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The Anti-Candida and the Cytotoxic Activity of Aloe Vera Gel Extracts

Linda H Al-Ghazali
Department of Clinical Laboratories, College of Applied Medical Sciences, University of Kerbala, Iraq

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Corresponding Author:
Linda H Al-Ghazali

Email:
linda.ahmeed@uokerbala.edu.iq

ABSTRACT

***Purpose**: The research paper studies the in vitro anti-candida activity and cytotoxic effects of Aloe vera (Linn) leaves extract against melanoma and normal cell lines.*

***Subjects and Methods:** The traditional Soxhlet apparatus was used to prepare the crude plant extract using organic solvents. The agar well diffusion method was used to explore the in vitro anti-candida, and the MTT assay was used to assess the cytotoxic activity.*

***Results:** With IC50 values of 250 g/ml and more than 1000 g/ml, respectively, crude extract demonstrated anti-Candida activity against Candida ((kefyr, glabrata, and albicans) in varying potencies and cytotoxic effect in B16 cell line and vero cell line.*

***Conclusions:** This study unequivocally establishes that the crude extract of Aloe vera leaves with bioactive metabolites is capable of supplying high-quality biological material for anti-Candida and anti-cancer therapeutic programs.*

INTRODUCTION

The most frequent oral fungal infection in humans is candidiasis, which is brought on by yeasts of the genus Candida. Candida albicans is the most common of at least 15 species of Candida yeast that can infect people (McCarty & Pappas, 2016; Muzyka & Epifanio, 2013). Healthy people have commensal Candida species, which are typically observed colonizing the oral mucosa. Additionally, they are widely distributed throughout the rest of the human body. However, due to these species' high adaptability to various host niches, Candida infection (CI) only appears in immunocompromised individuals (Sardi et al., 2013). The mouth, vagina, glans penis, esophagus, liver, gastrointestinal tract, respiratory tract, and skin are typically affected by CI. The most prevalent opportunistic oral infection and kind of fungal infection in the mouth is oral candidiasis (Neville et al., 2015; Lalla et al., 2013).

Nearly 75% of adult women in Western nations get vaginal yeast infections at some point in their lives. A weakened immune system, underlying diseases, drug addiction, prolonged antibiotic usage, decreased digestive secretions, dietary variables, vitamin deficiencies, poor liver function, and altered intestinal flora are all risk factors for CI (Martins et al., 2014). Cancer and cancer-related therapies frequently result in CI, which may also actively contribute to the development of cancer. It is quite concerning how microbial illness and

cancer are related. Since many years ago, researchers have been examining the relationship between microbial contamination and the chance of developing cancer (Karin et al., 2006; Momin & Richardson, 2012; Mesri et al., 2014; Snow & Laudadio, 2010; Forman, 1998). Consideration of the relationship between candidiasis and specific forms of cancer and the immunocompromised state of the host (Nasca & Pastides, 2001), The potential link between CI and the development of cancer has also been studied by researchers, who have primarily focused on oral tumors (Mohd et al., 2010; Salazar et al., 2012; Sankari et al., 2015).

An earlier cross-sectional study in Denmark showed that CI raises both short- and long-term risks for several cancers other than oral cancer (Norgaard et al., 2013). Recent research has shown that C. Albicans can cause cancer through a number of plausible methods (Ramirez-Garcia et al., 2016). There are numerous cancer treatments accessible, however, because multi-drug resistance is developing, current or newly developed chemotherapies have comparatively low success rates. This underlines how crucial it is to find brand-new melanoma-fighting substances that are both secure and efficient (Chan et al., 2007). Additionally, more studies are implementing the use of medicinal plants in the treatment of cancer because of their antioxidant and cytotoxic effects on cancer cells, which can be caused by phytochemicals with anti-inflammatory, immuno-modulatory, and anti-oxidant properties. These phytochemicals typically have the highest potential to exhibit chemo-preventive behavior in various cancers (Katiyar, 2011; Kwon et al., 2010).

