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Original Research

FRUITS OF HAVEN AND THEIR ROLE IN CANCER PREVENTION

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Abstract

Apart from spiritual, behavioral and social guidance to the world, the Holy Qur'an has also prescribed a number of medicines and therapeutic methodologies to treat and prevent numerous human ailments. In addition to the nutrition, food and dietary supplements the Holy Qur'an has directly emphasized several fruits for their health benefits and curative effects. Among the medicinal fruits, banana, grape, date, fig, olive and pomegranate are prominently discussed in the Holy Qur'an. Thus, in the present study an attempt is made to explore the therapeutic potentials of the fruits. Different parts of the mentioned fruits were subjected to sequential extraction method started with n-hexane then followed by ethanol and water. Cytotoxicity of the extracts was determined by dimethylthiazol-2-yl)- 2,5diphenyl tetrazolium bromide (MTT) assay on 2 human cancer (colon and breast) and normal endothelial cell. The antioxidant potencies were assessed using DPPH (1,1-diphenyl-2-picrylhydrazyl) and FRAP (Ferric reducing antioxidant power) assays. The results indicated that all the fruits tested in the study exhibited remarkable in vitro anticancer activity by against human breast (MCF-7) and colon (HCT 116) cancer cells. The IC50 values were ranged between 11.42 and 58.60 µg/ml. The significant antiproliferative effect of the fruits could probably due to the strong antioxidant effect, as all the tested fruits, except banana, displayed lowest IC50 values in DPPH and FRAP free radicals. The fruits extracts displayed IC50 values range between 6.06 and 70.50 µg/ml against DPPH, whereas, 10.20 to 95.20 µg/ml against FRAP. These results are in good agreement with the medicinal uses of the fruits suggested in the Holy Qur'an to cure the human ailments.

Keywords

Fruits; Prevention; Holy Quran; Science.

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1. INTRODUCTION

Arial (99,141). The unity and diversity of more than 250,000 flowering plant species distributed over the world (Kong. et al, 2003), cannot be emerged by chance from inanimate matter as the theory of evolution was claimed, the theory which denies the creation process has failed to explain how life originated on earth (Yahya, 2006). There is some truth to the old adage that human diseases is as old as human race, Life and diseases are equally striking, where there is life diseases are bound to exist . Over the centuries, humans have deepened on plants for basic needs such as food, clothing, shelter, transportation, hunting weapon and medicine .The empirical findings of Traditional Arabic and Islamic Medicine (TAIM) that have been held, and still holds, an important position in primary health care system. Owing to the statement of prophet Muhammad Peace Be Upon Him (PBUH) *"The one who sent down the disease sent down the remedy."* and *"For every disease, Allah has given a cure."* The sentence of prophet (PBUH), was a clear message to search for those remedies (Ahmad et al., 2009; Azaizeh et al., 2010; Zaid et al., 2011). Recently, it has been ascertained that oxidative stress produced by free radicals has been significantly associated with several diseases development such as cardiovascular, cancer, and neurodegenerative diseases (Covas, 2008). On the other hand, there is now substantial evidence indicating that fruits have generated increased interest in putative protective dietary factors in coronary heart diseases, cancer and Alzheimer's disease (Ness and Powles, 1997; Hung et al., 2004; Dai et al., 2006). Natural phenolic compounds and antioxidant substances in the fruits has played an important role in disease prevention and treatment (Huang et al., 2009).

The Federal Drug Administration (FDA) has permitted 23 g of olive oil daily to reduce the risk of coronary heart disease (Covas, 2008). Several scientific studies has recommended regular consumption, five or more serving of fruits and vegetables per day for a better health program (Subar et al., 1995). Despite the advantage of new approaches in drug discovery methods, there is still shortage of lead compounds progressing in clinical trials. The extensive frequency of wide range of fruit bioactive compounds has provided a new and important lead compound. The major phytochemicals derived from fruits that have potential to prevent cancer includes carotenoids, vitamins, resveratrol, silymarin, quercetin, indole-3-carbinol, and sulphoraphane. These phytoconstituents usually target multiple cell signaling pathways of cancer, they are safe, and they lack the side effects of conventional chemotherapies.

