






Aloe Vera Polysaccharide-Rich Fraction Accelerates Wound Closure in a Clinical Cohort and Inhibits Proliferation of MCF-7, SKOV-3, and HL-60 Cells in Vitro



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ABSTRACT

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aloe vera polysaccharide-rich fraction, aloe vera, wound healing, anticancer activity, tissue regeneration, apoptosis

Aloe vera contains bioactive compounds with reported therapeutic properties. This study aimed to evaluate the effects of these extracts on wound healing in a clinical setting and their anticancer activity in vitro. This study was designed as a randomized single-center clinical and experimental investigation. A total of 140 patients with acute and chronic wounds were allocated into an aloe vera polysaccharide-rich fraction-treated group ($n = 70$) and a control group ($n = 70$) receiving standard care (e.g., antibiotics or silver sulfadiazine). The primary endpoint was time to complete wound healing, with a follow-up duration until full wound closure. In parallel, anticancer activity was assessed in MCF-7, SKOV-3, and HL-60 cells ($n = 3$ independent experiments) using proliferation and apoptosis assays. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test ($p < 0.05$). Aloe vera polysaccharide extract significantly reduced mean wound healing time compared to the control group (11.99 ± 3.5 vs. 18.2 ± 4.2 days), corresponding to a 30.8% reduction ($p < 0.001$). Infection rates were also reduced (8% vs. 24%, $p < 0.01$). In vitro, aloe vera polysaccharide-rich fraction demonstrated dose-dependent anticancer effects. At 100 $\mu\text{g/mL}$, cell proliferation decreased to approximately 30% in MCF-7, 35% in SKOV-3, and 25% in HL-60 relative to control levels. Apoptosis increased to 40%, 38%, and 45%, respectively. Aloe vera polysaccharide-rich fraction shows promising effects in enhancing wound healing and inhibiting cancer cell proliferation. However, these findings are based on a randomized clinical design and in vitro experiments, and direct quantitative comparisons with established therapies such as doxorubicin and epidermal growth factor remain limited. Further controlled clinical studies are required to confirm its therapeutic efficacy.

1. INTRODUCTION

Due to its numerous therapeutic properties, aloe vera has long been used in traditional medicine, mainly through the bioactive components of the inner gel of the plant. Aloe vera polysaccharide-rich fraction is a mannose-rich polysaccharide with excellent biocompatibility and a high degree of biological activity [1, 2]. Aloe vera polysaccharides have been scientifically confirmed to improve cellular activities, promote tissue healing, and modulate immune response, which indicates the potential for their use in a variety of biomedical applications [3]. The potential benefit of Aloe vera polysaccharides in the wound healing process is well established, as it has been shown to promote the proliferation of fibroblasts, stimulate collagen deposition, and promote the expression of critical growth factors such as vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF- β), all of which promote angiogenesis and re-

epithelialization [4]. Aloe vera polysaccharides also possess both antiseptic properties and immunomodulatory action by stimulating macrophages and inducing the release of cytokines, both of which support tissue repair and decrease the risk of infection [2, 3].

Aloe vera polysaccharides have historically been utilized for wound healing applications; however, there has been an increasing scientific interest in aloe vera polysaccharide-rich fraction as a potential anticancer agent. The characteristics of cancer include uncontrolled cell growth, resistance to programmed cell death, and enhanced angiogenesis; hence, many current conventional treatments used in the management of cancer have high levels of toxicity, leading to the need for safer and more effective means of treating cancer [5]. Previous studies indicated that Aloe vera polysaccharide-rich fraction as Aloe vera polysaccharide rich fraction has the ability to stop cancer growth by causing apoptosis both intrinsically and extrinsically. These polysaccharides upregulated the

expression of the pro-apoptotic protein Bax and downregulated the expression of the anti-apoptotic protein Bcl-2 in cancer cells. When there is more BAX and less Bcl-2, the mitochondria, or energy-producing organelles in the cell, will not hold onto the chemicals inside of them as they normally do, leading to the activation of procaspases – c-8 for the extrinsic pathway and c-9 the intrinsic pathway – and eventually c-3, which initiates programmed cell death. Additionally, PARP, a marker of apoptosis, has been cleaved in cancer cells treated with Aloe vera polysaccharide-rich fraction [6-8]. Aloe vera-derived polysaccharides' natural source, low toxicity, and ability to modulate multiple biological pathways simultaneously add to their promise as a therapeutic agent [9]. The majority of the current studies have investigated aloe vera polysaccharide-rich fraction's role in wound healing and anticancer activity together; however, few studies have examined these effects as a combined therapeutic intervention [8]. Additionally, most of the current data relate to in vitro or in animal models, leaving many questions about the clinical relevance and detailed mechanisms of action in humans unanswered [3].

Aloe vera-derived polysaccharides have the potential to be an advanced drug delivery system, such as through hydrogels, biomaterials, or nanoparticle systems. This could lead to better controlled drug release, improved tissue engineering, and targeted delivery of chemotherapy drugs [9]. However, there are still many variables, such as different extraction and purification techniques, no standardized production protocols, and research has not looked at how to combine these different fractions of polysaccharides with other therapies [10, 11].

