Anticancer Effects of Copper (II) Hydrazone Schiff Base Complex: A review
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A B S T R A C T
Cancer treatment has traditionally consisted of established treatments such as radiation, surgical excision, and chemotherapy, which can be used alone or in combination. Many therapeutic factors have been extracted from minerals, plants, and animals. The majority of them have been synthesized in the lab, making them a valuable source of innovation pharmacologically. A growing interest in metal complexes in cancer treatment is due to their cytotoxic effects in vitro. The electronic nature of metals, modifications in ligands, and conformational changes in functional groups give rise to the discovery of drugs with different cytotoxic and pharmacokinetic properties. In recent decades, the number of people receiving chemotherapy has increased considerably. Medicinal inorganic chemistry can take advantage of the unique properties of metal ions to generate new drugs. This has prompted chemists to use various approaches to create novel metal-based anticancer drugs with various mechanisms of action, which are significant in the pharmaceutical industry due to their potent anticancer properties. Schiff base ligands and transition metals are the most researched coordination chemicals. Their applications as anticancer medicines are becoming more significant. This review analyzes various publications on copper complexes based on Schiff base hydrazone ligand in cancer treatment.

Keywords: Anticancer, Copper (II) complexes, Hydrazone, Schiff base ligands
INTRODUCTION:

According to scientific studies, cancer and cardiovascular disease are considered the top two medical concerns facing the scientific community in the twenty-first century. They are the leading causes of death globally [1]. Cancer is a significant public health hazard, particularly in developed countries, despite significant biomedical research and technology breakthroughs [2]. The global burden of cancer is anticipated to increase to 21.7 million people in ten years. Sedentary behavior, cigarette smoking, urbanization and associated pollution, changing food choices, and other environmental variables may contribute to the worldwide cancer pandemic [3, 4]. On a biological level, cancer spreads when genetic alterations disrupt the orderly processes of apoptosis and mitosis, and living creatures’ cells begin to grow uncontrollably, forming a tumor that can be malignant. The difference between a benign and malignant tumor is that a benign tumor can grow but not spread. However, a malignant tumor can develop and spread to other parts of the body [5-7]. Chemotherapy medications such as cabazitaxel, letrozole, paclitaxel, doxorubicin, granisetron, docetaxel, and platinum-based therapies like carboplatin, nedaplatin, oxaliplatin, and lobaplatin, are now used to treat cancer. Most of them have various adverse effects, including taste changes, exhaustion, appetite loss, sore mouth, anxiety, fever, infection, depression, nausea, and vomiting [8]. Current efforts in creating contemporary metallo-drugs have concentrated on using transition metal complexes to improve these conditions and lessen adverse effects [9, 10]. Organometallic compounds, intermediate between traditional inorganic and organic materials, offer new possibilities in medicinal chemistry. Both metal complexes and organic compounds are extensively utilized in cancer therapy. Extensive research has been conducted on the role of complexes and ligands in cancer treatment. The ligand amount, ligand type, and coordination architecture significantly affect the anticancer properties of metal-based complexes [11]. Hydrazones are a significant category of Schiff base ligands due to pharmaceutical activities, like DNA binding (Fig. 1) and antimicrobial (Fig. 2) activities [12-15]. They can form stable chelate combinations with transition metals, catalyzing physiological activities [16-20]. Due to their importance in biological studies, hydrazones can act as molecular binding in drug discovery, increase the therapeutic effects against cancer, and reduce its side effects [21]. Furthermore, hydrazones can form azomethine imine and are considered the main class of reagents in synthesizing organic compounds due to their significant advantages, such as easy availability, stability, and different reactivity depending on the structure and reaction conditions [20, 22]. In particular, hydrazone derivatives of isoniazid and other hydrazides have been created and studied for diagnostic antibacterial activity.

