cisplatin-sensitive, cisplatin-resistant, and Epstein-Barr virus (EBV)-carrying nasopharyngeal carcinoma (NPC) cells through the induction of cellular apoptosis. [Au(TPP)]Cl showed 100-fold higher potency than cisplatin in killing NPC cells, including cisplatin-sensitive and cisplatin-resistant variants and also a variant harboring the EBV. [Au(TPP)]Cl has the capability of noncovalently binding to DNA and targeting tumor activities as antitumor and has no major side effects, and hence it is a promising chemotherapeutic agent against NPC cells. In this work, a very important point is the porphyrin ring and its derivatives should be recommended for complexing Au(III); otherwise it is decomposed to Au(I), which is less effective and has side effects on normal cells [112].

3.5. SAHA- and VPA-Conjugated Metal Complexes. Grift and coauthors [44] studied the histone deacetylase (HDAC) enzyme-targeting molecules such as suberoylanilide hydroxamic acid (SAHA) and valproic acid (VPA), which are substitutes for the chlorido of trans-platinum planar amine (TPA) complex (Figure 8). Histones are perhaps the most significant protein constituent of chromatin, which is responsible for wrapping DNA around it. HDACs are zinc-containing enzymes or metalloenzymes that result in



Scheme 2: Synthesis of the erlotinib-gold (I) conjugate.

chromatin constriction and transcriptional suppression by deacetylating core histone lysine residues. Therefore, inhibiting HDAC activity has a significant impact on chromatin structure and its functions. As a result, cis-[Pt(NH3) 2(malSAHA-2H)], a bifunctional anticancer Pt therapeutic candidate with dual DNA binding and HDAC inhibitory action, was developed, and the IC_{50} was calculated as shown in the aforementioned study [43] (Table 3).

SAHA (Figure 9) is composed of a hydroxamic acid group that chelates Zn^{2+} in the enzyme's active site cavity, a hydrophobic chain that passes through the narrow cavity, and a phenyl head group at the cavity's entrance. This head group's structural changes may result in a change in binding affinity 34 or an expansion of inhibitor activity. For example, SAHA analogues with fluorescent head groups have been developed and could be utilized in optical microscopy to track HDAC-dependent events in real time [113].

3.6. Biotin-Conjugated Metal Complexes. Among vitamin compounds, biotin is the most promising targeting agent. Biotin absorbed by human peripheral blood mononuclear cells (PBMCs) is dependent on the regular activity of the Na-K-ATPase enzyme. Biotin is transported with Na ions in and out of the cell [114]. Babak and

co-authors [115] synthesized ruthenium(II)-arene complexes bearing biotin-containing ligands. As a result, a new drug delivery system based on endocytosis through tumor-specific vitamin receptors has emerged (Scheme 3). Ruthenium coordination resulted in dramatically increased cytotoxicity, despite the fact that Ru(II)-biotin complexes had a lower affinity for avidin than unmodified biotin. According to in vitro anticancer activity data, these unique half-sandwich ruthenium(II)-biotin conjugates may operate as biological vectors to cancer cells, notwithstanding the lack of a strong link between the existence of cellular metal complexes, cytotoxicity, and the biotin moiety. The purpose of this vector is to limit toxicity by targeting and accumulating the complex in cancer cells [115].

Biotin (vitamin H) is required for cell proliferation, and many rapidly increasing cancer cells have a high concentration of a particular vitamin receptor on their surface (sodium-dependent multivitamin transporter, SMVT). Ferrocenyl-biotin conjugates may have improved anticancer effects. As a result, biotin could be used as a biological vector

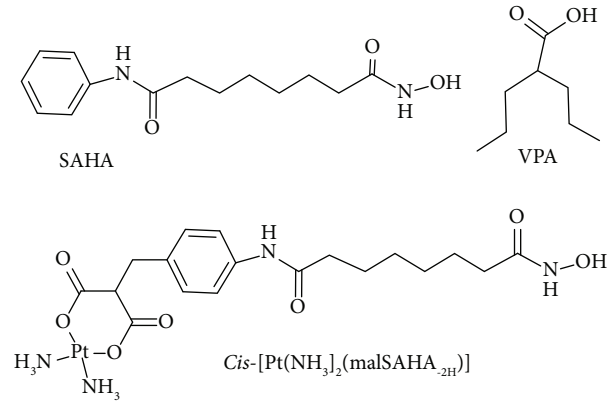


Figure 8: Structures of SAHA and VPA (HDAC inhibitors) and cis-[$Pt(NH_3)_2$(malSAHA-$_{2H}$)].

