https://doi.org/10.48047/AFJBS.6.15.2024.9408-9433

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

The Roles Of MicroRNAs In High-Risk Human Papillomavirus Related To Cervical Cancer: An Overview And Potential Biomarkers.

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Volume 6, Issue 15, Sep 2024

Received: 15 July 2024

Accepted: 25 Aug 2024

Published: 05 Sep 2024

doi: 10.48047/AFJBS.6.15.2024.9408-9433

Abstract

Human papillomavirus (HPV) is associated with the development of several malignancies including cervical cancer. Cervical cancer risk is increased by persistent high risk-HPV (hrHPV) infection. MicroRNAs (miRNAs) have become recognised as significant regulators in the pathogenesis of many diseases including cervical cancer. MiRNAs are short, non-coding RNA molecules that play pivotal roles in controlling gene expression, and affecting several biological processes including cellular activities such as proliferation, apoptosis, and immune response. This review examines the roles of miRNAs in the development of cervical cancer associated with hrHPV. We investigate how HPV infection alters the expression pattern of miRNAs, therefore contributing to the malignant transformation of cervical epithelial cells. Moreover, the review also explores the potential of miRNAs to serve as diagnostic and prognostic biomarkers for patients with cervical cancer. The discovery of miRNA signatures associated with HPV-related cervical cancer offers promising avenues for personalised medicine and targeted therapies. As research advances, understanding the intricate relationship between miRNAs and HPV could lead to novel strategies for combating this malignancy, ultimately improving patient prognosis. This review underscores the need for further investigation into miRNA-based interventions as part of the broader effort to reduce the global burden of cervical cancer.

Keywords: MicroRNA, human papillomavirus, cervical cancer, biomarker

Introduction

Human papillomavirus (HPV) is a primary etiological factor for infection-related cancer, mostly transmitted via sexual intercourse. It is also the predominant cause of cervical malignancies (Serrano et al., 2018)**.** There are more than 200 HPV types known to exist. HPV can be grouped into low-risk and high-risk types. Low-risk HPV types (HPV-6, -11, -42, -43, and -44) infection causing benign genital warts without inducing malignancy. Opposite to the high-risk types, there are16 high-risk types (HPV-16, -18, -31, -33, -34, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68, and -70) and are reported to be carcinogenic. High-risk HPV (hrHPV) has been associated to the development of cervical cancer (Causin et al., 2021). Persistence infection of hrHPV genotypes, an oncogenic, may produce cervical cancer and other forms of carcinomas (Gupta et al., 2018). HPV-16 and HPV-18 were the two most common high-risk genotypes that can become cancerous over time where these two high-risk types have become major risk factors that account for 70% of total cervical cancer cases (Bañuelos-Villegas et al., 2021; Okunade, 2020; Szymonowicz et al., 2020).

According to GLOBOCAN 2022 data, cervical cancer is ranked as the eight most prevalent cancer worldwide. Among women, it is the fourth most common type of cancer, following breast, lung and colorectal. In 2022, more than 650,000 new cervical cancer cases were diagnosed among women (Bray et al., 2024). Although not all HPV infections result in cervical cancer, 99.7% of cervical cancer cases are caused by persistent infection from hrHPV genotypes (Na et al., 2023). This information suggests the presence of several factors that promote tumor progression in persistent infections with hrHPV genotypes including epigenetics. Epigenetics changes can impact gene expression without altering DNA sequence. These changes encompass DNA methylation, demethylation, histone modification and regulation by RNA-mediated targeting regulators (Durzynska et al., 2017; Laengsri et al., 2018).

MicroRNAs (miRNAs) are short, non-coding RNA (≈28 nucleotides) that function at the post-transcriptional level in the regulation of cellular processes such as cell development, differentiation, proliferation, and apoptosis (Bañuelos-Villegas et al., 2021). MiRNA binds to the 3’ untranslated region (3’ UTR) of target mRNAs. This interaction leads to the repression of gene expression through mRNA degradation and translational inhibition. Numerous studies have documented the dysregulation of miRNAs in a variety of diseases including malignancies

(Arif et al., 2020; Condrat et al., 2020; Dragomir et al., 2022; Franczyk et al., 2022; Lee et al., 2021; Zhou et al., 2018). Aberrant miRNAs expressions are reported in various cancers such as breast, colorectal, lung, blood malignancies as well as cervical cancer (Harden et al., 2017; Iqbal et al., 2019; Loh et al., 2019; Luo et al., 2015; Mohammadi et al., 2016; Moloudizargari et al., 2021). MiRNAs act as tumour suppressors (tsmiRs) or oncogenes (oncomiRs) based on their regulating effects on the expression of their target genes (Snoek et al., 2019).

