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Short Communication

Clematis erecta Extract Inhibits Migration, Invasion and Induce Apoptosis in Breast Cancer Cells

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ABSTRACT

Migration and invasion of breast cancer cells to distant parts of the body is a hallmark of the disease. The disease becomes difficult to manage and treat with an increased invasion by cancer cells. Some drugs kill the cancer cells but causes general cytotoxicity but no drugs are known to inhibit the invasive potential of cancer cells. Previously, the natural components have been proven to exhibit anticancer and invasive potential. *Clematis erecta* L. (Ranunculaceae) Leaves infusion is traditionally used to treat syphilitic, cancerous and other foul ulcers. Moreover, methanolic extract and and ethyl acetate fraction exhibited significant analgesic and anti-inflammatory activity. The scientific literature still lacks support for the anticancer potential of *C. erecta***.** Therefore, it was envisaged to investigate the anticancer activities of *C. erecta* aerial parts on breast cancer cells. The results obtained suggest that *C. erecta* has anti-invasive potential on triple-negative human breast cancer cells (MDA-MB-231). Three different extracts (chloroform, methanol and water) of aerial parts of *C. erecta* were evaluated for their effect on the growth and migration of human breast cancer cells MDA-MB-231. Interestingly, aqueous extract inhibits cell growth by more than 50% and also inhibits migration and invasion by 40 and 50%, respectively. DNA fragmentation of extract treated cells further suggested that *C. erecta* has the potential to kill cancer cells.

INTRODUCTION

Cancer is a multifactorial and fatal disease; it is one of the biggest healthcare issue and is the leading cause of death.[1] Despite advanced scientific techniques, early diagnosis, treatment and preventive measures, the disease remains a challenge to cure.[2-4] The uncontrolled division of cancer cells, because of genetic instabilities and other cell alterations, leads to the transformation of normal cells into malignant ones.[4] Among all cancers, breast cancer is most commonly diagnosed among women worldwide.[5] The ability of breast cancer cells to invade and metastasize challenges the diagnosis and treatment of the disease.[6,7] Cancer cells, because of mutations in the genome, develop the ability to detach from the primary tumor site and degrade the surrounding extracellular matrix (ECM), and cells invade the stromal tissues.[8,9] These cells then intravasate and transit through lymph or vascular channels and extravasate in distant tissues, initiate homing themselves at the new site.[10-12]

Metastasis is a complex process involving the whole cell machinery and the inhibition of metastasis has the potential to reduce the disease's mortality. The scientific search is on to explore a variety of drugs and compounds to inhibit metastasis by blocking the elements inherent to the adhesion, migration, and invasion of cancer cells.[6,13-15] It is now increasingly accepted that the invasion and metastatic process provides an abundant novel target for the development of newer drugs that may act as inhibitions by controlling invasion and metastasis.[16]

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Phytochemicals from the human diet has been shown to be chemopreventive compounds and several studies have also suggested the role of bioactive natural components with anticancer potential.[17-19] Numerous medicinal drugs have been developed from natural sources comprising of anticancer components.[20, 21] Recently, scientific studies have focused on these compounds' bioactive components and cell death-inducing mechanisms.[22-24] Therefore, natural phytochemicals seem viable in preventing, delaying or curing cancer.

Recently, the anticancer effects of genus *Clematis* have attracted much attention.[25-28] Therefore, for our current study we selected *Clematis erecta* L. *C. erecta* is commonly known as upright virgin's bower and belongs to family Ranunculaceae. Infusion of the leaves of *C. erecta* is traditionally used in the treatment of syphilitic, cancerous and other foul ulcers.[29,30] The methanol extract and ethyl acetate fraction exhibited significant analgesic and anti-inflammatory activity and the aqueous extract of the plant exhibited bactericidal and fungicidal effects.[30,31] Studies on the anticancer potential of *C. erecta* are lacking in the literature. Therefore, it was envisaged to investigate anticancer activities of *C. erecta* aerial parts. Different extracts of the plants were evaluated for *in-vitro* anticancer study on selected cancer cell line, and thus the anticancer potential of the plant extracts were determined in the induction of apoptosis and inhibition of migratory and invasive ability.

