The Libyan International Medical University

Faculty of Basic Medical Science

Effect of snake venom on ovarian cancer

Taima Mohamed Shein

Supervised by: Dr. Eman Layas

Assisted by: Dr. Awali Nashad

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Abstract:-

Ovarian cancer, the second most common gynecological is still ranked among the top 5 of female cancer death in word. The proliferation of tumor cell, angiogenesis, and the relationship between the cancer cell and the component of extracellular matrix and important in events of carcinogenesis, and these pathways are being use as targets for new anticancer treatment. Various venoms and their toxins have shown possible anticancer effect on ovarian cancer cell line, providing new perspectives in drug development. In this report searcher observed the effect of natural toxins from snake venom and mechanisms through which they can inhibit the growth and proliferation of ovarian cancer cell. This approach could improve the efficiency of normal therapies and could allow the administration of decreased dose of chemotherapy natural toxins from snake venom could become potential candidates for future treatment of ovarian cancer.

Keywords: snake venom; ovarian cancer; carcinogenesis; human epithelial cell lines

1.0 Introduction:-

Cancer is one of the most life treating multi-faceted diseases that occur on account of uncontrolled cell production, accompanied by attack of local tissues and their metastasize ability. Cancer is ranking third for leading death source after infectious and cardiac diseases [1].

Two factors are involved which can caused cancer. These factors include external factors such as, radiations, chemicals, tobacco, viruses etc. Internal factors which involves, immune conditions, hormones and mutations (genetic alterations give rise to changes in expression, activation or localization of regulatory proteins in cells, affecting the signaling pathways that alter their response to regulatory stimuli and allow the unrestricted cell growth). This may act together or in sequence to instigate or promote carcinogenesis [1].

Ovarian cancer, the second most common gynecological cancer is still ranked among the top 5 of female cancer deaths in the world. Because ovarian cancer is often asymptomatic, the majority of patients with newly diagnosed ovarian cancer present the disease in its advanced-stage. Ovarian cancer is a result abnormal cells that have the ability to invade or spread to the other parts of the body [1].

Among the therapies used for ovarian cancer, chemotherapy remains the major option in cases where surgical treatment cannot be performed. The chemotherapeutic resistance or incapacity of administrating chemotherapy because of the poor health status of the patient is important issues in these cases. Development in oncology field of new drugs from natural resources holds an important role in modern medicine, mostly because the standard treatments have serious side effects. In some experimental studies, several plants and their compounds with possible anticancer effects have been reported, with their mechanisms being explained through the inhibition of angiogenesis, decreased cell growth and proliferation, apoptosis, and prevention of oxidation and inflammation. However compounds from plants are not enough nowadays.
Therefore, in the last year, studies have focused on the anticarcinogenic effects of toxins from animal venom. Snake venoms are the secretion of venomous snakes which are synthesize in venom gland. Snake venom are complex mixture of enzyme, toxins, nucleotides and proteinaceous and peptidyl toxins [1].

These proteins may be toxic or non-toxic. snake venom contain a number of bioactive substance which have pharmacological importance, snake venoms have been classified as 3 groups (neurotoxins, hemotoxin & cytotoxicity) according to its mode of action and effect. Neurotoxins target central nerves system causing heart failure and breathing problems. They have the ability to inhibit ion movement across the cell membrane and block the communication between the neurons. Hemotoxins are the toxins the cause destruction of RBC it affects cardiovascular system and blood functions. Cytotoxicity venom target specific cellular sites or muscles also inducing apoptosis and platelets activation through CLEC-2 platelet targeting and inhibition DNA and RNA production [1].

Enzymes present in snake venom hydrolyze protein and membrane component leading to blood clotting and tissue necrosis. Snake venom toxin increased the expression of pro-apoptotic protein Bax and caspase-3 but down-regulated anti-apoptotic protein Bcl-2 and inhibition of p50 and p65 translocation into the nucleus. Snake venom toxin also inhibited DNA binding activity of the signal transducer and activator of transcription 3 (STAT3). Snake venom toxin from Vipera Lebetina Tturanica and Agkistrodon Contortrix [CN] caused apoptotic cell death of ovarian cancer cells through the inhibition of STAT3 and OVCAR-5 signal and suggested that snake venom toxin may be applicable as an anticancer agent for ovarian cancer and the Bothrops Jararacussu [BJcuL] can Inhibit proliferation and growth ovarian cancer [1].

The aim of this report is to study the effect (mechanism and results) of snake venom on the treatment of ovarian carcinoma.

2.0 Materials and methods:-

They used Agkistrodon Contortrix [CN] (type of snake venom) on human ovarian cancer cell injected intraperitoneally into 40 female mice, they concluded after examination that the group treated with CN showed a decrease in the number and size of tumors formed and also have less adverse effect the liposomal encapsulation of CN possesses a high efficiency in inhibiting tumor dissemination and angiogenesis in human ovarian cell cancer [2].

