"Bioprospecting *Bauhinia variegata* L. For Anti-Cancer Properties."

Synopsis for Ph.D. Thesis

To be Submitted

Under the guidance of

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by

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Introduction

Cancer is the second largest killer after cardiovascular pathologies making neoplasia as a topic of major concern for the modern world. Analysis of cancer statistics worldwide suggests the emergence of cancer cases to 18.1 million and 9.6 million cancer deaths. Of the various types of cancers, Breast cancer alone accounts for 8.6 million new cases and death of 4.2 million females world-wide (Bray *et al*., 2018). In India, incidence rate of breast cancer is 1.4 lakhs and whereas the mortality rate is around seventy thousand. According to Mathur *et al*. (2020) for the ongoing year 2020, the projected occurrence of breast cancer in India is 1,392,179. High speed of urbanization and incompetence of the healthcare system in the developing countries will escalate breast cancer incidences to 2 million cases (Gupta *et al*., 2015).

Breast cancer originates either in ducts or lobules of breast. Depending on the origin of the tissue and invasive ability, they can be categorized into: Ductal carcinoma in-situ or Invasive Ductal carcinoma and Lobular carcinoma in-situ or Invasive lobular carcinoma. In situ refers to benign cancer whereas invasive refers to cancer types having metastatic capability. Apart from these types of breast cancer, incidences of inflammatory breast cancer is about 1% to 3% of breast cancers. Breast cancer can also be divided into hormone receptor positive and negative based on presence of hormone receptors on cancerous cells. About 80% of breast cancers displays estrogen receptors whereas 65% have presence of progesterone receptors, respectively referred as "ER-positive" and "PR-positive". Apart from role of hormones in breast cancer, mutations also result in greater prevalence of breast cancer. Her2 gene amplification or over-expression is responsible for about 15-30% of breast cancers. It has been proved that, HER2 (human epidermal growth factor receptor type 2), binds to growth factor and promotes cancer cell growth. Presence or absence of these three receptors is also used to categorize breast cancer. Triple Negative breast cancers lacks expression of all three receptors attributing to aggressive phenotype of the breast cancer, which is strongly accountable for the poor prognosis and increased disease recurrence (Podo *et al.*, 2012). The predisposing risk factors associated with breast cancer are exposure to Radiation, Family history (Genetics), Alcohol consumption, Menstrual cycle (early menarche, late menopause), lack of breastfeeding habits in mothers and use of oral contraceptives.

Cytokines present around the tumor microenvironment plays an important role in progression of cancer cells. Tumor necrosis Factor-α synthesized as a membrane bound protein (pro-TNF), is a 17-kDa protein comprising of 157 amino acids. It is cleaved by TNF converting enzyme (TACE) and released in active form. It has diverse physiological roles in vital processes such as cell differentiation, inflammation, cell survival and apoptosis. On cellular level TNF-α exercises its effects through its receptors to activate distinct signaling pathways that regulates cell survival, proliferation or death. There are two receptors for TNF-α, TNF-receptor 1 (TNFR1) present ubiquitously and TNF-receptor 2 (TNFR2) present mainly on immune cells. TNFR1 is an important member of death receptor family that is competent enough to induce apoptotic cell death. Upon binding of the homotrimer TNF-α, trimerization

of TNFR-1 occurs that further binds to TNFR-associated death domain (TRADD). It recruits the receptor interacting protein (RIP), TNFR-associated factor 2 (TRAF-2) and key molecules essential for downstream intracellular signaling (Rath and Aggarwal, 1999). When TNFR-1 signals apoptosis, TRADD binds pro-caspase-8, initiating apoptosis cascade involving the mitochondria along with caspases as key regulators (Degterev *et al.*, 2003). Tumour necrosis factor-α is a crucial pro-inflammatory cytokine found in breast tumor microenvironment (Komori *et al.*, 1993). TNF-α is known to inhibit proliferation and induce apoptosis of MCF-7 breast carcinoma cells (Jeoung *et al*., 1995; Cai *et al.*, 1997). TNF- *α* regulates metastasis related genes enhancing the invasive ability of MCF-7 cells (Chen *et al.*, 2008). Hence TNF-α acts as a dual edged sword in case of cancer including breast cancer, therefore, the balance of TNF-α in inducing survival and death-signaling is pivotal in determining the fate of TNF-α responding cells. Modulating this balance could help to prevent cancer development and facilitate using TNF-α for cancer therapy (Cruceriu *et al*., 2020)

Notable advancement has been made in our understanding of breast cancer and its progression at molecular level. Despite advances in curative measures like surgery, radiotherapy and chemotherapy; high mortality associated with cancer has not been restrained. Moreover, multidrug resistance (MDR) is also one of the factors hindering anticancer therapy. These hurdles are the driving force for the quest of novel anti-cancerous compounds. Identification of newer therapeutic agents is crucial to effectively inhibit cancer progression with minimal side effects, which at present is associated with the stringent treatment regime for this challenging disease.

