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A systematic review of oncologic pathways in cervical cancer and the correlation with dietary factors: insights into molecular mechanisms and nutritional influences

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ABSTRACT

Introduction: Cancer is currently the second greatest cause of death worldwide. Cervical cancer, the second most common malignancy in women worldwide, is characterized by dysregulated oncologic pathways contributing to its progression.

Goals: This systematic review aims to explore the role of different oncologic pathways in cervical cancer progression and the impact of diet on these pathways.

Methods: A systematic literature review was conducted using the PRISMA system and flow charts for quality assurance. The PICOS framework was used for inclusion criteria. Keywords used in six databases included ("signaling pathway") AND ("pathology") AND ("oncogenic") AND ("cervical cancer"). A risk of bias assessment was conducted on selected studies using the QUIN tool for in vitro studies.

Results: Nineteen studies were analyzed. Desired outcomes included induced proliferation, inhibited apoptosis, invasion-metastasis promotion, and angiogenesis. Identified oncologic pathways based on these outcomes include P53, TNF-mediated, FOXM1/WNT/β-catenin, EGFR, VEGF, NF-κB, Her-2, Histone 3, ERCC1, JAK/STAT, TGF-β, ErbB, BMP4/Hippo/ YAP1/TAZ, and ERK/c-Myc pathways. Nutritional factors, such as a western diet with processed meats, salty foods, chips, red meat, and instant foods, were found to affect the hyperactivation of these oncologic pathways, increasing cervical cancer risk.

Discussion: Each oncologic pathway has distinct mechanisms but some share similarities in triggering tumorigenesis. Increased proliferation results from heightened cell cycle activity and reduced tumor suppressor gene function. The suppression of caspase activity and pro-apoptotic proteins causes apoptosis inhibition. Metastasis and angiogenesis are driven by elevated expression of EMT and MMP proteins, promoting cancer cell invasion, migration, and new blood vessel formation. Nutritional factors influence these pathways, emphasizing the role of diet in cervical cancer progression and prevention.

Conclusion: Various and interconnected mechanisms underlie specific oncologic pathways impacting cervical cancer. Diet significantly influences the hyperactivation or inactivation of cancer-related pathways, affecting cervical cancer risk.

KEYWORDS

Cervical neoplasms, molecular signaling, oncogenic signaling pathways, tumor progression, nutrient-cancer interaction

ABBREVIATION LIST

AKT: Protein Kinase B.

Bcl-2: B-cell leukemia /lymphoma 2 protein.

Bcl-XL: B-cell lymphoma-extra-large.

BMP 4: Bone Morphogenetic Protein 4.

CC: Cervical Cancer.

CIN: Cervical Intraepithelial Lesion.

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CIN: Cervical Intraepithelial Neoplasia.

Cip1: Cyclin-Dependent Kinase Inhibitor Protein 1.

c-Myc: cellular-Myelocytomatosis.

DLL 4: Delta-like ligand 4.

EGFR: Epidermal Growth Factor Receptor.

EMT: Epithelial Mesenchymal Transition.

ErbB: Erythroblastic Oncogene B.

ERCC1: Excision Repair Cross- Complementing 1.

ERK: Extracellular signal Regulated Kinase.

FGF: Fibroblast Growth Factor.

Fox M1: Forkhead box protein M1.

HIF-1 alpha: Hypoxia Inducible Factor a alpha.

HPV: Human Papilloma Virus.

IL: Interleukin.

IκB-α: Inhibitor kappa B-alpha.

JAK/STAT: Janus Kinase/Signal Transducer and Activator of Transcription.

MEK: Mitogen-activated Extracellular signal-regulated Kinase.

mTOR: mechanistic Target Of Rapamycin.

NF-κB: Nuclear Factor Kappa B.

NICD: Notch Intraseluler Domain.

PAI2: Plasminogen Activator Inhibitor Type 2.

PI3K: Phosphoinositide 3-Kinase.

RTK: Receptor Tyrosine Kinase.

TAZ: Transcriptional coactivator with PDZ- binding motif.

TEAD: Transcriptional Enhanced Associate Domain.

TGF-β: Transforming Growth Factor- Beta.

TNF: Tumor Necrosis Factor.

VEGF: Vascular Endothelial Growth Factor.

VEGFR2: Vascular Endothelial Growth Factor Receptor 2.

