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Anti-cancer activity of *Moringa oleifera* Lam. seed oil on oral cancer

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Abstract

Background Despite recent advances in the diagnosis and treatment of oral cancer, relative survival rates have not changed significantly. *Moringa oleifera* (*M. oleifera*) Lam. is one such plant with its anticancer properties being proved in its leaves, stem, flowers but no studies are yet reported proving the anticancer property of its seed oil on oral cancer. This study aimed to evaluate the anti-proliferative and cytotoxic effect of *M. oleifera* seed oil against two Oral squamous cell carcinoma cell lines CAL27 and SCC15 using MTT assay.

Results 2D GC-TOF Mass spectrometry revealed a total of 199 compounds, among which the majority were alkanes (68.2016%) and fatty acid esters (11.1399%). The MTT assay report showed good dose-dependent activity. A significant reduction in cell viability within 24 h with IC50 value of 17.78 µg/mL and 24.28 µg/mL for all treatment groups was observed for both the cell lines CAL27 and SCC15.

Conclusion MTT assay showed a significant decrease in cell viability with an increase in the oil dose, thereby revealing the cytotoxic and anti-proliferative activity of *M. oleifera* seed oil on oral cancer cell lines namely CAL27and SCC15. The results of this study indicate that *M. oleifera* seed oil can be used as a potent anti-cancer agent in the treatment of Oral cancer.

Keywords *Moringa oleifera*, MTT assay, Cytotoxic, Anti-proliferative activity, CAL27 and SCC15 cell lines

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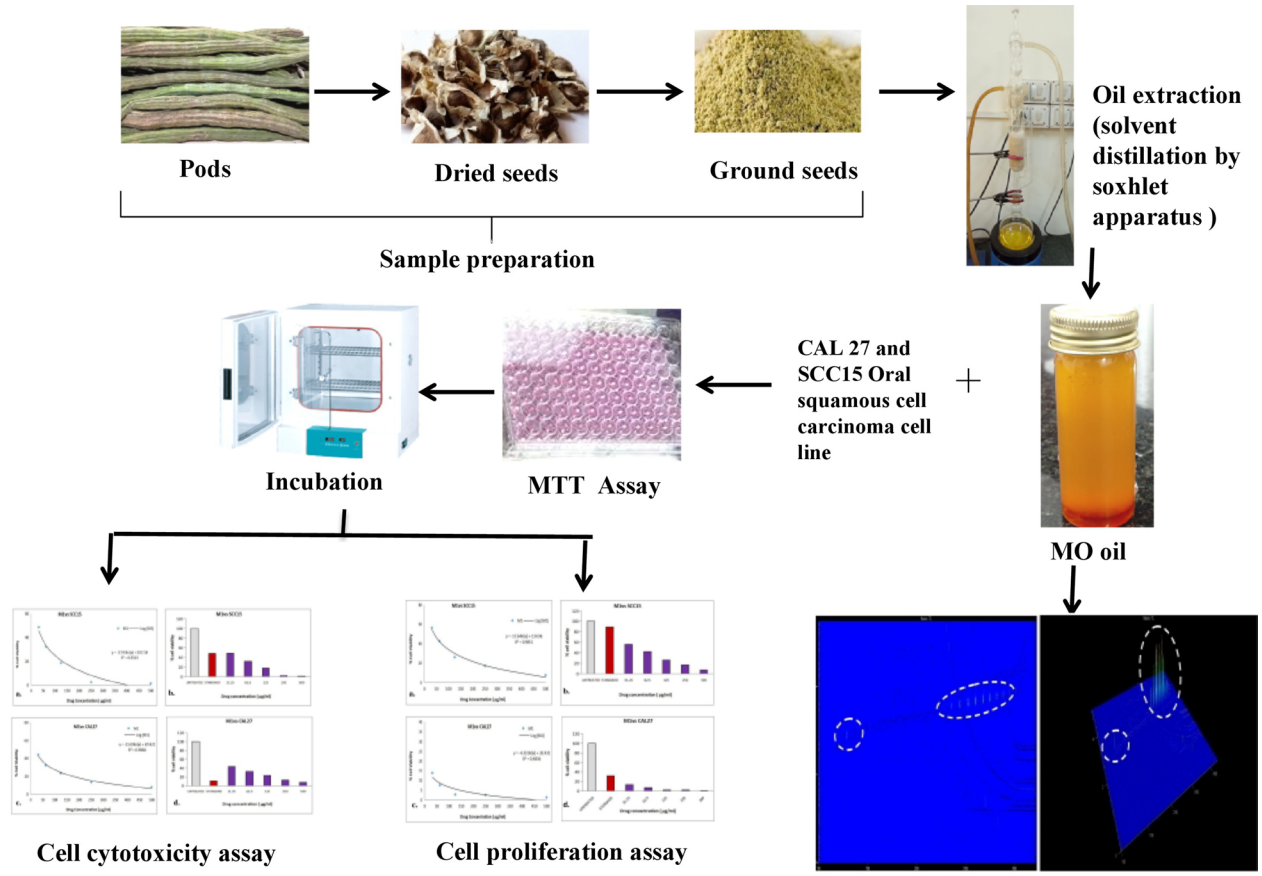
Graphical abstract