With the strong evidences of medicinal value of the fruits, the present study was conducted to analyze the antioxidant and cytotoxic properties of 33 extracts prepared from six fruits; banana *Musa sapientum* (Musaceae), dates *Phoenix dactylifera* (palmae), fig *Ficus carica* (Moraceae), grape *Vitis vinifera* (Vitaceae), olive *Olea earopoae* (oleaceae) and pomegranate *Punica granatum* (punicaceae).

This study is the first to report the antioxidant and cytotoxic properties of combined fruits (fig and olive) biased on the mentioned criteria of Quran

2. METHODS:

2.1. FRUIT MATERIAL

Six fruits; banana *Musa sapientum* , dates *Phoenix dactylifera* , fig *Ficus carica* , grape *Vitis vinifera* , olive *Olea earopoae* and pomegranate *Punica granatum* were selected for the study, fruit material was collected during the period of March-April 2014 from Istanbul-Turkey, except grape *Vitis vinifera* (white and red) was collected from well known market in Pinang-Malaysia during August 2015.

2.2. PREPARATION OF EXTRACTS

The fruit materials were dried in oven (35-40 ºC) and powdered mechanically. The pulverized plant material (50 g) was subjected to sequential extraction method started with n-hexane and followed by ethanol and water. All the extracts were prepared by 250 mL of the solvents using hot maceration (40 ºC) method with intermittent shaking. The extracts were filtered and concentrated at 45 ºC under vacuum by rotary evaporator (Buchi, USA) and further dried overnight at 45 ºC. Stock solutions of the extracts were prepared at 10 mg/mL in 100% dimethyl sulfoxide (DMSO). Further serial dilution of the stock was performed with cell culture media to obtain a range of desired concentrations of the extracts.

2.3. DPPH RADICAL SCAVENGING ACTIVITY

DPPH (1,1-diphenyl-2-picrylhydrazyl) assay was carried out to evaluate the scavenging activity of the extracts (Dahham at al, 2016). The stock solution of DPPH was prepared at a concentration of 200 µM in absolute methanol while stock solutions of the extracts were prepared at concentration of 10 mg/mL. DPPH was dispensed into 96-well plate (100 µL/well) and immediately, 100 µL of test12 samples were added at final concentrations of 12.5, 25, 50, 100, 200 µg/mL. Methanol alone and methanol with DPPH were used as blank and negative control, respectively. Ascorbic acid was used as positive control. The mixtures were incubated at 30 °C for 30 min in the dark and then the absorbance was measured at 517 nm. The dose response curves were obtained and then used to calculate the median inhibitory concentration (IC50). The results are expressed as mean ± SEM(n = 6).

2.4. FERRIC REDUCING ANTIOXIDANT POWER (FRAP) ASSAY

The FRAP assay was conducted according to (Dahham et al., 2015) method with minor modification. The FRAP reagent consists of 10 mM TPTZ (2,4,6- tripyridylstriazine) in 40 mMHCl, 20 mM FeCl3, and300 mM acetate buffer (pH 3.6) in proportions of1:1:10 (v/v/v). Various concentrations (3.25 – 100 µM) of fruit samples (50 µl) was added to 1.5 ml of freshly prepared FRAP reagent. The absorbance was measured at 593 nm using a TECAN Multi-mode microplate reader Model Infinite® 200 (Mannedorf, Switzerland) after 45 min of incubation. A standard curve was constructed using FeSO4 solution. The results were expressed as µM Fe2+/mg. All measurements were carried out in triplicate and the mean values were calculated.

