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Bergenin, Isolated Compound from *Crassula ovata* Plant, Its Role as Synergistic Effect With Docetaxel Against Prostatic Cancer (PC-3) Cell Lines

Hawraa Kareem Lifta [1] and Enas Jawad Kadhim [*,2]

[1]Department of Pharmacognosy and Medicinal Plants, College of Pharmacy, University of Babylon , Babylon , Iraq
[2]Department of Pharmacognosy and Medicinal Plants, College of Pharmacy, University of Baghdad , Baghdad , Iraq
***Corresponding Author.**

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Abstract

The synergistic effect of the bergenin compound, derived from the *Crassula ovata* plant, and the docetaxel drug *in vitro* cell line was assessed in this study. The bergenin compound was extracted using a Soxhlet device and 85% ethanol, then was identified and isolated using a high-performance liquid chromatograph. Docetaxel is regarded as a potent chemotherapy treatment that was licensed in 1996 to treat a variety of cancers, including prostate cancer, by preventing microtubular depolymerization and reducing the impact of bcl-2 and bcl-xL gene expression. It is considered one of the most effective chemotherapy treatment for prostatic cancer. However, it has adverse effects, including febrile neutropenia or myelosuppression. This study aim to combine the docetaxel with new natural compound as there is no previous study on combination between the docetaxel and bergenin to reduce the therapeutic dose as much as possible and obtain same therapeutic effect .The results demonstrated that bergenin exhibits a good synergistic effect against prostatic cancer with IC_{50} equal to 26 as a phenolic compound that can induce G0/G1 cell cycle arrest, enhance the expression of Bax, decrease the expression of Bcl-2, and inhibit the PI3K/AKT/mTOR pathway. As revealed by the results, the inhibition effect of the combination (bergenin and IC_{50} docetaxel equal to 89,8) was 64, compared to an inhibition effect of 62 for 100 mcg of docetaxel and the data obtained were analyzed by one-way ANOVA with a significance level of "$p < 0.05$" .

Keywords : Bergenin , *Crassula ovata*, Cytotoxicity , Docetaxel ,Prostatic cancer .

Introduction

One of the main causes of death worldwide is cancer and the onset of carcinogenesis is aided by the accumulation of genetic alterations or mutations in certain key proteins in cells caused by a particular genetic backgrounds, long-term exposure to different environmental pressures. Chemotherapy is a main treatment for cancer, but include unfavorable side effects and drug resistance that leads to multi-drug resistance (MDR)[(1)]. Prostate cancer (PCa) is common disease causing 250,000 deaths each year and based on clinical stage and prostate-specific antigen values, prostatic cancer is identified as organ-confined or locally progressed in 90% of cases.Even though prostatic cancer can be identified in its early stages, some patients experience metastases following localized radiation or surgery treatment [(2)].One of the most effective chemotherapy treatment available right now is docetaxel (Taxotere®). Docetaxel is thought to exert its antitumor effects through two distinct mechanisms: preventing microtubular depolymerization; and reducing the impact of B-cell lymphoma (Bcl-2) and B-cell lymphoma (Bcl-xL) gene expression [(3)]. Although it only offers a slight survival advantage and most patients eventually advance because to intrinsic or acquired drug resistance including microtubule mutations, the evolution of cancer stem cells, the upregulation of the PI3K-AKT signaling cascade, the elevation of the Multi-Drug Resistance (MDR) family of efflux transporters, the reactivation of androgen receptor (AR) signaling, and the dysregulation of peroxisome proliferator-activated receptor α (PPARα) signaling [(4)].

So the combination therapies are a valuable alternative for the treatment of castration-resistant prostate cancer because they frequently improve therapeutic efficacy and postpone the onset of undesirable effects. For instance, the synergistic anti-proliferative impact of docetaxel and capsaicin might be ascribed to two separate effects: one side's inhibition of the PI3K/Akt/mTOR signaling pathway and the other side's stimulation of AMPK.

