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The Effect of *Ficus Religiosa* Chloroform Extract on Suppression of Acquired Docetaxel Resistance in Prostate Cancer

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Abstract:

Most of the currently used cancer therapeutics are natural products. These agents were generally discovered based on their toxicity to cancer cells using various bioassays. Ficus religiosa (FR) plant is important medicinal plant and traditionally used to treat various diseases including mastitis, otitis media, pharyngolaryngitis, urethritis, dysmenorrhea and diabetic. Accordingly, it was aimed to investigate the cytotoxic effect of Ficus religiosa chloroform extract on Patch1 and Gli2 gene expression in Hedgehog pathway and Id1, Id2 and Id3 genes expression in inhibition differentiation pathway on prostate cancer cells, which are resistance to docetaxel (PC3-TxR) in vitro. Chloroform extract of Ficus religiosa plant leaves was performed to tested cytotoxic effect on PC3-TxR by using Sulforhod-amine-B assay and its ability to inhibition genes expression on PC3-TxR cells by using RT-PCR assay. The results showed that F. religiosa chloroform extract display high cytotoxic effect (IC50= 0.3±0.02 mg/ml), and inhibition effect of Id2 and Id3 gene expression more than, Patch1 and Gli2 gene expression on PC3-TxR cells. The present study showed anticancer effect of F. religiosa chloroform extract which target Id pathway on PC3-TxR cells.

Key words: *Ficus religiosa plant, Prostate cancer cells lines, gene expression, RT-PCR, Hedgehog, inhibition differentiation, Signalling pathway, Cytotoxicity*

Introduction:

Prostate cancer causes substantial morbidity and mortality worldwide and is the second leading cause of cancer death in men in developed countries (1). Metastatic prostate cancer initially responds to anti-androgen therapy; however, it eventually becomes resistant to hormonal manipulation. Chemotherapy remains the only treatment option in the setting of resistant prostate cancer providing modest survival and palliative benefits. Only half of all patients will respond to docetaxel, a mitotic spindle poison that is the current mainstay of chemotherapy. Docetaxel improves median survival by 2 months at the cost of significant toxicity, particularly in elderly patient population (2, 3). Inevitably, resistance to first line chemotherapy will develop and the disease then becomes difficult to control. Although, identifying patients who will not benefit from chemotherapy prior to their exposure will avoid unnecessary toxicity and allow them to move on to alternative treatment options. Targets for further drug development may also arise (4, 5).

Combination chemotherapy with nature products could provide new cancer therapy against of cancer resistance to chemotherapy and provide safe way with fewer side effects than other therapy (6). In this era of personalised cancer therapy, significant treatment advances have occurred through indeed, many of the pathways implicated in prostate cancer chemoresistance may well be applicable to other cancer types.

The majority of the world's population in developing countries still relies on herbal medicine to meet their health needs in cases when synthetic medicine could not relieve patients who suffer from painful, illnesses like cancer. In the modern system of medicine, chemotherapy is one of the most extensively studied methods in anticancer therapies, its efficacy and safety remain a primer concern as toxicity and other side effects of chemotherapy are sever (7).

Ficus religiosa one of the traditional medicinal plants used widely in the middle east because it has ayurvedic proprieties

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,antidiabetic, nootropic effect, wound healing, antihyperlipidemic, anticonvulsant, antiflammatory, analgestic, antimicrobial, antiviral, immunostimulant, parasympathetic modulatory and antitumor activities (8, 9, 10, 11, 12). It contains a number of important phytochemicals, which are phytosterols (stigmasterol, lupeol, campesterol and triterpene), tannic acid, flavonoids, serotinin and phenol compounds (13). Also the leaves are rich in minerals like calcium, phosphorous, iron, zinc; sodium, manganese and potassium, as well as amino acid are present in the leaves. Extracts obtained from the plant showed applications in pharmaceuticals (14, 15).

Therefore this study was designed to assess the cytotoxic effect of Ficus religiosa leaves chloroform extract on different pathways against prostate cancer cell resistance to docetaxel drug (PC3-TxR).

Materials and Methods:

Cell line and Reagents:

Fresh leaves of Ficus religiosa (FR) were collected between April to June 2012 in the city of Baghdad (Iraq) and authenticated by Dr. Ali Al-Mosauy, Professor in Plant Taxonomy, Department of Biology, Collage of Science, University of Baghdad (Baghdad, Iraq).

