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A Comparative study for Antioxidant and anticancerous potential of Moringa oleifera leaves extract against cervical cancer HeLa cells

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ABSTRACT

A number of pharmacological properties attributed to several parts of Moringa oleifera have been widely accepted by both Unani and Ayurvedic practices of medicines. Therefore, the current study is projected to explore the antioxidant and anticancerous potential of various sequentially extracted fractions of Moringa oleifera leaves (including aqueous, ethanolic, methanolic and hexane extract) against HeLa cervical cancer cells. Our result showed that among different fractions of Moringa oleifera, MMLE (Moringa oleifera leaves methanolic extract) extract has higher phenolic content and also exhibited significantly more radical scavenging (DPPH and Superoxide) and antioxidant (FRAP) capacity. Moreover, MMLE also exhibited significantly higher anticancerous potential by reducing cell viablility in cervical cancer HeLa cell line. Our results support the potent antioxidant and anticancerous activity of methanolic extract of Moringa oleifera which adds one more positive attribute to its known pharmacological importance. Further in vivo studies are needed to utilize these experimental findings towards developing a potent lead compound against cervical cancer cells.

Keyword: *Moringa oleifera, Antioxidant, anticancer, apoptosis, Cervical cancer, HeLa*

1. INTRODUCTION

Drug development using plant derived compounds has been enormously utilized by researchers [1]. Phytocompounds obtained from these medicinal plants holds a significant position in the global and Indian traditional medicinal system for their beneficiary role in the treatment of several diseases, either in the individual or combined form [2-4]. Sequential extraction of plant parts with different solvents followed by isolation and characterization of active components has gained a greater attention by several researchers and scientists. Several researches suggested that these bioactive compounds possess remarkable antioxidant, antimicrobial and anticancerous potential [5-9]. Thus, this study was designed to establish a possible correlation of phenolic contents with anticancerous and antioxidant potential in Moringa oleifera leaves.

The antioxidant potential of plants is due to the presence of such bioactive compounds (phenols, flavonoids, alkaloids, saponins, tannins etc). Oxidative substances such as ROS (Reactive oxygen species) and RNS (Reactive nitrogen species) are constantly synthesized in aerobic cells as by-products during normal metabolic activities [10]. Excessive generation of these prooxidants above its normal level leads to oxidative stress that ultimately results in cell death due to destruction of several macromolecules including lipids, proteins and nucleic acids [11]. Plant derived compounds have exhibited a strong reducing potential either in the form of free radical scavengers or hydrogen donators and pro-oxidative enzyme inhibitors [12-14]. Furthermore, these compounds also exert antitumor activities via interference with Reactive oxygen species, which has been associated with proliferation and invasion of cancerous cells [15, 16]. Recent experimental studies suggested the role of phytocompounds in inhibition of cellular inflammation and cancer progression through deactivation of numerous pro-oxidative enzymes [17-19].

Moringa oleifera, commonly known as the drumstick tree, is naturally found in India and worldwide [20]. Various parts of Moringa have been used as a health food across the world due to its high nutritional content. Moringa plant is also used as the multibeneficial therapeutic agent in traditional medicinal system [21, 22]. In India, it has been extensively used in ayurvedic and unani medicine for the treatment of several diseases such as heart strengthening, blood and liver detoxifier, neurodegenerative and cancer [23-27].

Taking into account the use in folk medicine of Moringa oleifera and its widespread claims of the medical effectiveness and the lack of comparative experimental studies of various sequentially extracts on its anticancerous potential, the present investigation was undertaken to evaluate the antioxidant and

antiproliferative effects of Moringa oleifera leaves grown in the Greater Noida region of India against cervical HeLa cancer cell line.

2. MATERIAL AND METHODS

2.1 Plant material and preparation of extracts

Moringa oleifera leaves were collected from the Noida Institute of Engineering and Technology Campus, Greater Noida, India. The leaves of Moringa oleifera were shed dried and converted into fine powder. Twenty grams of dried powders of leaves was sequentially extracted with n-hexane, ethanol, methanol, and aqueous solvents in soxhlet apparatus until it turned colorless [28]. The solvent was removed by rotary vacuum evaporator, filtered, and dried at room temperature. The extract was freeze dried and stored in a vacuum desiccator for further use. The percentage yield of different extracts of Moringa oleifera leaves were as follows: Moringa oleifera leaves n-hexane extract (MHLE)-5.84%, Moringa oleifera leaves ethanolic extract (MELE)-11.35%, Moringa oleifera leaves methanolic extract (MMLE)-16.68%, Moringa oleifera leaves aqueous extract (MALE)-8.56%.

