Study the Inhibitory effectiveness of Bee Glue (Propolis) on growth of the Prostate cancer cell lines to manifest the scientific miracles in the Quran

Lina Abdul-Fattah Kurdi

Department of Biology "Zoology", Faculty of Sciences - Al Faisaliah- King Abdul Aziz University, P.O. Box. 4938, Jeddah 21412, KSA
dr.lina_kurdi@hotmail.com

Abstract: The current study was designed to determine the effectiveness of the inhibitory effect of propolis against cytotoxicity on prostate cancer cell lines being considered the second- essential cause of cancer death in men. Compared with the effect of cyclophosphamide (CP) - anti-cancer pharmacological compound - *in vitro*. The cytotoxic activity of propoliswas assessed using SRB-U assay against prostate cancer cells PC3. Cells were exposed to serial dilution (0.1 to 1000 µg/ml) of the test propolisfor 72 h; IC_{50}: 50% to kill half of cells and R-fraction was calculated using Emax model. propolisshowed gradual logarithmic cell kill effect starting at 30 µg/ml. The calculated IC_{50} was found to be 73.1 µg/ml with resistance fraction of 3.27%. By comparison to positive control cytotoxic agent cyclophosphamide, it showed gradual cell kill from concentration 0.3 µg/ml with IC_{50} of 0.58 µg/ml. however, the resistance fraction of PC3 cells to cyclophosphamide was found to be 7.7%. despite the relatively high IC_{50} of propolis. The results showed that the treatment with propolis has made a marked improvement in the standards measured by this study. From the results of our study, we see that the therapeutic efficacy of anti-cancer for treatment with propolis is useful for therapy for prostate and perhaps other types of cancers.
[Lina Abdul-Fattah Kurdi. **Study the Inhibitory effectiveness of bee glue (propolis) on growth of the Prostate cancer cell lines to manifest the scientific miracles in the Quran.** *Nat Sci* 2016;14(10):144-152]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 23. doi:10.7537/marsnsj141016.23.

Keywords: Propolis, Cyclophosphamide, Prostate cancer cell lines, Apoptosis

in vitro and to provide data for the mechanisms of action while the treatment of cancer cell lines, and based on this data, promising anti-cancer for the future *in vivo* are being selected. In general, the functional tests require exposing the cancer cell lines to various concentrations of drugs and the usage of one of tincture ways such as: Sulforhodamine Btincture to assess the vitality of cells and then to evaluate the effect of drugs on cancer cells. To calculate the value of IC_{50} concentration of the drug that is necessary to reduce the proportion of 50% of the cells compared to cells control, the value of IC_{50} allows comparing the effect of drugs on cell lines, which can assess whether the drug is applicable to animal models (Zips *et al*., 2005).

From this point, the evidence about the integration of antioxidants have been increased with certain types of chemotherapy due to its effectiveness in reducing neoplastic toxicity and free radicles resulting from chemical treatment as there are factors that act as antimutagens prevent the transformation of mutagenic compounds to mutations, disrupt the mutations and inhibit the interaction between mutagenand DNA, and can Scavengers free radicles easily, such as carotenoids and flavonoids and phenolic compounds (Drisko *et al*., 2003; Bhattacharya, 2011; 2012).

The propolis as a natural element consists of 55% of flavonoids associated by phenolic acids compounds

1. Introduction

The primary goal of chemical treatment is to kill malignant cells without affecting normal tissue so it must be focus on specific molecules in the carcinogenic cells to be eliminated, many anti-cancer medications have been used for several decades, which are highly efficient in killing cancer cells proliferating by interfering with the replication of DNA through a range of different mechanisms, but the main mechanism which realizes the genotoxicity lie in obstructing the work of Replication Fork in DNA and show a response of DNA damage to anti-cancer factors either by stopping both of: cell cycle and the operations of damage repair, or the resumption of apoptosis. (Helleday., 2008; Weber., 2015).

Although the effectiveness of anti-cancer drugs on cancer cells have negative effects represented in: Stimulate the production of free radicles and therefore influential negatively on normal cells (Sahin *et al*., 2010), studies have indicated strong effects such as potential mutagen, teratogen and carcinogen (yoshizawa *et al*., 2000).

To assess the most anti-cancer agents, the initial step is the cultivation of cancer cells due to its low cost and because it is less time-consuming compared to tumors models in animal, allowing evaluation of large amounts of new anti-cancer factors. Many drugs abilities lies in their impact on molecular target, making it easier to choose a sophisticated anti-cancer

Bee glue (propolis) substance collected by bees from the buds of trees and have multiple benefits have been obtained from the wild honey company in Riyadh, Saudi Arabia.

