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The Effects of Ficus carica Latex on SH-SY5Y Neuroblastoma Cells and L929 Fibroblast Cells

Ficus carica Lateksinin SH-SY5Y Nöroblastoma Kanser Hücreleri ve L929 Fibroblast Hücreleri Üzerine Etkileri

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ABSTRACT

Aim: This study aims to evaluate the anti-cancer effect of latex obtained from Ficus carica on SH-SY5Y neuroblastoma cells and its wound healing potential on L929 fibroblast cells.

Materials and Methods: The effects of Ficus carica latex were investigated *in vitro*. A scratch wound model was created on L929 cells and treated with 1-1000 µg/mL of Ficus carica latex. Microscopic images were taken at 0 and 48 hours to measure the wound areas. In SH-SY5Y cells, cytotoxicity was assessed using the MTT assay, and the IC_{50} value was determined.

Results: Ficus carica latex promoted significant wound healing in L929 cells, particularly at concentrations of 5 µg/mL and above, associated with increased proliferation. In SH-SY5Y cells, no cytotoxic effects were observed at 1-50 µg/mL, whereas cytotoxicity was evident at 100 µg/mL and 1000 µg/mL.

Conclusion: Ficus carica latex significantly promoted wound healing even at low doses, mainly by enhancing cell proliferation. On the other hand, it exhibited marked cytotoxic effects on neuroblastoma cells at high doses. These findings suggest that Ficus carica latex could be a potential therapeutic agent for wound healing but should be used in a dose-controlled manner for cancer cells like neuroblastoma.

Keywords: Anti-cancer, Ficus carica latex, SH-SY5Y, L929, wound healing

ÖZ

Amaç: Bu çalışmada, Ficus carica bitkisinden elde edilen lateksin, SH-SY5Y nöroblastoma hücreleri üzerindeki antikanser etkisi ile L929 fibroblast hücreleri üzerindeki yara iyileştirici potansiyelinin değerlendirilmesi amaçlanmaktadır.

Gereç ve Yöntem: Ficus carica lateksinin etkileri *in vitro* olarak incelenmiştir. L929 hücrelerinde oluşturulan yapay yara modeli, 1-1000 µg/mL Ficus carica lateks ile işlenmiş, 0. ve 48. saatlerde mikroskobik olarak yara alanları ölçülmüştür. SH-SY5Y hücrelerinde MTT testi uygulanarak hücre canlılığı ve IC_{50} değeri belirlenmiştir.

Bulgular: Ficus carica lateks L929 hücrelerinde 5 µg/mL ve üzeri konsantrasyonlarda proliferasyona bağlı yüksek yara iyileşmesi sağlamıştır. Ayrıca Ficus carica lateks SH-SY5Y nöroblastoma hücrelerinde 1-50 µg/mL arası düşük dozlarda sitotoksik etki göstermemiş, ancak 100 µg/mL ve 1000 µg/mL gibi yüksek dozlarda sitotoksisite gözlemlenmiştir.

Sonuç: Ficus carica lateks, düşük dozlarda bile yara iyileşmesini anlamlı şekilde teşvik etmiş ve bu etkisi özellikle proliferasyon artışıyla desteklenmiştir. Öte yandan, nöroblastoma hücreleri üzerinde yapılan çalışmalarda, Ficus carica lateks yüksek dozlarda belirgin sitotoksik etkiler gösterdiği tespit edilmiştir. Bu bulgular, Ficus carica lateksinin yara iyileşmesi açısından potansiyel bir tedavi ajanı olabileceğini, ancak nöroblastoma gibi kanser hücreleri üzerinde doz-kontrollü kullanılması gerektiğini göstermektedir.

Anahtar Kelimeler: Antikanser, Ficus carica lateksi, SH-SY5Y, L929, yara iyileşmesi

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INTRODUCTION

Neuroblastomas are malignant solid tumors formed from the progenitor cells of the sympathetic nervous system[1]. Neuroblastoma is responsible for about 7-10% of all cancers occurring in children and primarily affects infants and young children. It represents approximately 8-10% of all pediatric malignancies, with an estimated incidence of one case per 7000 live births[2-4]. Neuroblastoma is a type of cancer that typically lacks disease-specific symptoms. Symptoms usually appear when the tumor grows and begins to compress surrounding organs or when metastasis occurs[1]. The goal of treatment is to fully restore the patient's health while minimizing side effects that may develop during the disease course or treatment. Care is adapted to reflect the stage of the disease, distinct clinical features, and the likelihood of the condition returning. In certain cases, surgical excision of the tumor may be adequate, whereas others may need further interventions such as drug therapy and radiation treatment. For patients with a significant risk of recurrence, autologous stem cell transplantation and antibody-based immunotherapy are also applied in addition to these treatments[1].

