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Assessment of Anticancer Capacities of (Ceftriaxone/Zn) Drug Complex with Chemical Characterization against Three Cancer Cell Lines of Breast, Hepatic and Large Cell Lung Cancer (MCF-7; HepG-2; H460)

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ABSTRACT

Background: Ceftriaxone (CF) shows high and wide range of the potent antibacterial activity with rare some side effects, a long half-life. Now new transition metal drug complex attract more attention for evolving of new capacities with multi-therapeutic approach such as anticancer activities.

Methods: CF/Zinc (CF/Zn) complex was prepared and characterized *via* the transmission and scanning electron microscope. CF/Zn complex was prepared in (1:1) ceftriaxone: Zn^{+2} ratio.

Result: (CF) coordinated as a tetradentate ligand towards zinc metal ion with the molecular formula $[Zn(CF)(H_2O)_2].2H_2O$. The particle size and morphological surface for zinc complex was examined by using of many analyses: SEM, EDX, TEM, TGA/DTG and X-ray diffraction. This study investigated the effect of CF/Zn metal complex as a potent anticancer agent against three cancer cell lines (Breast adenocarcinoma MCF-7, Hepatocellular carcinoma HepG-2 and large cell lung cancer H460). The synthesized complex showed great anticancer capacities against the three cell lines at conc. 10 ug/ml and the living percentages were: 95.44, 90.6 and 94.04 µg/ml respectively and inhibited the proliferation of the cancer cells at conc.100 ug/ml and the living percentages were 90.35, 80.25 and 84.26 µg/ml. Exposure to CF/Zn complex even at very low concentrations elevated anticancer capacities of CF against three dangerous and common cancer types worldwide.

Key words: Antibiotics, Antioxidant activity, Bacterial resistance, Ceftriaxone.

INTRODUCTION

Despite tremendous advancements in treatment, cancer continues to be a major global health concern, taking millions of lives each year. Drug resistance, toxicity and inadequate efficacy are some of the issues that highlight the need for innovative therapeutic approaches. The repurposing of antibiotics that chelate with certain transition metals to function as anti-cancer drugs has been an intriguing avenue for research in this regard (Karamanolis *et al*., 2025).

One of the biggest threats to world health is cancer, which has a major negative influence on people's quality of life. Almost one in five people between the ages of 0 and 74 will be diagnosed with cancer and the number of new cases and related deaths is continuously increasing. Around 18 million new instances of cancer were reported globally in 2018 and by 2020, that number had increased to almost 20 million, with 9.7 million deaths from cancer. Forecasts for 2040 show a significant increase, with an anticipated 15.3 million cancer-related deaths and 29.9 million new diagnoses (Global Cancer Observatory, 2024; Mattiuzzi and Lippi, 2019). Lung and breast cancers continue to be the most frequent cancer forms, but other malignancies, like colorectal cancer (CRC), are on the rise (Banerjee *et al*., 2024).

Numerous antibiotic classes have demonstrated encouraging anti-cancer effects in both *in vitro* and *in vivo* investigations. These methods include the production of reactive oxygen species, the activation of apoptosis and cell cycle arrest and the suppression of important regulators of cell migration and proliferation. Angiogenesis is also disrupted and important processes like inflammation, immunological response, mitochondrial dynamics and autophagy are altered. Antibiotics have also shown promise in improving the effectiveness of treating treatment-induced toxicities (Karamanolis *et al*., 2025).

In this regard, finding new therapeutic uses for already-approved medications, or repurposing them, has become a viable method to speed up and reduce the cost of drug development (Corsello *et al*., 2020; Wang *et al*., 2023) offer

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an intriguing illustration of drug repurposing research. Using the PRISM molecular barcoding technique, they discovered numerous non-oncology medications that exhibited anti-cancer activity. Furthermore, it is anticipated that artificial intelligence (AI) will help reposition outdated medications in the treatment of cancer, reducing the need for intensive preclinical screening.

Antibiotics are among the most interesting possibilities for repurposing because of their surprising but noteworthy anti-cancer activity. In addition to their conventional use in treating many infections, a number of antibiotics have demonstrated the capacity to stop the growth of cancer cells, trigger apoptosis and obstruct angiogenesis and metastasis two processes that are essential to the advancement of tumors. For repurposing attempts, antibiotics are especially appealing due to their well-established safety profiles and well-characterized pharmacology. Machine learning developments have strengthened this approach even more by providing cutting-edge instruments to find and verify repurposing candidates, such as antibiotics with underutilized or unique anti-tumor properties (Pushpakom *et al*., 2019).

