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Original Article

Evaluation of *Berberis aristata* Extract and Berberine for Anti-Oral Cancer Potential

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ABSTRACT

Background: Traditional ayurveda medication *Berberis aristata* possesses a wide range of biological activities, including antipyretic, anti-inflammatory, anti-diabetic, and anticancer, etc. Protoberberine, berberine, and bis-isoquinoline are the three primary alkaloids discovered in *Berberis aristata*, however, berberine is generally considered to be the main one. Extract of *Berberis aristata* has been shown to have the ability to stop the spread of cancer cells. **Aim:** To evaluate the ability of *Berberis aristata* to combat the human oral cancer cell line (SCC-29B). **Materials and Methods:** A methanolic extract of *Berberis aristata* stem was prepared. The alkaloidal fraction was separated from the extract. Through preparative TLC, berberine was isolated. UV, HPLC, HPTLC, and LCMS/MS were used to characterise the extract, alkaloidal fraction, and isolated berberine in order to validate its presence. The SRB assay method was used to evaluate the anticancer potential of extract and berberine against human oral cancer cell line SCC-29B. Statistical analysis was done. Docking studies were conducted to understand binding affinity of berberine with different targets of oral cancer. Berberine showed comparable binding affinity to Adriamycin with tested targets. **Results:** *Berberis aristata* stem extract was found to significantly control % cell growth of SCC-29B cell line. It may be deduced that *Berberis aristata* stem extract has the potential to have anticancer properties against oral squamous cell carcinoma. **Conclusion:** *Berberis aristata* can be thought as a possible therapeutic plant having anticancer efficacy against oral squamous cell carcinoma.

Keywords: SRB assay, Daruhaladi, *Berberis aristata*, Oral squamous cell carcinoma, cytotoxicity.

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INTRODUCTION

Oral cancer is a major cause of global morbidity and mortality. Squamous cell carcinoma accounts for more than 90% of oral malignancies and occurs most frequently in middle-aged to elderly patients who are habitual to smoking and drinking. The overall outlook for patients diagnosed with Oral Squamous Cell Carcinoma (OSCC) remains poor, largely due to delayed clinical presentation. Early lesions are frequently unrevealed due to the lack of accompanying symptoms. Early detection, diagnosis and treatment of OSCC significantly increase patient survival and minimise the need for extensive surgery.[1]

The National Cancer Institute has evaluated over 35000 plant species for anticancer properties. Around 3,000 plant species have been discovered to exhibit anticancer activities that can be reproduced. Various researchers have identified plant species having anticancer characteristics, including those that have been used in traditional therapy.[2] Suppression of cancer cell activity by different plant species was proposed by decreasing cancer cell proliferation and triggering apoptotic cell death.[3]

The American Cancer Society's most up-to-date estimation for carcinoma within the United States for 2022 is, about 54,000 new cases of mouth or bodily cavity cancer and about 11,230 deaths from the mouth or bodily cavity cancer. Oral cavity and bodily cavity cancers occur most frequently within the sites like gums, tongue, tonsil and cavity, floor of the mouth, etc.[4]

Berberis aristata DC, plant name has been checked with MPNS on 5 Jan 2022, is typically known as Tree turmeric, Daruharidra, Chitra, Daru Haldi and Indian barberry.[5,6] The roots of the plant are taken into account as the official source of drug. Traditionally, the plant is used as a demulcent,[7,8] tonic, diaphoretic,[9] anti-diarrhoeal,[10] diuretic[11] and a substitute to treat diseases like wound healing, immunomodulatory, skin diseases, rheumatism, snakebite, menorrhagia, jaundice, eyes problem, etc.[12,13] Recent literature reports antioxidant,[14] hypoglycemic,[15] and hepatoprotective[16] properties of *Berberis aristata*. Berberine is the main alkaloid component of the plant present in stem bark, leaves, rhizomes and roots.[17-19] Official publications like The Ayurvedic

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Pharmacopoeia of India (1999) reports therapeutic uses of plant for dysentery, obesity, diseases of ear, eyes and mouth, etc. Quality standards of Indian medicinal plants published by Indian Council of Medical Research (2005), reported preventive and curative effects of plant on chemical induced carcinogenesis.[20] Authors have already published a review article reporting anticancer potential of *Berberis aristata* against breast, cervical, brain, colon cancer[21] which includes research studies published from 2009 to 2022. There is not a single report of the anticancer activity of *Berberis aristata* against oral cancer. Therefore, the present study involved determination of cytotoxic effect of *Berberis aristata* stem extract against human oral cancer cell line SCC 29B.