Traditional medicine systems have been using medicinal plants as a source of therapeutic tools showing effectiveness against many diseases including cancer. Nevertheless, the lack of scientific evidence to substantiate the molecular basis of the efficacy of the said natural plants acts as an impediment in its wider acceptability especially in the developed countries and among allopathic physicians. The contemporary world is eagerly looking for more plant-derived compounds like vinblastine, vincristine, and paclitaxel with more efficacy against various types of cancer. Thus, the medicinal plants have started to gain global importance due to exceptional diversity of secondary metabolites they possess which could contribute in the discovery of newer drugs with greater efficacy and lesser side effects by use of processes through modern science. From extensive literature survey, it has been found that *Bauhinia variegata* L. is a plant with multitude potentials. It has also good anti-oxidant and radical scavenging property, a property which has been seen in most molecules with good therapeutic value (Pandey *et al*., 2012). Ethanolic extract of Bauhinia has shown an increase survival time of Swiss albino mice with Dalton's ascetic lymphoma (DAL), proving its efficacy against tumors (Rajkapoor *et al.*, 2003). Additionally, there is a report depicting the decrease in cyclophosphamide induced micronucleus formation in Swiss Mouse Bone Marrow cells (Pandey *et al.*, 2010). The bark of stem is also known to possess anti-carcinogenic property as described in an investigation where it was observed that there was reduction and delayed papilloma formation in the skin papilloma Swiss Albino Mice model, treated with Bauhinia extract (Agrawal and Pandey, 2009). Antitumour activity of ethanolic extract of *B. variegata*

was also reported against N-nitrosodiethylamine induced liver tumour in rats (Rajkapoor *et al*., 2006)

In vitro studies have also been reported with the leaves of this plant which demonstrates that aqueous extract of *Bauhinia variegata* L. has significant cytotoxic potential on MCF-7 and MDA-MB-231 cell lines compared to other extracts (Mishra *et al*., 2013 and Sharma *et al*., 2015). Gunalan and Vijayalakshmi, 2016 reported n-hexane and ethyl-acetate-methanol fractions of *B. variegata* leaf exhibited good cytotoxicity against colon cancer cells. It induced DNA damage and cell cycle arrest at sub G1 and G2/M phase respectively in COLO 320 cells. ID7 fraction isolated from *Bauhinia variegata* L. stem was found to inhibit cell viability, migration, invasion in the 4T1 and MDA-MB-231 cells. It increased the late apoptosis, adhesion, expression of PARP, caspase-7, caspase-8, RIP and TNF-R1 and reduced the secreted active gelatinases indicating attenuated tumour volume and weight, reduced inflammation in the liver and metastasis in lung (Santos *et al*., 2019). Similar results with *Bauhinia variegata* stem fraction on human peripheral blood mononuclear cells (PBMCs) and human cervical tumor cells (HeLa), inducing cell death process by activating Caspase-3, TNF-R1 and RIP have also been reported (Santos *et al*., 2018). *Bauhinia variegata* L. ethanolic bark extract showed the cell cycle arrest of HeLa cell lines in G0/G1 phase and apoptotic cell death by flow cytometric analysis (Shyamkumar and Ishwar, 2014). The pure fractions obtained from methanolic bark extract exhibited cytotoxicity against C-6 glioma rat brain, HCT-15 colon cancer and MCF-7 breast cancer cell lines (Sharma *et al*., 2019).

The study of published work has shown that *Bauhinia variegata* L. has anticancer potential which needs to be studied systematically with delineating the molecular basis of action. With this in mind, the proposed study has been aimed to identify the active phytocomponent/s from leaves of *Bauhinia variegata* L. which are accountable for the anti-cancerous activity against breast cancer cell lines.