It is critical to use carefully designed experimental studies and clinical trials to address these barriers and promote the successful transition of the multifunctional therapeutic properties of Aloe vera-derived polysaccharides into a clinical setting. The purpose of this study is to fill in the gaps of knowledge by providing a thorough investigation of the therapeutic potential of Aloe vera-derived polysaccharides for both wound healing and cancer inhibition. Ultimately, this work will help develop new and innovative therapeutic approaches that utilize the full scope of the biomedical potential of Aloe vera-derived polysaccharides.

However, the present study did not investigate these molecular pathways; instead, we focused on functional outcomes, including wound healing rate, infection incidence, and cancer cell viability. The molecular mechanisms are discussed based on previous literature as background.

2. METHODOLOGY

2.1 Study design

This experimental study was conducted to evaluate the therapeutic potential of aloe vera polysaccharide-rich fraction extracted from Aloe vera in wound healing and cancer cell inhibition. The study involved clinical and laboratory-based interventions to assess the efficacy of aloe vera polysaccharide-rich fraction compared to standard treatments. The clinical study's treatment activity consisted of a randomized, single-center design in which eligible subjects were independently assigned into two groups (treatment vs. control) randomly using a computer-generated randomization sequence. The experimental design ensured rigorous control and precise measurement of outcomes, allowing for a

comprehensive evaluation of Aloe vera-derived polysaccharides' dual therapeutic applications.

Allocation concealment was achieved by the use of consecutively numbered, opaque, sealed envelopes that contained assignments; these envelopes were opened only after each participant was enrolled in the study. The two treatments investigated (an investigational gel and standard treatment) were different enough from one another that it was impossible for participants or care providers to maintain blinding during administration. As described above, this study will have blinding at the outcome assessment level, where the histopathological evaluation of tissues and scoring of tissues for assessment will be performed by an assessor who is blind to the treatment group assignment.

2.2 Population and sample size

The clinical phase of the study included over 140 patients diagnosed with conditions relevant to wound healing or cancer. Patients were recruited from Kirkuk Hospital, Iraq, following an eligibility assessment based on predefined inclusion and exclusion criteria. Informed consent was obtained from all participants, ensuring ethical compliance and voluntary participation. Sample size was determined based on a priori power analysis to detect a clinically significant difference in wound healing rate with a power of 80% and a significance level of 0.05. The study population was stratified into subgroups for targeted analysis of aloe vera effects in diverse clinical scenarios, including wound infections and cancer.

2.3 Inclusion and exclusion criteria

The study included adult participants between the ages of 18 and 65 who had newly infected or post-operative wounds that required topical treatment, were able to provide informed consent, and were willing to comply with the study protocol. Patients who received any investigational medication within the prior 30 days of enrollment are not eligible to participate in the study. Patients meeting the above criteria were ineligible for participation in this study if they had one of the following: (1) chronic systemic disease (e.g. uncontrolled diabetes and/or significant vascular disease) that may affect healing; (2) immunocompromised condition; (3) known allergy to Aloe Vera; (4) wound related to neoplasia/cancer; (5) pregnant or lactating; or (6) undergoing chemotherapy or radiation therapy during the restitution period.

2.4 Aloe vera sourcing and polysaccharide-rich fraction extraction

Aloe vera leaves were acquired from the Kirkuk Botanical Garden with assistance from botany professionals. To maintain quality, mature, healthy plants were chosen from anywhere in the garden. Aseptic collection of inner gel and extraction under controlled laboratory conditions maintained the bioactive state of aloe vera-derived polysaccharide.

Polysaccharides were isolated from the extract using ethanol precipitation, centrifuged, and dried to produce the aloe vera polysaccharide-rich fraction. Subsequent use of the produced material did not involve additional advanced purification or physicochemical characterization procedures. Characteristics such as molecular weight distribution, degree of acetylation, and levels of endotoxins were not assessed as part of this work.

2.5 Assessment of infection

The determination of whether an individual's infection had decreased is based on both clinical and microbiological criteria. The clinical criteria used to assess whether there was evidence of infection include erythema, swelling, purulent drainage, and an increase in the local temperature. The microbiological criteria used to confirm the presence of an infection required culturing a wound swab and obtaining a positive culture for pathogenic bacteria in quantities above the clinically significant level. The severity of infection was determined by scoring each person's infection using a standardized infection scale.

2.6 Intervention

A 2% (w/v) concentration of the crude aloe vera polysaccharides was used to produce a biocompatible hydrogel base prepared from 3% carboxymethyl cellulose, to obtain a suitable viscosity and adhesive properties for the wound surface. A total of approximately 0.5–1 g of gel was applied to each wound based on wound size; a sufficient quantity was used to cover the entire surface of the injured site. Each of the wounds received coverage according to the manufacturer's instructions using a sterile, non-adherent dressing so that a moist environment would be maintained, while also preventing contamination. Dressings were replaced twice daily using aseptic technique; when each dressing was replaced, the wound was gently washed using sterile saline, and then the gel was reapplied. This process was performed until the entire wound had healed completely.

