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Original Article

Improvement of the Selectivity Index (SI) and Cytotoxicity Activity of Doxorubicin Drug by *Panax ginseng* Plant Extract

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Abstract

In China, Japan, and Korea, *Panax ginseng* has been used in traditional medicine for thousands of years. Panax is a plant used as a general tonic or adaptogen for chronically ill patients. The current study evaluated the cytotoxicity of Panax ginseng extract (PGE). Different cell lines (HCT-116, LNCaP, and normal cell line VERO) were treated with different inhibitory agentsat different concentrations (1000, 500, 250, 125, 62.5, and 31.25 µg/ml) as follows: G1 (Methanol *Panax ginseng* extract, PGE), G2 (Doxorubicin, DOX), and G3 (Methanol *Panax ginseng* extract +DOX, PDD). Each inhibitory agent group was used to treat the cancerous cell lines HCT-116, LNCaP, and normal cell line (VERO) to obtain IC50% by MTT assay. The inhibitory ability of the 1000 µg/ml PGE was significantly increased in all the three-cell lines compared with other concentrations. The recorded data revealed that the inhibition ability of PGE and Doxorubicin towards the HCT-116 cell line significantly increased compared with the other cell lines. The interaction between different PGE concentrations and cell lines showed that the 1000 µg/ml PEG had the highest inhibitory effects on HCT-116 compared with other combinations. The interaction between different DOX concentrations and different types of cell lines showed that the 1000 µg/ml DOX had the highest inhibitory effects on LNCap compared with other combinations. The PGD inhibition ability reflected a significantly higher difference toward the HCT-116 cell line as compared with other cell lines. IC50% is the concentrations (µg/ml) to kill 50% of cell line. It was calculated by MTT assay for three cell lines: HCT-116, LNCaP, and VERO. The rate of effectiveness of the inhibitory factors (PGE, DOX, and PGD) showed highly significant differences toward the cell line HCT-116 compared to the other cell lines. This indicates the safety of the PGE compound and its low toxicity toward normal cells, quite the opposite of cancer cells as compared to the common drug DOX and combined PGD (PGE+DOX). PGD combined with DOX (PGE + DOX) showed antagonistic results toward the HCT116, LNCaP, and VERO cell lines, while UDE combined with DOX (UDE+DOX) showed synergistic activity.

Keywords: *Panax ginseng*, HCT-116, LNCap, VERO, doxorubicin, interaction index, selectivity index

Amélioration de l'Indice de Sélectivité (IS) et de l'Activité de Cytotoxicité du Médicament Doxorubicine par l'extrait de Plante *Panax ginseng*

Résumé: En Chine, au Japon et en Corée, le *Panax ginseng* est utilisé en médecine traditionnelle depuis des milliers d'années. Panax est une plante utilisée comme tonique général ou adaptogène pour les patients atteints de maladies chroniques. La présente étude a évalué la cytotoxicité de l'extrait de *Panax ginseng* (EPG). Différentes lignées cellulaires (HCT-116, LNCaP et lignée cellulaire normale VERO) ont été traitées avec différents agents inhibiteurs à différentes concentrations (1000, 500, 250, 125, 62.5 et 31.25 µg/ml) comme suit: G1 (Extrait méthanol *Panax ginseng*, EPG), G2 (Doxorubicine, DOX) et G3 (Extrait méthanol *Panax ginseng* +DOX, PDD). Chaque groupe d'agents inhibiteurs a été utilisé pour traiter les lignées cellulaires cancéreuses HCT-116, LNCaP et la lignée cellulaire normale (VERO) pour obtenir une CI50% par dosage MTT. La capacité inhibitrice de l'EPG à 1000 g/ml a été significativement augmentée dans toutes les lignées à trois cellules par