Molecular docking is a type of computational modelling that aids to determine the appropriate binding orientation of ligand and receptor during interaction to form a stable complex. Due to its capacity to determine the conformation of ligands within the suitable target binding site with a high degree of accuracy, molecular docking is very commonly used method in structure-based drug design.[22] The detailed mechanism by which Berberine act as an anticancer agent is still not fully understood. Docking studies of Berberine with different oral cancer targets will help to understand the anti-cancer mechanism.

MATERIALS AND METHODS

Reagents and chemical

All the solvents, reagents and chemicals utilised were of analytical quality.

Instrument

UV (Shimadzu), HPLC (Cyberlab), HPTLC (Camag TLC Scanner, Linomat Sample Applicator, UV chamber) were used for analysis.

LC-MS/MS (UHPLC-UV-HRMS-ESI-POS-MS/MS TOF/Q-TOF Mass with ion source: Dual AJS ESI) was used to obtain LC-MS and LC-MS/MS spectrum.

Molecular docking was done using Auto dock Tools, Auto dock Vina, PyMol, Discovery studio, Avogadro's, etc.

Plant material collection

Plant material was gathered from the ayurvedic firm located near Lonavala (Batch number 03/21, Mfg Date: Nov 2021, Exp. Date: Apr 2025). It was authenticated by certified botanist with specimen number SS 05. The stem part of the wild *Berberis aristata* plant was procured, transported to the lab in a sealed container, cleaned, dried in the shade, and stored.

Identification and authentication

Berberis aristata plant part was collected. Later, identified and authenticated as per the Ayurvedic Pharmacopoeia.[5]

Preparation of extract

The stem was thoroughly washed and dried and then smashed using the mortar and pestle. A soxhlet extractor was used to extract the powdered stem in HCl and Methanol (2:3, v/v) at 45-50°C. Using filter paper, the resulting extract was filtered and any remaining solvent was recovered by distilling it below 50°C. The remaining syrupy liquid was dried on a water bath at 40°C and % yield was determined.

Isolation of alkaloidal fraction

A predetermined amount of plant extract was agitated with 5% glacial acetic acid for 30 min at intervals.[23] Once the solution turned acidic on the litmus paper, it was filtered and 10% sodium hydroxide solution was added. It was transferred to a separating funnel and extracted thrice with chloroform, the combined chloroform extract was allowed to evaporate on a water bath at 40°C to generate the dried fraction.

Phytochemical screening

As per usual protocol, tests were conducted to determine the presence of carbohydrates, glycosides, steroids, alkaloids, saponins, flavonoids, tannins and polyphenols.[24]

Development of thin layer chromatography for detection and isolation of Berberine by preparative TLC

Various combinations of solvents were tried to detect Berberine in extract and alkaloidal fraction. Silica Gel G was used as a stationary phase.

Characterization by various analytical methods

Characterization by UV spectroscopy

The reference standard and samples were dissolved in methanol to get stock solutions, which were then further diluted to obtain solutions of the necessary concentrations. All the solutions were scanned using a Shimadzu UV spectrophotometer in a range of 200-400 nm.

Characterization by RP-HPLC

The separation was performed using a C18 column. 20 µL of the sample and standard solutions were manually injected, and eluted through the column using the mobile phase of o-Phosphoric acid: Acetonitrile (70:30, V/V) at a flow rate of 1 mL/min. Detection was done at 348 nm.

Characterization by LC-MS/MS

Isolated Berberine was characterized by LC-MS/MS. Following conditions were used for LC-MS/MS study,

Auxiliary Sampler: Inj. Volume: 3.00 µL.