1 Background

The number of oral cancer cases in India is the highest worldwide and accounts for one-third of the total burden of the disease. Approximately one-fourth of all global incidences are reported in India, with 77,000 new cases and 52,000 deaths a year [1]. As a result of the disease's high prevalence, treating it has been a long and challenging endeavor. Systematic cancer therapy includes surgical removal, radiation, and chemotherapy [2]. The commonly used chemotherapeutic agents are DNA-interactive agents (e.g., doxorubicin, cisplatin,) anti-metabolites (e.g., methotrexate), molecular targeting agents, anti-tubulin agents (taxanes), and hormones. On the other hand, various disadvantages have been noticed with cancer therapy, like drug resistance, toxicity on normal body cells, and recurrence of cancer. There is a need for a better anti-cancer agent with fewer side effects to overcome the limitations of current cancer therapies [3].

Several ancient plant species are used in traditional medicine. Herbs like ginger, curcumin, saffron, and cinnamon have anti-cancer efficacy against OSCC cell lines [4]. *Moringa oleifera* (*M. oleifera*) is one such miracle plant, as it is rich in vitamins, proteins, carbohydrates, fatty acids, fibers, trace elements, and phytochemical compounds [5]. Various biological activities have already been studied, including the anti-cancer activity of leaves, fruits, flowers, bark, and roots of *M. oleifera* [6].

The anti-cancer activity of *M. oleifera* is accredited to niazimicin, Quercetin, niazinin, glycerol-1(9-octadecanote, (A-L-rhamnosyloxy) benzyl) carbamate [7]. *Moringa oleifera* exhibited an anti-proliferative effect on Hep-2 cells by initiating apoptosis by upregulating caspase 3 apoptotic marker [8]. Abd-Rabou et al. [9]. observed that *M. oleifera* seed oil induced apoptosis in colorectal cancer cells Caco-2 and HCT116 without affecting normal cells. Anti-cancer potency of *M. oleifera* leaf extract was found to regulate Caspase3, VEGF, HSF1 expression in mice induced with oral squamous cell carcinoma [10–12]. In this study, we aim to examine the anti-proliferation and cell cytotoxicity by MTT assay against SCC 15 and CAL 27 oral squamous cell carcinoma cell lines. To our knowledge, this study is the first of its kind.

2 Methods

2.1 Plant material collection

Fresh matured pods of *M. oleifera* were obtained from Keonjhar district of Odisha. The collected pods were cleansed 2–3 times with distilled water and shade dried. The seeds kernels were separated and ground into coarse powder.

2.2 Oil extraction and phytochemical analysis

Oil was extracted using Soxhlet apparatus (BOROSIL, India) at 30 °C. 100 g of powdered sample was taken in the thimble with 500 mL of ethanol (solvent). The extraction process continued for 8 h. The oil dissolved in ethanol was collected and evaporated using water bath. The extracted oil was then collected in sterile container and stored in 4 °C. The component identification was achieved by GCGC-TOF–MS analysis (Leco, Regasus 4D) with Agilent 7890B GC, and the compounds were identified from the NIST library following standardized methods.

2.3 Cell line culture

SCC 15 and CAL 27 human tongue squamous cell carcinoma cell lines were procured from American Type Culture Collection (ATCC). Cells were cultured in Dulbecco's modified Eagle's medium (DMEM) (AL007 HiMedia) and supplemented with Fetal Bovine Serum (FBS) 10% (L1006 HiMedia). Cells were incubated at 37 °C in CO_2 incubator (Healforce, China) in CO as 5% and humidity atmosphere as 95% [13].

