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RESEARCH ARTICLE

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Diosgenin promotes cisplatin-induced apoptosis through oxidative DNA damage in A549 non-small cell lung cells

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Abstract

The efficacy of cisplatin-based chemotherapy in malignancy is limited by the occurrence of innate and acquired drug resistance. Clinical observations suggest that targeting phytopharmaceuticals is the right choice to enhance the effectiveness of conventional chemotherapy. We aimed to evaluate the effects of diosgenin (DG) combined with cisplatin on apoptosis and its underlying mechanisms in the A549 non-small cell lung cells. Cell viability was measured using an MTT assay. Western blot was used for the measurement of γ-H2AX and 8-Hydroxy-2'-deoxyguanosine expression level. DCFH-DA fluorescence dye was used to detect reactive oxygen species (ROS) in cells. The activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and glutathione S-transferase were also assessed. For evaluation of apoptosis, TUNEL assay was used. DG significantly increases the cytotoxic effects of cisplatin. Besides, DG considerably increased the expression levels of γ-H2AX in cells. Upon melatonin treatment, ROS levels were increased, and antioxidant enzymes expression levels were significantly decreased. Co-treatment of DG and cisplatin resulted in increased cellular cytotoxicity through increasing ROS levels, inducing oxidative DNA damage, and decreasing cellular antioxidant defense, hence led to potent induction of apoptosis in tumor cells.

KEYWORDS

apoptosis, cancer, chemotherapy, cisplatin, diosgenin, DNA damage

1 | INTRODUCTION

Non-small cell lung cancer (NSCLC), which accounts for the approximately 85% of lung cancer cases, is reported to have high incidence and mortality rate (Zhang et al., 2020). Surgery and chemotherapy with cisplatin are the first-line therapeutic modalities in treating NSCLC (Torre et al., 2015). Cisplatin-mediated cytotoxicity is via binding to nuclear DNA, creating intrastrand DNA crosslinks, which finally leads to the promotion of apoptosis in tumor cells (Siddik, 2003). Although, application of cisplatin is demonstrated to improve overall survival of patients, however, in similar to other therapeutic options, development of drug resistance fails the complete removal of tumor cells, hence increase the possibility of tumor recurrence (Liu et al., 2020; Patel et al., 2020). The underlying mechanism for the development of drug resistance against cisplatin is a multifacet process, which is not fully understood (Galluzzi et al., 2014; Shtivelman et al., 2014; Wang et al., 2013). Numerous mechanisms are suggested for the appearance of drug resistance in cancer cells, some important of them include, dysregulation of drug transporters, resistance to apoptosis, aberrant activation of DNA repair machinery, as well as disruption in DNA damage response. In this regard, elaboration of new therapies and strategies are of utmost importance in combating NSCLC. Over the years, navigating labyrinth of chemoresistance, clearly underscores chemosensitization as promising strategy to overcome this burden. Accordingly, mechanisms of overcoming are based on enhancement of one drug activity using another agent through modulation of different resistance mechanisms. Natural agents are among the most suitable candidates because of having desirable properties such as low toxicity, multitargeting effects, low cost,

and less side effects (Cao et al., 2019). Furthermore, accumulating of investigations provide evidence that compounds represent antioxidant, antiproliferative, and proapoptotic effects are excellent anticancer agent in association with chemotherapy drugs (Abotaleb et al., 2019). Diosgenin, a key steroidal sapogenin used for the production of steroid drugs, has recently gain an increasing amount of attentions via its anti-inflammatory, antioxidant, antiproliferative, and anticancer impact in numerous types of human malignancies (Corbiere et al., 2004; Mohammad et al., 2013; Raju et al., 2004; Srinivasan et al., 2009). In NSCLC, previous studies have reported the potent anticancer effects of diosgenin. However, to the best of our knowledge, the effects of diosgenin on the sensitization of NSCLC cells to cisplatin are not yet studied. Therefore, we aimed to evaluate the effects of combination of cisplatin and diosgenin on sensitizing of A549 NSCLC cells to apoptosis and its underlying mechanism through assessing oxidative DNA damage.

