Journal of Agricultural and Marine Sciences 2024, 29(2): 33 - 41
DOI: 10.53541/jams.vol29iss2pp33 - 41
Received 12 August 2022
Accepted 28 August 2024

RESEARCH PAPER

Marine Natural Products with Cytotoxic Properties against Epithelial Ovarian Cancer

I. A. Burney[1,2*], Y. Tamimi[3], N. Abdulla[3], N. Al Balushi[3], B. Al Dhahli[3], S. Al Bahlani[3], S. I. Hasan[4], S. Dobretsov[5]

المنتجات البحرية الطبيعية ذات الخصائص السامة للخلايا في مكافحة سرطان المبيض الظهاري

إكرام بيرني، يحيى التميمي، ندى عبدالله، نجوى البلوشي، بثينة الذهلي، شادية البهلاني، سيد عمران حسن، سيرجي دوبريتسوف

Abstract. Epithelial ovarian cancer (EOC) is a common gynecological cancer and a leading cause of death, especially because the tumors develop resistance to cisplatin. New compounds are needed to achieve better disease control and survival. We examined the cytotoxic effect of Gallic acid (GA), Hymenialdisine, and Malformin A1 (MA1) on human ovarian cancer cells. Cytotoxicity was tested using cisplatin-sensitive (A2780s) and cisplatin-resistant (A2780cp) ovarian cancer cell lines, and a normal ovarian tissue cell line (HOSE6-3) using AlamarBlue assay, Hoechst dye, and flow cytometry, and the genes and proteins of interest were assessed using western blot, and qRT-PCR. The IC_{50} of Hymenialdisine was 146.8 µM for A2780s cells and >300 µM for A2780cp cell lines. Both GA and MA1 decreased cell viability in a concentration-dependent manner. The IC_{50} of GA was 103 µM for A2780s cells, 189 µM for A2780cp cells and 262 µM for HOSE6-3 cell lines, for MA1 IC_{50} was 0.23 µM for A2780s and 0.34 µM for A2780cp. This was in comparison to IC_{50} of 31.4 µM and 76.9 µM, for A2780s cells, and A2780cp cells respectively for cisplatin. The combination of GA and MA1 with cisplatin revealed synergistic action, especially in A2780cp cell lines. The results suggest that both GA and MA1 may help overcome the resistance to cisplatin through the synergistic effect. Hence, the cytotoxic potential of GA and MA1 merit further investigation.

Keywords: Ovarian cancer, Marine, Natural products, Cytotoxicity, Apoptosis, Oman

الخلاصة: سرطان المبيض الظهاري (EOC) هو سرطان نسائي شائع ومسبب رئيسي للوفاة، خاصة بسبب تطوّر المقاومة للسيسبلاتين في الأورام. هناك حاجة ملحّة لمركبات جديدة لتحقيق سيطرة أفضل على المرض وزيادة فرص البقاء على قيد الحياة. قمنا بدراسة تأثير السمية على الخلايا لثلاث منتجات بحرية طبيعية وهي حمض الغاليك (GA)، هيمينياليديسين، ومالفورمين A1 (MA1) على خلايا سرطان المبيض البشرية. تم اختبار السمية الخلوية باستخدام خطوط الخلايا الحساسة للسيسبلاتين (A2780s) والمقاومة للسيسبلاتين (A2780cp)، وخط الخلايا الطبيعية للأنسجة المبيضية (HOSE6-3) باستخدام AlamarBlue ، صبغة هويشت، وتدفق الخلايا، وتم تقييم الجينات والبروتينات ذات الاهتمام باستخدام التحليل الغربي وتقنية QRT-PCR. وكانت قيمة IC50 للهيمينياليديسين 146.8 ميكرولتر لخلايا A2780s وأكثر من 300 ميكرولتر لخطوط الخلايا A2780cp. أما حمض الغاليك ومالفورمين A1 فقد تناقصت قدرة الخلايا على البقاء بشكل يعتمد على التركيز. وكانت قيمة IC50 لـ GA هي 103 ميكرولتر لخلايا A2780s، و189 ميكرولتر لخلايا A2780cp، و262 ميكرولتر لخطوط الخلايا HOSE6-3، وأما بالنسبة لـ MA1 فقد كانت قيمة IC50 هي 0.23 ميكرولتر لـ A2780s و0.34 ميكرولتر لـ A2780cp. وكانت هذه القيم مقارنة للسيسبلاتين بقيم IC50 تبلغ 31.4 ميكرولتر و76.9 ميكرولتر بالنسبة لخلايا A2780s و A2780cp على التوالي. أظهرت المزيج من GA و MA1 مع السيسبلاتين تأثيرًا تآزريًا، خاصة في خطوط الخلايا A2780cp. تشير النتائج إلى أن كلًا من GA و MA1 قد يساعدان في التغلب على مقاومة السيسبلاتين من خلال التأثير التآزري. وبالتالي، فإن إمكانات السمية الخلوية لـ GA و MA1 تستحق المزيد من البحث والاستكشاف

الكلمات الرئيسية: سرطان المبيض، البحرية، المنتجات الطبيعية، السمية الخلوية، موت الخلايا المبرمج، عمان