However, the specific role of miRNAs in the progression of cervical cancer caused by hrHPV infection is not fully understood. The goal of this review is to summarise the involvement of miRNAs in the progression of cervical cancer caused by persistent hrHPV infection. Lastly, our findings might shed light on the application of miRNAs as biomarkers in the development of miRNA-based cervical cancer therapies as well as in the prediction or diagnosis of the disease.

2.0 Association between HPV infection with cervical lesion and progression to cervical carcinogenesis.

HPV consist of over 200 genotypes with approximately 15 of these genotypes, categorised as hrHPV, were linked to cervical lesion and cancer. Following HPV infection, cross-protective antibody is unable to be generated inside the hosts. This is due to the difference in the capsid proteins across different genotypes of HPV. This incapability contributes to the condition of reoccurrence infection as well as multiple genotypes infection (Li et al., 2024). Cervical lesion is an infectious condition, and several research findings have confirmed that this condition is caused by multiple HPV genotypes infection whereby this condition has been reported to be associated with persistent HPV infection. Research has shown that the risk of developing cervical lesions is higher with multiple HPV infections compared to a single infection (Bello et al., 2009; Della Fera et al., 2021; Kim et al., 2021; Rousseau et al., 2001).

Progression into cervical carcinogenesis from HPV infection is a lengthy process that involved the gradual advancement in the severity of cervical intraepithelial neoplasia (CIN). About 70% to 75% of women infected with HPV were diagnosed with HSIL, and approximately 1% to 4% of them may progress to become chronic and potentially lead to dysplastic changes in the cervix or precancer thus turns into cancer (Azimi et al., 2021; Rs, 2021). CIN, the precancerous squamous epithelium lesion of the cervix, is a histologic diagnosis of a cervical biopsy

specimen based on tissue examination. CIN is classified as grade 1, 2**,** and 3 (CIN1, CIN2, CIN3) based on the extent of cellular abnormalities observed in the cervix. Similarly, during a pap smear, cytologists interpret the results as low-grade squamous intraepithelial lesions (LSIL) or high-grade squamous intraepithelial lesions (HSIL) based on Bethesda System. CIN1 corresponds to LSIL or mild dysplasia, while CIN2 and CIN3 correspond to HSIL or moderate and severe dysplasia, respectively. HSIL is likely to further progressed into carcinoma (Bruno et al., 2021). CIN1, or mild dysplasia, is usually seen within 6 to 12 months and often spontaneously regresses by immune system (Shanmugasundaram & You, 2017), while CIN2 is characterized by cellular atypia affecting about two-thirds of the cervix's epithelial thickness. At this stage, the process remains reversible with approximately 40% of the cases with poor treatment will regressing spontaneously. Whereas, the condition of the cervix is graded as CIN3 where more than two-thirds of the epithelial thickness shows atypia, is more likely to lead to malignancy, though about one-third of these lesions may heal on their own (Salcedo et al., 2022). It is commonly known that persistent HPV infection, particularly from high-risk genotypes is the primary cause of CIN. The severity of CIN may progress to become cancerous in certain women, leading to cervical cancer while it may be completely eradicated in others.

Among hrHPV genotypes, HPV-16 infection was reported to be a relatively high incidence in high-grade lesions due to this infection presenting a high viral load. Noticeably, other hrPHV types for CIN risk include HPV-18, -31, -33, -45, -52, and -58. Previous research also found that the probability of high-grade CIN was affected by both the HPV genotype and its viral load (Adcock et al., 2019). A study has observed that a single infection from a hrPHV genotype causes the highest risk of cervical lesions. However, it has been observed in cases where co-infection of multiple HPV genotypes, in regards to high-risk or low-risk HPV genotypes, the cervical lesion was not higher. This has proven that there is no such synergistic effect in any of the multiple combinations of HPV infection patterns (Liang et al., 2019; Salazar et al., 2015).