2 | MATERIALS AND METHODS

2.1 | Cell culture and cell proliferation assay

A549 non-small cell lung cells, provided from Institute Cell Culture Collection, were grown in RPMI 1640 medium supplemented with 10% fetal bovine serum, 100 unit/ml penicillin, and 100 µg/ml streptomycin were provided from Gibco. Cells were incubated at 37°C with 5% CO_2. Cell viability was analyzed by applying MTT assay. Briefly, 1×10^4 cells were cultured in 96-well plates. After 24 h, cells were treated with diosgenin (up to 100 µM) and combination of cisplatin and diosgenin for 48 h. Then, 10 µl of MTT solution was added to each well and was incubated for 4 h at 37°C. For solving formazan crystals, 150 µl dimethylsulfoxide (DMSO) was added to each well and the absorbance was measured in a spectrophotometer at 570 nm.

2.2 | Measuring 8-Hydroxy-2'-deoxyguanosine contents

8-Hydroxy-2'-deoxyguanosine (8-OH-dG) is an important marker of oxidative DNA damage. 8-OH-dG levels in A549 cells were measured using enzyme-linked immunosorbent assay (ELISA) assay. For this purpose, the cellular contents of DNA were extracted from A549 cancer cells by commercial DNA extraction kit, and then ELISA kit (Abcam) was used for quantification of this marker in accordance to manufacturers' guidelines.

2.3 | Western blotting

Another potential marker used for assessing DNA damage in cells is γ-H2AX. For measuring the protein expression levels of this protein, we used western blotting. Briefly, after extraction and quantification, proteins were subjected to separation by10% SDS-PAGE. Following transferring to polyvinylidene fluoride (PVDF) membranes and incubation with 5% skim milk, membranes incubated with primary antibodies against, γ-H2AX and β- catenin. Then incubation with horseradish peroxidase (HRP)-labeled secondary antibody was also applied and detection was achieved by chemiluminescence. Anti-β-actin antibody was used as a control.

2.4 | Measurement of reactive oxygen species (ROS) levels

The effect of various treatments on intracellular ROS level was evaluated using reactive oxygen species assay kit. For this purpose, after treatments, cells were incubated with 10 µM 2, 7-dichlorofuorescin diacetate (DCFH-DA) for 45 min at 37°C in the dark. Intracellular ROS was reacted with DCFH-DA and highly fluorescent compound dichlorofluorescein (DCF) will be produced. DCF fluorescence intensity was assessed with excitation wavelength at 485 nm and emission wavelength at 525 nm. Results are presented as relative DCF fluorescence (ratio DCF-induced fluorescence/DCF-induced control fluorescence).

2.5 | Evaluating the activities of cellular antioxidants

The effects of combination treatment of cisplatin and diosgenin on cellular activities of antioxidants were evaluated using specific assay kits. In this regard, the activities of catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione S-transferase (GST), and superoxide dismutase (SOD) were measured using commercial assay kits. All procedure was applied in accordance to the provided protocols.

2.6 | Evaluation of apoptosis: TUNEL

For apoptosis detection, terminal uridine deoxynucleotidyl nick end labeling (TUNEL) was performed using in situ cell detection kit (FITC) following the manufacturer's guidelines. Briefly, A549 cells were grown on coverslips, then were fixed by paraformaldehyde solution (4% in PBS, pH) and were incubated in room temperature for 1 h. After washing with PBS, coverslips were placed in a solution containing 0.1% Triton X-100, 0.1% sodium citrate in ice for 2 h. Following this step, 50 µl TUNEL solution was added and incubated in the dark for 1 h at 37°C. Subsequently, to analyze total cell count and apoptotic cell count, five visual clear fields randomly were examined. The apoptotic index was calculated by apoptotic cells/total cells.

2.7 | Statistical analysis

Results were expressed as mean ± SD and $p < .05$ were considered as statistically significant. Kolmogorov–Smirnov and Levene tests were used to evaluate the normality of the data. To compare the groups, One-way ANOVA POST HOC (Tukey and Dunnett) tests were considered.