The human prostate cancer, which is docetaxel resistant cell line (PC3-TxR) was kindly provided by supplied by Department of Medicine, University of Pittsburgh and Partners Healthcare in USA.

The RPMI 1640 medium, glutamine, trypsin-EDTA, and fetal bovine serum were obtained from Cellgro (Manassas, VA, US) and Invitrogen (Grand Island, NY, US).

Methods

Preparation plant extract:

The plant leaves were dried in an oven at 60ºC and crashed into small chips. The crashed dry leaves (50 g) were macerated in 1L of 80% methanol under sonication for one hour and the FR was extracted by stirring the mixture for 24 hours. The extract was filtered and the solvent in the filtration was evaporated using a rotary evaporator (BUCHI, Germany). After that, the remaining aqueous phase was freeze dried. The product was extracted using 1 L chloroform by stirrer for 24 hours. Then, it was filtered and solvent was evaporated. Finally, obtained brown powder plant extract was kept at -20°C until used

Cytotoxicity of Ficus religiosa (FR) chloroform extracts:

The IC50 of the FR chloroform extract was determined using the SRB assay. The PC3-TxR cell line was maintained in RPMI-1640 medium supplemented with 10% FBS and 1% penicillin/streptomycin, and incubated at 37˚C in an atmosphere of 5% CO2. After 80% confluent, the cells were seeded to a 96-well plate at cell density of 3×103 cells/well and incubated for 24 hours (16). The cells were treated with the FR extracts with concentrations range of 0.002 to 2 mg/ml. After incubation for another 72 hours, the cell viability was determined using the SRB assay. The IC50 for extract was calculated using the sigmoidal model with aid of GraphPad Prism (GraphPad software, La Jolla, CA, USA).

Sulforhod-amine-B (SRB) assay:

To evaluate the growth inhibitory potential of test compound against various human prostate cancer cells, SRB assay was performed after 72hours. Cells were fixed with 10% trichloroacetic acid solution for prostate cancer cell lines , then PC3-TxR cells were incubated for one hour at 4˚C, washed 3-4 times with tap water, and air dried. Cells were stained with 0.4% SRB, and washed with 1% acetic acid solution after dry; then cells stain were dissolved with 10mM Tris (PH 10.0) and absorbance was measured at 565nM (17).

Gene expression determination:

Prostate cancer cells, which are resistance to docetaxel, were seeded into 6 well plates (5×10^{4} cells/well) and incubated for 24 hours, and afterwards, the cells were treated with FR chloroform extract at two concentrations (0.125 and 0.25) mg/ml, docetaxel (20 nM), and the combination FR (0.125 mg/ml) + docetaxel (10 nM) for another 24 hours. The total RNA was extracted using the Trizol reagent (Invitrogen, Carlsband, CA, US) according to the manufacturer's instruction.

For RNA extraction after collection the cells was centrifuged 12000 rpm, at 4˚C for 15 minutes, then extract with 200 µL chloroform, 500 µL isopropyl alcohol then washed with 75% ethanol to get RNA pellet which dissolved with 55˚C RNase free water.

To prepare RNA used DNase I treatment Kit (Invitrogen, US). Total RNA was subjected to cDNA synthesis in 10 µL of mixture containing Taq Man RT buffer (Applied biosystem, US), 0.8 µL of dNTP mix (100mM), 2 µL RT Random primers, 1 µL Multiscribe Reverse transcriptase, and 4 µL nuclease-free water. The reverse transcription reaction was performed sequentially for 10 minutes at 25˚C, for 120 minutes at 37˚C and 5 minutes at 85˚C.

Quantitive real time reverse transcription PCR (RT-PCR), Quantitive RT-PCR assays were carried out by using ABI PRISM 7300 (Applied Biosystem, US) with SYBR-green fluorescence. Real Time PCR amplification was performed in 24 µL of reaction mixture containing 10.5 µL of RNase free water, 12.50 µL of RT2SYBR Green/Rox PCR master mix and specific primer sets for hedgehog pathway (patch1 and Gli2) genes and Inhibition differentiation pathway (ID1, ID2 and ID3) genes, as shown in table 1.