Figure 1. The crystal structure of the Cu complex with DNA binding properties
Until recently, transition metal hydrazone complexes have been acknowledged to provide good models for explaining their prospective therapeutic uses. In addition, the anticancer activity of a range of substituted hydrazones has been reported, with some encouraging findings. Hydrazones complexes have been discovered to enhance the selectivity of certain specific anticancer drugs by creating drug carrier systems [23]. It has been shown in some literature that the biological activity, particularly relevant for anticancer activity, of ligands alone, was lower than that of hydrazone copper complexes. Many copper complexes have recently been created, and many have shown promising anticancer action. These studies offered an overview of copper-based anticancer drugs with hydrazone ligands.

Copper is a bio-essential metal that may be used as a structural and catalytic cofactor in all living organisms. As a result, it plays a crucial role in organism function, redox chemistry, developmental pathways, and growth [24]. Brain, breast, and prostate cancer tissues absorb more copper than normal tissues [25-27]. Many copper-based anticancer treatments have been studied as potential anticancer drugs [28-30]. Copper's homeostasis and metabolism are essential in many human cancers, making it one of these valuable metals. Copper levels in cancer patients' tumor tissues are significantly greater than normal tissue [31]. Another benefit of copper metal is that it affects malignant cells' metabolism and has a different reaction to tumors than healthy cells [32]. Copper complexes have shown outstanding potential and are being studied as viable replacements to platinum medications in this field [33]. Schiff base copper complexes may enhance intracellular reactive oxygen species via binding to DNA or damaging DNA, activate the mitochondrial pathway, and induce caspase-dependent apoptosis [34-36]. The durability of Schiff’s...
base compounds relies on the intensity and conjugate base of the azomethine group and steric effects, which rely on the substituents. Hydrazones are made by reacting aldehydes with hydrazines in analytical chemistry. They may create alternative complexes with metal cations such as Fe(III), Cu(II), and Zn(II) and may coordinate in the form of monoanionic, dianionic, or neutral [37]. Hydrazonemolecules with ONO and NNO donor atoms have been presented in coordination chemistry such as (E)-N’-(2-hydroxybenzylidene)benzohydrazide and (E)-N’-(pyridine-2-ylmethylene)benzohydrazide. Hydrazones have antioxidant, antibacterial, antifungal, anticancer, antitubercular, and anti-inflammatory physiological and biological properties [38]. Copper, cobalt, and nickel Schiff base complexes formed from hydrazones have attracted much attention. Due to their structural variety and numerous applications, Schiff base complexes have remained one of the most popular stereo-chemical models in transition-metal coordination chemistry. Copper complexes may induce the production of reactive oxygen species (ROS) in human cells [39]. For instance, they may accumulate in malignant cells due to their preferential membrane permeability to copper compounds. For instance, they may accumulate in malignant cells due to their membranes’ preferential permeability to copper compounds. Also, copper (II) complexes are extensively used in metal-mediated DNA cleavage for producing activated oxygen species [40-42]. The anticancer effect of metal complexes derived from hydrazones, such as nickel, cobalt, and copper complexes, has been reviewed in many recent publications. Various hydrazone derivatives were also synthesized and evaluated for antibacterial effectiveness against Gram-negative and Gram-positive bacteria [43]. The compounds’ cytotoxic effects on AGS and SW742 cancer cell lines were examined [44-46].