2.5. CELL LINES AND CULTURE CONDITIONS

Human Umbilical Vein Endothelial Cell line HUVEC, catalogue number (C2517A); human colorectal carcinoma cell line HCT-116, catalogue number (CCL-247) and human hormone sensitive and invasive breast cancer cell line MCF-7, catalogue number (HTB-22) were purchased from ScienCell USA. HUVEC were maintained in endothelial cell medium (ECM) (ScienCell, USA) supplemented with endothelial cell growth supplements (ECGS), 5% HIFBS and 1% PS. HCT-116 cells were maintained in RPMI whereas, MCF-7 was maintained in DMEM medium. The media were supplemented with 5% heat inactivated fetal bovine serum and 1% penicillin/streptomycin. Cells were cultured in a humidified incubator at 37 °C supplied by 5% CO2. Cell culture work was done in sterile conditions using Class II biosafety cabinet (ESCO USA)

2.6. CYTOTOXICITY ASSAY

The MTT cytotoxicity assay was performed according to the method developed by Mosmann1983 with minor modifications (Dahham et al., 2014). Cells were seeded at 1.5×104 cells in each well of 96-well plate in 100 µL of fresh culture medium and were allowed to attach for overnight. For screening, the cells (70 - 80% confluency) were treated with the extracts at the final concentration of100µg/mL. Later on, in order to obtain a dose-response curve, the most active extracts were tested for cytotoxicity at 3.12, 6.25, 12.5, 25, 50 and 100 µg/ml concentrations. After 48 h of the treatment the medium was aspirated and the cells were exposed to MTT solution prepared at5mg /mL in sterile PBS was added to each well at 10% v/v in the respective medium and was
incubated at 37°C in 5% CO2 for 3 h. The water insoluble formazan salts was solubilized with200 µL DSMO/well. Absorbance was measured by infinite® Pro200 TECAN Group Ltd., (Switzerland) at primary wave length of 570 nm and reference wavelength of 620 nm. Each plate contained the samples, negative control and blank. DMSO (1% v/v) was used as a negative control. 5-fluorouracil and Tamoxifen were used as standard reference control for HCT 116 and MCF-7 cell lines, respectively. The assay was performed in quadricate and the results were presented as a mean percent inhibition to the negative control ± SEM.

3. RESULTS

3.1. PLANT EXTRACTION

Three exacts were prepared from each fruit material, starting with n-hexane followed by ethanol and water. The yield of each extract was calculated and presented in Table 2 as w/w percent yield. Among all the extracts, hexane extracts of all the tested plants produced the lowest yield except for red grape skin extract (2.6%). However, the water extracts of the tested plants showed the highest yield followed by ethanol extracts. For instance, the highest yield recorded was 4.30% for water extract of pomegranate peel.