Material and Methods

Collection and Identification of Plant Material

The aerial parts of *C. erecta* were purchased from KR Indo German, Kurukshetra in September 2018. The identity of plant has been confirmed in Pharmacognosy laboratory of DPSDR, Punjabi University Patiala by comparing its macroscopic and microscopic characters with authentic sample of *C. erecta* already identified from Raw Material Herbarium and Museum, National Institute of Science Communication and Information Resources, New Delhi, India (Ref. No. NISCAIR/RHMD/ Consult/-2008-09/1192/224, dated 09/04/2009).

Solvents

Methanol (S.D. Fine Chemicals, Mumbai, India), *n*-hexane, and chloroform (E Merck, Delhi, India), of LR grade, were used for the preparation of various crude extracts of *C. erecta* leaves.

Preparation of Extracts

C. erecta aerial parts were dried under sunlight and powdered in a grinder. Dried powdered plant material (1.4 kg) was extracted successively by refluxation process using solvents (3 X 4 L each) in increasing order of polarity viz., n-hexane, chloroform and methanol on a water bath maintained at temperature of 80°C. Solvents from crude extracts were recovered using a distillation assembly to get n-hexane extract (HE), chloroform extract (CE), methanol extract (ME). The marc left was then extracted with distilled water (4L) by decoction process on a hot plate. The water/aqueous extract (WE) was dried in hot air oven at 70 to 80°C. Yields of HE, CE, ME and WE were found to be 4.50, 2.32, 4.07 and 2.14% w/w, respectively.[32]

Cell Lines and Cell Culture

Breast cancer cell lines (MDA-MB-231) were purchased from National Centre for Cell Science, Pune, India. Cell lines were cultured in DMEM containing 10% FBS (GIBCO), 100 IU of penicillin G/mL and 100 µg of streptomycin/mL at 37°C in humidified atmosphere containing 5% CO_2.[33]

Cytotoxicity Assay

Cell viability assay was performed by intensity-based measurement of blue formazan metabolized by only live cells from colorless 3-(4,5- imethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) by the action of mitochondrial dehydrogenase enzyme.[33] Cancer cells MDA-MB-231 were seeded (5×10^4) in a 96 well microtiter plate for 24 hour at 37°C and then treated with different concentrations (0, 20, 40, 80, 100, 200 µg/mL) (triplicate of each) of the extracts for 24 hours. After the treatment, the media containing drug was discarded and 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma Aldrich) was added to each well (10 µL/well) at a concentration of 5 mg/mL diluted in 1X PBS. The plate was incubated in the dark or wrapped with aluminum foil at 37°C for 2 to 3 hours, after which 200 µL DMSO was added to each well, and the plate were kept on a rocker for 30 to 60 minutes. The formazan crystals were solubilized in DMSO. After incubation, the absorbance was measured at 570 nm for each well using a microplate reader. The data is presented as percent post-treatment recovery (%live cells), whereas the absorbance from untreated control cells is defined as 100% live cells. The general formula used for estimating the percentage of viable cells is as below.

%Cell viability = (absorbance of treated cells/absorbance of untreated cells) × 100

The IC_{50} concentrations were interpolated from the graph by plotting % cell viability on Y-axis against the concentration on X-axis.

Invasion and Migration assay

MDA-MB 231 cells were treated with 200 µg of the extract. 50 µL geltrex (In-Vitrogen) was applied to 8 µm pore size polycarbonate membrane filters. After 24 hours of treatment, the surviving cells were trypsinized and seeded at upper part of the Boyden chamber (Sigma) containing geltrex at $5x10^3$ cells/well in serum-free medium and then incubated at 37°C for 24 hours. The bottom chamber contained a standard medium with 10% FBS. After

24 hours,cells that had invaded through the geltrex to the lower surface of the membrane filters were fixed with 4% paraformaldehyde, air-dried for 5 hours in a laminar flow hood and stained with DNA binding dye DAPI. Cell numbers were then counted using a fluorescent microscope. To determine the effect of aqueous extract on migration of the cells, cells were seeded on the upper Boyden chamber membrane without any geltrex coating. The migration of treated and untreated cells was assessed as described in the invasion assay.[34]

DNA Fragmentation Assay

After the treatment of the cells, the genomic DNA was isolated by phenol-chloroform and was be run on the 2% agarose gel to see any digestion of DNA. 100 bp ladder was used as a marker.[35]