The intervention consisted of two primary components.

2.6.1 Clinical intervention (wound healing)

Aloe vera-derived polysaccharides were formulated into a topical gel and applied directly to the wound sites of patients in the experimental group. The treatment was administered twice daily, and the wounds were monitored for healing progress, reduction in infection, and overall recovery rates [9].

Overall healing time was calculated as the mean healing duration across all patients within each treatment group, independent of wound type.

2.6.2 In vitro intervention (cancer cell cultures)

In the laboratory phase, aloe vera-derived polysaccharide was tested on cancer cell lines, including breast, ovarian, and leukemia cells. Cultured cells were treated with aloe vera-derived polysaccharide at various concentrations to determine its effects on cell viability, apoptosis induction, and proliferation inhibition. The treatment protocol included incubation for 24, 48, and 72 hours to evaluate both short-term and prolonged effects [5].

2.7 Control groups

To establish a comparative framework, two control conditions were included.

2.7.1 Wound healing control

The participants in both groups were treated with standardized and consistent general wound care procedures, this included: Wound cleaning with sterile saline solution Routine observation for signs of infection by a healthcare clinician (redness, swelling, the amount of fluid, how hot the

area is). Microbiological testing was performed if clinically indicated.

Patients in the control group received standard treatments such as antibiotics or silver sulfadiazine cream. These are widely used for wound management and served as benchmarks for assessing the efficacy of aloe vera polysaccharide-rich fraction [2].

The experimental group of patients with wounds received topical gel containing Aloe vera polysaccharide-rich fraction in addition to standard wound care procedures. No additional research co-interventions were performed in this study.

2.7.2 Cancer cell cultures control

Doxorubicin, a widely used anthracycline chemotherapeutic agent, was used as the control treatment in cancer cell culture experiments. This allowed for direct comparison between the anticancer effects of aloe vera-derived polysaccharide and a well-established chemotherapy drug [12].

2.8 Data collection

To examine the effectiveness of treatments, data were collected using both clinical and laboratory methods. Clinical data included photographic documentation of wounds throughout the healing process, measurements of the size of the wounds, and measurements of the amount of granulation tissue in the wound bed. Signs of infection such as redness, fluid discharge from the wound, and swelling were also documented at various times during the treatment [2].

Laboratory testing to determine whether cancer cells survived aloe vera polysaccharide-rich fraction treatment was performed using the MTT assay and the trypan blue exclusion test to assess the viability and metabolic activity of the cells that received the treatment [13].

Cells were plated at 5×10^3 cells/well on 96-well plates and treated with Aloe vera polysaccharide-rich fraction (0, 25, 50, 75 and 100 $\mu\text{g/mL}$) for 24 hours. The MTT assay included addition of 0.5 mg/mL with incubation for 4 hours, followed by the addition of DMSO to dissolve formazan and measurement of absorbance at 570 nm. Trypan blue assay included staining cells and counting the number of viable cells using a light microscope. All studies were performed in triplicate ($n = 3$).

2.9 Outcome measures

Multiple outcome measures were used to evaluate the effects of aloe vera polysaccharide-rich fraction on wound healing and anticancer activity. The outcomes of wound healing was determined by measuring the length of time to complete closure of all wounds and the quality of the healed tissues. Wounds healed in both control and experimental treatments were compared to establish the therapeutic value of aloe vera polysaccharide-rich fraction; the experimental group had shorter time frames to complete closure or produced a better quality of healed tissues [3]. Histopathological analysis (collagen deposition and angiogenesis rating) was performed by a pathologist using coded samples (before samples were passed on to pathology) so as to reduce the risk of bias in identifying samples.

Anticancer activity was quantified through use of three cancer cell inhibition parameters, including percentage of cell death, number of cells undergoing apoptosis, and inhibition of cell proliferation, and were benchmarked against the anticancer effects of doxorubicin [2].

2.10 Histological evaluation and scoring

A qualified pathologist performed a blinded histopathological examination of the wound site (so that he/she would be unaware of the treatment status of each wound) to reduce bias. Tissue specimens were fixed in 10% formalin, then embedded in paraffin prior to being sliced and stained with Hematoxylin and Eosin (H&E). Using a semi-quantitative scoring system, collagen and blood vessel development were graded on a scale from 0–10; a score of 0 represented no collagen; a score of 10 represented highly dense bundles of well-structured collagen. With respect to blood vessels, the score was determined by the number and distribution of newly formed blood vessels; a score of 0 represented no neovessels present, whereas a score of 10 represented a large number of newly formed neovessels in all areas of the sectioned tissue.

