**RESEARCH ARTICLE**

**Aloe vera Inhibits Proliferation of Human Breast and Cervical Cancer Cells and Acts Synergistically with Cisplatin**

Arif Hussain¹*, Chhavi Sharma¹, Saniyah Khan¹, Kruti Shah¹, Shafiul Haque²

**Abstract**

Many of the anti-cancer agents currently used have an origin in natural sources including plants. *Aloe vera* is one such plant being studied extensively for its diverse health benefits, including cancer prevention. In this study, the cytotoxic potential of *Aloe vera* crude extract (ACE) alone or in combination with cisplatin in human breast (MCF-7) and cervical (HeLa) cancer cells was studied by cell viability assay, nuclear morphological examination and cell cycle analysis. Effects were correlated with modulation of expression of genes involved in cell cycle regulation, apoptosis and drug metabolism by RT-PCR. Exposure of cells to ACE resulted in considerable loss of cell viability in a dose- and time-dependent fashion, which was found to be mediated by through the apoptotic pathway as evidenced by changes in the nuclear morphology and the distribution of cells in the different phases of the cell cycle. Interestingly, ACE did not have any significant cytotoxicity towards normal cells, thus placing it in the category of safe chemopreventive agent. Further, the effects were correlated with the downregulation of cyclin D1, CYP 1A1, CYP 1A2 and increased expression of bax and p21 in MCF-7 and HeLa cells. In addition, low dose combination of ACE and cisplatin showed a combination index less than 1, indicating synergistic growth inhibition compared to the agents applied individually. In conclusion, these results signify that *Aloe vera* may be an effective anti-neoplastic agent to inhibit cancer cell growth and increase the therapeutic efficacy of conventional drugs like cisplatin. Thus promoting the development of plant-derived therapeutic agents appears warranted for novel cancer treatment strategies.

**Keywords:** *Aloe vera* - bax - cisplatin - cyclin D1 - cytochrome P450 mono-oxygenases - synergistic - p21

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**Introduction**

*Aloe vera* (*Aloe barbadensis*) is one of the herbal remedies with a longstanding history for its curative and therapeutic properties for various ailments. Till date more than 75 active components with medicinal value have been identified in *Aloe vera* and have been suggested to possess synergistic action in alleviating the diseased conditions (Scalbert and Williamson, 2000; Hamman, 2008; Nejatzadeh-Barandozi, 2013). Its various biological activities include improving the bioavailability of co-administered vitamins and absorption of poorly absorbable drugs, and also possess purgative, anti-microbial, immunostimulatory, wound healing, anti-inflammatory, anti-tumor, and anti-diabetic activities (Azam et al., 2003; Nejatzadeh-Barandozi, 2013).

Accumulating scientific evidence suggests that *Aloe vera* possesses remarkable preventive and therapeutic potential against various cancers (Niciforovic et al., 2007; Joseph and Raj, 2010). The bioactive constituents of *Aloe vera* with chemopreventive potential such as lectin, aloin, barbaloin, aloe-emodin and aloesin have shown to possess immune-potentiating, antimitogenic, anti-proliferative, apoptosis-inducing, anti-oxidant and anti-metastatic potential (Choi and Chung, 2003; Akev et al., 2007; Niciforovic et al., 2007; Joseph and Raj, 2010). The aforementioned activities of *Aloe vera* (or its constituents) are mediated via targeting various effector molecules such as ER-α, STAT3 protein, STAT3-regulated anti-apoptotic (Bcl-xL), MMP-2, urokinase plasminogen activator (u-PA), VEGF receptor (VEGFR) 2, c-Myc, and VEGF (Chen et al., 2010; Huang et al., 2013; Pan et al., 2013). Interestingly, various studies have shown that the prophylactic use of *Aloe vera* can reduce the intensity of radiation-induced inflammation (Ahmadi, 2012; Haddad et al., 2013). Moreover, the combined use of anticancer agents, especially at low concentrations, and aloes constituents potentiated the growth inhibitory effect of the former on cancer cells (Fenig et al., 2004; Tabolacci et al., 2013).