Maximum flow gradient: 100.00 mL/min 2.

Diode Array Detection.

Solvent Composition: 0.1% Formic acid in water: ACN (98:2, V/V).

Quantification by HPTLC

Amount of Berberine from the extract was quantified using HPTLC. Following are the conditions used for HPTLC study,

Mobile Phase: Toluene: Ethyl acetate: Formic acid [5:4:1, V/V/V].

Saturation Time: 15 min.

Stationary Phase: HPTLC plates silica gel 60 F 254.

Band length: 6 mm.

Wavelength of detection: 348 nm.

Cytotoxicity test

Cytotoxicity test was carried out by Sulphorhodamine B (SRB) assay method using SCC 29B cell line.[25] For the cytotoxicity testing 96-well microtiter plates were used. Cell lines were cultured in RPMI 1640 medium. After inoculation, microtiter plates were incubated under specified conditions. Test samples were dissolved and diluted in dimethyl sulfoxide to get a concentration of 10(µg)/mL, 20(µg)/mL, 40(µg)/mL, and 80(µg)/mL. After addition of test samples plates were incubated for 48 hr. Cells were fixed in plate by using TCA. Sulforhodamine B was added and plates were incubated at RT for 20 min. After washing, the plates were read on a plate reader at wavelength 540 nm with a reference wavelength of 690 nm. By comparing with test wells to control wells average absorbance, percent growth was calculated. Two way (ANOVA) followed by Bonferroni *Post hoc* test was used for statistical analysis.

Molecular docking study

Molecular docking studies were performed to understand the binding affinity of Berberine to various targets of oral squamous cell carcinoma. The Protein Data Bank (PDB) structures for the ligands like berberine, 5-fluorouracil and adriamycin were downloaded from https://pubchem.ncbi.nlm.nih.gov/. or utilising smileys in Avogadro's. Based on previous literature, nine different targets for oral cancer were selected. The PDB structure for the chosen targets were retrieved from rcsb.org. Later, the PDB format was cleaned by eliminating heteroatoms from the receptors. Using Auto dock Tools, the PDB structures of the ligand and target receptors were converted to PDBQT format.

The following procedures were used to further purify the selected receptors' structures,

1) Bonds (build by distance).

2) Atoms (assign AD4 type).

3) Charges (add Koll man charges).

4) Hydrogen (add polar only).

For docking, the ligands and target receptors were defined using Auto dock Vina and Auto dock Split. With regard to the ligand, Auto dock Vina evaluates the receptor's binding sites and provides the binding affinity. Utilizing Discovery Studio, which provides information on the binding site and the binding interaction of the ligand to the receptor, the data interpretation of the ligand to the receptor was carried out.

RESULTS

Berberis aristata alcoholic extract was tested against a human oral cancer cell line SCC 29B to determine its anticancer potential.

Identification and authentication

Berberis aristata a member of the Berberidaceae family authenticated using the parameters like macroscopy, microscopy, and evaluation done as mentioned in the Ayurvedic Pharmacopoeia.[5,26] The macroscopic evaluation of plant material for organoleptic characteristics showed yellow-brown colour pieces with irregular cuts, variable lengths and thickness, rough surface and had bitter taste. Whereas, microscopic examination showed presence of xylem vessels, fibrous sclereids, stone cells, medullary rays prismatic crystals of calcium oxalate and simple starch grains. Results of Ayurvedic Pharmacopoeial tests were found to be within limits. Outcomes are mentioned in Table 1.

Extractive value

Methanol and HCl were used as a solvent for the extraction of *Berberis aristata* stem and the estimated extractive value for the stem extract was 17.77% w/w.

Table 1: Pharmacognostic evaluation as per Ayurvedic pharmacopoeia.

SL. No	Tests	Observations	Limits
1	Foreign matter	2%	NMT 2%
2	Total Ash	13%	NMT 14%
3	Acid insoluble extractive	4.8%	NMT 5%
4	Alcohol soluble extractive	12.8%	NLT 6%
5	Water soluble extractive	23.3%	NLT 8%
6	Loss on drying	8.66%	NMT 12%

Separation of alkaloidal fraction

The fractionation procedure was used to isolate the alkaloidal fraction from the stem extract and the % yield of alkaloid fraction was found to be 5.33% w/w.

