Clinical and Experimental Health Sciences

Effects of Curcumin and its Metal Complexes on Cell Viability, Apoptosis, and Cell Cycle Phases in MCF-7 Cells

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ABSTRACT

Objective: To obtain metal complexes of curcumin and determine their effects on MCF-7 cell viability.

Methods: We have first obtained Cu^{+2}, Co^{+2}, Zn^{+2} complexes of curcumin. We then compared their effects on MCF-7 cell viability and observed that Zn^{+2}-curcumin complex was the most effective and safe one. Experiments were carried out with two different Zn^{+2}-curcumin complexes (Zn-CUR-I and Zn-CUR-II) to further determine their effects on cell viability, apoptosis, and cell cycle phases.

Results: The results of different metal-curcumin complexes showed that they had a significant effect on MCF-7 cell viability. We chose Zn^{+2}-curcumin rather than Cu^{+2}-curcumin or Co^{+2}-curcumin since the latter metals might have toxic effects on healthy cells. Another Zn^{+2}-curcumin complex (Zn-CUR-II) was prepared and the effects of the two Zn^{+2}-curcumin complexes on MCF-7 cells were compared. Zn-CUR-II was much more effective than Zn-CUR-I in inducing apoptosis. There was no significant difference between the effects of the two complexes on cell cycle phases.

Conclusion: Zn^{+2}-curcumin complex (Zn-CUR-II) applied to MCF-7 cells induced apoptosis suggesting that it may be used as adjuvant therapeutic in breast cancer treatment.

Keywords: Curcumin, Zinc chloride, Metal complex, MCF-7, Apoptosis.

1. INTRODUCTION

Turmeric (*Curcuma longa*) is a perennial herbaceous plant with rhizomes from the Zingiberaceae family. Curcumin, which is also called diferuloylmethane, is a yellow-colored polyphenol found in the rhizome of turmeric and other species of *Curcuma*. Curcuminoids are "Generally Recognized as Safe" (GRAS) by the FDA [1]. Curcumin has a wide variety of biological activities including antioxidant, anti-inflammatory, anticancer, antigrowth, antiarthritic, anti-atherosclerotic, antidepressant, antiaging, antidiabetic, antimicrobial, wound healing and memory-enhancing activities [2]. In addition, it shows chemo-preventive, chemo-sensitization and radio-sensitization effects [3,4].

Metal complexes are becoming increasingly important in diagnosis and treatment. Platinum-based chemotherapeutics used in the treatment of various cancers have been recognized as standard first-line treatment agents against tumor progression and metastasis. Unfortunately, narrow therapeutic index of platinum drugs often resulted in severe nephrotoxicity, neurotoxicity, myelosuppression, and irreversible ototoxicity, limiting the widespread application of platinum drugs. Therefore, research and development of new metal-based anticancer drugs to reduce toxicity and alleviate clinical treatment is sought [5].

Curcumin inhibits the chemotherapeutic effect of some drugs while increasing the effectiveness of others. Although

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curcumin is effective against tumor promotion, angiogenesis, and tumor growth; it has limited use because of its hydrolytic instability and low bioavailability [6]. Curcumin has poor water solubility and is poorly absorbed by the gastrointestinal tract after oral administration due to its hydrophobic nature. Various approaches have been sought to overcome these obstacles including conjugation with various metals, i.e. Zn, Cu, Mn, Co, Fe. Metal-curcumin complexes increase solubility, cellular absorption and bioavailability of curcumin. In addition, metal complexes have improved the antioxidant, anti-inflammatory, anti-microbial and antiviral properties of curcumin [7].

In this study, we have first obtained curcumin complexes of Cu^{+2}, Co^{+2}, Zn^{+2}. We then compared their effects on cell viability and observed that Zn^{+2}-curcumin was the most effective and safe one. Further experiments were carried out with two different Zn^{+2}-curcumin complexes (Zn-CUR-I and Zn-CUR-II) to determine their effects on cell viability, apoptosis, and cell cycle phases.