Evaluation of the anticancer activity of Copper (II) complexes based on cytotoxicity assay
Targeting tumor cells to inhibit their proliferation with anticancer drugs is dependent on various factors [47]. Different methods can be used to assess the cytotoxicity of copper complexes based on the Schiff base hydrazone ligand as a transition metal. MTT assay is essential for determining the cell viability of cell lines in various drug concentrations and determining the IC50 of the desired drug [48]. The half-maximal inhibitory concentration IC50 is an essential value for determining a drug’s efficacy. It demonstrates how much drug is required to inhibit a biological process by half. A low IC50 value indicates that the drug is less likely to cause side effects and more effective treatment [44, 45]. This section reviews articles investigating the cytotoxicity of various Copper (II) hydrazone Schiff base complexes on various cancer cell lines. Copper (II) complexes based on quinoline-derived Schiff-base ligands show anticancer activity and non-covalent interactions with HSA in the C1–C3 complexes via sub-domain IIA and IIIA cavities. Kun Hu et al. studied synthesis, characterization, HSA/DNA binding ability, and anticancer effectiveness of copper complexes. Chemical complexes C2 and C3 demonstrated stronger antiproliferative activities against HeLa cells than C1, indicating that benzocaine’s medicinal chemical was more effective than 4-aminobenzoic acid methyl ester in enhancing anticancer activity. The complexes bind to DNA and fit well into the curved contour of the target DNA in the minor groove region [46]. HSA fluorescence has a significant dampening ability and a high binding activity. The complexes showed less cytotoxicity in normal HL-7702 cell lines, implying that they are more effective on HeLa cells. According to mechanistic studies, C3 may affect the interpretation of CDKs and cyclins and capture the cell cycle during the G0/G1 phase [49]. C3 can activate the Bcl-2 protein family while causing apoptosis in HeLa cells through ROS-mediated mitochondrial pathways [50]. Adding active medications to ligands may enhance the biological effects of copper complexes containing quinoline-derived Schiff bases, according to DNA/HSA affinity and cell cytotoxicity [46]. Shanshan Shen et al. studied the synthesis, characterization, and anticancer properties of transition metal complexes containing a nicotinohydrazone ligand to create efficient anticancer medications [51]. According to Annexin V/PI staining and western blot analysis, the complexes have a
significant cytotoxic effect on three cancer cell lines and induce apoptosis in cancer cells. This research aimed to find a new therapy for non-small cell lung cancer [51]. Furthermore, whereas L-Cu and L-Zn complexes had a substantial cytotoxic effect on the A549 cell line, they were ineffective on the healthy lung cell line BEAS2B even at greater doses [52]. When their other benefits are considered, these chemicals, which work selectively against A549 cancer cells, have the potential to be excellent anticancer medications [52]. Qian Zhang and colleagues studied a wide range of physiologically active porphyrin and hydrazine Schiff base ligands. Three Cu(II) complexes were shown to have a strong affinity for calf thymus DNA. The cytotoxicity of the complexes and ligands against several cancer cells (A549, H-1975, HepG2, and T47D) was also studied. According to the findings of this study, the complexes had a stronger cytotoxic impact than the ligands. Furthermore, another study examined the cytotoxicity of ligands and complexes against the normal cell line Hs 578Bst, and complexes were found to be less dangerous than ligands [53]. Sulekh Chandra and colleagues studied Ni(II) complexes with hydrazine carboxamide, 2-[3-methyl-2-thienylmethylene]. These complexes were characterized and assessed their inhibitory potential using spectroscopic methods [54]. Khlood Abou-Melha synthesized a Schiff base N-allyl-2-(2,4-dinitrophenyl) hydrazine-1-carbothioamide ligand and their metal complexes. Spectral analysis was used to characterize these complexes. The Cu(II) complex had square planar structures, whereas the Co(II), Ni(II), and Cd(III) complexes were octahedral. This author also looked into antioxidant and anticancer activity of complexes, which revealed that Schiff base and four metal complexes are very active in cancer cell death [55]. Fathy A. El-Saied et al. created Schiff bases hydrazone-oxime ligands from 3-(hydroxylimino)butan-2-one by condensation of acetohydrazide and pyridylhydrazide. The architectures