[1]Sultan Qaboos Comprehensive Cancer Care & Research Center, Muscat, Oman
[2]Panjwani Center of Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences, University of Karachi, Pakistan
[3]College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman
[4]Department of Chemistry, College of Science, Sultan Qaboos University, Muscat, Oman
[5]UNESCO Chair,Centre of Excellence in Marine Biotechnology, Sultan Qaboos University, Muscat, Oman
[6]Department Marine Science and Fisheries, College of Agricultural and Marine Sciences, Sultan Qaboos University, Muscat, Oman
*Corresponding author (Email: i.burney@cccrc.gov.om; ikramburney@hotmail.com)

CC BY ND

Introduction

Ovarian cancer is the 8th most common cause of death from cancer among women worldwide and the 2nd most common cause of death from gynecological cancer (Sung et al., 2021). Epithelial ovarian cancer (EOC) accounts for 90% of all ovarian cancers, and high-grade EOC accounts for the majority (Kurman et al., 2014). The vast majority of patients with high-grade EOC are diagnosed with stage III/IV disease (Matulonis et al., 2016). A combination of debulking surgery and cisplatin-based chemotherapy with or without anti-angiogenic therapy has been the standard of care (McGuire et al., 2003). More recently, a subset of patients with mutations in the BRCA1 or BRCA2 gene or those with homologous reconstitution deficiency has been shown to respond to inhibitors of the poly (ADP-ribose) polymerase (PARP) enzyme, leading to a prolongation of disease-free survival (Konstantinopoulos et al., 2010; Ledermann et al., 2012). However, despite a consistent rate of initial responses, cisplatin treatment often results in the development of chemoresistance, leading to a therapeutic failure (Galluzi et al., 2012). Five-year survival is reported to be 15-25% (Sung et al., 2021). Since cisplatin constitutes the major therapeutic option, new compounds are urgently needed to overcome resistance to cisplatin, ultimately leading to better disease control and survival.

Marine organisms represent a reservoir of natural resources rich in novel bioactive metabolites that can be potential anticancer drugs (Cragg et al., 1999; Reinhardt, 2000; Pandey et al., 2013). Marine drug research has evolved rapidly in the last decade, as marine organisms have been shown to acquire remarkable cytotoxic properties. Several cytotoxic chemotherapeutic agents of marine origin, such as cytarabine, trabectedin, and eribulin, are in routine clinical use, and several others are in different stages of clinical trials (Donoghue et al., 2012; Swami et al., 2012; Poveda et al., 2011).

In our previous study, the anticancer activity of 8 marine natural products and 32 extracts of marine organisms from Oman waters were studied (Dobretsov et al., 2016). Among the tested pure compounds, gallic acid (GA), MalforminA1 (MA1), and hymenialdisine (HYM) showed potent cytotoxic activity against the MCF-7 breast cell line. In this study, we investigated the cytotoxic effect of GA, MA1 and HYM in ovarian cancer cell lines for effectiveness, and if they were cytotoxic in cisplatin-resistant ovarian cancer cell lines.