Antibiotic use in cancer is still a very new and experimental area, despite its potential. As of the now, their anti-cancer qualities lack a generally recognized classification scheme. Antibiotics are generally categorized in modern medicine according to their manufacturing process, spectrum of antibacterial activity, or mechanism of action. Antibiotics are among the most interesting possibilities for repurposing because of their surprising but noteworthy anti-cancer potential in experimental settings (Kapoor *et al*., 2017). In addition to their conventional use in treating infections, a number of antibiotics have demonstrated the capacity to stop the growth of cancer cells and obstruct processes that are essential to the spread of tumors, such metastasis. For repurposing attempts, antibiotics are especially appealing due to their well-established safety profiles and well-characterized pharmacology (Pushpakom *et al*., 2019) .

Three lung cancer cell lines have been demonstrated to have their proliferation suppressed by the cephalosporin drug ceftriaxone. These results have been confirmed *invivo* in murine models, which adds credence to its anti-cancer potential (Li *et al*., 2012). By upregulating the oxidative stress response gene HMOX1, a number of cephalosporins, such as cefotaxime and ceftazidime, preferentially caused ferroptosis in naso-pharyngeal cancer cells either *in vivo* and *in vitro* (He *et al*., 2021).

Cell cycle arrest, angiogenesis and metastasis suppression and apoptosis induction are further hypothesized anti-cancer actions of cephalosporins. The downregulation of MUC1 and FZD (He *et al*., 2021) and the positive regulation of genes like DDIT3 and GADD45A corroborated these effects. Cefotaxime metal complexes exhibited potent, dose-dependent cytotoxicity against cells that cause liver cancer. Scientists ascribed this impact to the chemicals' antioxidant qualities, pointing to a possible dual function in hepatoprotection and cytotoxicity(Al-Thubaiti *et al*., 2022).

Because of their beta-lactam ring structure, beta-lactam antibiotics are among the oldest and most important types of antibacterial drugs. They work against both Gram-positive and Gram-negative bacteria by preventing the production of bacterial cell walls (Lima *et al*., 2020). By reducing cell proliferation and causing cell death, penicillin G has demonstrated significant anti-cancer effectiveness against leukemic and cervical cancer cell lines *in vitro*. It works by down regulating signal transducer and activator of transcription 5A (STAT5A) and matrix metalloproteinase (MMP)-11. MMPs are key proteins in the development of cancer, affecting angiogenesis, apoptosis and cell proliferation. They were first discovered to have a part in the breakdown of extracellular connective tissue.

Additionally, an apoptotic pathway may be involved, as evidenced by the increase of p53 expression after penicillin G therapy. The drug's potential for selective anti-cancer activity was highlighted by the dose-dependent cytotoxic effects, which showed that cancer cells were more sensitive than non-cancerous ones (Banerjee *et al*., 2013).

Metal ions like copper and zinc are essential to keep the human body healthy due to several biological functions especially when complexed with some antibiotics (El-Megharbel *et al*., 2025). Zinc (Zn) belongs to the transition metal element. Zn is an essential element due to its strong binding to proteins (Gupta, 2018). The importance of metals in conjugation with CF has been proved chemically in alleviating oxidative stress and providing high hepatic protection and as approved by the previous study of (El-Megharbel *et al*., 2022) who confirmed that CF metal complexes, especially (CF/Zn CF/Mg and CF/Se), ameliorated greatly the hepatic enzyme functions and enhanced the antioxidant activities with significant reduction in the reactive oxygen species as compared with ceftriaxone-treated groups alone. These previous results were promising in providing protection for against the severe oxidative stress induced by antibiotics.

Therefore, by reacting CF with (Zn^{+2}), the current work aims to synthesize a metal complex of antibiotic drug/Zn (CF/Zn) complex with investigating its new anticancer activities. The drug metal complex was investigated using electron microscopy and other spectroscopic techniques.

MATERIALS AND METHODS

Chemicals used

All used chemicals were pure (CF): Which is a sodium salt of ceftriaxone, $ZnCl_2$ were obtained from Sigma-Aldrich Company, USA.

