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Irham Nugroho, Insih Wilujeng, Pujaningsih Pujaningsih, Muis Sad Iman, Witanti Witanti, Ani Arifah

This research aims to analyze science process skills (SPS) and higher order thinking skills (HOTS) questions in Natural Science textbooks for elementary school students in Indonesia. Using a qualitative approach, data was collected from independent curriculum student and teacher handbooks for grade IV...

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Within the past five years, or since the end of COVID-19, traditional performances have resurfaced in a variety of formats and forms. One such performance is the Jaran Thek, which is one of the Reyog Ponorogo arts that is most well-known to us and is practiced in the southern and eastern parts of the...

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Staphylococcus aureus and Escherichia coli are mainly two commensal and pathogenic human bacteria that cause skin infections in tropical regions. Flavonoids found in Soursop leaf's have been shown to have antibacterial effects. The aim of this research was to assess the antibacterial effectiveness of...

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An unpleasant encounter can act as a trigger for the development of psychological issues. Bullying among adolescents is on the rise, which increases the risk of psychosocial issues developing in those who are bullied. Bullying victims may experience long-lasting psychosocial issues, such as post-traumatic...

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Leila Nisya Ayuanda, Nur Intan Kusuma, Nur Izzah, Nur Chabibah

During the Covid-19 pandemic, pregnant women became a vulnerable group, so pregnant women were worried about their pregnancy. Pregnant women required special attention and services related to preventing anxiety so that it did not manifest in more severe psychological disorders. In this case, midwives...

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Purple sweet potato is a plant that having a purple pigment which is an anthocyanin pigment that functions as antioxidant. Antioxidants themselves are compounds that can inhibit free radicals. With the inhibiting oxidation reactions in easily oxidizable materials and resisting substrate oxidation due...

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Tia Laelasari, Neni Sri Gunarti, Eko Sri Wahyuningsih, Aliffia Dwi Rahma, Dinda Revalina Putri, Tiurdia Pandiangan, Zahra Adisty Rahma

Kombucha is a probiotic fermented drink produced through a consortium of bacteria and yeast known as Soby (Symbiotic Culture/Colony Bacteria & Yeast), serving as an initial culture that aids in the fermentation process. Kombucha also contains organic acids, including ascorbic acid, which is also...

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Every religion has guidelines for overcoming psychological problems, including by reaching the peak of spirituality (peak experience). Islam, Buddhism and Catholicism have different guidelines for achieving "peak experience", Islam with the path of Sufism, Buddhism with Hasta Ariya Magha or the eight...

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Alvionita Kogoya, Monica Dwi Hartanti

The fourth most common type of cancer in women, cervical cancer is brought on by the Hu-man Papillomavirus. Numerous genes, including KLF5, FHIT, and DLG2, have been linked to the advancement of cervical cancer, according to earlier research. The link between the KLF5, FHIT, and DLG2 genes in cervical...

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# Correlations of Expression of KLF5, FHIT and DLG2 with Cervical Cancer

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**Abstract.** The fourth most common type of cancer in women, cervical cancer is brought on by the Human Papillomavirus. Numerous genes, including KLF5, FHIT, and DLG2, have been linked to the advancement of cervical cancer, according to earlier research. The link between the KLF5, FHIT, and DLG2 genes in cervical cancer tissue is the focus of this investigation. Using a biopsy, cancer tissues were recovered. The RNA isolation, nanophotometer, and PCR methods were used to gather the cDNA samples. qPCR was used to analyse each sample. KLF5, FHIT, and DLG2 gene expression did not significantly correlate with cervical cancer ( $p > 0.05$ ). The results of the Spearman's correlation test study indicated that the expression of the genes KLF5, FHIT, and DLG2 did not significantly correlate with the advancement of cervical cancer. This research may be a resource used in biomedical science to learn more about the genes linked to the development of cervical cancer. The KLF5, FHIT, and DLG2 genes can still be established as biomarkers for cervical cancer by increasing the sample size.