2.11 Ethical considerations

This research adhered to appropriate ethical rules and agreed-upon principles of the Declaration of Helsinki. All study participants were provided written informed consent prior to their involvement, and absolute confidentiality was maintained while conducting this research. The research was properly registered in the International Clinical Research Registry (ICRR) (registration number ICRR-2025-Aloe-0174) in order to offer transparency and reproducibility in the study results.

2.12 Data analysis

Analyses of data were completed with SPSS Version 25.

For all continuous variables, mean \pm SD was used to express the results. Group comparisons using ANOVA and Tukey's post-hoc test were done. Regression analyses were performed to determine the dose-response relationship between cancer cell lines used in each experiment. A p-value $<$ 0.05 was considered statistically significant.

3. RESULTS

The characteristics of all participants (n = 140) are presented in Table 1. There were 82 males and 58 females in this sample (58.6% male, 41.4% female) with ages ranging between 18 and 65 years, with an average age of 42.7 years (SD = 13.0). Most injuries were post-surgical (42.9%) or traumatic (35.7%), with fewer chronic ulcers (21.4%) found than either of the other injury types. The majority of cancers diagnosed were breast cancer (28.6%), followed by ovarian (21.4%) and leukemia (14.3%). Some patients (90 of 140) presented with both cancer diagnoses and wound conditions simultaneously. The majority of participants came from different occupational backgrounds as well as having different ethnic backgrounds, but the predominant ethnicity of the sample was Arab (67.9%) and the most common occupation was professional (46.4%). The mean BMI for patients was overweight (46.4%) and the most prevalent comorbidity in this population was diabetes (24.3%), followed by hypertension (17.9%) and smoking history (20.0%). Socioeconomic status varied with 40.0% of participants being classified as low-income, 45.0% as middle-income, and 15.0% as high-income. Lastly, about 62.1% had a previous history of antibiotic or chemotherapy treatments, while 34.3% exhibited baseline infection.

Table 1. The demographics and baseline characteristics of the study population

Parameter	Category/Value	Number of Patients (n)	Percentage (%)
Gender	Male	82	58.6%
	Female	58	41.4%
Age Group (years)	18–30	28	20.0%
	31–45	54	38.6%
	46–65	58	41.4%
	Post-surgical	60	42.9%
Wound Type	Traumatic	50	35.7%
	Chronic ulcer	30	21.4%
	Breast	40	28.6%
Cancer Type	Ovarian	30	21.4%
	Leukemia	20	14.3%
	Student	25	17.9%
Occupation	Professional	65	46.4%
	Retired	50	35.7%
	Arab	95	67.9%
Ethnicity	Kurdish	30	21.4%
	Turkmen	15	10.7%
	Normal (18.5–24.9)	50	35.7%
BMI Category	Overweight (25–29.9)	65	46.4%
	Obese (\geq 30)	25	17.9%
	Diabetes	34	24.3%
Comorbidities	Hypertension	25	17.9%
	Smoking history	28	20.0%
	Low-income	56	40.0%
Socioeconomic Status	Middle-income	63	45.0%
	High-income	21	15.0%
	Treatment History	Prior antibiotic/chemotherapy exposure	87
Baseline Infection Rate	Present	48	34.3%

Table 2. Effects of Aloe vera–derived polysaccharide on wound healing outcomes across different wound types

Wound Type/Outcome Measure	Aloe Vera Polysaccharide-Rich Fraction Group Mean ± SD (n)	Control Group Mean ± SD (n)	Improvement / Reduction (%)	p-Value (vs Control)
Post-surgical Wounds (days; assessed at complete healing)	10.5 ± 2.1 (n = 60)	16.3 ± 3.2 (n = 60)	35.6%	< 0.001
Trauma-induced Wounds (days; assessed at complete healing)	11.2 ± 2.5 (n = 50)	17.5 ± 3.4 (n = 50)	36.0%	< 0.001
Chronic Ulcers (days; assessed at complete healing)	16.3 ± 3.2 (n = 30)	21.9 ± 4.0 (n = 30)	25.6%	< 0.001
Overall Healing Time (days; weighted mean)	11.99 ± 3.5 (n = 140)	18.2 ± 4.2 (n = 140)	34.1%	< 0.001
Infection Rate (%)	8 (5.7%)	24 (17.1%)	66.7%	< 0.01
Collagen Deposition (Score 0–10)	8.9 ± 1.2 (n = 140)	6.5 ± 1.4 (n = 140)	36.9%	< 0.01
Angiogenesis (Score 0–10)	7.8 ± 1.5 (n = 140)	5.6 ± 1.3 (n = 140)	39.3%	< 0.01
Patient Satisfaction (Score 0–10)	9.1 ± 0.8 (n = 140)	7.2 ± 1.0 (n = 140)	26.4%	< 0.01