The genus *Ficus* (Moraceae) ranks among the most extensive groups of flowering plants and consists of approximately 800 species worldwide[5,6]. These species are critical genetic assets, appreciated for both their economic worth and nutritional contributions[7]. The healing properties of Ficus carica have been recognized across traditional medical practices such as Ayurveda, Unani, and Siddha. This species has been traditionally employed in managing a wide spectrum of disorders, including metabolic conditions like diabetes, respiratory ailments such as asthma, cough, and liver-related problems, gastrointestinal issues including ulcers and vomiting, reproductive disorders like menstrual pain, as well as infectious and dermatological diseases such as scabies, gonorrhea, and other skin conditions[8]. Ficus carica holds therapeutic importance in Unani medicine due to its mild purgative, diuretic, and expectorant actions, and is employed to alleviate obstructions and inflammation in hepatic and splenic conditions[8]. The latex found in *Ficus* species has long attracted attention due to its medicinal properties and has been used as a drug[9]. Owing to its antiseptic and anti-inflammatory properties, it is applied topically in the treatment of skin disorders such as warts, boils[10], and dermatitis[11]. Historically, latex has been used as a wound-healing agent for rabid dog bites, snake and scorpion stings, and has also been employed in the treatment of wasp stings and hard swellings[12]. Latex has been applied in various mixtures for the treatment of diverse dermatological conditions[12]. Phytochemical studies on Ficus carica have revealed that various plant tissues, particularly latex, as well as leaves, fruits, and roots, contain isolated bioactive compounds including phytosterols, anthocyanins, phenolic derivatives, amino and organic acids, fatty acids, aliphatic alcohols, volatile compounds, hydrocarbons, and various secondary metabolites[13]. According to the literature, numerous studies have investigated the anti-cancer properties of Ficus carica latex (FCL). These studies demonstrate the antiproliferative effects of FCL in cancers such as gastric[14], brain[15], cervix[16], breast, liver cancer, and acute myeloid leukemia[17]. This suggests that FCL is a promising agent in cancer treatment, in addition to its traditional uses. In this study, based on its traditional use in wound healing, it is aimed to investigate the wound healing-supportive effects of FCL on the L929 fibroblast cell line to provide new insights for the literature; additionally, since its antiproliferative effects have been shown in many cancer studies, it is aimed to evaluate, for the first time, the antiproliferative and cytotoxic effects of FCL on the SH-SY5Y neuroblastoma cell line.

MATERIALS AND METHODS

In this study, the cytotoxic and wound healing effects of FCL were investigated *in vitro* on SH-SY5Y human neuroblastoma and L929 fibroblast cell lines. FCL was obtained from (aydindansoframa.com, Aydın, Türkiye). According to the description of the supplier: the latex was collected in September from the stalks of unripe fig fruits in the Aydın region, stored in amber-colored vials at 3 mL per vial. All experiments were performed using material from the same batch to ensure consistency within the study. Until the work was done, FCL was kept at +2-4 °C. FCL was weighed as 100 mg into eppendorf tubes, and 10 mL of Roswell Park Memorial Institute (RPMI) medium (Thermo Fisher Scientific, Gibco) was added to prepare a stock solution at a concentration of 10,000 µg/mL. The solution was sterilized by filtration through a 0.22 µm pore-sized polytetrafluoroethylene filter. The resulting stock solution was used for subsequent dilutions, and the unused portion was stored at -80 °C. Serial dilutions of this stock solution were prepared to obtain concentrations of 1, 2, 5, 10, 50, 100, and 1000 µg/mL, which were used for all cell culture experiments. The concentration range selected in this study was based on previously reported concentrations used for the evaluation of FCL in different cell lines. Indeed, the literature has shown that FCL exerts cytotoxic effects at concentrations ranging from 25 to 100 µg/mL in various cell lines[18]. An additional high concentration (1000 µg/mL) was included to evaluate potential non-specific cytotoxicity and to define the upper limit of the response curve. A broad range encompassing both low and high concentrations was chosen to enable a detailed investigation of the potential dose-response relationship in the cells. The study was conducted using cells previously obtained commercially from the American Type Culture Collection (ATCC) and available in stocks of the Department of Pharmacology at Atatürk University Faculty of Pharmacy and cultured under the same laboratory conditions. Cells were used within passages 12-15 for all experiments.

