Original Article

Evaluation of Anticancer Activity of Sitagliptin against Hepatocellular Carcinoma: An *In Vitro* Study

Ruqaya A. Ameen, Ahsan F. Bairam, Haider F. Al-Zubaidy[1]

Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Kufa, Kufa, Iraq, [1]Department of Clinical Laboratory Sciences, Faculty of Pharmacy, University of Kufa, Kufa, Iraq

Abstract

Background: Hepatocellular carcinoma is a malignant liver tumor constituting greater than 90% of liver primary tumors. Most of chemotherapeutic drugs used nowadays are cytotoxic, which rise the necessity to find newer agents with anticancer activity and better safety profiles against normal cells. Sitagliptin, a dipeptidyl peptidase 4 inhibitor, has been shown to have antitumor properties through specific suppression of dipeptidyl-peptidase 4, a glycoprotein produced in many tissues that have been thought to promote metastasis and tumorigenesis. **Objectives:** This study aims to assess the anticancer activity of sitagliptin on liver cancer (HepG2) cell line. **Materials and Methods:** Five groups of cell lines were included in the study: Control group (untreated HepG2 cells), cisplatin-treated HepG2 group, sitagliptin-treated HepG2 group, cisplatin plus sitagliptin-treated group which received combination of different concentrations of cisplatin plus sitagliptin (250 µg/mL), and the fifth group treated with a combination of different concentrations of sitagliptin plus cisplatin (25 µg/mL). After exposure period, these groups were incubated for 48 h and then were used for performing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay for evaluating cells viability and cytotoxicity. Data were finally collected and analyzed statistically. **Results:** MTT assays findings indicated that sitagliptin significantly reduced the viability of HepG2 cells and it produced important cytotoxic effect against this cancer cells. Moreover, sitagliptin plus cisplatin combination showed significant reduction in HepG2 viability in addition to greater cytotoxicity for this cell-line in comparison with sitagliptin or cisplatin alone. **Conclusion:** Sitagliptin revealed anticancer properties against HepG2 cancer cell-line based on MTT assay, which would probably indicate its cytotoxic effect against this cell-line.

Keywords: Cell-line, cisplatin, HepG2, MTT assay, sitagliptin

Introduction

Hepatocellular carcinoma (HCC) is a malignant liver tumor accounting for greater than 90% of the liver primary tumors of the liver. HCC results in up to 85% of individuals with liver cirrhosis. Cytological features depend on the differentiation of hepatocytes from well-differentiated to poorly differentiated HCC.[1] HCC is the seventh most common cancer globally and second leading cause of death due to cancer. Indeed, it accounts for approximately 75% of all instances of liver cancer worldwide.[2] In Iraq in 2020, the estimated incidence rate was 713, and the number of new deaths was 686.[3]

The primary treatment modalities of HCC are surgery, ablation, trans-arterial chemoembolization, and chemotherapies including cisplatin. A recent study showed that treatment of hepatoma cells with cisplatin for 24 and 48 h resulted in a dose-related decrease in cell viability as measured by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay in Hep3B, Huh7, and HepG2.[4]

Cisplatin uptake in yeast and humans is mediated by the copper transporter copper transporter-1.[5] When cisplatin enters a cell, it becomes active. In order to induce cell death by apoptosis, cisplatin interacts with DNA in

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_830_23

Address for correspondence: Dr. Ahsan F. Bairam, Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Kufa, Kufa 540011, Iraq.
E-mail: ahsanf.bairam@uokufa.edu.iq

Submission: 24-Jun-2023 **Accepted:** 17-Jul-2023 **Published:** 30-Apr-2026

How to cite this article: Ameen RA, Bairam AF, Al-Zubaidy HF. Evaluation of anticancer activity of sitagliptin against hepatocellular carcinoma: An *in vitro* study. Med J Babylon 2026;23:126-31.

the cell nucleus. When it comes into contact with DNA, especially guanine (G) and adenine (A), it forms adducts that significantly disrupt the molecule's double helix shape, degrade DNA in tumor cells, preventing proliferation and leading to apoptotic cellular death.[6]