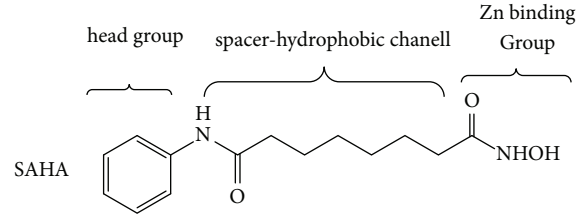


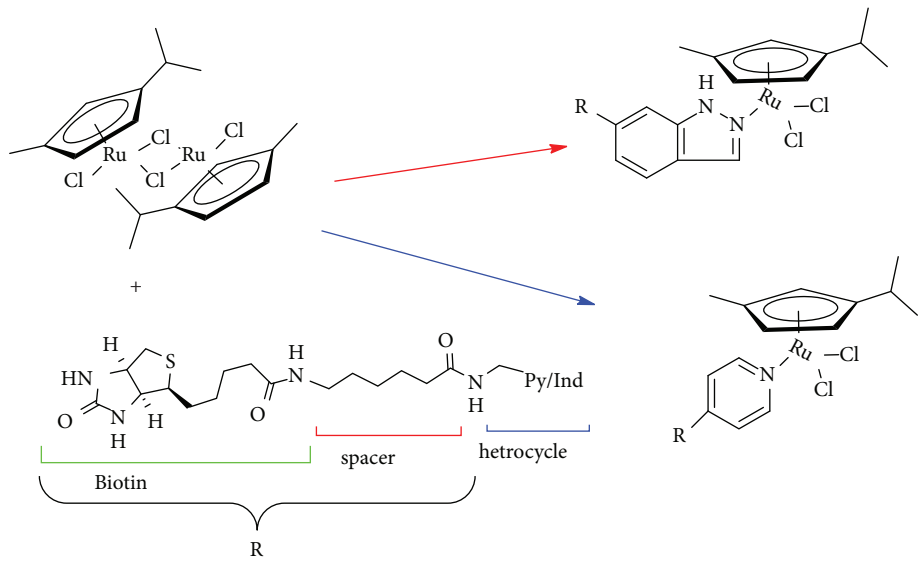
Figure 9: Chemical structural relationship of suberoylanilide hydroxamic acid (SAHA).

Table 3: IC_{50} values (μM) for test agents determined using A2780 and A2780*cis*R following 72 h of incubation.

Cytotoxicity mean $IC_{50} \pm$ SEM		
Test agent	A2780	A2780*cis*R
Cisplatin	2.9 ± 0.1	28.5 ± 1.5
Transplatin	>100	>100
Sodium valproate	>100	>100
Trans-[$PtCl_2(py)_2$]	>100	>100
Trans-[$Pt(VPA\text{-}1H)_2(py)_2$].	>100	95.1 ± 7.30
Trans-[$PtCl_2(NH_3)(py)$].	>100	>100
Trans-[$Pt(VPA\text{-}1H)_2NH_3(py)$].	86.5 ± 1.20	76.3 ± 04.20

to transport deadly chemicals to cancer cells selectively. Desthiobiotin and biotin-derived acids with aminoacyl linkers are used to the acylation of ferrocene. The conjugates and molecules produced by the acylation of ferrocene with biotin (Figure 10) have a high affinity for avidin and are cytotoxic to cancer cell lines, demonstrating that the biotin receptor is well expressed. This suggests that the biotin moiety could be employed as a biological vector to carry cancer cells with lethal ferrocenyl groups [116].

Kallus and coauthors [117] described the anticancer effects of triapine- and biotin-conjugated copper(II) and iron(III) complexes (Figure 11), in which triapine is the most well-known anticancer drug of thiosemicarbazone chemical class. The biotin metal complexes of the biotinylated derivative exhibited dramatically lowered anticancer activity. This phenomenon might be due to the metals utilized (Cu and Fe), and biotins are very important elements/molecules for cancer cell proliferation, which leads to cancer cell



Scheme 3: Biotinylation of half-sandwich Ru (II) complexes (anhydrous DMF, ratio of [{Ru(h6-p-cymene)Cl_2}$_2$] to ligand.