The objectives of the study are as under:

1) **Extraction, Activity guided fractionation and characterization of the crude extract from *Bauhinia variegata* L.**

   A. Extraction from *Bauhinia variegata* L. leaves and evaluation of its anti-oxidant potential.

      i. Phytochemical Extraction from *Bauhinia variegata* L. leaves.

      ii. Phytochemical profile of *Bauhinia variegata* L. extracts.

      iii. Evaluation of the anti-oxidant potential of *Bauhinia variegata* L. extracts.

   B. Activity guided fractionation of crude extracts from *Bauhinia variegata* L.

      i. To check the cytotoxic effect of *Bauhinia variegata* L. extracts on MCF-7 and MDA-MB-231 cells in time and dose dependent manner.

ii. To check the cytotoxic effect of different fractions of active extract on MCF-7 and MDA-MB-231 cells.

C. Isolation and characterization of the phytocomponents in active extract/fraction by Flash Chromatography/HPLC/LC-MS.

2) To analyse the effect on breast cancer cell migration, invasion and TNF- α regulated cell growth in response to active extract/fraction/isolated phytocomponent/s of *Bauhinia variegata* L.

A. To assess the effect of active extract on Cell Invasion, Migration, Wound healing and Clonogenic ability in MCF-7 and MDA-MB-231 cells.

B. To study the effect of *Bauhinia variegata* L. active extract on cellular spheroids.

C. To evaluate the effect of active extract on cell proliferation in absence and presence of TNF-α in MCF-7 and MDA-MB-231 cells.

3) To analyse the effect of active extract/fraction /isolated phytocomponent/s of *Bauhinia variegata* L. on cell death parameters in breast cancer cell lines.

A. Analysis of mitochondrial membrane potential in MCF-7 and MDA-MB-231 cells in response to *Bauhinia variegata* L. active extract.

B. To examine the effect of *Bauhinia variegata* L. active extract on type of cell death in MCF-7 and MDA-MB-231 cells.

Results:

1) Extraction, Activity guided fractionation and characterization of the crude extract from *Bauhinia variegata* L.

Leaves from *Bauhinia variegata* L. were procured from Waghai Botanical Garden, Waghai, Dang. For authentication, the collected material was sent to Botany Department, The M.S. University of Baroda. The voucher specimen is stored for future reference. The material was then weighed and kept for shade drying. The powder was then weighed and placed into a thimble. The Soxhlet Exaction was carried out using different solvents (petroleum ether, n-hexane, chloroform, ethyl acetate, methanol) of increasing polarity. After this eluotropic series, cold maceration using water was carried out to obtain aqueous extract. The antioxidant potential of the extracts was determined by performing DPPH radical scavenging assay and it was seen that Petroleum ether and n-hexane extracts had least antioxidant activity. Methanol and Aqueous extract showed maximum antioxidant activity. Cytotoxic effect of each extract was checked using MTT assay by exposing the MCF-7 and MDA-MB-231 cells to varying concentration and time period (24 hours, 48 hours, 72 hours) of the extract. Aqueous extract showed good cytotoxicity against both the cell-lines. IC 50 was found to be 10 µg/ml for 72hrs treatment for MCF-7 cells and 48hrs for MDA-MB-231 cells respectively. To decrease the incubation time, cells

were exposed to high concentration of aqueous extract which showed IC50 of 35 µg/ml for MCF-7 cells and 1300 µg/ml for MDA-MB-231 cells. Phytochemical analysis (qualitative) of the extracts obtained was done.

As aqueous extract showed good cytotoxicity, it was decided to take it for further studies. TLCs were run to find out the solvent system suitable for the Flash Chromatography. Different fractions were collected from Flash chromatography of aqueous extract and TLC was done. Again, MTT was performed from the fractions on MDA-MD-231 cells which showed cytotoxic activity. HRLC-MS analysis revealed the presence of three known anti-cancer compounds: Berbamine, 4'-Desmethylpapaverine and Rhapontin in the aqueous extract. These compounds are known to possess cytotoxic property against various cancer cells. Berbamine was found to block the fusion between autophagosome and lysosome fusion by impeding the interaction of SNAP29 and VAMP8 (Fu *et al.*, 2018). Papaverine has ability to reversibly inhibits mitochondrial complex I and sensitizing EO771 breast tumor cells to radiation therapy (Benej, M. *et al.*, 2018). Literature suggests Rhapontin suppresses cell-growth of KATO III by apoptosis (Hibasami *et al*., 2007).

