RESEARCH ARTICLE Indian Journal of Animal Research, Volume 60 Issue 5: 816-823 (May 2026)

Antioxidant Activity of Cefotaxime with Mg (II) Metal Ion and Novel Evaluation of its Anticancer Capacity against PANC-1 with Chemical and Spectroscopic Characterization

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10.18805/IJAR.BF-2074

ABSTRACT

Background: Cefotaxime (CF), a semisynthetic cephalosporin, exhibits a broad antibacterial spectrum. The World Health Organization identifies antimicrobial resistance as a significant threat, necessitating the development of new antibiotics with diverse metal chelation mechanisms to mitigate side effects. Pancreatic cancer, a leading cause of cancer mortality, may be linked to magnesium (Mg), which could lower incidence risk due to its inverse relationship with type II diabetes mellitus, a pancreatic cancer risk factor. Recent studies on metallic complexes present promising therapeutic agents against various diseases.

Methods: Cefotaxime magnesium (CF/Mg) complex was characterized using C,H, N and S elemental analysis, conductivity value, IR, UV, XRD, SEM and TEM “Scanning and transmission electron microscope”, this paper explain the effect of CF and CF/Mg on oxidative stress by many antioxidant assays such as “ABTS, DPPH and metal chelation” assay and inhibition of viability of cancer cells (PANC-1).

Result: The lower value of conductivity refers to that complex is non-electrolyte. The FT-IR for CF/Mg proved that antibiotic cefotaxime compound act as monoanionic tridentate ligand. In conclusion, CF/Mg complex exhibited high antioxidant activities. CF/Mg novel inhibited PANC-1 cellular viability. Thus, CF/Mg triggered promising results and acting as a potent agent with antioxidant capacities, with anticancer activity against the PANC-1 at suitable concentration.

Key words: Antioxidant, Cefotaxime, Magnesium, Metal complex, Pancreatic cancer cells.

INTRODUCTION

Antibiotics are considered as important environmental pollutants because of their excessive use in the human therapies, including the aquaculture (Pang *et al*., 2024). Presence of the antibiotics in the ecosystem naturally has a large effect on all the living organisms. The previous studies have confirmed that a lot of antibiotics can provoke harmful reactive oxygen species and also induced the excessive oxidative injury (Dwyer *et al*., 2014).

Antibiotics-induced oxidative injury and their toxic effects have been notified in animals and plants, leading to the inhibition of their growth and reproduction, tissue, physiological and biochemical alterations (Zhang *et al*., 2019; Liang *et al*., 2020; Jin *et al*., 2022; Huang *et al*., 2023). Low-levels of the antibiotic exposure could alter the general environmental composition significantly for the microbial communities (Quinlan *et al*., 2011). Additionally, Antibiotic pollution caused by altered microbial community could affect the bacterial enzyme activities and then leading to an increment in the parasites and pathogens (Kraemer *et al*., 2019).

Cefotaxime (CF), a new semisynthetic cephalosporin derivative that are major antimicrobials used to treat serious infections (Himani *et al*., 2025), showed a broad spectrum of antibacterial activity against clinically isolated strains of gram (+ve and -ve) bacteria. CF was the most active compound against members of the Enterobacteriaceae (Ennis and Glenn, 1995).

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How to cite this article: Albaqami, J.J. (2026). Antioxidant Activity of Cefotaxime with Mg (II) Metal Ion and Novel Evaluation of its Anticancer Capacity against PANC-1 with Chemical and Spectroscopic Characterization. *Indian Journal of Animal Research.* **60(5):** 816-823. doi: 10.18805/IJAR.BF-2074.

Submitted: 29-09-2025 **Accepted:** 30-01-2026 **Online:** 01-04-2026

Cephalosporin (CEPH) categories belongs to the 3rd-generation, are used essentially for the treatment of the bacterial diseases, for example, the respiratory system inflammation and infections in animals (Ribeiro *et al*., 2018). CF is the most common CEPH especially in the water environment (Ribeiro *et al*., 2018).

In the USA, pancreatic cancer ranks as the 4th most common cause of cancer-related mortality for both men and women (Strimpakos *et al*., 2010; Klein, 2012). The death rate of this type of cancer elevated by an average of 0.4% each year (National Cancer Institute, 2014).

Antimicrobial resistance has been identified as one of the great threats according to the “World Health Organization” (WHO). Thus, it is essential to develop new antibiotics with different modes of action. Thus, the metallic

complexes are very promising agents against the different types of diseases (Jastaniah *et al*., 2025).

