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Leaf Hexane Extracts of Two Turkish Fig (*Ficus carica* L.) Cultivars Show Cytotoxic Effects on a Human Prostate Cancer Cell Line

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Abstract

The world-famous Turkish fig, grown in Aydin, is also used for the treatment of various diseases with its leaves and latex. Studies have shown that fig leaf has antioxidant, antiviral, antidiabetic, antimicrobial, and anticancer effects. The objective of the study is to examine the anticarcinogenic and antimicrobial effects of nonpolar extracts from the leaves of two fig cultivars (Sari Lop and Aydin Black) that are the most widely grown in Aydin. The fig leaves collected in the summer of 2017 were dried in shade at room temperature and crumbled. The n-hexane extracts of the dried fig leaves obtained with manual soxhlet and semi-automated soxhlet apparatus were applied on PC3 human prostate cancer cell line for 24h. The antimicrobial activities of the extracts were examined on *Escherichia coli* and *Bacillus cereus* using disc and agar well diffusion methods. As a result, antimicrobial activity of the n-hexane extracts on the bacteria was not detected at the highest dose tested (100 mg/ml). The n-hexane extracts showed cytotoxic effect on PC3 cells in a dose-dependent fashion and caused close to 100% death at 1000 µg/ml. No significant difference was observed between the cytotoxic effects of n-hexane extracts of two fig cultivars and the extraction methods (P>0.05).

Keywords: *Ficus carica*, Fig leaf, Hexane extract, Prostate cancer, Cytotoxicity, Antimicrobial.

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Contents

1. Introduction

Fig (*Ficus carica* L.), a fruit tree of the Moraceae family, is a small tree with a height ranging from 1 to 10 m. *F. carica* plant is grown mostly in the city of Aydin in Aegean Region of Turkey [1]. The fig is cultivated worldwide for its nutritive and medical properties. It is widely used in Ayurveda, siddha, and homeopathy medical systems [2]. Fruits, leaves, and roots of fig plants are some of the remedies people resort to in various illnesses. While fig fruit is used for the prevention of indigestion, anorexia, cardiovascular problems, and cancers; fig roots and leaves are used against indigestion and anorexia. In addition, fig leaf is also used against the anemia [3]. The total phenolic substance, organic acid content, and antioxidant potential in the fig leaf have been reported to be higher than in fig pulp and crusts [4].

It is claimed that *F. carica* is useful in treating liver and spleen disorders and gout disease. Fig leaves were also tried for the treatment of jaundice. *F. carica* leaves boiled in hot water were reported to be used in kidneys and liver, in diabetes and calcification, and as well as in hemorrhoid treatment [5, 6]. *F. carica* leaves have also been used in the treatment of vitiligo due to the presence of furanocoumarins, psoralen, and daidzein [7]. The fig leaf is also reported to be used in asthma, cough, sexual disorders, diarrhea, hematuria, earache, toothache, migraine, eye problems, stomach problems, and scabies [8]. In traditional medicine, the use of *F. carica* leaf, fruit, and root is a reality due to the antibacterial, antifungal, antioxidant, and antiviral activities it has [3].

In 1998, when the aqueous decoction of fig leaf was administered to Type I diabetic patients, hypoglycaemic effect was revealed as the postprandial (after the meal) glycemia decreased significantly in the patients [9]. Following this, Canal et al. showed that chloroform extract obtained from aqueous decoction of *F. carica* leaves was successfully used to decrease cholesterol levels and hyperglycemia on the rats with experimentally-induced diabetes [10].

It was reported that fig leaf methanol extract (500 mg/kg) decreased the aspartate aminotransferase, alanine aminotransferase, total serum bilirubin, and malondialdehyde levels, and showed liver protective effect by reducing lipid peroxidation in the liver [11]. This activity of the fig leaf extract is comparable to slymarine [12] which is known as a liver protective agent.

The petroleum ether extract of *F. carica* leaves provided promising results in the treatment of rifampicin-induced hepatic damage in rats [13]. A study conducted on Wistar albino rats showed that the petroleum ether, chloroform, and ethanol extracts of *F. carica* leaves had anti-imflammatory properties [8]. In a recent study, ethyl acetate extract of fig leaf was shown to be controlling the glucose and fat levels in type 2 diabetic rats, thus being effective in controlling the carbohydrate metabolism [14]. While promising results were obtained with *F. carica* leaf extracts, ethanol extract of *F. carica* fruit (fig) up to 1000 ug/ml for 72 h did not show any toxicity on U87 glioblastoma cells [15].

