

**ABSTRACT**

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**TITLE: Evaluation of LIMD1-VHL targeting microRNA as biomarker in Uterine Cervical Carcinogenesis****Submitted by: FARHIN SULTANA**

Cervical cancer (CaCx) remains a major health concern, especially in low- and middle-income countries (LMICs), due to limited screening and treatment options. It is the fourth most common cancer globally and the second most prevalent in India, primarily driven by persistent high-risk human papillomavirus (HR-HPV) infection. HR-HPV promotes tumor progression by stabilizing hypoxia-inducible factor-1 alpha (HIF-1 $\alpha$ ), which is normally regulated by tumor suppressor genes (TSGs) LIMD1 and VHL. While their downregulation is often linked to genetic or epigenetic alterations, some cases suggest alternative regulatory mechanisms.

This study identifies microRNAs (miRNAs) as potential regulators of LIMD1 and VHL suppression. Through in silico analysis, miR-135b-5p (targeting LIMD1) and miR-21-5p (targeting VHL) were found to be overexpressed in cervical lesions, correlating with disease progression. The study also highlights MIR135B locus amplification as a key genetic mechanism driving miR-135b-5p upregulation. These findings suggest that these miRNAs contribute to HIF-1 $\alpha$  dysregulation and cancer progression.

Given their distinct expression patterns, miR-135b-5p and miR-21-5p were evaluated as potential biomarkers for cervical cancer screening. A validation study in 243 cervical swab samples confirmed their ability to differentiate between low- and high-grade cervical dysplasia with high sensitivity (90.4%) and specificity (94%). To enhance accessibility, a fluorescence-based miRNA detection method for miR-135b-5p was developed, offering a cost-effective alternative to quantitative real-time PCR (qRT-PCR).

Mechanistic studies revealed that miR-135b-5p and miR-21-5p regulate LIMD1 and VHL expression, affecting cancer cell proliferation, apoptosis, and metastasis. Dual inhibition of these miRNAs restored tumor suppressor activity, induced cell cycle arrest, and reduced migration and invasion of cervical cancer cells. These effects were linked to the suppression of HIF-1 $\alpha$  target genes, including VEGF, MMP9, TGF- $\alpha$ , and CCND1.

By bridging the gap between HR-HPV screening and clinical interventions, miR135b-5p and miR-21-5p-based triaging hold significant potential in early detection of clinically relevant cervical lesions, thereby, minimizing overtreatment in low resource settings.

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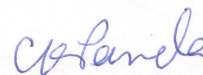
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