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In vitro apoptotic effect of Zinc(II) complex with N-donor heterocyclic ligand on breast cancer cells

N-donör heterosiklik ligandlı çinko(II) kompleksinin meme kanseri hücreleri üzerinde *in vitro* apoptotik etkisi

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Abstract

Background: The synthesis of new ligand and transition metal complexes have drawn great attention in cancer treatment due to excellent DNA cleavage activities and high antitumor activity.
Objective: The purpose of this study was to synthesize a new Zn(II) complex with 2,2′-bipyridine (bpy) ligand, $[Zn(bpy)_2(H_2O)]2(ClO_4)$, and to investigate the potential therapeutic activity against breast cancer.
Materials and methods: Zn(II) complex was obtained and structurally characterized using crystallography and other spectroscopic methods. The cytotoxic and apoptotic effects of Zn(II) complex on MCF7 breast cancer and HUVEC control cells were evaluated by WST-1, Annexin V and cell cycle analysis.
Results: The spectroscopic data demonstrated that Zn(II) complex was successfully synthesized. Furthermore, Zn(II) complex exhibited significant cytotoxic effect on MCF7 breast cancer and HUVEC cells ($p < 0.01$). MCF7 and HUVEC cells proliferation was reduced to 11.0% and 52.6%, respectively at 10 μM for 48 h. Additionally, Zn(II) complex significantly induced apoptotic cell death (84.87%) and caused S phase arrest (36.4%) in MCF7 cells at 10 μM ($p < 0.01$).
Conclusions: Zn(II) complex has great therapeutic potential for the treatment of breast cancer. However, further studies are warranted to identify the underlying mechanisms of apoptotic cell death and to reduce the toxicity of Zn(II) complex on control cells.

Keywords: Metal complex; Zinc; 2,2′-Bipyridine; Breast cancer; Apoptosis.

Öz

Amaç: Yeni ligand ve geçiş metali komplekslerinin sentezi, DNA kırılması aktiviteleri ve yüksek antitümör aktivitesi nedeniyle kanser tedavisinde önemli derecede dikkat çekmektedir. Bu çalışmanın amacı 2,2′-bipiridin (bpy) ligandı, $[Zn(bpy)_2(H_2O)]2(ClO_4)$ ile yeni bir Zn(II) kompleksi sentezlemek ve meme kanserinde potansiyel terapötik etkisinin araştırılmasıdır.
Gereç ve Yöntem: Zn(II) kompleksi elde edildikten sonra yapısal olarak kristalografi ve diğer spektroskopik yöntemler kullanılarak karakterize edilmiştir. Zn(II) kompleksinin MCF7 meme kanseri ve HUVEC kontrol hücreleri üzerindeki sitotoksik ve apoptotik etkileri, WST-1, Annexin V ve hücre döngüsü analizi ile değerlendirilmiştir.
Bulgular: Spektroskopik veriler, Zn(II) kompleksinin başarıyla sentezlendiğini göstermektedir. Zn(II) kompleksi, MCF7 meme kanseri ve HUVEC hücreleri üzerinde önemli sitotoksik etki göstermiştir ($p < 0.01$). 48 saat boyunca 10 μM Zn(II) kompleksi uygulanan MCF7 ve HUVEC hücrelerinde canlılık oranlarının sırasıyla %11.0 ve %52.6'ya azaldığı belirlenmiştir. Ayrıca, 10 μM Zn(II) kompleksi MCF7 hücrelerinde apoptotik hücre ölümünü (%84.87) önemli ölçüde arttırmıştır ve hücrelerde S fazında tutulmaya (%36.4) neden olmuştur ($p < 0.01$).
Sonuç: Zn(II) kompleksinin, meme kanseri tedavisinde önemli terapötik potansiyele sahip olduğu belirlenmiştir.

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Ancak, apoptotik hücre ölümüne neden olan mekanizmaları tanımlamak ve Zn(II) kompleksinin kontrol hücreleri üzerindeki toksisitesini azaltmak için ileri çalışmaların yapılması gereklidir.