Cervical cancer carcinogenesis is caused by persistent hrPHV infections, which lead to a progressive transition from precursor lesions to invasive cancer. This process is facilitated by the dysregulation of both host and viral gene expression due to the integration of viral DNA into the host genome, resulting in epigenetic modifications. The risk of developing cervical cancer and cervical lesions varies based on the potential of various subtypes of HPV infection and the variations in their pathogenicity. Up to 80% of the incidence of cervical cancer can be

reduced among women presented with precursor lesions with high compliance to treatment and regular follow-up (Basu et al., 2018).

The HPV proteins, E6 and E7 are the primary oncoproteins contributing to the development of cervical carcinogenesis by associating with p53 and pRb tumor suppressor protein, respectively. These two proteins function by targeting various downstream modulators, thereby affecting critical pathways involved in the development of cancer such as MAPK-, mTORC-, Wnt-, Notch-, Akt-, and STAT-dependent cascades (Bonab et al., 2021; Pal & Kundu, 2020). Additionally, these oncoproteins also interact with some other crucial functional proteins (i.e., transcription factor and epigenetic regulator) causing some alteration in the activity of gene expression which could results in cell invasion and tumor progression (*as illustrated in Figure 1*) (Harden et al., 2017).

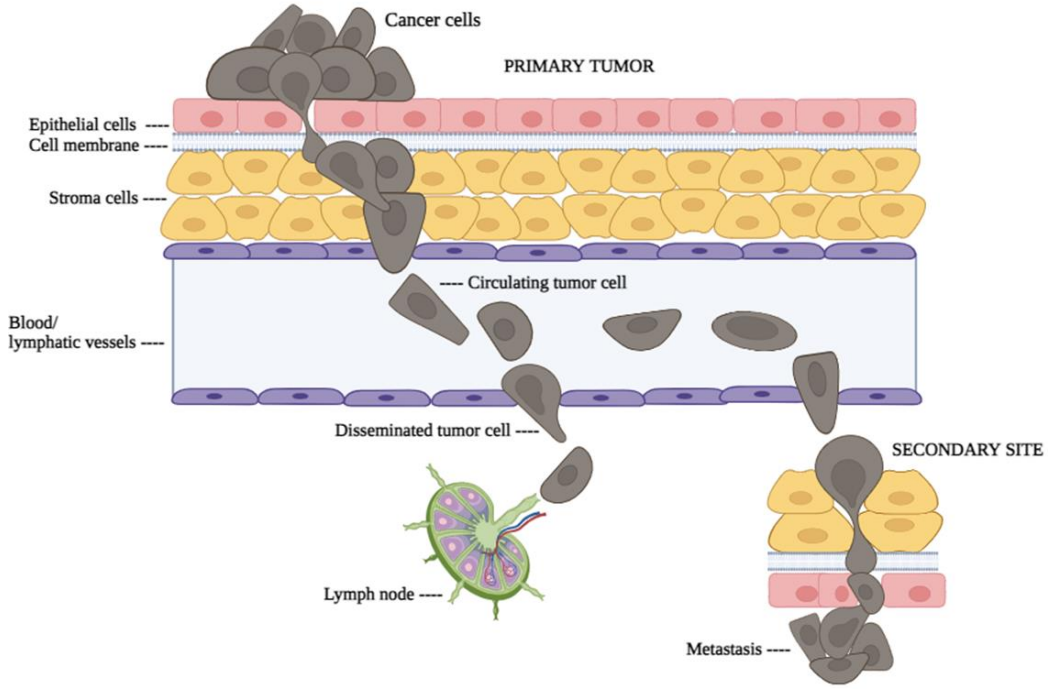

Figure 1*: Invasion of cancer cells and progression to metastatic stage in cervical carcinogenesis.*

A study focused on phylogeny and polymorphism in the E6 and E7 gene variants for 14 common HPV genotypes, consist of -16, -31, -33, -52, -58, -51, -53, -66, -18, -39, -59, -68, -6 and -44 were successfully classified into five species groups: α-9 (HPV16, 31, 33, 52, 58), α-5 (HPV51), α-6 (HPV53, 66), α-7 (HPV18, 39, 59, 68) and α-10 (HPV6, 44). The analysis

revealed that the incident of HSIL was significantly increased in patients infected with α-9 HPV compared to other groups, especially HPV-16 (Zhao et al., 2019).