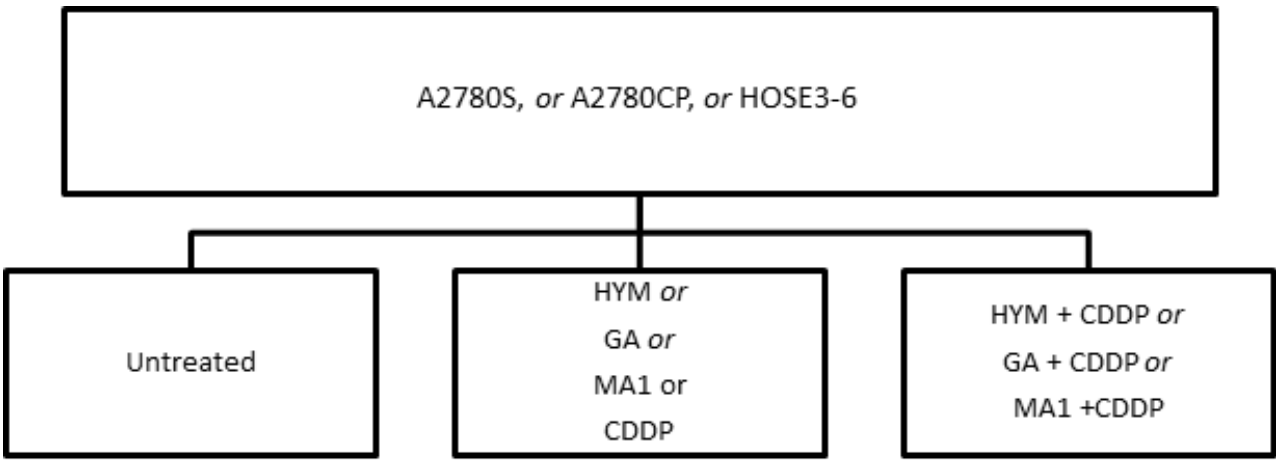
Materials and methods

Reagents

HYM was purchased from Boc Science (USA) and dissolved in dimethyl sulfoxide (DMSO) (Sigma, USA) to make a stock solution of 3085.2µM. GA monohydrate, $C_6H_2(OH)_3COOH H_2O$, M.W.= 188.14 g/mol, was purchased from Cica reagent, Kanto Chemicals, Japan. A stock solution of GA monohydrate (188.14 g/mol) was prepared in absolute ethanol (EMD Millipore) at 531.52µM and stored at 4˚C. MA1 was purchased from Boc Science (USA), and dissolved in dimethyl sulfoxide (DMSO) (Sigma, USA) to make a stock solutions of 1887.9 µM. Cis-dichlorodiammineplatinum (CDDP or cisplatin) solution (1 mg/ml) solution was obtained from Mylan, France, at a concentration of 3333.2 µM.

Cisplatin-sensitive (A2780S) and cisplatin-resistant (A2780CP) ovarian cancer cell lines were generous gift from Dr. Benjamin K. Tsang (University of Ottawa, Ottawa, Canada). The immortalized normal ovarian cell line HOSE3-6 was a generous gift from Professor GSW Tsao, Hong Kong University. Cell lines were seeded in a 96-well plate and cultured in Dulbecco's Modified Eagle's Medium (DMEM/F12). All culturing media were supplemented with 10% fetal bovine serum (Gibco) and 1% penicillin-streptomycin (Gibco) in a humidified incubator (5% CO_2) at 37˚C. The cell lines in the medium were maintained as described earlier (Al Bahlani et al., 2011).

Figure 1. Study Design. Cisplatin-sensitive A2780S cells, cisplatin-resistant A2780P cells, which were either left untreated (control) or treated with single agents HYM, GA, MA1 or CDDP at their respective IC_{50} concentrations. Combination of HYM+CDDP, GA+CDDP, or MA1+CDDP were administred. The immortalzed normal ovarian cell line (HOSE3-6) was not treated with either CDDP as a single agent or in combination with HYM, due to its high IC_{50} value in both A2780S and A2780CP cell lines. Therefore, further investigation of HYM was not pursued



Cell Viability Assay

AlamarBlue (Invitrogen, USA) was used to determine the IC_{50} values of HYM, GA, and MA1 in A2780S, A2780CP and HOSE6-3 cell lines. Briefly, cells were seeded at a density of 15,000 cells/well in a 96-well plate (Corning) for 24 h. Following the removal of growth media, the cells were treated with various concentrations of HYM, GA, and MA1 in serum free media for 24 hours. Subsequently, then detection dye AlamarBlue was added, and the plate was incubated for 3 hours before being read using a Multiskan spectrum plate reader (ThermoFisher Scientific, USA) at 570/600 nm. The viability of the negaa tive control cells was set as 100%. Each exper riment was performed in triplicate and repeated three times to ensure thr reability of the results.

Hoechst Dye Staining of Cells

Apoptosis was determined, as described previously. Briefly, A2780S and A2780CP cell lines were cultured in a 24-well plate (Corning) at a density of 150,000 cells/well and incubated overnight. Growth media was refreshed and different concentrations of HYM, GA, and MA1 were added to cells and incubated for 24 h. On the third day, cells were harvested, washed with Dulbecco's phosphate-buffered saline, with no calcium and no magnesium (DPBS) (GIBCO, Thermo Fisher), stained with Hoechst 33258 dye (Sigma-Aldrich) in 10% formalin (1:50), and then preserved in the dark at 4°C until visualization (within 1-2weeks). Apoptotic cells were identified based on their morphology (smaller size and fragmented DNA) under a fluorescent microscope with a DAPI filter. We estimated the percentage of cells undergoing apoptosis by microscopic examination of different random fields at 40X and 100X magnification. We examined at least three different areas for each experiment, and the number of apoptotic cells was counted to estimate the percentage of survival.

Annexin V-FITC Apoptosis Assay

Flow cytometry was used to examine cell apoptosis. The cells were plated in 6 well plates at a density of 5×10^5 cells/well and incubated for 72h in the presence or absence of Malformin A_1. The apoptosis assay was performed using Annexin V-FITC Apoptosis Detection Kit (Guava Nexin® reagent, Millipore Sigma, USA) and analysed with flow cytometry according to the manufacturer's protocol. Briefly, the cells were detached using 2% EDTA in PBS, and Annexin V and 7-amino-actinomycin-D dyes were added.

The samples were then incubated in the dark at room temperature for 20 mines. A flow cytometer (Beckman Coulter Life Sciences, USA) equipped with Navios Cytometer Software 1.3 was used to measure the percentage of apoptotic cells. Finally, the data were analyzed using Kaluza software 2.1.

Statistical Analysis

All experiments were performed in triplicate and repeated at least three times. The results are reported as the mean ± standard error of the mean (SEM). Means were compared using one-way ANOVA followed by a Tukey or Dunnett 2-sided post-hoc tests. Prior to analysis, the normality of the data and homogeneity of the variables were tested. The difference between means was considered significant at $p < 0.05$ (*P < 0.05, **P < 0.01, ***P < 0.001).