Phytochemical screening

By performing preliminary phytochemical analysis for several secondary metabolites, the extracted substances were described. The presence of proteins, saponin glycosides and amino acids could not be detected in stem extract, but tannins, steroids, alkaloids, flavonoids, anthraquinones, and cardiac glycosides were present.

Development of thin layer chromatography and isolation by preparative TLC

Berberine was detected in the extract and alkaloid fraction by using n-butanol: water: glacial acetic acid (7:1:2, V/V/V) as mobile phase and Silica Gel G as stationary phase. Berberine was isolated by preparative TLC using the same stationary and mobile phase.

Characterization by UV

The overlay spectrum of extract, alkaloidal fraction and isolated berberine in comparison to standard berberine was recorded for the selection of wavelength and also for the prediction of the presence of berberine in all samples shown in Figure 1.

Characterization by HPLC

In comparison to the Berberine, the chromatogram of the extract exhibited the same retention time of 5.43±0.05min at 348 nm shown in Figure 1.

Characterization by LC-MS/MS

The LC-MS spectra of standard and isolated Berberine both displayed a molecular ion peak with an m/z of 336.12 (Figure 2a and 2c). When compared to the Berberine standard, the MS/MS spectra revealed a comparable sort of fragmentation pattern, which supports the isolated fraction of pure Berberine shown in Figure 2b and 2d. Fragmentation pattern of Berberine was proposed from LC-MS/MS spectra (Figure 3).

Characterization by HPTLC

The densitogram of extract, alkaloidal fraction and isolated Berberine in comparison with standard Berberine was taken at 348 nm using mobile phase, Toluene: Ethyl acetate: Formic acid (5:4:1, V/V/V/) (Figure 4). The R_f value of Berberine was found to be 0.68±0.05. The linearity of standard Berberine was also taken for the quantification of extract (Table 2, Figure 5a and 5b). Using the regression equation, % Berberine content was calculated.

Cytotoxicity testing

Berberis aristata stem extract and Berberine when tested against human oral cancer cell line SCC 29B showed highly significant activity compared to control with *p*-value <0.001 at all concentration levels (Table 3). Comparison between growth curve of SCC 29B cell lines on treatment with berberine and *Berberis aristata* stem extract is shown in Figure 5. An inverse relationship between concentration and % control growth was observed. Decrease in density of viable cells as compared to control (Figure 6 c) was observed for *Berberis aristata* stem extract (Figure 6 a) and berberine (Figure 6 b) treated wells.

Molecular Docking

The docking analysis of berberine against nine distinct targets of OSCC in comparison to Adriamycin and 5-flurouracil has been presented in Table 4. The docking analysis showed that all of the ligands had a binding affinity for the OSCC targets, which results in a variety of interactions with the amino acid chains of receptors, including van der Waals, hydrogen bonding and Pi-Pi bonds. It was evident from this binding affinity values, that berberine has comparable affinities to Adriamycin and higher binding affinities than 5-fluorouracil for tested targets.

Table 2: Linearity data.

SL. No	Parameters	Observations
1	Linearity range	100-500 ng/band
2	Rf value	0.68±0.05
3	Regression equation	Y= -820.3 + 28.91x
4	R^2 value	0.997
5	% Berberine content in extract	2.869%

n=3.