WNT: Wingless and Int-1.

YAP1: Yes Associated Protein 1.

INTRODUCTION

Cancer is currently the second greatest cause of death worldwide[1]. The second most common malignant tumor in women worldwide is cervical cancer, which poses a major threat to their health. With an estimated 604,000 new cases and 342,000 deaths worldwide in 2020, cervical cancer is the fourth most common cancer diagnosed in women and the fourth leading cause of cancer-related deaths in women[2].

Cervical cancer shares characteristics with other cancers in that it is marked by dysregulation of different oncologic pathways. Cancer is a result of dysregulated signaling pathways, which allow tumor cells to go through dysregulated mitogenesis, resist apoptosis, and invade nearby tissues[3]. The transcriptional programs of epithelial cells undergo significant alterations when a persistent human papillomavirus (HPV) infection persists, impacting entire signaling pathways and influencing cervical carcinogenesis[4]. However, the complex interactions between genetic, environmental, and lifestyle factors, particularly diet, influence their activity and efficacy[5].

According to epidemiological research, several dietary categories or nutrients may be able to stop precursor lesions from developing into cervical cancer. The European Prospective Investigation into Cancer and Nutrition (EPIC) study found a significant inverse relationship between daily fruit intake and cervical cancer. Specifically, eating more fruits and vegetables and getting enough nutrients (such as vitamins A, C, and E, folates, carotenoids, and minerals) has been linked to a lower risk of HPV infection, cervical intraepithelial neoplasia (CIN), and cervical cancer[6].

Finding dysregulated genes in cancer-associated pathways may help to understand the molecular processes behind tumorigenesis and lead to the development of novel tumor therapy approaches. By conducting a comprehensive systematic review, this study aims to produce existing evidence on the intersection of oncologic pathways and dietary influences in cervical cancer, providing valuable insights for future research directions and clinical interventions to reduce the global burden of this disease.

METHODS

Study Eligibility

We conducted a systematic literature review using the PRISMA system and flow charts to ensure the quality of the study. This study evaluates the relationship between diet and nutrition to cervical cancer oncology pathways and looks at what oncology pathways are involved and their effects on cervical cancer signalling pathways. The literature search was identified using ScienceDirect, PubMed/NCBI, Springerlink, and Wiley databases. Exclusion criteria included: 1) non-Research articles; 2) Not in English; 3) Not published in the last 10 years. Inclusion criteria based on the PECOS principle, namely 1) Problem = cervical cancer; 2) Exposure = oncology pathway; 3) Comparison = no comparison; 4) Outcome: metastasis, angiogenesis, induction of cell proliferation, inhibition of apoptosis, cell migration; 5) Research Design: an experimental study in vitro. The keywords used in the search strategy were "signaling pathway" AND "oncogenic" AND "cervical cancer" OR "CC" AND "pathology".

Inclusion Criteria

The PICOS framework was used as the basis for inclusion criteria consisting of 1) Problem: cervical cancer; 2) Intervention: Oncological pathway in the pathogenesis of cervical cancer; 3) Comparison: - ; 4) Outcome: metastasis,

angiogenesis, induce proliferation, inhibit apoptosis, and cell migration; 5) Study design: in vitro experimental study.

Exclusion Criteria

Exclusion criteria were adopted: 1) non-in vitro studies; 2) non-English studies; 3) published last ten years.

Data Sources

The literature search was conducted by three independent researchers (AZV, DCK, and NLC) from May 3, 2024, to June 20, 2024. Several databases were used, including Pubmed, ScienceDirect, and SpringerLink. The keywords used in six databases included ("signaling pathway") AND ("pathology") AND ("oncogenic") AND ("cervical cancer").

Study Selection and Data Extraction

The selected studies were extracted independently by three independent researchers (AZV, DCK, and NLC) into Mendeley and Google Sheet. Subsequently, all the authors evaluated their eligibility and accuracy. Any disagreements that arose during the writing process were resolved through discussions.

Risk of Bias Assessment

A risk of bias assessment was conducted on the selected studies using the QUIN tool for in vitro studies by AZV, DCK, and NLC. The tool evaluates twelve criteria: clearly stated aims/objectives, thorough explanation of sample size collection, detailed description of the sampling technique, comparison group details, comprehensive methodology explanation, operator details, randomization, outcome measurement method, outcome assessor details, blinding, statistical analysis, and result presentation. To assess the study's quality, the article was classified into three categories: low, moderate, and high.