of the Cu(II), Ni(II), and Co(II) complexes have been discovered through spectral studies. The novel complexes' in vitro effectiveness against three human cell lines was verified. The complexes' cytotoxic activity was compared to the anticancer medication doxorubicin [56]. Elif Eda Sengül et al. studied the consequences of DNA binding and cleavage of several copper complexes. All chemicals, according to UV-vis spectroscopy data, may be coupled to DNA via intercalation mode. Electroreduction experiments revealed that these chemicals have concentration-dependent cleavage activity on plasmid DNA in the absence and presence of hydrogen peroxide [57]. Ummuhan O. Ozdemir et al. synthesised N-acetyl butane sulfonic acid hydrazide and its Cu(II) complex \(\text{[Cu(Absh)\,(CH}_3\text{COO)}\text{]^{\text{2-}}}\). The spectrometric methods (\(\text{^{1}H-}^{13}\text{C NMR, FT-IR, LC-MS}\), thermal analysis, magnetic susceptibility, and conductivity tests were used to characterize the chemical. The complex showed one irreversible reduction and one irreversible oxidation potential and half-wave reduction [58]. The anticancer effects of Schiff base ligands derived from hydrazone (HL= (E)-N’-(pyridin-2-ylmethylene)benzohydrazide) were compared to those of a synthetic Copper (II) complex with HL. Human gastric cancer (AGS) and human colon cancer (SW742) cell lines were tested using the MTT assay. Increasing the Copper (II) complex with HL resulted in a stronger cytotoxicity effect on cancer cell lines, reducing cell viability [59]. Higher Copper (II) complex activity may be connected to a reduction in metal ion polarity due to positive charge partial sharing of the metal ion with donor groups. It can penetrate delocalization over the entire ring. As a result, the complex's lipophilicity increases, allowing it to penetrate cell plasma membranes [60, 61]. Patel et al. produced copper (II) hydrazone complexes using (Z)-2-(phenyl(2-(pyridin-2-yl)hydrazono)methyl pyridine (L) and tested their anticancer capabilities. Complex 1 is mononuclear, whereas the solid-state structure of complex 2 contains a mixture of co-crystals of the mono- and binuclear complexes 2a, \([\text{Cu}(L)(\text{H}_2\text{O})(\text{SO}_4)})\], and 2b, \([\text{Cu}_2(L)_2(\text{l-SO}_4)_2]\). Using MTT assay for evaluating the anticancer activity of the ligand HL against four human cancer cell lines, including IMR 32 (neuroblastomas), MCF 7 (breast tumors), HepG2 (hepatocellular carcinoma), and A549 (lung cells) revealed that the IC50 values of complexes 1 and 2 effectively killed selected cell lines, particularly HepG2
Copper compounds have cytotoxic potential due to the transition between Cu(II) and Cu(I) ions, producing superoxide and hydroxyl radicals and inducing cell death. In addition, antiproliferative experiments revealed a similarity in the logGI50 of a copper complex with cisplatin and doxorubicin [63]. The anticancer effects of three copper (II) complexes (Cu(L)2, [Cu(L)(bpy) (H2O)] NO3, and [Cu(L)(Phen)(H2O)] NO3) on MCF-7 (human breast cancer) cell lines demonstrated that complex cytotoxicity was greater than metal-free ligand, showing the importance of Cu(II) in cell death. The third complex had the highest activity in cell death due to the strong DNA binding ability of the planar “phen” co-ligand and deeper insertion between the DNA base pairs. Copper (II) complexes caused morphological alterations such as cell detachment and shrinking. Furthermore, lipid peroxidation and glutathione depletion were examined to better understand the complexes’ mechanism of action, which demonstrated a substantial role for ROS generation in cytotoxicity [64]. Chang et al. studied the anticancer activity of Cu(II), Zn(II), and Cd(II) complexes with isonicotinohydrazide-derived hydrazone Schiff base on human lung cancer (A549) and human gastric cancer (SGC7901 and BGC823) cell lines. In the A549 cell line, it lowered the antiapoptotic factor Bcl-2 while enhancing the pro-apoptotic proteins Bax and caspase-3 [65]. Ebrahimipour et al. studied the antitumor activity of tridentate ONO ligand (E)-N’-((2-hydroxynaphthalen-1-yl) methylene) acetohydrazide [HL] and its cationic Cu(II) complex [Cu(L)(H2O)]NO3 on human breast cancer (MCF-7) and discovered that copper has a better anticancer function than ligand [66]. The production of Cu(L)(H2O)(NO3) and assessment of its cytotoxicity indicated that it has a significant impact in the cell death of the human skin carcinoma cell line A431. However, as compared to standard medications like cisplatin or doxorubicin, this compound is slightly less effective [67].