Authentication of the cell line was performed by ATCC using short tandem repeat (STR) profiling prior to distribution. No additional authentication was performed in our laboratory. The cytotoxic effect of FCL on SH-SY5Y cells was evaluated, while its wound healing-supportive effects on L929 cells were analyzed. There are no cells obtained from any living being in the study. The cells were purchased commercially. Therefore, informed consent and ethics committee approval are not required. For cell culture, RPMI 1640 medium containing 10% FBS (Gibco) was used to maintain the L929 cells, and 1% penicillin, streptomycin, amphotericin B antibiotic-antifungal mixture containing penicillin, streptomycin, and amphotericin B (Gibco), whereas SH-SY5Y cells were cultured in Kaighn's modification of Ham's F-12 medium (Thermo Fisher Scientific, Gibco). Standard protocols were applied to support cell proliferation and viability; incubation of cells occurred at 37 °C in a humidified atmosphere of 5% CO_2, with culture media renewal every 48 hours. After reaching confluence, cells forming a monolayer were washed with phosphate-buffered saline (PBS) (Thermo Fisher Scientific, Gibco), detached using trypsin, centrifuged, resuspended in fresh medium, and transferred to new culture flasks. Viable and dead cells were distinguished by 0.4% trypan blue staining, and cell counts were performed using a Thoma counting chamber. Cells were seeded at a density of 5×10^3 cells per well in 96-well plates for SH-SY5Y cytotoxicity assays and 1×10^6 cells per well in 12-well plates for the wound healing assay using L929 cells. All procedures were carefully performed to ensure reliable analysis of FCL's biological effects on the cells. The number of cells per 1 mL was calculated using the formula: cell count (in 1 mL)=n (number of cells counted in 0.1 mm^3) × dilution factor × 10^4.

MTT Cytotoxicity Assay

The MTT assay relies on viable cells' function in transforming MTT to insoluble formazan crystals. In the MTT assay, SH-SY5Y cells were divided into experimental groups, including a control group without FCL exposure and groups treated with FCL at concentrations of 1, 2, 5, 10, 50, 100, and 1000 µg/mL. SH-SY5Y cells underwent exposure to a range of concentrations of FCL (1-1000 µg/mL) and incubated for 24 hours. Afterwards, 100 µL of medium and 10 µL of MTT reagent (Acros Organics, China) were applied to all wells, with incubation conducted at 37 °C for 4 hours. The medium was then aspirated, and the formazan deposits were dissolved in 100 µL of dimethyl sulfoxide (Interlab, Türkiye). Using an enzyme-linked immunosorbent assay reader (Multiscan Sky, Thermo, Singapore), optical density at 570 nm was used to determine cell viability. Viability percentages were calculated relative to the untreated control group (% cell viability=(sample absorbance)/(mean control absorbance) × 100) and bar graphs were generated using GraphPad Prism 6 software. The same data were used to perform IC_{50} analysis. Thus, IC_{50} values were calculated in GraphPad Prism 6 using the "log (inhibitor) vs. normalized response" equation, which corresponds to a three-parameter logistic regression model (with the Hill slope fixed at -1). Data were normalized prior to curve fitting, and IC_{50} values are reported as best-fit estimates with 95% confidence intervals. The relationship between log concentration and viability was plotted as a line graph.