SRB Cells Cytotoxicity Assay

The cytotoxicity of propolis was examined against PC3 prostate cancer cells by SRB assay and compared to cyclophosphamide as previously described (Skehan *et al*., 1990; Houghton *et al.*, 2007). Exponentially growing cells were collected using 0.25% Trypsin-EDTA and plated in 96-well plates at 1000-2000 cells/well. Cells were exposed to test extract and cyclophosphamide for 72 h and subsequently fixed with TCA (10%) for 1 h at 4 ºC. After several washings, cells were exposed to 0.4% SRB solution for 10 min in dark place and subsequently washed with 1% glacial acetic acid. After drying overnight, Tris-HCl was used to dissolve the SRB-stained cells and color intensity was measured at 540 nm.

Data analysis

The dose response curve of compounds was analyzed using E_{max} model.

$$\%\,\text{Cell viability} = (100 - R) \times \left(1 - \frac{[D]^m}{K_d{}^m + [D]^m}\right) + R$$

Where R is the residual unaffected fraction (the resistance fraction), [D] is the drug concentration used, K_d is the drug concentration that produces a 50% reduction of the maximum inhibition rate and m is a Hill-type coefficient. IC_{50} was defined as the drug concentration required to reduce fluorescence to 50% of that of the control (i.e., $K_d = IC_{50}$ when R=0 and E_{max} =100-R) (Mahmoud *et al.*, 2012).

Statistical Analysis:

The Statistical Analysis applicated by the student 't' test, to calculate the significant results which get from the test Under examination**.**

3. Results:

The Effects of different concentrations of the Treatment with Propolis on Prostate cancer cell line PC3 after 72 h:

The results obtained from table 1 shows that the treatment with 0.3 µg/ml of propolis caused a highly significant decrease ($P \leq 0.01$) on the mean of Prostate cancer cell line PC3 their value (2.646 ±0.039) and extremly significant decrease ($P \leq 0.001$) at different concentration (1,3,10,30,100,300,1000 µg/ml) of propolis their values were(2.451±0.029, 2.473±0.053, 2.436±0.080,2.204±0.060,1.639±0.074, 0.248±0.022, 0.065±0.004) respectively compared with control sample mean (3.005±0.076) (Fig:1).

- resinous materials with Biologic effect - 30% wax, 10% essential oils, 5% pollen (Kalogeropoulos *et al*., 2009).

The evidence suggests that natural factors can inhibit carcinogenesis process and have an active influence on the risk of cancer, where prostate cancer represents an ideal model to develop preventive and chemical strategies due to Long latency, delay in its appearance and the rate of its progress is relatively slow and high rates of infection. It is considered the second most important type of cancer-causing death for men (Scifo *et al*., 2006; Díaz-Carballo *et al*., 2012; Szliszka *et al*., 2013).

Studies have indicated that the propolis has several pharmacological activities such as: an anti-microbial, anti-oxidant, anti-inflammatory, and has an anti-cancer activities such as: it prevents significantly the growth of prostate cancer cells from it as it works the work of chemotherapy and has a protective role as prostate cancer anti-cancer (Cuesta-Rubio *et al*., 2002; Paredes-Guzman *et al*., 2007; Premratanachai and Chanchao, 2014; Salim *et al*., 2015).

As for recent studies, they have shown that dietary supplements that is rich with polyphenols compounds such as propolis play an important role in chemoprevention in prostate cancer such as: Caffeic acid phenethyl ester (CAPE) compound, it is a useful anti-mutagenic and anticarcinogenic, in addition to the ethanolic extract of propolis that has chemical protective properties through its direct anti-cancer, and indirect immunological properties. It also suppresses the spread of the tumor and urges to stop the cell cycle and apoptosis in prostate cancer cells (Barlak *et al*., 2011; Chuu *et al*., 2012; Szliszka *et al*., 2013).

On that basis, the aim of this study is to observe the effective role of propolis compound as one of the natural compounds in reducing the toxic effects at the cellular cell line of prostate cancer cells to show the scientific miracles in the therapeutic capability set by Allah, Exalted be He, in this natural material.

2. Materials and Methods

Cell Culture

Experiments were conducted on Prostate cancer cell lines PC3(ATCC® CRL-2422™), obtained from King Fahd research center at King Abdul-Aziz university.

Cyclophosphamide (CP)

Cyclophosphamide, commercially known as Endoxan, is a drug used for anti cancer chemotherapy and is obtainable as powder then its melted in a physiological solution, and it was purchased from Baxter Oncology, Halle, Germany.

Propolis

Table (1): The Effects of different concentrations of Treatment by Propolis on the mean of Prostate cancer cell line PC3 after 72 h.