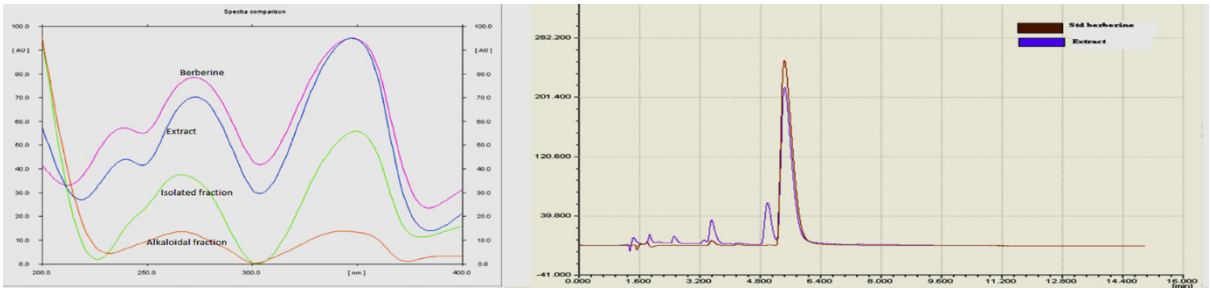

Figure 1: UV-visible and HPLC overlay of standard berberine and extract.

Figure 2: a) LC-MS spectra of standard berberine. b) LC-MS/MS spectra of standard berberine. c) LC-MS spectra of isolated berberine. d) LC-MS/MS spectra of isolated berberine.

Table 3: Result of cytotoxicity testing of stem extract against Human Oral Cancer Cell Line SCC 29B.

Concentration (µg/mL) Sample	% Control Growth (Mean±SEM)				GI_{50} (Concentration of drug in µg/mL causing 50% inhibition of cell growth)
	10	20	40	80	
Berberis Aristata stem extract	74.300*** ±0.458	61.467*** ±0.259	56.667*** ±0.259	30.500*** ±0.190	47.31
Berberine	31.900*** ±0.073	25.300*** ±0.110	11.900*** ±0.073	9.733*** ±0.056	< 10
Adriamycin (Positive Control)	-52.20*** ±0.281	-53.80*** ±0.249	-56.50*** ±0.414	-66.40*** ±0.297	<10
Negative Control	101.225±0.000				

Data expressed as Mean±SEM; n=6; Two way (ANOVA) followed by Bonferroni's *Post hoc* test, *p<0.05, **p<0.01, ***p<0.001 and ns- non-significant, when compared with the control group

DISCUSSION

Berberis aristata plant material was identified and authenticated as per Ayurvedic Pharmacopoeia. Methanol with hydrochloric acid was selected as a solvent for the extraction based on Pharmacopeial procedure. Presence of berberine in extract, alkaloidal fraction was confirmed by HPLC, TLC and UV spectroscopy. Quantitative analysis of extract for berberine was done by HPTLC. LC-MS/MS studies confirmed purity of isolated berberine. Berberine has reported cytotoxicity against various cancer cell lines and same was observed for SCC 29B.

As per the literature Berberine was reported to alter cell morphology and cause genomic DNA fragmentation as well as nuclear condensation in KB oral cancer cells. It had also increased expression of the FasL death receptor ligand and proapoptotic factors like Bax, Poor, and Apaf-1, Bcl-2, and Bcl-xL.[38] Berberine has been reported to exhibit an anticancer effect also by inducing

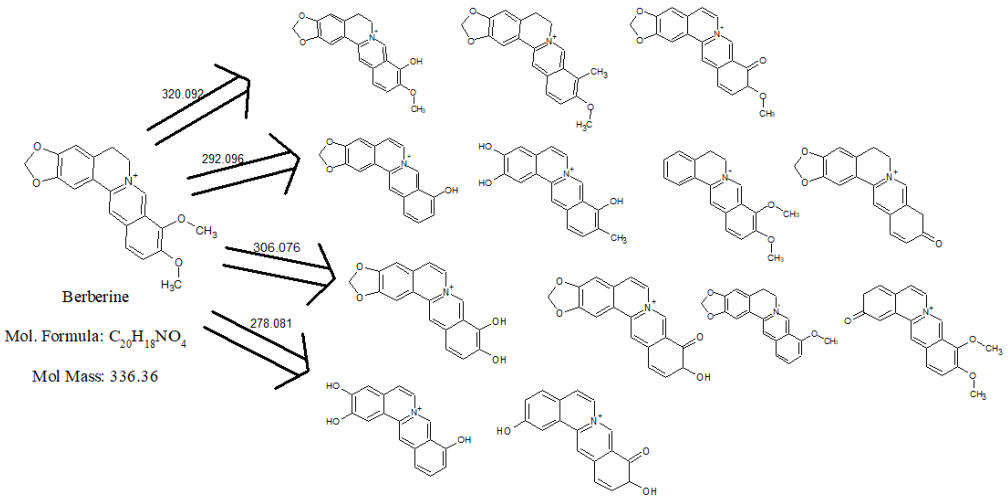

Figure 3: Proposed fragmentation pattern of berberine.