3.0 Results:-

A preliminary study was carried out using different snake venoms (Agkistrodon Contortrix and Vipera Lebetina Turanica) venoms were chosen because of their effect on the morphology of OVCAR-5 and SK-OV-3 cells. About 100 ovarian cancer cell lines are available. Genomic differences between cancer cell lines and tissue samples have been pointed out in several studies. The most commonly used cell line models for ovarian cancer are SK-OV-3, A2780, OVCAR-3, CAOV3 and IGROV1. The two most frequently used ovarian cancer cell lines SK-OV-3 and OVCAR-3.

Effect of Agkistrodon Contortrix [CN] on OVCAR-5

This tissue was controlled by CN, were formalin fixed for histological examination, the histological section were stained with antibody against factor-VIII related antigen as a specific marker of vascular endothelial cell one of the most remarkable differences between CN-treated and control group was complete absence of tumor, the findings indicate that the level of angiogenesis was dramatically decreased by CN [2].

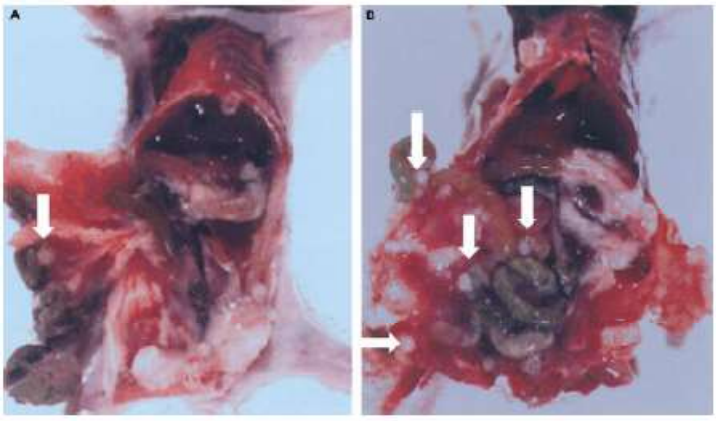

***Fig 1* : (A) shown normal cell, (B) shown nodules effect of CN on OVCAR-5**

Effect of Vipera Lebetina Turanica on Sk-OV3

The SK-OV3 human ovarian cancer cells the inhibition of growth and proliferation and induces programmed cell death by effect metalloproteases on the cell [3].

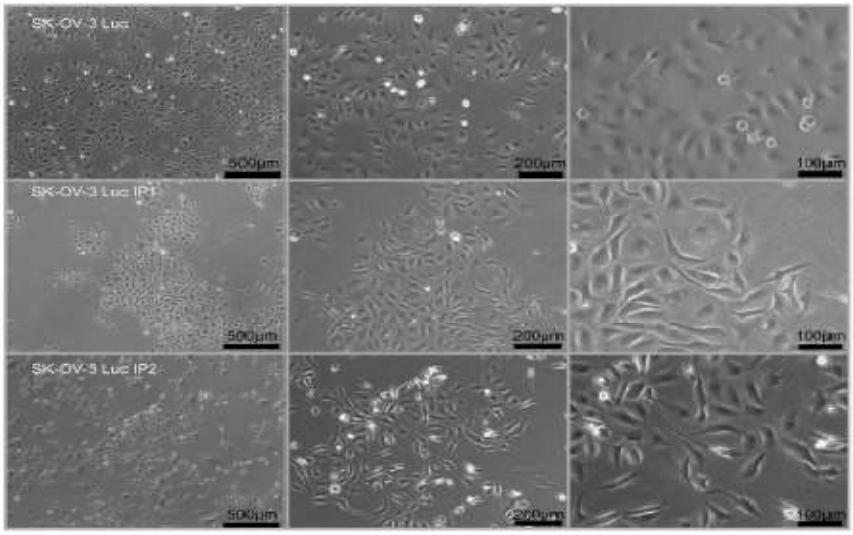

***Fig. 2* : Shown gradually decrease of tumor cells due to the effect of type III proteases**

Effect of Bothrops Jararacussu [BJcuL] on OVCAR-5

BJcuL had a differing effect on viability of tumor cells depending on concentration a BJcuL at concentration lower than 1μM didn't have cytotoxic effect on cell even at 96h ,but was cytotoxic to the cell at concentration higher than 1μM in 24h so can effect rabidly on OVCAR-5 to suppresses proliferation and growth . [4]