Con. (ug/ml)	Treatment Groups	No. cell line	Mean ± Std.Error	Std.Deviation	Inhibition %
0	C	1 2 3 4 5 6 Mean ± Std.Error	3.005±0.076	0.186	___
0.1	P	1 2 3 4 5 6 Mean ± Std.Error	2.800±0.035	0.086	3.462
0.3	P	1 2 3 4 5 6 Mean ± Std.Error	2.646±0.039 **	0.094	11.917
1	P	1 2 3 4 5 6 Mean ± Std.Error	2.451±0.029 ***	0.071	18.409
3	P	1 2 3 4 5 6 Mean ± Std.Error	2.473±0.053 ***	0.130	17.676
10	P	1 2 3 4 5 6 Mean ± Std.Error	2.436±0.080 ***	0.197	18.908
30	P	1 2 3 4 5 6 Mean ± Std.Error	2.204±0.060 ***	0.148	26.631
100	P	1 2 3 4 5 6 Mean ± Std.Error	1.639±0.074 ***	0.180	45.439
300	P	1 2 3 4 5 6 Mean ± Std.Error	0.248±0.022 ***	0.054	91.744
1000	P	1 2 3 4 5 6 Mean ± Std.Error	0.065±0.004 ***	0.009	97.836

C:Control, P: Propolis p* significant<0.05 p** highly significant<0.01 p***extremly significant<0.001

Table (2): The Effects of different concentrations of Treatment by cyclophosphamide on the mean of Prostate cancer cell line PC3 after 72 h.

Con. (ug/ml)	Treatment Groups	No. cell line	Mean ± Std.Error	Std.Deviation	Inhibition %
0	C	1 2 3 4 5 6 Mean ± Std.Error	1.793.0 ± 041	0.101	___
0.1	CP	1 2 3 4 5 6 Mean ± Std.Error	1.742.0 ± 042	0.103	2.844
0.3	CP	1 2 3 4 5 6 Mean ± Std.Error	1.630±0.029 **	0.070	9.091
1	CP	1 2 3 4 5 6 Mean ± Std.Error	1.446±0.037 ***	0.091	19.353
3	CP	1 2 3 4 5 6 Mean ± Std.Error	0.953±0.031 ***	0.076	46.905
10	CP	1 2 3 4 5 6 Mean ± Std.Error	0.804±0.021 ***	0.050	55.159
30	CP	1 2 3 4 5 6 Mean ± Std.Error	0.488±0.015 ***	0.037	72.783
100	CP	1 2 3 4 5 6 Mean ± Std.Error	0.307±0.009 ***	0.022	82.878
300	CP	1 2 3 4 5 6 Mean ± Std.Error	0.112±0.003 ***	0.006	93.753
1000	CP	1 2 3 4 5 6 Mean ± Std.Error	0.071±0.001 ***	0.002	96.040

C:Control, P: Propolis p* significant<0.05 p** highly significant<0.01 p***extremly significant<0.001

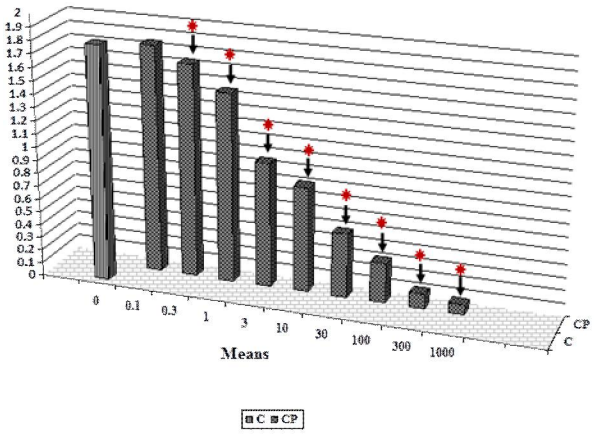

Fig (2): Effects of different concentrations of Treatment with cyclophosphamide on the Means of Prostate cancer cell line PC3 after 72h.

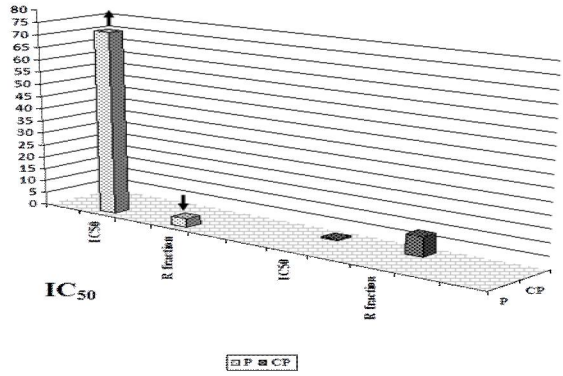

Fig (3): Effects of different concentrations of Treatment with Propolis and cyclophosphamideon the IC_{50} values of Prostate cancer cell line PC3 after 72h.

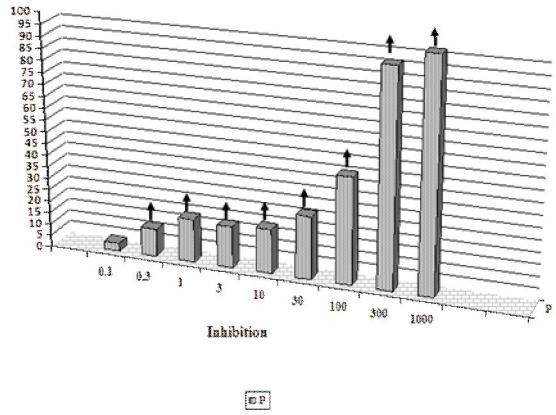

Fig (4): Effects of different concentrations of Treatment with Propolis on the Inhibition rate of Prostate cancer cell line PC3 after 72h.