2.4 Cell viability assay (MTT assay)

Cytotoxic and anti-proliferation activity of *M.oleifera* seed oil was determined by MTT assay. The assay control included medium control (only medium), negative control (cells and medium) and a positive control (medium with Cisplatin − 5 mg and cells). SCC15 and CAL 27 cells were seeded into 96-well microtiter plate (Corning, USA) at cell density 20,000 cells per/200 µl DMEM medium without the test compounds and incubated overnight. Test agents were incubated in cell culture medium without addition of fetal bovine serum (RM10432, HiMedia) at 37 °C for 24 h (since the test samples were insoluble in nature). This made the test materials' constituents to release into the medium, which was further used for cytotoxicity assay and cell proliferation assay. After removal of the spent medium from 96 well microtiter plate, the cells were left for incubation with serum free medium for 3 h. After serum starvation, the five concentrations of test samples were added as 31.25, 62.5, 125, 250, 500 µg/mL and incubated for 24 h at 37 °C in a 5% CO_2 0.5 mg/mL of MTT reagent (4060 HiMedia) was added to the spent media after removing the spent media. The plate was then wrapped with aluminum foil and left for 3 h of incubation. After removal of MTT reagent, 100 µL of DMSO (solution for solubilisation) was added and dissolved properly until MTT formazan crystals appeared. The absorbance was recorded on a spectrophotometer at 570 nm as reference wavelength.

2.5 Statistical analysis

All data were analyzed using Minitab version 17 software. The data were presented in mean and Standard deviation. The significant difference was evaluated using regression analysis. A linear regression equation was used to determine the half maximal inhibitory concentration IC50 from the linear part of sigmoid curve in order to analyze cell viability, i.e. $y = mx + c$, $y = 50$, M and C values were derived from the viability graph. R^2 values ≥ 0.95 were considered to be statistically significant.

3 Results

3.1 GC × GC-TOF–MS analysis of *M. oleifera* seed

Light brown color oil was obtained from 100 g of dried seeds of *M. oleifera* with 28% of total oil yield. The oil was analyzed using two dimension gas chromatography time of flight mass spectrometry and chemical profiles were identified using NIST libraries and subsequently grouped under chemical classes with reference to PubChem and Human metabolome database (Fig. 1).

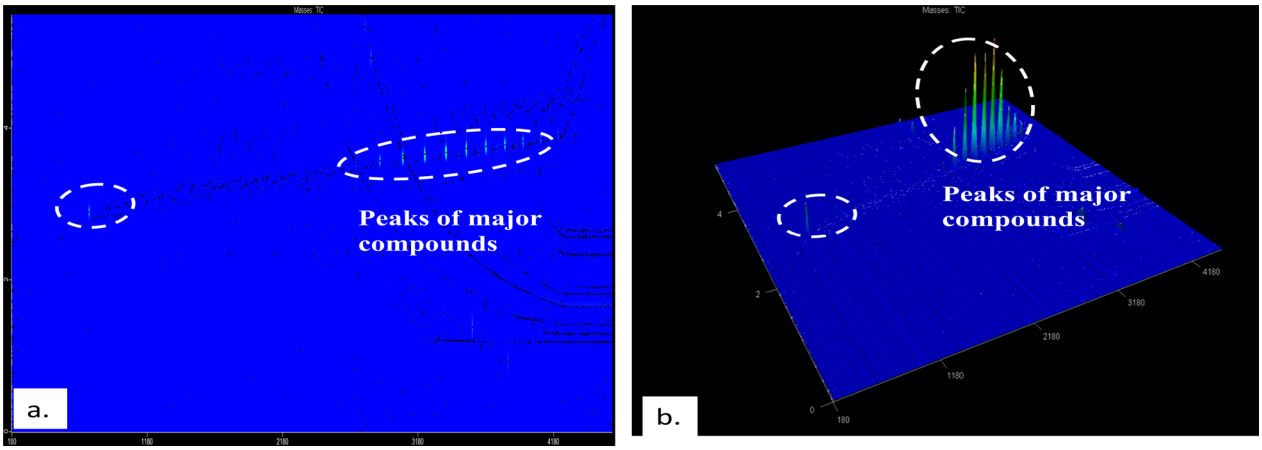


Fig. 1 **a** Contour plot of 2D GC-TOF–MS showing the peaks of major phytochemicals; **b** 3 dimensional plot representing major compounds

Table 1 Major constituents identified from seed oil of *M. oleifera* by GC × GC TOF–MS analysis