Anahtar kelimeler: Metal kompleks; Çinko; 2,2′-bipiridin; Meme kanseri; Apoptoz.

Introduction

Metal complexes have received considerable attention in the treatment of cancer due to their ability to induce catalytic processes, to provide higher selectivity and to exhibit a broader spectrum of biological activity [1–3]. Zinc(II) is an essential trace element that requires for the functionality of more than 300 enzymes and immune system, the stabilization of DNA, gene expression, cell proliferation, etc. Zn(II)-based hydrolytic cleavage promises therapeutic potential in cancer treatment due to its low toxicity, redox inertness, hard Lewis acid character and good biocompatibility of Zn ions [4, 5].

In the literature, different Zn(II) complexes have been synthesized and the anti-proliferative effects of these complex on different cancer cells (prostate, breast and lung) have been determined [6–10]. Furthermore, there is an evidence that Zn may play role in carcinogenesis depending the dose and cell type. For example, decreasing in cellular Zn levels may be the risk factors for breast, prostate and ovarian cancer, pancreatic adenocarcinoma and hepatocellular carcinoma [11–13]. In this context, new zinc-ligand modifications have received much attention in recent years. For this purpose, we prepared a $[Zn(bpy)_2(H_2O)]2(ClO_4)$ complex and characterized with single crystal X-ray, FT-IR and UV-vis. Finally, the therapeutic effects of Zn(II) complex on MCF7 breast cancer and human umbilical vein endothelial cells (HUVEC) were investigated.

Materials and methods

Synthesis of $[Zn(bpy)_2(H_2O)]2(ClO_4)$

To a solution of 2,2′-bipyridine ligand (0.940 g, 0.60 mmol) in methanol (10 mL) was added a solution of $Zn(ClO_4)_2 \cdot 6(H_2O)$ (0.100 g, 0.27 mmol) in methanol (15 mL). The mixture was stirred at 60°C temperature for 6 h. After the mixture was filtered, slow evaporation at room temperature afforded colorless crystals. Yield 0.136 g (85% based on Zn). M.p. 255°C Anal. Calc. for C12H10Cl2N2Zn: C, 40.40; H, 3.05; N, 9.42. Found: C, 40.62; H, 3.12; N, 9.49%. IR [(KBr, ν cm^{-1})] selected bonds: ν(O–H) water 3200–3400 (b), ν(C–H) 3060(m), ν(C=C), ν(C=N) 1600(s), 1554(m), and ν(ClO_4) 1089 (vs.), 625 (s). UV–Vis λ_{max} nm (CH_3CN): 198, 243, 297 and 308.

Determination of X-ray structure

Crystals of Zn(II) complex for X-ray crystal-structure were obtained by slow evaporation. The data for complex was measured at room temperature on a Bruker ApexII area-detector diffractometer using Mo Kα radiation (λ = 0.71073 Å) from a fine-focus X-ray. The data collection and refinement parameters were summarized in Table 1. Data reduction was performed using the Bruker SMART program package [14]. The structure was solved by direct methods using *SHELXS97* and refined SHELXL-2014 [15]. The molecular structure was visualized by MERCURY [16]. PLATON was used for geometric calculations [17].

Cell culture

MCF7 and HUVEC cell lines were purchased from ATCC. MCF7 breast cancer and Human umbilical vein endothelial

Table 1: Crystal data and structure refinement for complex.

Empirical formula	C40 H36 Cl4 N8 O18 Zn2	
Formula weight	1189.31	
Temperature	108(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P 21/n	
Unit cell dimensions	a = 9.0137(3) Å,	α = 90°
	b = 12.9132(5) Å,	β = 101.4730(10)°
	c = 19.6330(7) Å,	γ = 90°
Volume	2239.54(14) $Å^3$	
Z, calculated density	2, 1.764 Mg/m^3	
Absorption coefficient	1.398 mm^{-1}	
F(000)	1208	
Crystal size	0.29 × 0.20 × 0.12 mm	
Theta range for data collection	1.90–28.40°	
Limiting indices	$-8 \le h \le 12$, $-17 \le k \le 13$, $-20 \le l \le 22$	
Reflections collected/unique	11,829/4469 [R(int) = 0.0226]	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8502 and 0.6873	
Refinement method	Full-matrix least-squares on F^2	

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cell (HUVEC) lines were maintained in a humidified incubator at 37°C with 5% CO_2. These cells were grown in Dulbecco's Modified Eagle's Medium (DMEM), containing 10% fetal bovine serum (FBS) and penicillin (100 U/mL) and streptomycin (100 μg/mL).