The inhibitory effects that kills the half of cells (IC_{50}) was calculated for each treatment with different concentration of propolis, it was equal to 73.1 µg/ml with resistance fraction of 3.27% (Fig:3).

when calculating the inhibition ratio of cancer cells (PC3) as a result of different concentration it was 3%, 11%, 18%, 17%, 18%, 26%, 45%, 91%, 97% respectively (Fig:4), and the inhibition ratio was inversely proportional to the rate of vitality, as the rate of vitality increased the rate of inhibition decreased (Fig:6).

The Effects of different concentrations of the Treatment with cyclophosphamide on Prostate cancer cell line PC3 after 72 h:

Tabulated results obtained from table 2 revealed that treatment by 0.3 µg/ml of cyclophosphamide caused highly significant decrease ($P \leq 0.01$) on the mean of PC3, its value was(1.630±0.029) and extremely significant decrease ($P \leq 0.001$) at different concentration (1.3 to 1000 µg/ml) of cyclophosphamide their values were(1.446±0.037, 0.953±0.031, 0.804±0.021, 0.488±0.015, 0.307±0.009, 0.112±0.003, 0.071±0.001) respectively compared to median of control sample (1.793±0.041) (Fig:2).

The value of Inhibiting Cellular Proliferation by 50% to kill half of cells (IC_{50}) for each different concentration cyclophosphamide calculated and it was 0.578 µg/m with resistance fraction of 7.7% (Fig:3).

When calculating rate of cancer cells growth inhibition PC3, results of different concentration were at a value of 2%,9%,19%,46%,55%,72%,82%, 93%,96% respectively(Fig:5), and the rate of inhibition is inversely proportional to vitality rate, the more the vitality rate the less the inhibition (Fig:7).

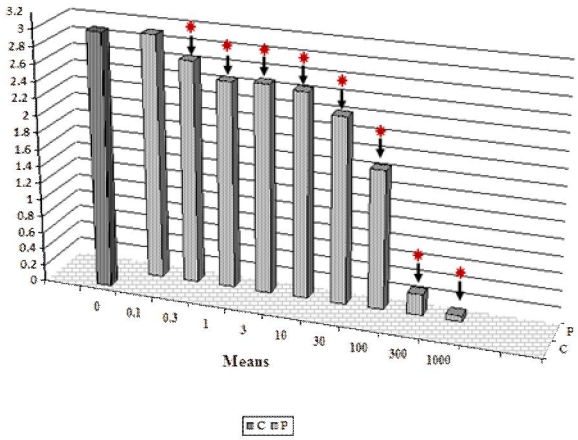

Fig (1): Effects of different concentrations of Treatment with Propolis on the Means of Prostate cancer cell line PC3 after 72h.

cancer tumors-. In order to achieve the objective of the study, a line from cancer lines has been chosen it is the cellular cancer line in prostate cancer cells PC3, where all treatments recorded results at different concentrations (0.1,0.3,1,3,10,30,100,300,1000 µg/ml), after a period of incubation took (72h).

The effectiveness of these treatments by various concentrations in the inhibition of cancer cell line growth of prostate cancer cells PC3, depending on the concentration and compared with control samples. After incubation for a period of 72 hours for the cells of prostate cancer, the inhibitory effect of various concentrations of Propolis showed a marked improvement and a compatible increase with concentrations increase, also all concentrations have recorded a high drop ($P \leq 0.01$) at (0.3 µg/ml) and ($P \leq 0.001$) at (1,3 to1000 µg/ml) in the average appearance of prostate cancer cells values compared to the average control sample.

Results obtained from this study indicate that these treatments were associated with clear improvement of the inhibitory impact on Prostate cancer cell line PC3, which is directly proportional to concentrations, posting the best inhibitory impact at a concentration of 1000 µg/ml for all treatments and as compared with the control sample. and there was a linear relationship between the inhibitory efficacy with concentration.

It becomes clear through this study that the results of treatment with drug and the results of treatment with propolis were so close, also (IC_{50}) values calculation have been adopted in order to show treatments effective concentration compared with control samples, so the best recorded value was the treatment with propolis then the treatment with drug.

Such findings are consistent with the findings of many previous studies as a result of treatment for prostate cancer cells PC3 using Propolis or any of its effective components.

In a study on evaluating the effect of Propolis extract on prostate cancer cells using MTT assay, it was found that different concentrations(5,10,20µg / ml) of Propolis extract lowered the vital cancer cells by up to 24.5-75.00%. Most of the toxic effect was against prostate cancer cell sat the concentration of 20µg / ml, which indicates the anti-proliferative effect resulting from the antioxidant abilities of Propolis (Barlak *et al*., 2011).