*Aloe vera*, due to its multifaceted approach towards targeting cancer cells and less undesirable side effects, may prove to be an agent of choice for treatment of human carcinomas. Therefore, the present study was designed to evaluate the potential of favorable interactions in the novel combination of cisplatin with *Aloe vera* crude extract.

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Anti-Proliferative Effects of *Aloe vera* against Human Cervical and Breast Cancer Cells

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leaves were

inhibitory concentration) values were calculated from the

proportional to the number of viable cells. The IC50 (50%

×100, considering that the colorimetric signal is directly

the drug-treated sample/OD of the non-treated sample)

as percent cell viability and was calculated as (OD of

The effect of ACE on growth inhibition was assessed

incubator, MTT (5 mg/ml in PBS) was added to each

C2=5 µM) for 24 h in 96-well microtiter plates. After

of ACE alone for 24 and 48 h or a combination of ACE

complete culture medium containing 1-60% concentrations

use. Further dilutions were made from the stock in

μm filters. Filtrate was considered to be 100% extract

store in complete medium to required concentrations between

1-60% for the treatment of MCF-7 cells, HeLa cells and

Cytometry (Beckman Coulter Flow Cytometer FC500,

mg/ml of RNase A. The cells were analyzed using flow
cytometry (Beckman Coulter KALUZA 1.1 analysis software).
The data was analyzed using the Beckman Coulter KALUZA 1.1 analysis software.

Calculation of Combination effects of cisplatin and ACE
Combination effects were calculated and expressed as a

combination index (CI) as previously described (Hussain et al., 2012). CI analysis provides qualitative information

on the nature of drug interaction, and CI, a numerical

value, was calculated according to the following equation:

\[
CI = \frac{C_{A,x} + C_{B,x}}{IC_{A,y} + IC_{B,y}}
\]

Where, CA,x and CB,x are, respectively, the concentrations of drugs A and B used in combination to achieve x% drug effect. ICx,A and ICx,B are the concentrations for single agents to achieve the same effect. A CI value <1, =1, or >1 represents, respectively, synergy, additivity, and antagonism of cisplatin and ACE, respectively.

Detection of apoptosis in MCF-7 and HeLa cells after treatment with ACE

Microscopic examination: morphological changes in MCF-7 and HeLa cells were observed on treatment with ACE at different concentrations (40, 50 and 60%) for 24 and 48 h using a normal inverted microscope (Labomed, USA). The untreated cells were used as negative control.

Nuclear morphological studies
ACE-induced nuclear morphological changes in MCF-7 and HeLa cells were analyzed using propidium iodide staining. Briefly, ~10^6 cells/ml were seeded on glass coverslips and incubated overnight in complete medium at 37°C. Further, cells were treated with ACE at its IC50 for a series of time periods (0, 6 and 24 h). At the end of the desired time interval, cells were fixed in a mixture of acetone: methanol (1:1) at -20°C for 10 min, washed with 1X PBS (pH 7.4) twice and stained with propidium iodide (10 mg/ml in PBS) for 30 s in dark at room temperature. The coverslips were thoroughly washed with PBS and placed upturned onto a glass slide with mounting media (DPX). Slides were viewed at 515 nm under the Progress Fluorescent Microscope (Olympus, USA). The images were captured at 40X magnification.

Quantification of apoptotic cells by flow cytometry
ACE-induced apoptosis in MCF-7 and HeLa cells was determined by flow cytometric analysis as described earlier (Hussain et al., 2012). After treatment of synchronous cultures of MCF-7 and HeLa cells with ACE at their respective IC50 for 0 and 24 h, both adherent and floating cells were harvested, washed with phosphate buffered saline (PBS, pH 7.2) and fixed with ice-cold absolute ethanol at -20°C overnight. Cells were then washed with PBS prior to re-suspending in a buffer containing PI (50 mg/ml), 0.1% sodium citrate, 0.1% Triton X-100 and 100 mg/ml of RNase A. The cells were analyzed using flow cytometry (Beckman Coulter Flow Cytometer FC500, CXP Version 2.2). The data was analyzed using the Beckman Coulter KALUZA 1.1 analysis software.
Expression analysis of various genes targeted by ACE