2.2 Total Phenolic Estimation

The total phenolic content of different extract of Moringa oleifera was evaluated in terms of gallic acid equivalence by Folin-Ciocalteau reagent [29]. Briefly, different extracts of Moringa oleifera leaves were mixed with Folin's reagent and 7.5% Na2CO3 and further incubated at 370C for 90 min. Finally optical density of sample was measured at 765 nm.

2.3 Experimental Analysis of antioxidant activity

2.3.1 DPPH Free Radical Scavenging Assay

The radical scavenging activity of different extract of Moringa oleifera leaves were analysed by the DPPH method with slight modifications [30, 31]. DPPH when mixed with ethanol, is dark violet coloured radical. Various doses of Moringa oleifera leaves extracts (50, 75, 100, 200, and 400 µg/mL) were mixed with 100 µM of DPPH and incubated at 370C for 30 min in dark. Finally, the absorbance was measured at 515 nm and percent free radical scavenging activity was measured by:

Percent inhibition = [(control absorbance − sample absorbance)/control absorbance] × 100.

2.3.2 Superoxide Radical Scavenging Activity

Furthermore, superoxide radical scavenging activity of different Moringa oleifera leaves extracts was analysed according to the previously described protocol with some modifications [32]. Different concentrations of leaves extracts were mixed with EDTA (40.2 mg/ml), ethanol, riboflavin (0.2 mg/ml) and NBT (1 mg/ml) and were diluted to 3 ml with phosphate buffer. After that, sample mixtures were incubated for 15 min at room temperature and absorbance was read at 560 nm. Finally, the superoxide percentage inhibition was estimated according to the following equation:

Percent inhibition= [(Absorbance of sample− Absorbance of control)/Absorbance of sample] × 100.

2.3.3 Ferric Reducing Antioxidant Power Assay

The ferric ions reducing potential of Moringa oleifera leaves extracts was done by using the method of [33, 34]. In brief, 100 μL of different leaves extract was mixed with 3mL of FRAP reagent (300mM sodium acetate buffer with pH 3.6, 10 mM 2,4,6- Tri(2-pyridyl)-s-triazine solution, and 20mMFeCl3 in the ratio of 10:1:1).Then sample mixture was incubated at 370C for 30 min and absorbance measured at 593 nm. The results were represented as μM Fe (II)/mg dry weight of leaves extract.

2.4 Experimental Analysis of anticancerous potential

2.4.1 Cell line and Culture

Human cervical cancer cell line HeLa were procured from the National Centre for Cell Sciences (NCCS), Pune, India and cultured in DMEM media along with 10% FBS (fetal bovine serum) and 1% antimycotic solution in a CO2 incubator.

2.4.2 Cell proliferation assay

MTT assay was used to analyze the effect of different doses of Moringa oleifera leaves extracts on cervical cancer HeLa cell. Briefly, 5x103 cells/well were cultured 96-well culture plates, in a total volume of 100 µL for 24 h [35]. After incubation, cells were treated with different concentrations of MMLE (50-400 µg/ml) for 24 h. Thereafter, 20 µl of MTT dye (5 mg/ml MTT in PBS) was added to each well for 4 h in dark and the absorbance was recorded at 490 nm by using a microplate reader (BIORAD, USA).

2.5 Statistical analysis

In this study all the experiments were performed in triplicates and the respective data were depicted as the mean±SE of three individual experiments. One way ANOVA was employed to perform the statistical analysis using Dunnett's multiple comparison test, two-tailed, and paired Student's t-test (*$p < 0.01$, **$p < 0.001$ represent significant difference compared with control).

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3. RESULTS

3.1 Total Phenolic Content

Phenolic substances can be considered as free radical terminators or chain-breaking antioxidants [40, 41]. Therefore, we have calculated the total phenolic content in Moringa oleifera leaves extract. Our results clearly showed that MMLE extract has exhibited the highest phenolic content (282.04±7.21) in comparison to other extracts including MELE (226.57±5.97), MALE (129.42±5.81) and MHLE (48.36±4.47) respectively.