In a study conducted in Iran, the anti-angiogenic effects of fig leaf ethanolic extract was evaluated on human umbilical vein endothelial cells (HUVEC). After 24 hours of incubation with the extract at 25 µg/ml, a statistically significant cytotoxic effect on HUVECs was reported compared to the control group [16].

The antimicrobial effects of *F. carica* leaf extracts have been examined in several studies. The methanol extract of fig leaves collected and dried in South Korea was detected to have antimicrobial activity on oral bacteria [17]. In 2016, total phenolic and flavonoid contents of the methanol extracts from ten different varieties of *F. carica* in Algeria were examined and antimicrobial effects of the extracts were determined by disk diffusion test. As a result, all extracts were rich in phenolic compounds and had antimicrobial effect against Gram-positive and Gram-negative bacteria. *Staphylococcus aureus* and *Bacillus cereus* were reported to be the most susceptible bacteria to *F. carica* extracts [18]. In another study, the ethanol extract of fig leaf showed growth inhibitory effect against the bacteria *Staphylococcus aureus*, *Salmonella typhi*, and the mold *Fusarium oxysporum*. Also, fig latex was tried in this study and reported to have a stronger effect. *Aspergillus niger* and *E. coli* were more resistant to ethanolic extract and fig latex [19].

To the best of our knowledge, no results were reported on the essential oil and n-hexane extracts of fig leaves. The objectives of this study, were to assess the antibacterial and antiproliferative effects of nonpolar extracts from leaf of two Turkish fig cultivars on two bacterial samples and on PC3 human prostate cancer cell line, respectively.

2. Materials and Methods

2.1. Preparation of Fig Leaves

The research material fig leaves were collected from the *F. carica* cultivar Sari Lop trees grown in the Aydin Adnan Menderes University Central Campus (37°51'28.3"N 27°51'23.8"E) and *F. carica* cv. Aydin Black (also known as Bursa Black) leaves were collected from a fig orchard in Gencelli village of Kuyucak district in the city of Aydin (37°56'04.5"N 28°39'28.9"E) in the summer of 2017. The collected leaves were visually inspected not to have damage due to sunburn, plant pests, or human handling. The leaves were shade-dried at room temperature for a week and crushed. The resulting leaf pieces were stored in dry and cool room conditions.

2.2. Determination of Water Content of the Fig Leaves

Fresh, mature or young (leaf length < 10 cm) fig leaf pieces ranging between 4 and 10 gr was weighed into a pre-weighted crucible. After 3 hours at 105°C in lab oven, the crucible with the sample was cooled in a desiccator and weighed again to determine the water contents.

2.3. Essential oil extraction

Essential oil was extracted from 100 gr of crushed dry fig leaves mixed with 800 ml of distilled water by 6-hr hydrodistillation using the Clevenger-type apparatus.

2.4. Hexane Extraction Methods

In the first manual method, classical, glass soxhlet extraction system was used. Dried and crushed (24 gr) fig leaf samples in the cellulose thimbles were extracted with 300 ml of n-hexane for 2.5 hours. The resulting extract

was filtered twice through Whatman No. 1 filter paper and concentrated by rotary evaporator (Büchi Labortechnik AG, R-100, Flawil, Switzerland) at 55°C at about 70 bar vacuum pressure. The resulting solid extract mass was weighed, diluted in n-hexane to a concentration of 0.1 gr/ml (10%), and stored at -18°C.

For the second extraction method, dried and crushed Sari Lop and Aydin Black fig leaves (a total of 24 gr in 3 cellulose thimbles) were extracted with a total of 150 ml of n-hexane in a semi-automated soxhlet device (Velf Scienfitica, ser 148/3, 20865 Usmate, Italy). The extraction program is composed of 40 min immersion, 80 min washing, and 3 min recovery. At the end of the extraction, the leftover n-hexane was removed and the resulting solid extract mass was stored as described above.

2.5. Bacterial Species

Antimicrobial assays were performed on *E. coli* ATCC 35218 and *B. cereus* ATCC 11778 (gifted by Prof. Dr. H. Halil Bıyık, Aydın Adnan Menderes University). Bacteria were cultured in tryptic soy broth (TSB) (Merck) and tryptic soy agar (TSA) media consisting of TSB supplemented with 15% agar agar (Sigma Aldrich).

2.6. Disc Diffusion and Agar Well Diffusion Methods

Fifty µl of *E. coli* or *B. cereus* culture grown in TSB for 6-8 hours was transferred onto Mueller Hinton Agar (MHA) plates (Merck) and spread over the entire surface to form a thin film layer. Ten µl of the n-hexane extract of fig leaf dissolved in n-hexane or acetone at 0.1 gr/ml concentration was impregnated into sterile 6 mm antimicrobial susceptibility disks (Oxoid) on the surface of MHA plate, and the discs were pressed down gently to ensure complete contact with the agar surface. The n-hexane or acetone (10 µl) and a Gentamicin (Oxoid) disk were used as negative and positive controls, respectively. Plates were incubated at 37°C for up to 48 h and the bacterial growth inhibition zones around the discs were observed and measured.