Another study also showed that when Propolis extract was incubated by the concentrations (20-50µg / ml) with prostate cancer cells for a period of 48 hours, it appeared that the toxic effects was against prostate cancer cells by between (0.84 ± 3.38% & 0.95 ± 8.27%) in addition to apoptosis between (4.71 ± 0.47%) and (10.64 ± 0.73%). The studies also showed that Propolis extract enhances the expression of

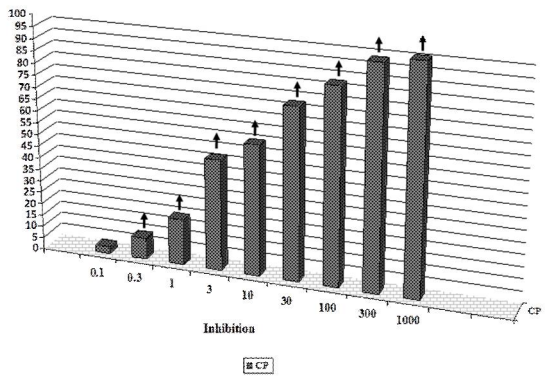

Fig (5): Effects of different concentrations of Treatment with cyclophosphamide on the Inhibition rate of Prostate cancer cell line PC3 after 72h.

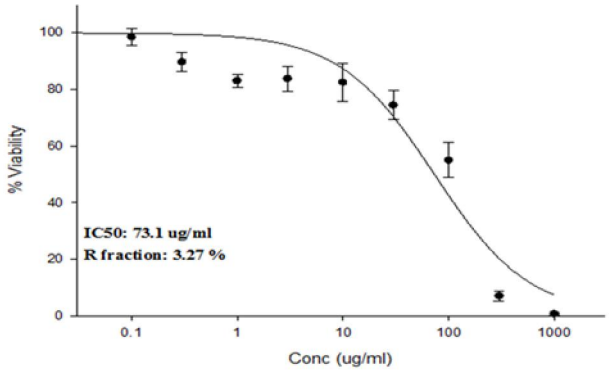

Fig (6): Effects of different concentrations of Treatment with Propolis on the cell viability of Prostate cancer cell line PC3 after 72h.

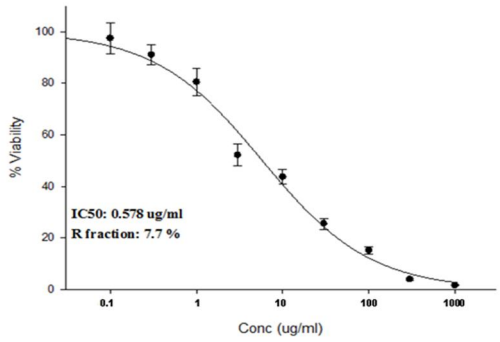

Fig (7): Effects of different concentrations of Treatment with cyclophosphamide on the cell viability of Prostate cancer cell line PC3 after 72h.

4. Discussion

This study aimed to monitor the inhibitory effectiveness of both Propolis as - a natural therapeutic product from bees - compared to treatment with Cyclophosphamide as - a chemotherapy drugs for

through 2 different types of cell death: necrosis and apoptosis, respectively (Scifo *et al*., 2004).

The results of one of the studies also revealed that the treatment prostate cancer cell line (DU145) with propolis ethanolic extract alone or a combination treatment with Vinorelbine - a drug widely used in prostate cancer therapy and its known to induce apoptosis - it is probability to be useful for prostate cancer therapy through cell cycle distribution, increasing p53 levels (Scifo *et al*., 2006).

Also indications calculations explained synergistic interaction by Combination treatment of Caffeic acid phenethyl ester (CAPE) with docetaxel (DOC) and (CAPE) with paclitaxel (PTX) cotreatments on cytotoxicity in prostate cancer cells, that treatment with CAPE enhances the cytotoxic effects of (DOC) and (PTX) in prostate cancer cells by increased caspase-3 activity and significantly elevated Estrogen receptor-β (ER-β) (Tolba *et al*.,2013).

By analyzing the results of cellular study through SRB Assay on human prostate cancer cell line PC3 treatment with ethanolic extract and doxorubicin drug (DOX) - an established chemotherapeutic drug- for 24 & 72 h with different doses (0, 0.01, 0.1, 1, 10 and 100 µg / ml), Combination treatment appeared significant anti-tumor potential as well as high antioxidant properties of nitric oxide (NO), superoxide dismutase (SOD), catalase (CAT), total antioxidant capacity (TAC) and reduced glutathione (GSH) levels compared with the untreated cells (Salim *et al*., 2015).

When testing cellular toxicity on prostate cancer cells that was treated with various concentrations (0-200µg / mg) of Propolis and (0-25µg / mg) of quercetin compound as one of the main flavonoids compounds in Propolis and with an incubation at a temperature of º37 for 24 hours, found that the effect of Propolis on prostate cancer cells values are higher than quercetin. This result has interpreted the harmonious effect of all Propolis components in anti-cancer effect, as it demonstrated that Propolis is a good source of antioxidants and a natural anti-tumorfactor that is able to limit the spread of cancer cells (Turan *et al*., 2015).