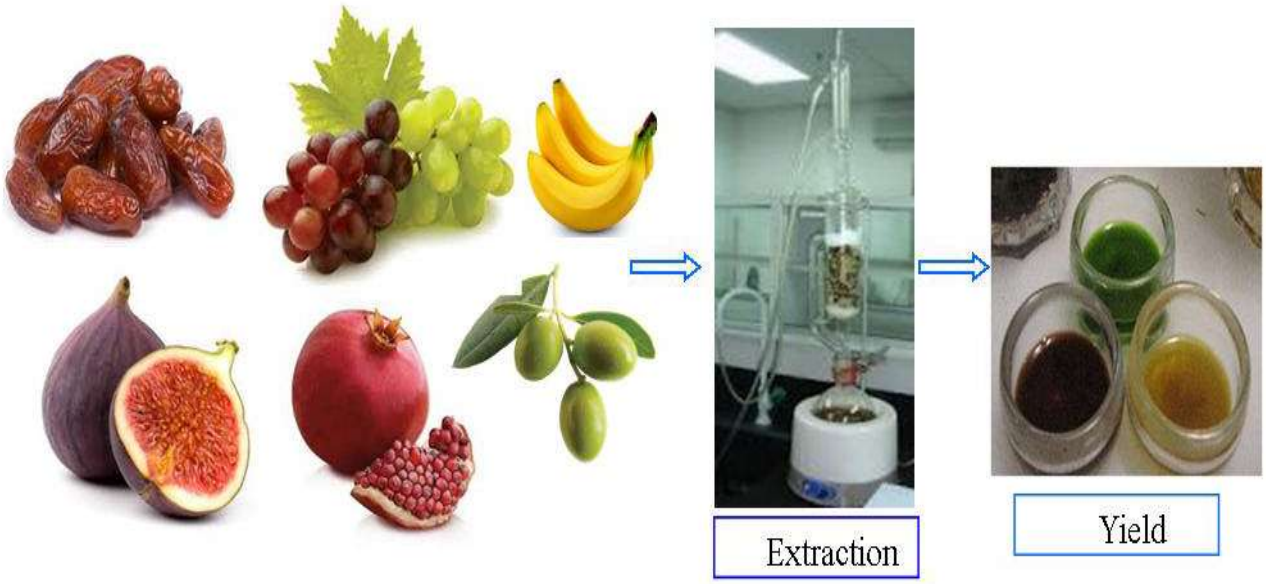

Fig 2 The selected fruits, subjected to extraction method and the resulted yield.

3.2. ANTIOXIDANT ACTIVITY

The result of radical scavenging capability of fruit extracts which was determined by DPPH and FRAPS scavenging methods is depicted in Table 1. In general, the extracts prepared from ethanol demonstrated the most potent antioxidant activity, whereas the extracts prepared from the solvent hexane displayed poor or moderate DPPH and FRAP scavenging activity. Among the tested fruits, pomegranate peel exhibited significant ($p<0.01$) antioxidant activity as lowest IC50 values were calculated for ethanol extract (IC50 = 6.06 µg/ml). Moreover, red grape skin and olive for ethanol extract also demonstrated significant ($p<0.05$) with IC50 values 9.60, 10.11 µg/ml, respectively. For water extracts of combined 1:7 fig+ olive showed the highest value with (IC50 = 12.01 µg/ml), the other fruit extract for n-hexane displayed either moderate or insignificant DPPH scavenging activity. Similarly, the ethanol extract of pomegranate peel demonstrated remarkable FRAP radical scavenging effect with IC50 10.20 µM of Fe2+/mg.(Table 1).

3.3. ANTI-PROLIFERATIVE EFFECT OF THE EXTRACTS AGAINST CANCER CELLS

The MTT assay was used to screen the possible cytotoxic activity of 33 extracts against two human cancer cells lines (HCT-116 and MCF-7) and one normal cell lines (HUVEC) .For screening, the cells were treated with the extracts at 50 µg/mL concentration. The extracts with more than 60% inhibition of cell proliferation were considered as active extracts. Hexane extracts of pomegranate exhibited the highest cytotoxicity on all the tested cell lines, while hexane and ethanol extracts of fig and red grape seed showed selective antiproliferative effect against colon cancer cell line (HCT116) with 61.43 and 74.01.%, respectively. Moreover, the ethanol extract of red grape seed showed selective cytotoxicity towards HCT-116 and MCF-7 with 65.33 and 60.03%. respectively. Interestingly, all the extracts of the fruit showed poor cytotoxicity against the normal cell line (Table 2). Moreover, the combination of fig and olive 1:7 which based on the mentioned criteria of Quran, were fig has mentioned only one time. Whereas, olive cited seven time. However the combined extract of n-hexan exhibited selective cytotoxicity against MCF-7 with 62.40%. The morphological alteration of the treated cancer cells presented clear evidence of significant cytotoxicity of some fruit extracts. Figure 2 showed the treated cells with vehicle (1% DMSO) displayed a compact monolayer of aggressively growing cancer cells with prominent nuclei and intact cell membrane. Whereas the images taken from the extracts treated group showed a severe reduction in the number of cells because of the anti-proliferative activity of the extracts. In addition, the extracts strictly affected the pseudopodial projections the cells which rendered

the cells no adherent and become round shaped. Interestingly, all the extracts studied showed either poor or no sign of cytotoxicity towards the normal cell line (HUVEC), which used as the model cell line for the normal human cells.