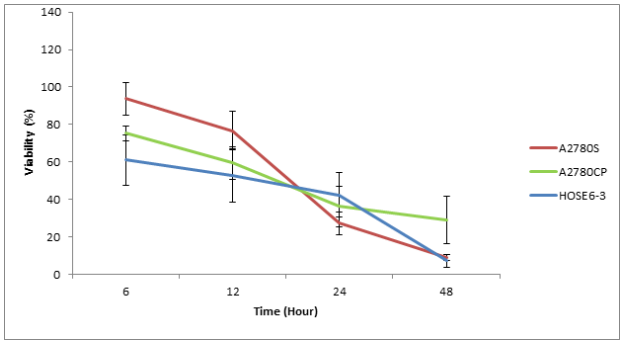
Results

Determination of IC_{50}

We used AlamarBlue to assess cytotoxicity in A2780S, A2780CP, and HOSE6-3 cell lines exposed to different doses of the three compounds and cisplatin. The recorded IC_{50} values (in µM) are shown in Table 1.

Due to its high $IC_{50,}$ particularly in the A2780CP cell line, the HYM compound was not studied further. However, the IC_{50} values for each cell line were determined for subsequent experiments. The three cell lines were exposed to the IC_{50} concentrations of the three compounds at different time points (6, 12, 24, and 48 hours). Figure 2 displays the cell viability in response to GA treatment at different time points. Although data for MA1 and HYM are not shown, they exhibited a similar viability pattern. Consequently, exposure at 24 hours was chosen for subsequent experiments.

Figure 2. Time-dependent decrease in cell viability following the administration of GA at the IC50 concentrations specific to each cell line: 262 µM for HOSE3-6, 103 µM for A2780S, and 189 µM for A2780CP.



Apoptosis

Apoptosis was confirmed through the observation of distinct morphological changes, such as nuclear fragmentation and reduction in cell size. Figure 3 shows these changes in response to the administration of MA1, while similar changes were observed with GA treatment as well.

The degree of apoptosis was determined by exposing A2780S and A2780CP cells to different concentrations of GA and MA1 for 24 hours, followed by Hoechst dye staining. The

Table 1. Cytotoxicity of A2780S, A2780CP, and HOSE6-3 cell lines exposed to different doses of the three compounds and cisplatin

	CDDP	HYM	GA	MA1
HOSE3-6	29.39	Not studied	262	0.07
A2780S	31.4	146.8	103	0.23
A2780CP	76.9	300<	189	0.34

results revealed a dose-dependent increase in the number of apoptotic cells in response to GA treatment (Figure 4).

Figure 3. The induction of apoptosis in A2780S and A2780CP cell lines following a 24-hour application of MA1