The combined effects of docetaxel and capsaicin in inhibiting PC-3 cell tumor growth were validated by *in vivo* investigations [5].So the medicinal plants have been used to treat a variety of illnesses. In fact, in some countries, the use of medicinal plants is closely associated with "witchcraft" [6] and Approximately 70% to 90% of people in affluent countries take herbal treatments that are referred to as "complementary," "alternative," or "nonconventional."[7,8] .

Over 3,000 plant species have been identified in Iraq; approximately 1500 are considered commercially important, which is classified as "medicinal plants". These plants are needed for medicine, Drug industry purposes and food [9]. Due to the existence of several active ingredients in medicinal plants can be used directly or indirectly as extract forms for the management of a variety of diseases[10]. The majority of natural compounds extracted from medicinal plants are thought to be the starting point for modern drug discovery[11] .

Scientists are now more interested in finding novel compounds with medical value for use in pharmaceuticals than just figuring out the chemical structure for a plant's use. they depended on the folkloric uses which is enabling them and other researchers to focus on plants that may be medicinally valuable rather than depending on trial and error, as in random screening processes. It is possible to test for biological activity using a variety of tests, including *in vitro* and *in vivo* testing of crude or fractionated extracts[12] .

This paper is dealing with a plant belong to Crassulaceae family ,one of family not mentioned in the flora of Iraq[13], also known as the stonecrop family, contains a wide variety of species, from tiny, inconsequential annual herbs to perennial shrubs and trees. About 35 genera and 23 hybrid genera make up the complete family, making a total of 305 intraspecific taxa and 1410 species. *Sedum* (stonecrop, wall pepper), has 428 species, is the largest genus. *Aeonium* (36 species), *Crassula* (195 species), *Echeveria* (139 species), *Kalanchoe* (140 species), and *Dudleya* (47 species) [14] .

Crassula ovata is a perennial succulent plant that can grow between one and three meters tall. It has strong branches and smooth, spherical, fleshy leaves that develop on either side of the stem. The color of the leaves is a deep Green, 30–90 mm long, and 18–40 mm wide large, elliptical to egg-shaped, frequently with a red border and a somewhat pointed end. Fresh stem growth is identical to the original in terms of color and texture, as are the leaves, but as they age, they turn brown and woody under ideal condition clusters of tiny white or pink star-shaped flowers to bloom. Pollinated flowers develop a tiny seed capsule when conditions are favorable [15,16] .

The secondary metabolites that are typically present in plant parts are responsible for the biological activity and therapeutic effects of those parts. Among the most prevalent are phenolic[17] . Secondary metabolites such as phenolic compounds exhibit remarkable cytotoxic effects on various cell lines because of their ability to scavenge free radicals, exhibit antioxidant features, and influence multiple pathways, including apoptosis, cell proliferation, metastasis, and angiogenesis[18] .The bergenin as phenolic compound also show anticancer effect according to other study against cervical cancer cells involves apoptosis, cell cycle arrest, inhibition of cell migration and the STAT3 signaling pathway[19] . Docetaxel (Taxotere, sanofi-aventis) has considered as one of the most important cytotoxic agents with serious side effect , the most common in all approved regimen is Febrile neutropenia or Myelosuppression which is dose-limiting toxicity[20] . Combination of natural compound with synthetic one allows to reduce such a side effect.

Materials and Methods

Materials and plant authentication

This study was experimental research using ethanol(Alpha chemicals 99.7-100%), n-hexane(BDH ,ltd., poole ,England), ethyl acetate(Alpha chemicals 99.5%), prostatic cancer (PC-3) Cell line , bergenin standard Macklin (CAS no :477-90-7) and the sample consists of whole plant (leaves ,steam ,root) of *Crassula ovate* were collected from Babylon nursery plantation in march 2023.The plant was identified and authenticated by Dr. Esraa Abdel AL Razzaq Majeed / Department of Biology /College of Sciences / University of Baghdad.