3 | RESULTS

3.1 | Combination of diosgenin and cisplatin synergically suppressed A549 cell viability

As represented in Figure 1, A549 cells were treated with various concentrations of diosgenin in alone and in combination with cisplatin. Diosgenin significantly suppressed cellular viability, in a dose-dependent manner. The IC50 value for diosgenin in A549 cell was 43.7 μM. On the other hand, combination of diosgenin with cisplatin caused a significant increase in the antiproliferative effects of cisplatin. This is approved by the left shift of the cisplatin proliferation plot in the presence of diosgenin. In A549 cells, the IC50 value for cisplatin was 6.13 μM. Co-treatment of cells with 43 μM diosgenin and 0–10 μM cisplatin resulted in the significant reduction in the IC50 value of cisplatin. The IC50 value of cisplatin in the presence of diosgenin was 3.51 μM. Therefore, diosgenin successfully increased the cytotoxic effects of cisplatin in A549 cells.

3.2 | Combination of diosgenin and cisplatin increased intracellular levels of ROS

For evaluating the underlying mechanism of diosgenin effects on cisplatin cytotoxicity, the cellular levels of ROS were measured. We found that both diosgenin and cisplatin resulted in the significant enhancement in the intracellular levels of ROS ($p < .05$; Figure 2). Moreover, the intracellular levels of ROS were significantly higher in cells treated with the combination of diosgenin and cisplatin, as compared to cells treated with either cisplatin or diosgenin ($p < .05$).

3.3 | Effects of diosgenin and cisplatin and their co-treatment on DNA damage

For evaluating the cellular contents of DNA damage, the expression levels of 8-OH-dG and γH2AX were measured. Our results showed that diosgenin and cisplatin increased the 8-OH-dG levels in A549 cells ($p < .05$; Figure 3a). Importantly, diosgenin and cisplatin in combination exerted more potent effect on increasing DNA damage ($p < .05$; Figure 3a). Furthermore, the expression levels of γH2AX that plays substantial role in DNA damage response were also evaluated in our study. Our findings demonstrated that mono-treatment of diosgenin or cisplatin resulted in the significant increment in γH2AX levels in both groups ($p < .05$; Figure 3b). Additionally, co-treatment of diosgenin and cisplatin increased γH2AX levels more potently ($p < .05$; Figure 3b).

3.4 | Combination of diosgenin and cisplatin decreased the activity levels of antioxidant enzymes

To investigate the suppressive effect of diosgenin on antioxidant status of A549 cell line, which is considered as a main mechanism of it in cancer treatment, we evaluated the activity of antioxidant enzymes including CAT, SOD, GST, GR, and GPx. As shown in Figure 4, our results showed that diosgenin and cisplatin combination significantly suppressed the abovementioned enzymatic activities in comparison to mono-treatment ($p < .05$).

3.5 | Effects of diosgenin and cisplatin and their combination on apoptosis

To evaluate the effect of mono-treatment and concomitant treatment of diosgenin and cisplatin on the apoptosis of A549 cell lines, we

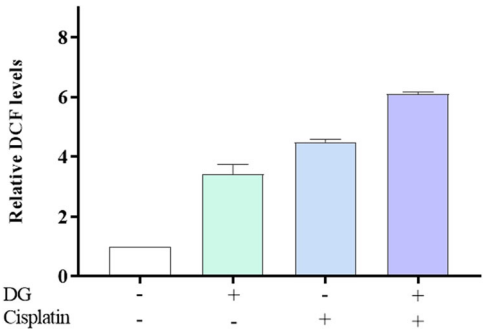

FIGURE 2 The effects of DG and Cis-platin and their co-treatment on ROS levels. All values are shown as mean ± SD. ROS, reactive oxygen species.