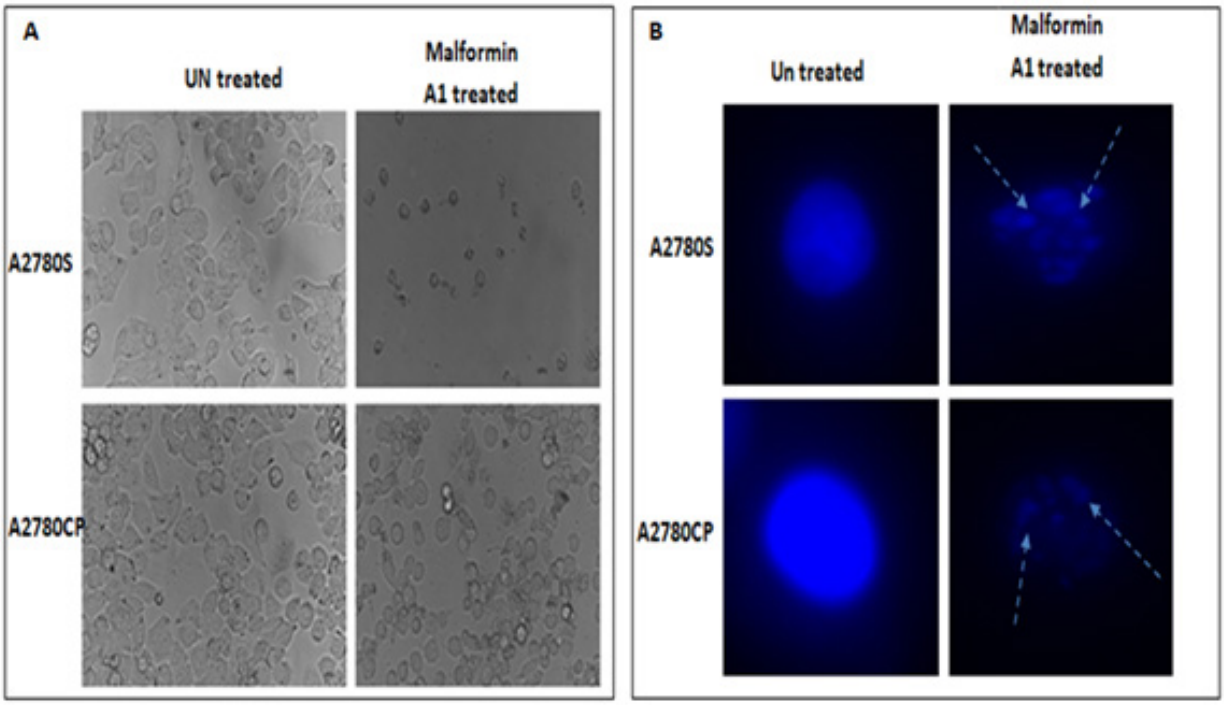
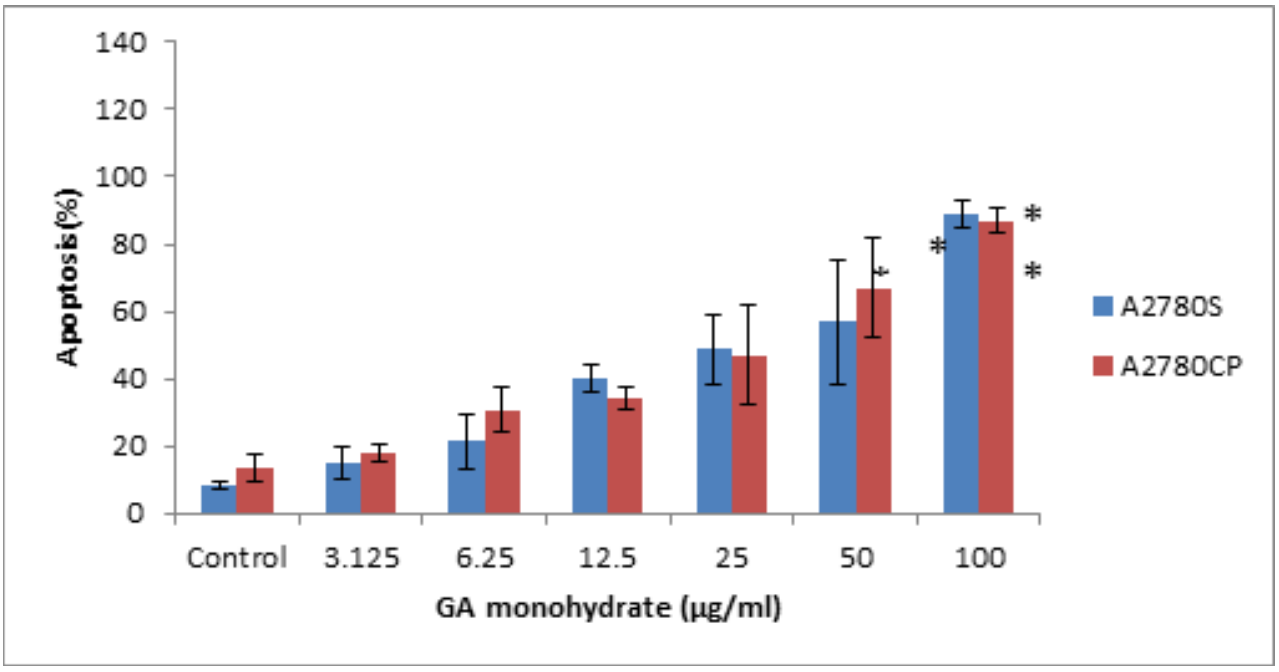


Figure 4. A dose-dependent increase in the degree of Apoptosis was observed in both A2780S and A2780CP cell lines following a 24- hour application of GA at different concentrations



Cell Viability of Single Agents and in Combination

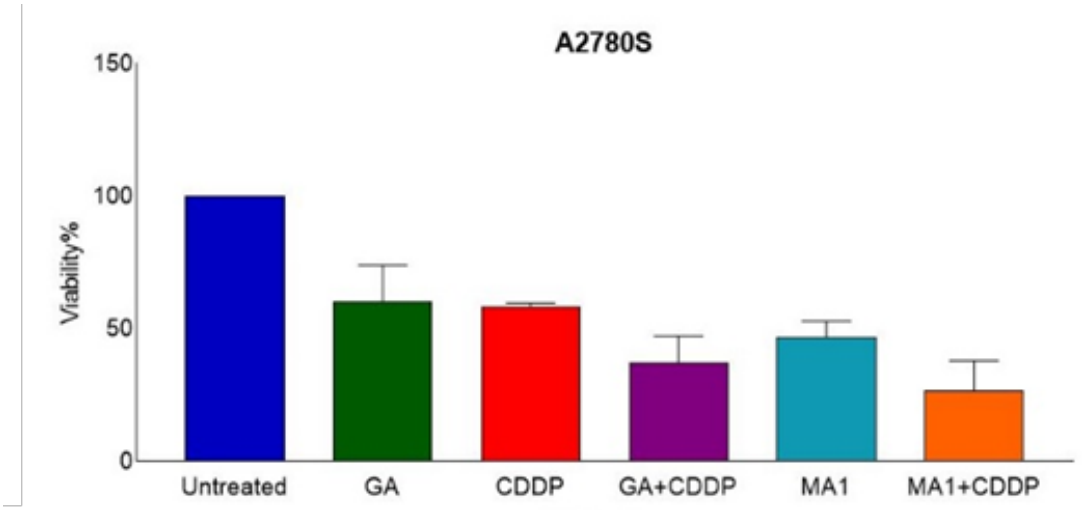
Cell viability was determined using the Alamar-Blue assay with the viability of control cells set at 100%. The cells were exposed to either CDDP, GA, or MA1, or in combination (GA+CDDP) and MA1+CDDP), and the results are shown below. It is evident that all agents led to a significant reduction in cell viability. In the A2780S cell line, viability was reduced to 20% with a combination of MA1+CDDP in the A2780S cell line, and 35% in the A2780CP cell lines, and this was significantly lower than the two agents separately. Viability was reduced to 15% with the combination of GA+CDDP.