2) **To analyse the effect on breast cancer cell migration, invasion and TNF- α regulated cell growth in response to active extract/fraction/isolated phytocomponent/s of *Bauhinia variegata* L.**

Effect of different concentration of aqueous extract was check on wound healing ability of ER/PR +ve and ER/PR -ve cells. Wound closure was observed in control cells within 72 hrs by cell migration whereas breast cancer cells treated with different concentrations of aqueous extract showed impairment in migration.

Clonogenic cell survival assay was carried out to determine the effect of active extract on clone forming ability of MCF-7 and MDA-MB-231 cells. The cells treated with extract of *Bauhinia variegata* L. showed decreased clonogenic ability in concentration dependent manner, suggesting loss of cloning ability of both the cell-lines.

Effect of Aqueous extract was checked on both ER/PR positive and negative cell-lines in presence of TNF-α and estradiol by MTT assay, and it was seen that the extract showed decreased cell proliferation when exposed for 24 hours. Similar results were seen in 3D tumor model called spheroids. It was found that migration was arrested in extract treated spheroids compared to untreated spheroids of MCF-7 cells. Effect of aqueous extract was also checked on MCF-7 spheroids in presence and absence of TNF-α and estradiol. Cells migrated from the periphery of the spheroid when treated individually with TNF-α and Estradiol. The cells showed decreased migration in presence of TNF-α and Estradiol both as compared to the independent exposure of the TNF-α and Estradiol. It was concluded that the aqueous extract has the potential to inhibit the migration of cancer cells. Migration was monitored for different time intervals (24, 48 and 72 hours). It was difficult to generate spheroids from MDA-MB-231 cells owing to its invasive property.

3) To analyse the effect of active extract/fraction /isolated phytocomponent/s of *Bauhinia variegata* L. on cell death parameters in breast cancer cell lines.

Apart from its well-established role in cellular energetics, mitochondria are important mediators of cell death due to the presence of apoptogenic factors. Aberrations in the mitochondrial membrane are the initiators of cell death. Analysis of mitochondrial membrane potential in MCF-7 and MDA-MB-231 cells in response to *Bauhinia variegata* L. aqueous extract was performed using TMRM dye. Significant reduction in mitochondrial membrane potential was observed in MCF-7 cells treated with 10 µg/mL and 35 µg/mL of extract. MDA-MB-231cells showed significant reduction in fluorescence when treated with 1300 µg/mLof aqueous extract suggesting loss of mitochondrial membrane potential.

Effect of active extract /isolated phytocomponent/s from *Bauhinia variegata* L. on mitochondrial membrane potential and cell death parameters in both breast cancer cell-lines needs to be analysed.

Conclusion:

Bauhinia variegata L. leaves methanolic and aqueous extract possesses good anti-oxidant property. The aqueous extract possesses most cytotoxic activity compared to other extracts on both ER/PR+ and ER/PR- breast cancer cell lines. The aqueous extract was tested for its anti-cancer properties against breast cancer cell-lines MCF-7 and MDA-MB-231. Both these cell lines differ in their hormonal profile and invasive ability. Aqueous extract showed inhibition of cell migration of MCF-7 and MDA-MB-231 cells, along with MCF Spheroids. Clonogenic ability of both the ER/PR +ve (MCF-7) and ER/PR -ve (MDA-MB-231) cell-lines was decreased when exposed to aqueous extract of *Bauhinia variegata* L. TNF-α is known to possess dual property of increasing cell proliferation and inducing cell apoptosis depending on which pathway it activates. It was observed that cell growth was restricted by TNF-α in presence of our active extract. It suggests that Aqueous extract modulates TNF-α induced cell growth and migration in both the cell-lines and also in MCF-7 spheroids. *Bauhinia variegata* L. aqueous extract also showed loss of mitochondrial membrane potential in both the cell-lines.

In conclusion, aqueous extract is efficient in inhibiting the cell migration and invasion of breast cancer cell lines, indicating presence of anti-cancer phytocomponents in the extract which possess TNF- α modulating properties. Three anti-cancerous compounds Berbamine, 4'-Desmethylpapaverine and Rhapontin were detected in aqueous extract and anti-cancerous property of our extract might be due to synergistic effects of these compounds or either individual effect.

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Achievements

Publications:-

Mononuclear copper (II) and binuclear cobalt (II) complexes with halides and tetradentate nitrogen coordinate ligand: Synthesis, structures and bioactivities.