2. METHODS

2.1. MCF-7 cells and cell culture conditions

Cells were obtained from American Type Culture Collection (ATCC, USA) and cultured in DMEM supplemented with 10% FBS (Sigma, USA) [8]. Cell viability was determined using MTT Cell Viability Assay (Roche, Mannheim, Germany) and calculated from absorbances at 560 nm. IC50 values were obtained using the CalcuSyn software program (the median inhibitory concentration at which cell growth is inhibited by 50%).

2.2. Synthesis of metal-curcumin complexes (Cu-CUR, Co-CUR, Zn-CUR-I)

Twenty ml of curcumin solution (2 mM, in methanol) was added to 20 ml of aqueous solution of 1 mM $CuCl_2$, $ZnCl_2$ and $CoCl_2$. Then 1 M ammonium hydroxide solution was added drop by drop to bring the pH around 8.5. The red-brown solution was stirred at 60°C for 15-20 minutes. It was observed that the substance precipitated in the reaction medium. After filtration, the precipitate was washed with methanol several times to eliminate impurities. A brown powdery substance was obtained [9].

2.3. Synthesis of Zn-CUR-II complex

$ZnCl_2$ and 1,10-phenanthroline were added to 50 ml of chloroform. A white suspension was obtained and incubated at room temperature for 24 hours, then filtered and washed with chloroform. After this a red solution was obtained by adding triethanolamine under nitrogen and at room temperature to the orange solution of curcumin in MeOH. An intermediate complex solution in DMSO was added to this solution. The resulting orange suspension was mixed under nitrogen overnight and leaching with orange solid MeOH was performed after filtration [10].

2.4. Fourier transform IR spectroscopy

A Shimadzu FT-IR spectrometer (QATR-S) was used to measure the % transmittance for the characterization of synthesized metal-curcumin complexes.

2.5. Spectroscopic analysis and curcumin quantification

Stock standard of curcumin (1 mg/ml in DMSO) was prepared at room temperature. This solution was diluted to obtain working standards. The UV-VIS spectrum was taken in the wavelength range of 300-700 nm and the maximum absorbance of curcumin was determined as 440 nm. The absorbance of the standards was used to plot a standard calibration curve. The curcumin content of curcumin derivatives was then calculated using this curve [10,11].

2.6. Determination of cell viability

A stable tetrazolium salt (MTT) was used to determine cell viability [8]. After the cells were propagated and counted, they were planted in 96-well plates containing 200 µl of medium and 10,000 cells/well and incubated at 37°C for 24 h in each well. To examine the effects of different groups on cell viability over time, 100 µl of MTT was added 48 h after application. Cell viability was measured at 560 nm using a multiplate reader after incubation for 3-4 h. The absorbances obtained were substituted in the formula given below and the cell viability rate (%) of each group was calculated.

Viability (%) = (A_{560} Sample – A_{560} Blank / A_{560} Control – A_{560} Blank) x 100

2.7. Determination of apoptosis and necrosis

The effects of metal-curcumin complexes on apoptosis and necrosis were determined by staining the cells with Annexin V/PI [8]. After the administration of metal-curcumin complexes in determined amounts, apoptosis and necrosis rates at 48 hours were analyzed by flow cytometry.

2.8. Cell cycle analysis

Cell cycle analysis was performed at 48 hours after the application of metal-curcumin complexes [8]. DNA extraction was performed in phosphate-citric acid buffer, and the extracted DNAs were stained with PI and analyzed by flow cytometry.

2.9. Reactive oxygen species (ROS) analysis

Reactive oxygen species were detected using 5-(and-6)-chloromethyl-2',7'-dichlorodihydrofluorescin diacetate (CM-H2DCFDA) staining. Cells were seeded into 6-well plates ($1x10^5$ cells/well) and treated with curcumin and metal-curcumin complex for 24 h. Cells treated with hydrogen peroxide were used for positive control. After treatment cells were washed and incubated with phenol red-free DMEM medium containing 10 µM CM-H2DCFDA for 30 min at 37°C, in the dark. Stained cells were analyzed by flow cytometry.