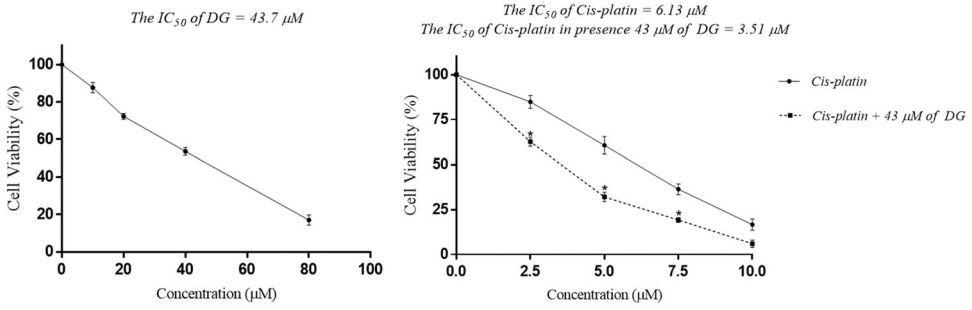

FIGURE 1 Effects of DG and Cis-platin and their co-treatment on cell viability. All values are represented as mean ± SD.

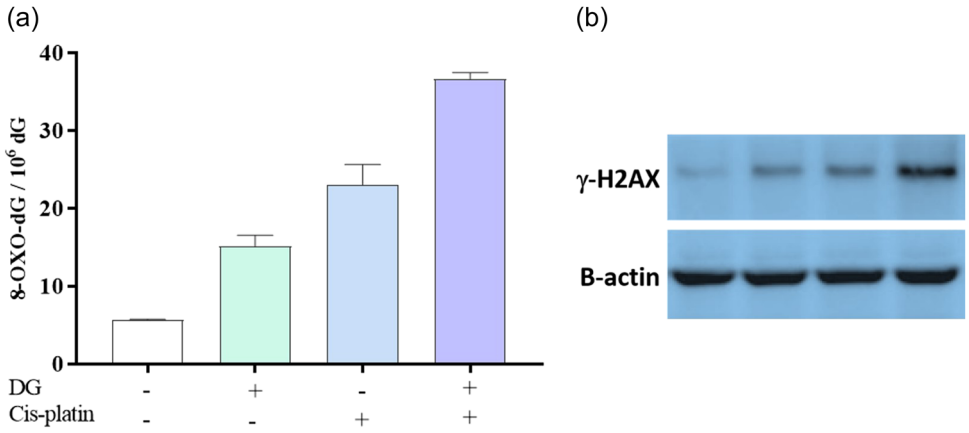

FIGURE 3 Effects of DG and Cis-platin and their co-treatment on DNA damage. (a) Levels of 8-oxo-dG, (b) protein levels of γ-H2AX in A549 cells. All values are depicted as mean ± SD.