**Keywords:** KLF5, FHIT, DLG2, Cervical Cancer.

## 1 Introduction

In the world, cervical cancer is the fourth most prevalent neoplasm and the fourth leading cause of cancer-related deaths in women [1,2]. Globally, there were 342,000 fatalities and 604,000 new instances of cancer in 2020, according to Global Cancer Statistics [2]. With 36,633 cases and 21,003 deaths from breast cancer, Indonesia came in second [2,3]. Cervical cancer mortality is correlated with diagnostic delay. Roughly 75% of fatalities have an advanced diagnosis that goes undetected [4], happens frequently in underdeveloped nations as a result of low socioeconomic position, ignorance, and insufficient vaccination and screening programme implementation [5].

The most common cause of cervical cancer is due to the abnormal growth of cells in the cervix as well as other cellular changes. Invasion will occur more quickly if there is the influence of epigenetic factors [5]. More than 70% of cancer cases cervical caused by Human Papillomavirus (HPV) types 16 and 18 [6,7]. When the virus is infected,

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there will be a mutation in host deoxyribonucleic acid (DNA) with certain environmental conditions. The Virus enters the host cell's DNA and activates proteins E6 and E7 so that can avoid cellular defense mechanisms and the immune system. The E2 Protein is also expressed to increase replication of viral DNA. Within a certain period, increased expression of HPV will inhibit some proteins are cellular and affect biological processes such as cell proliferation, cell cycle, and cellular apoptosis can accelerate and aggravate the carcinogenesis of cancer cells [4, 5].

A previous study by Hu et al "in 2015, found some "new spots" like KLF5, FHIT and DLG2 genes were involved in the carcinogenesis of cervical cancer [8] HPV integration sites in the introns and exons of these genes can increase or decrease protein expression, which can affect the rearrangement or amplification of surrounding genes [9,10]. Cells can experience DNA Replication Stress (DRS) due to exposure to many cellular changes that create gene mutations. Gene mutations can be compensated for by the p53 protein by detection and elimination by cellular apoptosis. However, the increased expression of Krüppel Like Factor 5 (KLF5) inhibits p53 so the mutation process takes place continuously [11]. The KLF5 gene is a DNA-binding transcriptional regulator that contributes to several cellular processes such as proliferation, differentiation, angiogenesis, migration, and cytoskeleton polymerization by regulating platelet-derived growth factor (PDGF)- $\alpha$ , cyclin D1, survivin, p21, p27 in gene targets [12]. In a study conducted by Ma et al in 2017, there was an increase in KLF5 gene expression in the tissues of cervical cancer. Elevated KLF5 expression activates the p38 signal pathway of tumor necrosis factor receptor superfamily member 11a (TNFRSF11a) by binding to the cyclin D1 promoter which enhances the proliferation, migration, and invasion of cervical cancer cells [11,12].

Fragile Histidine Triad Diadenosine Triphosphatase (FHIT) acts as a tumor suppressor gene that regulates apoptosis and suppresses tumor metastasis [13]. FHIT is overlapped by a fragile site FRA3B which is one of the 90 chromosomes Common Fragile Sites (CFS) fragile and easily damaged in the metaphase phase of chromosomes under high stress in DNA replication. Dysfunction of FHIT leads to increased expression of cyclin D1 thus accelerating the cycle of uncontrolled cell proliferation [14]. Decreased copy number and expression level of FHIT are associated with carcinogenic cervical cancer, especially at higher stages [15]. Discs Large MAGUK Scaffold Protein 2 (DLG2) gene derived from MAGUK (Membrane-Associated Guanylate Kinases) families that serve to regulate polarity, cellular structure, and cell growth [16]. The DLG2 gene also functions as a checkpoint in the G2/M cycle. It is believed that DLG2 promotes cell proliferation by accelerating the cell cycle phase G1 as well as cyclin A and cyclin B proteins [17]. This study aims to analyse the relationship between KLF5, FHIT, and DLG2 in cervical cancer.