The use of therapeutic plant preparations is supported by both scientific research and the knowledge of previous generations. Due to their medicinal or cosmetic benefits, herbal medicines are currently included in a wide range of commercial items. Among these, Aloe vera (Aloe barbadensis Miller (Liliaceae)) is a perennial succulent that has a reputation for being a potent natural medicine (Choi & Chung, 2003). Aloe vera is applied to people both internally and externally as a type of complementary medicine and in the home for first aid. Aloe vera has been demonstrated to exhibit benefits that promote the healing of wounds and burns as well as immunomodulatory, anti-inflammatory, antiparasitic, UV protection, antioxidant, antiviral, anticancer, and antidiabetic actions (Choi & Chung, 2003; Lee & Weintraub, 200; Sarkar et al., 2005; Yoo et al., 2008; Kigondu et al., 2009; Ozsoy et al., 2009).

METHODOLOGY

Collection of Plants

Aloe vera (Linn) leaves were purchased from the Imam Husain nursery and employed in the current investigation. Green leaves were cleaned of impurities and dust by being washed in tap water and then distilled water. They were then cut down the middle, the gel was separated by scratching with a spoon, the pulp was cut into small pieces, and they were allowed to dry at room temperature. Finally, they were crushed with an electric grinder, ground into a fine powder, and stored in a small container to avoid the effects of humidity.

Test Microbes

The study included the investigation of three species of Candida (kefyr, glabrata and albicans) which were obtained from the Postgraduate Laboratory in the Biology department, college of sciences at the University of Kerbala.

Preparation of Plant Extract

A Soxhlet extraction system (BUCHI Extraction System Model B-811) was used to extract the fine powder of dried Aloe vera leaves gel, employing 150 ml of diethyl ether for 20 g of plant powder (the extraction process was carried out in the College of Pharmacy/university of Kerbala).

Chloroform, ethyl acetate, and ethanol were employed in this extraction method in a 1:1:1 ratio. The heating power was set to two cycles/h so that six extraction cycles could be completed in 3 hours. The resulting liquid crude extracts were next concentrated by removing the organic solvents in a vacuum rotary evaporator (BUCHI Rota vapor Model R-144) operating at a temperature of 60 °C and then dried in an atmosphere oven. To lessen the deterioration of the compounds, high-temperature treatment was discontinued. The extract was then maintained in a small container at 25 C° (Kumoro et al., 2009).

The Anti-Candida Activity Test

To assess the extract's anti-candida activity, the agar well-diffusion test was utilized. A suspension was created in a sterile saline solution (0.85%) using Candida (glabrata, kefyr, and albicans) from a 24-hour culture on Sabouraud dextrose agar. A spectrophotometer at 530 nm was used to adjust the suspension's turbidity to get a final concentration that was equal to a 0.5 McFarland standard (0.5—2.5 103). One milliliter of the Candida suspension was added to 20 milliliters of melted SDA after it had been cooled to 55 °C. The assay plate (9 cm in diameter) was filled with the inoculated agar, which was then let to cool on a level surface. Four wells, each 4 mm in diameter, were drilled once the medium had solidified, which contained 20 µl of the extract (anti-Candida drug), and were carved out of the agar. Each plate had five different concentrations (25, 50, 100, 200, and 400 mg/1000 ml) and was incubated at 35 °C for 24 hours.

For each studied Candida species, positive (Clotrimazole) and negative controls (20% Dimethyl sulfoxide) were made in place of the extracted sample under investigation. Three measurements, taken in three distinct directions, were averaged to determine the growth inhibition diameter. Three duplicates of each test were run (De Magaldi & Camero, 1997; Magaldi et al., 1998; Mata et al., 1999; Magaldi et al., 2001; Magaldi et al., 2001).

In Vitro Cytotoxic Activity

The cytotoxicity of the extract on melanoma cancer cells (B16 cell line) and normal cells (vero cell line) was evaluated using the previously reported 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) test [33]. The MTT assays was done in the Al- Phadel foundation for training and evolution/Babylon) In a nutshell, 7000 cells were plated each well onto a 96-well plate. The plating medium was taken out and replaced with fresh medium with or without extract treatment after a 24-hour incubation and attachment period. For 24, 48, and 72 hours at 37°C, the cells were exposed to medium alone or various doses (31.95-1000 g/ml) of plant extract. Positive control was performed using oxaliplatin (0.25 g/ml). Following incubation, the plates were incubated at 37°C for 4 hours with 20 l of MTT solution (5 mg/ml) added to each well.