WST-1 assay

The cytotoxic effects of Zn(II) complex on MCF7 and HUVEC cells were assessed by WST-1 assay (BioVision, San Francisco, CA, USA). Briefly, MCF7 and HUVEC cells (2×10^4 cells/well) were treated with Zn(II) complex at various concentrations (1.25, 2.5, 5, 7.5, 10, 25 and 50 μM) for 24 and 48 h. Then, 10 μL/well of the WST-1 reagent was added. After incubation for 1–3 h, the absorption at 450 nm was measured using an Elisa reader (Allsheng, China).

Annexin V analysis

To determine the effect of Zn(II) complex on apoptotic cell death, the minimum (1.25 μM) and the maximum (10 μM) concentration were selected as a similar inhibition rate was observed at 25 and 50 μM in MCF7 cells according to WST-1 results. To analyze the apoptotic effect of Zn(II) complex, MCF7 cells were seeded into 6-well plates (1×10^5 cells/well) and treated with Zn(II) complex. After 48 h of incubation, cells were trypsinized, stained with Muse Annexin V and Dead Cell Assay Kit (Millipore, Darmstadt, Germany) and analyzed with Muse Cell Analyzer (Muse™ EMD Millipore Co., Hayward, CA, USA) (n = 3). Additionally, the apoptotic effects of 1.25 and 10 μM of Zn(II) complex was further confirmed by Multi Caspase Assay (Millipore, Darmstadt, Germany) including caspase-1, 3, 4, 5, 6, 7, 8, and 9 activity according to manufacturer protocol and analyzed by Muse Cell Analyzer (Muse™ EMD Millipore Co., Hayward, CA, USA) (n = 3).

Cell cycle analysis

To analyze the effects of Zn(II) complex on the G0/G1, S and G2/M arrest, MCF7 cells were seeded into 6-well plates (5×10^5 cells/well) and treated with 1.25 and 10 μM concentrations of Zn(II) complex for 48 h. After fixation with cold 70% ethanol for at least 3 h, the cells were stained with Muse Cell Cycle Assay Kit (Millipore) for 30 min in the dark and each group was analyzed by Muse Cell Analyzer (Muse™ EMD Millipore Co., Hayward, CA, USA) (n = 3).

Statistical analysis

SPSS 22.0 software was used for all statistical analysis. A one-way analysis of variance (ANOVA) and post-hoc test were carried out to determine the differences between the means of three or more independent groups. *$p < 0.05$ and **$p < 0.01$ were considered statistically significant.

Results

Structural description of the complex

The perspective view of the structure along with the crystallographic numbering was shown in Figure 1A. The crystallographic data and some selected bond lengths and angles were summarized in Tables 1 and 2. XRD data demonstrated that the complex was monoclinic crystal system with space group P 21/n. The Zn(II) complex contained two molecules of bpy and one molecule of water. The metal ion was coordinated by four N (N1, N2, N3 or N4) from two bpy, one O (O5) from water molecule. The coordination geometry may be approximated as a strongly distorted trigonal bipyramid in which the Zn, N1, N4 and O5 atoms defined the basal trigonal plane and the N2 and N3 atoms occupied apical positions (Figure 1A). The N-Zn-N angle was the widest (N2ZnN3 = 178.82) and the equatorial region angles were in the range of 121.14–118.36 deviating from 120°. The bite angle of bpy ligands were in the range of 78.83°–102.45°. The axial bond distances between N-Zn (N1-Zn = 2.0693 Å and N4-Zn = 2.0646 Å) was longer than equatorial N-Zn distances (N2-Zn = 2.0993 Å and N3-Zn = 2.0858 Å). The bond length of Zn-N was similar to analogues published structures [18–22]. The bpy ligands were almost planer [torsion angle (N1C5C6N2 = 0.1° (2) and N3C11C16N4 = 0.7° (2)]. The uncoordinated perchlorate molecules link adjacent complexes through hydrogen bonds with coordinated water molecule. In the unit cell structure, mononuclear units were linked by two O–H…O hydrogen bonds between O-H of the coordinated water molecule and oxygen atoms of perchlorate ion, with an O5…O2 distance of 2.935 (2) Å (O5-H21A…O2) and O5…O6 distance of 2.746 (2) Å (O5-H21B…O6) (Figure 1B).