Table 1. A review of studies on the anticancer effect of copper complexes

<table>
<thead>
<tr>
<th>Compound</th>
<th>cell line</th>
<th>IC50 value</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu(L1)(NO3)2</td>
<td>HeLa</td>
<td>18.72 ± 1.03</td>
<td>[46]</td>
</tr>
<tr>
<td>Cu(L2)Cl2</td>
<td>HeLa</td>
<td>15.76 ± 1.19</td>
<td></td>
</tr>
<tr>
<td>Cu(L2)SO42·H2O</td>
<td>HeLa</td>
<td>9.98 ± 0.87</td>
<td></td>
</tr>
<tr>
<td>Cu(penh)2</td>
<td>A549, BGC823, Eca109</td>
<td>7.3, 9.7, 6.5</td>
<td>[51]</td>
</tr>
<tr>
<td>Na[CuL(H2O)]H2O</td>
<td>A549</td>
<td>12</td>
<td>[68]</td>
</tr>
<tr>
<td>CuP1</td>
<td>A549, H1-1975, HepG2, T47D</td>
<td>18.82, 17.34, 13.62, 34.51</td>
<td>[68]</td>
</tr>
<tr>
<td>CuP2</td>
<td>A549, H1-1975, HepG2, T47D</td>
<td>14.64, 13.52, 26.98, 43.81</td>
<td>[53]</td>
</tr>
<tr>
<td>CuP3</td>
<td>A549, H1-1975, HepG2, T47D</td>
<td>19.16, 17.07, 27.85, 31.68</td>
<td>[53]</td>
</tr>
<tr>
<td>Cu(II) complex</td>
<td>HepG2</td>
<td>26.71 ± 0.28</td>
<td>[55]</td>
</tr>
<tr>
<td>Cu(HL)2</td>
<td>MCF-7, Hep-G2, HL-60</td>
<td>28.9 ± 2.10, 5.8 ± 0.71, 62.1 ± 18.91</td>
<td>[55]</td>
</tr>
</tbody>
</table>
3. Mechanisms underlying the anticancer effects of the copper complexes
Copper (II) Schiff base complexes have anticancer properties through various processes, including cell cycle arrest, apoptosis, and autophagy, leading to cell death. Copper complexes release anticancer action by causing DNA damage, generating ROS, inhibiting topoisomerase, and changing the expression level of molecules involved in the cell cycle, apoptosis, and autophagy activation or inhibition [73, 74] (Fig.3).

