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The therapeutic effects of *Ficus carica* extract as antioxidant and anticancer agent

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ABSTRACT

Natural extracted ingredients are evolutionarily selected molecules and are used to control inflammation, and cancerous progression and transformation. Several studies have evaluated the beneficial properties of certain pharmaceutical molecules extracted from *Ficus carica* (FC). The current study aimed to investigate the antioxidant and anticancer properties of FC ethanolic leaves extract. The dried coarse powder of *F. carica* leaves was exhaustively extracted with ethanol. The resulting crude ethanolic *F. carica* extract (FCE) was assayed for total phenolic content and, antioxidant and anticancer activities, since both are interrelated. The antioxidant activity of the FCE was determined using DPPH as a standard stable free radical. The anticancer activity of the extract was determined against breast cancer (MCF7), hepatocellular carcinoma (HepG2), Colon cancer (CaCo-2), and a human laryngeal carcinoma (Hep-2) cell lines. The obtained results indicated a strong antioxidant activity of the extract with 1 mg/ml having 75.7% DPPH scavenging ability. The anti-cancer activities of the extract showed strong inhibition percentages against all the selected cell lines. The FCE had potent effects against both Hep2 and HepG2 cells with inhibition percentages ranged 80.7–66.9%. The properties of the FCE demonstrated here support our proposal of the validity of the traditional health claims of medicinal plants.

1. Introduction

Fruits and vegetables are considered to be the most important sources of phytochemicals in the human diet. Approximately 20,000 phytochemicals of the known 200,000 originate from fruits, vegetables and grains Patra (2012) recently, phytochemicals have been used as antioxidants to treat several diseases. Phytochemicals have antibacterial, antifungal, antiviral, antithrombotic, anti-inflammatory, and cholesterol lowering properties Schreiner and Huyskens-Keil (2006). One of the largest causes of the death in the world is cancer. So far, anomalies have been demonstrated in about 350 genes in human cancers (Futreal et al., 2004; Broadhead et al., 2010). Epidemiologically, one in eight of deaths worldwide is due to cancer (Wolf and Davidovici, 2010) Research in the use of natural products has increased in recent years in response to high cancer related death rates (Gheldof et al., 2003; Liu et al., 2000; Laandrault et al., 2001; Siddhuraju and Becker, 2003; Zuo, 2002).

Fig (*Ficus carica*) is seasonal fruit that is may be originated from the Middle East, which is one of the early cultivated fruit species and currently is an important crop worldwide. The common fig grows in natural ecosystems of the Mediterranean basin. Dried figs are available to consumers worldwide, at any time of the year. The fig tree is a member of the mulberry family (Moraceae). Fig products are excellent examples of natural products that are widely used as a food source and a source of traditional medicine. In folk medicine, Fig root is used in the treatment of leucoderma and ringworms. The fruit of the fig tree has antipyretic, purgative, and aphrodisiac properties which have been shown to be useful in treating inflammation and paralysis (Jeong and Lachance, 2001).

Many bioactive molecules from the plants have been found to have anti-cancer activities. In the United States, about 50–60% of cancer patients use extracts derived from different plant species (alternative medicine), entirely or concurrently with common traditional therapeutic treatment such as chemotherapy and/or radiation therapy (Gutheil et al., 2011).

Many studies on *F. carica* have confirmed the presence of various bioactive compounds such as phenolic compounds, phytosterols,

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organic acids, anthocyanin composition, triterpenoids, coumarins, and volatile compounds such as hydrocarbons, aliphatic alcohols. Phenolic compounds, organic acids, and volatile compounds are very common in most cultivars of *F. carica* (Oliveira et al., 2009; Gibernau et al., 1997). Phenolic compounds are favorable to human health, since they are able to act as antioxidants, the consumption of which is associated with favorable health outcomes (Alis et al., 2011).

Some recent reports explored the anticancer activities of *F. carica* leaf extracts. A mixture of 6-O-acyl-β-d-glucosyl β-sitosterols showed in-vitro inhibitory effects on the proliferation of various cancer cell lines (Svetla et al., 2005; Khadabadi et al., 2007; Rubnov et al., 2001) .

The current study aims to determine the cytotoxic effects of *F. carica* leaf ethanol extracts on breast cancer (MCF7), hepatocellular carcinoma (HepG2), Colon cancer (CaCo-2) and human laryngeal carcinoma (Hep-2) cell lines.