Extraction of plant material

About 200 gram of powdered plant were defatted for 48 hours in n-hexane to remove wax and fatty material, The plant material was filtered, dried at room temperature, and then begin the extraction process. Each 50 gram of dried, powdered, defatted plant materials were put in a thimble and extracted by a Soxhlet apparatus until complete exhaustion (9 hr.) ,300 ml of 85% aqueous ethanol was used as a solvent extractor, then by filtration to remove boiling chips and other residues and get crude extract by rotary evaporator under reduced pressure. The crude extract (37.421 g) was dissolved by 300 ml of water, then partitioned with ethyl acetate in separatory funnel(3*300ml)[21] . The ethyl acetate fraction (1.95% yield) was dried with anhydrous sodium sulfate, filtered, and evaporated to dryness under reduced pressure using rotary evaporator after that was sending to HPLC.

HPLC qualitative and quantitative analysis

High-performance liquid chromatography (HPLC) analysis was conducted on a SYKAM HPLC system (Germany) equipped with a C^{18}-ODS column .The mobile phase was composed of 95% acetonitrile + 0.01% Triflouroacetic acid (solvent A) and 5% acetonitrile + 0.01% Triflouroacetic acid (solvent B) at 1 ml/min. The gradient program was as follows: 0-5min (10%A+90%B), 5-9min (25%A+75%B) , 10-20 min (40%A+60%B) then returning to initial conditions. Detection of phenolic compounds was carried out with a UV-visible detector at 278 nm[22] .The isolation of bergenin was done by a modified PHPLC in the Ministry of Science and Technology in Baghdad. The modified part is that, during the analytical part the injection volume is 100 µL, while in the preparative part, instead of changing the column, there will be an increase in the injection volume to 700 µL with changing only the loop and collecting the compound that matches bergenin standard's R_t during the analytical procedure manually. Instead of automatically collecting, which occurs in a normal preparative HPLC run, the isolated compound is re injected to compare with the R_t of bergenin standard[23] .The quantification was done by calibration curve through determination of the relationship between detector response and the sample concentration where different concentrations of the standard (5, 10, 15, and 20) µg/ml vs. detector response (peak area) was plotted. Using linear regression analysis to construct the standard curve, the (R^2) correlation coefficient of the regression line is determined for bergenin [24].

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay

(MTT) assay done through using 96-well plate that implanted with cell line when a confluent monolayer was reached apply the sample . DMSO was used as the solvent in the stock solutions for docetaxel and bergenin, which were 13.3 and 20 mg/ml, respectively. By dilution prepare different concentrations for both compound as (100 ,50 , 25 ,12.5,6.25,3.1) mcg\ml and applied to well plate after remove the media from all cell except the negative control[19] . After 48 hrs. , apply the MTT dye . After 4hrs remove the media and dissolve the formazan violet crystal by DMSO. By micro plate reader at 570nm measure the absorbance with cell viability and cytotoxicity then by axel program the IC_{50} was calculated for bergenin and docetaxel, the next step of combination between bergenin and calculated IC_{50} of docetaxel was done, as the negative control is a cancer cell with media , the positive control represent the IC_{50} of docetaxel and the combination of same concentrations of bergenin (100 ,50 , 25 ,12.5,6.25,3.1) with of IC_{50} of docetaxel.

Statistical analysis

The data was analyzed by one-way ANOVA with a significance level of "$p < 0.05$" , after testing the data with a normality test and ensuring a normal distribution, using the Levene test to assess variance homogeneity and post hoc analysis to explain the significant difference between the means.

Results and Discussions

The presence of about 69.868 PPM of bergenin in this plant crude extract (37.421 g) first identified by the HPLC chromatogram of ethyl acetate(1.95% yield) figure 1 show all compounds present in them, about eleven compounds were found, bergenin R_t (5.60) while bergenin standard figure 2 R_t (5.69) from the two close R_t values confirm the compound while figure 3 illustrates the re injection of isolated bergenin chromatogram to confirm the isolated compound as bergenin .