Real time-polymerase chain reaction was carried out starting with a 15 minutes hot start at 95˚C followed by a denaturation step at 94˚C for 15 seconds, an annealing step at 60˚C for 30s, and an extension step at 72˚C for 1min. Data were analyzed by using sequence detector system version 1.4 software (AppliedBiosystem, US) (18).

Table1: List primers for quantitative RT-PCR

Genes	Forward	Reverse
GAPDH	Agccacatcgctcagacac	Gcccaatacgaccaaatcc
Patch1	cttcgctctggagcagattt	Acccagtttaaataagagtct
Gli2	cacgctctccatgatctctg	Cccctctccttaggtgctc
ID1	ttggagctgaactcggaatc	Gagacccacagagcacgta
ID2	gctatacaacatgaacgactgct	Aatagtgggatgcgagtccag
ID3	catcgactacattctcgacctg	Tccttttgtcgttggagatgac

Results:

The chloroform extract of F. religoiosa showed high cytotoxic effect on PC3-TxR cells (IC50= 0.30±0.02 mg/ml). The Patch1 gene expression was not significantly affected by the treatment of FR extract at high concentration (0.25 mg/ml) and low concentration (0.125 mg/ml) and there was not any effect displayed when treated with FR chloroform extract companied + docetaxel. As well as, Gli2 gene expression was not displayed any affected when treated with FR extract. However, the docetaxel was found to have no effect on the two genes tested (Figure 1).

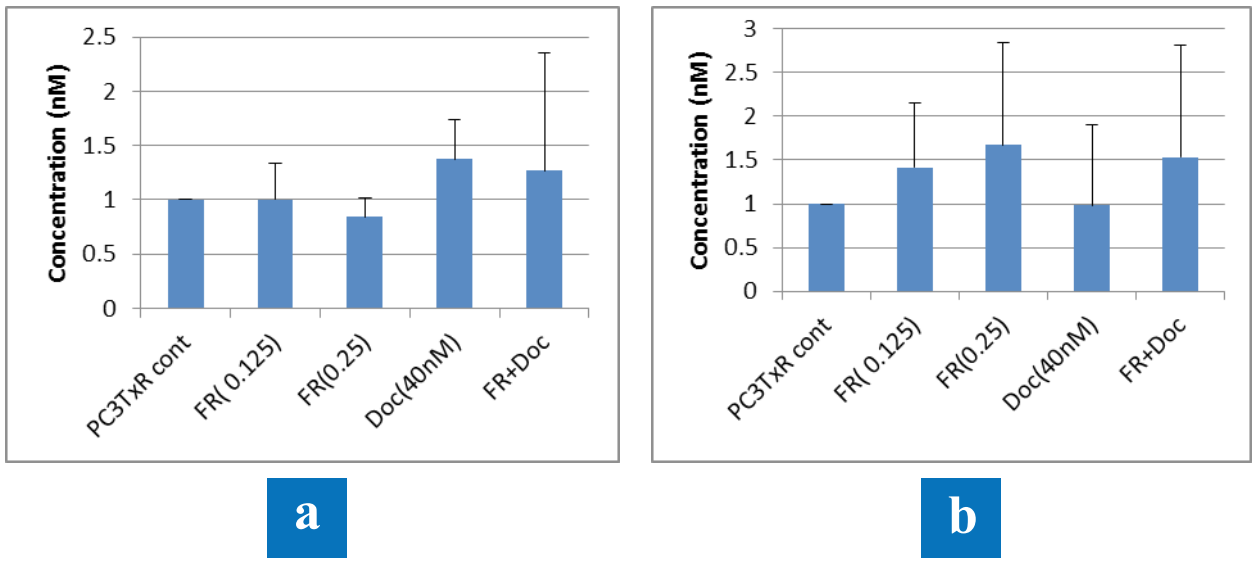

Figure 1: Effect of F. religiosa chloroform extract and docetaxel on genes expression of hedgehog pathway (a) Patch1 gene (b) Gli2 gene on PC3-TxR cancer cell lines.

In figure 2, FR chloroform extract caused non-significant effect in regulation of Id1 gene expression in a dose dependent manner. As well as the combination of FR (0.125 mg/ml) + docetaxel (10 nM) was (0.68±0.02), while docetaxel (20 nM) alone display non-significant effect in regulation of Id1 gene expression (0.64±0.25) compared with control (PC3-TxR cancer cells).