3.0 MicroRNA and cancer

MiRNAs are short, non-coding RNAs (≈28 nucleotides) that regulate the expression of coding genes. This gene is essential for various biological processes such as cell growth, proliferation, and cell death. MiRNAs act as negative modulators of gene expression via post-transcriptional mechanisms (Ge et al., 2018; O'Brien et al., 2018). The activity of microRNA is characterised by either the degradation of mRNA or the repression of translation (*Figure 2*).

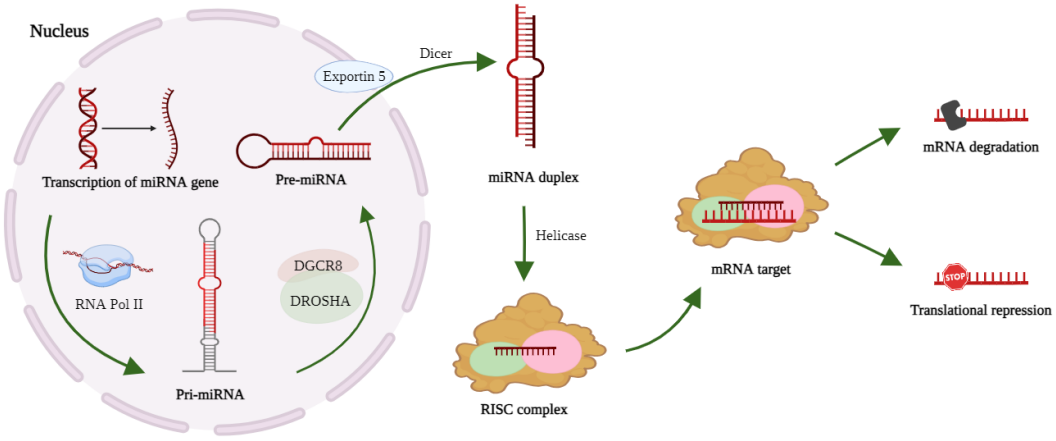

Figure 2: *Biogenesis of miRNA.*

The primary miRNA (Pri-miRNA) is generated in the nucleus before initiating the standard pathway to form miRNAs. Subsequently, the poly AAA tail's end was cleaved due to the interaction between the Drosha enzyme and the DGCR8 cofactor, which is associated with the characteristic hairpin shape of pri-miRNA. This will result in the formation of the precursor miRNA (Pre-miRNA). With the aid of exportin 5, pre-miRNA is exported out from the nucleus to the cytoplasm. Hence, in this stage, the Dicer enzyme cleaved the pre-miRNA and removed the terminal loop to produce a mature miRNA duplex. With the presence of helicase, the RISC complex will only guide one of the matured strand miRNAs to the target mRNA. The interaction of the matured strand of miRNA with target mRNA will lead to translational activity either to stop or alternatively lead to degradation of mRNA in this condition occurs when perfect pairing between both miRNA and mRNA occurs (O'Brien et al., 2018; Wu et al., 2018).

Researchers have been increasingly interested in studying the significant roles of microRNAs in disease progression particularly in relation to cancer development and progression. In addition, recent findings have also revealed that long noncoding RNAs (IncRNAs) play a vital role in the development and progression of cancer by interacting with various regulatory proteins, including ribonucleoprotein (RNP) complexes, transcriptional factors/co-activators, and epigenetic modifiers (Vafadar et al., 2019; Zhang et al., 2020). Initial evidence of miRNA involvement in cancer emerged in 2002, shortly after the discovery of the first human miRNA, the let-7 family (Lee et al., 2016). This discovery spurred further investigation into the functions of miRNAs in disease advancement (Reddy, 2015).