Sl. no	Name of compound analyzed by 2DGC-TOF–MS	R.T. (s)	R.T. (s)	Total area % of compounds	Formula	Class
1	Dodecane	752	2.9	2.8758	C12H26	Alkane
2	Hexadecane	1709	3.33	2.4666	C16H34	Alkane
3	Heptadecane, 2-methyl-	2721	3.53	1.5833	C18H38	Alkane
4	Heptacosane	3386.5	3.68	52.932	C27H56	Alkane
5	2-Bromotetradecane	3782.5	3.75	1.2784	C14H29Br	Alkane
6	Nonadecane, 2-methyl-	3766	3.72	1.2485	C20H42	Alkane
7	5,7-Dodecadiene, (Z,Z)-	4547	1.69	4.5438	C12H22	Alkene
8	Bis-(3,5,5-trimethylhexyl) phthalate	3579	1.38	2.6576	C26H42O4	Acid ester
9	Phthalic acid, bis(7-methyloctyl) ester	3843	0.93	1.6458	C26H42O4	Acid ester
10	Z-10-Tetradecen-1-ol acetate	4580	1.67	4.8984	C16H30O2	Ester
11	1,3-Dioxolane, 2-(3-bromo-5,5,5-trichloro-2,2-dimethylpentyl)-	4486.5	1.16	2.2499	C10H16BrCl3O2	Acetal

The identified compounds were segregated into classes namely—Alkanes, Alkene, Aldehyde, Amine, Acid esters, Fatty acids, Alcohols, Carbohydrates, Terpenoids, Ketones, Esters and others (Table attached as Additional file 1). A total of 199 compounds constituting total area of 94.7298% among which majority were alkanes (68.2016%) and fatty acid esters (11.1399%). The complete list of all 199 phytochemicals is present in Additional file 1. The peaks in the 3D plot and contour plot represent the major phytochemicals with more concentration (Table 1).

3.2 Cellular toxicity of *M. oleifera* seed oil on CAL27 and SCC15 cells

Treatment with *M. oleifera* seed oil showed decrease in the cell viability with IC50 value is 17.78 µg/mL on CAL27 and 24.28 µg/mL on SCC15 cell line. Data illustrated in (Figs. 2, 3) show the percentage viabilities of both the cell lines after 24 h incubation with treatment versus controls. Figure 2 represents the regression graph for calculation of IC50 value, and the column graph represents the decrease in viability percentage with increase in concentration of the oil in comparison to the standard (Cisplatin). Figure 3 represents the microscopic images of both the cell lines showing decrease in cancer cells with increase in dose of the oil. 31.25 µg/mL of oil