Discussion

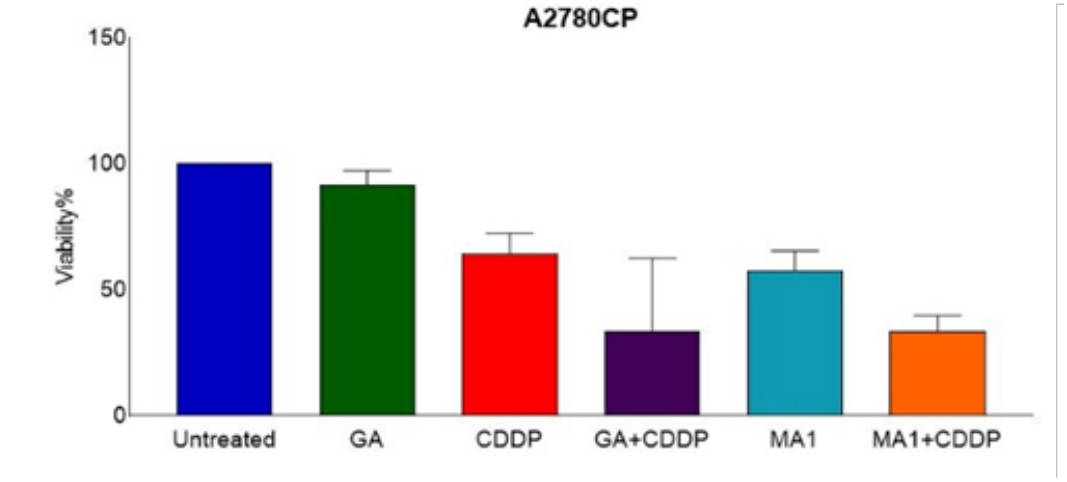
Both GA monohydrate and MA1 demonstrated significant cytotoxicity in cisplatin-sensitive and cisplatin-resistant cell lines. Their cytotoxicity effects were attributed , at least in part, to the induction of apoptosis. Interestingly, when cisplatin was combined with GA or MA1, a significantly greater level of cytotoxicity was observed compared to the use of either agent alone, suggesting a potential synergistic action. The selection of HYM, GA and MA1 for this study was based on a previous screening of anticancer compounds derived from Omani marine natural products against the MCF-7 breast cancer cell line (Dobretsov et al., 2016).

Figures 5A and 5B depict the cell viability of A2780S and A2780CP cell lines following a 24 hour application of the test compounds. A significant reduction in cell viability was observed when the combination of GA+CDDP and MA1+CDDP were administred, compared to the application of a single compound or CDDP alone. The results are presented as the mean ± SD of three independent experiments, with untreated cells serving as controls

(A)



(B)



The three compounds have been reported to exhibit anticancer activity in different types of cancer cell lines. The IC_{50} value of HYM in our experiments, leading to its exclusion from further investigation. On the other hand, GA is a polyphenolic compound commonly found in many plants (Kahkeshani et al., 2019). GA has demonstrated anticancer activity in various types of cancer, including lung cancer, breast cancer, prostate cancer, leukaemia, and cervical cancer (Madlener et al., 2007; Kaur et al., 2009; You et al., 2010a; You et al., 2010b; Wang et al., 2014). It has also been shown to induce apoptosis in stomach cancer and acute lymphoblastic leukemia (Yoshioka et al., 2000; Sourani et al., 2016). MA1 was found to exhibit cytotoxic activity against HeLa, prostate cancer cell lines, and human colorectal cancer cells (Liu et al., 2016; Park et al., 2017; Notarte et al., 2017). Notably, the cytotoxicity of all three compounds in ovarian cancer is reported by us for the first time (Abdullah et al., 2021; Abdullah et al., 2021., Al Balushi et al., 2022). The cytotoxicity of these compounds in cisplatin-resistant cell lines has not been previously reported.

The A2780 cell line, derived from an untreated ovarian cancer patient, serves as the parental cell line. The cisplatin-resistant cell line A2780CP was developed by chronic exposure of A2780 to cisplatin; A2780CP had a 6-fold resistance to cisplatin, compared with A2780S cells. An increased activity of efflux mechanisms, especially the intracellular copper ion transporters, leading to a reduction in the intracellular impact of cisplatin is considered to be the major mechanism of developing resistance (Pan et al., 2002; Kalayda et al., 2008). Post-translational modification has been suggested to be yet another important mechanism (Zhu et al., 2005).