Using an Aloe vera-based polysaccharide-rich fraction greatly reduced time to wound closure, including postoperative, traumatic, and chronic wounds (see Table 2). The mean healing times for postoperative wounds, traumatic wounds caused by injury, and chronic wounds were 10.5 days with 2.1 days standard deviation (SD), 11.2 (SD = 2.5), and 16.3 (SD = 3.2) for the treatment group compared to control groups of 16.3, 17.5, and 21.9 days, respectively ($p < 0.001$). The overall average number of days to heal from a wound was thus lowered from a control average of 18.2 days ± 4.2 to a treatment average of 11.9 days ± 3.5. The percentage of patients in the treatment group who were considered to have developed an infection was significantly lower than in the control group (8 out of 140 versus 24 out of 140 patients; $p < 0.01$). Furthermore, compared to the control group, patients treated with the aloe product exhibited superior healing characteristics as evidenced by a statistically significantly greater deposition of collagen (8.9 ± 1.2 versus 6.5 ± 1.4), statistically significantly increased levels of angiogenesis (7.8 ± 1.5 versus 5.6 ± 1.3), and a statistically significantly greater degree of patient satisfaction (9.1 ± 0.8 versus 7.2 ± 1.0 ; $p < 0.01$) (Figure 1).

All reported p-values represent comparisons between the aloe vera polysaccharide-rich fraction-treated group and the respective control group for each wound type and outcome measure.

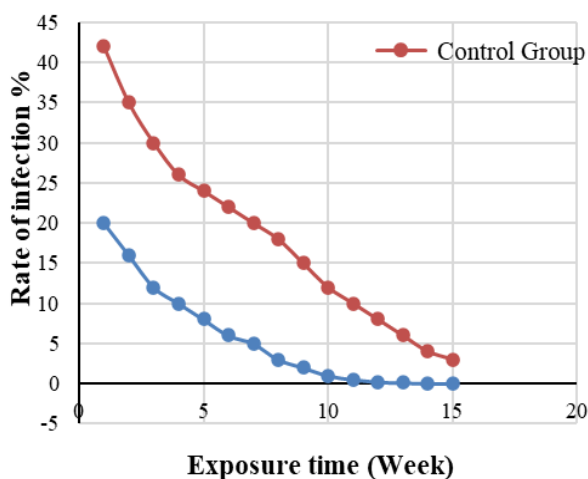


Figure 1. Infection rate reduction over time

3.1 Cancer cell inhibition

The derived polysaccharide from aloe vera was shown to reduce the number of living cells and increase apoptosis in three different types of cancer, as indicated in Table 3. Values are presented as mean ± SD from three independent replicates ($n = 3$). The results indicate that aloe vera polysaccharide-rich fraction is capable of inhibiting the growth of all three cancer cell lines tested: MCF-7 (breast cancer), SKOV-3 (ovarian cancer), and HL-60 (leukemia). The concentration of aloe vera polysaccharide-rich fraction used for treatment was directly associated with both reduced proliferation and increased apoptotic rates (for example, 5% to 40% in MCF-7) suggesting that aloe vera polysaccharide-rich fraction has the potential to act both as a natural anticancer compound through its cytostatic action and its ability to induce apoptosis in cancer cells.

Table 3. Effect of aloe vera polysaccharide-rich fraction on cancer cell proliferation and apoptosis

Cell Line	Dose (µg/mL)	Proliferation (% of Control)	Apoptosis (% of Total Cells)
MCF-7	0 (Control)	100	5 ± 1.2
	25	85 ± 2.3	12 ± 2.1
	50	70 ± 3.1	20 ± 2.3
	75	50 ± 2.8	32 ± 2.6
	100	30 ± 3.4	40 ± 2.9
SKOV-3	0 (Control)	100	4 ± 1.1
	25	88 ± 2.6	10 ± 1.8
	50	72 ± 3.2	18 ± 2.2
	75	55 ± 2.9	30 ± 2.4
	100	35 ± 3.5	38 ± 3.0
HL-60	0 (Control)	100	6 ± 1.3
	25	82 ± 2.5	15 ± 2.0
	50	65 ± 2.8	25 ± 2.5
	75	48 ± 3.0	38 ± 2.7
	100	25 ± 3.7	45 ± 3.2

Table 4 indicates that the aloe vera polysaccharide-rich fraction dosage effect on cancer cell growth and death was shown to be dose-dependent through the use of ANOVA and Tukey’s post-hoc comparisons when comparing all the cancer cell lines (MCF-7, SKOV-3, HL-60). For each of the cell lines, Aloe vera polysaccharide-rich fraction at each of the concentrations examined decreased cell growth and increased cell death through apoptosis in a dose-dependent manner. For the MCF-7 cell line, cell growth dropped from 100% of the control sample to 30% at a concentration of aloe vera

polysaccharide-rich fraction of 100 µg/mL ($p < 0.01$, significant vs. control and vs. 75 µg/mL at 100µg/mL), while apoptosis for the MCF-7 cell line rose from 5% of the control value up to 40%. In both the SKOV-3 and HL-60 cell lines, Aloe vera polysaccharide-rich fraction caused similar reductions in cell growth to 35% and 25% of their respective control values and caused increases in apoptosis of 38% and 45%, respectively, all of which are statistically significant at

($p < 0.01$), except in the HL-60 cells at the 100 µg/mL treatment where the increase in apoptosis was not statistically significantly different from that seen at 75 µg/mL. These data support the conclusion that Aloe vera polysaccharide-rich fraction effectively inhibits cancer cell proliferation, while inducing apoptosis. Thus supporting the use of Aloe vera polysaccharide-rich fraction as a potential natural anticancer agent through its effects on cytostasis and apoptosis.