The formazan crystals were then solubilized by adding 100 l of DMSO to each well after the supernatant had been removed. Using an ELISA reader, the amount of absorbance was measured at 570 nm. Experiments were performed in triplicate. The results are expressed as the percentage of cell viability concerning the media-treated cells {The percentage of viable cells (VI) determined with the equation:
VI = (Absorbance of the treated cells ÷ Absorbance of the control cells) ×100}

IC50 determination

The half maximal inhibitory concentration (IC50) gauges a substance's ability to effectively block a certain biological or metabolic function.

The percentage of cell viability in cells containing the vehicle dimethyl-sulfoxide (DMSO), which was employed as the control and represented 100% survival, was calculated from the

absorbance readings of the treated cells. Using a dose-response curve and the CalcySynTM (USA) program, the cytotoxic concentrations of extracts that give a 50% inhibition of cell growth (IC50) were determined. By contrasting the IC50 values of different cell lines, the cytotoxic effect of A. vera extracts and the control were assessed.

Statistical analysis

Each experiment was carried out three times, and one-way ANOVA was used to compare the outcomes statistically. Based on mean values, an analysis of variance for each parameter was conducted to establish its significance at $p < 0.05$. The means and standard deviations of the data were reported.

RESULTS AND DISCUSSION

By using the MTT assay, the gel extract from aloe vera (Linn) leaves was examined for its anti-Candida activity against the three species of Candida (kefyr, glabrata, and albicans), as well as its cytotoxic action on the melanoma cell line (B16) and its activity on normal cell line (Vero).

The results in table 1 showed clearly that there is a positive relationship between the increased concentrations of the extract and the inhibition zones diameters, in addition to that there is a difference in the anti-Candida activity of the extract against tested Candida strains at the same concentrations, it was the highest against C. glabrata and C. kefyr when compared with which against C. Albicans.

Table 1: The inhibition zone diameters (mm) of Candida species (glabrata, kefyr and albicans) by the effects of diethyl ether extract of Aloe vera (Linn) leaves concentrations) mg\1000ml)

***Candida* species**	***Aloe vera (Linn)* leaves gel extract Concentrations(mg\1000ml)**					**Clotrimazole**	**DMSO 20%**
	25	**50**	**100**	**200**	**400**		
C. glabrata	5.33±1.15	8.67±2.52	13.33±3.51	23.33±4.73	33.00±3.61	53.67±3.79	00.00
C. kefyr	4.33±0.58	5.33±1.53	6.67±2.08	10.00±2.65	25.00±6.24	46.33±1.53	00.00
C. albicans	3.33±1.53	4.33±0.58	5.67±2.31	8.33±3.06	18.00±4.58	33.00±2.00	00.00

Source: Authors

The inhibition zones' diameters gradually increased from the lower concentration of 25mg/1000ml, where they were (5.331.15, 4.330.58, 3.331.53) mm, to the higher concentration of 400mg/1000ml, where they were (33.003.61, 25.006.24, 18.004.58) mm, respectively, demonstrating the anti-candida effects of aloe vera extract on the C. glabrata, C. kefyr. The results in figure 2 revealed that the viability of the melanoma cell line (B16) was 100% when treated with plant extract in the concentration of 31.95µg/ml and began to decrease gradually whenever the concentration was increased until reached 45.05% in concentration 1000µg/ml in the same time the viability of its was 18.14% when oxaliplatin (standard drug) was used in a concentration of 0.25 µg/ml.

In addition to that the results in the same figure showed the viability of the normal cell line (vero) was 96.36% when plant extract was used in a concentration of 31.95µg/ml and began to decrease gradually) Unconsciously (, When compared to the viability percentage caused by the influence of oxaliplatin at a concentration of 0.25 g/ml, which was 68.50%, the concentration was increased until it reached 73.97% at a concentration of 1000 g/ml.