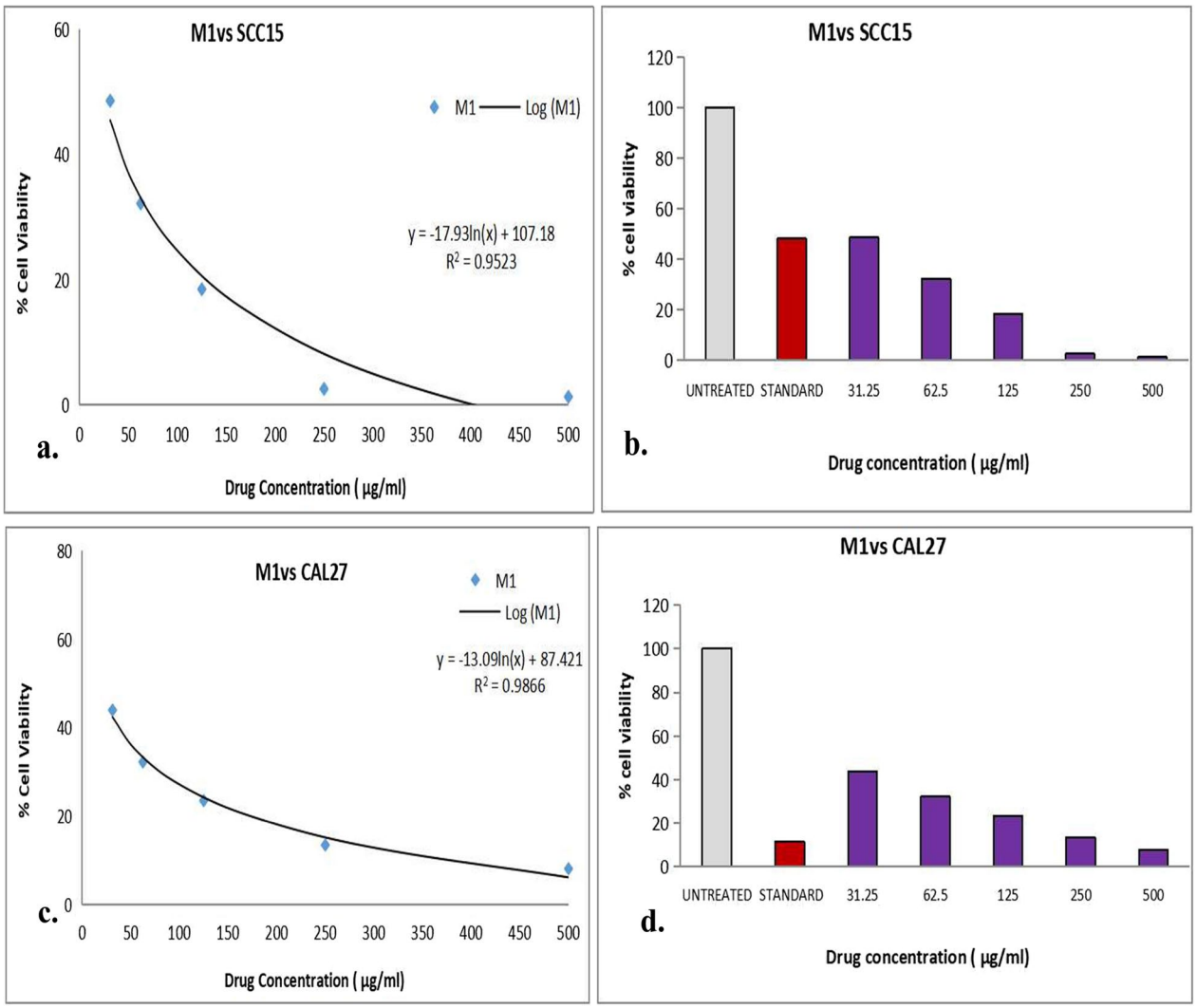


Fig. 2 Graphical representation showing cytotoxic effect of *M. oleifera* seed oil. **a** and **b** Cytotoxic effect of *M. oleifera* against cisplatin on SCC15 is represented by linear decrease in cell viability along with increase in concentration; **c** and **d** cytotoxic effect of *M. oleifera* against cisplatin on CAL 27 is represented by linear decrease in cell viability along with increase in concentration

showed the minimum cytotoxicity and 500 µg/mL of oil showed maximum cytotoxicity on both the cell lines (Table 2).

3.3 Effect of *M. oleifera* seed oil on proliferation of CAL27 and SCC15 cell lines

The results of cell proliferation assay exhibited remarkable difference between the control groups and *M. oleifera* seed oil. A gradual and significant decrease in the cell viability was observed after 24 h incubation in both the cell lines when treated with *M. oleifera* seed oil in dose-dependent manner (Figs. 4, 5). Figure 4 represents the regression graph for calculation of IC50 value and the column graph represents the decrease in viability percentage with increase in concentration of the oil in comparison to the standard (Cisplatin). Figure 5 represents the microscopic images of both the cell lines showing decrease in cancer cells with increase in dose of the oil. 500 µg/mL of oil showed maximum anti-proliferative