Outcome of Interest

This review focused on analyzing the oncologic pathways involved in cervical cancer and the potential influence of diet and nutrition on these pathways. This study identifies key pathways like PI3K/AKT/mTOR, HIF-1A, NF-κB, and others and discusses their roles in proliferation, apoptosis inhibition, angiogenesis, invasion, and metastasis in cervical cancer.

RESULTS

Study Selection and Identification

After the literature search, 2.119 studies published in the last ten years were obtained from six databases: ScienceDirect, PubMed, and SpringerLink, using boolean operators with the main keywords "oncogenic" and "cervical cancer."

Fig 1 shows the search for studies concerning the oncologic pathway of cervical cancer. There are 19 valid articles included.

Twenty-one articles were removed from consideration due to duplication in their research. Additionally, 462 articles were excluded because they did not meet the inclusion criteria, did not cover oncological pathways in cervical cancer and did not align with the intended research design leading to their exclusion, particularly review articles and books. Furthermore, 129 journals were inaccessible for analysis due to subscription limitations.

Summaries of The Included Studies

(Table 1) provides an overview of all studies that were a part of this scoping review. The study examined the oncologic pathways involved in the development of cervical cancer using a variety of cervical cancer cell lines and human cervical cancer tissue. The systematic review identified twenty one oncologic pathways, including PI3K/AKT/m-TOR, P53, (TNF)-mediated, FOXM1/WNT/β-catenin, EGFR, VEGF, Hif 1-alpha, Her-2, Histone 3, ERCC1, JAK/STAT, ErbB, NF-kB, BMP4/Hippo/YAP1/TAZ, and ERK/c-Myc

Risk of Bias Assessment

The QUIN tool comprises twelve questions, totalling twenty-four points, and categorizes articles based on these points: 1) low risk >70%; 2) moderate risk 50-70%; and 3) high risk <50%. The risk of bias assessment indicated that fourteen articles had a moderate risk of bias due to a lack of detailed explanations regarding sample size collection, randomization, operator details, and blinding. Five articles had a high risk of bias. Specifically, based on the twelve questions, four articles did not explain comparison group details and sampling technique, and one article did not explain statistical analysis, methodology, and outcome measurement. Table 2 displays the results of the QUIN risk analysis using the bias tool. Despite the varying degrees of bias in the studies, most of the analyzed data were thoroughly discussed. Reviewers concluded that these studies are sufficiently suitable for analysis.

DISCUSSION

Induce proliferation

Based on the involvement of oncologic pathways in inducing proliferation, there are 9 oncologic pathways involved as shown in figure 2, namely: 1) PI3K/AKT/mTOR; 2) NF-κB; 3) TNF-mediated; 5) Wnt/β-catenin; 6) HIF-1A; 7) EGFR; 8) BMP4/Hippo/YAP1/TAZ; and 9) ERK/c-Myc; The oncology pathway was described in the 14 articles included[7–11,15,16,18,20–23,25].

PI3K/AKT/mTOR induces proliferation by upregulating EGFR, which in turn activates MAPK/ERK. The transcription of