Wound Healing Assay

The wound closure assay was implemented on the L929 fibroblast cell line to evaluate cell migration and wound closure. Cells were seeded at 100,000 cells per well in 12-well plates, with eight different concentrations of FCL (1, 2, 5, 10, 50, 100, 1000 µg/mL, and control), each in triplicate. In the wound healing experiment, L929 cells were divided into experimental groups, including a control group without FCL treatment and groups treated with FCL at concentrations of 1, 2, 5, 10, 50, 100, and 1000 µg/mL. After formation of a confluent monolayer, a 100 µL yellow pipette tip was used to produce the scratch to create an artificial wound model (the average wound area in the initial scratches was calculated as 30,000 μm^2). The medium was aspirated. Following a PBS wash, the medium was replaced with fresh high-glucose culture medium[19]. The wound closure process was monitored at 0, 24, and 48 hours using an inverted microscope (Zeiss Axio Vert A1). The scratch area reduction was quantified, and wound closure area percentage calculated through analysis of images with ImageJ software[20]. For 24 hours: % wound closure=$[(A_0-A_{24})/A_0] \times 100$, for 48 hours: % wound closure=$[(A_0-A_{48})/A_0] \times 100$ (A_0=mean wound area at 0 hours A_{48}=mean wound area at 48 hours).

Statistical Analysis

IBM SPSS Statistics version 27 was employed for statistical analysis. Group means ± standard deviations are reported. One-way ANOVA and Duncan's post-hoc test were used to compare groups, considering p-values under 0.05 as statistically significant. Graphs were generated with the help of GraphPad Prism 6 software.

RESULTS

Wound Healing Findings in L929 Cells

Migration of L929 fibroblast cells in response to FCL treatment was evaluated through the scratch assay method (Figure 1). After 24 hours of incubation, wound closure rates in the control group and 1 µg/mL and 2 µg/mL FCL groups were calculated as 50.36%, 49.08%, and 50.85%, respectively. No statistically significant difference was found among these groups at 24 hours. In contrast, statistically significant increases in wound closure rates were observed at concentrations of 5, 10, 50, 100, and 1000 µg/mL FCL groups when compared to the control group at 24 hours. The closure rates at these concentrations

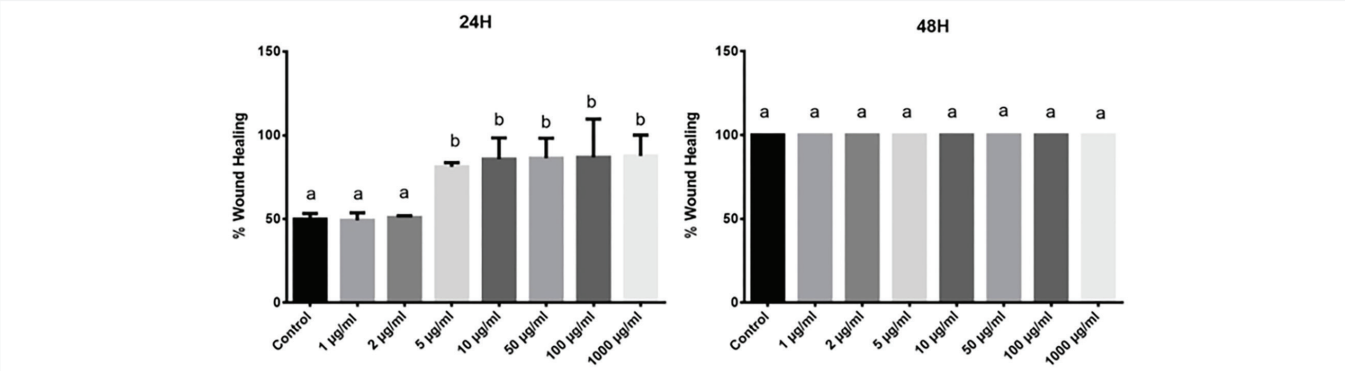

Figure 1. Effects of Ficus carica latex on the percentages of wound healing in L929 cells at 24 and 48 hours. The groups marked with the same letters (a,b) do not differ statistically significant from each other, whereas groups labeled with different letters indicate statistically significant differences ($p<0.05$). Data are expressed as mean ± standard deviation. Statistical significance was determined using one-way analysis of variance with Duncan's post-hoc test for each time point (24 and 48 hours) separately

were 81.05%, 85.72%, 86.23%, 86.74%, and 87.59%, respectively. After 48 hours of incubation, wound closure reached 100% in all groups. Wound closure images are given in Figure 2.