Cytogenetic studies have shown that Propolis has an active role in the inhibition of cancer in a variety of cancer cell lines and that effect lies in its phenolic compounds, it may be polyurethane compounds phenols and flavonoids in propolis as a catalyst and an effective complement to chemotherapy and radiation therapy in treating cancer (Suzuki *et al*., 2002; Chen., 2003), because Flavonoids compounds in Propolis can play an important role in chemoprevention against cancer, It is likely that its anti-cancer ability lies in curbing DNA synthesis in cancer cells and their ability to cause apoptosis and activate the phagocytosis process for the production of factors capable of factor's molecules (TRAIL tumor necrosis factor related apoptosis ligand) which is an important factor in monitoring and immunization In defense mechanisms against cancer cells which are autologous stimuli urge on apoptosis in cancer cells without any toxic against normal cells, but some cancer cells have a resistance to apoptosis caused by these particles. The studies also demonstrated the role of phenol and polycarbonate natural compounds in alerting TRAIL molecules to fight cancer cells and increase their effectiveness in activating apoptosis, after adding (100ng / ml) of (TRAIL) molecules with (50µg / ml) of Propolis extract, the percentage of apoptosis in prostate cancer cells increased to (1.2 ± 65.8%) and caused a major disruption in prostate cancer cells, and found that Propolis extract has helped to overcome the resistance of cancer cells to (TRAIL) molecules thus, this data showed the important role of Propolis and its biologically active compounds in the chemical prevention against prostate cancer through significant activation of protein TRAIL and caspase-8 caspase-3 (Szliszka *et al*., 2011a; 2011b; Szliszka *et al*., 2012).

Immunological characteristics and anti-cancer properties of Propolis are attributed to its: ability to scavenge free radicals, organization of protein expression of cycling D1, B1 and cycling dependent kinase (CDK), its strong inhibitory effectiveness to stop cancer cell cycle in phase G2 & S, damping the spread of tumor, inhibit prostate tumor cell growth and tumors derivative from it, and causes the apoptosis in prostate cancer cells. When incubating prostate cancer cells with (25 - 50µg / ml) of Propolis and for (24h), it was observed that the rate of apoptosis was close to zero, indicating that it works as chemotherapy and that it has a protective role as anti factor for prostate cancer (Russo *et al*., 2004; Li *et al*., 2007; Paredes-Guzman *et al*., 2007; barlak *et al*., 2011; Szliszka *et al*., 2013).

It also should be noted of the results of many previous cellular studies in the treatment alone or combination with Propolis or one of Flavonoids compounds derived from Propolis, so when applying (MTT assay) on prostate cancer cells (DU145) - a cell line similar the last phase of prostate cancer - and observing many biochemical indicators resulting from the treatment with Navelbine - a drug usually used in the treated of prostate cancer - alone or treatment a drug with ethanolic extract of propolis: such as integrity of the cell membrane (lactate dehydrogenase emancipation), status of cell redox (production of reactive oxygen species, nitric oxide formation, reduce the levels of glutathione), genomic DNA fragmentation, and possible mitochondrial trans membrane, potential alteration (deltapsi), so the results of propolis extract in human prostate cancer concluded that anti-cancer activity, and their anti-cytotoxicity

inhibition of p70S6K and Akt signaling networks. Cancer. Prev. Res (Phila).,5(5):788-97.
7. Cuesta-Rubio O, Frontana-Uribe BA, Ramírez-Apan T, Cárdenas J.(2002): Polyisopreny-lated benzophenones in cuban propolis; biological activity of nemorosone. Z Naturforsch C.;57(3-4):372-8.
8. Díaz-Carballo D, Gustmann S, Acikelli AH, Bardenheuer W, Buehler H, Jastrow H, Ergun S, Strumberg D. (2012):7-epi-nemorosone from Clusiarosea induces apoptosis, androgen receptor down-regulation and dysregulation of PSA levels in LNCaP prostate carcinoma cells. Phytomedicine. 19(14):1298-306.
9. Drisko, J. A., Chapman, J., & Hunter, V. J. (2003): The use of antioxidant therapies during chemotherapy. Gynecologic oncology, 88(3), 434-439.
10. Fraga, C. G., &Oteiza, P. I. (2011): Dietary flavonoids: role of (−)-epicatechin and related procyanidins in cell signaling. Free Radical Biology and Medicine, 51(4), 813-823.
11. Helleday, T., Petermann, E., Lundin, C., Hodgson, B., & Sharma, R. A. (2008): DNA repair pathways as targets for cancer therapy. Nature Reviews Cancer, 8(3), 193-204.
12. Houghton, P., Fang, R., Techatanawat, I., Steventon, G., Hylands, P. J., & Lee, C. C. (2007): The sulphorhodamine (SRB) assay and other approaches to testing plant extracts and derived compounds for activities related to reputed anticancer activity. Methods, 42(4), 377-387.
13. Kalogeropoulos, N., Konteles, S. J., Troullidou, E., Mourtzinos, I., & Karathanos, V. T. (2009): Chemical composition, antioxidant activity and antimicrobial properties of propolis extracts from Greece and Cyprus. Food.Chemistry., 116(2), 452-461.
14. Li H[1], Kapur A, Yang JX, Srivastava S, McLeod DG, Paredes-Guzman JF, Daugsch A, Park YK, Rhim JS. (2007): Antiproliferation of human prostate cancer cells by ethanolic extracts of Brazilian propolis and its botanical origin. Int. J. Oncol.,31(3):601-6.
15. Noel, S., Kasinathan, M., &Rath, S. K. (2006): Evaluation of apigenin using *in vitro* cytochalasin blocked micronucleus assay. Toxicology *in vitro*, 20(7), 1168-1172.
16. Mahmoud, A.M[1]., Al-Abd, A.M., Lightfoot, D.A., El-Shemy, H.A. (2012):Anti-cancer characteristics of mevinolin against three different solid tumor cell lines was not solely p53-dependent.J Enzyme Inhib Med Chem. ;27(5):673-9.
17. Orsollæ, N., Bašæ, I., Singh, V. K., Govil, J. N., & Arunachalam, C. (2007): Cancer chemoprevention by propolis and its polyphenolic compounds in experimental animals. Phytochemistry and pharmacology III, 55-113.