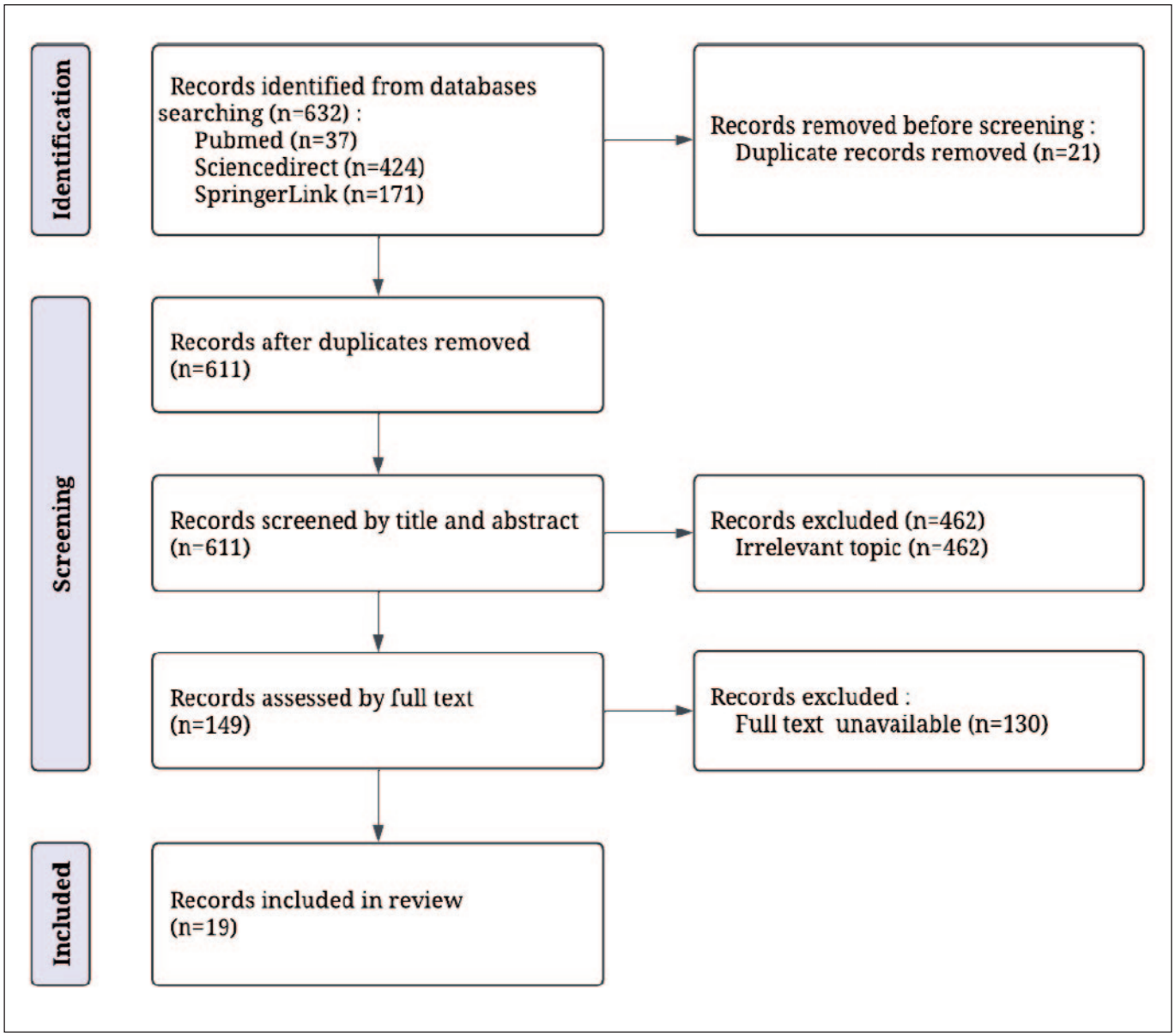

Figure 1. PRISMA flowchart by a Systematic Review of Oncologic Pathways in Cervical Cancer and the Correlation with Dietary Factors: Insights into Molecular Mechanisms and Nutritional Influences

several genes crucial for controlling the cell cycle and promoting cell division is changed due to MAPK/ERK activation[26]. NF-kB can promote the transcription of genes that control proliferation, such as C-MYC and cyclin D1[27]. TNF-mediated signalling pathway activates the transcription factor nuclear factor-κB (NF-κB). The freed NF-κB translocates to the nucleus and activates the transcription of its downstream target genes, which are involved in cell survival, proliferation, and migration[9]. Wnt/β-catenin pathway induces proliferation by targeting β-catenin, cyclinD1 and c-myc gene. The HIF-1A pathway stimulates proliferation in cervical cancer cells by upregulating YAP/TAZ[28]. Egfr stimulates cell proliferation through the processes of dimerization, autophosphorylation, and activation of downstream signaling pathways[16]. YAP/TAZ controls the metabolism of deoxynucleotides in cancer cells, promoting cell proliferation and inhibiting senescence[29]. Increased proliferation may also occur by expression and stabilization of c-Myc through phosphorylating ERK1/2[23].

Inhibit apoptosis

Based on the involvement of oncologic pathways in inhibiting apoptosis, there are 3 oncologic pathways involved, namely: 1) PI3K/AKT/mTOR; 2) NF-κB; and 3) Wnt/β-catenin. The oncology pathway was described in the 3 articles included[10,11,25].