rapport aux autres concentrations. Les données enregistrées ont révélé que la capacité d'inhibition de l'EPG et de la doxorubicine envers la lignée cellulaire HCT-116 a considérablement augmenté par rapport aux autres lignées cellulaires. L'interaction entre différentes concentrations de l'EPG et des lignées cellulaires a montré que le PEG à 1000 ug/ml avait les effets inhibiteurs les plus élevés sur HCT-116 par rapport à d'autres combinaisons. L'interaction entre différentes concentrations de DOX et différents types de lignées cellulaires a montré que la DOX à 1000 g/ml avait les effets inhibiteurs les plus élevés sur LNCap par rapport à d'autres combinaisons. La capacité d'inhibition du PGD reflétait une différence significativement plus élevée envers la lignée cellulaire HCT-116 par rapport aux autres lignées cellulaires. IC50% est la concentration (µg/ml) pour tuer 50% de la lignée cellulaire. Il a été calculé par dosage MTT pour trois lignées cellulaires: HCT-116, LNCaP et VERO. Le taux d'efficacité des facteurs inhibiteurs (EPG, DOX et PGD) a montré des différences très significatives envers la lignée cellulaire HCT-116 par rapport aux autres lignées cellulaires. Cela indique la sécurité du composé EPG et sa faible toxicité envers les cellules normales, tout à fait le contraire des cellules cancéreuses par rapport au médicament commun DOX et au PGD combiné (EPG + DOX). Le PGD combiné à la DOX (EPG + DOX) a montré des résultats antagonistes envers les lignées cellulaires HCT116, LNCaP et VERO, tandis que l'UDE combiné à la DOX (UDE + DOX) a montré une activité synergique.

Mots-clés: *Panax ginseng*, HCT-116, LNCap, VERO, doxorubicine, indice d'interaction, indice de sélectivité

1. Introduction

Ginseng (*Panax ginseng Meyer*) is a perennial plant in the *Araliaceae* family that has been used medicinally or as a natural tonic for over 2,000 years in Asia (1). However, just four nations produce more than 99% of the world's ginseng: China, Korea, Canada, and the USA. The global ginseng market is projected to be worth $2,084 million, with Korea being the largest market at $1,140 million (2). In 2012, Korea produced 26,057 tons of ginseng, of which 50% was fresh. Red ginseng and processed goods such as nutritional supplements, medications, beverages, soups, and jellies (2) utilized another 44% of the ginseng produced (3). Ginseng is recognized to have immunostimulant, anticancer, antiemetic, antioxidant, and antiproliferative effects, among other health advantages (4-8).

According to the World Health Organization (WHO) World Cancer Study 2014, about 14.1 million new cancer cases occurred worldwide in 2012, causing 8.2 million deaths, which is about 14.6% of all human deaths (9). More than 250 cancers in the world, including breast, prostate, colon, rectal, blood cellular, bladder, ovary, uterus, stomach, liver and gastrointestinal tract, and blood, are recorded as major and common diseases (10). There are many internal and external causes of cancer, including foods, smoking, viral diseases, remains of labs, industry, laboratory testing, or some harmful things such as abnormal exposure to radiation or alcohol. Nonetheless, the main cause of cancer remains unknown (11). Internal factors include the development of the antibody responsible for stopping the protein suppressor of tumor (p53) antigens by the body (12). Chemotherapy, surgery, radiation, immunology, and gene therapy are used in cancer care (13). Chemical therapies have side effects, such as hair loss, weight loss, liver damage induced by chemical toxicities, respiratory ailments, cardiac toxicity, etc. (14). The extreme toxicity of most anticarcinogenic medicines speeds up the search for new medicines and attempts to develop new agents that can prevent or slow down the growth of cancer with less toxicity and more safety (15). Alternative drugs have been used in many breast, colon, and skin cancers to mitigate toxicity and the adverse effects of chemotherapy to achieve positive and appropriate outcomes (16). Numerous phytonutrients found in fruits, herbs, and spices act as powerful and effective cancer prevention agents by preventing the overproduction of toxic chemicals within the body (17). Doxorubicin has the ability to reduce the cardiac toxicity (18). The aims of this study were to evaluate the cytotoxicity of *Panax ginseng* extract (PGE) and improvement in the selectivity index of doxorubicin (DOX) by PGE bystudying the interaction index between DOX and PGE.