It is hypothesized that taking of Mg may reduce the risk of incidence of the pancreatic cancer because previous studies indicate that it is associated inversely with type-II diabetes mellitus, a risk factor for pancreatic cancer (Ben *et al*., 2011; Li *et al*., 2011).

According to two case-control studies, pancreatic cancer was negatively correlated with Mg consumption (Jansen *et al*., 2013). However, no correlation was discovered in a previous study (Manousos *et al*., 1981). Studies demonstrated that Mg is correlated inversely with the risk of incidence of different types of diabetes mellitus, this is of a high risk factor of incidence of "PANC-1" cancer type "Pancreatic cancer". Meanwhile, previous studies confirmed the direct correlation between metal ions like "Mg" and the pancreatic cancer are very rare till now (Dibaba *et al*., 2015).

Thus, the essential aim of the current study was to assess both the antioxidant and anticancer activities for CF/Mg prepared complex and assessment of it's chemical characterization beside it's biological activity.

MATERIALS AND METHODS

All used chemicals purchased from Sigma were of reagent grade and used without further purification. Complex [Mg (CF) Cl]. H_2O was prepared by dissolving of 2 mmol CF in ~ 20 ml EtOH -and 1 mmol magnesium chloride dissolved in 15 ml EtOH. Reaction mixture was stirred at room temperature for ~ 5 h. The precipitate was filtered and finally dried (Al-Thubaiti *et al*., 2022).

Experiment of the chemical characterization

IR spectra measured as KBr disks using spectrophotometer infrared Bruker. Electronics spectra were examined using DMSO solvent. Elemental analysis of carbon, hydrogen, nitrogen and sulphur were measured using a Perkin Elmer CHN 2400 instrument. Conductivity measured using HACH conductivity meter. SEM captures were taken in Joel JSM-6390. XRD were recorded on "X-ray" powder diffraction. TEM images were performed using JEOL 100s microscopy.

Assessment of the antioxidant capacity

Assay of ABTS

Antioxidant assay of CF and its (Mg) metal ion complex was carried out according to Arnao *et al*. (2001). 192 mg of ABTS reagent were dissolved in distilled H_2O. About "1 mL" of the previously prepared solutions were added to 17 µL of $K_2S_2O_8$ (140 mM) and, then it was left in the dark for 24 hrs. 1 mL of this mixture was then immediately made up to 50 mL, with MeOH to obtain the final ABTS prepared solution, this reaction was then incubated at 37°C for 1/2 hr in the dark. The decline in ABTS color absorbance was measured at 734 nm.

DPPH assay

The antioxidant activity of cefotaxime and its metal complex with (Mg) was measured by using DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) free radical's assay (Boly *et al*., 2016). 100 µL of the recently freshly prepared DPPH reagent, then all were added to 100 µL of CF and its metal ion complex (Mg). The reactions were then incubated for 1/2 hr at 37°C in the dark. The resulting reduction in DPPH colour intensity was measures at 540 nm.

Metal chelation assay

Metal chelation assay was carried out according to Santos *et al*. (2017). A 20 µL of freshly prepared $FeSO_4$ was mixed with 50 µL of CF and its metal complex in the sterilized wells plate. Then, addition of 30 µL of ferrozine. Afterwards, the plates were incubated at 37°C for 10 minutes. After incubation, the decline in the colorimetric intensity was immediately measured at ~ 562 nm (Santos *et al*., 2017).

Cell culture

PANC-1 was freshly obtained from Scientific Inc. The cells were promptly maintained in the suitable ″DMEM″ supplemented with 100 mg/mL streptomycin, 100 units mL^{-1} penicillin and 10% fetal bovine serum in a humidified, 5% carbon dioxide ″CO_2″ atmosphere at the optimum temperature ~″37°C″. The cells of "PANC-1" were authenticated by STR method analysis (Promega, Madison, WI, USA) (Algehani *et al*., 2021).