Table 1. Summary of Studies

No	Authors	Oncologic Pathway	Samples	Effect
1	Peng, et al. 2020[7]	AKT and P53 signaling pathway	Normal cervical cell lines Ect1/E6E7 and cervical cell lines (Hela, SiHa, C-33A and Caski)	Proliferation, invasion, migration, and apoptosis
2	Wang, et al. 2024[8]	PI3K/AKT/mTOR signaling pathway	C-33A, HeLa, SiHa, and CaSk	Proliferation and migration
3	Liu, et al. 2021[9]	(TNF)-mediated signaling pathway and ErbB signaling pathway	HeLa, SiHa, C33A, ME180, HeLa 229, MS751, and CaSki.	Cell development, differentiation, and proliferation
4	Kang, et al. 2024[10]	Wnt/β-catenin signaling pathway	Normal cervical epithelial cell line (HCerEpiC) and cancer cell lines (including HeLa, Caski and SiHa)	Proliferation, migration and apoptosis
5	Li, et al. 2024[11]	PI3K/AKT signaling pathway	CC cell lines (ME-180, SiHa, CaSki, and C-4I), control cell line (End1/E6E7)	Proliferation, apoptosis, migration and invasion
6	Zhang, et al. 2023[12]	FOXM1/Wnt/β-catenin signaling pathway	The triggering human cervical cancer cells (ectocervical Ect1/E6E7), HeLa, SiHa, C-33A, CaSki	Migration and invasion
7	Meyer, et al. 2019[13]	EGFR, VEGF, Hif 1-alpha, Her-2 and Histone 3 signaling pathway	squamous cell cervical carcinoma	cell growth, cell proliferation
8	Li, et al. 2024[14]	HIF - 1A down-regulation signaling pathway	dataset GSE63514 from the Comprehensive Gene Expression Database (GEO).	Migration, and invasion
9	Chen, et al. 2016[15]	hif-1a signaling pathway	locally advanced cervical cancer (LACC) patients	Angiogenesis, proliferation, tumor growth, invasive, metastasis
10	Almeida, et al. 2018[16]	EGFR, ERCC1 and p53 signaling pathway	cervical cancer cell line (CASKI, C33A)	Cell proliferation, survival, transformation,
11	Jiang, et al. 2022[17]	JAK3/STAT5 signaling pathway	PBMC cervical cancer patient	suppress imune function, cell proliferation, cell invasion
12	Tan,et al. 2024[18]	PI3K/AKT signaling pathway	HeLa cell line (adenocarcinoma and HPV type 18)	Cell proliferation, migration, survival of cervical cancer
13	Chen, et al. 2024[19]	PI3K/AKT/mTOR and EMT signaling pathway	HeLa and SiHa cell lines	Cell adhesion, invasion, migration.
14	Shi, et al. 2020.[20]	PTEN/PI3K/AKT signaling pathway	cervical cancer tissues and cervical cancer cell lines	Proliferation and progression
15	Li, et al. 2023[21]	VEGFR2/PI3K/AKT signaling pathway	cervical cancer HeLa cells	Proliferation, migration, and invasion
16	Huang, et al. 2023.[22]	BMP4/Hippo/YAP1/TAZ signaling pathway	Human cervical cancer cell lines HeLa and SiHa	Proliferation, colony formation, migration, and invasion
17	Ma, et al. 2021[23]	ERK/c-Myc signaling pathway	cervical cancer tissues	Proliferation, metastasis, and cisplatin resistance
18	Xu, et al. 2020.[24]	Wnt/β-catenin signaling pathway	Human cervical cancer cell lines HeLa and SiHa	Drive oncogenesis and radioresistance
19	Feng, et al. 2016[25]	NFkB signaling pathway	HeLa and CaSki	Proliferation

ErbB (Erythroblastic Oncogene B); TNF (Tumor Necrosis Factor); JAK/STAT (Janus Kinase/Signal Transducer and Activator of Transcription); NF-kB (Nuclear Factor Kappa B); PI3K/AKT (Phosphatydil-Inositol-3-Kinase/Serine-Threonine Kinase); RAS/RAF/MAPK (Mitogen-Activated Protein Kinase); VEGF (Vascular Endothelial Growth Factor); EGFR (Epidermal Growth Factor Receptor); BMP4/Hippo/YAP1/TAZ (Bone Morphogenetic Proteins 4 /Hippo/Yes-Associated Protein 1/Transcriptional Coactivator with PDZ-Binding Motif); Wnt/β-catenin (Wingless-Type MMTV Integration Site Family/β-catenin); HIF - 1A (Hypoxia-Inducible Factor-1Alpha); ERCC1 (Excision Repair Cross-Complementing 1); ERK/c-Myc (Extracellular signal-regulated kinase/c-mýkēs).