Synthesis

(CF/Zn) complex was prepared by adding 1.0 mmol of $ZnCl_2$, in C_2H_5OH (30 ml solvent) with CF (1.0 mmol) in C_2H_5OH (30 mL) of. Then, make refluxing for about 5 hr till white

precipitate produced. Then cooling, filtration washing using with hot ethanol and finally drying as shown in Fig (1).

Instrumentations

All the instruments used and easurments performed as showin in the following (Table 1).

Anticancer activity

Cell culture

MCF-7, HepG-2 and H460 cell lines were freshly taken from Scientific Inc. The cells were maintained at around 37°C in DMEM media with fetal bovine serum, streptomycin and penicillin in an environment with 5% CO_2. The Gene Print 10 system (Promega corporation, Madison, WI, USA) was used to validate the cell lines by STR analysis (Algehani *et al*., 2021).

Cytotoxicity assay

The study used a cytotoxicity assay to assess the viability of MCF-7, HepG-2 and H460 cells. The cells were maintained in a DMEM medium containing (fetal bovine serum, streptomycin and penicillin). After 24 hours, the cells were treated with a CF/Zn metal drug complex. After 3 days, the cells were highly fixed by replacing the DMEM medium with 10% TCA and incubated for 1 hr at 4°C. The cells were washed 5 times with distilled H_2O, added SRB solution and incubated at 37°C in the dark for 10 minutes. The well plates were washed 3 times with TCA and air-dried. The protein-bound SRB stain was then dissolved with 150 µL of TRIS. The absorbance was measured at 540 nm using a "BMGLABTECH®-FLUOstar" Omega (microplate reader) (Gholamhoseinian *et al*., 2009).

RESULTS AND DISCUSSION

Chemical characterization of CF/Zn

$ZnCl_2$ with CF at equal molar ratios resulted in a white CF/Zn combination. The non-electrolytic nature of the CF/Zn new formula complex, which has the general formula $[Zn(CFE)(H_2O)_2]$ $2H_2O$, is demonstrated by (C, N and H) analyses of data and molar conductance (Λm = 22 Ω^{-1}. cm^2. mol^{-1}). The resulting complex is soluble in DMSO but insoluble in the majority of organic and inorganic solvents.

One crucial method for determining the type of crystallinity in metal complexes is XRD examination. The Zn (II) combination exhibits clear amorphous structure with a nano range structure, as seen by the X-ray diffraction patterns obtained at a range of 2θ = 10-70° (Table 2). Using full width at half maximum, which has ranged between 70 to 80 nm, the size of the particle was determined[16] based on the Scherrer relationship.

One essential method for characterizing the complexity of metal with drugs is thermal analysis. The high successful chelation of CF with Zn metal is confirmed by TGA (Fig 2). The CF/Zn complex was subjected to thermogravimetric (TGA) and its differential (DTG) examination in a N_2 environment at temperatures ranging from 30 to 800°C. Crystalline water molecules were lost during the first endothermic step of breakdown, which took place at temperatures between 30 and 120°C. Due to the loss of coordinated water, the 2nd cracking stage was conducted between 140 and 220°C. The 3rd step of breakdown, which was associated with the loss of the CF ligand, took place at temperatures between 390 and 550°C. ZnO is the last leftover product.

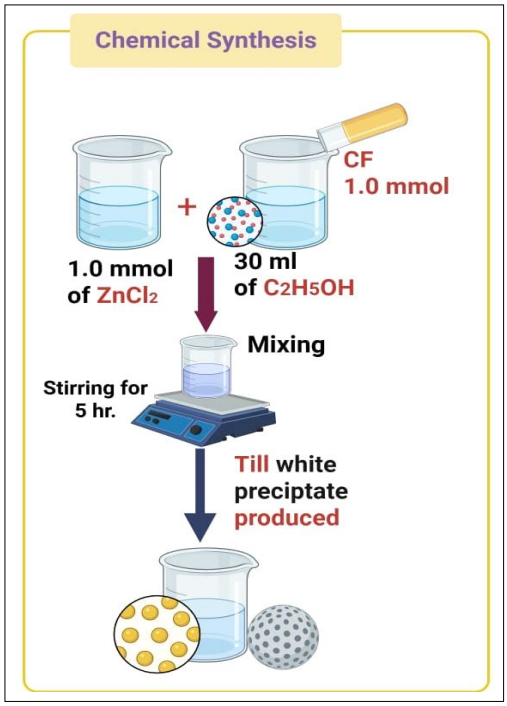


Fig 1: Synthesis of CF/Zn complex.