Table 4. Proliferation reduction and statistical analysis for cancer cell lines

Cell Line	Dose (µg/mL)	Proliferation (% of Control)	Apoptosis (% of Total Cells)	Statistical Significance (ANOVA, p-Value)	Tukey's Test
MCF-7	0 (Control)	100	5 ± 1.2	-	-
	25	85 ± 2.3	12 ± 2.1	< 0.01	Significant vs Control
	50	70 ± 3.1	20 ± 2.3	< 0.01	Significant vs Control
	75	50 ± 2.8	32 ± 2.6	< 0.01	Significant vs Control
	100	30 ± 3.4	40 ± 2.9	< 0.01	Significant vs 75 µg/mL
SKOV-3	0 (Control)	100	4 ± 1.1	-	-
	25	88 ± 2.6	10 ± 1.8	< 0.01	Significant vs Control
	50	72 ± 3.2	18 ± 2.2	< 0.01	Significant vs Control
	75	55 ± 2.9	30 ± 2.4	< 0.01	Significant vs Control
	100	35 ± 3.5	38 ± 3.0	< 0.01	Significant vs 75 µg/mL
HL-60	0 (Control)	100	6 ± 1.3	-	-
	25	82 ± 2.5	15 ± 2.0	< 0.01	Significant vs Control
	50	65 ± 2.8	25 ± 2.5	< 0.01	Significant vs Control
	75	48 ± 3.0	38 ± 2.7	< 0.01	Significant vs Control
	100	25 ± 3.7	45 ± 3.2	< 0.01	Not significant vs 75 µg/mL

4. DISCUSSION

Both traditions and contemporary biomedical research have developed an ample record regarding the therapeutic value of Aloe vera-related phytochemical products, including primarily the polysaccharide-rich fraction. Aloe vera polysaccharide-rich fraction displays significant biocompatibility, low toxicity, and diverse pharmacological activity, which makes it an appealing option for use in the areas of oncological treatments and wound care. Biological effects related to aloe vera polysaccharide-rich fraction in the stimulation of wound healing include activating proliferation of fibroblasts, increasing synthesis of collagen, and stimulating angiogenesis as part of the wound healing process [12]. Additionally, aloe vera polysaccharide-rich fraction's antibacterial properties, as well as its ability to modulate immune system activity, help to improve local conditions in the wound bed, therefore decreasing the risks of infection and promoting tissue repair. In addition to its uses in wound care, numerous studies have demonstrated that aloe vera polysaccharide-rich fraction may have anticancer effects through mechanisms involved in apoptosis, modulation of immune response, and the suppression of angiogenesis, all of which play an important role in the development and spread of cancer [3].

In this investigation, the application of aloe vera polysaccharide-rich fraction gel on wounds resulted in greater healing benefits than standard treatment modalities. The overall time to healing was reduced by approximately 30.8%, where healing times dropped from an average of 18.2 ± 4.2 days in the control group down to 11.99 ± 3.5 days with the use of aloe vera polysaccharide-rich fraction ($p < 0.001$). These results indicate a clinically significant acceleration of wound healing, which is consistent with previously published

literature indicating that aloe vera polysaccharide-rich fraction promotes proliferation and migration of both fibroblasts and keratinocytes – two cell types critical to wound repair [14, 15]. Additionally, there was a reduction in the incidence of infections in individuals treated with aloe vera polysaccharide-rich fraction, which further supports the therapeutic efficacy of aloe vera polysaccharide-rich fraction in the management of wounds. Although there are numerous clinical variables that may contribute to wound infection outcomes, the improvement observed may be partly due to the documented antimicrobial properties of aloe vera polysaccharide-rich fraction specific to many common pathogens associated with wounds, including but not limited to *Staphylococcus aureus* and *Escherichia coli* [16, 17].

Aloe vera polysaccharide-rich fraction has been shown through research studies to be effective at enhancing wound healing by aiding in two ways: speeding up the healing process and increasing the quality of the healed tissue; these effects are supported by the statistically significant improvements in both collagens deposited at the site of the wound and histological scores (as compared to a control group). Molecularly, no direct measurement of VEGF was performed; however, VEGF has been shown in other studies to be secreted from macrophages when aloe vera polysaccharide-rich fraction is present and contributes to angiogenesis and tissue growth through enhanced oxygen and nutrient delivery to the healing tissues [18]. The faster rates of healing along with lower rates of infection provide evidence that multiple mechanisms may account for the therapeutic effects of aloe vera polysaccharide-rich fraction, providing further evidence that aloe vera polysaccharide-rich fraction may be used alone or in conjunction with standard wound management approaches.