IC_{50} Findings of FCL on SH-SY5Y Cells

FCL was applied to SH-SY5Y human neuroblastoma cell cultures subjected to a concentration range of 1 to 1000 µg/mL, and cell viability was assessed by the MTT assay after 24 hours of incubation. As shown in Figure 3, viability rates were normalized and a dose-response curve was generated. The analysis revealed a decrease in cell viability with increasing FCL concentration, demonstrating a dose-dependent cytotoxic effect on SH-SY5Y cells. According to the 24-hour MTT data, the IC_{50} value of FCL was determined as 577.9 µg/mL.

MTT Findings of FCL on SH-SY5Y Cells

The results of the 24-hour MTT assay conducted on the SH-SY5Y cell line with various concentrations of FCL showed no statistically significant effect on cell viability at 1, 2, 5, 10, and 50 µg/mL concentrations. The cell viability rates at these concentrations were determined as 101.78%, 101.42%, 100.39%, 98.15%, and 95.09%, respectively. The average cell viability in 1-50 µg/mL concentration groups remained around 100%, and had no statistically significant differences compared with the control group. However, as shown in Figure 4, a statistically significant decrease in cell viability was detected at the concentration of 100 µg/mL, with the viability rate dropping to 75.85%. We found that the 100 µg/mL concentration had a statistically significant antiproliferative effect on SH-SY5Y cells. When exposed to the maximum concentration of 1000 µg/mL, cell viability was calculated as 40.67%, falling below the 50% threshold and indicating a marked cytotoxic effect of FCL. These findings demonstrate that FCL statistically significantly reduces cell viability in the SH-SY5Y cell line at 100 and 1000 µg/mL concentrations and that this effect occurs in a dose-dependent manner.

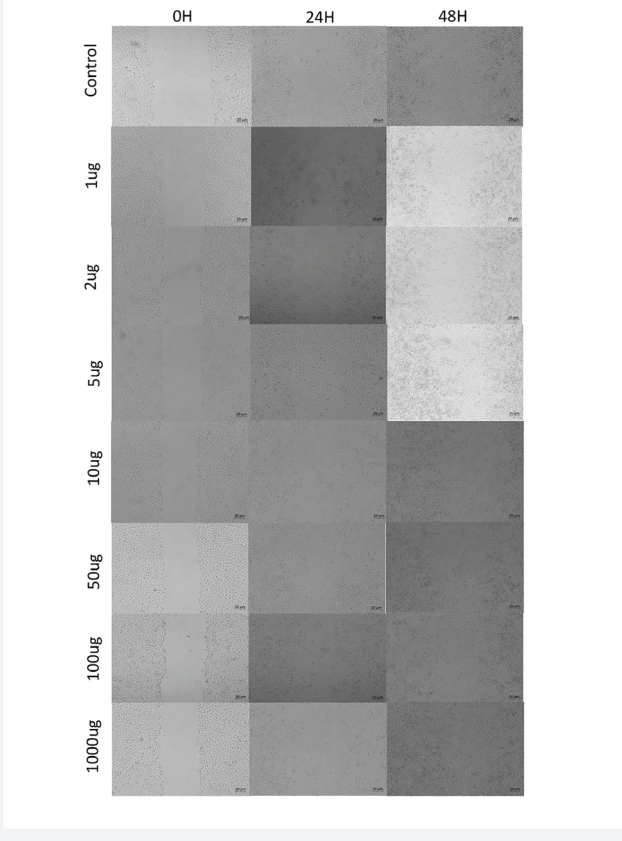

Figure 2. Effects of Ficus *carica* latex on wound healing in L929 cells at 24 and 48 hours

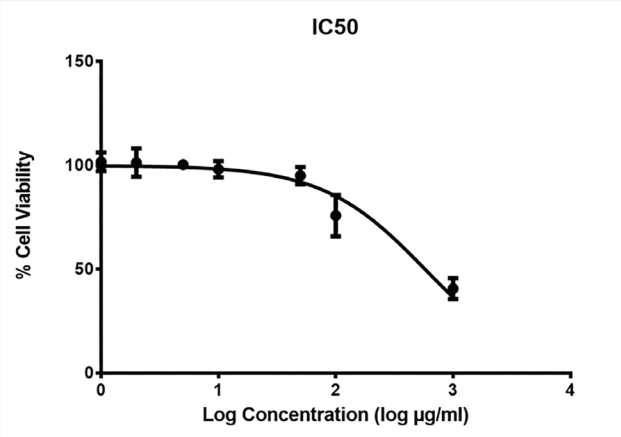

Figure 3. The effects of Ficus carica latex on SH-SY5Y neuroblastoma cells (IC_{50})