Table 2. Result of QUIN Tools

No	Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Overall
1	Peng, et al. 2020	2	0	0	2	2	0	0	2	0	0	2	2	MEDIUM
2	Wang, et al. 2024	2	0	0	0	2	0	0	2	0	0	2	2	HIGH
3	Liu, et al. 2021	2	2	2	2	2	0	0	2	0	0	2	2	MEDIUM
4	Kang, et al. 2024	2	1	1	2	2	0	0	2	0	0	2	2	MEDIUM
5	Li, et al. 2024	2	0	2	2	2	0	0	2	0	0	2	2	MEDIUM
6	Zhang, et al. 2023	2			2	2	0	0	1	0	0	2	2	HIGH
7	Meyer, et al. 2019	2	2	0	0	2	0	0	2	1	0	2	2	MEDIUM
8	Li, et al. 2024	2	2	2	2	2	0	0	1	0	0	2	2	MEDIUM
9	Chen, et al. 2016	2	1	2	0	2	0	0	2	0	0	2	2	MEDIUM
10	Almeida, et al. 2018	2	0	2	2	2	0	0	2	0	0	0	2	MEDIUM
11	Jiang, et al. 2022	2	2	2	2	2	0	0	2	0	0	2	2	MEDIUM
12	Tan,et al. 2024	2	1	1	1	2	0	0	2	0	0	2	2	MEDIUM
13	Chen, et al. 2024	2	0	1	0	2	0	0	2	0	0	0	2	HIGH
14	Shi, et al. 2020.	2	0	2	1	2	0	0	2	0	0	2	2	MEDIUM
15	Li, et al. 2023	2	1	2	1	2	0	0	2	0	0	2	2	MEDIUM
16	Huang, et al. 2023.	2	0	0	1	2	0	1	2	0	0	2	2	MEDIUM
17	Ma, et al. 2021	2	0	2	2	2	0	0	1	0	0	2	2	MEDIUM
18	Xu, et al. 2020.	2	0	1	0	1	0	0	2	0	0	2	2	HIGH
19	Feng, et al. 2016	2	0	0	0	1	0	0	0	0	0	0	2	HIGH

Q1: clearly stated aims/objective; Q2: thorough explanation of sample size calculation; Q3: detailed description of the sampling technique; Q4: comparison group details; Q5: comprehensive methodology explanation; Q6: operator details; Q7: randomization; Q8: outcome measurement method; Q9: outcome assessor details; Q10: blinding; Q11: statistical analysis; Q12: result presentation.

PI3K/AKT pathway inhibits apoptosis by stopping the cell cycle from progressing by repressing downstream factors, such as p27Kip and p21Waf1/Cip1, which are members of the cyclin-dependent kinase family. Additionally, it has the ability to phosphorylate and inactivate a number of targets, including caspase-9 and Bad, which are crucial components of the mitochondrial apoptosis pathways (Xu, et al. 2017). NF-κB, an important inducible tumorigenesis modulator, causes tumor cells to avoid apoptosis by evading cell cycle checkpoint[30]. It can induce expression of antiapoptotic proteins, such as PAI2 and Bcl-xL[31]. Wnt/β-catenin signaling activates Cyclin D1 and survivin, which can induce the inhibition of caspase 3 expressions, and consequently can inhibit[32]. The mechanism of inhibiting apoptosis is summarized in Figure 3.

Angiogenesis

Angiogenesis is the process of forming new blood vessels in the body. Cancer sends signals for more nutrients and oxygen supply, hence more new blood vessels are formed to fulfill this. Inhibition of angiogenesis-forming factors can cause tumor cells to become dormant[33].