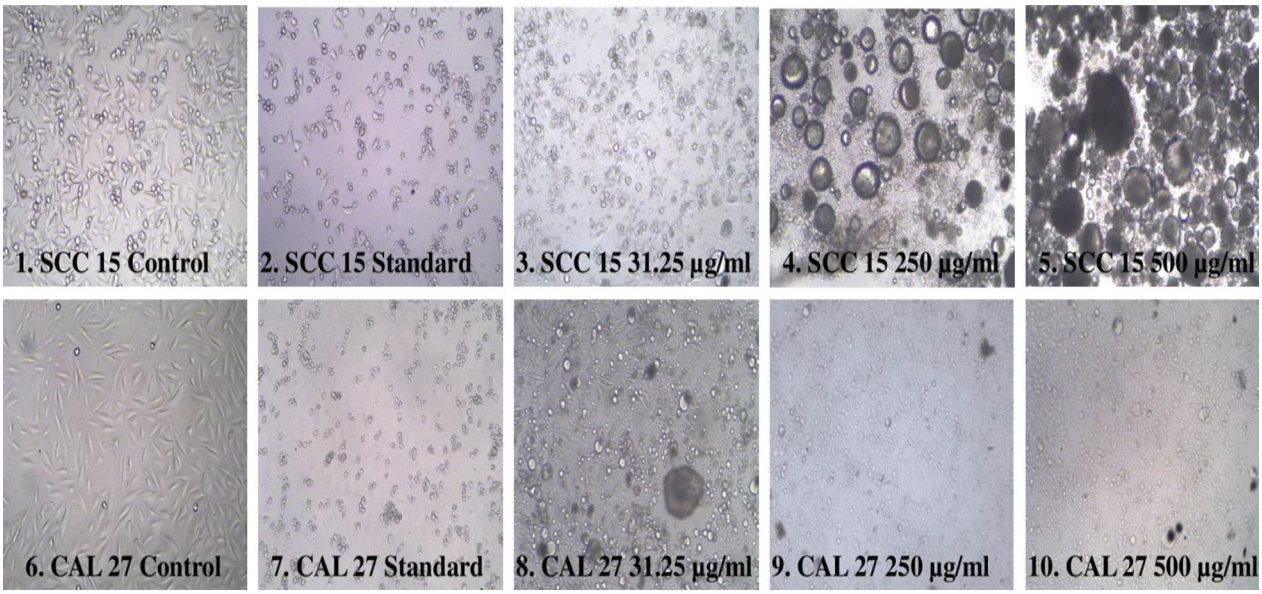


Fig. 3 (1) SCC 15 cell control (2) 5 mg cisplatin as standard (positive control) (3–5) SCC 15 cell toxicity activity in *M. oleifera* seed oil at concentration of 31.25, 250 and 500 ug/mL of test sample after 24 h incubation (6) CAL 27cell control (7) 5 mg cisplatin as standard (positive control) (8–10) CAL 27 cell toxicity activity in *M. oleifera* seed oil at concentration of 31.25, 250 and 500 ug/mL of test sample after 24 h incubation

Table 2 Percentage viability of SCC 15 and CAL 27 cells against *M. oleifera* seed oil showing its cytotoxic effect

OSCC cell lines	Viability%							
	Negative control	Cisplatin	Incubation time (h)	Concentration of *M. oleifera* seed oil in µg/mL				
				31.25	62.5	125	250	500
SCC 15	100	48.10	24	48.5	32.1	18.4	2.5	1.2
CAL 27	100	11.51	24	43.9	32.2	23.4	13.3	8.0

effect on both the cell lines with viability percentage of 7.5 in SCC15 and 1.2 in CAL27 (Table 3).

4 Discussion

Many studies have been conducted recently to support the beneficial effects of *M. oleifera* on health [6]. *Moringa oleifera* exhibits chemo-preventive properties, which help in inhibition of the growth of human cancer cells. Various studies have recognized the pro-apoptotic and anti-proliferative effects of *M. oleifera* extracts [14]. There are reports revealing the anti-cancer potential of different parts of *M. oleifera,* namely leaves, stem, flower and roots [15–19]. Studies have shown that pod extract has medicinally and biologically active compounds [20]. As compared to other parts, in *M. oleifera* seeds flavonoids, glucosides, and glucosinolates compounds are significantly high, which are responsible for various biological activities [21, 22]. The seed oil has shown strongest activity as antimicrobial, anti-oxidant, and anti-inflammatory properties as reported earlier [23, 24].

Moringa oleifera seed oil has also shown cytotoxicity on other cell lines, likely HeLa, HepG2, MCF-7, CACO-2, and L929 by MTT assay [25, 26]. Positive cytotoxic effects were studied in *M. oleifera* against EAC and Hep2 cell lines using MTT assay [16]. Other work on ethanolic extracts of *M. oleifera* exhibited anti-cancer activity and acted as potent growth suppressive agents against human breast cancer MDA-MB-231 cells [27]. The potential chemo-preventive activity of *M. oleifera* was demonstrated in a human tumor (KB) cell line [28].

In our study, cell proliferation and cytotoxicity assay results suggested that *M. oleifera* showed toxicity on CAL27, SCC15 cell line. *Moringa oleifera* oil exhibited anti-proliferation effect in both types of oral squamous