Current research indicates that over 50% of miRNA genes are located in cancer-associated genomic regions. MiRNA dysregulation has been documented in various cancers, highlighting their potential role in malignancy. Specifically, miRNAs can either promote or inhibit tumor development by modulating tumor suppressor genes or oncogenes (Chakrabortty et al., 2023). Tumor-suppressive miRNAs (tsmiRs) are generally under-expressed in malignancies, whereas oncogenic miRNAs (oncomiRs) are overexpressed. Depending on the type of cancer and the miRNAs involved, there may be a considerable reduction in cancer cell proliferation, metastasis, and/or survival when these oncomiRs or tsmiRs are stimulated or inhibited, respectively (Svoronos et al., 2016). MiRNA-21 is one of the most frequently expressed miRNA in various cancers (Elghoroury et al., 2018; Feng & Tsao, 2016; Huang et al., 2013; Qu et al., 2017; Seputra et al., 2021; Wang et al., 2011; Zamani et al., 2019). Table 1 summarises the differential expression of miRNAs in various cancers.

Table 1: Differential Expression of miRNAs in Various Cancers.

Types of Cancer	MiRNA Expression		References
	Upregulated	Downregulated	
Breast	miR-9 miR-10b miR-21 miR-29 miR-182-5p miR-221/222 miR-373 miR-374b-5p miR-942-5p	miR-145 miR-199a-5p miR-200 family miR-203 miR-205 miR-329 miR-362-3p	(Kang et al., 2016; O'Bryan et al., 2017; Piasecka et al., 2018; Zhang et al., 2017)
Lung	miR-17-92 cluster miR-21 miR-93 miR-106b miR-155 miR-196b-5p miR-210 miR-372 miR-373	let-7 family miR-15a/16-1 miR-29 family miR-34a miR-126 miR-145 miR-200 family miR-335 miR-451a	(Frydrychowicz et al., 2023; Wu et al., 2019; Yan et al., 2022; Zhong et al., 2021)
Colorectal	miR-10b miR-17 miR-31-5p miR-106b/93/25 cluster miR-106a/363 cluster miR-145-5p miR-183/96/182 cluster miR-301a-3p miR-452	let-7 family miR-29 family miR-34a miR-101 miR-145 miR-152-3p miR-125b miR-488	(Cui, 2019; Lu et al., 2020; Ma et al., 2015; Ramzy et al., 2015)

Hematological Malignancies	miR-21 miR-17-92 cluster miR-125b miR-146a miR-150 miR-155 miR-196b	miR-15a/16-1 miR-29b miR-34a Let-7 family miR-143 miR-9	(Anelli et al., 2021; Gupta & Rahman, 2019; Marco et al., 2018; Mendiola-Soto et al., 2023; Testa et.al., 2022; Trino et al., 2018; Yeh et al., 2016)

With advancement of high throughput technology for detection of miRNA quantification such as next-generation sequencing, microarray, Northern blot-based platforms, and real-time polymerase chain reaction has made it possible to explore global miRNA profile in the whole cancer genome and results from a previous investigation have demonstrated that the miRNA profiles of cancer cells differ significantly from those of normal control cells in the same tissue. Furthermore, these important discoveries regarding miRNA dysregulation in human cancer have proven to be a strong diagnostic, classification, and prognostic tool (Dave et al., 2019; Ouyang et al., 2019; Zhu et al., 2019). It is also demonstrated in many studies, a large high throughput of miRNA profiling among cancer cases was done for diagnosis and prognosis. Besides, many researchers utilize potential miRNA as a great biomarker in both cancer diagnostic and therapeutic targets in cancer management and prognosis (Bertoli et al., 2015; Cho, 2010; Florczuk et al., 2017; Hasanzadeh et al., 2019; Heneghan et al., 2010; Tan et al., 2018).

3.1 Roles of miRNAs in the development and progression of cervical cancer associated with HPV.

MiRNAs have a significant effect on the formation and progress of cervical cancer, especially in cases caused by hrHPV infection. Biological processes in cervical cancer involve the modification of miRNA expression by hrHPV oncoproteins, specifically E6 and E7, which play a role in the development of cancer (Lo Cigno et al., 2024; Malla & Kamal, 2021).