Table 4: Result of docking studies.

Sl. No.	Target name (Abbreviation)	PBD ID	Binding affinity of ligands (kcal/mol)			Interaction of Berberine with OSCC Receptors
			Ber-berine	Adria-mycin	5-Fluro-uracil	
1	Phospho-inositide-3-Kinase[27](PIK3R1)	1H9O	-6.1	-7.2	-4.3	Pi-Pi T shaped: TYR 76, Pi- alkyl: LEU 84, van der Waals: LEU 75, HIS 85, HIS 88, GLU81, SER 77.
2	SRC proto-oncogene[28] (SRC)	1FMK	-6.6	-8.6	-5.1	Pi-sigma: LEU 120, VAL 111, Pi-alkyl: TRP 119, Pi-Donor Hydrogen Bond: ASN 112, van der Waals: THR 114, GLY 116.
3	Serine/threonine Kinase1[29] (AKT1)	4GV1	-8.0	-8.4	-5.5	Pi-sigma: LEU 295, Pi-Anion/Cation: ASP 292, LYS 179, Conventional Hydrogen bond: HIS 194, van der Waals: LYS 276, ASP 274, CYS 310.
4	Mitogen-activated protein kinase 3[30-33] (MAPK3)	4QTB	-9.0	-10.3	-4.9	Pi-sigma: VAL 56, Pi-Pi stacked: TYR 53, Pi-alkyl: LEU 173, ALA 69, C-H bond: ASP 128, Conventional hydrogen bond: LYS 168, SER 170, van der Waals: ASP 184, ASN 171.
5	Vascular endothelial growth factor A[34] (VEGFA)	3QTK	-5.8	-6.2	-4.1	Pi-sigma: THR 24, Pi-alkyl: VAL 26, Conventional hydrogen bond: ARG 49, van der walls: ASP 27, LEU 25 etc.
6	Filamin A, alpha[35] (FLNA)	3HOP	-5.6	-7.4	-4.4	Pi-alkyl: LYS 58, ARG 51, ARG 63, van der Waals: SER 61, GLU 55, ASN 54, LYS 62
7	Calmodulin 3[35] (CALM3)	2F3Z	-5.8	-5.7	-4.5	Amide-Pi- stacked: LYS 75, Pi-sigma: MET 76, Pi-alkyl: MET 76, LYS 75, C-H bond: THR 79, van der Waals: THR 146, ILE 85, SER 81 ASP 78 etc.
8	Huntingtin[35] (HTT)	3IO4	-6.7	-8.0	-4.7	Pi-Pi stacked: TYR 171, Pi-alkyl: ILE 329, Pi-anion: GLU 328, C-H bond: GLU 328, van der Waals: GLN 325, PHE 92.
9	Janus kinase 2[36] (JAK2)	2B7A	-6.5	-7.5	-5.3	Pi-Pi T shaped: PHE 1019, TRP 1020, Pi-alkyl: ILE 1018, Conventional hydrogen bond: ARG 938, van der Waals: ILE 1074, ARG 980, SER 1016.