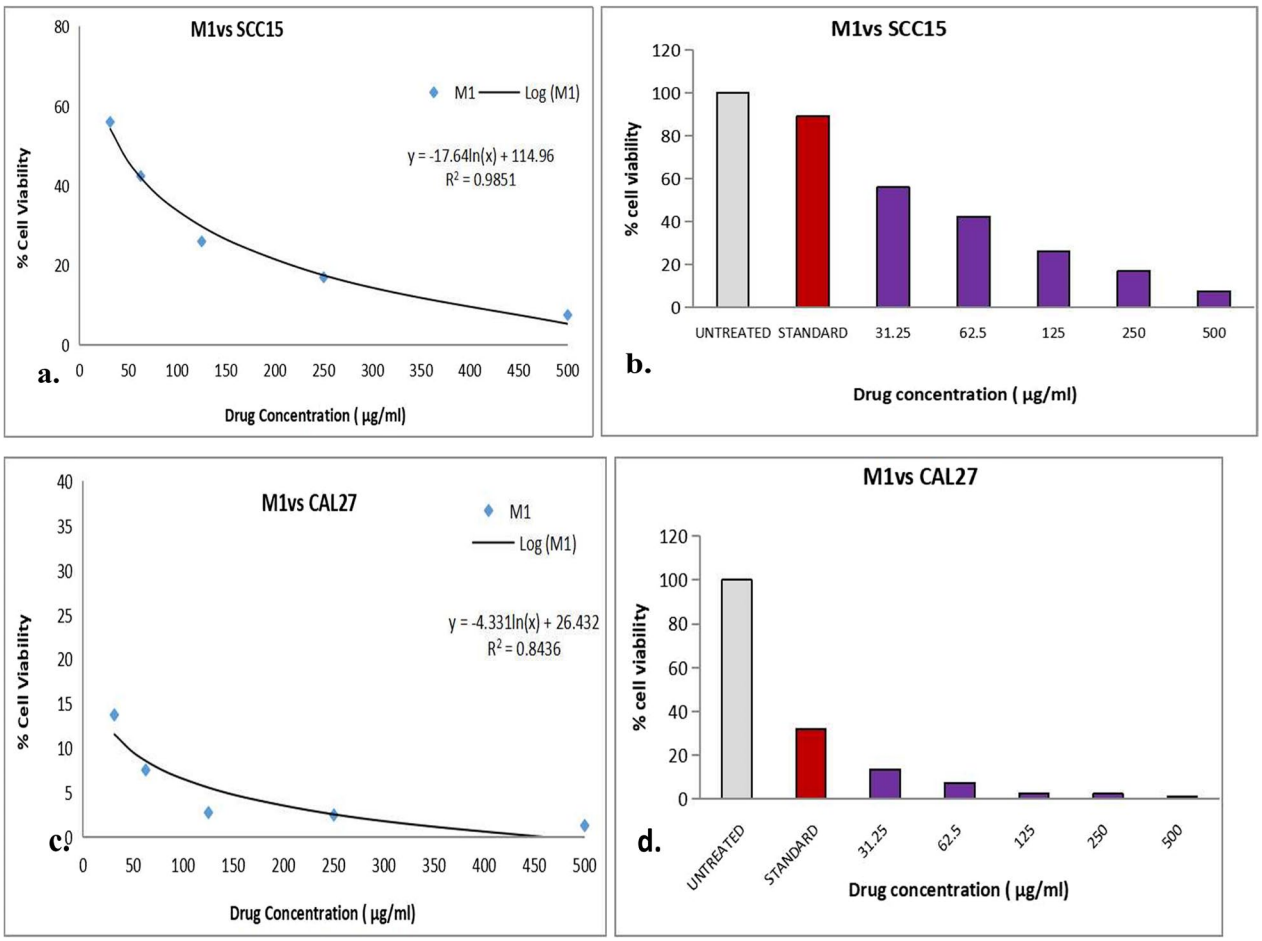


Fig. 4 Graphical representation showing anti-proliferative effect of *M. oleifera* seed oil. **a** and **b** Anti-proliferative effect of *M. oleifera* against cisplatin on SCC15 is represented by linear decrease in cell viability along with increase in concentration; **c** and **d** anti-proliferative effect of *M. oleifera* against cisplatin on CAL 27 is represented by linear decrease in cell viability along with increase in concentration

cell carcinoma cells. Heptacosane (52% area) was found to be the major component in our sample which is similar to a study reported in *Achyranthes aspera* L, the chloroform leaf extract showed the highest anticancer activity, in which Heptacosane, 1-chlor exhibited anticancer activity [29]. Heptacosane also acts as a substrate and P-gp inhibitor, retaining the substrate chemotherapeutic drug inside the cell and thus enhancing its cytotoxic effects [30]. Many studies have reported and validated the anti-cancer property of *M. oleifera* leaves extracts on oral squamous cell carcinoma but to our knowledge, this is the first study proving the anti-cancer property of its seed oil on OSCC. This implies the application of *M. oleifera* seed oil on cancer therapy but with more quantitative testing to estimate the dose and further evaluation on in-vivo studies.

5 Conclusion

Anti-cancer activity of *M. oleifera* seed oil is yet to be reported on oral cancer. Since, the seeds shows more oil yield with wide range of phytoconstituents and is easy to obtain we tried to evaluate its anti-cancer activity on two oral cancer cell lines. *Moringa oleifera* seed oil exhibits anti-cancer activity by decreasing cell proliferation and exhibiting cytotoxicity in CAL27 and SCC15 cells. A low cell survival was detected on treatment with different concentrations in a dose-dependent manner. Thus, our findings provide growing evidence supporting the promising role of *M. oleifera* seed oil as a potent anti-cancer agent. Additionally, the present work provides a preliminary platform for further investigation of the possible mechanism and role of *M. oleifera* seed oil on Oral cancer.