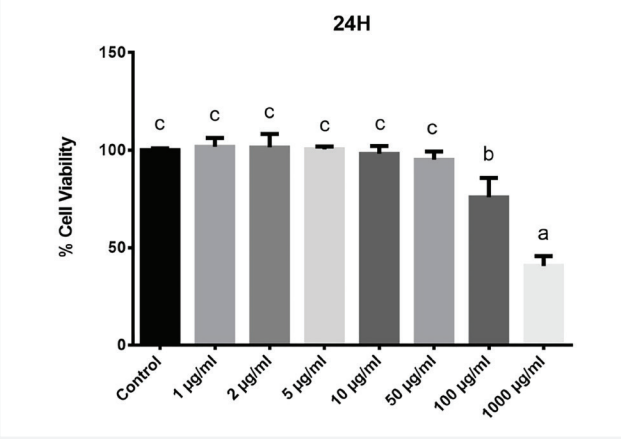

Figure 4. MTT results of Ficus carica latex on SH-SY5Y cell line after 24 hours of incubation. Statistical significance was determined using one-way analysis of variance with Duncan's post-hoc test for each time point 24 hours. In the figures, groups marked with the same letters (a,b,c) do not differ statistically significant from each other, whereas groups labeled with different letters indicate statistically significant differences ($p<0.05$)

DISCUSSION

Neuroblastoma is one of the most common malignant solid tumors in childhood, arising primarily from the adrenal glands and the sympathetic nervous system[1]. Despite advances in treatment, relapse and therapy resistance remain significant challenges, highlighting the need for new therapeutic approaches and natural product-based alternatives. In this context, many studies are being conducted to find cheaper drug alternatives (especially of plant origin) with fewer side effects in the treatment of neuroblastoma[21-25]. Some studies investigating the anticancer effects of FCL suggest that FCL exhibits antiproliferative effects. Therefore, in this study, we examined the antiproliferative effects of FCL on SH-SY5Y cells. In addition to the antiproliferative effects of FCL in the literature, FCL is widely used in traditional medicine, including Ayurveda, Unani, and Siddha, for wound healing and dermatological purposes. A study on a diabetic rat wound model reported that FCL accelerated wound healing by affecting the survival capacity of pathogenic bacteria and biofilm formation, as well as increasing β-defensin-1 and platelet endothelial cell adhesion molecule-1 expression and collagen production, thereby supporting the healing process[26]. In another study, topical application of FCL on pigeons infected with avian pox resulted in complete lesion regression and clinical healing comparable to 3% tetracycline ointment, demonstrating strong antiviral and healing effects[27]. Since FCL is used in traditional medicine for dermatological diseases, in this study we investigated the effects of FCL on wound healing for the first time in the literature. L929 human fibroblast cells are frequently preferred in biocompatibility, cytotoxicity testing, and *in vitro* wound healing models. Literature review reveals limited studies evaluating the effects of FCL on wound healing in the human fibroblast L929 cell line. For these reasons, we used the L929 cell line in our study, and our results showed that FCL's effect on promoting cell migration in L929 fibroblast cells is dose-dependent, with wound healing effects particularly at concentrations of 5 µg/mL and above at 24 hours. Moreover, we observed that at higher concentrations, this effect plateaued, showing no further dose-dependent increase. These findings suggest that FCL supports effective cell migration in the early phase of wound healing and that the concentration range of 5-10 µg/mL may be optimal in terms of both efficacy and low toxicity. In addition, in this study, the effects of FCL on the SH-SY5Y neuroblastoma cell line were investigated. A review of the literature reveals that the anticarcinogenic effects of FCL have been clearly demonstrated in many studies. Based on these properties, this study was conducted to investigate the potential effects of FCL on the SH-SY5Y cell line, which has not yet been studied in the literature. Our data showed that FCL exerts dose-dependent antiproliferative and cytotoxic effects on SH-SY5Y cells, with antiproliferative effect observed at concentrations of 100 and 1000 µg/mL. In addition, we observed that at a concentration of 1000 µg/mL, viability dropped below 50% and cytotoxic effects occurred at this concentration. At lower concentrations, no change in the proliferation of SH-SY5Y cells was observed. Other studies investigating the anticancer potential of FCL support our findings. This natural product has shown promising cytotoxic and antiproliferative effects in many different cancer cell lines. In one study, it has been shown that FCL decreased survival, inhibited DNA synthesis, causing cell cycle arrest at