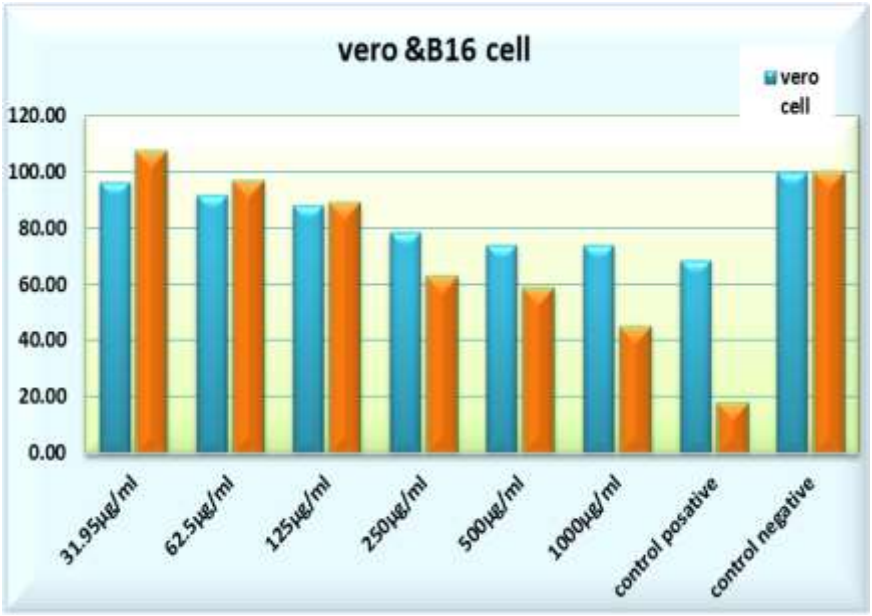

Figure 1: The viability percentage of melanoma cell line (B16) and normal cell line (vero) by the effect of Aloe vera (Linn) leaves gel extract

Positive control: (Oxoplatin (0.25 µg/ml))
Negative control: The cells were treated with media alone

The half maximal inhibitory concentration (IC50) was determined depending on the results of absorbance values of treated cells after converting it to the percentage of cell viability in cells with the presence of the vehicle dimethyl-sulfoxide (DMSO).

Figure 2 showed the results of (IC50) for the melanoma cell line (B16), in which the IC50 value was 250 µg/ml.

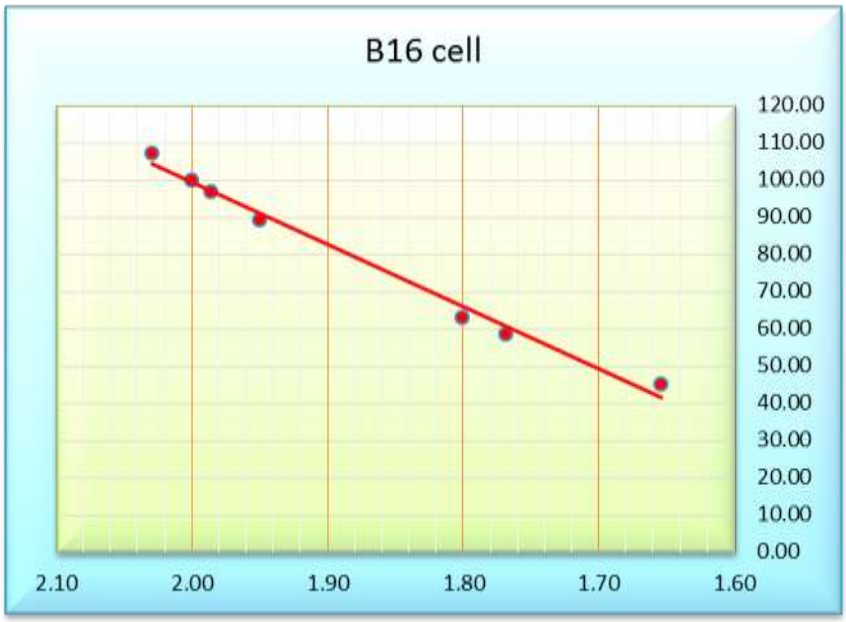

Figure 2: Half maximal inhibitory concentration (IC50) of Aloe vera (Linn) leaves gel extract on melanoma cancer cell line (B16)

On the other hand, Figure 3 showed the results of (IC50) for normal cell line (vero), in which the IC50 value was very high over than 1000 µg/ml.