## 2 Method

### 2.1 Collecting Samples

Cervical tissue sampling was performed at Dr. Cipto Mangunkusumo Hospital from citologically confirmed cervical cancer patients. Participating patients were not in any

stage of therapy. The tissue sample was taken by biopsy at a size of 0.5 x 0.5 x 0.5 cm<sup>3</sup>. The DNA/RNA buffer was used to store the samples in order to maintain the integrity of the RNA. Samples then transferred into the laboratory in a cool box and stored in the -80°C freezer for further analysis.

## 2.2 Extracting the RNA

RNA was extracted using the Quick-RNA Miniprep Plus Kit (Zymo Research Corp., Irvine, CA, USA) according to the manufacturer's protocol. Briefly, tissue was homogenized with a bead beater homogenizer then transferred to a microcentrifuge tube. The RNA lysis buffer was added and mixed accordingly. The mixture was then transferred into a spin-way™ Filter in a collection tube and centrifuged at 130,000g for 30 seconds to remove genomic DNA. Ethanol (95-100%) was then added to the flow through and the mixture was transferred to Zymo-Spin™ III CG Column in a new collection tube and centrifuged. DNase was used to treat samples from genomic DNA. RNA Prep Buffer and RNA Wash Buffer were used for washing the spin column containing RNA. The column was then transferred into a nuclease-free tube and DNase/RNase-free water was added directly on the column matrix and RNA was collected.

## 2.3 Synthesising the Complementary DNA

The reaction was prepared by mixing 200ng of RNA, 4 µl trans amp buffer, 1 µl reverse transcriptase, and DNase/RNase-free water to 20 µl. The mixture was then incubated in 25°C for 10 minutes, 42°C for 15 minutes, and 85°C for 5 minutes for inactivation.

## 2.4 Quantitative Real Time PCR (qRT-PCR)

The mixture was prepared in a PCR tube containing 5 µl 2x SensiFAST SYBR® No-ROX Mix reagent, 0.4 µl of 10 µM of each primer, DNA template and water until the final volume reaches 20 µl. The PCR condition was 95°C for 2 minutes, 95°C for 5 seconds, 60°C for 10 seconds and 72°C for 10 seconds. Forty cycles was used to amplify the DNA template.

## 2.5 Data Analysis

Data were analyzed using the GraphPad Prism 8.2.0 program and Microsoft excel 2019. Due the small sample size, the Shapiro-Wilks normality test was used to determine the normality of the data distribution. The Kruskal-Wallis test and Spearman test were carried out to analyze the differences and the correlations in gene expression levels, respectively. The value of  $p < 0.05$  was considered significant.