The IR spectra of the complex demonstrated two bands at 1089 cm^{-1} and 625 cm^{-1}, an indication of the perchlorate anion. A broad absorption band centered at 3433 cm^{-1} due to the $\nu_{sym/asym}$ vibration of the OH group in the water molecule. The bands of around 1600 cm^{-1} and 767 cm^{-1} were observed due to the ν_{bpy} vibration of

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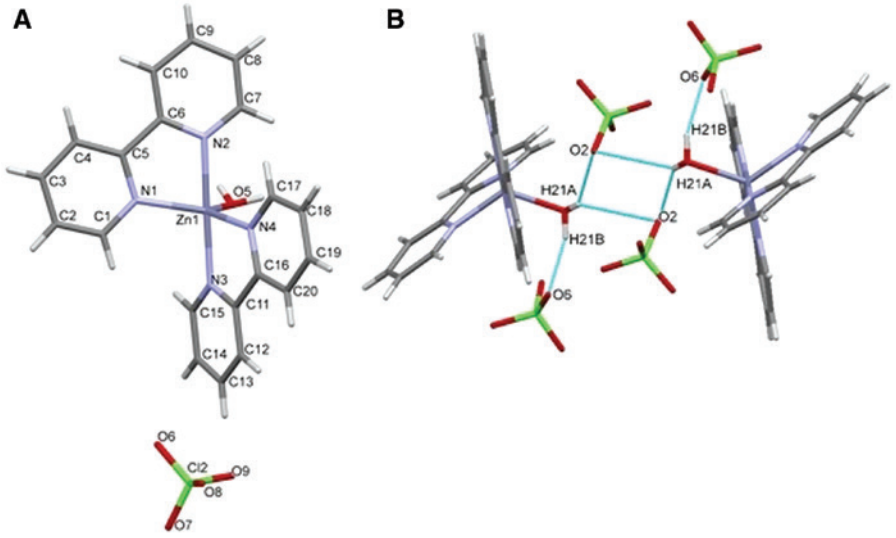


Figure 1: (A) Trigonal bipyramidal molecular structure of Zn(II) complex with 2,2′-bipyridine ligand. (B) Hydrogen bonding interactions between uncoordinated perchlorate and coordinated water molecule (O5…O2 distance of 2.935 (2) Å (O5-H21A…O2) and O5…O6 distance of 2.746 (2) Å (O5-H21B…O6).

Table 2: Some selected bond lengths (Å) and bond angles (°) for Zn(II) complex.

Zn1-O5	2.0502(16)	O5-Zn1-N1	120.50(7)
Zn1-N1	2.0692(17)	O5-Zn1-N2	90.64(6)
Zn1-N2	2.0993(16)	O5-Zn1-N3	88.80(6)
Zn1-N3	2.0859(16)	O5-Zn1-N4	121.14(7)
Zn1-N4	2.0647(16)	N1-Zn1-N2	78.73(6)
N4-Zn1-N1	118.36(6)	N1-Zn1-N3	102.45(6)
N4-Zn1-N2	100.28(6)	N3-Zn1-N2	178.82(7)

bpy ligand. The UV spectrum of the complex in acetonitrile showed that the lower wavelength bands maximum absorptions at 198–308 nm may be assigned to π–π* transitions of the aromatic rings and the charge transfer band to ligand from metal (MCLT) [23].