Cisplatin is a cytotoxic drug that is not specific only to cancer cells but also affects normal cells; hence it may be harmful to the normal cells in the body and has several warnings, including gastrointestinal toxicity, myelosuppression, neurotoxicity, nephrotoxicity, ocular toxicity, and ototoxicity.[7]

Thus, there is a need to identify new anticancer medicines with a reduced potential for side effects in healthy tissues. Significant anticancer effects of dipeptidyl peptidase 4 (DD4) inhibitors in cancer cells have been observed. In particular, the antidiabetic medication named sitagliptin was approved by the United States Food and Drug Administration in 2006 an inhibitor of (DPP4). Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide are incretin hormones that are deactivated by the enzyme DPP-4. The hormone incretin increases insulin secretion from beta cells while decreasing glucagon secretion from beta cells.[8] Since sitagliptin blocks DPP-4 activity, it also extends the effects of incretin hormones. Consequently, significant postprandial augmentation of insulin secretion and reduction of glucagon secretion is observed.[9] In addition to antidiabetic action, sitagliptin has been shown to improve the prognosis of several types of cancers, including breast,[10] kidney,[11] ovarian,[12] and colon.[9] In accordance with that, our study attempts to assess the anticancer activity of the DPP-4 inhibitor (Sitagliptin) in HepG2 cell-line and compare the resultant activity with the standard chemotherapeutic agent used in anticancer protocols, cisplatin.

Materials and Methods

Study design

This study was performed on HepG2 cell-line utilizing a previously mentioned protocol.[13] In detail, the cells were cultured into a (96-well) plate and then incubated for 24 h to promote the formation of a cellular monolayer (80% growth phase). The old medium was discarded, and 200 µL of medium containing the test medicines was added. Four primary groups were utilized in addition to the control group, which are: cisplatin-treated HepG2 group, sitagliptin-treated HepG2 group, cisplatin plus sitagliptin-treated group which received combination of different concentrations of cisplatin plus sitagliptin (250 µg/mL), and the fourth group treated with a combination of different concentrations of sitagliptin plus cisplatin (25 µg/mL). The plates were then kept in an incubator for 48 h. After exposure to drugs, the medium was discarded, and the wells were washed with phosphate-buffered saline. Formazan conversion was detected using a blank control. To achieve the final target concentration of MTT (0.5 mg/mL), 10.8 mL of medium was combined with 1.2 mL of stock-MTT solution (5 mg/mL). Next, 200 µL of the resultant MTT solution was applied to each well. After 3 h in the incubator, the plate had intracellular-purple formazan crystals, easily observed using an inverted microscope. The supernatant was discarded, and 100 µL of Dimethylsulfoxide was added to each well to dissolve the formed-formazan crystals. After 30 min in a room-temperature incubator, the cells had lysed, and the crystals had disintegrated. Using a microplate reader set to 570 nm to determine absorbance. Data were finally collected and analyzed statistically. This study was performed at the Cell Culture Lab in the Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Kufa, and it lasted about 2 months in total.

Statistical analysis

The data were gathered and analyzed using "Microsoft Office Excel 2019" (Microsoft Corporation, Redmond, WA, USA) and "IBM SPSS Statistics" (IBM, Chicago, IL, USA) version 20. Means were compared using one-way ANOVA (Post-Hok-Tukey), and probability less than 0.05 ($P < 0.05$) or lower was regarded as statistically significant.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The study protocol was reviewed and approved by a local ethics committee according to the document number 1127 dated August 20, 2022.

Results

The impact of sitagliptin on HepG2 cell-line

The results showed a significant decrease in cell viability of HepG2 cell-line which is directly proportional with increasing the sitagliptin concentration ($P \leq 0.001$) as shown in Figure 1. In addition, sitagliptin further showed significant cytotoxicity against the corresponding cell-line ($P \leq 0.001$) for all concentrations in comparison with the control group, as listed in Table 1.