2. Materials and methods

2.1. Plant material and extraction

Leaves of *F. carica* were collected from the local farms in Borg Al-Arab, Alexandria, Egypt The collected leaves were washed with distilled water and air dried in the shade for one week, then they were cut into small pieces, ground into a coarse powder using a mechanical grinder, and stored in an air tight container. About 30 g of leaf powder was mixed with 500 ml of 70% ethanol 99% for 24 h at room temperature 25 ± 2 °C with occasional stirring (Nadia et al., 2017). The extract was then filtered with Whatman No. 1 filter paper and concentrated under reduced pressure below 50 °C using a rotary vacuum evaporator. The recovered extract was lyophilized and the recovered fine powder was stored at −20 for further use.

2.2. Determination of total phenolics content (TPC)

The TPC of fig leaves extracts was determined using the Folin–Ciocalteu micro method (Waterhouse, 2009). The reaction mixture contained 40 μL of extract, 3160 μL of pure water, 200 μL of the Folin–Ciocalteu reagent, and 600 μL of 20% sodium carbonate solution. After 30 min of incubation at 40 °C, the absorbance was read at 765 nm. The TPC is expressed as Gallic acid equivalent per a dry basis of fig leaves (mgGAE/gdb).

2.3. Mammalian cell lines

Four types of human cancer cell lines were used in this study; colon cancer cells (CaCo-2), laryngeal carcinoma (Hep-2), Hepatocellular carcinoma (HepG2) and Brest cancer (MCF7). Colon cancer cells (CaCo-2) and laryngeal carcinoma (Hep-2) were cultured on DMEM media, while Hepatocellular carcinoma (HepG2) and Brest cancer (MCF7) cells were cultured on RBMI media. All Medias were supplemented with 200 mM L-glutamine and 10% fetal bovine serum (FBS) (Gibco BRL).

2.4. Cytotoxicity assay

Peripheral blood mononuclear cells (PBMCs) were isolated by Gradient centrifugation. Then 2 $\times 10^5$ cells/ml were cultured in RPMI medium and seeded into round bottom 96-well plates. Nontoxic doses of *Ficus carica* crude extract were determined using the PBMCs. Leaf extracts were prepared in serial dilutions of (5000, 2500, 1250, 625, 312.5 and 156 μg/ml). A cell suspension of (6×10^4 cells/ml) was cultured on the 96-well plates and treated with 100 μl of each of the extract dilutions. After 48 h, the cellular cytotoxic effects were quantified using a neutral red assay protocol (Borenfreund and Puerner, 1985).

2.5. Anticancer activities of F. carica extract

The anticancer activities of *Ficus carica* against HepG2, CaCo2, MCF7, and Hep2 cells was determined using the previously described assay (Borenfreund and Puerner, 1985). and compared to 5fluorouracil (5FU) as a positive control. A cell suspension (6×10^4 cells/ml) was cultured on 96-well plates and treated with about 100 μl of each of serially diluted extracts (5000, 2500, 1250, 625, 312.5 and 156 μg/ml). After 48 h, the cellular cytotoxic effects were quantified using a neutral red assay protocol.

2.6. Determination of antioxidant capacity (DPPH)

Leaf extract was diluted in pure methanol at different concentrations (0–1 mg/mL). A total of 0.3 mL of extract was mixed with 2.7 mL of methanol solution containing DPPH radicals (6×10^{-5} mol/L). The mixture was shaken for 20 s and the absorbance was measured at 517 nm after a 60 min incubation at room temperature in the dark. Pure methanol was used as blank solution and the DPPH solution was used as a control. The inhibition percentage of the absorbance was calculated using the following equation.

Percentage of DPPH scavenging activity was calculated as: $[(AC - AE)/AC] \times 100$

Where:

AC: The mean of absorbance of negative control

AE: The mean of absorbance of extract

2.7. The total antioxidant capacity assay

The total antioxidant capacity of leaf extract was measured calorimetrically and the results were expressed as vitamin C equivalents in mg/g of extract. Briefly, 100 μL of leaf extract or serial concentrations of vitamin C (0–1 mg/mL) was added to 1.9 mL of the reagent solution (0.6 M H_2SO4, 28 mM sodium phosphate and 4 mM ammonium molybdate). The mixtures were incubated in oven at 95 °C for 90 min; then the absorbance was measured at 695 nm (Prieto et al., 1999).