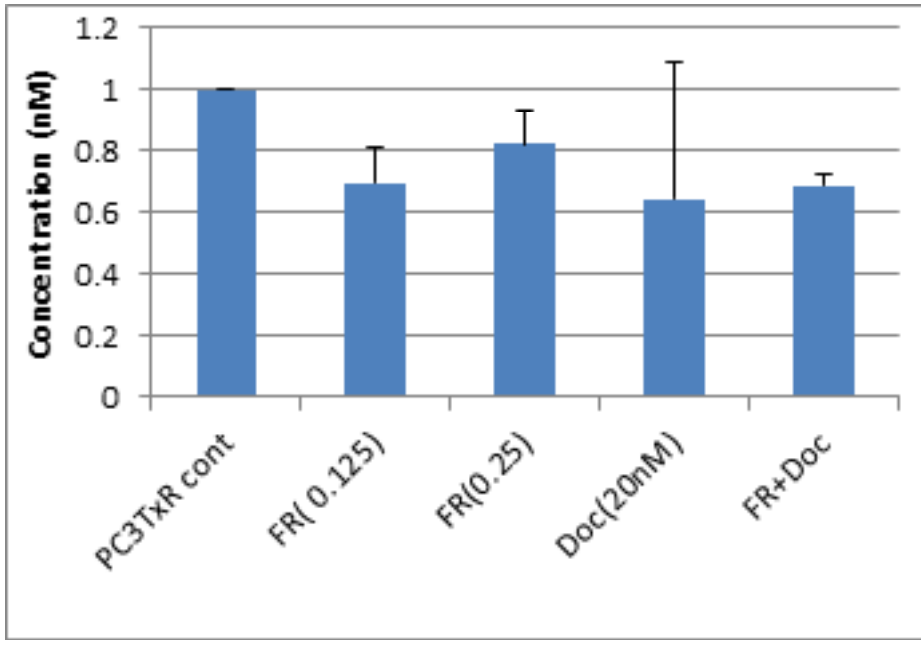

Figure 2: Effect of Ficus religiosa chloroform extract and docetaxel on Id1 gene expression in PC3-TxR cancer cell lines

Moreover, figure 3 displayed that chloroform extract caused down-regulated of Id2 gene expression at concentration 0.125 mg/ml was (0.76±0.10) and at concentration 0.25 mg/ml was (0.85±0.06), in a dose dependent manner, and the combination of docetaxel (10 nM) + FR (0.125 mg/ml) was significantly down-regulation Id2 gene expression (0.67±0.07) but docetaxel (20 nM) alone showed no significant effect on PC3-TxR cells (0.93±0.13).

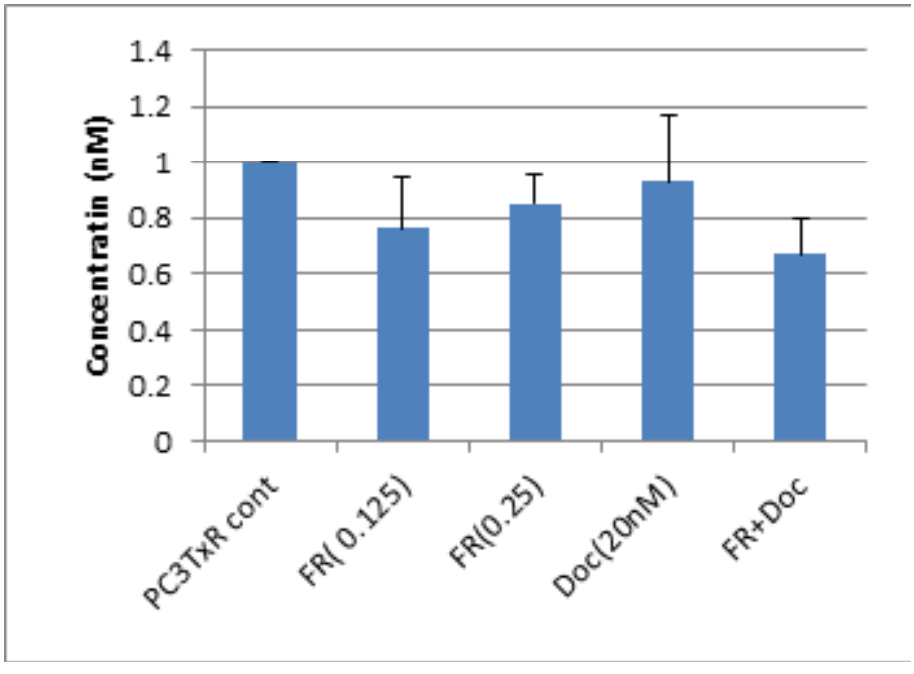

Figure 3: Effect of Ficus religiosa chloroform extract and docetaxel on Id2 gene expression in PC3-TxR cancer cell lines