One of the major issues in the treatment of ovarian cancer is development of resistance to platinum agents. Almost 80% of patients with high-grade EOC respond to cisplatin at the time of diagnosis, and even at the time of relapse. If the relapse occurs more than one year after the last dose of platinum compounds, the reponse rate to further platinum-based chemotherapy is between 30-70%. However, if the disease relapses within the 6 months from the last dose of platinum containing chemotherapy, the reponse rates to subsequent lines of chemotherapy are between 10 and 30% (Matulonis et al., 2016; McGuire et al., 2003; Galluzi et al., 2012). Once the disease relapses, almost all patients develop resistance to platinum compounds, leading to cancer-related mortality. The major aim of this study was to see whether the addition of HYM, GA, or MA1 would be active against cisplatin-resistant cell lines, and would overcome the resistance to cisplatin. HYM produced cytotoxicity in A2780s and A2780CP cell lines at a high IC_{50} value and hence was not tested in combination with CDDP. However, both GA monohydrate and MA1 produced cytotoxicity at a relatively low IC_{50} value. The IC_{50} for CDDP was 31.4 and 76.9 μM for A2780s and A2870CP cell lines respectively. The addition of GA monohydrate and MA1 led to a significant reduction in cell viability and an increase in the proportion of apoptotic cells, suggesting a synergistic action of apoptosis-mediated cytotoxicity.

In conclusion, this study highlights the significant cytotoxic activity of GA and MA1 in both cisplatin-sensitive and cisplatin-resistant cell lines. The addition of GA or MA1 to CDDP demonstrates a synergistic effect, resulting in increased citotoxicity. The combinations need to be explored further using in-vivo models and possibly in clinical trials.

Acknowledgments

We are thankful to Dr. Benjamin K. Tsang (University of Ottawa, Ottawa, Canada) for providing A2780S and A2780CP cell lines, and Professor GSW Tsao, (Hong Kong University) for providing the immortalized normal ovarian cell line HOSE3-6. The work was supported by the generous His Majesty's Trust Fund Grant (SR/MED/MEDE/17/01), entitled, "High Grade Epithelial Ovarian Cancer: Overcoming Chemotherapy Resistance with Omani Marine Compounds"

References

Abdullah N, Al Balushi N, Hassan SI, Al Bahlani S, Dobrestsov S, Tamimi Y, Burney IA. (2021a). Hymenialdisine is cytotoxic against cisplatin-sensitive but not against cisplatin-resistant cell lines. Sultan Qaboos University Medical Journal 21(4): 632–634.

Abdullah N, Tamimi Y, Dobretsov S, Balushi N, Shukeili J, Al Balushi H, Alkindi M, Hassan SI, Al Bahlani S, Tsang B, Burney IA. (2021b). Malformin-A1 (MA1) sensitizes chemoresistant ovarian cancer cells to cisplatin-induced apoptosis. Molecules 26: 1-13 (Article 3624).

Al Bahlani S, Fraser M, Wong AY, Sayan BS, Bergeron R, Melino G, Tsang, BK. (2011). P73 regulates cisplatin-induced apoptosis via a calcium/calpain-dependent mechanism. Oncogene 30(41): 4219-4230.

Al Balushi N, Hasan SI Abdulla N, Al Dhahli B, Al Bahlani S, Ali I, Tsang B, Dobretsov S, Tamimi Y, Burney I. (2022). Addition of gallic acid overcomes resistance to cisplatin in ovarian cancer cell lines. Asia Pacific Journal of Cancer Prevention 23(8): 2661-2669.

Cragg GM, Newman DJ. (1999). Discovery and development of antineoplastic agents from natural sources. Cancer Investigations 17(2): 153-163.

Dobretsov S, Tamimi Y, Al-Kindi MA, Burney I. (2016). Screening for Anti-Cancer Compounds in Marine. Sultan Qaboos University Medical Journal 16(2): 168-174.

Donoghue M, Lemery SJ, Yuan W, et al. (2012). Eribulin mesylate for the treatment of patients with refractory metastatic breast cancer: use of a "physician's choice" control arm in a randomized approval trial. Clinical Cancer Research 18(6): 1496-1505.

Galluzzi L, Senovilla L, Vitale I, Michels J, Martins I, Kepp O, Castedo M, Kroemer G. (2012). Molecular mechanisms of cisplatin resistance. Oncogene 31(15): 1869-83.

Kahkeshani N, Farzaei F, Fotouhi M. (2019). Pharmacological effects of gallic acid in health and disease: A mechanistic review. Iranian Journal of Basic Medical Science 22: 225-237.

Kalayda GV Wagner CH, Bub I, Reedijk J. Jaehde U. (2008). Altered localisation of the copper efflux transporters ATP7A and ATP7B associated with cisplatin resistance in human ovarian carcinoma cells. BMC Cancer 8: 175-186.

Kaur M, Velmurugan B, Rajamanickam S, Agarwal R, and Agarwal C. (2009). Gallic Acid, an Active Constituent of Grape Seed Extract, Exhibits Anti-proliferative, Pro-apoptotic and Anti-tumorigenic Effects Against Prostate Carcinoma Xenograft Growth in Nude Mice. Pharmaceutical Research. 26: 2133-2140.