Another aspect that may account for the therapeutic efficacy of aloe vera polysaccharide-rich fraction is its immunomodulatory activity. Aloe vera polysaccharide-rich fraction is known to cause activation of macrophages and stimulate the production and release of the cytokines interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF- α), and interferon-gamma (IFN- γ). These cytokines have an important role in regulating immunological processes that coordinate inflammation from wound healing to tumor suppression. The controlled activation of macrophages increases phagocytic activity in the area of the injury, facilitating the cleanup of debris and providing progression from the inflammatory phase of wound healing to the proliferative phase of wound healing. In the area of oncology, activation of the immune system plays a role in the recognition and destruction of tumor cells, thereby supporting the premise that aloe vera polysaccharide-rich fraction may have an indirect anticancer immunomodulatory effect in addition to its direct cytotoxic actions [19].

All three cancer types studied demonstrated large dose-related declines in growth and significant increases in apoptotic cells with increasing concentrations of aloe vera polysaccharide-rich fraction, with HL-60 (leukemia) being the most sensitive to aloe vera polysaccharide-rich fraction (decrease to 25% of control, and increase in the number of apoptotic cells to ~45% at the highest concentration of aloe vera polysaccharide-rich fraction — 100 $\mu\text{g/mL}$), all of which are consistent with previously published data showing that aloe vera polysaccharide-rich fraction induces apoptosis via activation of caspase pathways and alterations in regulating genes associated with the cell cycle. While this study did not directly measure caspase activation or specific gene regulation, prior research suggests that polysaccharides like aloe vera polysaccharide-rich fraction may promote apoptotic pathways and modulate cell cycle regulators [13]. Tukey's post-hoc analysis indicates that the MCF-7 and SKOV-3 cell lines had significant differences between the intermediate (75 $\mu\text{g/mL}$) and highest (100 $\mu\text{g/mL}$) doses of aloe vera polysaccharide-rich fraction. However, HL-60 showed no significant growth response above either concentration of aloe vera polysaccharide-rich fraction. This finding suggests that either receptor-mediated responses have reached a saturation point, or that activation of intracellular signaling cascades is at maximum levels; a common finding for polysaccharide-based therapies. Moreover, differences in sensitivities among cell lines may also be affected by the level of expression of membrane receptors, intracellular signaling pathways, and cellular metabolic rates. Most of the *in vitro* studies conducted reported notable effects (as high as 100 $\mu\text{g/mL}$), however, there is no evidence to support that such concentrations could exist *in vivo* due to the combined absorption/distribution/metabolism/excretion issues related to aloe vera polysaccharide-rich fraction itself, thus pharmacokinetic and toxicological research must be conducted in order to determine the clinical relevancies of these results.

Recent developments in research on biomaterials indicate that Aloe vera polysaccharide-rich fraction has the potential to be an effective constituent in applications associated with tissue engineering and drug delivery systems. Aloe vera polysaccharide-rich fraction stockpiled to create hydrogels, scaffolds, and nano-carriers for use in tissue engineering and cancer treatment has shown improved mechanical stability, regulated release, and greater cell compatibility. Thus, these forms of delivery systems show great potential for use in

regenerative medicine and targeted therapy for cancer. Aloe vera polysaccharide-rich fraction incorporated into modernized delivery systems may be able to increase the therapeutic effect of aloe vera polysaccharide-rich fraction by increasing its bioavailability and by keeping concentrations at the treatment site for a longer time duration. These methodologies may be important avenues for translational future uses. Aloe vera polysaccharide-rich fraction is thought to exert its antitumor effects through activation of extrinsic and intrinsic pathways leading to apoptosis. Studies using Aloe vera polysaccharide-rich fraction have found that the substance will upregulate pro-apoptotic proteins like Bax while downregulating anti-apoptotic proteins like Bcl-2, resulting in inducing programmed cell death [13]. In addition, inhibiting angiogenesis via suppression of VEGF also decreases both tumor growth and metastasis potential. The results above demonstrate a statistically significant decrease in cell proliferation with concomitant statistically significant increase in cell apoptosis, which supports the proposed mechanism for aloe vera polysaccharide-rich fraction [18].