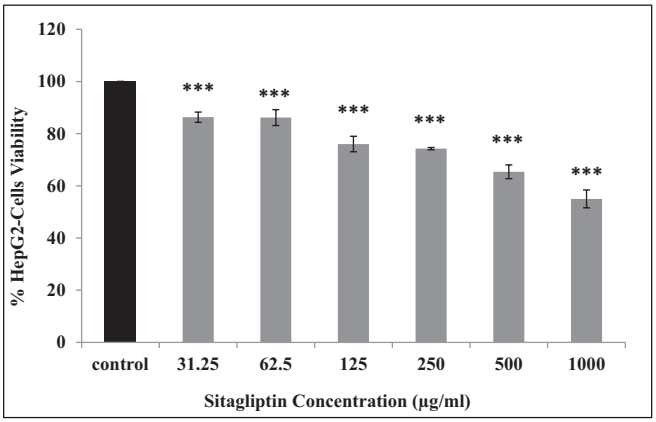

Figure 1: The impact of sitagliptin on cell viability of HepG2 cell-line. *** $P \leq 0.001$

Inhibitory concentration (IC50) value of sitagliptin against HepG2 cell-line

As shown in Figure 2, the IC50 of sitagliptin was determined to be 1440 µg/mL.

The impact of cisplatin on HepG2 cell-line

The results showed a significant decrease in cell viability of HepG2 cell-line ($P \leq 0.001$) after exposure to cisplatin, and this reduction increases gradually as the concentration of cisplatin increase, see Figure 3. Furthermore, cisplatin produced significant cytotoxic effect on the corresponding cell-line ($P \leq 0.001$) at all concentrations in comparison with the control group, as listed in Table 2.

Table 1: Cytotoxic effect of sitagliptin against HepG2 cell-line

Sitagliptin concentration (µg/mL)	Cytotoxicity %
Control	0 ± 0
31.125	13.69 ± 1.97
62.25	13.83 ± 3.05
125	23.96 ± 2.97
250	25.73 ± 0.44
500	34.60 ± 2.64
1000	45.00 ± 3.43

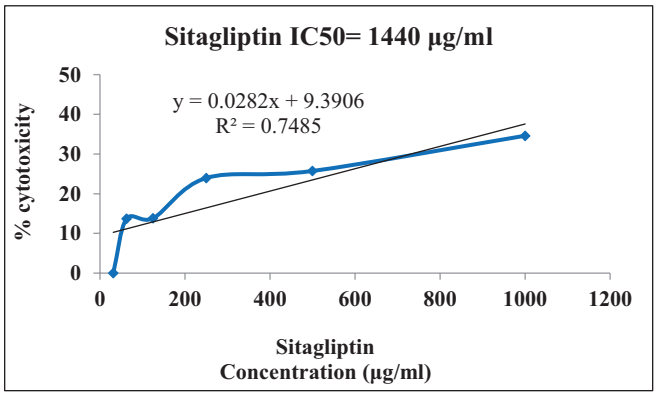

Figure 2: 50% inhibitory concentration value of sitagliptin against HepG2 cell line

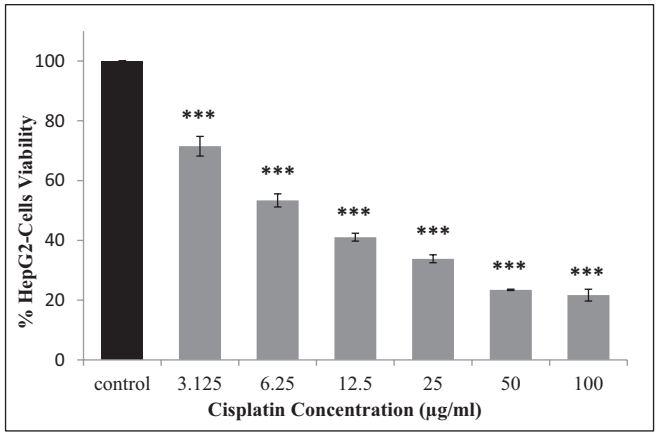

Figure 3: The impact of cisplatin on the cell viability of HepG2 cell-line. *** $P \leq 0.001$

The impact of combination of cisplatin plus sitagliptin on HepG2 cell-line

In this part of the study, cells of HepG2 cell-line were exposed to different concentrations of cisplatin in combination with a fixed concentration of sitagliptin (250 µg/mL). Results showed a significant decrease in cell viability of HepG2 cells ($P \leq 0.001$) at all concentrations tested as shown in Figure 4. Moreover, a significant cytotoxic effect ($P \leq 0.001$) was detected on cells of HepG2 after exposure to different concentrations of cisplatin plus sitagliptin in comparison with the control group as listed in Table 3.