Reverse transcription-PCR was used to detect the expression of bax, cyclin D1, p21, CYP 1A1, and CYP 1A2 and in response to treatment with ACE at IC50 for varying time points (0, 6 and 24 h). Total RNA extraction from untreated and ACE-treated MCF-7 and HeLa cells was carried out as per the manufacturer’s instructions (GenElute Mammalian Genomic Total RNA Kit, Sigma, USA) at various time intervals. Further, total RNA was subjected to first strand synthesis as per manufacturer’s protocol (ProtoScript M-MuLV Taq RT-PCR Kit, New England Biolabs, USA) followed by PCR using gene-specific primers (Hussain et al., 2012; Tatemichi et al., 1999; Alao et al., 2004; Wang et al., 2005; Nishimura et al., 2007). β-actin was taken as an internal control. The PCR cycle was as follows: initial denaturation at 95°C for 5 min, followed by 35 amplification cycles (denaturation at 94°C for 30 s, annealing at 55°C for β-actin and p21, 56°C for Bax, CYP 1A1 and CYP 1A2 and 54°C for cyclin D1 for 30 s, and extension at 72°C for 45 s), with final extension at 72°C for 7 min. Amplified products were visualized on a 2% agarose gel containing ethidium bromide.

Statistical analysis

All data are expressed as means ±SD of at least 3 experiments. Fisher’s exact test was adopted for statistical evaluation of the results. Significant differences were established at P < 0.05.

Results

ACE shows selective cytotoxic effects towards MCF-7 and HeLa cells

The growth inhibitory effects of different concentrations of ACE on MCF-7 cells, HeLa cells and lymphocytes were assessed by the MTT assay. MCF-7 and HeLa cells treated with increasing concentrations of ACE ranging from 1%-60% for 24 and 48 h showed a dose and time-dependent increase in cell death (Figure 1 A and B). The IC50 was found to be at 60% after 24 h treatment with ACE in both the cell lines (Figure 1 A and B).

In order to determine whether ACE shows selective toxicity, lymphocytes were treated with similar doses (1%-60%) of ACE. No significant cytotoxic effect on cell viability was observed after the treatment with ACE for 24 h at the above mentioned concentrations (Figure 1C), thereby supporting the safe toxic profile of ACE.

ACE induces cell death via apoptosis in MCF-7 & HeLa cells

Morphological examinations of MCF-7 & HeLa Cells: Morphological characteristics of ACE treated MCF-7 (40%, 50% and 60%) & HeLa cells (30%, 40% and 60%) were visualized by using inverted microscope for 24 and 48 h respectively. In comparison to untreated, ACE treated cells showed typical features of cell death at the morphological level such as rounding off of cells, cell shrinkage and detachment from the substrate which accumulated in a dose and time-dependent manner, thus indicating that ACE induces cell death by apoptosis in these cells (Figure 2 A and B).

Aloe vera induced nuclear morphological changes in MCF-7 & HeLa Cells

ACE induced nuclear morphological changes characteristic of typical cell undergoing apoptosis were studied in MCF-7 and HeLa cells at their respective IC50 at various time-points. Untreated MCF-7 and HeLa cells appeared uniform in chromatin density with an intact nucleus (yellow arrows). However, on treatment of MCF-7 cells with ACE for 6 and 24 h resulted in

Figure 1. Differential Cytotoxicity of ACE on MCF-7 and HeLa Cells. (A & B) MCF-7 and HeLa cells treated with ACE at varying concentrations (1-60 %) results in dose and time dependent growth inhibition after 24 and 48 h treatment whereas treatment of lymphocytes with ACE at similar concentrations for 24 h was found to be minimally cytotoxic (C). Values are means +SD of three independent experiments. Each value with ACE treatment differs from the control value (p<0.05)
apoptosis-associated nuclear morphological changes like chromatin condensation and fragmentation (blue arrows) along with appearance of apoptotic bodies (pink arrows) (Figure 3A). Also, HeLa cells treated with ACE showed similar changes in nuclear morphology including blebbing (green arrow) (Figure 3B). With an increase in duration of ACE exposure, there was a cumulative accrual of the said features consistent with apoptosis in both the cell lines (Figure 3 A and B).