(Fig. 1).

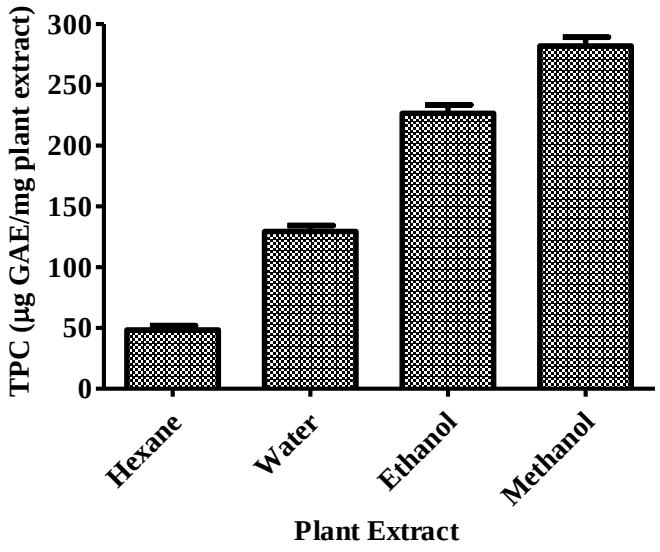

Figure 1: Total phenolic estimation of different extract of Moringa oleifera leaves (MHLE: Moringa oleifera hexane leaves extract, MALE: Moringa oleifera aqueous leaves extract MELE: Moringa oleifera ethanol leaves extract, and MMLE: Moringa oleifera methanol leaves extract). Each value represented as mean±SEM of three independent experiments and assessed in terms of gallic acid equivalence.

3.2 Effect of Moringa oleifera leaves extract on DPPH free radical

The free radical scavenging activity of DPPH radical was examined by reduction of DPPH (stable radical) to diphenylpicrylhydrazine (yellow colored product). Experimental observations clearly revealed that methanolic extract of Moringa oleifera displayed higher free radical scavenging activity in a dose dependent manner as shown in Figure 2. Thus it can be concluded that MMLE extract could be a better scavengers than MELE, MALE and MHLE.

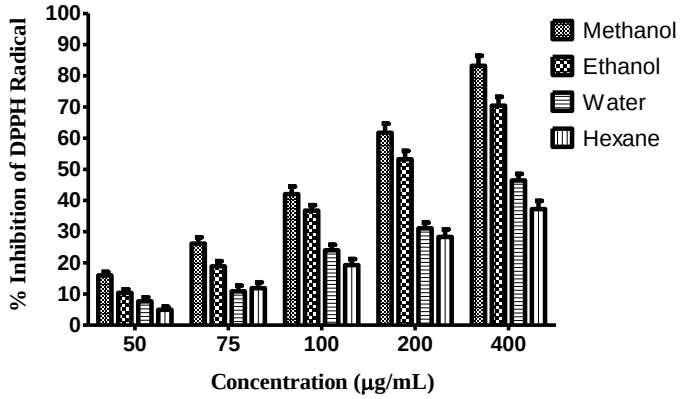

Figure 2: Dose dependent inhibitory effects of MHLE, MALE, MELE and MMLE on free radical scavenging (DPPH) activity. Each value represented as mean±SEM of three independent experiments.

3.3 Effect of Moringa oleifera leaves extract on Superoxide radical

Superoxide radicals are considered to be the precursor of the ROS generation responsible for several diseases [42]. Therefore in our study we have evaluated the superoxide radical scavenging activity Moringa oleifera leaves extracts. Our results exemplified that methanolic extract has the highest superoxide radical scavenging ability followed by other different extracts (Fig. 3).