The results presented in figure 4, displayed that docetaxel alone caused more down-regulation of Id3 gene expression (0.63±0.12) was displayed, and the combination FR chloroform extract at concentration (0.125 mg/ml) + docetaxel (10 nM) (0.73±0.09), but the cells treated with FR extract at concentration (0.25 mg/ml) alone displayed non-significant effect (1.01±0.04) while FR at concentration (0.125mg/ml) alone was detected (0.83±0.1) when study FR extract on PC3-TxR cells.

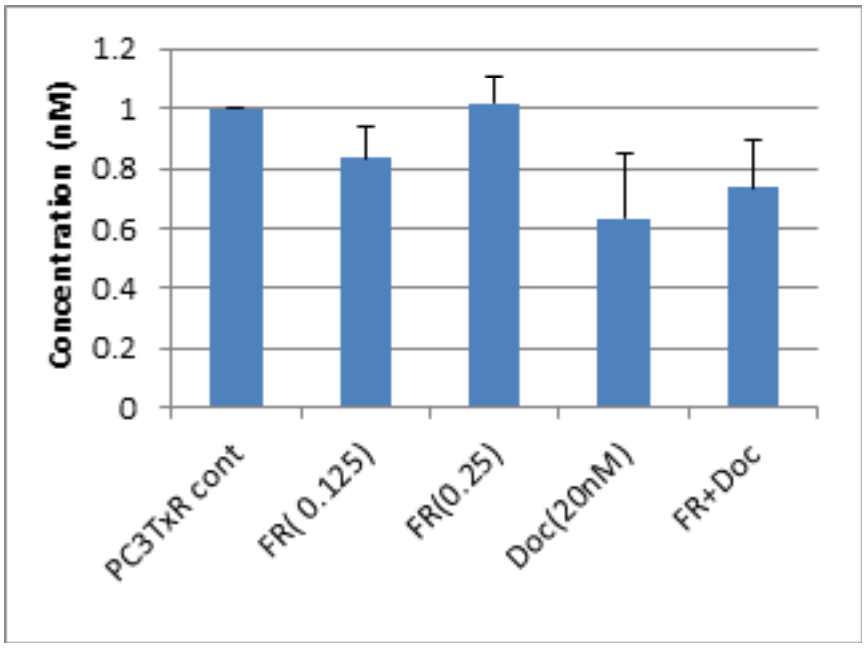

Figure 4: F. religiosa chloroform extract effect on Id3 gene expression on PC3-TxR cells

Discussion:

The chloroform extract of F. religiosa showed cytotoxic effect on PC3-TxR cells which confered by down-regulation of inhibition differentiation pathway (ID), as well as the combination of FR chloroform extract with docetaxel display interesting inhibition effect on PC3-TxR cells. Dependent on previous studies, methanol extract of FR plant is rich in phenolic contents, which have been shown to possess antimutagenic and antimalignant effects (19,20).

Various studies indicate that Ficus species are widely used in the management of various types of diseases like respiratory disorders, sexual disorders, central nervous system disorders (CNS), cardiovascular disorders (CVS), gastric problems, skin infections and diabetes (20,21,22). Most of the pharmacological studies were aimed on validating its traditional uses (23). Although modern drug design single agents with specific targets, but whole extract with multiple compounds has been shown to be more efficacious than its individual components (24). Killing of tumor cells through the induction of apoptosis is now recognised as a strategy for identifying anti-cancer drugs (25). However FR extract exhibited significant cytotoxic activity in cervical cancer cell lines and human breast cancer cell lines (MCF7) (26,27,28), as well as FR extract displayed antiproliferative effect in multiple breast cancer cells and showed low toxicity to non- tumorigenic mammary epithelial cell (28).