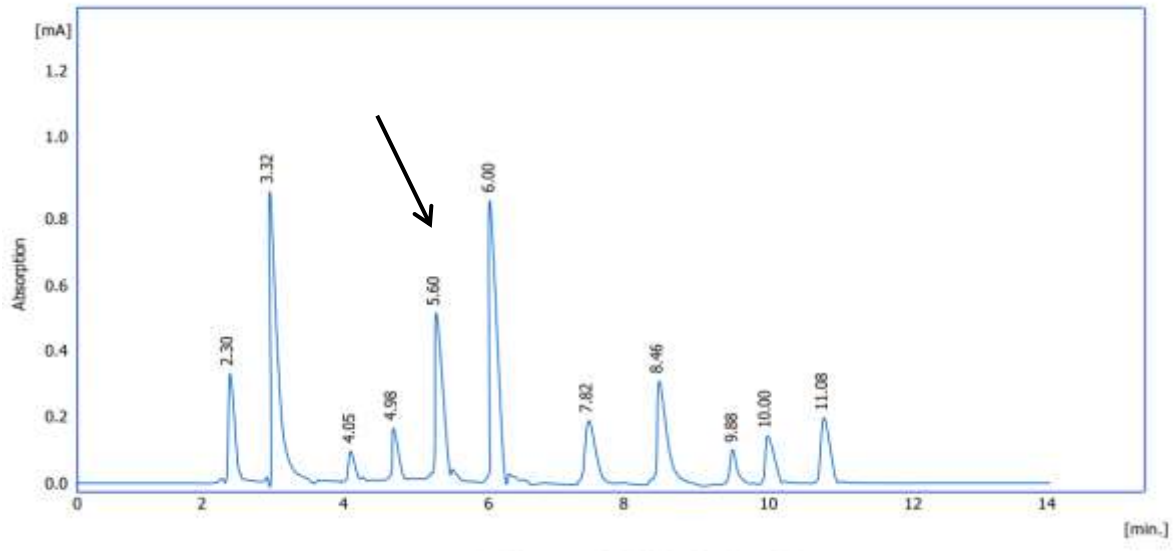

Figure 1 . HPLC chromatogram of ethyl acetate fraction

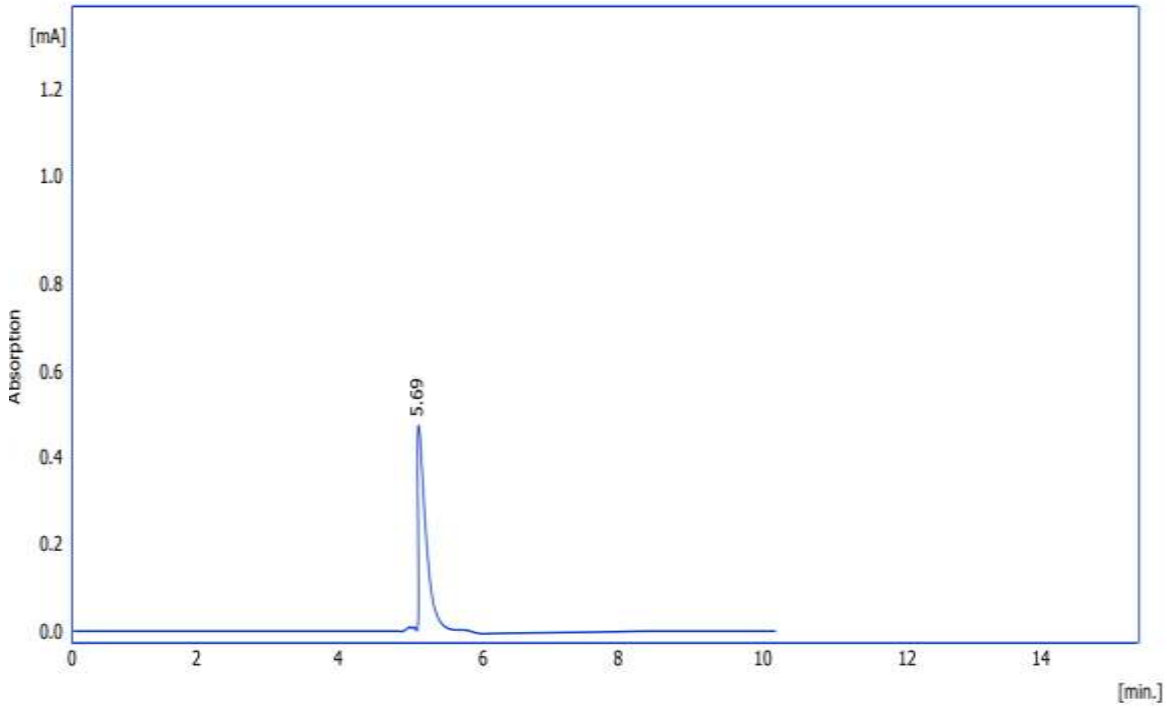

Figure 2 . HPLC chromatogram of bergenin standard

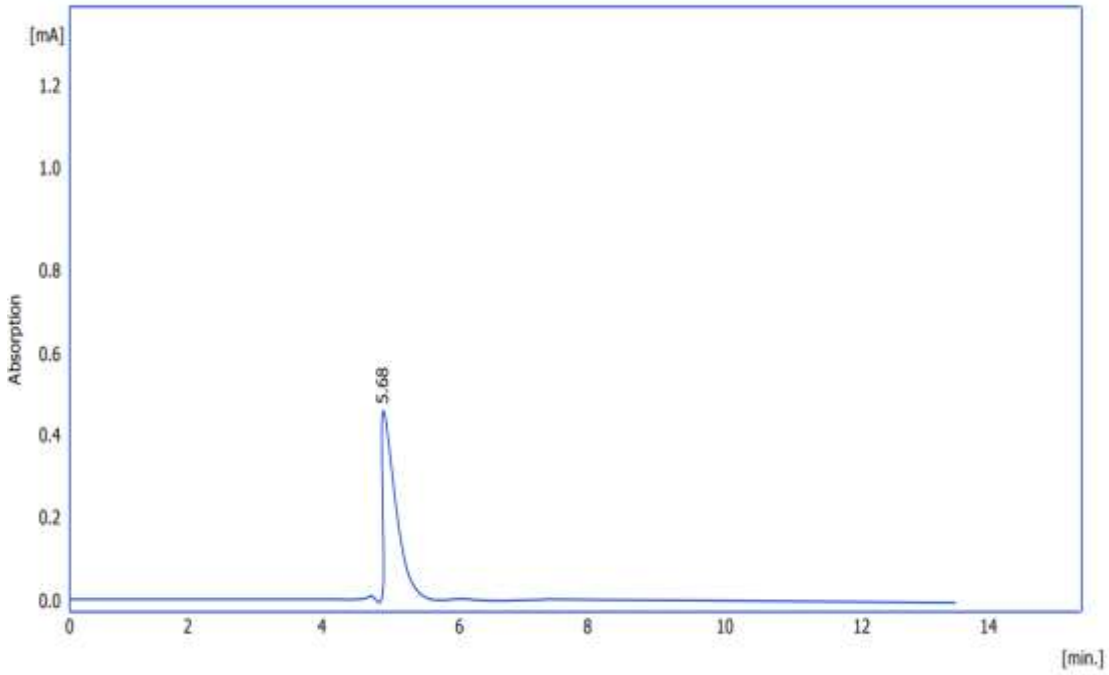

Figure 3 .HPLC chromatogram of isolated bergenin compound

MTT assay

The results demonstrate that a very noteworthy synergistic effect between bergenin and docetaxel against the prostatic cell lines as represent in the data that was analyzed by one-way ANOVA with a significance level of "$p < 0.05$" . The first results of docetaxel and bergenin alone against the prostatic cell showed each compound has the ability separately to curb the growth of prostatic cancer cell line and significantly, in concentration dependent manner figure 5 and 6 . The second results of combination (bergenin and IC_{50} of docetaxel) against the prostatic cells figure 7 , showed that each compound has significant ability to curb the growth of prostatic cancer cells . The data was tested using Shapiro-Wilk tests since the number of cases was less than 2000. The null hypothesis is accepted for most concentrations

since their p-values surpass 0.05. so the data is normally distributed. The variance homogeneity assessed by the Levene show significant differences (not equal). Post hoc analysis using the Games-Howell test shows a significant difference ("p < 0.05") among groups, in particular, 100 and 50 ug/ml.