Therapeutic effects that were observed for the first time in this study were corroborated by previous studies showing the immunomodulatory and regenerative actions of aloe vera polysaccharide-rich fraction. For instance, aloe vera polysaccharide-rich fraction has been shown to enhance the healing of wounds by modulating inflammatory cytokine levels as well as accelerating fibroblast migration [3]. Additionally, its anticancer potential is shown within many cancer models, including cervical cancer, where it induced apoptosis [3]. However, this research extends previously published work by combining measured clinical wound healing outcomes with evaluated anticancer effects within one experimental model and allows for a more complete understanding of aloe vera polysaccharide-rich fraction's potential versatility as a therapeutic agent [10]. The variable sensitivity observed by the tested cancer cell lines illustrates the importance of tumor heterogeneity on response to treatment. Susceptibility of cancer cells to polysaccharide-based agents, such as aloe vera polysaccharide-rich fraction, may result from variations in receptor expression on the cell membrane, manipulations of intracellular signaling pathways, and differences in metabolic activity. The plateau effect seen at the higher doses in some cell lines may result from receptor saturation or maximal activation of apoptotic pathways. The understanding of dose-response relationships is crucial for establishing optimal dosing strategies for therapies and is useful to assist future *in vivo* studies and clinical use of therapies.

The study's integration of both clinical and experimental approaches to examine wound healing and response to cancer cell lines simultaneously is a significant strength of this research. Including different types of wounds and cancer cell lines will increase the likelihood that findings are applicable to other wound types [4]. By utilizing ANOVA and Tukey's post hoc analyses, statistical significance has been shown to be reliable and valid for the effects observed. Limitations of this research, which must be taken into consideration, include the need for additional cancer studies in the laboratory setting and through long-term follow-up clinical evaluation; there was only short-term follow-up available for this study, which limits our ability to assess recurrence and wound healing success over time. Molecular signal pathways were not quantified; therefore, it is not possible to infer how the biological effects of this study occurred based on the results obtained. Further

research, including studies using animal models of cancer, molecular analysis of signal pathways, and extended long-term clinical follow-up, will lend further validity to these findings [20-22].

The growing attraction of acquiring natural bioactive substances with multiple modes of action arises from their capacity to simplify overall treatment and reduce any negative side effects associated with the use of current approaches. The documented combination of tissue formation, ability to inhibit germs, effect on the immune system, as well as anticancer effect for aloe vera polysaccharide-rich fraction in this investigation suggests the need for further research not only into the use of aloe vera polysaccharide-rich fraction as an individual treatment but also as an adjunct treatment to other existing methods of care. Sadly, further definitive clinical trials utilizing larger sample sizes and additional mechanistic molecular investigations are required to assess efficacy, safety, as well as optimal therapeutic formulation of aloe vera polysaccharide-rich fraction prior to becoming commonplace in clinical practice [23].

The impact of these findings generates an extraordinary opportunity for patients. For example, aloe vera polysaccharide-rich fraction's proposed ability to stimulate the healing process and lower the chance of developing a secondary infection may lead to reduced dependency on antibiotic use and provide a solution for public health challenges related to drug-resistant microorganisms. Aloe vera polysaccharide-rich fraction's source from nature, its low toxicity, and its ability to stimulate cellular death point toward consideration of use as an adjunct treatment to traditional forms of oncology treatments, therefore improving outcomes while decreasing adverse reactions resulting from these treatments [10]. Additionally, the potential creation of advanced delivery mechanisms (e.g., aloe vera polysaccharide-rich fraction-loaded nanoparticles or biomaterial scaffolds) could also increase the bioavailability of, and/or enhance the overall effectiveness of, aloe vera polysaccharide-rich fraction as a therapeutic agent [24].

Collagen deposition and angiogenesis were determined through semi-quantitative histological scores based on H&E-stained sections. They were not evaluated using techniques that can be quantitatively measured, such as Masson's Trichrome staining for collagen or anti-CD31 immunohistochemistry for vascular endothelium. Future studies should utilize one or both of these more accurate methods to assess quantitatively the amount of collagen deposited and the amount of new blood vessels formed spontaneously in tissue undergoing regeneration.

Aloe vera polysaccharide-rich fraction was not identified or quantified by any characterisation methods during this study, which limits our understanding of the physicochemical properties (such as purity, molecular weight, degree of acetylation, and endotoxins) of aloe vera polysaccharide-rich fraction. These aspects are known to influence their biological activity. Future studies will need to include an extensive array of analytical techniques, including but not limited to chromatographic methods and spectroscopic analysis of aloe vera polysaccharide-rich fraction, so that data can be reproduced and standardised.

5. CONCLUSION

The findings of this research indicate that aloe vera

polysaccharide-rich fraction has the potential to be a new treatment option for promoting wound healing and inhibiting cancer cell proliferation. Aloe vera polysaccharide-rich fraction was shown to promote tissue regeneration, decrease the incidence of infection, stimulate apoptosis, and be associated with faster healing. Furthermore, the novelty of this research is the integrative assessment of aloe vera-derived polysaccharide having both clinical wound healing and in vitro cancer growth inhibition, in contrast to the limited evaluations of it in past literature. Additionally, the side-by-side comparisons with standard treatments and a chemotherapeutic agent highlight that the polysaccharide-rich fraction from aloe vera has translational significance. Ultimately, these findings suggest that the crude-derived aloe vera polysaccharide has potential as an innovative treatment approach that addresses issues within regenerative medicine and oncology and provides an avenue for continued mechanistic studies and clinical trial evaluation prior to implementation in patient care.

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