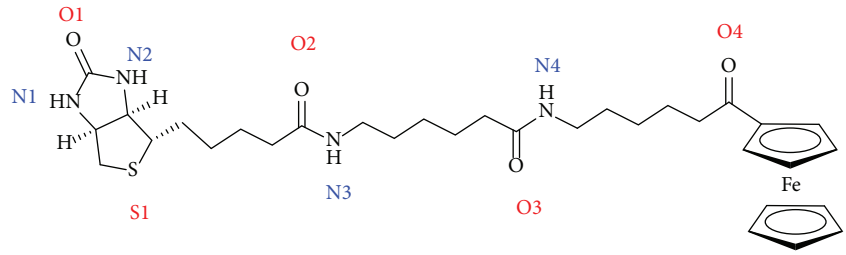


Figure 10: Chemical structure of acylation of ferrocene with biotin.

resistance to death. On the other hand, the metal-free biotin-conjugated ligands were comparable to the reference drug triapine in terms of activity [117].

A tumor-targeting compound might be linked to Pt complexes to develop targeted therapies, potentially improving efficacy while reducing negative effects. Some vitamins are highly sought after by cancer cells, and vitamin uptake receptors are overexpressed on the cell surface. As a result, vitamin-bound Pt compounds can enter easily into cancerous cells and could be used as anticancer agents that lead the cancer cell apoptosis. Biotin (vitamin H or B7) has recently gained a lot of interest because cancer cells absorb it more than normal cells. Biotin can be synthesized from an ureido, tetrahydrothiophene, and valeric acid. It is a coenzyme for carboxylases, which are involved in the synthesis of amino acids and fatty acids as well as signal transduction and gene expression. Biotin is largely absorbed by the SMVT, which has previously been discovered to be overexpressed in cancer cells from the kidney, lung, breast, and ovary. Biotin-bound drug delivery methods boost drug cellular absorption while also allowing for safer and more focused medication administration to tumor areas [115, 118].

Muhammad and coauthors [119] developed and investigated mono- and dibiotinylated Pt(IV) complexes for cancer treatment (Figure 12). Pt cellular absorption in breast cancer cells is greatly improved by tethering the biotin moiety to the Pt(IV) scaffold, but Pt accumulation in breast epithelial cells is significantly reduced. The mono-biotinylated Pt(IV) complex is more active than the dibiotinylated Pt(IV) complex in terms of reactivity and cytotoxicity. Pt-Bio-I inhibits cisplatin-resistant MDA-MB-231 cells much more effectively than cisplatin and inhibits MCF-7 cancer cells similarly to cisplatin. Due to its low toxicity to mammary epithelial cells, Pt-Bio-I may offer certain advantages over cisplatin in the breast cancer treatment. One hydroxyl ligand in axial position of Pt(IV) complexes appears to enhance DNA response and cancer cell cytotoxicity [119].

3.7. Hyaluronic Acid (HA)-Conjugated Metal Complexes. Hyaluronic acid (HA) is a sequential anionic polymer composed of 1,4-D-glucuronic acid and 1,3-N-acetyl-D-glucosamine repeating disaccharide units (Figure 13). It is a nonsulfated glycosaminoglycan present in neuronal, epithelial, and connective tissues. HA is made up of hydroxyl, carboxylic acid, and N-acetyl groups and can be coupled with a variety of different compounds [120]. HA has a variety of applications in medicine, cosmetics, and nutraceuticals due to its outstanding viscoelasticity, high moisture holding capacity, and high biocompatibility. It is frequently utilized for ophthalmology surgery, arthritis treatment, tissue