2.8. Statistical analysis

All statistical analyses were performed using Minitab ver. 17 software. One way ANOVA was used for data analysis and Tukey test ($p<0.05$) for the multiple means comparisons.

3. Results and discussion

3.1. Total phenol content (TPC)

F. carica leaves may constitute an excellent source of bioactive compounds, specifically, phenolic compounds. The efficiency of extraction of bioactive molecules from the plant tissues is affected greatly by the solvent type and temperature (Confidence and Doga, 2020; Tramelli and Faveri, 2007)

It is well known that alcohol mixed with water can affect the extractability of phenolic compounds greatly compared to monocomponent solvents (Manuel et al., 2005; Spigno, 2007). In this study, the phenolic compounds of fig leaves were extracted at room temperature for 24 h using 70% ethanol and measured using the Folin–Ciocalteu micro method. After 30 min of incubation at 40 °C, the absorbance was read at 765 nm where the total phenols content was 3.8 mgGAE/gdb. Phenolic contents in this study was lower than the sum of the determined phenolic compounds obtained by Oliveira et al. (2009) where 42 mg/g extracted by pure methanol by soxhlet for eight hours). The value of total phenolics in fig leave obtained here is similar with the result of 4.5 mg/g obtained by Konyalıoğlu et al. (2005) who extracted the total phenolic compounds over two days using ethanol.

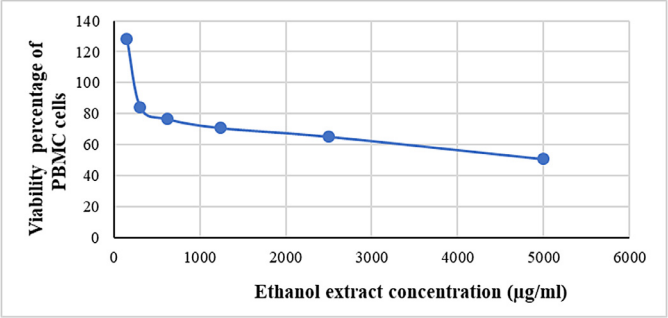

Fig. 1. The cytotoxic effect of different concentrations of FCE extract on peripheral blood mono nuclear cells (PBMC).

3.2. Cytotoxicity

From a toxicological point of view, using ethanol and water in place of other organic solvents for extraction is safer because it makes the extracts more suitable for the food processing (James et al., 2002).

The cytotoxic effect of FCE on normal human cells was determined by treating peripheral blood mono nuclear cells (PBMC) with serial dilutions of FCE. The FCE was prepared by incubating fig leaves in 70% ethanol for 24 h.

Results revealed that, there were no cytotoxic effects under lowest concentrations of *Ficus carica* extract (5000, 2500, 1250, 625, 312.5 and 156 μg/ml) (Fig. 1). Interestingly, there was an increase in the number of PBMCs compared to the untreated cells, which was reflected as an increase in the percentage of cellular viability. The lowest concentration of FCE (156 μg/ml) promoted the PBMCs proliferation percentages to 127% relative to the untreated cells.

3.3. Anticancer activity

Different concentrations of FCE were tested for their potential as anticancer agents using a variety of cancer cell lines. The cancer cell lines tested included colon cancer (CaCo-2), laryngeal carcinoma (Hep-2), Hepatocellular carcinoma (HepG2) and Brest cancer (MCF7). Analysis of variance revealed that all crude extract concentrations (5000, 2500, 1250, 625, 312.5 and 156 μg/ml) inhibited the viability of the four types of cancer cells significantly (Table 1). In addition, the interaction of the four cancer cell lines and the six FCE concentrations was significant indicating that the cell lines responded to the different leaf extract concentrations differently.

In the present study, there is significant inhibition (decrease in viability) between the mean of six concentrations on four different cancer cell lines. The mean cancer cell inhibition increased from 47.91% to 78.61% with increasing concentration of FCE.

3.4. Hep2 cell

With regards to the Hep2 cells lines, the minimum cell viability was reached when treated with the highest extract concentration

Table 1
Analysis of variance of the effect of six different ethanol crude extract concentrations on the activity of four cancer cell lines.