Zn(II) complex inhibits the proliferation of breast cancer cells

The anti-proliferative effects of Zn(II) complex on the viability of MCF7 and HUVEC cells were determined by WST-1 assay (Figure 2). As shown in Figure 2A, MCF7 cell viability significantly decreased to 40.9%, 11.0% and 12.2% at a concentration of 1.25, 10 and 50 μM Zn(II) complex ($p < 0.01$), respectively for 48 h. However, the viability of HUVEC cells considerably reduced to 42.3%, 52.6% and 40.7% at a concentration of 1.25, 10 and 50 μM Zn(II) complex, respectively for 48 h ($p < 0.01$, Figure 2B).

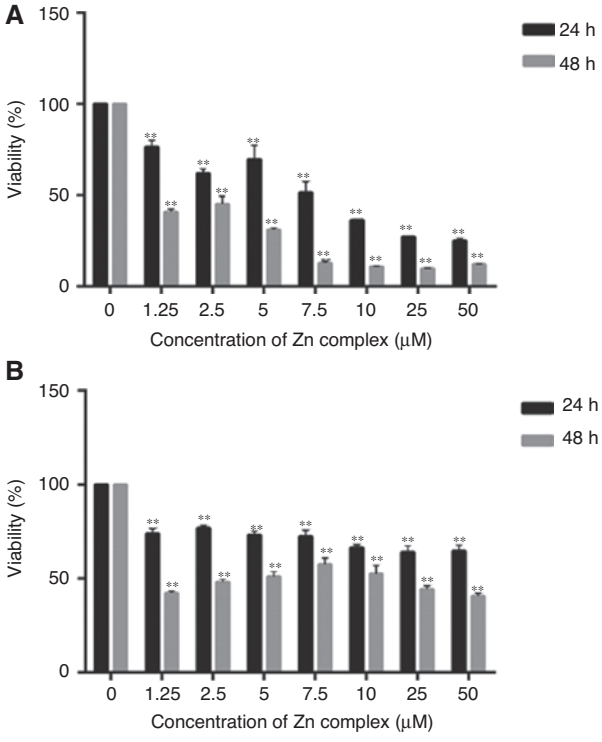


Figure 2: The anti-proliferative effects of Zn(II) complex on the viability of MCF7 and HUVEC cells were determined by WST-1 assay. The viability of (A) MCF7 breast cancer and (B) HUVEC cells after 24 and 48 h exposure to 1.25, 2.5, 5, 7.5, 10, 25 and 50 μM Zn(II) complex (**$p < 0.01$).

Therefore, an inhibitory effect of Zn(II) complex on MCF7 proliferation was detected in a dose and time-dependent manner.

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Zn(II) complex induces apoptosis in breast cancer cells

To reveal a possible apoptotic inducing effect of Zn(II) complex on MCF7 breast cancer cells, we carried out Annexin V assay and our findings were summarized in Figure 3. At a concentration of 1.25 and 10 μM Zn(II) complex, the percentage of total apoptotic cells was 50.45% and 84.87%, respectively for 48 h. Thus, the total number of apoptotic cells remarkably increased 13.8- and 23.2-fold, respectively ($p < 0.01$) as compared with control cells. Furthermore, we explored the activity of apoptotic cell death by multi-caspase assay (Figure 3). After incubation with 1.25 and 10 μM Zn(II) complex, the rate of caspase positive/dead cells was 23.44% and 69.89%, respectively in MCF-7 cells ($p < 0.01$). Thus, Zn(II) complex significantly induced apoptotic cell death through multi-caspase activity in breast cancer cells.

Zn(II) complex induces cell cycle arrest

To explore the effects of Zn(II) complex on cell cycle arrest, the cells were stained with cell cycle assay. As shown in Figure 4, Zn(II) complex caused a remarkable increase in the percentage of S phase (from 11.3% to