2.10. Statistical analysis

GraphPad Prism 8.0.1 software was used. All results were presented as mean ± standard deviation. Pairwise comparisons were made using Student's t-test and multiple comparisons using the One-Way ANOVA test. The Tukey test was used for intergroup significance with the following thresholds: p values less than 0.001 were reported as $p < 0.001$; p values less than 0.01 were reported as $p < 0.01$ and p values less than 0.05 were reported as $p < 0.05$.

3. RESULTS

The synthesized complexes were found to be stable at room temperature with brown-to-red colors, and they were soluble in DMSO. The structures of metal-curcumin complexes were confirmed by FT-IR spectroscopy measurements (Table 1 and Figure 1). UV-VIS spectra of different metal-curcumin complexes revealed the presence of curcumin (results not shown).

Table 1. *FT-IR spectral bands (cm^{-1}) for curcumin and their metal complexes.*

	(OH)	(C=O)	(C=C)	(CO) (C=C)	(CO)	(C=CH)	MO
CUR	3504	1626	1506	1428	1273	807	-
CoCUR	3504	1589	1490	1424	1266	815	467
CuCUR	3504	1617	1505	1419	1273	812	469
ZnCUR-I	3504	1622	1505	1395	1274	816	462
	(OH)	**(C=O)**	**(C=N)**	**(C-C-C)**			
ZnCUR-II	3400	1624	1582	1518			

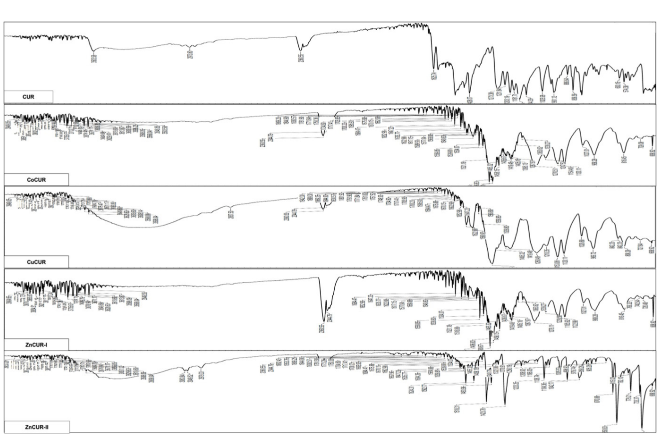

Figure 1. *FT-IR measurements of different metal-curcumin complexes CUR: Curcumin; CoCUR: Cobalt-curcumin complex; CuCUR: Copper-curcumin complex;*
ZnCUR-I: Zinc-curcumin complex-I; ZnCUR-II: Zinc-curcumin complex-II

The results obtained from characterization studies agreed with the literature [9,12].

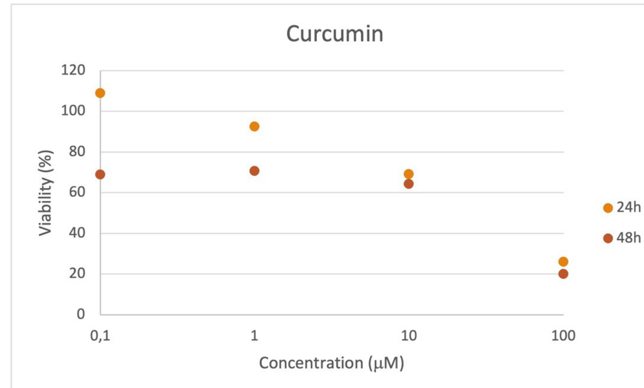

Figure 2. *MCF-7 cell viability 24 h and 48 h after treatment with different concentrations of curcumin.*