The assay of cytotoxicity

PANC-1 cells which were immediately preserved in the suitable medium called :"DMEM" which were supplemented with streptomycin, 100 units mL^{-1} of penicillin and 10% of heated fetal bovine serum, 5% CO_2 atmosphere at 37°C. 100 µL of cell suspension (5×10^3 cells) were seeded and incubated for ~ 24 hr_s. The pancreatic cells were then immediatley treated with 100 µL of "DMEM" medium containing CF/Mg at differnt concentrations. After 72 hr_s , the cells were immediately fixed with TCA "150 µL" and then immediately incubated for 1 hr at 4°C. The PANC-1 cells were then washed for at least for 5 times withdistilled.H_2O. 70 µL SRB solution was added and incubated at 25°C for 10 min. The plates were then washed time with 1% acetic acid. Then 150 µL of TRIS was immediately added to dissolve the bounded stain of "SRB". The absorbance was measured at 540 nm via using the plate reader "Omega" (Germany) (Abdel-Hameed *et al*., 2012).

RESULTS AND DISCUSSION

The analyses of C, H, N and S are convenient with the stoichiometry of Mg^{+2}: CFX is in molar ratio (1:1) (Mg:CFX). Molar conductivity value (19 $\Omega^{-1}cm^2\,mol^{-1}$) that convenient within the range of the non-electrolytic characters (Geary, 1971) proposing that chloride ion is inside the chelation sphere.

Infrared spectra

IR for CF and CF/Mg are shown in (Fig 1) are similar in the range of 3400-2600 cm^{-1} due to vibrational stretching of (O-H), (N-H) and (C-H) aromatic (Al-Thubaiti *et al*., 2022). The IR spectrum of cefotaxime has a band appears at

1775 cm^{-1} characterized to lactam (carbonyl group C=O), while the amide and ester (C=O) bands are appeared and then interfered at "1642 cm^{-1}"; while magnesium complexity the range of bands at of 1700-1652 cm^{-1} appeared so CF coordinated *via* the "O" atom of (C=O) lactam group other than (C=O), amide and then ester groups due to the bands of (C=O) lactam group, which were then shifted towards less frequencies (15-40 cm^{-1}). The bands ranged between 664-553 cm^{-1} for CF complexity are assigned to ν (M-O), that are not monitored in the spectra of CF alone.

New bands that appeared for Mg/CF complexity at 490-521 cm^{-1} might assigned to υ (M-N) (from NH_2 group) that are not present in CF suggesting that CF chelated as a chelating agent with tridentate with characters as monoanionic (Nakamoto, 1986). Based on the obtained data, CF chelates with metal ions as a tridentate *via* the β-lactam carbonyl group, carboxylate and amino groups.

The UV-Vis spectra

The "uv-vis" spectra for both CF and CF/Mg complex is presented in Table (1). Cefotaxime has three absorption maxima at 274 nm which is assigned to $\pi \rightarrow \pi^*$, 325 nm due to intraligand of $\pi \rightarrow \pi^*$ transitions with heterocyclic moiety (Franchini *et al*., 1985; Hadjikostas *et al*., 1987). Band at 355 nm is due to intraligand transition of sulphur atoms of $n \rightarrow \pi^*$. The band due to S atoms is not shifted suggesting that S atom is not chelated with CF. The magnesium (II) show weak bands at 280,320 and 385 nm may be assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions.

XRD, SEM and TEM analysis

X-ray diffraction analysis confirm the structure of CF/Mg complex Fig 2. Diffractograms XRD confirmed that CF/Mg has formulating (Amorphous) structure.

The CF/Mg complex was characterized by the X-ray diffraction at 25°C using the Cu Kα radiation. The diffraction characterization of the prepared CF/Mg complex was in between 10° to 80°. The semi crystalline nature of CF/Mg determined by using "Scherrer formula" (Cullity, 1972). The complex semi crystalline size was calculated and has the value of 24 nm.

The image of SEM gives an explanation for the morphological surface of Mg (II) CF that is shown in Fig 3. The image was scanned for Mg (II) using SEM, which made a full check for the morphological phase. (A) CF: The image of SEM shows homogeneity in size with one-piece plate. Meanwhile, (B) CF/MG: showing aggregation shape and size with many grooves and protruded circular formations due to chelation between CF and Mg metal ions.

TEM images for CF and CF/Mg compound Fig 4. (C): CF, which clarifies that CF complexity has a homogeneity in phase material. (D) CF/Mg: Spherical black spots like shapes are shown in magnesium cefotaxime chelates with a particle size range of 16-24 nm.

Antioxidant capacities of CF and it's Mg metal complex

The estimated percentages obtained of the chelating activity *via* using 3 different assays are shown in Table 2. Metal chelation, the assay of ABTS and the assay of DPPH were used. The capacity of the CF and CF/Mg complex to scavenge the free radicals of ABTS was 300.51-fold, which is more than CF itself. Meanwhile, the metal chelating activity of CF/Mg was higher than CF itself by 13.06% (μM EDTA eq/mg), respectively.