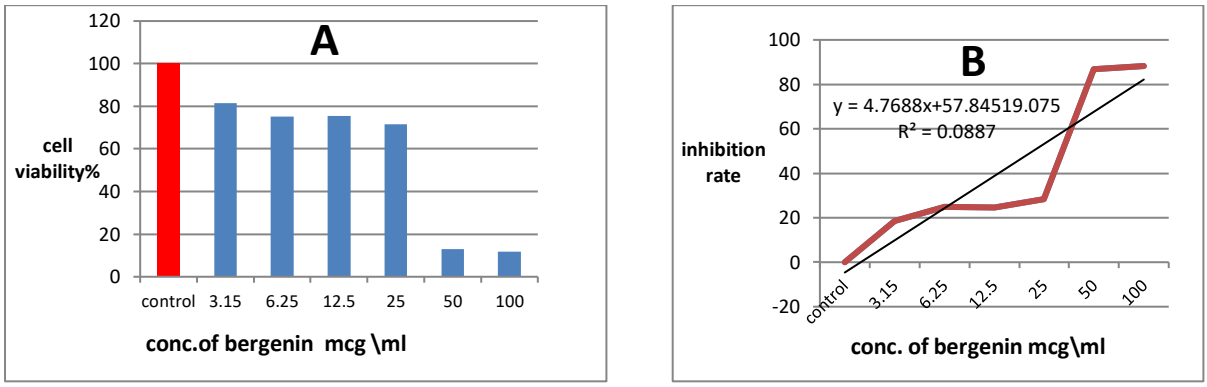

Figure 5 . A- Cytotoxic effect of bergenin against PC-3 cells line . B- IC_{50} (half inhibition concentration) of bergenin equal to 26 mcg

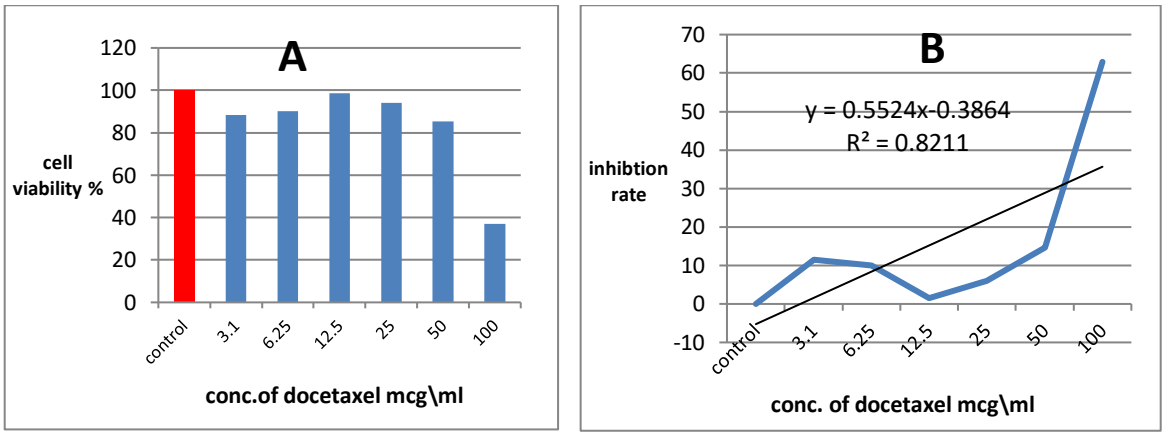

Figure 6 . A- Cytotoxic effect of docetaxel against PC-3 cells line . B- IC_{50} (half inhibition concentration) of docetaxel equal to 89.8 mcg