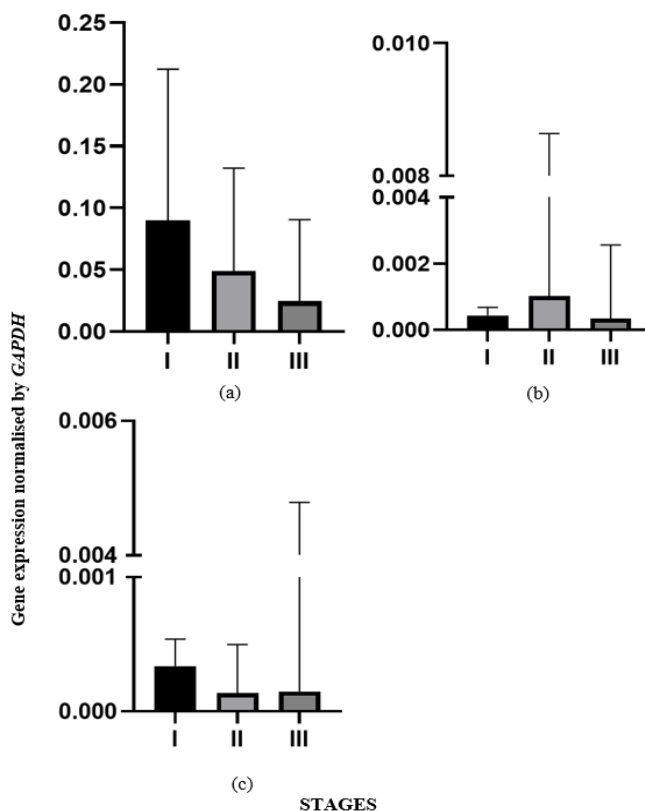
### 3 Result and Discussion

#### 3.1 Expression of *KLF5*, *FHIT*, and *DLG2* genes in cervical cancer

The results of the Shapiro-Wilk normality test show that  $P < 0.0001$  suggesting that the data was not normally distributed (Table 1). For comparing the expression of the *KLF5*, *FHIT*, and *DLG2* genes, the Kruskal Wallis test was used. The significant values obtained for each of the *KLF5*, *FHIT*, and *DLG2* genes were 0.1069, 0.4326 and 0.6845 respectively, presented in Table 1. The results of statistical analysis concluded that the expression of the *KLF5*, *FHIT*, and *DLG2* genes was not statistically significant.

**Table 1.** Median value of *KLF5*, *FHIT* and *DLG2* gene expression based on stages I-III of cervical cancer

Genes	Stadium I	Stadium II	Stadium III	<i>p</i> -value
<i>KLF5</i>	0,0899	0,0489	0,0245	0,1069
<i>FHIT</i>	0,0004	0,0010	0,0003	0,4326
<i>DLG2</i>	0,0003	0,0001	0,0001	0,6845



**Fig. 1.** Expression of (a) *KLF5*, (b) *FHIT* and (c) *DLG2* genes in cervical cancer. Median  $\pm$ CI was used to represent the data.

Fig. 1. shows that the median KLF5 gene expression decreases as cervical cancer progresses, while the median FHIT gene expression increases in stages I to II but decreases in stage III. On the other hand, the DLG2 gene expression value decreased from stage I to II but increased in stage III.

When cervical cancer cells invade normal cervical tissue, there will be changes in the cycle of the infected cells. These changes in the cell cycle create a state of DNA Replication Stress (DRS) thereby accelerating gene mutations, especially in the G1 phase. Gene mutations can be inhibited by activating the p53 checkpoint by DNA Damage Response (DDR) to detect and eliminate mutated cells through the apoptosis process. However, cancer cells can intervene molecularly in this process by changing the function of several genes to exacerbate cervical cancer cell mutations [18,19].

We observed that the expression level of KLF5 was decreasing throughout cervical cancer stages, however, no significant difference was detected. Similar results were observed by another study comparing the level expression of KLF5 in normal and cancerous cervical tissues [20]. This might be due to the lack of other supporting factors, such as TNFRSF11a. KLF5 activates the p38 tumor necrosis factor receptor superfamily member 11a (TNFRSF11a) protein signaling pathway by binding to the cyclin D1 promoter thereby increasing the proliferation and invasion of cervical cancer cells [11]. Cyclin D1 is a co-regulator of cyclin-dependent kinase which functions carries out the G1 phase of the cell cycle. ko-ekspresi KLF5 dan TNFRSF11a secara signifikan mempengaruhi tumoregenesis dari jaringan serviks. Dimana KLF5 menunjukkan korelasi positif dengan ekspresi dari mRNA dan protein TNFRSF11a [11]

Fragile Histidine Triad Diadenosine Triphosphatase (FHIT) is a tumor suppressor gene that functions to regulate apoptosis and suppress tumor metastasis [21]. In HPV invasion, the FHIT gene is suppressed, leading to a decrease in its expression, hindering the apoptosis process, and increasing cyclin D1 cycle, thereby enhancing cancer cell proliferation [22]. In a study conducted by Wang et al in 2017, a significant decrease in FHIT expression was observed, particularly from CIN III to stage I cancer cells [14]. Statistical analysis of the data in this study showed no significant difference in FHIT expression in cervical cancer stages, possibly due to variations in the samples used in the research, specifically RNA samples.