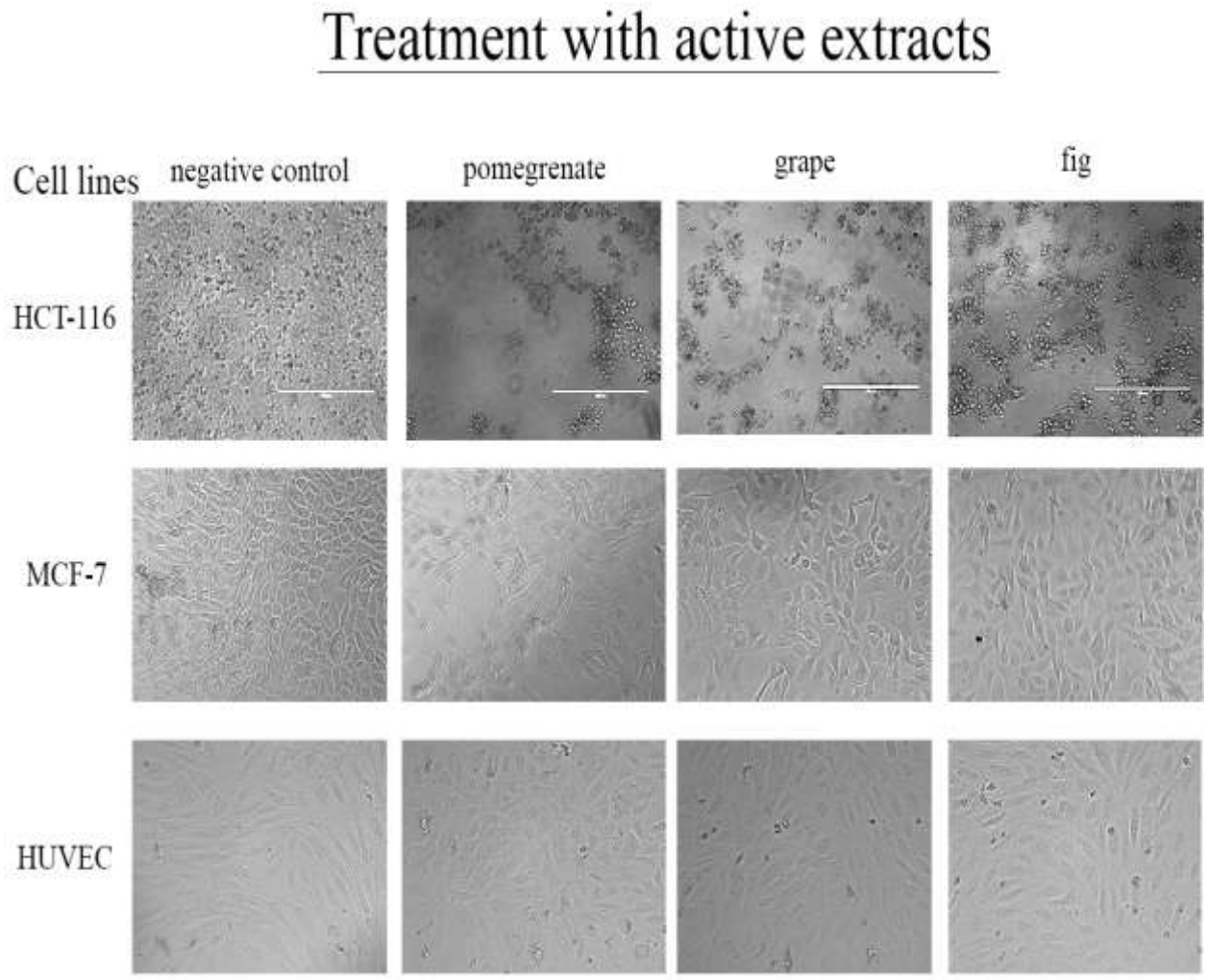

Fig 2. Effect of selected fruit extracts on cellular morphology of human cancer and normal cell lines. Photomicrographic images of cancer cell lines, taken under an inverted phase-contrast

Table 1. Yield and antioxidant activity of different extract of the selected fruits