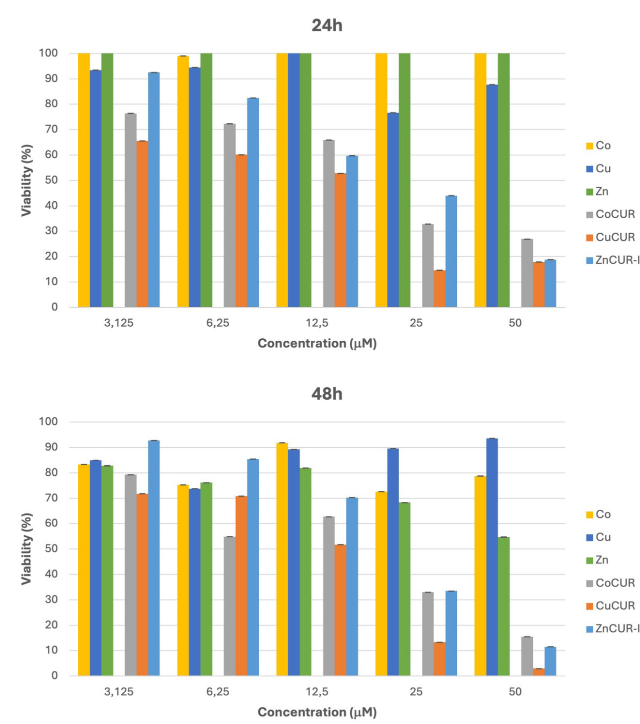

Figure 3. *MCF-7 cell viability 24 h and 48 h after treatment with Cu^{+2}, Co^{+2}, Zn^{+2} and their curcumin complexes.*
Co: Cobalt; Cu; Copper; Zn: Zinc; CoCUR: Cobalt-curcumin complex; CuCUR: Copper-curcumin complex; ZnCUR-I: Zinc-curcumin complex-I

The effect of curcumin and metal-curcumin complexes on cell viability was determined using MCF-7 cells (Figure 2 and Figure 3). The results of different metal-curcumin complexes showed that they had a significant effect on MCF-7 cell viability. After evaluating the results of cell viability experiments using CalcuSyn software we have decided to choose 35 µM curcumin and 48 h as standard assay conditions. In further studies the effects of metal-curcumin complexes on cell viability, apoptosis, and cell cycle phases were determined. We chose Zn^{+2}-curcumin rather than Cu^{+2}-curcumin or Co^{+2}-curcumin since the latter metals might have toxic effects on healthy cells [7,13]. A second Zn^{+2}-curcumin complex (Zn-CUR-II) was prepared and the effects of the two Zn^{+2}-curcumin complexes on MCF-7 cells were compared. Figure 4 shows that compared to Zn-CUR-I, Zn-CUR-II was more effective in decreasing cell viability (IC50 values: 18 µM vs 14 µM). The apoptotic effect of the two Zn^{+2}-curcumin complexes (Zn-CUR-I and Zn-CUR II) on MCF-7 cells was investigated by flow cytometry. Figure 5 shows that Zn-CUR-II was much more effective in inducing apoptosis (10.27% vs 76.31%). We also analyzed the effects of the two Zn^{+2}-curcumin complexes on cell cycle phases and observed that there was no significant difference between them (Figure 6). The effect of Zn-CUR-II on ROS production in MCF-7 cells was investigated by CM-H2DCFDA staining. It was observed that ROS production in Zn-CUR-II treated cells were significantly higher than controls (Figure 7).