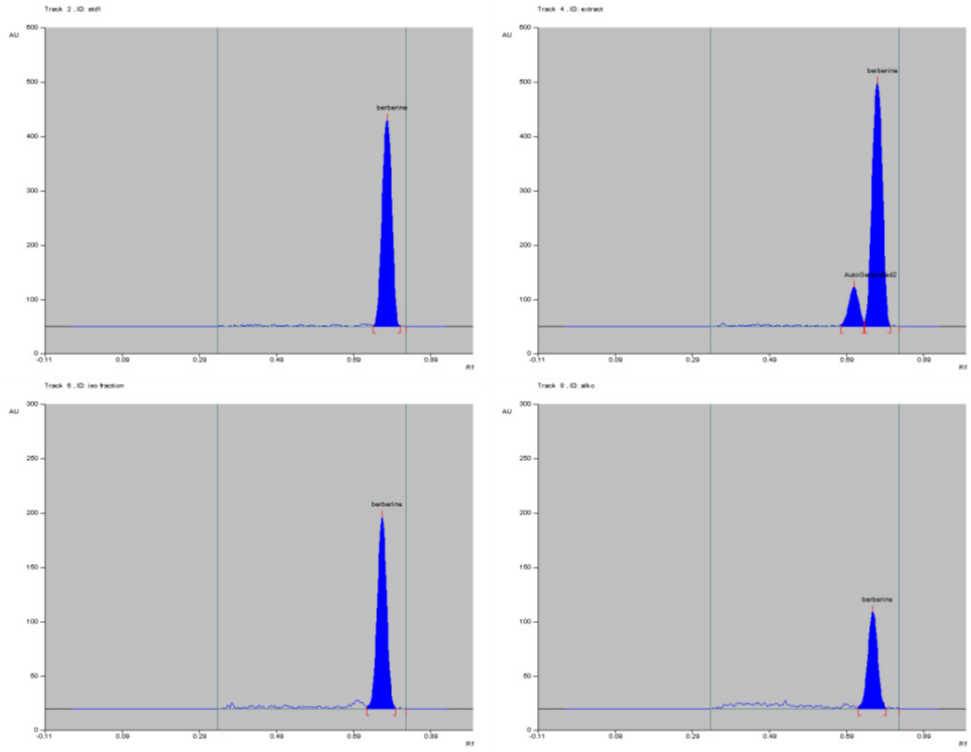

Figure 4: Densitogram of a) Standard Berberine b) Extract c) Isolated berberine d) Alkaloidal fraction.

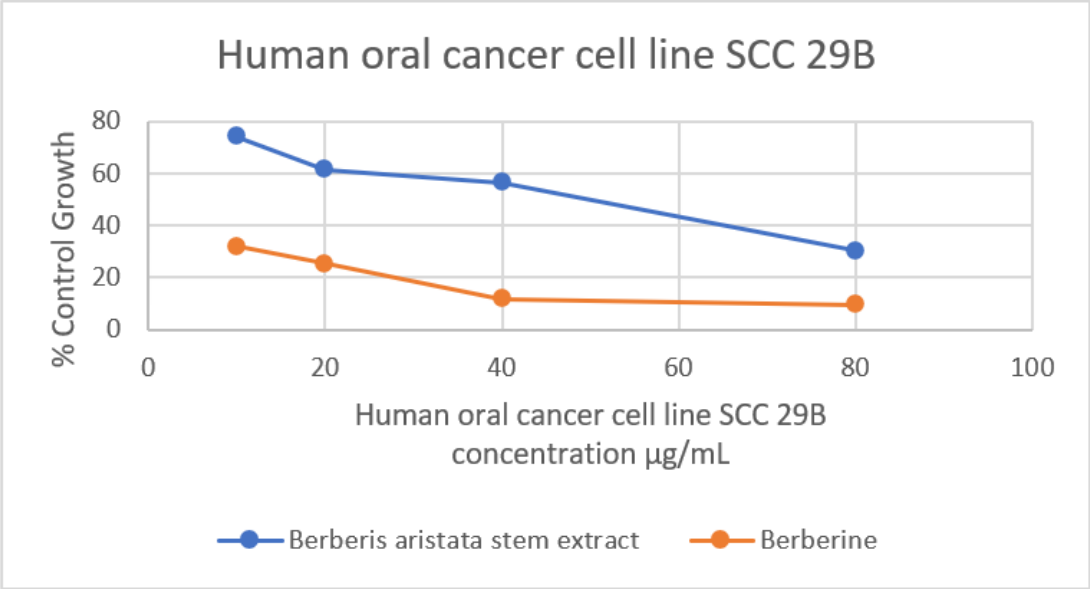

Figure 5: Growth curve of SCC-29B cell line on treatment with stem extract and berberine.