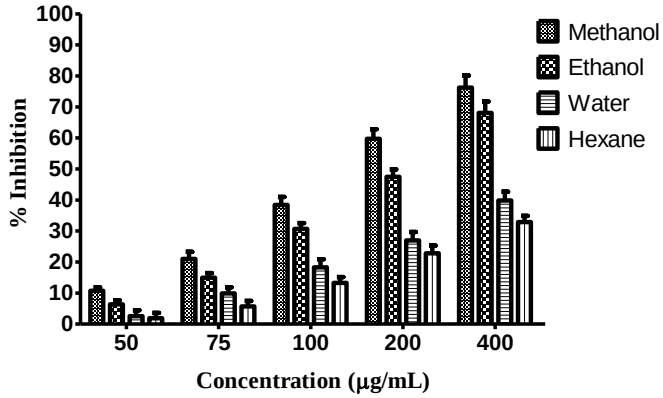

Figure 3: Dose dependent inhibitory effects of MHLE, MALE, MELE and MMLE on superoxide free radical. Each value represented as mean±SEM of three independent experiments.

3.4 Effect of Moringa oleifera leaves extract on Ferric ion reducing power

Ferric reducing antioxidant capability of Moringa oleifera leaves extract was expressed as equivalence of ferrous sulphate (mM/g of sample) and our results depicts that the ferric reducing antioxidant power of the extracts was in an increasing order with the concentrations (Figure 4).

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In the FRAP assay the absorbance of MMLE, MELE, MALE, and MHLE was found to be 0.21, 0.47, 0.74, 1.78, 2.27; 0.13, 0.29, 0.62, 1.22, 1.89; 0.07,0.18, 0.37, 0.71, 0.97 and 0.05, 0.11, 0.28, 0.63, 0.85 at 50, 75, 100, 200 and 400 µg/ml respectively. The observations of FRAP analysis also showed a positive correlation with results of the reducing power and DPPH radical scavenging analysis. The methanolic extract of leaves (MMLE) showed all the three activities with highest efficiencies followed by the other three extracts (MELE, MALE, and MHLE) (Fig. 4). Thus, we have selected MMLE for exploring the anticancer efficacy of Moringa oleifera plant.

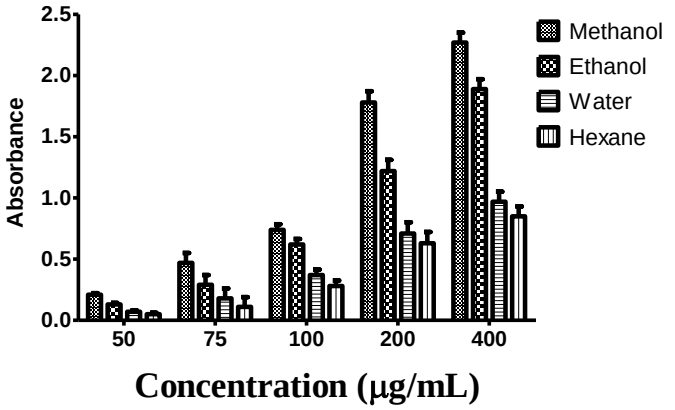

Figure 4: Dose dependent inhibitory effects of MHLE, MALE, MELE and MMLE on FRAP (ferric reducing antioxidant power). Each value represented as mean±SEM of three independent experiments.

3.5 Effect of Moringa oleifera leaves extracts on cell viability

The antiproliferative efficacy of Moringa oleifera leaves extracts on HeLa cells was evaluated by MTT assay after 24h of treatment. In figure 5, there is a significant decrease in cell viability of treated HeLa cells in a dose dependent manner with respect to untreated cells. Moringa oleifera leaves methanolic extract have shown the highest antiproliferative activity against cervical cancer HeLa cell line (88.67%, 65.71%, 52.56%, 39.43% and 18.85% inhibition, respectively). While, ethanolic, water and hexane extracts exhibited a moderate antiproliferative effects against cervical cancer HeLa cell line. Thus these results of cell proliferation assay strongly corroborate with the previous findings of medicinal benefits of Moringa oleifera plants.