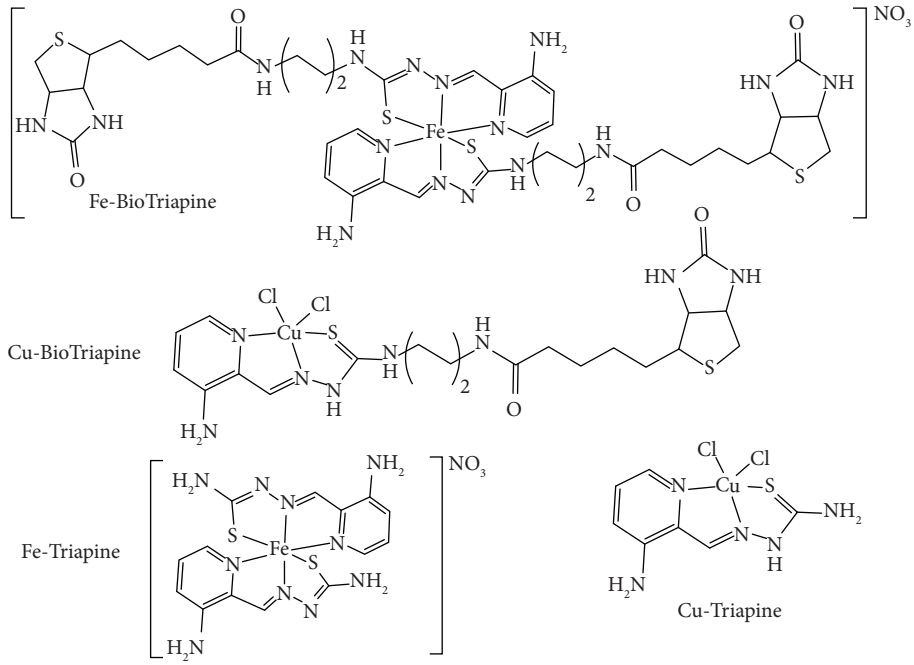


Figure 11: Chemical structure of Fe and Cu complexes with biotin and triapine.

engineering, and drug delivery since it is nonimmunogenic, nontoxic, noninflammatory, biocompatible, and biodegradable. As a drug delivery mechanism, HA has been combined with a range of drugs, such as paclitaxel (PTX) and doxorubicin (Dox), and other biopharmaceuticals. The enhanced permeability and retention (EPR) effect selectively transfers nanoparticles of HA medicine to cancer cells [121]. Furthermore, the interaction of HA with several receptors, such as cluster determinant44 (CD44), receptor for HA-mediated motility (RHAMM), and lymphatic vascular endothelial receptor-1, improves selective delivery (LYVE-1). The reticuloendothelial system (RES) cannot clear HA nanomedicines due to their negative surface charge. As a result, HA conducted research in the realm of drug delivery to improve material biocompatibility and drug delivery by passive and active targeting [122].

For drug administration and magnetic resonance imaging, Shu and coauthors [123] developed doxorubicin (DOX) loaded into a zeolitic imidazolate framework (ZIF) lined with polydopamine (PDA), chelated with Fe^{3+}, and coupled with hyaluronic acid (HA) (Figure 14). A Fe^{3+}-mediated coordination process linked the target molecule HA to DOX@ZIF-8. The integrated DOX might be released from the nanocarrier in a pH-dependent and sustained way. The inhibition experiment also revealed that DOX@ZIF-8-HA's ability to target CD44-overexpressed PC-3 cells effectively increased intracellular absorption and improved *in vitro* chemotherapeutic efficacy when compared with DOX. Furthermore, the Fe^{3+} chelation provided DOX@ZIF-HA a high contrast potential for MR imaging. The developed DOX@ZIF-HA might be used as a possible theranostic agent for chemotherapy and MR imaging of CD44-overexpressed PC-3 cells [123, 124].

4. Folate-Conjugated Metal Nanomaterials in Targeted Cancer Therapy

Folate (FA, pteroyl-L-glutamic acid) is a tiny organic biomolecule with unique properties. FA offers various advantages as a member of the vitamin B family, including cheap cost, immunogenicity, biocompatibility, molecular weight, and strong affinity for the folate receptor (FAR), a highly selective tumor marker overexpressed in over 90% of ovarian carcinomas. Moreover, the FA molecule contains many active sites, making it a typical ligand for metal coordination. FA was able to coordinate with metallic elements such as Fe(III) and Cu(II) via –COOH; however, the topologies and dimensions of these coordination complexes were erratic and unpredictable, which had a strong link to the coordination state [125–127].