Apoptosis and associated cellular events have profound effects on the progression of benign to malignant neoplasm and are considered as important target for the therapy of various cancers (29). It is a complex sequential process of genetically determined self-destruction that ultimately leads to the activation of proteases with certain substrate specificities, the Caspases and nucleases that produce membrane blebs, degrade DNA into nucleosome sized fragments and condensate cellular compartments (30). FR extracts induced conformational changes in Bax and triggers mitochondria mediated (28).

Resistance to docetaxel in human prostate cancer has been a subject of considerable interest, the development of therapeutic strategies that target docetaxel-resistant cells has remained an elusive challenge in clinical oncology (4, 5). Mechanistically, signaling pathway regulated canonical survival molecules with well-documented roles in chemotherapy resistance (31), as well as increased Id genes expression in Inhibition differentiation pathway has been associated with cell proliferation, immortalization, invasion and aggressive malignant phenotype in several human cell lines (32). Most importantly, expression of Id gene has been found in many types of human cancers and its expression level has been indicated as a marker for malignant progression in a number of human cancers including the prostate. These lines of evidence indicate that Id gene may play an essential role in prostate carcinogenesis and malignant progression. Although mechanisms responsible for Id gene mediated tumorigenesis are not clear (33,34). In this work try to establish the cytotoxic effect of FR extract on cancer cells that target of specific gene which play potent role in cancer cells.

Previously, it was reported that Id gene was able to initiate DNA synthesis and induce cell cycle G1 to S transition in a number of cell lines, these lines of evidence indicate that the role of Id gene in cell survival may depend on the origin of the cells as well as in vitro culture conditions. In this foundation indicate a reverse relation between Id protein and androgen receptor and it is possible that Id gene may be able to mediate androgen response through regulation of androgen receptor expression (35,36). In present study shows FR extract

has ability to inhibit growth of PC3-TxR cancer cells by down regulation of Id genes expression (Id2 and Id3 genes expression) which prevent growth progression of cancer cells.

In conclusion, FR chloroform extract provided evidence that inhibition of PC3-TxR cell growth by down regulation of ID signaling pathway in PC3-TxR depletes a subpopulation of cells responsible for acquired docetaxel resistance and tumor initiation, laying the foundation for a promising new therapeutic strategy.

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تاثير المستخلص الكلوروفوم لنبات لسان العصفور على تثبيط الخلايا السرطانية المكتسبة لمقاومة دوكسيتاكسيل في سرطان البروستات

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الخلاصه:

معظم العلاجات السرطانية المستخدمة حاليا هي منتجات طبيعية. تم اكتشاف هذه الاهمية بصفة عامة على أساس سميتها على خلايا السرطانية باستخدام مختلف اختبارات بيولوجية. نبات لسان العصفور (Ficus religiosa) هو من النباتات الطبية الهامة والتي تستخدم عادة لعلاج مختلف الأمراض بما في ذلك التهاب الضرع، التهاب الأذن الوسطى، التهاب البلعوم و الحنجرة، التهاب الإحليل، وعسر الطمث والسكري.

لدراسة تأثير السمي لمستخلص الكلوروفورم لاوراق نبات لسان العصفور على الخلايا السرطانية باستخدام SRB assay ودراسة تاثيره على التعبير الجيني لجينات Patch1) و(Gli2 في مسار hedgehog والتعبير الجيني لجينات (ID2، ID1 و ID3) في مسار Inhibition differentiation في خلايا سرطان البروستاتا المقاوم لدوسيتاكسيل (PC3-TXR) باستخدام تقنية RT-PCR في المختبر.

وأظهرت النتائج أن مستخلص الكلوروفورم لاوراق F. religiosa تأثير سمي عالي (IC50 = 0.3 ملغ / مل)، وتأثيره التثبيطي على التعبير الجيني للـ (ID1، ID2 و ID3) أكثر من تاثيره التثبيطي على التعبير الجيني لل(Patch1 و(Gli2 في خلايا البروستات السرطانية PC3 -TXR. ونستنتج من ذلك ان المستخلص الكلورفورم لاوراق نبات لسان العصفور له تأثير سمي ومثبط لسرطان البروستات المقاومة لعقار الدكسيتاكسيل (PC3-TxR).