Table 1: Instruments used in the experiment.

Instrument	Measurements
Shimadzu, DTG-60 series	This instrument varies the sample temperature in accordance with a program and simultaneously measures the change in mass of the sample (TGA) and the temperature difference between the sample and a standard substance (DTG).
X 'Pert PRO PAN analytical X-ray powder diffraction.	The XRD
Quanta "FEG" "250 equipment"	The images of (SEM)
JEOL 100s microscopy which is a high-performance transmission electron microscope (TEM), designed for detailed analysis of microscopic samples.	The images of (TEM)

TEM and SEM analysis are an important techniques to study the surface morphology for metal complexes. Images of TEM of CF (Fig 3A) and it's complex [Zn (CFE)$(H_2O)_2$]. $2H_2O$ as shown in (Fig 3B) which confirmed the complete formation of spherical black spots with nanorange, which is in agreement with XRD data. SEM images show a uniform homogeneity of CF (Fig 3C). Images of SEM for CF/Zn show the homogeneous and aggregation uniform. TEM images for CF/Zn complexity is shown in (Fig 3D). From EDX spectrum analysis it confirms the main composition elements of the complex (Fig 4). and refer to spherical black spots formation with nanoparticles in the rang 70-80 nm which agreement with XRD data.

Table 2: Data for XRD of [Zn (CFE) $(H_2O)_2]\cdot 2H_2O$.

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
23.8001	85.03	0.2047	3.73559	100

H460, HepG-2 and MCF-7 anticancer activity

Using three cancer cell lines (MCF-7: Breast adenocarcinoma; Hepatocellular carcinoma: HepG-2; and H460: Large cell lung carcinoma), this study examined the anticancer efficacy of the CF/Zn metal combination as a strong anticancer agent. Against the three cancer strains, the

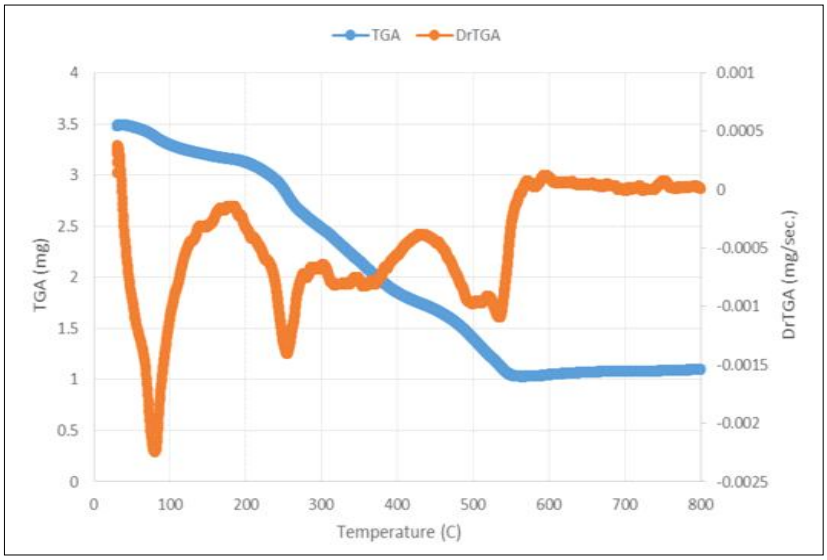


Fig 2: TGA/DTG of CF/Zn complex.