Fruits	Part used	solvent	Yield (%)	DPPH (IC50 µg/ml)	FRAP (µmol Fe2+/mg)
Banana	peel	n-Hexan	1.25	552.60	59.15
		Ethanol	0.9	19.10	55.10
		Water	2.25	54.11	79.28
	Fruit	n-Hexan	1.67	482.21	53.11
		Ethanol	1.05	123.07	46.40
		Water	3.90	151.09	190.50
Dates	Fruit	n-Hexan	1.50	120.05	33.13
		Ethanol	1.93	18.34	43.06
		Water	2.55	33.12	38.09
Fig	Fruit	n-Hexan	1.10	70.50	120.90
		Ethanol	2.8	16.09	20.42
		Water	3.7	22.10	50.30
Grape (red)	Skin	n-Hexan	2.06	18.35	163.01
		Ethanol	1.95	9.60	95.20
		Water	3.55	16.25	71.33
	Seed	n-Hexan	1.22	32.46	40.61
		Ethanol	1.95	11.53	22.03
		Water	0.9	22.50	66.89
(white)	Skin	n-Hexan	0.92	32.12	17.90
		Ethanol	2..42	20.52	29.27
		Water	1.67	19.10	14.19
Olive	Skin	n-Hexan	0.45	90.10	21.41
		Ethanol	1.00	10.11	13.21
		Water	2.34	13.09	33.02
Pomegranate	Peel	n-Hexan	1.32	53.49	26.76
		Ethanol	1.14	6.06	10.20
		Water	4.30	12.80	27.54
	Seed	n-Hexan	0.69	67.92	160.09
		Ethanol	1.50	23.30	88.52
		Water	1.99	34.06	73.11
Fig +Olive 1 : 7		n-Hexan	0.50	23.20	19.50
		Ethanol	1.43	11.05	13.49
		Water	2.59	12.01	20.18

Table 2. Cytotoxic effect of different extracts of the selected fruits

Fruits	Part used	solvent	% inhibition of cell proliferation		
			HCT-116	MCF-7	HUVEC
Banana	peel	n-Hexan	52.04	19.22	6.92
		Ethanol	16.14	44.62	20.12
		Water	11.80	20.53	4.65
	Fruit	n-Hexan	23.76	48.21	5.11
		Ethanol	18.20	12.07	4.40
		Water	11.42	15.09	1.50
Dates	Fruit	n-Hexan	58.60	39.20	6.43
		Ethanol	46.23	22.31	4.50
		Water	17.93	7.66	3.05
Fig	Fruit	n-Hexan	61.43	50.10	7.70
		Ethanol	47.85	34.06	5.84
		Water	38.09	30.15	5.55
Grape (red)	Skin	n-Hexan	55.20	63.89	8.50
		Ethanol	58.10	43.74	10.51
		Water	48.12	52.15	7.33
	Seed	n-Hexan	74.01	30.16	15.60
		Ethanol	65.33	60.09	9.03
		Water	39.40	22.50	6.20
(white)	Skin	n-Hexan	45.59	50.19	7.90
		Ethanol	39.04	38.52	9.22
		Water	25.60	19.10	4.12
Olive	Skin	n-Hexan	48.40	55.10	7.41
		Ethanol	39.05	30.71	5.99
		Water	22.80	10.00	3.08
Pomegranate	Peel	n-Hexan	83.98	62.55	14.50
		Ethanol	65.10	57.09	10.20
		Water	41.80	38.15	5.91
	Seed	n-Hexan	52.64	60.23	16.03
		Ethanol	42.10	51.19	8.52
		Water	26.07	34.50	6.11
Fig +Olive 1 : 7		n-Hexan	60.20	62.40	5.31
		Ethanol	52.35	34.15	6.49
		Water	25.12	16.12	4.18