Discs Large MAGUK Scaffold Protein 2 (DLG2) belongs to the MAGUK family and plays a crucial role in regulating polarity, cellular structure, and cell growth behavior [23]. DLG2 is also a tumor suppressor gene that functions to enhance programmed cell death in the event of cancer invasion. Keane et al's research indicates that the deletion of 11q, the location of DLG2, results in cell cycle progression, particularly in the G1 phase, leading to increased proliferation of cancer cells [24]. Statistical analysis of the data in this study revealed no strong significance between DLG2 expression and cervical cancer, and a decrease in gene expression from stage I to stage II, followed by an increase in stage III. DLG2 has been proven to be integrated in the presence of HPV, but its consistency may vary in more invasive stages [25]. Therefore, further research is needed to reevaluate DLG2 expression in cervical cancer.

### 3.2 Correlations of Expression of *KLF5*, *FHIT*, and *DLG2* in Cervical Cancer

To see the correlation between the *KLF5*, *FHIT* and *DLG2* genes, the Spearman test matrix was used. The results show that the correlation between each of the three genes was weak as shown in Fig. 2.

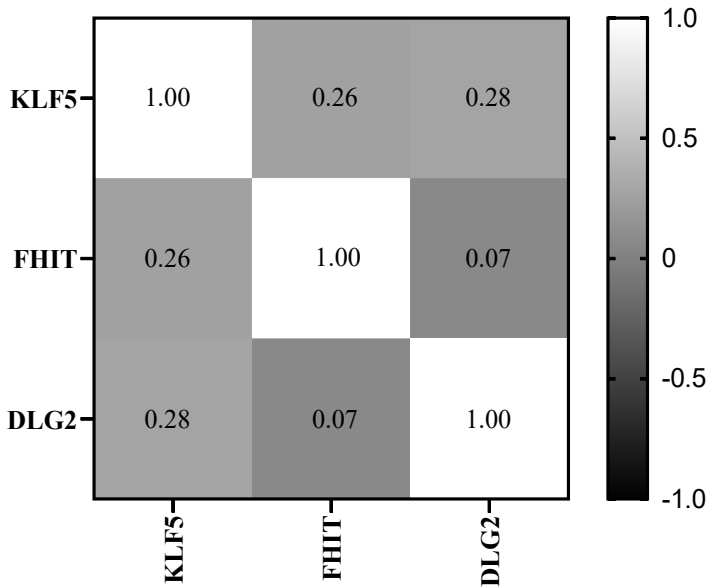


Fig. 2. Correlations of Expression of *KLF5*, *FHIT* and *DLG2* with Cervical Cancer

The *KLF5*, *FHIT*, and *DLG2* genes have a role in cell proliferation, especially in the G1 phase. In the G1 phase, an interaction occurs between cyclin-dependent kinase and cyclin D1. The expression of cyclin D1 itself is influenced by the interaction between the *KLF5* and *FHIT* genes in cervical cancer [15] In neuroblastoma cancer, reducing the expression of the *DLG2* gene will shorten the time in the G1 phase of cell proliferation [17]. Results of correlation analysis of the *KLF5*, *FHIT*, and *DLG2* through the Spearman correlation matrix in Figure 2, shows that there is no correlation with cervical cancer. This means that the expression of the three genes in the samples used does not correlate with influencing the progression of cervical cancer. This indicates that there is a possible interaction of other genes that facilitate the proliferation of cervical cancer cells, such as *HMG2* and *MYC*. The *KLF5* gene itself must bind to the *TNFRSF11a* promoter to increase the expression of cyclin D1 which is involved in the G1 phase of cell proliferation. In the results of this study, it is possible that *TNFRSF11a* is not involved in cervical cancer proliferation, which is indicated by decreased *KLF5* expression.

## 4 Conclusion

The expression of the KLF5, FHIT and DLG2 genes does not affect cervical cancer carcinogenesis. Also, there is no significant correlation between the expression of the KLF5, FHIT, and DLG2 genes in cervical cancer. Further studies are needed to explore other genes that involve in progression of cervical cancer.

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