**Cell cycle analysis of MCF-7 & HeLa cells**

Cell cycle distribution of MCF-7 and HeLa cells was determined by flow cytometry after the treatment of these cells with ACE at their respective EC50 concentrations for 24 h. Cell cycle analysis demonstrated that 60% ACE treated MCF-7 & HeLa show increased number of cells in sub G0/G1 phase with an associated decrease in the number of cells in S-phase and G2-phase of the cell cycle when compared to the untreated control. The untreated cells (0 h) showed appropriate distribution of cells in the different phases of cell cycle (Figure 4); while in case of ACE treated cells, there was a significant time-dependent increase in the number of cells in the sub-G0/G1 phase of the cell cycle. This confirms that ACE induces the cell death via apoptosis.

ACE treatment significantly modulates the expression of cyclin D1, bax, CYP 1A1, CYP 1A2 and p21

With the target of determining the effector genes involved in ACE mediated cellular responses in MCF-7 and HeLa cells, the expression of cyclin D1, bax, CYP 1A1, CYP 1A2 and p21 were analyzed before and after treatment with ACE at 6 and 24 h respectively. β-actin was used as an internal control for comparison of samples.

The aberrant expression of cyclin D1, a key player...
in the progression of the cells from G1 to S phase, has been associated with the deregulated cell cycle control in many human cancers. It was found to be over-expressed in both the untreated MCF-7 and HeLa cells (Figure 5 A and B). As shown in Figure 5 A and B, a significant, time-dependent inhibitory effect of ACE was observed on the expression of cyclin D1 in both the cell lines compared to untreated cells.

Bax, the first identified pro-apoptotic member of the Bcl-2 protein family, plays a major role in inducing apoptosis. In both untreated MCF-7 and HeLa cells, the expression of bax was found to be low which significantly increased in ACE treated MCF-7 and HeLa cells in a time-dependent manner in comparison to the untreated cells (Figure 5 A and B).

Progression through the cell cycle is regulated through activation and inactivation of cyclin-dependent kinase (Cdk)s that form sequential complexes with cyclins A-E during the different phases G1, S, G2, and M of the cell cycle. The activity of Cdk s is controlled by binding of Cdk inhibitors (CKIs) to Cdk-cyclin complexes. One such CKIs is p21, preferentially interact with Cdk2- and Cdk4-cyclin complexes and block their interaction with cyclin D and thus functions as a regulator of cell cycle progression at G1. In both untreated MCF-7 and HeLa cells, the expression of p21 was found to be low which significantly increased in ACE treated MCF-7 and HeLa cells in a time-dependent manner in comparison to the untreated cells (Figure 5 A and B).

CYP 1A1 and CYP 1A2 are the members of the cytochrome P450 enzyme superfamily, which act as drug metabolizing enzymes and leads to the accumulation reactive oxygen species forming ultimate carcinogens that are toxic to the cell and thereby leading to tumorigenesis. Expression of CYP1A1 and CYP2A2 was detected in untreated MCF-7 and HeLa cells (Figure 5 A and B). However, in comparison to the untreated cells, ACE treatment resulted in significant downregulation of these genes in both the cancer cell lines (Figure 5 A and B).

**ACE and cisplatin infusion act synergistically to inhibit the growth of MCF-7 and HeLa cells**

Since currently available chemotherapeutic drugs are associated with non-specific cytotoxicity towards normal cells as well as development of chemo-resistance, a combinational treatment with the natural dietary agents may serve as a better approach towards cancer treatment. In the present study, a combination of ACE and cisplatin was evaluated to potentiate the chemotherapeutic index of cisplatin.

The effect of concurrent treatment of MCF-7 and HeLa cells with different sub-lethal concentrations of cisplatin and ACE for 24 h was analyzed by cell viability assay. It was observed that 1μM of cisplatin (C1) used in combination with 30% (A1) and 40% (A2) ACE resulted in a significant decrease in cell viability (81 and 71% respectively) of MCF-7 cells as compared to either of the compounds alone (98.2% for C1, 92 and 90% for A1 and A2) (Figure 6 A). In HeLa cells, the combination of 1μM of cisplatin (C1) with 30% (A1) and 40% (A2) ACE resulted in 75 and 60% (for C1A1 and C1A2) significant decrease in cell viability while individual drugs decreased the cell viability by 84% for C1 and 88 and 82% with A1 and A2 respectively (Figure 6 B). Also, treatment of MCF-7 and HeLa cells with 5 μM of cisplatin (C2) combined with A1 and A2 respectively resulted in synergistic decrease in cell viability (78 and 70% for MCF-7; 61 and 55% for HeLa) as compared to individual doses (C2 =92.5% and 81% for MCF-7 and HeLa) (Figure 6 A and B). Combined indices (CI) were calculated and CI less than 1 were found to be less than 1 indicating a synergistic interaction between the two drugs at the doses used for both MCF-7 and HeLa cells.