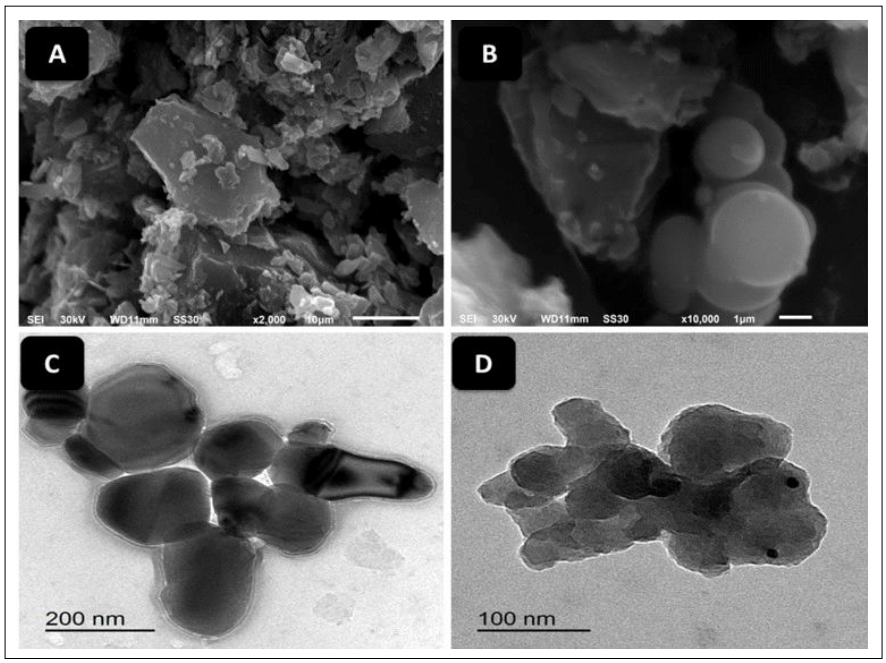


Fig 3: SEM (A: CF , B:CF/Zn) ; TEM (C:CF, D:CF/Zn).

produced CF/Zn combination demonstrated strong anticancer properties. Antibiotic metal complex's novel anticancer uses have drawn a lot of interest because of its anticipated ability to combat different kinds of cancer cells. The three cancer strains (MCF-7, HepG-2 and H460) have been tested against the CF metal combination with zinc. In the current study, the cytotoxic effects of CF/Zn showed cytotoxicity against MCF-7, HepG-2 and H460 cells at concentrations of 10 µg/ml, with living percentages of 95.44, 90.6 and 94.04 µg/ml, respectively. They also inhibited the proliferation of the cancer cells at concentrations of 100 µg/ml, with living percentages of 90.35, 80.25 and 84.26 µg/ml and inhibited the proliferation of the cancer cells at conc. 100 ug/ml, with living percentages of 85.35, 80.25 and 80.23 µg/ml. Increasing the concentrations of the tested complex also improved this. The growth inhibition of all cellular carcinoma and the decrease in the cell viability in the carcinoma cells treated with CF/Zn was showed higher at 100 ug/ml conc. than recorded at 10 ug/ml conc. as shown in (Fig 5).

Millions of people die from cancer every year, making it one of the most significant worldwide health issues (Karamanolis *et al*., 2025). Lung, liver and breast cancers continue to be the most common kinds of cancer (Global Cancer Observatory, 2024; Mattiuzzi and Lippi, 2019).

Accordingly, CF, a cephalosporin category of antibiotics, has been currently demonstrated to inhibit the cellular growth of 3 lung cancer lines this may be explained by

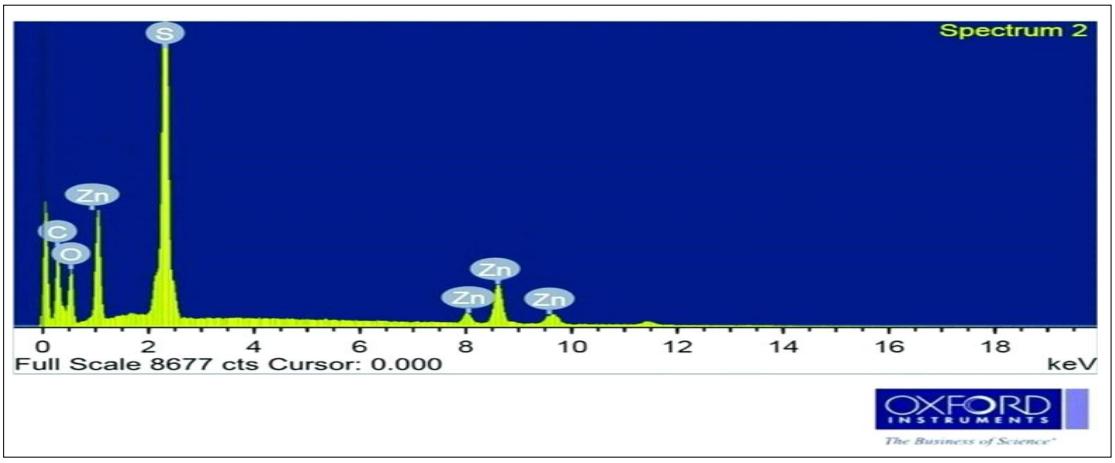


Fig 4: EDX of CF/Zn complex.