The impact of combination of sitagliptin plus cisplatin on HepG2 cell-line

Series of combinations have been used to evaluate cell viability of HepG2 cell-line, these combinations include different concentrations of sitagliptin plus a fixed concentration of cisplatin (25 µg/mL). The results showed a significant decrease in the studied cell viability of HepG2 cell-line ($P \leq 0.001$), as the level of sitagliptin increase, lower cell viability was reported as shown in Figure 5.

Table 2: Cytotoxic effect of cisplatin against HepG2 cell-line

Cisplatin Concentration (µg/mL)	Cytotoxicity %
Control	0 ± 0
3.125	28.52 ± 3.29
6.25	46.64 ± 2.19
12.5	58.94 ± 1.32
25	66.17 ± 1.32
50	76.56 ± 0.22
100	78.33 ± 1.97

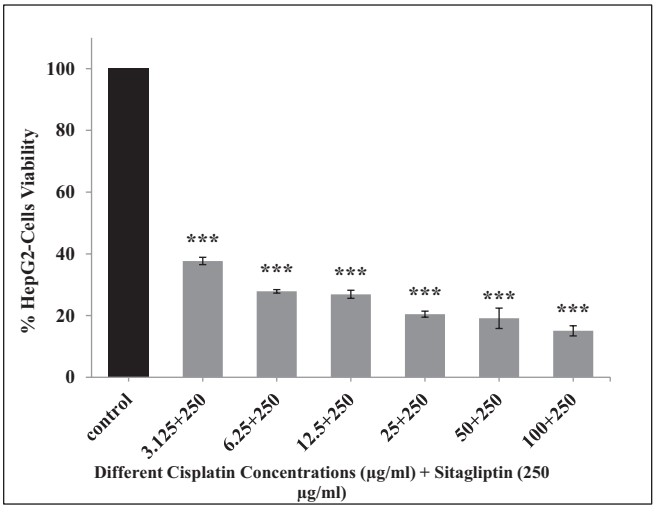

Figure 4: The impact of combinations of different concentrations of cisplatin plus sitagliptin (250 µg/mL) on the cell viability of HepG2 cell-line. *** $P \leq 0.001$

Table 3: Cytotoxic effect of combinations of different concentrations of cisplatin plus sitagliptin (250 μg/mL) against HepG2 cell-line

Cisplatin concentration (μg/mL)	Cytotoxicity %
Control	0 ± 0
3.125 + 250	62.31 ± 1.19
6.25 + 250	72.16 ± 0.57
12.5 + 250	73.11 ± 1.31
25 + 250	79.55 ± 0.98
50 + 250	80.89 ± 3.30
100 + 250	84.95 ± 1.65

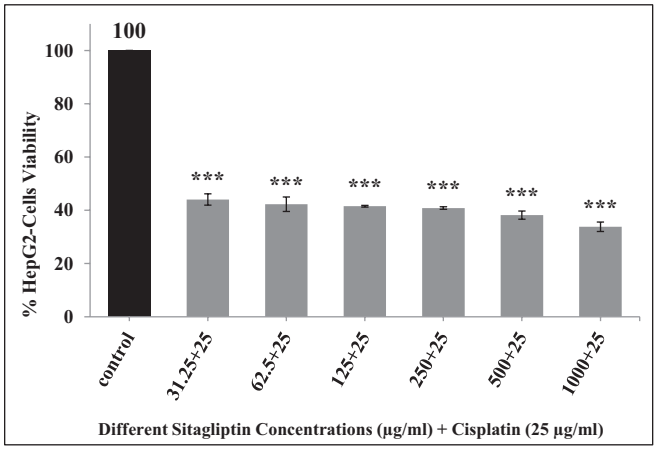

Figure 5: The impact of combinations of different concentrations of sitagliptin plus cisplatin (25 μg/mL) on cell viability of HepG2 cell-line. *** $P \leq 0.001$