MiRNAs that are dysregulated in cervical cancer have the ability to act as either oncogenes or tumour suppressors (Doghish et al., 2023). Certain miRNAs, known as oncomiRs, play a crucial role in the progression of cancer. They achieve this by specifically targeting genes that

suppress tumour growth, stimulating cell division, and preventing cell death. On the other hand, in cervical cancer, there may be a decrease in the expression of miRNAs that suppress tumour growth, resulting in uncontrolled cell proliferation and the development of cancer cells (Chakrabortty et al., 2023; Han et al., 2015; Tornesello et al., 2020).

MiRNAs play a crucial role in various cancer-related processes, including immune evasion, angiogenesis, and epithelial-to-mesenchymal transition (EMT), which contribute to the advancement of cancer (Wu et al., 2024). With their role as important regulators at the post-transcriptional level, miRNAs play a vital role in the molecular mechanisms responsible for cervical cancer caused by HPV. Moreover, they show promise as valuable diagnostic biomarkers and targets for therapeutic interventions (Babion et al., 2020; Tang et al., 2020).

3.2 Differential expression of miRNA in cervical cancer

The roles of oncomiRs and tsmiRs have been reported widely in hrHPV related cervical cancer (Abbas et al., 2021; Di Fiore et al., 2024; Xu et al., 2023). Hence, understanding both miRNA's functions and their roles on how they affect regulation in disease progression is important. The suppression and inhibition of oncomiRs are essential in inhibiting tumor progression whereas overexpression of tsmiRs may offer therapeutic benefits for anti-cancer therapy (Abd-Aziz et al., 2020).

Certain miRNAs are overexpressed in cervical cancer and functioning as oncomiRs, by targeting tumour suppressor genes, thereby, promoting carcinogenesis. MiR-21 is one the most significant upregulated miRNA in cervical cancer by inhibiting tumor suppressor genes (PTEN, RASA1, TIMP3 and AP-1), leading to enhance cell proliferation and invasion thus suppressing apoptosis (del Mar Díaz-González et al., 2019; Gao et al., 2021; Ruan et al., 2020; Xu et al., 2015; Zamani et al., 2019; Zhang et al., 2016).

Similarly, miR-155 is also upregulated in cervical cancer and is associated with poor prognosis as well as correlated with lymph nodes metastases and invasion (Fang et al., 2016). This finding was supported by another study conducted by Li et al. (2019), where miR-155 was significantly overexpressed in both SiHa and CaSki cervical cell lines.

In another study, miR-205 was found to be upregulated in human cervical cancer tissue. Subsequently, *in vitro* study using Hela cervical cell line revealed that this miRNA regulates CHN1 gene by promoting carcinogenesis (Liu et al., 2020). Recent study was done in cervical tissue sample also reported that this miRNA promotes cell viability and migration by targeting GATA Binding Protein 3 (GATA3) (Han & Xu, 2022). In contrast, miR-205 was found to be downregulated in breast cancer and human glioma (Huo et al., 2016; Yue et al., 2016). This suggests that similar miRNA can act either oncomiR or tsmiR in different diseases. This is because single miRNA can regulate multiples genes whereas one gene can be regulated by multiple miRNAs (Xu et al., 2020).

Conversely, some miRNAs were downregulated in cervical cancer including miR-100 and miR-375. Transfection of MiR-100 mimics successfully downregulates the expression of SATB1 gene in CaSki cervical cell line (Huang et al., 2020). Downregulation of miR-100 has also been reported in various cancer including breast, colorectal and prostate (Chen et al., 2014; Gong et al., 2015; Wang et al., 2014). On the other hand, upregulation of miR-100 was observed in acute myeloid leukaemia, renal cell carcinoma and pancreatic cancer (Sánchez et al., 2016; Sun et al., 2020; Wang et al., 2013). These studies suggest that the role of miR-100 may differ among different cancer types. Additionally, the expression level of miRNA in the same cancer could be different depending on different samples obtained such as blood, tissue or serum plasma (Pritchard et al., 2012). The discrepancies in these findings are still unclear and further investigation is warranted.

Likewise, a study conducted by Xiao & Zheng (2020), showed that the expression level of miR-375 was decreased in human cervical squamous cell carcinoma by targeting JAK2 gene. Similar study was conducted in several gastric cancer cell lines. In the study, miR-375 expression was substantially reduced in all cell lines derived from gastric cancers compared to the nonmalignant gastric cell line, GES-1. This finding suggests that miR-375 act as tsmiR in gastric carcinogenesis (Ding et al., 2010). It was also reported that the expression of this miRNA was downregulated in liver cancer (Xie et al., 2017). Likewise, miR-375 acts as oncomiR in promoting breast cancer (Tang et al., 2020).