Agar well diffusion assay was used to increase the amount of extract tested. After the test bacteria were spread on the MHA plates as described in the disc diffusion method, wells with 5 mm in diameter were formed on the agar under aseptic conditions. Each well was filled with the n-hexane extract of fig leaf dissolved in n-hexane or acetone at 0.1 gr/ml concentration. Plates were incubated and the bacterial growth inhibition zones around the discs were observed as described above.

2.7. Prostate Cancer Cell Line Culture

The anti-carcinogenic properties of the n-hexane extracts of the fig leaves were tested on PC3 human prostate cancer cell line (gifted by Prof. Dr. William H. Gmeiner, Wake Forest University). Cells were cultured in RPMI-1640 (Sigma-Aldrich) supplemented with 10% fetal bovine serum (FBS) (Biowest) in the presence of 5% CO_2 at 37°C. Cells were routinely passaged using Trypsin (Sigma-Aldrich) when they reached 80-90% confluence.

2.8. Cytotoxicity MTT Assay

PC3 cells were seeded at a density of 3000 cells/well in 96-well plate and incubated in CO_2 incubator. The following day, hexane extracts were applied to the cells at 250, 500, 750, and 1000 µg/ml concentrations for 24-48 hours, and cell viabilities were measured colorimetrically by 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) (Sigma-Aldrich). MTT was dissolved in sterile phosphate buffered saline (PBS) and further diluted in RPMI with 10% FBS to a final MTT concentration of 0.5 mg/ml. At the end of the fig leaf extract treatment, the used media was replaced with 120 µl of new media with MTT. After a minimum 3 hours of incubation, the violet colored formazan crystals inside the cells were observed under a microscope, and the MTT containing media was replaced with 100 µl of dimethyl sulfoxide (DMSO) (Merck). After the plate was shaken for 10 min to dissolve the formazan crystals, results were obtained with a spectrophotometer (Thermo Labsystems Multiskan Spectrum Mic) at 570 nm. All experiments were performed in triplicates and the experiments were repeated 3 times.

3. Results and Discussion

The water contents of fresh, mature fig leaves and the young leaves (leaf length < 10 cm) for both fig cultivars were found to be 70 and 78%, respectively. These values are correlated with the water content of mint leaves, which was reported as 70-80% [20].

Essential oil extraction from both fig cultivar leaves was not possible as no essential oil was observed after the water distillation method using Clevenger apparatus, possibly due to low amount of essential oil in the leaves. To check the equipment functionality, essential oil of *Thymus vulgaris* L. was successfully extracted. A larger volumed extraction system might help in extracting essential oil from fig leaves.

The n-hexane extraction yield rates of *F. carica* leaves in manual and semi-automated soxhlet methods were 1.55 and 2.30 mg/gr, respectively for the Sari Lop cultivar and 2.15 and 2.40 mg/gr, respectively for the Aydin Black cultivar.

First, the *F. carica* leaf extracts prepared at 10% concentration in n-hexane were used in disc diffusion tests Table 1. However, considering the low volume of extract used in discs and the fast vaporizing nature of n-hexane, no antibacterial effect of the extracts or the n-hexane negative control was observed. For this reason, the n-hexane extracts were solubilized in acetone at 10% concentration but no antimicrobial effect on the growth of *E. coli* and *B. cereus* was observed either Table 1. The negative control acetone showed greater antimicrobial effect than all of the extracts. None of the fig leaf extracts obtained by Semi-automated soxhlet system and dissolved in acetone had antimicrobial effect against *B. cereus*. Similar results were obtained in well diffusion tests (results not shown).

Table-1. Result of disc diffusion tests using the n-hexane extract of fig leaves dissolved in n-hexane or acetone.

Extraction solvent	Reagents tested	Diameter of growth inhibition zone (mm)	
		***E. coli* ATCC 35218**	***B. cereus* ATCC 11778**
None	Gentamicin (Pos. control)	12	21
n-hexane	n-hexane (Neg. Control)	6	6
	Sari Lop M	6	6
	Sari Lop S	6	6
	Aydin Black M	6	6
	Aydin Black S	6	6
acetone	Acetone (Neg. Control)	15	15
	Sari Lop M	12	12
	Sari Lop S	8	6
	Aydin Black M	10	10
	Aydin Black S	13	6

Note: M: Manual soxhlet; S: Semi-automated soxhlet.