the G_0/G_1 phase and activated apoptosis in U251 brain cancer cells[15]. In another study, FCL was shown to inhibit invasion in glioblastoma cell lines (U-138 MG, T98G, and U-87 MG) by inducing apoptosis through the regulation of Let-7d expression[28]. Additionally, treatment of MDA-MB-231 breast cancer cells with different concentrations of FCL (0.1%, 0.25%, 0.5%, and 1%) for 24 hours resulted in a reduction in cell proliferation[29]. A study on CaSki and HeLa cells reported that FCL plays a potential role in preventing the progression of cervical cancer by suppressing the proliferation of cervical cancer cells through the upregulation of tumor suppressor proteins p53 and pRb[16]. Studies in the literature show that FCL exhibits antiproliferative activity through many pathways. In general, FCL appears to reduce survival by decreasing DNA synthesis, arresting the cell cycle, upregulating tumor suppressor genes and inducing apoptosis. Many studies in the literature suggest that FCL is cytotoxic in cancer cells but not in healthy cells. Moreover, it is emphasized that when applied in certain formulations, FCL may be effective with fewer side effects. It has been reported that fig latex at 0.125 µg/mL exhibited cytotoxic effects on CaSki and HeLa cancer cells, whereas it did not cause toxicity in the normal HaCaT cell line[16]. In another study, fig latex suppressed proliferation of stomach cancer cells without causing toxicity, with an optimum inhibitory concentration of 5 mg/mL[14]. In a study conducted by Aysin et al.[30], they claimed that FCL induced cell death in a concentration-dependent manner, and high doses caused a more serious cytotoxic effect in cancer cells (A549, MCF-7, MDA-MB-231). The same study claimed that FCL showed less cytotoxicity in healthy cells (MRC-5 non-tumor lung cells) than cancer cells and FCL would have selective cytotoxicity to cancer[30]. In another study on the HT-29 colon cancer cell line, the bioavailability of FCL was enhanced by formulation in liposomal capsules, enabling controlled release and reducing toxic effects[31]. Moreover, FCL extracts have been shown to exhibit cytotoxic activity against MCF-7 breast cancer, HepG2 liver cancer, and HL-60 acute myeloid leukemia cell lines[17]. Animal model studies also support these findings. In a study on diabetic rats, application of fig latex reduced tumor size; hematocrit, hemoglobin, and erythrocyte parameters decreased, while platelet and leukocyte levels remained controlled compared to the cancer group. Moreover, no histopathological damage was detected in the liver and kidney of individuals treated with fig latex, indicating that latex can exert antitumor effects without systemic toxicity[32]. In studies conducted to determine the IC_{50} value of FCL, a separate investigation on colorectal cancer cells evaluated the effects of increasing concentrations of fig latex on HCT-116 and HT-29 cell proliferation; the 48-hour IC_{50} values were found to be 206 µg/mL and 182 µg/mL, respectively, and apoptosis was shown to be activated via PARP cleavage[33]. Additionally, in a study on HeLa cells, fig latex reduced viability in a dose-dependent manner even at low concentrations such as 2 µg/mL, with an IC_{50} of approximately 17 µg/mL[34]. IC_{50} values of FCL were found to be 1/26, 1/40, 1/45 in A549, MCF-7, MDA-MB-231 cancer cells, respectively, while this value was found to be 1/7 in MRC-5 non-tumor lung cells. This study suggested that FCL has less cytotoxicity in healthy cells than cancer cells[30]. In our study, we found the IC_{50} value of FCL in SH-SY5Y cells to be 577.9 µg/mL. It is understood from the literature that various cancer cell lines have been studied to elucidate the antiproliferative effects of FCL. However, the concentrations at which FCL exerts antiproliferative activity differ among many cell lines. For instance, while cytotoxic effects were observed in HeLa cells at 0.125 µg/mL, another study suggested that the optimum inhibitory concentration in gastric cancer cells was 5 mg/mL. In our study, we found that FCL at a concentration of 1000 µg/mL was cytotoxic in SH-SY5Y cells, whereas at 100 µg/mL it exhibited antiproliferative activity. Moreover, findings in the literature indicate that the IC_{50} value of FCL varies across different cell lines. Many studies have also demonstrated that the effects of FCL are dose-dependent. Furthermore, both our results and those reported in the literature show that FCL exerts varying levels of efficacy and cytotoxicity in different cell lines. Several studies have also shown that FCL may behave differently in cancer cells compared to normal cells. In our study, we observed that FCL at 100 µg/mL exerted antiproliferative effects on SH-SY5Y neuroblastoma cells, while the same concentration promoted wound healing in L929 cells. Based on our findings and existing literature, we suggest that the use of appropriate formulations or careful dose adjustment could enhance the efficacy of FCL while reducing its toxicity. In our study, FCL was evaluated on both L929 fibroblast and SH-SY5Y neuroblastoma cell lines. Our results indicate that concentrations of FCL 5 µg/mL and above promote wound healing in L929 cells, suggesting its potential as a component in future wound-healing formulations. On the other hand, its antiproliferative effect at a concentration of 100 µg/mL indicates that it may also be effective in the treatment of neuroblastoma. Furthermore, while the wound healing model in L929 cells provides new insights for the literature, the effects of FCL on the SH-SY5Y neuroblastoma cell line are demonstrated for the first time; thus, FCL contributes scientifically by revealing both its wound-healing potential and its antiproliferative effects on neuroblastoma cells, and the findings shed light on potential clinical applications, including wound-healing products and neuroblastoma therapy with careful dose control.