2. Material and Methods

2.1. Herb Collection and Extraction

Samples of three medicinal plantswere collected from the local Iraqi market of AL-Hikma Scientific Herbarium. The leaves of the herb were cleaned, dried in an oven at 50°C, pulverized to a fine powder using a mechanical grinder, and kept in a refrigerator at 4°C (19). Then the powder was extracted directly using a Soxhlet apparatus. From each plant, 100 mg of fine powder was taken and placed into an extraction thimble. Then, 1000 ml ethanol (100% concentration) was added, and the extract was allowed to sit for 24 hours. The final product of the extraction process was filtered through gauze and then through filter paper (Wattman No.1), and the supernatant was evaporated at 45°C under reduced pressure in a rotary evaporator.

2.2. Cytotoxicity Assay

2.2.1. The Experimental Design

The cell line treatments were allocated into three groups according to the type of inhibitory agent with varying concentrations (1000, 500, 250, 125, 62.5, and 31.25 µg/ml). Group one (G1) was treated with *Panax ginseng* extract (PGE), group two (G2) was treated with doxorubicin (DOX), and group three (G3) was treated with *Panax ginseng* extract +DOX (PDD). Each inhibitory agent was used to treat cancerous cell lines (HCT-116 and LNCaP) and a normal cell line (VERO) to first calculate the cytotoxicity and then the selectivity and interaction indices.

2.2.2. Cell Line Culture Procedure

In this study, two forms of cell culture media were used: growth media (GM) and maintenance media (MM). The pH was tested and modified to (1, 5, 7, 8). At the final concentrations of 100 IU/ml and 100 µg/ml penicillin G and streptomycin, respectively, antibiotics were added to the culture medium (1 ml of antibiotic solution to 100 ml of culture medium), and nystatin was also added to give a final concentration of 25 IU/ml. Media filtration was done using 0.22 µm Millipore filters in a biohazard safety cabinet. The components were 100 ml GM and MM (20). Every bottle was tightly sealed, labeled by name and date, and stored at 37 °C in the incubator. The bottles were checked 2-3 days later. If there was no turbidity and no sign of bacterial growth, they were moved to the refrigerator to be processed before they were used.Cell viability testswere performed by MTT (21).

2.2.3. The Interaction Index (IAI) of Drug Combinations

The interaction indices (IAI) of ARD (DOX + ART) were determined as 'combined'. It was used as an inhibitor against LS174, L20B, and NCL and calculated according to the following equation:

$$IAI = \frac{d1}{D1} + \frac{d2}{D1} \quad \{< 1, synergistic. = 1, additive. >, antagonistic\} \text{ (22)}$$

2.3. Statistical Analysis

In this analysis, the Genstat (version 10) software was used to evaluate the outcome of the cytotoxicity assaywith ANOVA p> 0.001 in one- and two-way.

3. Results

3.1. Dose Response Curve and Determination of $IC_{50\%}$ by MTT Assay

The results revealed a good inhibition ability (IC50%) of PGE and DOX compounds in addition to the combined compound UDD (UDE:DOX) and PGD (PGE:DOX). IC50% is the concentrations (µg/ml) which kill 50% of cell line.It was calculated by MTT assay for three cell lines, two cancerous ones(HCT-116 and LNCaP) and one normal cell line (VERO) (Table 1) (Figure 1). The IC50% of DOX toward HCT-116 was higher than that of PGE. The rate of effectiveness of the inhibitory factors (PGE, DOX, and PGD) showed highly significant differences toward the HCT-116 cell line compared to the others (VERO and LNCaP). The rate of IC50% of the three cell lines together was significant among all the inhibitory factors, with DOX having a clear, significant superiority; it has high inhibitory activity toward the three cell lines (Table 1).

Table 1. Inhibition concentration (µg/ml) of compounds to kill 50% of cell lines (IC50%) by MTT assay

Compounds (µg/ml)	Cancerous cell line		Normal cell line	Average b
	HCT-116	LNCaP	VERO	
PGE	32.89±2.27	41.98±2.10	217.45±2.51	97.44
DOX	28.80±1.34	45.00±1.29	88.23±1.28	54.01
PGD	39.11±2.12	43.54±0.98	155.59±1.21	79.413
Average a	47.088	343.526	245.458	
LSD,P<0.01	A=2.16	B=7.99	AB=15.63	