S.O.V.	DF	MS
Cell lines	3	2081.29*
Extract concentration	5	1588.20*
Cell line × Extract concentration	15	300.500*
Error	48	11.33

* Indicates significant differences under p value ($p<0.05$).

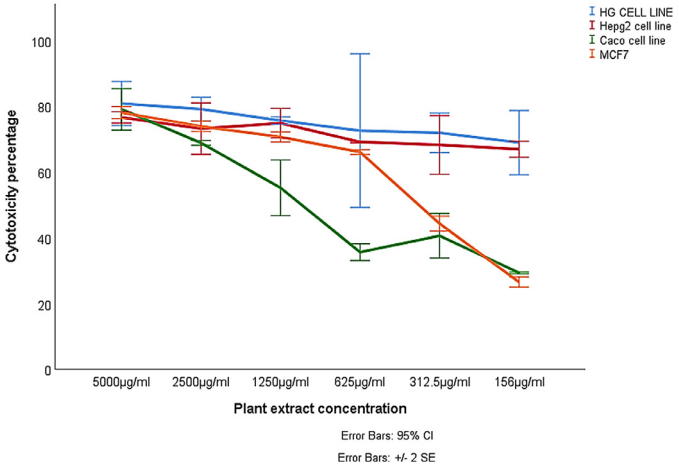

Fig. 2. Effect of fig leaves ethanol extracts on viability of different cancer cell lines; CaCo-2 Cell, HepG2, Hep2 cell and MCF7 cell.

(5000 μg/ml) of FCE while the maximum cell viability was at lowest concentration (156 μg/ml) of FCE. However, across the range of FCE concentrations used there were no significant differences in decreasing cancer cell viability except for the lowest concentration (156 μg/ml) where the inhibition of viability decreased to 68.92% from 80.78% for 5000 μg/ml. Therefore, FCE concentrations starting from 5000 μg/ml to 32 μg/ml inhibited cell viability significantly but with the same level based on the statistical analysis (Figs. 2 and 3).

3.5. HepG2

In the case of the cancer line HepG2, the lowest cell viability was obtained when FCE concentrations of 5000 μg/ml was used and the highest cell viability was at lowest concentration FCE concentration of 156 μg/ml. However, there were no significant differences in cell viability among all FCE concentrations (Fig. 2).

3.6. CaCo-2 cell

The highest inhibition in CaCo-2 cell viability was recorded under the highest concentration of FCE (5000 μg/ml). There was no significant differences in viability inhibition when crude extract with the two concentrations (5000 and 2500 μg/ml) while when the two concentrations (2500 vs both 1250 and 625 μg/ml) were used, the differences were significant (Fig. 2).

3.7. MCF7 cell

All FCE concentrations affected the viability of MCF7 cells significantly. However, the highest three concentrations (5000, 2500 and 1250 μg/ml) inhibited the cell viability equally, based on the statistical analysis. The last three concentrations (1250, 625 and 156 μg/ml) showed significant differences in cell viability (Table 2).

Therefore, the ethanol extract of leaves of *Ficus carica* exhibited reducing activity and anticancer activity in all cancer cell types used in this study. The current results suggest that ethanol leaf extract of fig have great potential as anti-carcinogenic and antioxidant agent. In general, the beneficial effect of plant products such as figs may be attributable to one or more phytochemicals including antioxidants. Fig leaf and fruit extracts contained several antioxidants, such as flavonoid and tannin. The presence of flavonoid, tannin, and other polyphenolic compounds can counteract free radicals by donating protons to free radicals and therefore terminate potentially damaging chain reactions. Saponin content in *Ficus carica* leaf and fruit extracts can also perform antioxidant functions through the reduction of