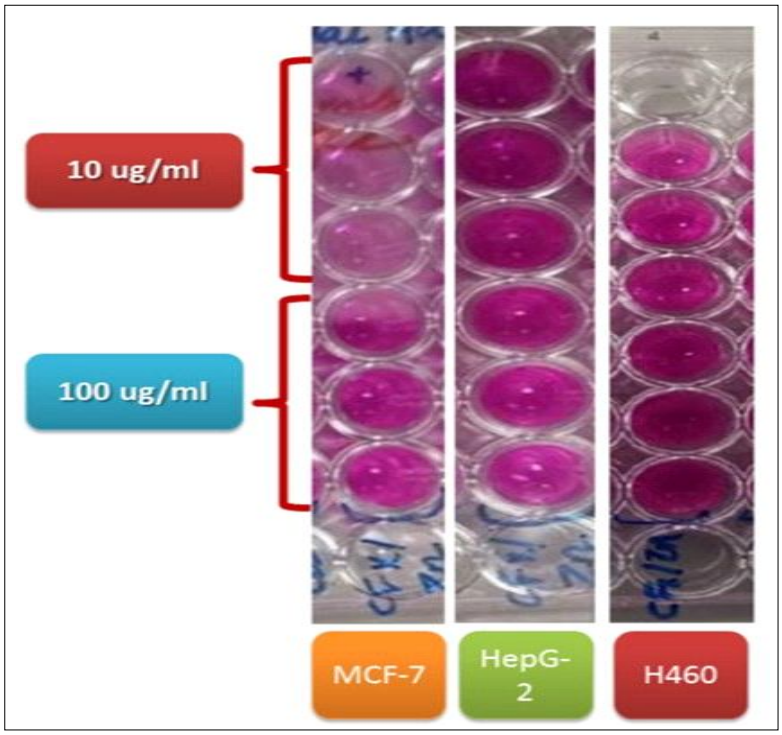


Fig 5: Anticancer activity of CF/Zn complex against MCF-7, HepG-2 and H460.

inhibiting Aurora B kinase, the essential protein that is vital during mitosis and controls cell division. The current study demonstrated the effectiveness of the synthesized complex (CF/Zn) against three lines of cancer cells (MCF-7, HepG-2 and H460) at both low concentrations (10 µg/ml and 100 µg/ml). These new findings have been validated in some models *in vivo*, additionally confirming its anti-cancer potential (Li *et al*., 2012) and this may explain the success of the complex CF/Zn in inhibition of three lines of cancer cells either hepatic, breast and lung cancers.

Additionally, prior research supports the current conclusion. (Al-thubaiti *et al*., 2022) revealed that cefotaxime metal complexes exhibited potent, dose-dependent cytotoxicity against liver cancer cells. They suggested a possible dual involvement in cytotoxicity and hepatoprotection (Al-thubaiti *et al*., 2022) and attributed this impact to the chemicals' new antioxidant capacities provided due to this metal chelation with the antibiotic drug.

Although antibiotics have great potential to cure cancer, there are a number of issues and debates around their use. They have been described as a "double-edged sword" (Yip and Papa, 2021) because the advantages must be balanced against the hazards, which include disturbance of the microbial resistance and interaction with some other cancer therapy. Antibiotics are also linked to additional negative consequences, such as harm to the reproductive systems of both sexes and the rise of bacteria species resistant to them. These side effects severely restrict their therapeutic uses, even though they have nothing to do with their ability to prevent cancer (Gao *et al*., 2020; Borovskaya and Gol'dberg, 2000) .

Reducing the toxicity of antibiotics is crucial to maintaining their effectiveness, regardless of whether they are used to treat cancer or germs. This can be accomplished through a variety of therapeutic approaches, including the combination of biocides or synergistic antibiotics, as well as the current use of the active compounds, essential active oils and some small molecules that directly combat pathogens, both synthetic and natural (Murugaiyan *et al*., 2022; Sakari *et al*., 2022) such as those employed in the current investigation by chelating the antibiotic medication CF with zinc metal. In addition to developing new anticancer actions, novel ways are improving antibiotics' antibacterial potency. These include medications that target exotoxins, bacterial genome editing and the use of clustered regularly associated protein (CRISPR-Cas) to eliminate microbial resistance genes. Bezlotoxumab, a monoclonal antibody that targets Clostridium difficile's toxin B, is a noteworthy example. However, additional research is still needed to determine how beneficial these treatments are in treating cancer (Murugaiyan *et al*., 2022; Sakari *et al*., 2022).