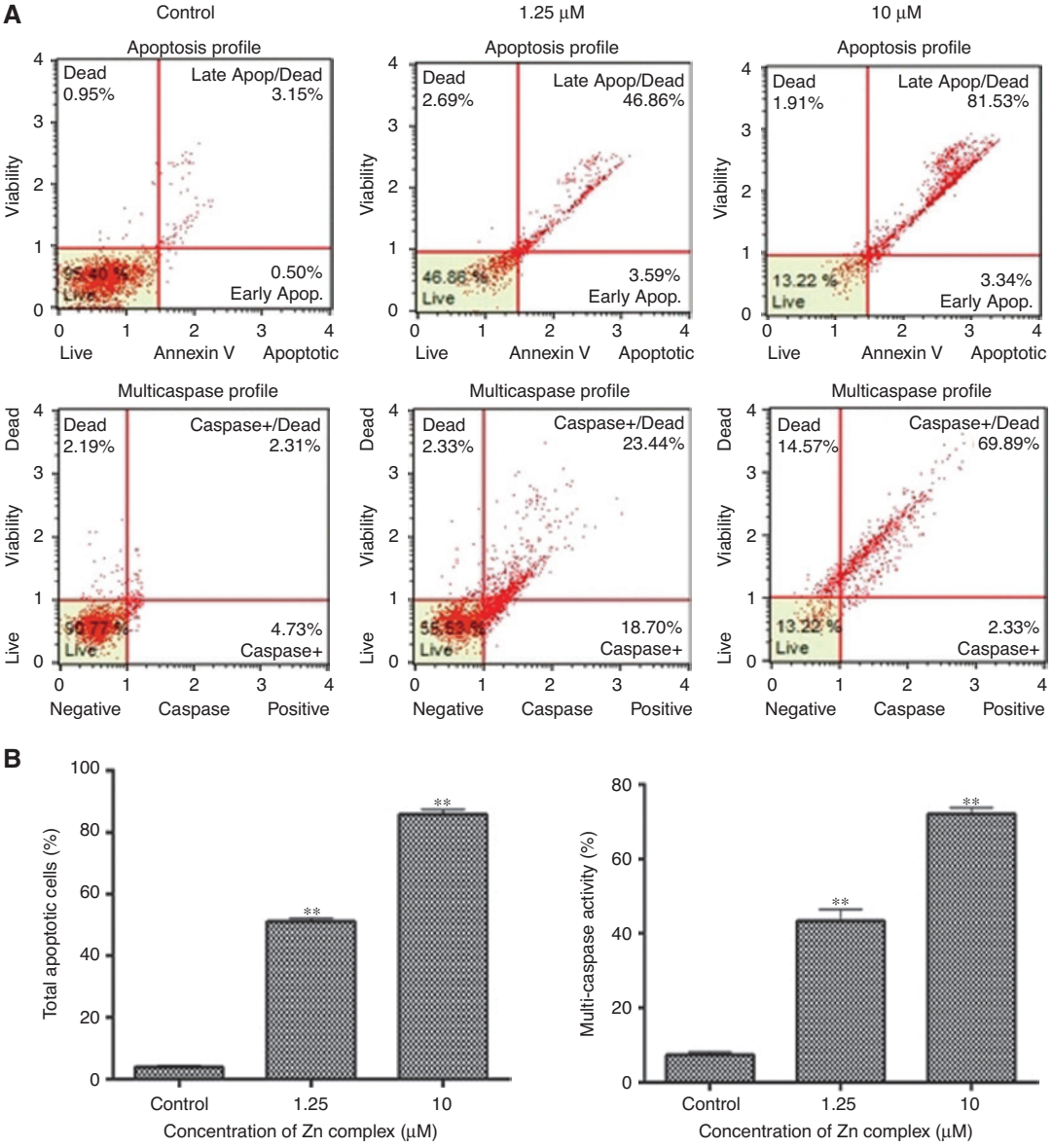


Figure 3: The apoptotic effect of Zn(II) complex on MCF7 cells was determined by Annexin V analysis.
(A) The results of Annexin V and multi-caspase analysis. (B) Statistical analysis of the results of total apoptotic cells after treatment with different concentrations of Zn(II) complex ($p < 0.01$**).