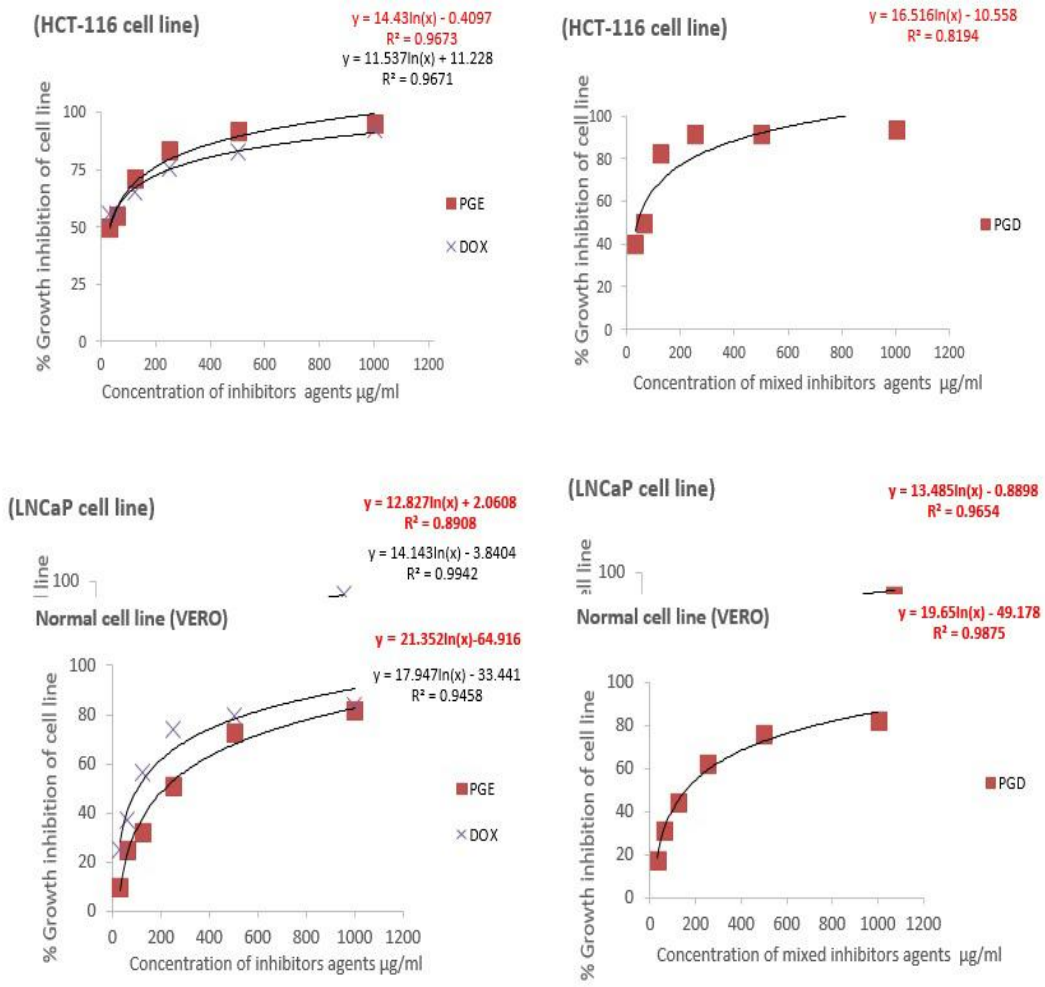

Figure 1. Dose-response curve of growth inhibition activity of PGE, DOX and PDE on cancerous cell

3.2. Selectivity Indexes (SI) of Inhibiting Agents

The current results demonstrated a selective index of all inhibitors (PGE, DOX, and PGD) towards HCT-116 and LNCap. The selectivity index of PGE (SI=6.62) was higher than that of DOX and PGD when used to treat HCT-116 and LNCaP. It has high toxicity toward the cancerous cell lines but low toxicity toward the normal cell line, VERO. This indicates the safety of the PGEcompound and its low toxicity toward normal cells, which is quite the opposite of its toxicity toward cancer cells as compared to the common drug DOX and combined PGD (PGE+DOX).