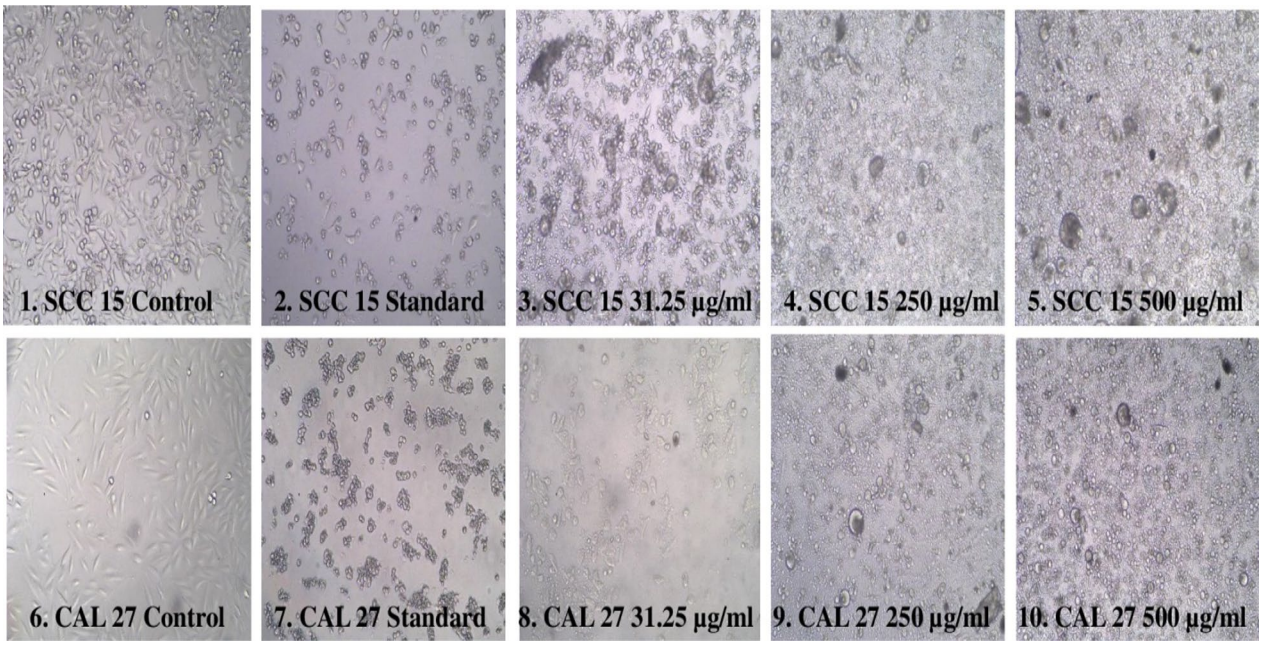


Fig. 5 (1) SCC 15 cell control (2) 5 mg cisplatin as standard (positive control) (3–5) SCC 15 cell proliferation activity in *M. oleifera* seed oil at concentration of 31.25, 250 and 500 ug/mL of test sample after 24 h incubation (6) CAL 27cell control (7) 5 mg cisplatin as standard (positive control) (8–10) CAL 27 cell proliferation activity in *M. oleifera* seed oil at concentration of 31.25, 250 and 500 ug/mL of test sample after 24 h incubation

Table 3 Percentage viability of SCC 15 and CAL 27 cells against *M. oleifera* seed oil showing its anti-proliferative effect

OSCC cell lines	Viability%							
	Negative control	Cisplatin	Incubation time (h)	Concentration of *M. oleifera* seed oil in µg/mL				
				31.25	62.5	125	250	500
SCC 15	100	89.11	24	55.9	42.4	26.0	17.0	7.5
CAL 27	100	31.88	24	13.7	7.5	2.7	2.4	1.2

Abbreviations

M. oleifera	*Moringa oleifera*
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
GLOBOCAN	*Global Cancer Observatory (GCO)*
OSCC	Oral squamous cell carcinoma
GCGC-TOF–MS	2D-gas chromatography-Time of flight–Mass spectrometry
DMEM	Dulbecco's modified Eagle's medium
FBS	Fetal Bovine Serum
ATCC	American Type Culture Collection
DMSO	Dimethyl sulfoxide
IC50	Half maximal inhibitory concentration

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43088-024-00475-z.

Additional file 1. Phytochemicals identified by 2D GC-TOF-MS analysis.

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Author contributions
RB and SKB contributed to conceptualization and supervision; RB and JNM done validation and review and editing; MD helped in original draft preparation.

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Availability of data and materials
All the data generated or analysed during this study are included in this article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Authors declare that there is no conflict of interest among the authors and has approved for publication.

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