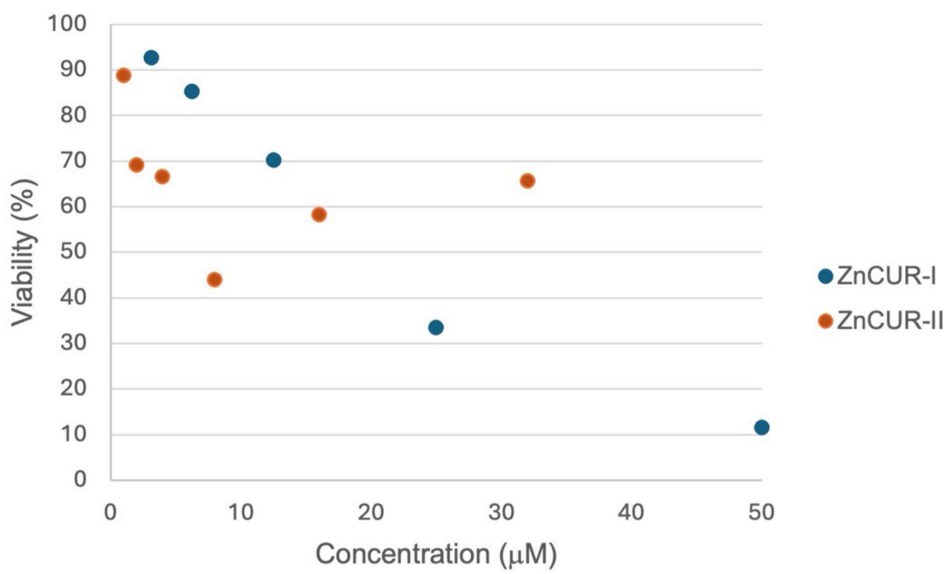

Figure 4. *MCF-7 cell viability 48 h after treatment with the two different Zn^{+2}-curcumin complexes (Zn-CUR-I and Zn-CUR-II).*

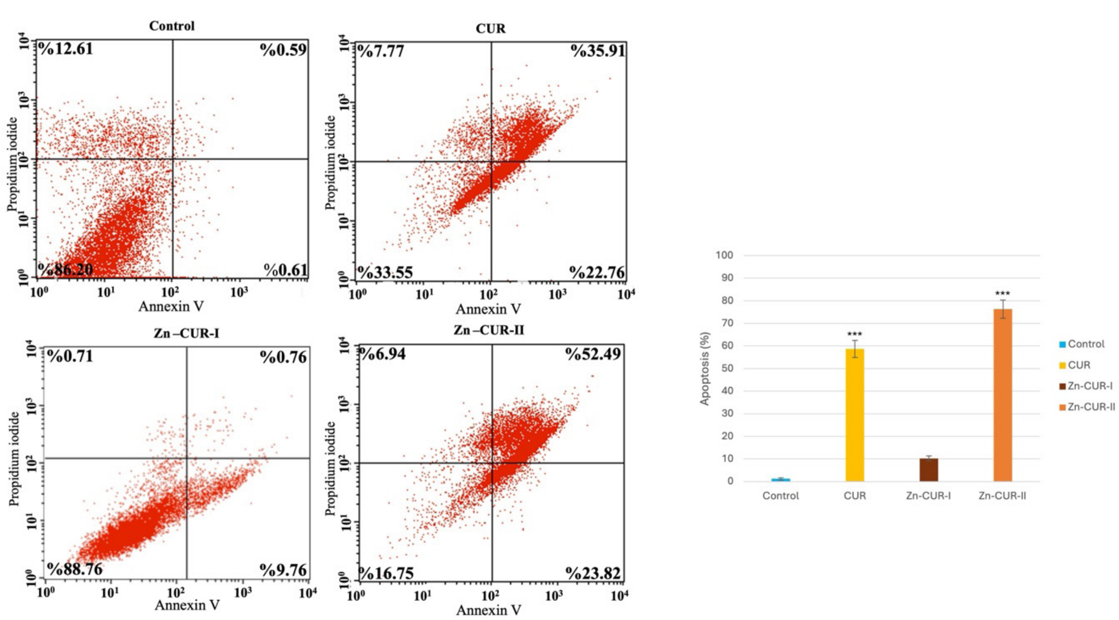

Figure 5. *Flow cytometric analysis for apoptosis and necrosis in MCF-7 cells after treatment with two different Zn^{+2}-curcumin complexes (Zn-CUR-I and Zn-CUR-II). The bar graph shows percentage apoptosis levels of MCF-7 cells after treatment.*