RESULTS

Cell Viability Assay

Anticancer activity was done by using cell viability assay (MTT Assay). MTT 3 - (4, 5-dimethyl thiazol-2-yl) -2, 5-diphenyl tetrazolium bromide] is a tetrazolium salt. The antiproliferative effect of chloroform, methanol, and water extract of *C. erecta* on human breast cancer metastatic cell line (MDA-MB-231) growth was studied. Cells were exposed to concentrations ranging from 20 to 200 µg/mL of chloroform, methanol, and aqueous extract of *C. erecta* followed by incubation for 24 hours. The cytotoxic potential of each extract is clearly indicated in Fig. 1. The percentage of cell viability upon treating the cells showed a trend of decrease as the concentration of the extract was increased. The results from this assay suggest the cytotoxic potential of the extract.

Invasion and Migration assay

In order to assess the properties of the aqueous extract of *C. erecta* (200 µg) to study its effect on migration and invasion of MDA-MB-231 cells, we employed the transwell assay. The cells were treated with 200 µg of the extract. The results indicated that the aqueous extract of *C. erecta* reduced the migration and invasion ability of MDA-MB-231 cell line significantly after 24 hours of treatment. The extract reduced the migration of MDA-MB-231 cells by 40% (Figs. 2A & 2B). A similar inhibition pattern was also observed for the invasion capacity of the cells where aqueous extract reduced the number of invaded cells to almost 50% (Figs. 3A & 3B). Our results indicated that the aqueous extract may inhibit the migration and invasion of the MDA-MB-231 cell lines.

DNA Fragmentation Assay

We further investigated the role of aqueous extract of *C. erecta* in the apoptosis of MDA-MB-231 cells. The effect of aqueous extract of *C. erecta* in apoptosis was examined using the DNA fragmentation assay. DNA fragmentation is one of the characteristic features of the cells undergoing apoptosis. In order to examine any changes in the DNA of the MDA-MB-231 cells, cells were treated with variable concentrations of the aqueous extract of *C. erecta*. The cells were plated in six well culture plates and after

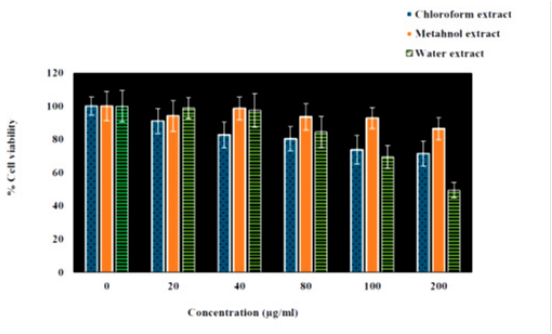

Fig. 1: Percent cell viability of MDA-MB-231 cell lines in different extracts of *C. erecta*

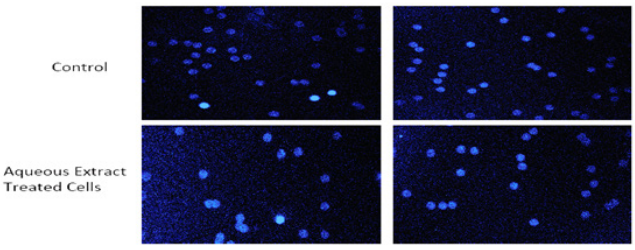

Fig. 2 A: Representative photomicrographs showing the inhibitory effect of aqueous extract of *C. erecta* on the migration of MDA-MB-231 cancer cells

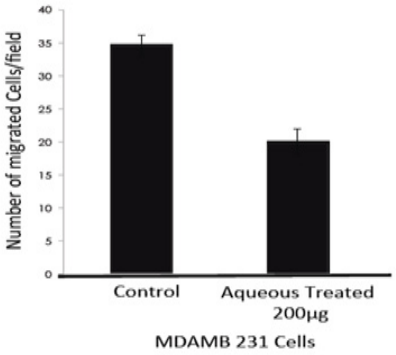

Fig. 2 B: Inhibitory effect of aqueous extract of *C. erecta* on the migration of MDA-MB-231 cancer cells