Study Limitations

This study presents important findings regarding the cytotoxic and wound healing effects of FCL; however, it has several limitations. Firstly, all experiments were conducted exclusively under *in vitro* conditions. The biological mechanisms

underlying the observed wound healing effects have not been fully elucidated. A limitation of the study is that we did not perform independent STR profiling in-house; however, all cells were obtained directly from ATCC, which authenticates lines prior to distribution, and were used only at early passages 12-15 to minimize variability. Moreover, we note that independent phytochemical profiling of FCL was not performed, which represents a limitation and will be addressed in future work. Another limitation of the study is that images of the cells were captured at 0, 24, and 48 hours. The complete closure of the wounds at 48 hours indicates that wound healing occurred at earlier stages. However, since no images were taken at earlier time points in our study, the exact timing of wound closure could not be determined with greater precision. This represents one of the limitations of our study. Additionally, although the SH-SY5Y cell line resembles human neuronal cells, it remains uncertain whether the observed cytotoxic effect would also occur in actual human brain cells. This uncertainty highlights the need for further research to ensure the safe use of FCL.

CONCLUSION

In this study, FCL was shown to statistically significantly promote wound healing even at concentrations of 5 µg/mL and above in L929 fibroblast cells, and this effect was supported by an increase in cell proliferation. On the other hand, evaluations on SH-SY5Y neuroblastoma cells revealed that FCL showed significant cytotoxic effects at a concentration of 1000 µg/mL, while it showed antiproliferative effects at a concentration of 100 µg/mL. Findings suggest that FCL might be effective as a treatment option for enhancing wound healing; however, its use on cancer cells such as neuroblastoma should be carefully dose-controlled. In addition, the proliferative properties of FCL in a healthy cell such as L929 and antiproliferative properties in SH-SY5Y cancer cells at a concentration of 100 µg/mL suggest that FCL may exhibit anticancer properties without damaging normal cells at certain concentrations.

Ethics

Ethic Committee Approval: There are no cells obtained from any living being in the study. The cells were purchased commercially. The active ingredients used were purchased and not extracted from plants. For these reasons, ethics committee approval is not required.

Informed Consent: Participant consent is not required.

Footnotes

Authorship Contributions

Concept: B.A., R.A.U., Design: B.A., Data Collection or Processing: B.A., A.A., Analysis or Interpretation: A.A., R.A.U., Literature Search: B.A., Writing: B.A., R.A.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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