**** $p < 0.001$ compared to controls*

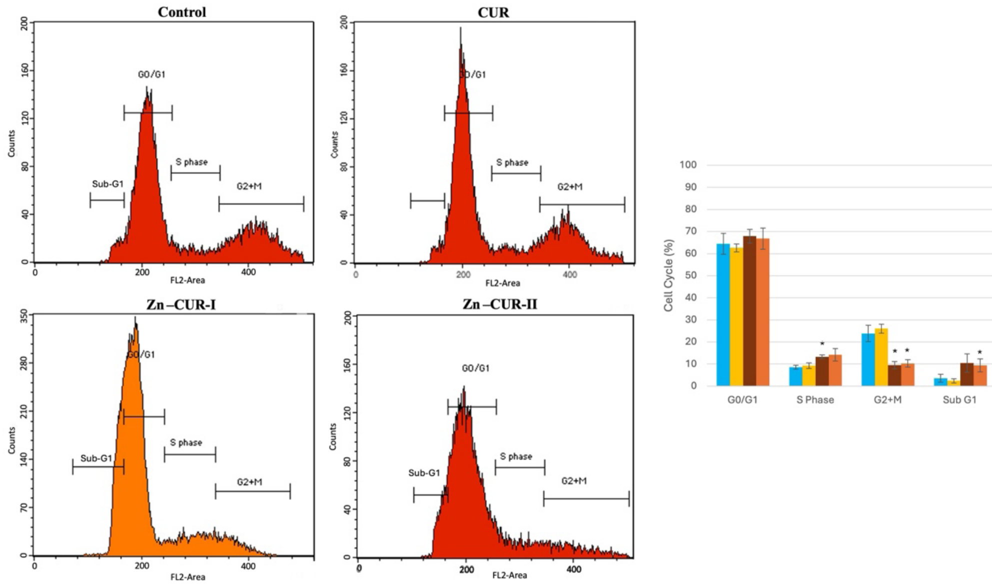

Figure 6. *Effect of two different Zn^{+2}-curcumin complexes (Zn-CUR-I and Zn-CUR-II) on cell cycle phase distribution in MCF-7 cells. The bar graph shows percentage of cells at different cell cycle phases.*
** $p < 0.05$ compared to controls*

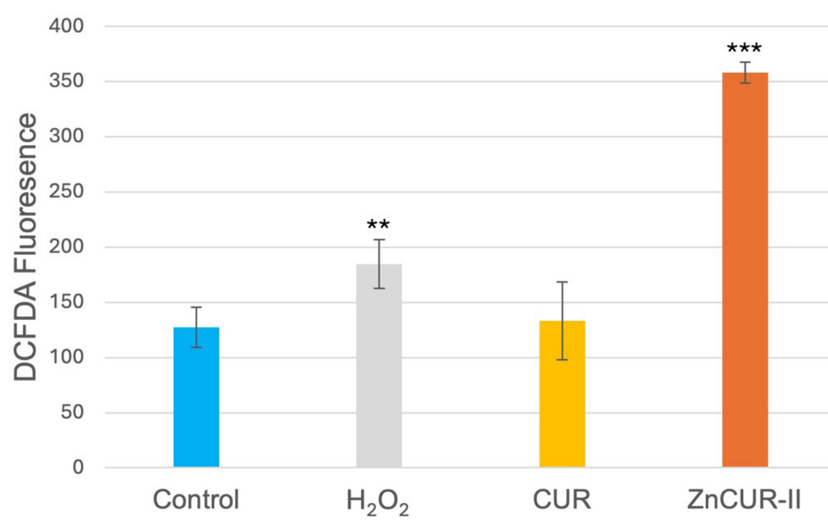

Figure 7. *Reactive oxygen species levels of Zn-CUR-II treated MCF-7 cells.*
*** $p < 0.01$ compared to controls; *** $p < 0.001$ compared to controls*

4. DISCUSSION

Extensive research has been conducted on cytotoxicity and genotoxicity of novel metal-based antitumor complexes that can overcome cis-platinum resistance and toxicity [14]. These studies have focused on transition metal complexes other than platinum that can offer unique properties and the ability to target DNA through non-covalent bonds [10]. Metal-based compounds have different physicochemical and biological properties. Particularly the presence of strong covalent bonds increases stability in the biological environment. In addition, metal complexes have the potential to overcome the limitations of drugs in terms of drug selectivity, resistance, and toxicity [15]. The therapeutic applications of different metal-curcumin complexes and creation of new metal-based organometallic compounds have attracted attention [13]. We have obtained metal-curcumin complexes with Cu^{+2}, Co^{+2} and Zn^{+2} using different preparation methods [9,10]. The results obtained from the characterization studies of the complexes agreed with the literature [9,12].