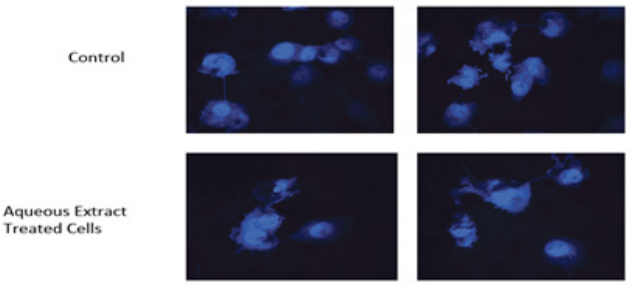

Fig. 3 A: Representative photomicrographs showing the inhibitory effect of aqueous extract of *C. erecta* on the invasion of cancer cells

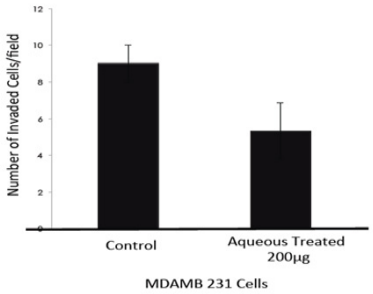

Fig. 3 B: Inhibitory effect of aqueous extract of *C. erecta* on the invasion of cancer cells

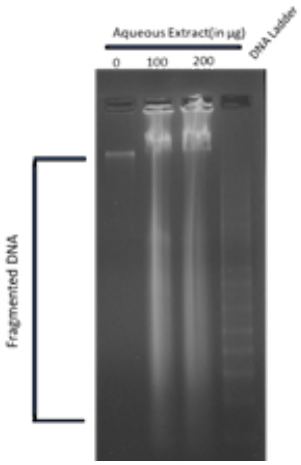

Fig. 4: Fragmented DNA of MDAMB 231 cells after treatment with aqueous extract of *C. erecta* DMSO is a non-treated control and the last lane shows DNA ladder

24 hours, cells were treated with indicated concentrations of the aqueous extract (Fig. 4). The cells treated with DMSO served as a control for the experiment. Then the cells were incubated for 24 hours for treatment. DNA of the treated cells was isolated with a DNA extraction kit (Thermo Fisher) as per the manufacturer's instructions. Then DNA was quantified by nanodrop to measure the concentration. An equal amount of DNA was loaded on the 1.8% of agarose gel containing ethidium bromide. The cells' treatment showed DNA fragmentation when the cells were treated with higher concentrations (100 and 200 µg) of aqueous extract of *C. erecta*. Fig. 4 indicate the fragmenting of DNA in smear form. These results suggest the role of extract of *C. erecta* in causing apoptosis of MDA-MB-231 cells.

Discussion

Breast cancer is the leading cause of death among women worldwide.[5] Breast cancer metastasis remains a cause of mortality,[2,6] various chemotherapeutic drugs are in clinic[36,37] but these drugs also induce toxic side effects.[38] Thus, an alternative approach using fewer toxic compounds such as medicinal plants and their formulations, may be of high value that induce less toxicity on normal cells.

Phytochemicals are important bioactive constituents of medicinal plants.[17, 18] Traditionally, a variety of plants and their extracts have been used in the traditional medicine system.[20] Humans practice these traditional medicines from ancient times to modern times. The chemotherapeutic drugs such as paclitaxel, etoposide and others are also originally purified from herbs.[39] Various parts of the different plants contain potential bioactive constituents for therapeutic purpose and chemoprevention. The need of the hour is to understand the mechanism of their action. Several breast cancer studies have shown that plant compounds are effective anticancer compounds.[24,27,40] In the present study, we *used C. erecta* to show that its extract has anticancer properties. The present study has revealed that the extract of *C. erecta* has significant cytotoxic potential and kill the breast cancer cells upon treatment with the extract. The treatment of MDA-MB-231 cells with extract of *C. erecta* has suggested its potential to kill these cells. These observations are consistent with various other studies where various plant extracts have been shown to have cytotoxic properties against cancer cells.[21, 39, 41] Previously, *Clematis* spp. have been shown to be antibacterial, anti-inflammatory and their uses against ulcers from syphilis and cancer.[29] Additionally, it was interesting to observe that *C. erecta* extract also has the property to inhibit the migration and invasive ability of the cancer cells. The migration and invasion assays showed significant inhibition, a similar kind of inhibition was also shown by the natural components previously. Mycalolide B (MycB) a natural molecule from algae suppressed the proliferation, migration and invasion of breast and ovarian cancer cells.[42] The inhibition of migration and invasion of *C. erecta* extracts can be utilized to isolate and purify the bioactive compounds that can inhibit these malignant abilities of cancer cells.

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