Table 4: Cytotoxic effect of combinations of different concentrations of sitagliptin plus cisplatin (25 μg/mL) against HepG2 cell-line

Sitagliptin concentration (μg/mL)	Cytotoxicity %
Control	0 ± 0
31.25 + 25	55.94 ± 2.13
62.5 + 25	57.72 ± 2.72
125 + 25	58.47 ± 0.31
250 + 25	59.15 ± 0.47
500 + 25	61.82 ± 1.54
1000 + 25	66.19 ± 1.77

In addition, a significant increase in cytotoxicity ($P \leq 0.001$) was seen after exposure to higher concentrations of sitagliptin compared with the control group, as listed in Table 4.

Impact of cisplatin alone versus combination of cisplatin plus sitagliptin on HepG2 cell-line

As demonstrated in Figure 6, cisplatin concentrations plus sitagliptin (250 μg/mL) combinations after they have been exposed to HepG2 cells, they significantly reduced cell viability of HepG2 cells ($P \leq 0.001$) in comparison

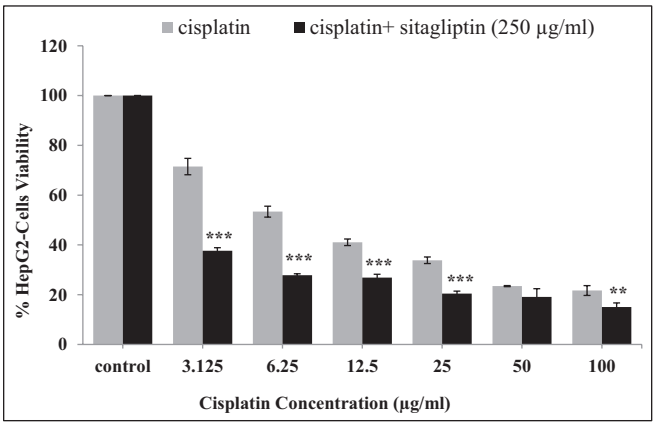

Figure 6: Impact of cisplatin alone versus combination of cisplatin plus sitagliptin on the viability of HepG2 cells. ** $P \leq 0.01$, *** $P \leq 0.001$

Table 5: Comparison between the cytotoxic effect of cisplatin alone and the combination of cisplatin with sitagliptin against HepG2 cell line

Cisplatin concentrations (μg/mL)	Cytotoxicity (%)	
	Cisplatin alone	Cisplatin plus sitagliptin*
Control	0 ± 0	0 ± 0
3.125 + 250	28.52 ± 3.29	62.31 ± 1.19
6.25 + 250	46.64 ± 2.19	72.16 ± 0.57
12.5 + 250	58.94 ± 1.32	73.11 ± 1.31
25 + 250	66.17 ± 1.32	79.55 ± 0.98
50 + 250	76.56 ± 0.22	80.89 ± 3.30
100 + 250	78.33 ± 1.97	84.95 ± 1.65

*Refers to different cisplatin concentrations plus fixed concentration of sitagliptin (250 μg/mL)

with cells exposed to cisplatin alone. Interestingly, high significant differences were reported at low cisplatin concentrations, particularly 3.125, 6.25, 12.5, and 25 μg/mL. However, 50 μg/mL + 250 μg/mL combination, although it produced lower cell viability, no statistically significant results were reported. Similarly, the same combinations precipitated higher cytotoxicity on the corresponding cell-line versus that seen with cisplatin alone, see Table 5.

Impact of sitagliptin alone versus combination of sitagliptin plus cisplatin on HepG2 cell-line

After 48 h incubation, HepG2 cells showed significantly lower cell viability when exposed to all sitagliptin plus cisplatin combinations in comparison with sitagliptin alone ($P \leq 0.001$), as demonstrated in Figure 7. Furthermore, a very high significant increase in cytotoxicity percent ($P \leq 0.001$) for all concentrations, compared with the sitagliptin alone administered group as listed in Table 6.