organizing chemical preventive activation in animal models and in cancer cell cultures, and that high doses of flavonoids have the ability to reduce oxidative damage of DNA and compositional changes of mitochondria and is working to retard growth in cancer cells and impeding the transfer of cellular signals and cause cell differentiation in oncology (Noel *et al*., 2006; Orsollae *et al*., 2007; Zhang *et al*., 2013). Also have the ability to modify inflammation signals and Oncogenic through interaction with the cell membrane proteins and fats and make a vital physical changes in cell membranes, modulating the redox and scavenging free radicles (Cavia-Saiz *et al*., 2010; Fraga and Oteiza., 2011; Wu *et al*., 2015). It is also greatly enhance the role of glutathione, superoxide dismutase (SOD) and catalase, and work to restore and increase the content of cells from glutathione (Wu *et al*., 2015; Panat *et al*., 2016).

After analyzing the results of this study, it was proved that treatment with Propolis may had a strong inhibition role against the growth of prostate cancer cell lines. Therefore, the current study recommends the need to educate and instruct cancer patients who are treated chemically with anti-cancer drugs for the need to eat natural materials that has proven curative and preventive effect through a variety of studies and researches.

References

1. Barlak, Y., Değer, O., Çolak, M., Karataylı, S. C., Bozdayı, A. M., &Yücesan, F. (2011): Effect of Turkish propolis extracts on proteome of prostate cancer cell line. Proteome science, 9(1).
2. Bhattacharya, S. (2011): Natural antimutagens: a review. Research Journal of Medicinal Plant, 5(2), 116-126.
3. Bhattacharya, S. (2012): Anticarcinogenic property of medicinal plants: involvement of antioxidant role. Medicinal Plants as Antioxidant Agents: Understanding their Mechanism of Action and Therapeutic Efficacy. Research Signpost, Trivandrum, 83-96.
4. Cavia‐Saiz, M., Busto, M. D., Pilar‐Izquierdo, M. C., Ortega, N., Perez‐Mateos, M., &Muñiz, P. (2010): Antioxidant properties, radical scavenging activity and biomolecule protection capacity of flavonoid naringenin and its glycoside naringin: a comparative study. Journal of the Science of Food and Agriculture, 90(7), 1238-1244.
5. Chen, C. N., Wu, C. L., Shy, H. S., & Lin, J. K. (2003): Cytotoxic prenylflavanones from Taiwanese propolis. Journal of natural products, 66(4), 503-506.
6. Chuu CP[1], Lin HP, Ciaccio MF, Kokontis JM, Hause RJ Jr, Hiipakka RA, Liao S, Jones RB. (2012): Caffeic acid phenethyl ester suppresses the proliferation of human prostate cancer cells through

Ethanolic extract of Polish propolis: chemical composition and TRAIL-R2 death receptor targeting apoptotic activity against prostate cancer cells. Evidence-Based Complementary and Alternative Medicine, 2013.