4. DISCUSSION

Fruits and their constituents represented an important element for human over the centuries. The impact of the fruits was also acknowledged in the Holy Qur'an which mentioned the beneficial effects of several fruit such as grape, dates, fig, olive and pomegranate. Prophet Muhammad (PBUM) recommended these fruit for different use. For instance, prophet mentioned about fig "*If I had to mention a fruit that descended from paradise I would say this is it because the paradisiacal fruits do not have pits. . .eat from these fruits for they prevent hemorrhoids, prevent piles and help gout*." (Zaid et al., 2011). Recently studies on fig *Ficus carica* showed antioxidant, immunostimulant, antimicrobial, anticancer and anti-inflammatory activities (Yang et al., 2009; Jeong et al., 2009; Lansky et al., 2008). Modern research studies showed that the grape, olive and pomegranate exhibited dynamic therapeutic application in cardioprotective effects, cancer prevention, antidiabetic and neuroprotective property (Yadav et al., 2009; Boskou, 2010; Jurenka, 2008). These disease is the most leading cause of morbidity and mortality worldwide, cancer is responsible for 6 million death annually (Amin and Mousa, 2007). In the cancer war, medicine has relied on the toxic compound (Blagosklonny, 2005). Unfortunately , the cytotoxicity properties of most chemotherapy drug is nonspecific and therefore do not distinguish between normal healthy cells and tumor cells , these events has lead to inappropriate and toxic therapeutic agents with a wide range of side effect that limit the maximum tolerated doses and the minimum effective doses of chemotherapy. In the present study, 33 extract were selected and extracted by using sequential extraction method with 3 solvents of different polarity. This study aimed to evaluate the anticancer and antioxidant activities of 6 Quranic fruits. MTT assay was used to assess the anticarciogenic properties of the fruit extract; this assay provides a preliminary method for determination of cell's viability via mitochondrial activity in living cells.

The results of the cytotoxic assay showed that among all the extracts, the highly non-polar solvent extract i.e., hexane extract exhibited higher cytotoxic activity than the other solvent extract (ethanol and water) Among the 6 fruit, the hexane and ethanol extracts of pomegranate *Punica granatum* showed most potent anti-proliferative effect on all the tested cancer cell lines.

Consistently the grape extract, both skin and seed non-polar and polar extract displayed selective cytotoxicity towards hormone dependent breast cancer cell line (MCF-7), and colon cancer cell line (HCT116).however, Non-polar extracts of fig exhibited significant inhibitory effect against the colon cancer cell line (HCT116). Interestingly, the combined extracts of fig and olive 1:7 showed a selective activity against (MCF-7). Noteworthily, the extracts of the most effective fruit (pomegranate, grape, fig) did not produced significant cytotoxicity against normal cell line (HUVEC). Altogether, the most biologically active fruit which showed significant cytotoxicity toward cancer cell lines as well as antioxidant activity were the pomegranate peel and grape seed. These findings conferm that the pomegranate fruit provide an inexhaustible source of many therapeutic application, as our previous study revealed the potent antimicrobial activity of *Punica granatum* (Dahham et al., 2010). The present study confirmed that the extracts of pomegranate, grape and fig) demonstrated selective cytotoxicity against human breast and colon cancer cell lines while being less cytotoxic against the normal cell. The selectivity may attributed to the substances interact with special cancer-associated receptors which can stimulate apoptosis mechanism that cause cancer cell death (Hacker, 2000). The microscope image of the treated HCT-116 and MCF-7 cells displayed typical signs of apoptosis such as cell membrane blebbing, nuclear condensation and crescent shaped nuclei (Figure 2). The results of the present study could be very helpful as preliminary data in the search for new anticancer and antioxedant compounds from the tested fruit . These fruits have the potential to be chemically standardized and used as herbal medicines or developed into pharmaceutical drugs for the treatment of various diseases.

5. CONCLUSION:

In conclusion the differences and similarities of the fruit properties were described in Quran "*he sends down water from the sky, and with it we bring forth the plant of every thing. from these we bring forth green foliage and composite grain, palmtrees laden with clusters of dates within reach, vineyards and olive groves and pomegranates alike and unlike. behold their fruits when they bear fruit and ripen. surely, in these there are signs for a nation who believe*" (Qur'an 6:99). The present study revealed that among the six fruits (pomegranate *Punica granatum*, grape *Vitis vinifera* and fig *Ficus carica*) *found* to be most biologically effective extract with significant cytotoxic effects and antioxidant activity. the selectivity and diversity of the fruits result

in this study were clearly compatible with the above verses (Qur'an 6:99). Were different extracts showed different activities

Furthermore, the extracts of these fruits displayed either negligible or no signs of cytotoxicity against the tested human normal cell , these fruit extract could be as promising candidates for the development of novel chemopreventive or chemotherapeutic formulations with no side effects. The results obtained in the present study justify the traditional use of these gifted fruits in health care system.

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