Discussion

The two main challenges of treating malignant disorders are drug side effects and treatment resistance. Through

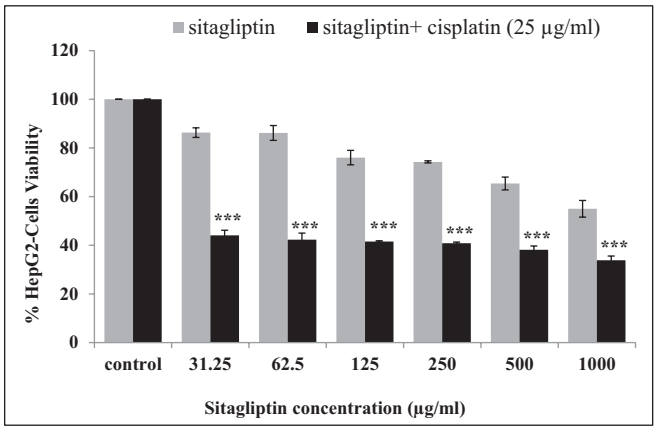

Figure 7: Impact of sitagliptin alone versus combination of sitagliptin plus cisplatin on the viability of HepG2 cells. *** $P \leq 0.001$

Table 6: Comparison between cytotoxic effect of sitagliptin alone and the combination of sitagliptin with cisplatin against HepG2 cell line

Sitagliptin concentrations (µg/mL)	Cytotoxicity (%)	
	Sitagliptin alone	Sitagliptin plus cisplatin*
Control	0 ± 0	0 ± 0
31.25 + 25	13.69 ± 1.97	55.94 ± 2.13
62.5 + 25	13.83 ± 3.05	57.72 ± 2.72
125 + 25	23.96 ± 2.97	58.47 ± 0.31
250 + 25	25.73 ± 0.44	59.15 ± 0.47
500 + 25	34.60 ± 2.64	61.82 ± 1.54
1000 + 25	45.00 ± 3.43	66.19 ± 1.77

*Refers to different sitagliptin concentrations plus fixed concentration of cisplatin (25 µg/mL)

a combination of treatments, researchers try to solve these issues.[14] Combination therapy may improve drug therapeutic effects[15] while lowering drug side effects of anticancer medications by lowering drug dose.[16]

This study aimed to evaluate the potential anti-tumor activity of sitagliptin in HepG2 cancer cell-line. To perform this study, we utilized sitagliptin alone as well as in combination with cisplatin to investigate the impact of combination therapy on the anti-tumor efficacy.

According to the findings of this study, the cell viability of HepG2 cells was significantly decreased, and its cytotoxicity was significantly increased ($P \leq 0.001$). These results are similar to that reported by Amritha *et al*.,[9] who used the MTT assay to compare sitagliptin at varying concentrations with control and they found that this drug has significant antitumor properties against colon cancer.

Recent study further showed that GLP-1 has a positive and protective role in both transplanted tumors and colon cancer cell-lines, suggesting that blocking the DPP-4 enzyme would increase the action of GLP-1.[17] According to Pinheiro *et al*.,[18] sitagliptin inhibited cell growth in cultured lymphocytes at 50 µg/mL and greater concentrations. Cytotoxic effect of sitagliptin is mediated by the specific suppression of DPP-4, a glycoprotein produced in many tissues that have been thought to promote metastasis and tumorigenesis via stimulating hypoxia-inducing factor-1α/vascular endothelial growth factor signaling.[19]

In addition, the anticancer activity of cisplatin is already approved and this chemotherapy is considered as one of the standard medicines widely used for the treatment of liver cancer. Previous MTT assay results demonstrated a dose-dependent decrease in cell viability after cisplatin treatment in HepG2, Hep3B, Huh7, and J7 cells.[4] However, some cells showed apoptotic signals, suggesting that the effect is likely concentration-dependent, and at a dose of 100 mg/mL, cisplatin was reported to cause primary necrosis in Hep3B and HepG2 cell lines.[20]

The cytotoxic effects of cisplatin are manifested when the drug penetrates the cell, links to DNA to form a DNA adduct, and disrupts DNA replication. It leads to cellular oxidative stress and reactive oxygen species release. Cell cycle arrest and alterations in mitochondrial potential at the membrane result from p53 signaling activation.[21]