30. Szliszka E, Zydowicz G, Mizgala E, Krol W. (2012): Artepillin C (3,5-diprenyl-4-hydroxycinnamic acid) sensitizes LNCaP prostate cancer cells to TRAIL-induced apoptosis.Int J Oncol.,41(3):818-28.
31. Szliszka, E., Zydowicz, G., Janoszka, B., Dobosz, C., Kowalczyk-Ziomek, G., &Krol, W. (2011b): Ethanolic extract of Brazilian green propolis sensitizes prostate cancer cells to TRAIL-induced apoptosis. International Journal of Oncology, 38(4), 941-953.
32. Tolba MF, Esmat A, Al-Abd AM, Azab SS, Khalifa AE, Mosli HA, Abdel-Rahman SZ, Abdel-Naim AB. (2013): Caffeic acid phenethyl ester synergistically enhances docetaxel and paclitaxel cytotoxicity in prostate cancercells. IUBMB Life.,65(8): 716-29.
33. Turan, I., Demir, S., Misir, S., Kilinc, K., Mentese, A., Aliyazicioglu, Y., & Deger, O. (2015): Cytotoxic effect of Turkish propolis on liver, colon, breast, cervix and prostate cancer cell lines. Tropical Journal of Pharmaceutical Research, 14(5), 777-782.
34. Weber, G. F. (2015): Molecular Therapies of Cancer. Springer.
35. Wu, P., Ma, G., Li, N., Deng, Q., Yin, Y., & Huang, R. (2015): Investigation of *in vitro* and *in vivo* antioxidant activities of flavonoids rich extract from the berries of Rhodomyrtustomentosa (Ait.) Hassk. Food chemistry, 173, 194-202.
36. Yoshizawa, K., Nambu, H., Yamamoto, D., Yang, J., Kiyozuka, Y., Shikata, N., &Tsubura, A. (2000): Time‐specific occurrence of alopecia in neonatal C57BL mice treated with N‐methyl‐N‐nitrosourea and the therapeutic efficacy of tacrolimus hydrate. Pathology international, 50(3), 175-184.
37. Zhang, S., Lu, B., Han, X., Xu, L., Qi, Y., Yin, L.,...& Peng, J. (2013): Protection of the flavonoid fraction from Rosa laevigata Michx fruit against carbon tetrachloride-induced acute liver injury in mice. Food and chemical toxicology, 55, 60-69.
38. Zips, D., Thames, H. D., & Baumann, M. (2005): New anticancer agents*: in vitro* and *in vivo* evaluation. *in vivo*, 19(1), 1-7.
18. Panat, N. A., Maurya, D. K., Ghaskadbi, S. S., & Sandur, S. K. (2016): Troxerutin, a plant flavonoid, protects cells against oxidative stress-induced cell death through radical scavenging mechanism. Food. Chemistry, 194, 32-45.
19. Paredes-Guzman, J. F., Daugsch, A., Park, Y. K., &Rhim, J. S. (2007): Antiproliferation of human prostate cancer cells by ethanolic extracts of Brazilian propolis and its botanical origin. International Journal of Oncology, 31, 601-606.
20. Premratanachai P, Chanchao C[2]. (2014): Review of the anticancer activities of bee products. Asian. Pac. J. Trop. Biomed.,4(5): 337-44.
21. Russo A, Cardile V, Sanchez F, Troncoso N, Vanella A, Garbarino JA.(2004): Chilean propolis: antioxidant activity and antiproliferative action in human tumor cell lines. Life Sci.,76(5):545-58.
22. Sahin, K., Sahin, N., & Kucuk, O. (2010): Lycopene and chemotherapy toxicity. Nutrition and cancer, 62(7), 988-995.
23. Salim EI, Abd El-Magid AD, Farara KM, Maria DS. (2015): Antitumoral and Antioxidant Potential of Egyptian Propolis Against the PC3 Prostate Cancer Cell Line. Asian. Pac. J. Cancer. Prev., 16(17):7641-51.
24. Scifo C, Cardile V, Russo A, Consoli R, Vancheri C, Capasso F, Vanella A, Renis M. (2004): Resveratrol and propolis as necrosis or apoptosis inducers in human prostate carcinoma cells. Oncol Res. ;14(9):415-26.
25. Scifo C, Milasi A, Guarnera A, Sinatra F, Renis M. (2006): Resveratrol and propolis extract: an insight into the morphological and molecular changes induced in DU145 cells. Oncol. Res.,15(9):409-21.
26. Skehan, P., Storeng, R., Scudiero, D., Monks, A., McMahon, J., Vistica, D.,...& Boyd, M. R. (1990): New colorimetric cytotoxicity assay for anticancer-drug screening. Journal of the National Cancer Institute, 82(13), 1107-1112.
27. Suzuki, I., Hayashi, I., Takaki, T., Groveman, D. S., & Fujimiya, Y. (2002): Antitumor and anticytopenic effects of aqueous extracts of propolis in combination with chemotherapeutic agents. Cancer Biotherapy and Radiopharmaceuticals, 17(5), 553-562.
28. Szliszka E[1], Czuba ZP, Bronikowska J, Mertas A, Paradysz A, Krol W. (2011a): Ethanolic Extract of Propolis Augments TRAIL-Induced Apoptotic Death in Prostate Cancer Cells. Evid Based Complement Alternat Med.,2011:535172.
29. Szliszka, E., Sokół-Łętowska, A., Kucharska, A. Z., Jaworska, D., Czuba, Z. P., & Król, W. (2013):