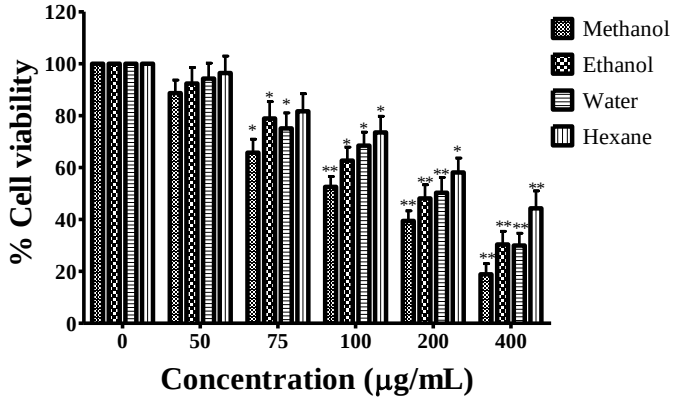

Figure 5: Dose dependent effect of MMLE on cell viability of cervical cancer HeLa cells for 24 as evaluated by MTT assay. Each value represented as mean±SEM of three independent experiments (*p <0.05 and **p< 0.001, represent significant difference compared with control).

4. DISCUSSION

Natural products including phytocompounds have emerged as a rich source for drug discovery [44]. For thousands of years, traditional medical practitioners have prescribed several parts of Moringa oleifera plants for the treatment of numerous diseases including ear and dental infections, skin diseases, hypertension, respiratory illnesses, diabetes, and cancer [45]. Moringa oleifera has also been promoted as a nutrient-rich food source [46, 47]. It is clearly stated in several research reports that antioxidants minimize or prevent oxidation, by scavenging free radical (excessive generation of ROS and RNS) and reducing oxidative stress. Oxidative stress plays a major role in the oxidation of various biomacromolecules such as enzymes, DNA, proteins, and lipids that could result in several human diseases including arthritis, cancer, and atherosclerosis [47, 48]. Antioxidant activity of plant extract has been associated with the phenolic compound present in it [49] therefore it is valuable to estimate the role of these sequentially extracted fractions in scavenging free radicals and determining the total antioxidant capacity. Herein, we report a comparative in vitro analysis of the antioxidant and anticancer effect of different extracts of Moringa oleifera leaves against cervical cancer HeLa cell line.

Several plant phytoconstituents such as flavonoids, alkaloids, saponins, and phenols are found to be responsible for their potential role as strong antioxidants that further contribute to their beneficiary medicinal potential including antimicrobial, anticancerous and anti-inflammatory activities [51]. Therefore, we have quantified the total phenolic content in Moringa oleifera

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leaves extract in sequentially extracted solvents and the results revealed the presence of a significant amount of phenols in all the extract of Moringa oleifera leaves although highest percentage found in the methanolic extract. Moreover, the antioxidant nature of the plant is also assessed by its ability to reduce ferric ion concentration into ferrous ions.

The sequentially extracts of Moringa oleifera leaves were then analysed for their anticancer activity against cervical cancer HeLa cells by MTT assay. Out of all the four leaves extracts, methanolic extract has shown more prominent anti-proliferative effects on HeLa cell lines of cervical cancer in a dose-dependent manner (Fig. 4). According to the current study, each extract differently inhibited cell proliferation in dose dependent manner which could be due to the different level of bioactive constituents in each type of extract.

An earlier study done by Mansour et al., also reported that bioactive compounds present in Moringa oleifera are having potentiality to modulate the antioxidant systems and inhibit growth of hepatocellular carcinoma cells in vitro [52]. Since these findings supported our work, it could be hypothesized that phytocompounds present in Moringa oleifera leaves extracts blocked the anti-oxidant system in cervical cancer HeLa cells, which subsequently leads to inhibition of cell growth and triggers apoptosis.

5. ACKNOWLEDGEMENT

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6. CONCLUSION

Based on our experimental findings, the methanolic extract of leaves of Moringa oleifera showed the highest phenolic content along with strong reducing power and free radical scavenging capacity. A high positive correlation was observed between all the three in vitro assays for antioxidative properties of sequentially extracted Moringa oleifera leaves. Also our results support the potent antioxidant activity of methanolic extract of Moringa oleifera which contributes one more positive attributes to its defined medicinal properties. Moringa oleifera exhibits an antiproliferative effect by inducing loss of cell viability in HeLa cells. Our data confirm the potential of Moringa oleifera leaves extract as a potent therapeutic agent in human cervical cancer. Altogether, these findings provide us a new way to utilize the potential of methanolic leaves extract of Moringa oleifera as a lead compound for the treatment of numerous chronic diseases.

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