Liu and coauthors [128] used FA as a ligand to make metal complexes in the nanoscale, such as folate-nickel nanotubes (FA-Ni NTs) and folate-cobalt nanotubes (FA-Co NTs) and studied their anticancer effects in vivo and in vitro. Unlike the widely used folate-drug conjugates, this complex nanotube's production technique is easy and straightforward, yielding in a constant form and uniform morphology. According to *in vitro* studies, folate-cobalt nanotubes (FA-Co NTs) exhibit remarkable anticancer effects against tumor cells with high rates of FAR expression, while causing minimal damage to normal cells. Furthermore, when encapsulating the anticancer medication doxorubicin via cell surface receptor-mediated endocytosis, certain types of NTs had a stronger antitumor capacity. Furthermore, pharmacokinetic parameters of FA-Co NTs in mice were explored, as well as its capacity to target tumor tissues in tumor-bearing animals. When administered separately *in vivo*, FA-

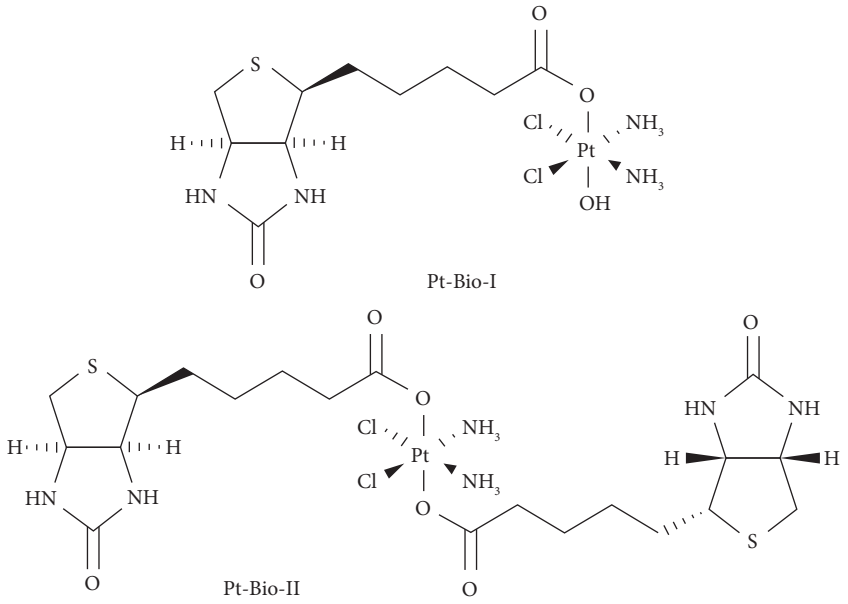


Figure 12: The structure Pt-Bio-I and Pt-Bio-II complexes.

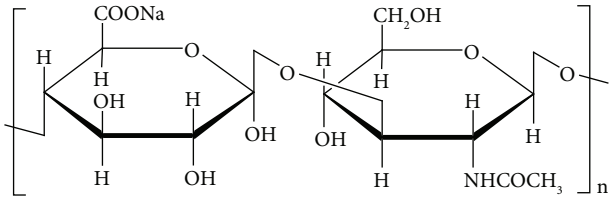


Figure 13: Chemical structure of hyaluronic acid (HA).