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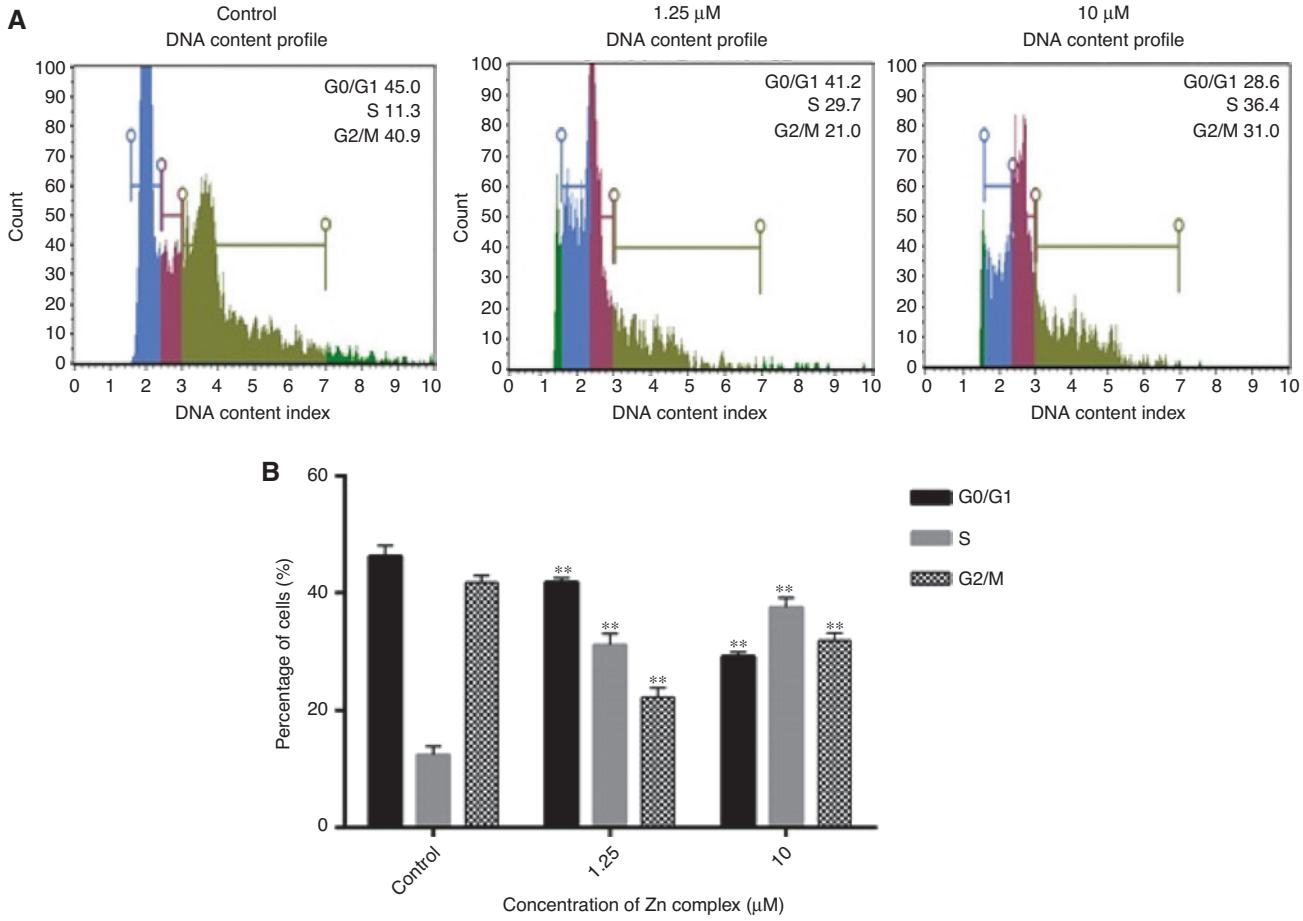


Figure 4: Effects of Zn(II) complex on cell cycle distribution in MCF7 cells.
(A) The results of cell cycle analysis. (B) Statistical analysis of the results of cell cycle distribution after treatment with different concentrations of Zn(II) complex ($p < 0.01$**).