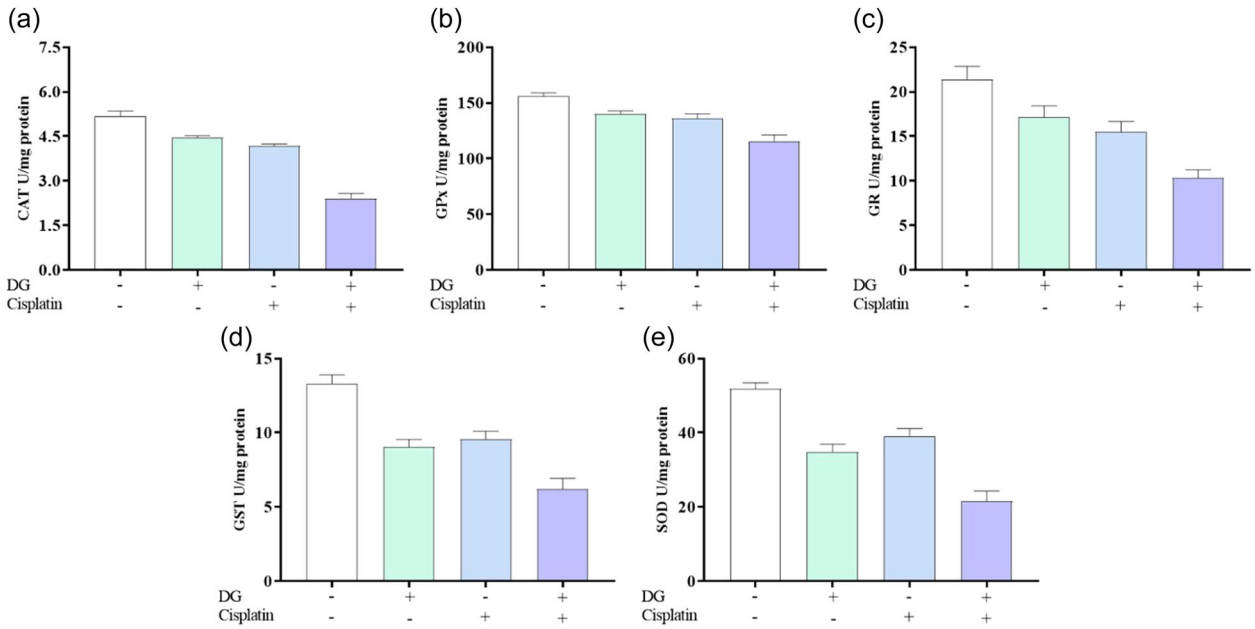

FIGURE 4 Effects of DG and Cis-platin and their co-treatment on the activity levels of antioxidant enzymes. (a)–(e) The CAT, GPx, GR, GST, and SOD levels, respectively in A549 cells. Results are shown as mean ± SD. CAT, catalase; GPx, glutathione peroxidase; GR, glutathione reductase; GST, glutathione S-transferase; SOD, superoxide dismutase.

performed TUNEL after 48 h treatment. As shown in Figure 5, diosgenin and cisplatin side induced apoptosis. Furthermore, diosgenin and cisplatin in combination resulted in increased apoptosis rate of A549 cells when compared with each drug in alone ($p < .05$; Figure 5).

4 | DISCUSSION

Development of drug resistance is still a big burden against complete combating of numerous human malignancies including NSCLC. Therefore, finding novel agents with high efficacy in increasing the cytotoxic effects of conventional chemotherapeutics, as well as decreasing their side effects are of utmost importance. Hence, we examined the effect of diosgenin combination with cisplatin as well as the underlying mechanisms on cell apoptosis of A549 NSCLC cells and found that combination of diosgenin and cisplatin led to significant increase in the suppression of cellular viability and induction of apoptosis, which was mediated with increasing oxidative DNA damage and decreasing cellular antioxidant defense system.

Diosgenin is one of the natural compounds gaining huge attention in recent years due to its potent anticancer activities in various human cancers. In addition, some studies have reported that diosgenin is able to inhibit tumor progression of NSCLC. For example, Ganesan et al. inhibited the cellular proliferation and induced

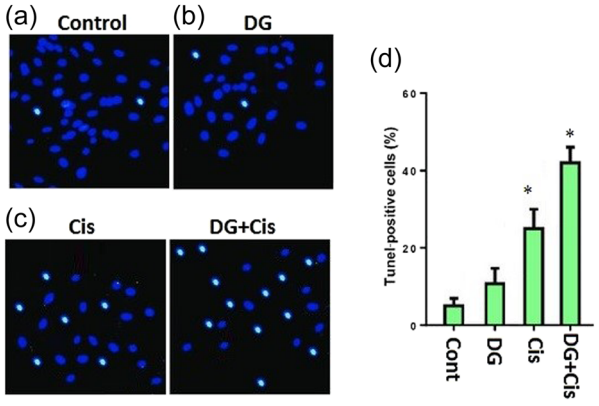

FIGURE 5 Effects of DG and Cis-platin and their combination on apoptosis. TUNEL staining of A549 cells in (a) control, (b) exposed with DG, (c) treated with Cis-platin, and (d) exposed with DG plus Cis-platin. All values are represented as mean ± SD.

apoptosis in A549 cells via promoting cholesterol efflux (Ganesan & Arockiam, 2019). In another study by Rahmati and coworkers, it was reported that diosgenin exerted potent anticancer effects in A549 cells through inhibiting telomerase activity by downregulating of hTERT gene expression (Mohammad et al., 2013). In agreement with these studies, our finding showed that diosgenin inhibited cellular proliferation and prompted apoptosis in A459 cells.