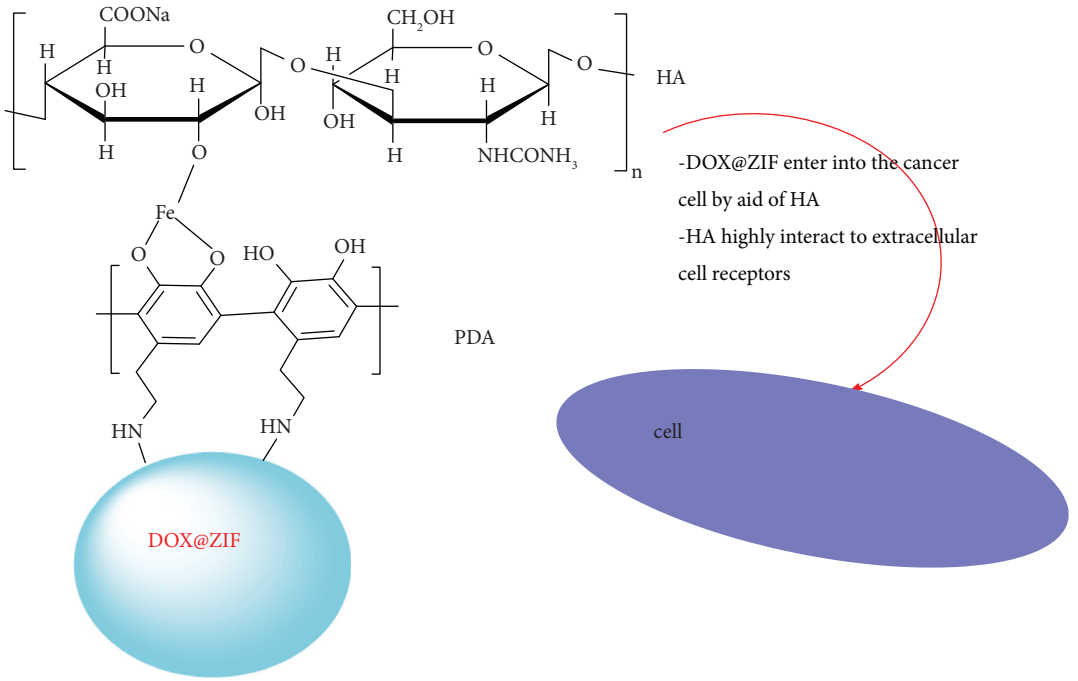


Figure 14: Mechanism of actions of the HA conjugated the DOX@ZIF through Fe3+ complexed dopamine on cell (adapted from Ref. [123]).

Table 4: Anticancer activities of folate-cobalt nanotubes (FA-Co NTs).

Drug	IC_{50} (mM)		
	HeLa	A549	L-O2
DOX	1.05		4.51
FA-Co NTs	1.49	5.43	20.32

Co NTs can significantly slow tumor growth with little side effects. As indicated, the IC_{50} capacity of cancer cells HeLa and A54, as well as a normal cell, L-O2, was investigated (Table 4). These findings will help researchers learn more about FA-based metal complex nanomaterials as a possible anticancer nanomedicine and targeted drug carrier [128, 129].

5. Conclusions

Anticancer medicines based on platinum (Pt) have received a lot of attention. However, substantial side effects, lack of target-specific actions, and drug resistance have restricted their use. Without promoting side effects and/or cancer cell resistance, cancer will continue to be one of the leading causes of death in humans around the world. Some of the receptors attach to biomolecule ligands such as biotin, folic acid, hyaluronic acid, and others, allowing them to enter the cell and promote cancer cell proliferation. Overexpressed receptors, such as EGFR, FAR, and biotin receptors, are known to play a role in cell differentiation, proliferation, and migration and have been identified as critical tumor-specific targets. In this aspect, metal complexes can engage in a wide range of different and novel modes of action, such as ligand exchange reactions, the generation of ROS, and the release of bioactive molecules, as well as interacting with cell membranes, nucleic acids, and organelles. As anticancer drugs, nonplatinum complexes containing metal ions (Zn, Fe, Ru, Cu, Au, and Ir) and lanthanide complexes must be utilized. Metal complexes that are more easily reduced are more cytotoxic. In the presence of biological reductants, the anticancer activities of ruthenium(III), cobalt(III), copper(II), and iron(III) complexes are thought to be dependent on their reduction to the next oxidation state, which improves their antimetastatic activity. Similarly, a combination of metal prodrugs with nano-vehicles can mediate transport of drug molecules to active targets of the cancer tissue. Metal-drug complex activation by light could become the most promising approach, allowing the use of highly inert complexes that are only activated where a light source is applied. In addition to drug development, conjugated biomolecules drug delivery systems with better pharmacokinetic and pharmacodynamic features, such as higher bioavailability, have emerged as viable options for the requisite therapeutic efficacy over the previous decade. Combining novel anticancer metal complexes with biomolecules that target the cancer cellular metabolomics pathway could open a new route for cancer treatment, that is, both effective and safe. It is clear that future research will focus on finding new molecular targets and thereby improving bioavailability, reducing adverse side effects, and improving the structural components of metal-drug complexes conjugated to biomolecules for cancer therapy.

Data Availability

The data used in this study can be accessed from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

The literature collection and the first draft writing were carried out by Gemechu Shumi. Dr Rajalakshmanan Eswaramoorthy, Dr Tegene Dessalegn, and Dr Taye B. Demissie supervised and edited the manuscript. All the coauthors participated in reviewing and editing the manuscript.

Acknowledgments

The authors are thankful to Adama Science and Technology University, Adama, Ethiopia, and the University of Botswana for supporting this work.

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