However, a recent study conducted in Algeria reported that methanol extracts of 10 different varieties of *F. carica* leaves showed antimicrobial properties against Gram positive and Gram negative bacteria [18]. Type of extraction solvent used, geographic and climatic differences between Turkey and Algeria, and the type of the fig trees may be counted as the potential reasons for the difference in antimicrobial effectiveness between the studies. Another study conducted in South Korea with fig leaf methanol extract also reported antimicrobial effect against the oral bacteria [17]. In 1998, hypoglycemic effect of fig leaf was investigated in type I diabetic patients [9] and in 2000, a chloroform extract from *F. carica* leaves was used to reduce cholesterol levels in diabetic mice [21].

In this study, cytotoxic effects of n-hexane extract of fig leaves collected from two local cultivars (Sari Lop and Aydin Black) grown in Aydin, Turkey were investigated on the PC3 human prostate cancer cell line. Fig leaf extracts were applied on cells at doses ranging from 0-1000 µg/ml for 24 h. Results reveal that fig leaf extracts showed cytotoxic effect on PC3 cells in a dose-dependent manner Figure 1. The leaf extracts started showing 50% cytotoxicity on PC3 cells after 24 h treatment at 250 µg/ml dose. Almost complete cytotoxicity was observed on PC3 cells after 24 h treatment at 1000 µg/ml. No statistically significant difference was available between the cytotoxic effects of Sari Lop and Aydin Black cultivars (t-test, P>0.05). Also, there was no significant difference in the comparison of the extraction type (manual soxhlet vs. semi-automated soxhlet device) (t-test, P>0.05).

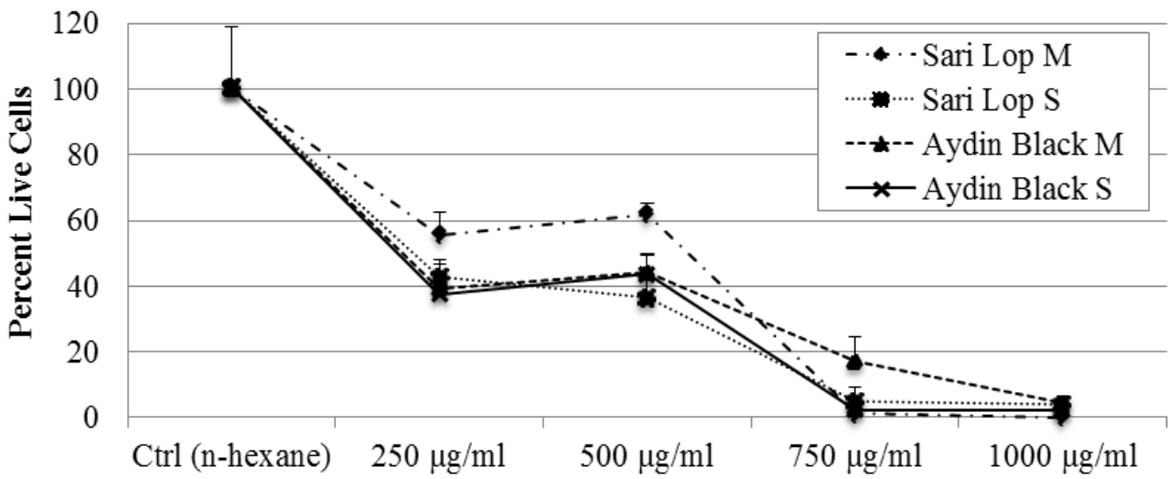

Figure-1. Treatment of n-hexane extracts of fig leaves on PC3 cells for 24 h. M: Manual soxhlet; S: Semi-automated soxhlet.

The petroleum ether extract of *F. carica* leaf was successfully used in rats to protect the liver from damage by rifampicin [13]. Similarly, hepatoprotective effects of fig leaf ethanol [22] and methanol [23] extracts were reported against hepatotoxicity caused by carbon tetrachloride. Ethanol extract of fig leaf was reported to have a curing effect against both cellular and humoral antibody response in mice [24]. It was also indicated that fig leaf ethanol extract has immunity stimulating effect. Additionally, the water extract of fig leaf is known to have toxicity against herpes simplex virus [25].

4. Conclusion

In conclusion, *F. carica* fruit, latex, and leaf have been researched for their beneficial effects by various studies. This study revealed that 24 h treatment of n-hexane extract of two fig cultivars shows cytotoxic effect on PC3 human prostate cancer cell line.

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