On the other hand, the scavenging ability of CF/Mg was also the highest by measuring the stability of the DPPH radical at 30.12% (μM trolox eq/mg). Thus, this metal complex has a greater chelating capacity than CF itself (Table 2).

Anticancer activity against PANC-1

The applications of treatment using the metal drug complex in the biomedical fields have been approved for the treatment of a lot of cancer types. The CF/Mg metal ion complex has been assessed against pancreatic cancer (PANC-1). In the current study, the cytotoxicity of CF/Mg was

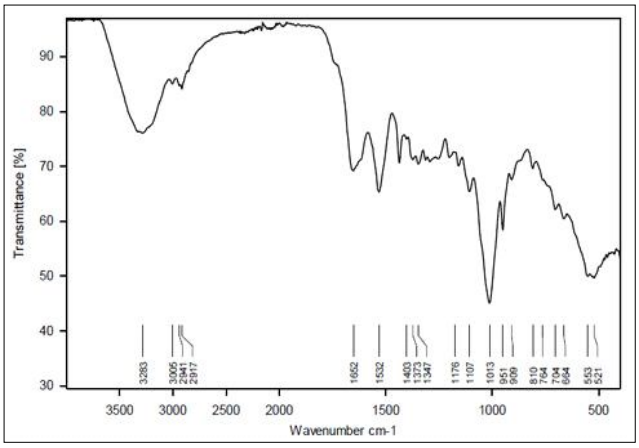

Fig 1: FT-IR of CF/Mg metal formula complex.

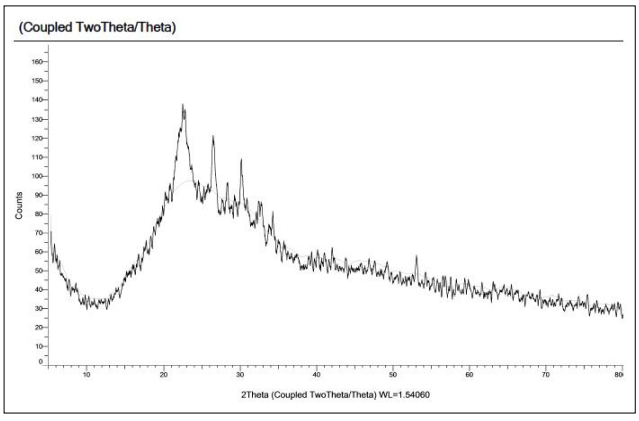

Fig 2: XRD of CF/Mg complex.

Table 1: Uv-Vs data of CF and CF/Mg complex.

Compound	$\pi \rightarrow \pi^*$	$n \rightarrow \pi^*$
CF	274,325	355
CF/Mg(II)	280,320	385

tested on PANC-1 (pancreatic ductal adenocarcinoma cells, which are a type of pancreatic cancer). It is an epithelioid, highly characterized cell line derived from a human pancreatic carcinoma that showed that the biosynthesized CF/Mg reported the measuring of the cytotoxicity against the PANC-1 cancer cells. This was also greatly reinforced by the increment of the concentration of the "CF/Mg" metal complex. The inhibition of pancreatic cancer cell growth and decrease in the cellular viability that appeared in PANC-1 cells treated with the metal complex "CF/Mg" was recorded at the following concentrations: 10 and 100 ug/ml as follows: 90.87 and 77.58 µg/ml, respectively, causing this loss in PANC-1 cellular growth and viability, as shown in Table 3.

CF is an antibiotic drug used to treat several of the bacterial infections in humans, animals and plant tissue culture. It is used in the humans to treat the joint infections, pelvic inflammation, urinary tract infections, meningitis, pneumonia and sepsis *via* I.V or I.P injection (The American Society of Health-System Pharmacists, 2016).

CF was firstly discovered in 1976 and it was in the commercial use in 1980 (Hamilton, 2015; Newbould, 2012). It is a broad-spectrum antibiotic with activity against numerous gram (+ve and -ve) bacteria with resistance to β-lactams such as penicillin (Al-Thubaiti *et al*., 2022).

Metals have an essential and vital key role in the actions of different metallo-antibiotics, as they are essentially involved in their interactions with specific proteins, cellular membranes and other biological molecules (Fischer and Ganellin, 2006).