Konstantinopoulos PA, Spentzos D, Karlan BY, Taniguchi T, Fountzilas E, Francoeur N, Levine DA, Cannistra SA. (2010). Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer. Journal of Clinical Oncology 28(22): 3555-3561.

Kurman RJ, Carcangiu M, Herrington CS, Young RH. (2014). WHO Classification of Tumours of Female Reproductive Organs. Fourth Edition ed. Vol. 6. Geneva, Switzerland, Geneva.

Ledermann J, Harter P, Gourely C. (2012). Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer. New England Journal of Medicine 366(15): 1382-1392.

Liu Y, Wang M, Wang D. (2016). Malformin A1 promotes cell death through induction of apoptosis, necrosis and autophagy in prostate cancer cells. Cancer Chemotherapy and Pharmacology 77: 63-75.

Madlener S, Illmer C, Horvath Z, et al. (2007). Gallic acid inhibits ribonucleotide reductase and cyclooxygenases in human HL-60 promyelocytic leukemia cells. Cancer Letters 245: 156-162.

Matulonis UA, Sood A, Fallowfield L, Howitt BE, Sehouli J, Karlan BY. (2016). Ovarian cancer. Nature Reviews Disease Primers 2(1):

1-48 (Article 16061).

McGuire W, Markman M. (2003). Primary ovarian cancer chemotherapy: Current standards of care. British Journal of Cancer 89(3): S3-S8.

Notarte KI, Nakao Y, Yaguchi T, Bungihan ME, Suganuma K and dela Cruz TE. (2017). Trypanocidal activity, cytotoxicity and histone modifications induced by malformin A1 isolated from the marine-derived fungus Aspergillus tubingensis IFM 63452. Mycosphere 8(1): 111-120.

Pan B, Yao KS, Monia BP, Dean NM, McKay RA, Hamilton TC, O'Dwyer PJ. (2002). Reversal of cisplatin resistance in human ovarian cancer cell lines by a c-jun antisense oligodeoxynucleotide (ISIS 10582): evidence for the role of transcription factor overexpression in determining resistant phenotype. Biochemistry and Pharmacology 63(9): 1699-707.

Pandey K, Chalamala C. (2013). Potent anticancer compounds from the ocean. Academic Journals 5(8): 455-460.

Park SY, Oh HH, Park YL, Yu HM, Myung DS, Cho SB. (2017). Malformin A1 treatment alters invasive and oncogenic phenotypes of human colorectal cancer cells through stimulation of the p38 signaling pathway. International Journal of Oncology 51(3): 959-66.

Poveda A, Vergote I, Tjulandin S. (2011). Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer: outcomes in the partially platinum-sensitive (platinum-free interval 6-12 months) subpopulation of OVA-301 phase III randomized trial. Annals of Oncology. 22(1): 39-48.

Rinehart KL. (2000). Antitumor Compounds from Tunicates. Medicinal Research Review 20(1): 1-27.

Sourani ZM, Pourgheysari BP, Beshkar PM, Shirzad HP, and Shirzad MM. (2016). Gallic acid inhibits proliferation and induces apoptosis in lymphoblastic leukemia cell line (C121). Iranian Journal of Medical Science 41: 525-530.

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. (2021). Global cCancer sStatistics 2020: GLOBOCAN eEstimates of iIncidence and mMortality wWorldwide for 36 cCancers in 185 cCountries. CA Cancer Journal for Clinicians 71(3): 209-249.

Swami U, Chaudhary I, Ghalib MH, Goel S. (2012). Eribulin- a review of preclinical and clinical studies. Critical Reviews in Oncology and Hematology 81(2): 163-184.

Wang K, Zhu X, Zhang K, Zhu L, and Zhou F. (2014). Investigation of Gallic Acid Induced Anticancer Effect in Human Breast Carcinoma MCF-7 Cells. Journal of Biochemistry and Molecular Toxicology 28: 387-393.

Yoshioka K, Kataoka T, Hayashi T, Hasegawa M, Ishi Y, and Hibasami H. (2000). Induction of apoptosis by gallic acid in human stomach cancer KATO III and colon adenocarcinoma COLO 205 cell lines. Oncology Reports 7: 1221-1224.

You BR, and Park WH. (2010a). Gallic acid-induced lung cancer cell death is related to glutathione depletion as well as reactive oxygen species increase. Toxicology in Vitro 24: 1356-1362.

You BR, Moon HJ, Han YH, and Park WH. (2010b). Gallic acid inhibits the growth of HeLa cervical cancer cells via apoptosis and/or necrosis. Food and Chemical Toxicology 48: 1334-1340.

Zhu K, Fukasawa I, Fujinoki M, Furuno M, Inaba F, Yamazaki T, Kamemori T, Kousaka N, Ota Y, Hayashi M, Maehama T, Inaba N. (2005). Profiling of proteins associated with cisplatin resistance in ovarian cancer cells. International Journal of Gynecological Cancer 15(5): 747-754.