In the NSCLC, effectiveness of cisplatin as worthwhile chemotherapeutic agent well defined previously; however, several undesirable side effects emphasize the needs for new strategies to tackle the challenges. There is various evidence supporting that combined chemotherapy possess effective role in combating drug resistance and induction of apoptosis (Housman et al., 2014). Additionally, numerous of studies have been described that application of natural products such as curcumin, Salvianolic acid, and Rosmarinic acid hampers cisplatin related drug resistance in NSCLC (Chen et al., 2015; X. Z. Liao, Gao, et al., 2020; Tang et al., 2017). In our study, we approved that combination of diosgenin and cisplatin increased the cytotoxic effects of cisplatin on A549 cells and led to a potent induction in apoptosis in comparison to mono-treatments with either diosgenin or cisplatin.

It is well documented that ROS exerts dual function in cellular process in a concentration-dependent manner, as in moderate levels play a role in cancer initiation and progression through inflammation, DNA mutation, and cellular damage, and in higher levels act as anticancer agent by induction of apoptosis (Spitz et al., 2003). Generally, ROS attacks the guanine in DNA and form; 8-OH-dg; therefore increased DNA damage is considered as a major consequence of ROS overproduction and is supported by the fact that higher levels of ROS have a direct correlation with increased levels of 8-OH-dG (Deavall et al., 2012; Mangal et al., 2009). Since 8-OH-dG is regarded as one of the suitable markers to assess DNA oxidation in vitro; in this study, we evaluated this factor in response to combination therapy and as mentioned above we found that 8-OH-dG increased in line with ROS overproduction. There is evidence that anticancer properties of cisplatin are mediated through induction of DNA damage (Cohen & Lippard, 2001), which is in accordance with our findings. As an early event in DDR, posttranslational modification of histone variant H2AX through phosphorylation of serine 139-a by ATM and ATR kinases produce of γH2AX which is crucial in recruitment of DNA repair proteins and effectors to damaged site (Schwertman et al., 2016). Our results showed that co-treatment of diosgenin with cispaltin results in the significant reduction in γH2AX levels. To the best of our knowledge, our study is the first investigation to show that diosgenin in combination with cisplatin exert stronger DNA damage in A549 cell line which subsequently bring about potent apoptosis. Cruz et al. showed that diosgenin increased DNA damage, hence suppressed cell proliferation in HepG2 cells (Cruz et al., 2018). Liao and coworkers revealed that the antiproliferative activity of diosgenin contributed to the induction of G2/M phase arrest via modulating the Cdc25C-Cdc2-cyclin B pathway of DNA damage response and apoptosis in human breast cancer cell lines (W.-L. Liao et al., 2020).

As another notable point in our findings, diosgenin in combination with cisplatin led to remarkable reduction in antioxidant levels including SOD, CAT, GPx, DR, and GST. It has been widely accepted that several chemotherapeutic agents and adjuvant therapies acting through limiting antioxidant capacity and blocking antioxidant defense which finally result in cell death (Sznarkowska et al., 2017). Furthermore, our results supported with this notion that programmed cell death is the consequence of ROS overproduction and inhibition of antioxidant defense which consider as one of the important mechanism in melatonin anticancer activity (Di Bella et al., 2013).

In conclusion, our results showed that combination of cisplatin and diosgenin resulted in the increased cellular cytotoxicity. In addition, we found that diosgenin increased ROS levels by inducing oxidative DNA damage and deceased cellular antioxidant defense, hence led to potent induction of apoptosis in A549 cell lines. Therefore, the combination treatment of A549 cells with diosgenin and cisplatin might be an effective strategy in inducing apoptosis and reversing developed drug resistance and more importantly decreasing the adverse side effects of these agents.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data available on request from the authors.

ETHICS STATEMENT

This study was approved by The First People's Hospital of Qujing, Qujing, Yunan, P.R. China.

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