CF interacts with metal ion (Mg) to give CF/Mg metal complex which was characterized by spectroscopic methods is suggested for its structure. CF behaves as monoanionic

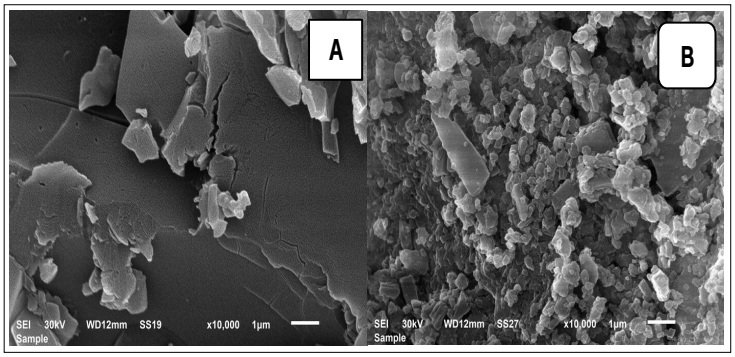

Fig 3: SEM of A: CF, B: CF/Mg.

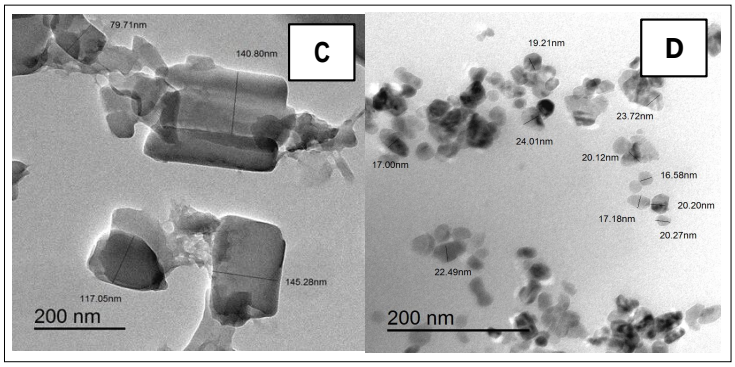

Fig 4: TEM of C: CF, D: CF/Mg.

Table 2: Antioxidant activity of CF and its metal complex (CF/Mg).

Test name	Metal chelation		ABTS		DPPH	
Name of the sample	(µM EDTA eq/mg)		(µM trolox eq/mg)		(µM trolox eq/mg)	
	Mean	SD	Mean	SD	Mean	SD
CF	2.77	0.44	280.15	11.17	18.00	0.37
CF/Mg	13.06	0.16	300.51	2.43	30.12	2.45

Trolox eq: "Equivalent to the trolox" Meanwhile, SD: "Standard deviation".

Table 3: Anticancer activity of CF/Mg (Cefotaxime/Mg) complex formula.

Viability %	PANC-1 (Pancreatic cancer)	
	CF/Mg (µg/ml)	
	Mean	SD
10 ug/ml	90.87	2.78
100 ug/ml	77.58	15.10

tridentate ligand. The complex has been screened for anticancer and antioxidant capacities against pancreatic cancer cell lines (PANC-1) and *via* testing the antioxidant activities by ABTS, metal chelation and DPPH tests.

The essential coordination of CF *via* the NH_2-thiazole, β-lactam (C=O) group and carboxylate; thus it may behave as tridentate ligands (Masoud *et al*., 2015). CF was coordinated via not only "O" atoms of β-lactam group "C=O" and group of amide but also via the N-atom of thiazole ring, thus it may act as tridentate ligand as proved in the current study (Alekseev *et al*., 2013).

Regarding the multi bacterial resistance, the recent discovery of the novel antibiotics is of a great effect. Many bacterial types, release β-lactamase enzyme in huge amounts, thus they have the ability to breakdown the β-lactam ring (Hamza *et al*., 2022; Anacona and Estacio, 2006).

The oxidative injury to the biomolecules is of an essential importance in highly risk diseases such as cancer and serious diseases and pandemic. Thus, it is an essential need to investigate the key and vital role of the metal drug complexes to diminish the severe oxidative damage.

The current results confirmed that the novel antioxidant activity of CF/Mg complex by investigating it's antioxidant capacities; this increased the efficacy of CF, as it acquire two capacities as antioxidant and anticancer agent also. Thus, synthesizing a novel CF/Mg is helping to alleviate the oxidative damage in a lot of infectious and cancer diseases.