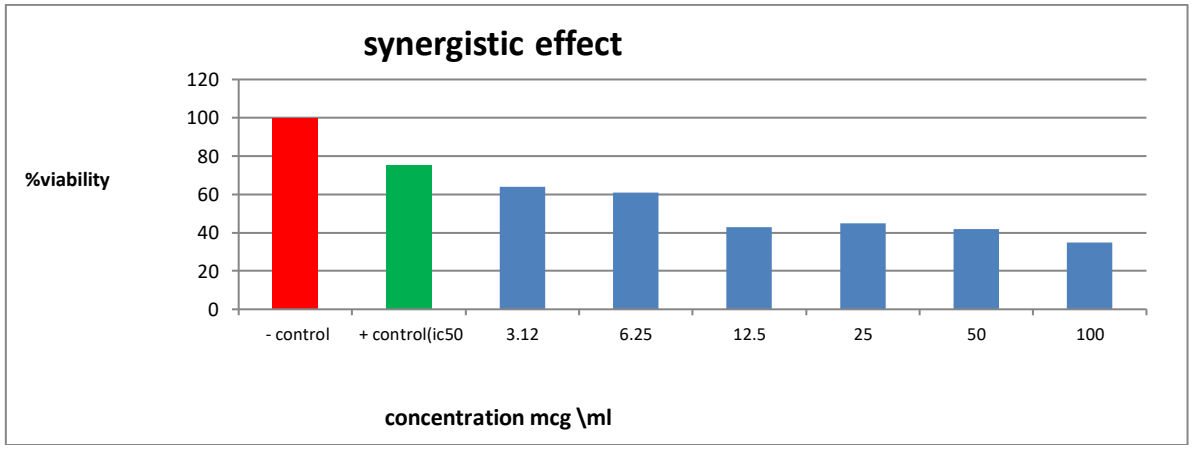

Figure 7 . Cytotoxic effect of combination (bergenin and IC_{50} of docetaxel equal to 89.8 mcg) against PC-3 cells

In this experiment the bergenin compound figure 8 show excellent anticancer effect against prostatic cancer, the inhibition effect of bergenin at 100 ug/ml is equal to 88 compared to docetaxel at same concentration which is give an inhibition effect equal to 62 , also in case of IC_{50} bergenin has a higher value than docetaxel this belong to that, the bergenin as phenolic compound which shows anticancer effect according to other study it induces G0/G1 cell cycle arrest, enhanced the expression of Bax , decreased the expression of B-cell lymphoma 2(Bcl-2) and inhibited PI3K/AKT/mTOR pathway[19] and inhibited PI3K/AKT/mTOR pathway[25] . At same time the synthetic or semi synthetic drug is still favorable despite the natural compound give less side effect .The reason for that belong actually for several points including: most natural compounds are lacking precise mechanism of action and solubility problem, in case of bergenin it is not water soluble ,it is difficult to dissolved it in DMSO and require long shaking and each drug to give an effect must be water soluble to be absorbed inside the body to solve this problem its required to convert it into nano particles, still these particle has many challenges inside the body including potential toxicity because can a cross the biological membrane especially blood brain barrier (BBB) ,probing the targeting efficiency , undergo changes or accumulation inside the body[26] , another way to use it is by combing it with synthetic or semisynthetic compound, this allow to reduce the dose required in the body and further allow to reduce the side effect which is the main problem associated with the synthetic drugs . In this study docetaxel, has been considered as one of the most important cytotoxic agents but has serious side effects .Combination with bergenin a natural compound will allow to reduce such a side effects. from the result of combination of IC_{50} of docetaxel (89.8 mcg) with bergenin(100 mcg) the inhibition effect is equal to 64 compared to using 100 mcg of the drug alone is equal to 62 This opens a window to further studies and used several values lower than the IC_{50} of docetaxel and try to combine with bergenin to obtain the best synergistic effect between the two compounds .