**Discussion**

The recent goal of cancer treatment is to reverse, suppress, or prevent carcinogenic progression through
the use of natural dietary agents (Oyagbemi et al., 2009; Kundu and Chun, 2014; Thumvijit et al., 2014). With this perspective, the present study was designed to utilize the anti-carcinogenic potential of Aloe vera, one of the oldest medicinal plants used extensively for its health benefits, including cancer prevention. Due to its tumor-inhibitory effect in vitro and in vivo and its ability to minimize the various side effects caused by conventional therapy including chemotherapy, Aloe vera has gained significant attention for providing new prospects for the development of novel therapeutics. The most important substances that make up the aloe are cinnamic acid, barbalonia, resistantol oil, calcium and aloin (Kuo et al., 2002; Esmat et al., 2005; Guo et al., 2008; Niciforovic et al., 2007; Chou and Liang, 2009).

In the present study it was observed that treatment of MCF-7 and HeLa cells with ACE at varying doses 1%-60% for 24 and 48 h decreased the viability of these cells in a dose and time dependent manner (Figure 1 A and B). On the contrary, there was no significant decrease in the viability of normal lymphocytes when treated with ACE at similar doses (Figure 1 C). These results are in accordance with previous studies which demonstrated that Aloe vera extract or its components significantly reduced proliferation of cancer cells in vitro and in vivo while being less toxic towards the normal cells (Kuo et al., 2002; Shimp et al., 2003; Shieh et al., 2004; Guo et al., 2008; Xiao and Guo, 2009; Chandu et al., 2012).

Since necrosis is often associated with an intense inflammatory response to surrounding tissue, apoptosis is the desirable mode of cell death by therapeutic drugs used in cancer treatment. Considering this fact, the cellular and nuclear morphological changes induced by ACE treatment in MCF-7 and HeLa cells were analyzed (Figure 2 and 3). It was observed that treatment of MCF-7 and HeLa cells with ACE resulted in significant changes in cellular morphology in a time and dose dependent manner characterized with rounding off of the cells, cell shrinkage and detachment from the matrix (Figure 2 A and B). At nuclear level, chromatin condensation and fragmentation along with appearance of apoptotic bodies intensified with increasing time of exposure of ACE (at EC50 doses) in both the cell lines in comparison to the untreated cells in which these changes were lacking indicating that cell death induced by AWE is through apoptotic pathway (Figure 3 A and B). Cell cycle analysis revealed a significantly increased proportion of cells in the sub-G0/G1 phase on treatment with ACE at EC50 dose while the untreated cells showed appropriate distribution of cells in the different phases of cell cycle (Figure 4). This confirms that ACE induces the cell death via apoptosis. Various other studies have also confirmed that the different constituents of Aloe vera induce cell cycle arrest and apoptosis in cancer cells (Jeon et al., 2012; Suboj et al., 2012; Huang et al., 2013; Ismail et al., 2013; Pan et al., 2013).

These anti-proliferative and apoptosis-inducing effects of Aloe vera were correlated with the expression of genes involved in these mechanisms such as bax, p21 and cyclin D1. Bax, a pro-apoptotic member of the bcl-2 family, its downregulation has been linked with evasion of apoptosis in cancer cells and is involved in mediating the response to a wide range of cytotoxic stimuli (Kagawa et al., 2000; Cuddeback et al., 2001). It was found that treatment of MCF-7 and HeLa cells with ACE resulted in increased expression of bax gene in a time dependent manner in comparison to untreated cells which showed very low expression of bax gene in both the cell lines (Figure 5). Thus, the downregulation of bax in these cells may be responsible in part for the apoptosis-inducing effects of Aloe vera. Various chemopreventive agents including Aloe vera constituents have been shown to induce apoptosis via up regulation of bax (Kuo et al., 2002; Chiu et al., 2009; Lin et al., 2010; Tomasin and Gomes-Marcondes, 2011; Chung et al., 2013; Li et al., 2013).