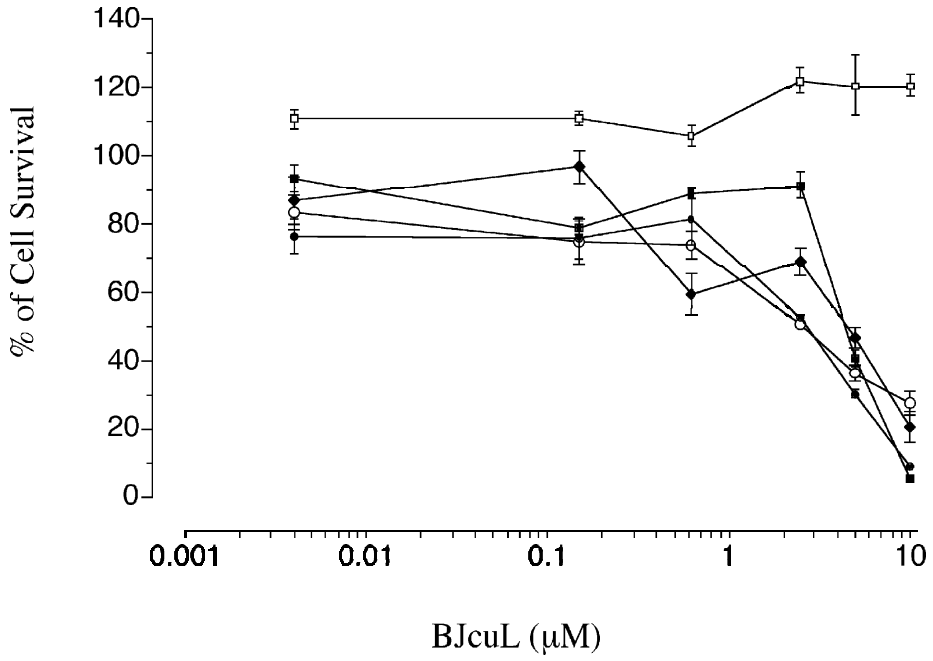

Fig. 3 **: Shown effect of (BJcuL) concentration with rabid suppresses proliferation and growth of OVCAR-5**

4.0 Discussion :-

Several type of snake venom can inhibit ovarian carcinoma, each type has its own way Markland et al used the (CN) one of the type of snake venom on OVCAR-5 (human epithelial carcinoma) it is effect on inhibits tumor cell invasion through anartificial basement membrane and adhesion cell through inhibition of vβ5 of OVCAR-5 to extracellular matrix and inhibited ovarian cancer dissemination and inhibited angiogenesis also can inhibits the platelet aggregation and preventing tumor migration by blocking the integrin signaling pathway. Platelet aggregation plays an important role in facilitating tumor metastasis [2].

Song et al used (Vipera Lebetina Turanica), it's the other type of snake venom which act on SK-OV3 (human epithelial carcinoma) effect on induces programmed cell death (apoptosis) by effect of metallooroteases type III which can inhibits platelet aggregation and can inhibits the proliferation and growth of ovarian cancer so they can increase the expression of the Bax and caspase 3 (pro-apoptotic) and decreased the expression of Bcl2 (anti-apoptotic protein) and increase DNA binding activity of NF-KB also inhibition of translocation of p65 and p50 into the nucleus as well phosphorylation of inhibitory κB [3].

De Carvalho et al investigation the effect of snake venom (Bothrops Jararacussu) on OVCAR-5, they observed a weak adherence of cancer cell to BJucL, this lectin (BJcuL) has been shown to bind to lactose moieties and induce agglutination of erythrocytes, so this type of snake venom didn't inhibit adhesion of this cell to extracellular matrix proteins of lectin but concluded that the viability of the tumor cells was suppressed by BJucL (can inhibit the proliferation and growth of tumor cell) [4].

5.0 Conclusion:-

Snake venom is a complex mixture of several protein and enzymes and organic and inorganic molecule. Snake venom used an anti-cancer agent the cytotoxic effect of snake venom have a potential to destroy tumor cancer cell by inhibits proliferation and causing cell death.

For the future work, It is importantly to continue these studies concerning therapeutic drugs from natural resource and, more importantly, to investigate their mechanism of action on cancer.

6.0 References:-

1- Moga M. A., Dimienescu O. G., Arvatescu C. A., Ifteni P., Ples L., "Anticancer activity of toxins from bee and snake venom – an overview on ovarian cancer". Molecules 2018, 23, 692.

2- Markland F. S., Shieh K., Zhou Q., Golubkov V., Sherwin R. P., Richters V., Sposto R. "A novel snake venom disintegrin that inhibits human ovarian cancer dissemination and angiogenesis is an orthotopic nude mouse model". Haemostasis 2001;31:183-191

3- Song J. K., Jo M. R., Park M. H., Song H. S., An B. J., Song M. J., Han S. B., Hong J. T. "Cell growth inhibition and induction of apoptosis by snake venom toxin in ovarian cancer cell via inactivation of nuclear factor κB and signal transducer and activator of transcription 3". Arch. Pham. Res. 2012; 35:867-876.

4- De Carvalho D. D., Schmitmeier S., Novello J. C., Markland F. S. "Effect of BJcuL (a lectin from the venom of the snake Bothrops jararacussu) on adhesion and growth of tumor and endothelial cells". Toxicon 2001;39:1471-1476.

5- De Vlieghere E., Carlier C., Ceelen W., Bracke M., De Wever O., "Data on in vivo selection of SK-OV-3 Luc ovarian cancer cells and intraperitoneal tumor formation with low inoculation numbers. Elsevier (2016), 542-549.