3.1. Cell cycle arrest
The cell cycle is a series of interconnected activities that enable a cell to grow and reproduce. Kinases and phosphatases are primary proteins involved in cell cycle progression. Cyclin-dependent kinases (Cdks) are essential kinases activated by cyclins and play an important role in cell cycle checkpoints. G1/S transition, G2/M, and mitotic spindles are three checkpoints that ensure proper
cell cycle progression [75]. Cancer cells disrupt the cell cycle and uncontrollably reproduce cells with defective DNA. Cell cycle arrest is a stage in the cell cycle in which the cell is no longer active in replication and division to repair the damage. As a result, blocking cell cycle checkpoints before DNA repair may initiate an apoptotic cascade, ending in cell death [76]. The anticancer impact of \([\text{Cu(L2)SO4}]_2\text{H}_2\text{O}\) based on quinoline-derived Schiff base ligand on HeLa cells was obtained in a concentration-dependent manner by lowering CDK2, cyclins D1 and E1, and cell cycle arrest in G0/G1-phase [77]. Cu(BrHAP)2 Schiff base compound also prevented HT-29 cells from entering the S phase, as demonstrated by an increase in G1 cell population after 24 and 48h [78]. Flow cytometry analysis of MDA-MB-231 cells treated with complexes \([\text{Cu(R-L 2}]_2\text{EtOAc}\) and \([\text{Cu(S-L 2} \text{)}_2\text{EtOAc}\) at a dose of 15 µM increased the number of cells in the G2/M phase compared to the G0/G1 and S phases, indicating G2/M arrest [79]. [N,N’ -bis(2’ -hydroxyphenylacetone ) - o -ethanediamine] copper complex inhibited cell proliferation by inhibiting DNA synthesis and increasing p21 protein expression level in a time and dose-dependent manner [73].

3.2. Apoptosis promotion

Schiff base Copper (II) compounds can trigger apoptosis by targeting proteins involved in apoptosis pathways while also producing ROS to boost ROS-mediated mitochondrial apoptosis pathways [80]. External signals that enter the cell via transmembrane death receptors, such as tumor necrosis factor, activate the extrinsic route (TNF) [81]. The intrinsic or mitochondrial-dependent signaling pathway affects the inner mitochondrial membrane, leading the mitochondria to lose transmembrane potential and permeability and release proapoptotic chemicals into the cytosol, including cytochrome c, Smac/DIABLO, and HtrA2/Omi [82]. P53 is another proapoptotic protein that pauses the cell cycle at the G1/S phase to detect DNA damage. If the DNA damage is irreparable, p53 directs the cell to apoptosis via the intrinsic pathway [83]. Caspase is a protein family essential for a cell to die. They are classified into three groups: initiators (caspases-8, -9, and -10), effectors (caspases-3, -6, -7), and inflammatory caspases (caspases-1, -4, and -5) [84]. Apoptosis is connected with morphological alterations such as DNA segregation, chromatin condensation, shrinkage, membrane blebbing, and organelle packing [85]. The protein family B-cell lymphoma-2 (BCL-2) regulates cell apoptosis. Some of them for example, BAX and BAK promote cell death, whereas others for example, Bcl-2 and BCL-XL have an antiapoptotic impact [86]. According to a study conducted by Kun Hu et al., copper (II) complexes based on Schiff-base ligands can lower mitochondrial membrane potential (MMP), increase oxidative damage, upregulate BAX, and downregulate Bcl-2 in HeLa cells to promote apoptosis in a dose-dependent way [77]. In a study on two separate gastric cancer cell lines, these complexes inhibited NF-B signaling, reduced Bcl-2, produced ROS, increased Bax, activated caspase-3, and cleaved PARP-1 in a time-dependent manner. Blebbing and chromatin condensation after 24 and 48 hours of treatment and late apoptosis after 72 hours also revealed the morphology of treated cancer cells [87]. Furthermore, the copper complex induces apoptosis in a colon cancer cell line by boosting ROS and, as a result, lowering MMP and cytochrome c levels in mitochondria and activating caspases 3/7 [78]. The production of \([\text{Cu4(L)4Cl4}]_5\text{H}_2\text{O}\) and in vitro apoptosis testing of the complex against the SGC7901 cell line revealed that it increases BAX and p53 while decreasing Bcl-2 [88]. Treating Eca-109 cells with \([\text{Cu(sal-trp) (phen)}]_0.5\text{H}_2\text{O}\)•0.5CH2Cl2•CH3OH caused apoptosis by mitochondrial dysfunction, generation of ROS, upregulation of Bad and Bax, and downregulation of Bcl-2 and Bcl-xL [74].