The anti-proliferative activity induced by Aloe vera in MCF-7 and HeLa cells was found to be linked with the expression of cyclin D1 and p21 (Figure 5). Cyclin D1, a proto-oncogene, is a key regulator of cell cycle and its aberrant expression has been associated with development and progression of several cancers (Alao, 2007; Musgrove et al., 2011; Stone et al., 2012). It can function as a transcriptional co-regulator in conjunction with its binding partners including p21, a cyclin-dependent kinase (cdk) inhibitor, which induces cell cycle arrest and is found to contribute to cancer preventive effect of certain dietary agents such as aloe-emodin, ellagic acid and zinc (Kuo et al., 2002; Chung et al., 2013; Yang et al., 2013). In the present study it was observed that ACE treated MCF-7 and HeLa cells showed time-dependent decrease in the expression of cyclin D1 in comparison to the untreated cells which showed high expression of this gene (Figure 5). Further, the untreated cells showed low expression of p21 which was found to increase in a time-dependent manner when treated with ACE (Figure 5).

Another important gene family member, CYP 1A1 and CYP 1A2 which are key players in phase I-dependent metabolism of drugs and other xenobiotics that often exert toxicity or carcinogenicity and thus modulation of their expression may be significant determinant of cancer therapy (Androutsopoulos et al., 2009; Kavitha et al., 2013; Kim et al., 2013; Jeena et al., 2014). Our results showed that ACE treatment of MCF-7 and HeLa cells induced substantial loss in the expression of CYP1A1 and CYP1A2 genes as the duration of treatment increased as compared to the untreated HeLa which had a higher expression of these genes (Figure 5). Increases in their expression have been linked to a higher risk of malignancies (Androutsopoulos et al., 2009). Chemopreventive agents including aloe constituents have been previously shown to modulate the expression of CYP genes including CYP1A1 and CYP1A2 (Tang et al., 2009; Kavitha et al., 2013; Kim et al., 2013; Jeena et al., 2014).

The emergence of resistant cells to chemotherapeutic agents, referred to as chemoresistance is one of the major problems of conventional cancer therapy necessitating the need to develop newer approaches for cancer prevention and treatment (Mijatovic et al., 2005; Sasabe et al., 2007). Therefore the combinatorial chemopreventive approach was carried out to hit more than one molecular target with the simultaneous treatment of Aloe vera and a chemotherapeutic drug, cisplatin to enhance the therapeutic index at low-dose combinations. It was found...
that cisplatin had nonspecific cytotoxicity towards both the cancer cell lines (MCF-7 and HeLa cells) along with the normal cells (data not shown). It was observed that sub-lethal doses of ACE and cisplatin in various combinations (C1A1, C1A2, C2A1 and C2A2 for MCF-7 and HeLa cells) showed significantly increased growth inhibition of these cells in comparison to the individual doses as reflected in the CI less than 1 indicating a synergistic interaction between these drugs at the doses used (Figure 6). These results are in line with other studies which showed that a synergistic effect of concurrent use of chemopreventive agents with other cancer therapeutic agents (Fenig et al., 2004; Mijatovic et al., 2005; Zeng et al., 2008; Lissoni et al., 2009; Tabolacci et al., 2013). Interestingly, a previous study correlated increased expression of bax with chemosensitivity of breast cancer cells towards chemotherapy (Sakakura et al., 1997). As discussed above, the overexpression of bax, induced by Aloe vera may be linked with its chemopotentiating effect in these cells.

In conclusion Aloe vera alone or its simultaneous use with cisplatin exhibits anti-neoplastic effects in breast and cervical cancers by inducing apoptosis and modulation of expression of effector molecules. Thereby, this study provides a rationale for future experiments that will shed new lights on the underlying mechanisms or potential targets of Aloe vera for its better utilization as anticancer agents.

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