Mehul H. Sadhu, Sujit Baran Kumar, Jaswinder Kaur Saini, Sejal S. Purani, Tanvi R. Khanna. Inorganica Chimica Acta 466 (2017) 219–227

Conference Abstract Published in Journal:

- **Purani S.**, P. Robin, S. Dave. Elucidating Therapeutic potential of *Bauhinia variegata* L. using breast cancer cell line. European Journal of Cancer 92, Suppl. 3 (2018) S17–S160

Poster presentation:

- Poster Presentation at 6th International Translational Cancer Research Conference – "Prevention and Treatment of Cancer: Hypes and Hopes" held during February 04-07, 2016 at Hyatt Regency, Ahmedabad, Gujarat, INDIA.

- Poster Presentation at "National Symposium on Current Research In cancer Biology & Therapy" from 7-8 October 2016 at School of Biological Science & Biotechnology, University & Institute of Advanced Research, Koba Institutional Area, Gandhinagar, Gujarat.

- Poster Presentation at 11th European Breast Cancer Conference (EBCC) held during 21st - 23rd March 2018 at Centre de Convencions International de Barcelona in Barcelona, Spain.

Conferences Attended:

- Attended UGC-DRS Sponsored Two day National Seminar on "MOLECULAR BASIS OF DISEASES" Organized on 1-2 AUGUST, 2014 at Department of Biochemistry, The Maharaja Sayajirao University of Baroda, Vadodara
- Attended a National conference on "Herbal Drug Research: Opportunities and Challenges" November 5-7, 2014 at B.V. Patel Education Trust & B.V. Patel PERD Centre, Ahmedabad, Gujarat.
- Attended Three day National Symposium on "Emerging Trends in Biochemical Sciences" Organized on 29th -31st December, 2014 at Department of Biochemistry, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat.
- National Symposium on "Current Research In cancer Biology & Therapy" from 7-8 October 2016 at School of Biological Science & Biotechnology, University & Institute of Advanced Research, Koba Institutional Area, Gandhinagar, Gujarat.
- National Symposium on "Omics to Structural Basis of Diseases" from September 30-October, 2016 at Department of Biochemistry, Faculty of Science, The M. S. University of Baroda, Sayajigunj, Vadodara, Gujarat.
- One Day International Seminar on "Advances in Cancer and Cell Biology" on 6th January 2018 at Department of Microbiology and Biotechnology Centre, The M. S. University of Baroda, Vadodara, Gujarat.
- 11th European Breast Cancer Conference (EBCC) held during 21st -23rd March 2018 at Centre de Convencions International de Barcelona in Barcelona, Spain.
- International Symposium on "Vaccine Development and Infectious Diseases" on 7th January 2019 at Department of Microbiology and Biotechnology Centre, The M. S. University of Baroda, Vadodara, Gujarat.
- National seminar on "Translational Research in Cancer" on 1st -2nd February, 2019 at Ramanbhai Patel college of pharmacy, Charotar University of Science and Technology, Changa, Gujarat.
- International Symposium on "Trends in Biochemistry" on 27th -28th September, 2019 at Department of Biochemistry, The M. S. University of Baroda, Vadodara, Gujarat.

- ❖ MSU PhD Conclave 2020 on 25th February 2020 at Faculty of Science, The M. S. University of Baroda, Vadodara, Gujarat

Workshops Attended:

- ❖ DST-MSUB-ILSPARE sponsored Four day workshop on "Advanced Techniques in Stem Cell Research" Organized from 31st December, 2014 – 3rd January, 2015 at Department of Biochemistry, The Maharaja Sayajirao University of Baroda, Gujarat.
- ❖ Attended One day Workshop on "Science Communication Workshop" Organized on 11th March, 2016 at Department of Microbiology and Biotechnology Centre, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat.
- ❖ One day Workshop on "Research Grant Writing" by GSBTM in collaboration with The National Academy of Sciences, India (NASI)on the 30th August, 2016 at Ahmedabad Management Association (AMA), Ahmedabad, Gujarat.
- ❖ Five-day workshop on Frontiers of NMR spectroscopy and MRI from 25th to 29th September 2017 at Shree M. & N. Virani Science college, Rajkot, Gujarat.
- ❖ Workshop on "Computer aided drug discovery and Microbiome analysis" Organized on 31st March, 2019 at Department of Biosciences, Veer Narmad South Gujarat University,Surat, Gujarat.
- ❖ Workshop on "Flow cytometry in Research and Health Care" held at Nirma University from 3-5th March,2020

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