DPPH and metal chelation assays are used to predict with the antioxidants that may act to scavenge the DPPH free radicals and capture the metals, therefore, evaluate the free-radical scavenging capacities (El-Megharbel and Hamza, 2022). The current results afforded that CF complex with Mg, scavenged significantly DPPH free radicals, thus CF/Mg complex had higher antioxidant activity.

A previous report confirmed that ABTS is vital for the antioxidant capacities, that evaluates the capacities of the synthetic antioxidant to eliminate the free radicals produced by ABTS which are generated in the liquid phase, compared with a Trolox (water-soluble vitamin E analogue) (El-Megharbel and Hamza, 2022); the current results proved that the CF/Mg complex exhibited strong antioxidant capacity.

Mg is essential to have several antioxidant mechanisms of preventing incidence of the pancreatic cancer. The recent evidences indicate that "Mg" deficiency is one of the risk factors for causing the case of insulin resistance and consequently incidence of the type-II diabetes mellitus (Wang *et al*., 2013). Previous trials proved that "Mg" supplementation enhances greatly the cellular sensitivity to insulin hormone (Guerrero-Romero and Rodriguez-Moran, 2011).

Some of the pancreatic cancer cells such as: PANC-1 and MIA- PaCa-2 tumors have a lot of IGF-1 receptors (Fisher *et al*., 1996). Previous study indicated that mice with deficient "IGF-1", with burden of pancreatic tumor cells "JC101" was markedly declined (Lashinger *et al*., 2011). In experimental models of "Mg" deficient, a high level of insulin secretion may have a deleterious effect on the pancreatic exocrine part in patients with type-II diabetes mellitus, leading to the mutation of tumors (Jansen *et al*., 2012).

Previous studies have shown that the PANC-1 cells with their main insulin receptors which have a high affinity for the hormone of insulin (Fisher *et al*., 1996). Previous studies also indicated that insulin hormone promotes the pancreatic cancer's growth in hamster " H2T" (Fisher *et al*., 1998) and several other pancreatic cancer types including MIA-PaCa-2, PANC-1 and BxPC-3 (Ding *et al*., 2000). It was confirmed that there is great association of "Mg" ion deficiency and also PANC-1 might be *via* the type-II diabetes mellitus and also the insulin resistance.

Mg deficiency is essentially associated with the free radicals levels' that has the ability to induc DNA damage and incidence of various types of carcinogenesis. Previously, it was found that "Mg" acts as an antagonist against the carcinogenic chemicals as: Pb, Cd and Ni (Anastassopoulou *et al*., 2019).

The current study proved that the novel CF/Mg complex inhibited PANC-1 cells, this promising results are in a great accordance with the previous study of Al-Thubaiti *et al*. (2022) who synthesized 5 metal complexes of CF and chemically characterized the following complexes: Ca^{2+}, Cr^{+3}, Cu^{2+}, Zn^{2+} and Se^{4+} and their results proved that the CF metal ion complexes with either Zn or Se inhibited greatly the hepatic cancer cells viability in HepG-2 cells, meanwhile other complexes with chromium , copper and calcium which greatly elevated the antioxidant capacities with different antioxidant assays such as: DPPH, ORAC, ABTS, FARAB and metal chelation tests. As previously proved in the studies of El-Megharbel *et al*. (2022); AlZahrani *et al*. (2025) and Al-Thubaiti *et al*. (2025), which proved this new scientific concept of the potency of metal complexes as potent antioxidant, antibacterial and anticancer activities. The present study results are very promising, since the current study demonstrated the provision of strong protection of CF/Mg against the pancreatic cancer (PANC-1) and a decline in the severe oxidative injury that could generated by excessive use of the antibiotics.

CONCLUSION

This study aimed to prepare one CF metal complex by reaction of CF with (Mg^2) ions. The structures of the CF/Mg complex have been chemically characterized via molar conductance, microanalytical, FT-IR, UV, TEM, SEM and XRD analyses. The obtained results clarified that the CF/Mg complex significantly inhibited pancreatic carcinoma

viability in PANC-1 cells and reinforced the antioxidant capacities with ABTS, DPPH and metal chelation tests as compared to the CF drug alone. These results are very promising, especially due to the novelty of this metal complex in providing inhibition percentage against pancreatic carcinoma (PANC-1) and declining the severe oxidative stress induced by antibiotics.

ACKNOWLEDGEMENT

The author would like to acknowledge the Deanship of Graduate studies and Scientific Research, Taif University for funding this work.

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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