The effect of curcumin on cell viability was determined using MTT cell proliferation assay [16]. Curcumin was found to exhibit strong cytotoxicity and antiproliferative effects against MCF-7 cells even when administered at low doses [17]. In this study curcumin was applied at varying concentrations and at two different times (24 and 48 hours) to MCF-7 cells and the IC50 values (36.72 μM) were in accordance with the literature [17-19]. In vitro anticancer activity of different curcumin compounds synthesized with Ni, Co, Cu and Zn was carried out against human cancer hepatocellular carcinoma (HepG2) using MTT method [20]. All complexes showed better inhibitory activity than curcumin and the highest antitumor activity was found for copper and zinc complexes. In another study, the cytotoxic effects of Fe^{3+}-curcumin and Cu^{2+}-curcumin complexes against MCF-7, MDA-MB-231, and 4T1 breast cancer cells were also observed and Cu^{2+}-curcumin complex was more cytotoxic [21]. In our studies, all metal-curcumin complexes were observed to exhibit significant cytotoxic behavior against MCF-7 cells after 24 and 48 hours of application [22]. The effect of Zn^{+2}-curcumin derivatives on cell viability in the human neuroblastoma cell line (SH-SY5Y) and the IC50 values obtained were 8.75 µM for 24 hours and 6.84 µM for 48 hours [10]. A dose-dependent viability-lowering effect was observed and reported to be superior to the previously reported reference compound. A similar effect of Zn-CUR-II complex on cell viability was evident in our study with an IC50 value of 14 µM.

Various mechanisms of action have been proposed for the anticancer activity of curcumin. Curcumin suppresses cancer cell proliferation, metastasis, and angiogenesis by inducing cell death and apoptosis [23-25]. Pucci et al. [10] have performed Annexin V and PI staining to see whether the cell response was due to apoptotic or necrotic mechanisms after the administration of various curcumin complexes. They found that the complexes gave high fluorescence intensity and suggested that this was evidence for apoptosis induction. Additionally, the investigation of apoptotic markers indicated that complexes induce cell apoptosis through a molecular mechanism involving the activation of JNK, caspase-3 and changes in MMP. On the other hand, Garufi et al. [26] showed that the antitumor activity of the Zn^{2+}-curcumin complex can induce DNA damage and conformational changes of some proteins, thereby leading to apoptotic cell death. Although cell proliferation is necessary for the growth, development and regeneration of eukaryotic organisms, it also causes cancer [27]. Since the DNA content in cells changes during the cell cycle, the cell population at various stages of the cell cycle can be estimated by flow cytometry using PI [27]. Ni^{+2}-curcumin complexes were able to stop A549 cells in G1 phase and induce apoptotic cell death when exposed to low-energy visible light [28]. Curcumin can regulate cancer cell proliferation by causing cell cycle arrest in the G2/M phase [29]. Also, curcumin complexes stopped the cell cycle in G2/M phase in MDA-MB-231 and MCF-7 cells [11,30]. The curcumin complex Cur@ZIF-8@HA applied to the human breast 4T1 cancer cell line caused cell cycle arrest, ROS production, and higher cytotoxicity with apoptosis in the G2/M and S phases. Our results also revealed that Zn-CUR-II increased intracellular ROS levels.

5. CONCLUSION

In our study, metal-curcumin complexes were obtained using different metals and methods to increase the bioavailability of curcumin. The effects of the metal-curcumin complexes on cell proliferation, apoptosis, and cell cycle phases were then investigated in MCF-7 cells. While Cu^{+2}, Co^{+2} and Zn^{+2} curcumin complexes affected cell proliferation and cell cycle phases, they did not show any significant effect on apoptosis. The effects of these complexes on cell death mechanisms needs to be further examined in more detail. We have shown that Zn-CUR-II was effective on inducing apoptosis of MCF-7 cells and believe that elucidating the cell death pathway(s) affected by Zn-CUR-II will be useful in determining the efficacy of the therapeutic effects of curcumin in different cancer cell lines.

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Author Contributions:

Research idea: GB, ASY

Design of the study: GB, AMYG, ASY

Acquisition of data for the study: GB, ZMO, AMYG

Analysis of data for the study: GB, ZMO, AMYG

Interpretation of data for the study: All authors

Drafting the manuscript: GB, AMYG, ASY

Revising it critically for important intellectual content: AMYG, ASY

Final approval of the version to be published: All authors

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