3.3. The Interaction Index (IAI) of Drug Combinations

The interaction indices (IAI) of PGD (DOX+PGE) combined on cancerous cell lines (HCT116 and LNCaP) and the normal cell line (VERO) were calculated using the following equation:

$$IAI = \frac{d1}{D_1} + \frac{d2}{D_1} \begin{cases} < 1, synergistic. \\ = 1, additive. \\ > 1, antagonistic. \end{cases}$$

The stock solution of the combination of DOX+PGE was prepared according to DOXPGE = (0.0166:0.9833) partition.

3.3.1. Human Colorectal Carcinomacell Line (HCT-116); Combined *P. ginseng* Extract and Doxorubicin (PGD)

IC_{50}%ofcompoundmixture=39.28µg/ml
$d_1=d_{DOX}$=0.0166 xIC_{50}%(39.28 µg/ml)
$d_{DOX=}$0.654 µg/ml.
$d_2=d_{PGE}$=0.9866xIC_{50}%(39.28µg/ml)
d_{PGE}=38.624µg/ml
$D_1=D_{DOX}$=28.80µg/ml
$D_2=D_{PGE}$=32.89µg/ml.
*I*AI=(d_{DOX}/D_{DOX})+(d_{PGE}/D_{PGE})
IAI=0.654/28.80+38.62/32.89=0.0227 + 1.174=1.197
1.197 >1,so there is antagonism.

3.3.2. Human Prostate Carcinoma (LNCaP); Combined *P. ginseng* Extract and Doxorubicin (PGD)

IC_{50}%ofcompoundmixture=43.54µg/ml
$d_1=d_{DOX}$=0.0166 xIC_{50}%(43.54 µg/ml)
$d_{DOX=}$0.722 µg/ml.
$d_2=d_{PGE}$=0.9866xIC_{50}%(43.54µg/ml)
d_{PGE}=42.95µg/ml.
$D_1=D_{DOX}$=45.00µg/ml
$D_2=D_{PGE}$=41.98µg/ml
IAI=IAI=(d_{DOX}/D_{DOX})+(d_{PGE}/D_{PGE})
IAI=0.722/45.00+42.95/41.98=0.016 + 1.035=1.03
1.35 >1,sothere isantagonism.

3.3.3. Normal Cell Line VERO; Combined *P. ginseng* Extract and Doxorubicin (PGD)

IC_{50}%ofcompoundmixture=155.59µg/ml
$d_1=d_{DOX}$=0.0166 xIC_{50}%(155.59 µg/ml)
$d_{DOX=}$2.592 µg/ml.
$d_2=d_{PGE}$=0.9866xIC_{50}%(155.59µg/ml)
d_{PGE}=152.99µg/ml.
$D_1=D_{DOX}$=104.51µg/ml
$D_2=D_{PGE}$=217.45µg/ml
IAI=IAI=(d_{DOX}/D_{DOX})+(d_{PGE}/D_{PGE})
IAI=2.592/2104.51+152.996/217.45=0.430+0.703=1.335
1.335>1, so there is antagonism.

The combination of PGD and DOX (PGE + DOX) showed antagonistic results toward the HCT116, LNCaP, and VERO cell lines, where IAI (1.19, 1.03, and 1.33, respectively) >one. This means that the PDE extract increased the IC50% of DOX, and this contradicts what was mentioned by Chen, Wang (23) who reported that *p ginseng* is able to improve many anticancer drugs, including doxorubicin, when used to treat HCT116 and LNCaP cell lines (Table 2).

Table 2. Selectivity indices (SI) and interaction index (IAI) of drug combinations of inhibitor agents

Compounds (µg/ml)	Cancerous cell line				Normal cell line
	HCT-116		LNCaP		VERO
	SI*	IAI**	SI	IAI	IAI
PGE	6.61	-	5.79	-	-
DOX	3.19	-	1.65	-	-
PGD	3.97	1.19	3.57	1.03	1.33

* SI >2 means present selectivity index; SI <2 means absent selectivity index.
** IAI<1 means synergistic; IAI>1 means antagonistic; IAI=1 means additive interaction