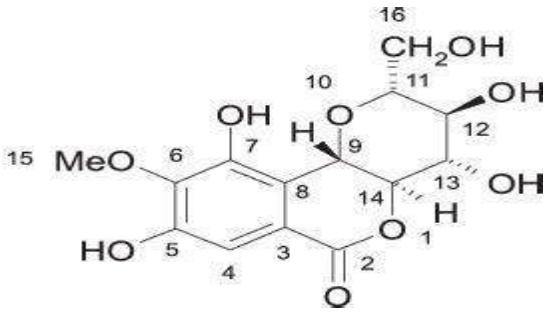

Figure 8 . Stricture of bergenin compound [27]

Conclusion

As observed from applying varying concentrations of "bergenin" to a prostatic cancer cell line with an IC_{50} equal to 89.8 mcg of docetaxel, the isolated bergenin and docetaxel had a good synergistic impact against prostate cancer. This is attributed to the ability of bergenin , which is according to other studies, inhibits the activation of the JAK2/STAT3 pathway and induces apoptosis and autophagy, induces the cleavage of PARP (an indicator of apoptosis), and the apoptosis molecular mechanism is done by the downregulation of ant apoptotic Bcl-2 and upregulation of the proapoptotic B-cell lymphoma 2 (Bcl-Fp132) associated X protein (Bax).

Acknowledgments

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Conflicts of Interest

No conflicts.

Funding

Self-funding.

Ethics Statements

In vitro study, no ethical statements are required.

Author Contribution

The authors confirm their contribution to the paper as follows: extraction, isolation ,structural analysis and cytotoxicity with statistical analysis : Hawraa K. lifta and Enass J. Kadhim reviewed the results and approved the final version of the manuscript.

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مركب البيرجنين المعزول من نبات المال، ودوره في التأثير التأزري مع الدوسيتاكسيل ضد خلايا سرطان البروستات

حوراء كريم لفته[١] و ايناس جواد كاظم [٢،*]

[١] قسم العقاقير والنباتات الطبية، كلية الصيدلة، جامعة بابل، بابل، العراق

[٢] قسم العقاقير والنباتات الطبية، كلية الصيدلة، جامعة بغداد، بغداد، العراق

الخلاصة

هذه الدراسة تقييم التأثير التآزري لمركب البرجينين المشتق من نبات الكراسولا البيضوية ودواء الدوسيتاكسيل على سرطان البروستاتا. تم استخلاص مركب البرجينين باستخدام جهاز سوكسلت و٨٥٪ إيثانول. ثم تم فصله وتحديده باستخدام كروماتوجرافيا سائلة عالية الأداء. يعتبر دوسيتاكسيل علاجًا كيميائيًا قويًا تم ترخيصه في عام ١٩٩٦ لعلاج مجموعة متنوعة من السرطانات، بما في ذلك سرطان البروستات ، عن طريق منع إزالة البلمرة الأنبوبية الدقيقة وتقليل تأثير التعبير الجيني bcl-2 وbcl-xL. ويعتبر أحد العلاج الكيميائي الأكثر فعالية لسرطان البروستات . ومع ذلك، فإنه له آثار ضارة، بما في ذلك قلة العدلات الحموية أو كبت نقي العظم. تهدف هذه الدراسة إلى دمج الدوسيتاكسيل مع المركب الطبيعي الجديد حيث لا توجد دراسة سابقة حول الجمع بين الدوسيتاكسيل والبيرجينين لتقليل الجرعة العلاجية قدر الإمكان والحصول على نفس التأثير العلاجي. أظهرت النتائج أن البرجينين يظهر تأثيرًا تآزريًا جيدًا ضد سرطان البروستات كمركب فينولي يمكن أن يحفز توقف دورة الخلية G0/G1، ويعزز التعبير عن Bax، ويقلل التعبير عن Bcl-2، ويمنع مسار PI3K/AKT/mTOR . وكما أظهرت النتائج، فإن معدل التثبيط للتركيبة (البرجينين وIC50 دوسيتاكسيل) كان ٦٤، مقارنة بمعدل تثبيط قدره ٦٢ لـ ١٠٠ ميكروغرام من دوسيتاكسيل. وتم تحليل البيانات إحصائيا التي تم الحصول عليها بواسطة ANOVA أحادي الاتجاه بمستوى دلالة $P < 0.05$.

الكلمات المفتاحية : بيرجنين ، دوسيتاكسيل ، نبات المال ،السمية الخلوية ، سرطان البروستات.