Besides miRNAs that have been discussed, dysregulation of other miRNAs was also reported in cervical cancer studies as summarized in Table 2.

Table 2: Summary of other miRNAs involved in cervical carcinogenesis.

MiRNAs	Expression	References
let-7i	Upregulated	(Wilting et al., 2013)
miR-25	Upregulated	
miR-29b	Upregulated	
miR-92a	Upregulated	
miR-106b	Upregulated	
miR-145	Upregulated	
miR-595	Upregulated	
miR-26b	Downregulated	
miR-195	Downregulated	
miR-199a-5p	Downregulated	
miR-365	Downregulated	
miR-617	Downregulated	
miR-770-5p	Downregulated	
miR-193b	Upregulated	(Jiménez-Wences et al., 2016)
miR-218	Downregulated	
miR-31	Upregulated	(Causin et al., 2021)
miR-93	Upregulated	
miR-96-5p	Upregulated	
miR-200a	Upregulated	
miR-1	Downregulated	
miR-107	Downregulated	
miR-143	Downregulated	
miR-361-5p	Downregulated	
miR-383-5p	Downregulated	
miR-1284	Downregulated	

miR-2861	Downregulated	
miR-9	Upregulated	(Zeng et al., 2015)
miR-21	Upregulated	
miR-376a	Downregulated	
miR-497	Downregulated	
miR-15b	Upregulated	(Wen et al., 2017)
let-7c	Downregulated	(Malta et al., 2015)
miR-20b	Upregulated	(Endale et al., 2024)
miR-27a	Upregulated	
miR-106a	Upregulated	
miR-146a	Upregulated	
miR-185	Upregulated	
miR-23b	Downregulated	
miR-203	Downregulated	
miR-375	Downregulated	
miR-479	Downregulated	

4.0 Future directions

The potential of miRNAs as diagnostic and prognostic biomarkers in cervical cancer shows great promise due to their stability in body fluids, ease of detection, and disease-specific expression profiles. Research is now more focused on identifying specific miRNA signatures that can differentiate between benign HPV infections, precancerous lesions, and invasive cervical cancer. This helps improve early diagnosis and minimise unnecessary treatments.

MiRNAs have the potential to be used as non-invasive biomarkers that can be detected in blood, cervical smears, or urine. This could potentially enhance the accuracy of current screening methods, such as the Pap smear and HPV testing. In addition, the identification of dysregulated miRNAs associated with hrHPV infection could potentially provide a more accurate way to assess the risk level for patients. This could lead to personalised monitoring and early intervention strategies.

Furthermore, miRNAs can predict clinical outcomes, including tumour aggressiveness, likelihood of metastasis, and patient survival. Understanding the interaction between miRNAs

and resistance to treatments such as chemotherapy or radiotherapy could provide valuable insights for making updated therapeutic decisions. Looking ahead, the incorporation of miRNA profiles into clinical practice can completely transform how we approach the early detection, prognosis, and personalised treatment of cervical cancer.

5.0 Conclusion

In conclusion, miRNAs have significant impacts on the development of hrHPV-related cervical cancer. They regulate crucial cellular functions including cell proliferation, apoptosis, immune response, and metastasis. Biological dysregulation of miRNAs, under the influence of hrHPV oncoproteins, plays both functions as oncogenes and tumour suppressors, thereby playing a significant role in the initiation and advancement of cervical cancer. Their unique expression profiles in cervical cancer offer exciting possibilities for their application as diagnostic and prognostic biomarkers. Further research should prioritise the improvement of miRNA-based biomarkers for early detection, monitoring disease progression, and tailoring treatment to individuals. This has the potential to revolutionise how hrHPV-associated cervical cancer is clinically managed.

Acknowledgement

This research was funded by Ministry of Higher Education (MoHE) Malaysia, under the Fundamental Research Grant Scheme (FRGS), grant number FRGS/1/2022/SKK10/UNISZA/02/1.

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