4. Discussion

The usage of herbal supplements is increasing, because they are regarded as less expensive and perhaps more effective than standard medication (24, 25). The limitations of existing conventional treatments have boosted the use of herbal medicines in prostate cancer. Compared to the conventional medication, DOX and PGD combined (PGE+DOX), the current study shows the safety of PGE compounds and their minimal toxicity toward normal cells. Hematological neoplasms and carcinomas, for example, are successfully treated with DOX (26). However, it is prone to multi-drug resistance (27). PGE ginseng may have anticancer properties. Because autophagy is a prosurvival cellular function, drugs that block it can be utilized as chemosensitizers in the treatment of cancer (28). Low dosages of ginseng also increase the cytotoxicity of docetaxel, cisplatin, and doxorubicin (29, 30). The observed impact may be caused by NF-B inhibition. NF-B promotes tumor growth, angiogenesis, metastasis, and chemotherapeutic resistance byactivating genes involved in malignant transformation and tumor promotion. Rg3 inhibits NF-B, reducing the expression of antiapoptotic genes (Bcl-2, Cox-2, c-Fos, c-Jun, cyclin D1, etc.) and increasing the sensitivity of colon cancer cells to docetaxel and other chemotherapeutics (29, 30). A pharmacokinetic interaction has been discovered that enhances some anticancer medicines. The elimination half-life of 5-FU increased by approximately 58.8% after pretreatment with 3.0 mg/kg *Panax ginseng* extract twice daily for 10 days (79.17 versus 125.72). The increase in 5-FU exposure induced by Panax ginseng extract may lead to a prolonged therapeutic effect (31). However, the exact process remains unknown. Ginseng may enhance medication exposure, including that of docetaxel. Ginseng and its ginsenosides, at clinically relevant doses, can mildly inhibit CYP1A1, CYP1A2, CYP1B1, CYP2D6, CYP2C9, CYP2C19, CYP2E1, and CYP3A4 in vitro using human liver microsomes (31). In rats, ginseng extract increases muscle and liver protein and RNA content, reducing the weight loss caused by anticancer medicines (31-35). Shengmai (a Chinese herbal preparation including red ginseng, lily turf root, and magnolia vine fruit) can protect diaphragm muscles against doxorubicin-induced toxicity, which is associated with a reduction in iNOS expression and lipid peroxidation (36). Shengmai also protects the liver and kidneys and increases white blood cell, platelet, and serum alanine aminotransferase levels (37). For over 2000 years, Chinese medicine has used and practiced herb-herb or herb-drug combinations to improve therapeutic effects (38). Recent research has shown that herbs used with anticancer medicines can re-sensitize chemoresistance (39). For example, in cancer treatment, herb-drug combinations can improve therapeutic efficacy.Few plants have garnered as much international attention as ginseng. Ginseng is commonly used in China, Japan, Germany, France, Austria, and the UK. It is frequently used as an adjuvant in cancer therapy in Asia and Western Europe (39). Interactions between herbs and medicines are clinically significant when they occur. Herbs should be labeled to warn consumers of potential medication interactions and refer them to their general practitioners or other medical professionals (40). P-glycoprotein overexpression is linked to MDR and chemotherapeutic failure (41). MDRl encodes p-glycoprotein, an ABC transporter superfamily member, and unloadsxenobiotics like DOX from cells, causing drug resistance (42, 43). In Asia, ginseng is largely utilized as a cancer tonic. Because of its low toxicity and favorable characteristics such as antiangiogenesis, antiproliferation, anti-inflammation, antioxidation, anti-apoptosis, and immunological modulation, ginseng has good promise as a chemotherapy adjuvant (44).

The *Panax ginseng* extract (PGE) has a safety index when used as a treatment compared with DOX. PGE revealed an antagonistic interaction when combined with DOX (PGD).

Using *Panax ginseng* extract (PGE) with doxorubicin is not recommended. This plant should be more extensively studied and the compounds purified to better understand its toxic cellular effects.

Authors' Contribution

Study concept and design: M. R. A. H.
Acquisition of data: N. J. K.
Analysis and interpretation of data: M. R. A. H.
Drafting of the manuscript: N. J. K.
Critical revision of the manuscript for important intellectual content: M. R. A. H.
Statistical analysis: N. J. K.
Administrative, technical, and material support: M. R. A. H.

Conflict of Interest

The authors declare that they have no conflict of interest.

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