G0/G1-phase arrest, promoting Ca^{2+} production, and generating reactive oxygen species. Apoptosis of Human HSC-3 oral cancer cells and cell death of KB oral cancer cells was mediated by berberine when both the death receptor-mediated and mitochondrial pathways are activated concurrently.[37,38] Same pathways were reported to be responsible for reduction of viability of SCC-4 cells by berberine.[39] Berberine modulates apoptosis in oral cancer cells by inhibiting the expression of cycloxygenase-2 and Mcl-1.[40]

Berberine was proposed to show direct effect on cancer cell growth and metastasis. As per literature Serine/threonine Kinase1 (AKT1), Mitogen-Activated Protein Kinase 3 (MAPK3), Janus Kinase 2 (JAK2), etc. are few of the cellular targets account to the anti-cancer effect of berberine, also proved through docking studies with various oral cancer targets.

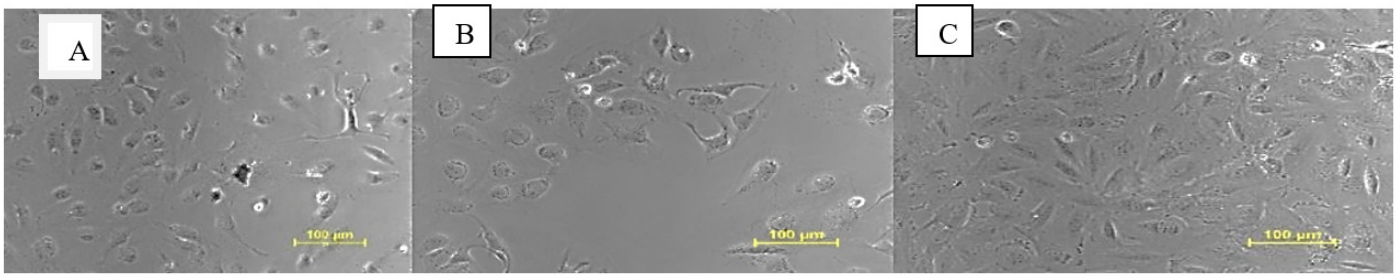

Figure 6: a) SCC-29B treated with *Berberis aristata stem extract*. b) SCC-29B treated with Berberine. c) SCC-29B Control.

SUMMARY

The methanolic extract of *Berberis aristata* stem was prepared and the extractive value was found to be 17.77% w/w. The phytochemical screening of the extract was done and the results showed the presence of reducing sugar, steroids, glycosides, tannins and polyphenols, flavonoids along with alkaloids. The alkaloidal fraction was separated from the extract and berberine was also isolated using preparative TLC. Characterization was done by UV, HPTLC, HPLC and LC-MS/MS methods. The extract and berberine has been tested for cytotoxicity testing against human oral cancer cell line SCC-29B. Both showed significant activity against tested cell lines. A docking study of Berberine in comparison with adriamycin and 5-fluorouracil was done against nine different targets of OSCC. Based on the binding affinity of all the ligands to the selected targets of OSCC, berberine showed comparable results to Adriamycin.

CONCLUSION

The anti-oral cancer potential of *Berberis aristata* stem extract and Berberine can be concluded from the cytotoxicity testing against SCC 29B cell lines by SRB assay method. Docking studies concluded Berberine has the ability to bind to OSCC receptors, and contribute to anticancer potential by various mechanisms. Further preclinical and clinical studies are need to be performed.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ANOVA: Analysis of Variance; **PDB:** Protein data bank; **SEM:** Standard Error Mean; **OSCC:** Oral Squamous Cell Carcinoma; **SRB:** Sulphorhodamine B; **RPMI:** Roswell Park Memorial Institute; **TCA:** Trichloro-aceticacid; **RT:** Room Temperature; **HCl:** Hydrochloric acid.

AUTHORSHIP CONTRIBUTION STATEMENT

Vijaya Vichare: Conceptualization, Supervision.

Manasi Rokade: Formal analysis.

Vaishnavi Ithape: Writing- Original draft.

Vrushali Tambe, Shashikant Dhole, Vishnu Choudhari: Writing-review and editing.

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