29.7% and 36.4%) at a concentration of 1.25 and 10 µM Zn(II) complex, respectively ($p < 0.01$). Furthermore, the proportion of MCF7 cells in G0/G1 arrest decreased from 45.0% to 41.2% and 28.6% at a concentration of 1.25 and 10 µM Zn(II) complex, respectively. Thus, Zn(II) complex significantly caused at S phase arrest in MCF7 cells.

Discussion

In the current study, we evaluated that a new Zn(II) complex successfully synthesized, characterized and significantly inhibited the proliferation of MCF7 breast cancer cells through induction of apoptosis and S phase arrest. On the other hand, Zn(II) complex exhibited toxic effects on control cells. Thus, there is an urgent need to improve new strategies for reducing undesirable effects of metal-ligand complexes on control cells.

Transition metals complexes with different ligands have provided cancer research with new insights to overcome the limitations of current chemotherapeutic agents. In this context, utilization of different transition metals (Mn, Fe, Cu, Co, Au and others, etc.) and their complexes have increasing attention for cancer treatment due to their anticancer activity. In the literature, different Zn complex (tetranuclear Zn complex $[Zn_4(\mu^3-OH)_2(PiCO)_6(H_2O)_4]$, $Zn(L)(OAc)\cdot 3H_2O$, $Zn(L)_2\cdot 2H_2O$, phosphido pincer-Zn(II) complexes [(PPP)ZnR], divinylzinc Zn complexes ($Zn[C(Me)=CH_2]_2$ and $Zn[C(H)=CMe_2]_2$), Zn(II) with 4,4′-bipyridine complex, $Zn_3(\mu_3\text{-}PO_4)$ and $Zn_3(\mu_3\text{-}CO_3)$, etc.] have been synthesized and structurally characterized [24–29]. However, there has been limited studies to assess the anticancer effects of Zn complexes on cancer cells. Milacic et al. found that pyrrolidine dithiocarbamate (PyDT)-zinc(II) complex induced apoptotic cell death by calpain activation in human breast (MDA-MB-231) and prostate cancer cell lines (PC-3) [7]. Cui et al. stated that two zinc(II) $\{[Zn(bibp)(MoO_4)](H_2O)_2\}_n$

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[bibp = 4,4′-bis(imidazol-1-yl)-biphenyl] and nickel(II) based coordination polymers exhibited anticancer activity on MDA-MB-231, MDA-MB-468, SK-BR-3, and MCF7 breast cancer cells [8]. Rundstadler et al. reported that zinc(II)-phenanthroline-indomethacin complexes could kill breast cancer stem cells and bulk breast cancer cells [9]. In the current study, a novel Zn(II) complex remarkably inhibited MCF7 cell proliferation by inducing apoptotic cell death and cell accumulation in the S phase. However, the underlying molecular mechanisms of Zn(II)-based apoptotic cell death need to be explored.

Furthermore, only one study, to our knowledge, investigated the potential cytotoxic and apoptotic effects of Zn-S-NVC complex on PC3 human prostate cancer and PNT1A human normal prostate epithelium cell lines [10]. They found that Zn-S complex and NVC induced high toxicity in both PC3 and PNT1A. However, Zn-S-NVC complex reduced the PC3 cell viability by 65% without damage to PNT1A control cells [10]. Thus, the cytotoxic and apoptotic effects of transition metal-complexes on control cell lines should be determined to provide information on the exact potential anticancer activities. In our study, Zn(II) complex inhibited the proliferation of HUVEC control cells. Therefore, there is need for discovery of new Zn complexes with different ligands to reduce the toxic side effects on control cells.

Consequently, Zn(II) complex coordinated with bpy ligand significantly suppress breast cancer cell growth in a dose-dependent manner and induce cell cycle arrest and apoptotic cell death. However, further studies are needed to identify the mechanism underlying its apoptotic effect and to reduce toxicity on control cells. Additionally, metal-based drug design studies could include *in vitro* experiments with cancer and control cell lines to assess therapeutic effects and toxicity of metal complexes on cancer therapy.

Supplementary material

CCDC 860726 contains the supplementary crystallographic data for Zn(II) complex. These data can be downloaded via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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Conflicts of interest: The authors declare that they have no conflicts of interest.

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