In this study, the combination of sitagliptin plus cisplatin showed a significant decrease in the viability HepG2 cells ($P \leq 0.001$) when compared with cisplatin alone. This indicates the synergism between cisplatin and sitagliptin which may elevate cytotoxicity against cancer cells more than that obtained when using cisplatin alone. The synergism between sitagliptin and chemotherapeutic agents has been mentioned by previous studies and it was suggested that pharmacological regulation of cellular transmission pathways could be achieved by this combination.[12]

In addition to cisplatin, the antitumor impact of sitagliptin, either alone or in combination with doxorubicin, was also demonstrated in mice model of cancer. Curiously, when doxorubicin and sitagliptin were taken together, tumor size reduction was much greater than that achieved with either medication alone.[22]

Several clinical trials have shown therapeutic benefits with the combination of chemotherapy and sitagliptin, adding support to the use of these two treatments together.[23] When treating rat models of clear cell renal cell carcinoma, the combination of sitagliptin with resveratrol is superior to either medication used alone. This could be because of the additive effects of their antioxidant and anti-inflammatory characteristics.[11]

Sitagliptin inhibits survivin synthesis and upregulates p53-mediated apoptosis.[24,25] P53 is a tumor suppressor gene product that suppresses BCL-2 expression while increasing Bcl-2-associated X protein expression.[26] Furthermore, sitagliptin has decreased survivin level, an

apoptosis-inhibiting protein that is, overproduced in a broad range of malignancies.[27] Survivin key roles include mitotic regulation and apoptosis suppression which are linked to cancer development.[28]

According to that, sitagliptin would probably play a role as cytotoxic agent in HepG2 cancer cell-line. Finally, anticancer activity of sitagliptin could enhance the cytotoxicity of cisplatin which may help in reducing the dose and subsequently the side effects of cisplatin in cancer patients.