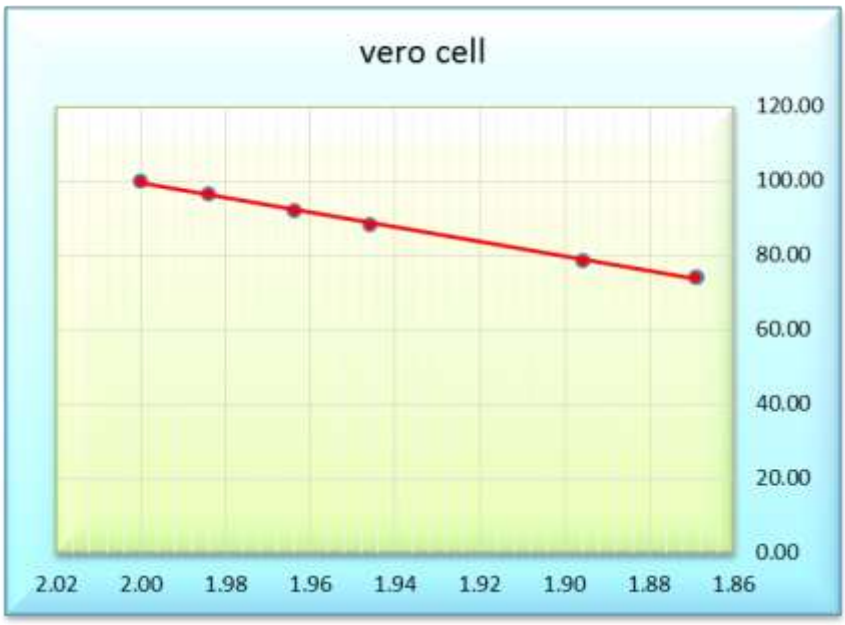

Figure3: Half maximal inhibitory concentration (IC50) of Aloe vera (Linn) leaves gel extract on normal cell line (vero).

Discussion

The gradual increase in inhibitory effects of Aloe vera (Linn) leaves extract against the same Candida species with the increasing extract concentration could be a result of the increase in phytochemical compounds quantity in tested extract concentrations. In addition to that, the differences in the potentiality of the extract in inhibition activity may be due to the differences in pathogen sensitivity for the Aloe vera (Linn) leaves extract. (Shilpa et al., 2020; Antonisamy et al., 2012).

In the present study, we noted the cytotoxic potentiality of Aloe vera (Linn) leaves gel extract with high specificity to melanoma cell line when compared with its effect on the normal cell which was the main purpose behind the present study. In addition, the IC50 concentration of plant extract was a moderate value in the melanoma cell line but this value was very high in the normal cell line so all that can support the goals of the present study.

Because of increased exposure to chemical carcinogens and UV radiation in the modern world, skin cancer poses a rising threat to humans. Research has been done on various cancer types in vivo (Corsi et al., 1998; Akev et al., 2007) and cell lines in vitro (Al-Oqail et al., 2016) to determine the anticancer impact of Aloe vera gel and leaf extracts. Aloe vera shields mice from DMBA/croton oil-induced cutaneous papilloma genesis, according to a different study (Saini et al., 2010).

CONCLUSION

This study uses machinery to demonstrate the ability of Aloe vera plant extracts to destroy malignant cells while shielding healthy cells from the cytotoxic effects of anticancer medications. Here, cancer cell culture is being carried out, and it is well shown how chemotherapeutic drug potency and molecular participation in cancer cells interact. Aloe vera displays strong anticancer action, according to an evaluation of an in-vitro antitumor activity. In the future, this effort can be automated to purify and identify the active components found in aloe vera utilizing a variety of analytical techniques. This research can also be expanded to include in-vivo studies of immune-modulatory and cytoprotective action, as well as anticancer activity by quantifying tumor volume.

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