The gut microbiota is essential for preserving physiological homeostasis, which includes immune system modulation and food metabolism. The current study's novel therapeutic approach, which involves chelating the antibiotic CF and zinc metal, may have a vital clinical role, particularly with regard to the gut mucrobiota and reduce the negative effects of antibiotics on the gut microbiota while enhancing the strong anticancer activities that were revealed in the current findings. Dysbiosis, or disruption of the gut microbiota, has been linked to a number of diseases, including inflammatory and neoplastic conditions (Rinninella *et al*., 2019; Sommer *et al*., 2017).

As a result, it has been established that the use of antibiotics significantly contributes to gut dysbiosis and that there is evidence linking this to the development of cancer (Dahiya and Nigam, 2023). According to a UK nested case-control research, exposure to penicillin more than ten years ago was linked with a marginally higher risk of developing this type of cancer, after repeated doses. These results have been confirmed by other research. For example, the Finnish cancer registries showed a high link between higher antibiotics usage and increasing most rates of most of the solid tumors including both lung and breast cancer types, whereas diabetic individuals treated with anti-anaerobic antibiotics showed an increased risk of cancer. However, these investigations have intrinsic limitations due to their retrospective characters (Boursi *et al*., 2015; Wang *et al*., 2014). All these findings greatly supported the current findings that proved the anticancer activities of the CF/Zn complex on breast, liver and lung cancer cells.

Additionally, a meta-analysis of (Boursi *et al*., 2015) observational studies with a combined patient population of almost 8 million found that antibiotic usage was associated with a moderate increment in the risk of cancer overall. Prolonged antibiotic exposure further exacerbated this link, which was especially strong in hematological, lung, pancreatic and genitourinary cancers (Petrelli *et al*., 2019). On the other hand, although confounding variables including smoking and chronic obstructive pulmonary disease make interpretations more difficult, previous antibiotic usage has been marginally linked to the development of lung cancer in prospective studies (Zhang *et al*., 2008).

Antibiotic usage during the therapy was linked to worse overall progression-free survival, according to the meta-analysis of patients treated from cancer, suggesting that antibiotics also appear to diminish the effectiveness of cancer treatment (Huang *et al*., 2019) and this significantly improved the concept of the current investigation, which discovered that chelating zinc with CF significantly increased the antibiotics' anticancer potency and, hence, reduced their severe side effects.

Notably, a characteristic of antibiotic innovation, modified β-lactams have a variety of anti-cancer actions. *In vitro* (Kuhn, 2004; Svensson *et al*., 1995), cephalosporins reduce toxicity and show similar efficacy to stand-alone therapies when used as prodrugs in conjunction with chemotherapeutics such as doxorubicin and nitrogen mustards. Furthermore, some antibiotics-based on the β-lactam have shown dual activity against concurrent infections, cancer cell lines, possibly treating infection and cancer (Yildirim *et al*., 2022; AlZahrani *et al*., 2025), the

results of the current work, which verified the anticancer effectiveness of the manufactured formula CF/Zn against three cancer cell lines (MCF-7, HepG-2 and H460), significantly approved all of these findings.

CONCLUSION

Utilizing spectroscopic analysis methods such as Thermal analysis, XRD, EDX, SEM and TEM for characterization of the complex CF/Zn was investigated to confirm its purity and small size range. For the CF/Zn complex induced high anticancer activity. The synthesized complex CF/Zn showed high anticancer capacities against the three cell lines at conc. 10 ug/ml and the living percentages were: 95.44, 90.6 and 94.04 µg/ml respectively and inhibited the proliferation of the cancer cells at conc.100 µg/ml and the living percentages were 90.35, 80.25 and 84.26 µg/ml. In conclusion, Exposure to CF/Zn complex even at very low concentrations elevated anticancer capacities of CF against three dangerous and common cancer cells. Thus, it is recommended that prospective studies could investigate the *invivo* effect of CF/Zn on experimental animals to explore more biological capacities of the synthesized complex.

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Conflict of interest

The author would like to confirm that there is no known conflict of interest associated with this publication.

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