3.3. DNA damage

Copper complexes based on Schiff base ligands can bind to the DNA and cleave it to block replication, cause DNA damage, cell cycle arrest, and apoptosis. For example, in an investigation, Schiff base copper (II) complexes increased DNA damage and repair marker γH2AX in both time and dose-dependent manners and p-Chk1/2 (checkpoint kinase 1/2) after 8 hours in HeLa cells. These findings indicate the DNA damage and DNA damage response induction of copper complexes [89].
In the presence of H2O2, DNA breakage was observed in four chiral mononuclear copper (II) complexes with mono-anionic bidentate Schiff-base ligands. They can all produce ROS and employ them to promote apoptosis and DNA cleavage [90].

Topoisomerases are enzymes necessary for proper DNA replication, recombination, and repair. They break DNA strands to prevent overwound or underwound DNA structure during replication or transcription. There are two types of topoisomerase enzymes: type I, which cleaves single-strand DNA, and type II, which cleaves two DNA strands and decatenates DNA [91]. Topoisomerase inhibitors cause DNA damage, inhibit DNA synthesis, arrest tumor cell proliferation and promote apoptosis [92]. Chew et al. demonstrated that copper (II) complexes based on hydrazone ligand could block topoisomerase I by binding to the enzyme and DNA in human lung cancer cell lines (A549) and human prostate adenocarcinoma cell line (PC-3) [71]. Studies revealed that the tridentate chiral Schiff base copper complexes (C21H31N5O6CuSn and Cu(Van-Val)(Pz)2Sn(CH3)2(H2O)2) can inhibit Topoisomerase I by binding to the major groove of DNA and as a result, DNA damage and cancer cell apoptosis on Hepatoma HuH7 and Hepatoma HepG2 cell lines [70, 93]. However, Schiff-based ligands have shown topoisomerase inhibitory action against cancer cell lines in two studies, but when combined with copper, no anticancer activity by topoisomerase inhibition was observed [94, 95].

3.4. Autophagy

Autophagy reduces cell survival and promotes cell death in cancer cells, inhibiting carcinogenesis. The autophagy pathway begins with the suppression of mTORC1 (one of the Mammalian targets of rapamycin (mTOR) complexes) and the activation of the Unc-51-like autophagy-activating kinase (ULK) complex [96]. Beclin-1 recruits many proteins involved in autophagosome formation and elongation, followed by LC3I to LC3II conversion, resulting in autophagosome-lysosome fusion and autophago-lysosome formation [97, 98]. Jianfang Dong et al. synthesized [Cu(sal-trp)(phen)]•0.5H2O•0.5CH2Cl2•CH3OH complex and treated the Eca-109 cells with it. They observed the autophagosome of cancer cells induced by p62 and LC3BI downregulation and Beclin-1 and LC3BII upregulation [74]. Furthermore, autophagy was promoted in gastric cancer cells treated with Schiff base copper coordinated compound (SBCCC) in a time-dependent manner [87]. Nazanin Kordestan et al. synthesized cop-

Figure 3. The general anticancer mechanism of Cu complexes
per complexes with tridentate halogen-substituted Schiff base ligand L1 (containing a 2-pycolylamine-type motif), including Cu(BrCl-L1)Cl, Cu(Cl2-L1)NO3, Cu(Br2-L1)Cl, and Cu(Cl2-L1)Cl. They exposed the A2780 cell line to IC50 concentrations of manufactured complexes and found that treated cancer cells with Cu(BrCl-L1)Cl and Cu(Cl2-L1)NO3 had a significantly higher autophagic cell number [99].

Conclusion
Schiff bases and their metal complexes are among the most significant chemical compounds, sharing many substances’ structural variety and active medicinal agent characteristics. This review intended to highlight the anticancer potential of Schiff base Copper (II) hydrazone complexes. These complexes, in general, have a promising future as anticancer medicines. However, more research into these compounds’ side effects and lipophilicity is needed to ensure their efficacy in cancer therapy.

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