However, because the MTT assay is a preliminary screening test. It does not totally confirm the anticancer action. Finally, additional future research studies are necessary to determine the influence of sitagliptin on various types of experimental cancer models and to further confirm the anticancer activity using other evaluation approaches such as flow cytometry.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Ioannou GN, Splan MF, Weiss NS, McDonald GB, Beretta L, Lee SP. Incidence and predictors of hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2007;5 :938-945.e4.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
3. IARC (International Agency for Research on Cancer). Iraq fact sheets, Globocan. 2020. Available from: https://gco.iarc.fr/today/data/factsheets/populations/368-iraq-fact-sheets.pdf. [Last accessed 26 Dec 2021].
4. Li CJ, Tsai HW, Chen YL, Wang CI, Lin YH, Chu PM, *et al*. Cisplatin or doxorubicin reduces cell viability via the PTPIVA3-JAK2-STAT3 cascade in hepatocellular carcinoma. J Hepatocell Carcinoma 2023;10:123-38.
5. Ciarimboli G. Membrane transporters as mediators of Cisplatin effects and side effects. Scientifica (Cairo) 2012;2012:473829.
6. Turel I, Kljun J. Interactions of metal ions with DNA, its constituents and derivatives, which may be relevant for anticancer research. Curr Top Med Chem 2011;11:2661-87.
7. Barabas K, Milner R, Lurie D, Adin CC. A review of toxicities and therapeutic applications. Vet Comp Oncol 2008;6:1-18.
8. Scott LJ. Sitagliptin: A review in type 2 diabetes. Drugs 2017;77:209-24.
9. Amritha CA, Kumaravelu P, Chellathai DD. Evaluation of anti cancer effects of DPP-4 inhibitors in colon cancer—An in vitro study. J Clin Diagn Res 2015;9:FC14-6.
10. Tseng CH. Sitagliptin may reduce breast cancer risk in women with type 2 diabetes. Clin Breast Cancer 2017;17:211-8.
11. Kabel AM, Atef A, Estfanous RS. Ameliorative potential of sitagliptin and/or resveratrol on experimentally-induced clear cell renal cell carcinoma. Biomed Pharmacother 2018;97:667-74.
12. Kosowska A, Garczorz W, Kłych-Ratuszny A, Aghdam MRF, Kimsa-Furdzik M, Simka-Lampa K, *et al*. Sitagliptin modulates the response of ovarian cancer cells to chemotherapeutic agents. Int J Mol Sci 2020;21:8976.
13. Meerloo JV, Kaspers GJ, Cloos J. Cell sensitivity assays: The MTT assay. In: Cree IA, editors. Cancer Cell Culture: Methods and Protocols (Methods in Molecular Biology). 2nd ed. London: Human Press; 2011. p. 237-44.
14. Kim KY, Kim SH, Yu SN, Park SK, Choi HD, Yu HS, *et al*. Salinomycin enhances doxorubicin-induced cytotoxicity in multidrug resistant MCF-7/MDR human breast cancer cells via decreased efflux of doxorubicin. Mol Med Rep 2015;12:1898-904.
15. Jin X, Wei Y, Liu Y, Lu X, Ding F, Wang J, *et al*. Resveratrol promotes sensitization to Doxorubicin by inhibiting epithelial-mesenchymal transition and modulating SIRT1/β-catenin signaling pathway in breast cancer. Cancer Med 2019;8:1246-57.
16. Nakashima T, Nagano S, Setoguchi T, Sasaki H, Saitoh Y, Maeda S, *et al*. Tranilast enhances the effect of anticancer agents in osteosarcoma. Oncol Rep 2019;42:176-88.
17. Koehler JA, Kain T, Drucker DJ. Glucagon-like peptide-1 receptor activation inhibits growth and augments apoptosis in murine CT26 colon cancer cells. Endocrinology 2011;152:3362-72.
18. Pinheiro MM, Stoppa CL, Valduga CJ, Okuyama CE, Gorjão R, Pereira RM, *et al*. Sitagliptin inhibit human lymphocytes proliferation and Th1/Th17 differentiation in vitro. Eur J Pharm Sci 2017;100:17-24.
19. Yang X, Zhang X, Wu R, Huang Q, Jiang Y, Qin J, *et al*. DPPIV promotes endometrial carcinoma cell proliferation, invasion and tumorigenesis. Oncotarget 2017;8:8679-92.
20. Brenes O, Arce F, Gätjens-Boniche O, Díaz C. Characterization of cell death events induced by anti-neoplastic drugs cisplatin, paclitaxel and 5-fluorouracil on human hepatoma cell lines: Possible mechanisms of cell resistance. Biomed Pharmacother 2007;61:347-55.
21. Dasari S, Tchounwou PB. Cisplatin in cancer therapy: Molecular mechanisms of action. Eur J Pharmacol 2014;740:364-78.
22. Salama MM, Zaghloul RA, Khalil RM, El-Shishtawy MM. Sitagliptin potentiates the anti-neoplastic activity of doxorubicin in experimentally-induced mammary adenocarcinoma in mice: Implication of oxidative stress, inflammation, angiogenesis, and apoptosis. Sci Pharm 2022;90:42.
23. Ramakrishnan R, Gabrilovich DI. Mechanism of synergistic effect of chemotherapy and immunotherapy of cancer. Cancer Immunol Immunother 2011;60:419-23.
24. Kumari N, Dwarakanath BS, Das A, Bhatt AN. Role of interleukin-6 in cancer progression and therapeutic resistance. Tumour Biol 2016;37:11553-72.
25. Cheteh EH, Sarne V, Ceder S, Bianchi J, Augsten M, Rundqvist H, *et al*. Interleukin-6 derived from cancer-associated fibroblasts attenuates the p53 response to doxorubicin in prostate cancer cells. Cell Death Discov 2020;6:42.
26. Ozaki T, Nakagawara A. Role of p53 in cell death and human cancers. Cancers (Basel) 2011;3:994-1013.
27. Sohn DM, Kim SY, Baek MJ, Lim CW, Lee MH, Cho MS, *et al*. Expression of survivin and clinical correlation in patients with breast cancer. Biomed Pharmacother 2006;60:289-92.
28. Lv YG, Yu F, Yao Q, Chen JH, Wang L. The role of survivin in diagnosis, prognosis and treatment of breast cancer. J Thorac Dis 2010;2:100-10.