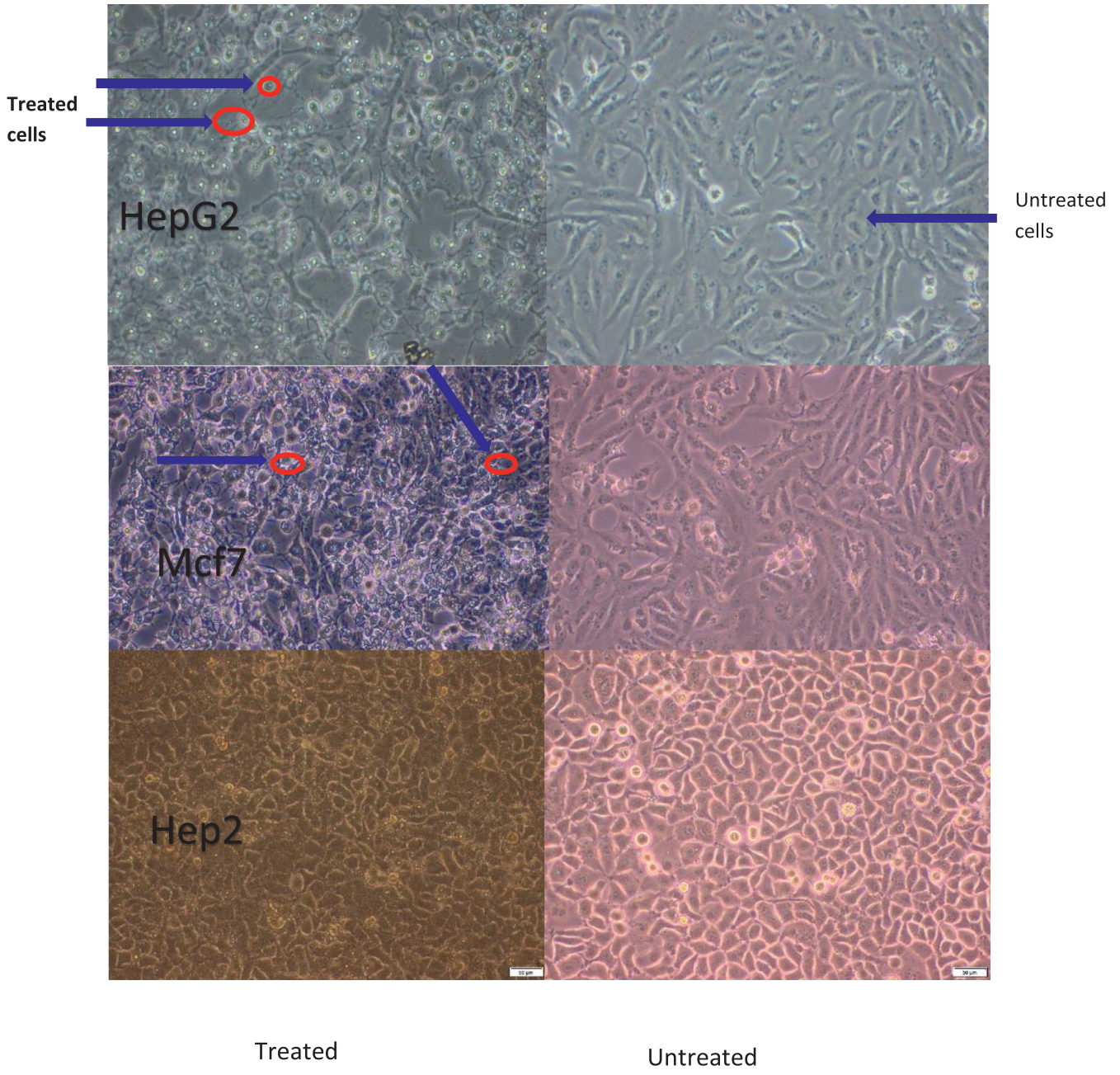

Fig. 3. The anticancer effect of FCE on HepG2, Mcf7 and Hep2, cells after 48 of treatment, cells undergoing apoptosis are characterized by cellular rounding up, shrinkage, membrane blebbing, and loss of cell adhesion

superoxide through the formation of hydroperoxide intermediates (Zhang et al., 2018).

All these results were comparable with the nontoxic dose of 5-fluorouracil (0.9 μg/ml) that showed inhibition percentages of 40.1%. These findings indicated that HepG2 and Hep2 cells were more sensitive to the lowest treatment concentrations (15.6 μg/ml) than both of CaCo-2 and MCF7 cells were.

3.8. Antioxidant activity

3.8.1. DPPH

In this experiment FCE was diluted in pure methanol at different concentrations (0–1 mg/mL). Extracts were mixed with methanol solutions containing DPPH. The mixture was shaken for 20 s and the absorbance was measured at 517 nm after a 60 min incubation at room temperature in the dark. The FCE showed good antioxidant potential when compared to standard ascorbic acid using the DPPH scavenging assay. Higher concentration FCEs captured more free radicals formed by DPPH. IC50 activity in this study was at concentration 0.259 mg from leaves extract Figure 4. This was higher than the antioxidant activity of 0.6 mg recorded by Souhila et al. (2016) who used Methanol with soxhelt apparatus for eight hours for extraction.

3.9. Total antioxidant activity

The total antioxidant capacity of FCE was measured calorimetrically and the results were expressed as vitamin C equivalents in mg/g of extract (Prieto et al., 1999). Total anti-oxidant activity obtained in this study at room temperature after 24 h by ethanol 70% was 0.569 mg/g.

Total antioxidant activity in this study was lower than that determined by Nadia et al. (2017) by using Ascorbic as standard. The fig plant extracted using ethanol. *Ficus carica* offered a higher reducing ability with 638.23 ± 0.43 mg GAE/100 g. *F. carica* has been

Table 2
Means of anticancer activity as affected by different concentrations of ethanol leave extracts.

Conc. μg/ml Cell line	5000	2500	1250	625	312.5	156	Mean
Hep2 cell	80.78^{A}	79.10^{AB}	75.62^{ABCD}	72.55^{ABCD}	71.90^{ABCD}	68.92^{BCD}	74.81^{A}
HepG2 cell	76.58^{ABCD}	73.16^{ABCD}	74.82^{ABCD}	69.10^{BCD}	68.23^{CD}	66.90^{D}	71.47^{B}
CaCo-2 cell	79.05^{AB}	68.81^{BCD}	55.18^{E}	35.62^{FG}	40.59^{F}	29.33^{G}	51.43^{C}
Mcf7 cell	78.03^{ABC}	73.87^{ABCD}	70.62^{ABCD}	66.02^{D}	44.30^{F}	26.52^{G}	59.89^{D}
Mean	78.61^{A}	73.735^{B}	69.06^{C}	0.822^{D}	56.255^{E}	47.917^{F}	

Means that do not share a letter are significantly different.

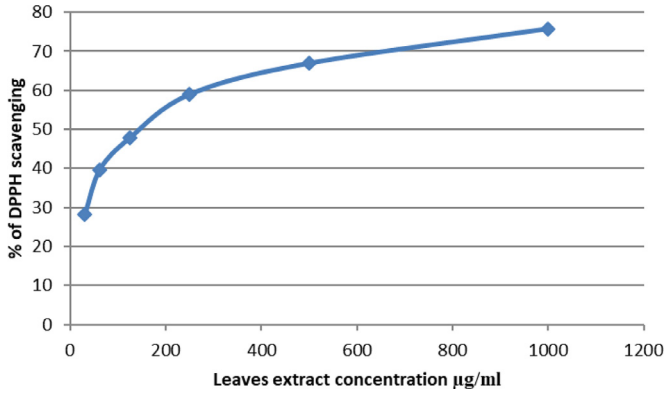

Fig. 4. Antioxidant activity of fig leaf extracts was measured calorimetrically and expressed as vitamin C equivalents in mg/g of extract.

traditionally used for its medicinal benefits as a metabolic, cardiovascular, respiratory, antispasmodic, and anti-inflammatory remedy (Werbach, 1993).

4. Conclusion

Antioxidant and anticancer properties of *Ficus carica* ethanolic leaves extract were investigated. The obtained results indicated a strong antioxidant activity of the extract at 1 mg/ml with 75.7% DPPH scavenging ability. The anti-cancer activities of the leaf extract showed strong inhibition percentages against the all selected cell lines with potent effect against both Hep2 and HepG2 cells with inhibition percentages of 80.7–66.9%. The obtained results support our suggestion of using traditional plant extracted agents for therapeutic purposes.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

CRediT authorship contribution statement

Raoufa Abdel-Rahman: Review & editing. **Eglal Ghoneimy:** Review & editing. **Abeer Abdel-Wahab:** Review & editing. **Nehal Eldeeb:** Review & editing. **Marwa Salem:** Review & editing. **Eman Salama:** Formal analysis, Writing – original draft. **Talaat Ahmed:** Formal analysis, Writing – original draft, Writing – review & editing.

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