As shown in Fig 4, in cervical cancer, the E6 protein in HPV inactivates p53, which results in angiogenesis through the mechanism of induction of pro-angiogenesis factors such as VEGF (Vascular Endothelial Growth Factor), FGF (Fibroblast Growth Factor), and angiopoietins, and inhibits the production of thrombospondin-1, which acts as an angiogenesis inhibitor. Activation of VEGF activates the formation of new blood vessels resulting in endothelial cell proliferation and migration.

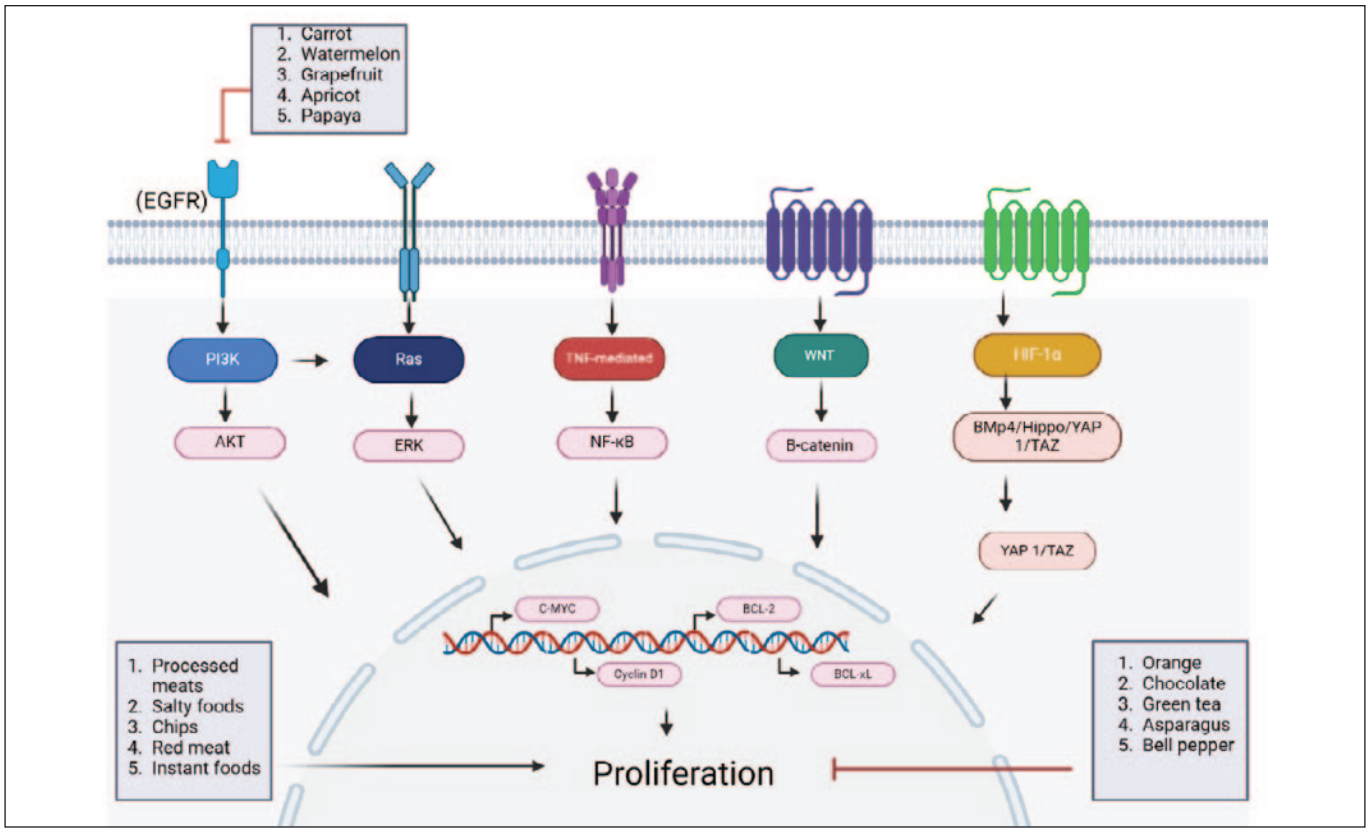

Figure 2. Mechanism of proliferation influenced by PI3K/AKT/mTOR, NF-κB, TNF-mediated,Wnt/β-catenin, HIF-1A, EGFR, BMP4/Hippo/YAP1/TAZ, ERK/c-Myc, and some nutrition

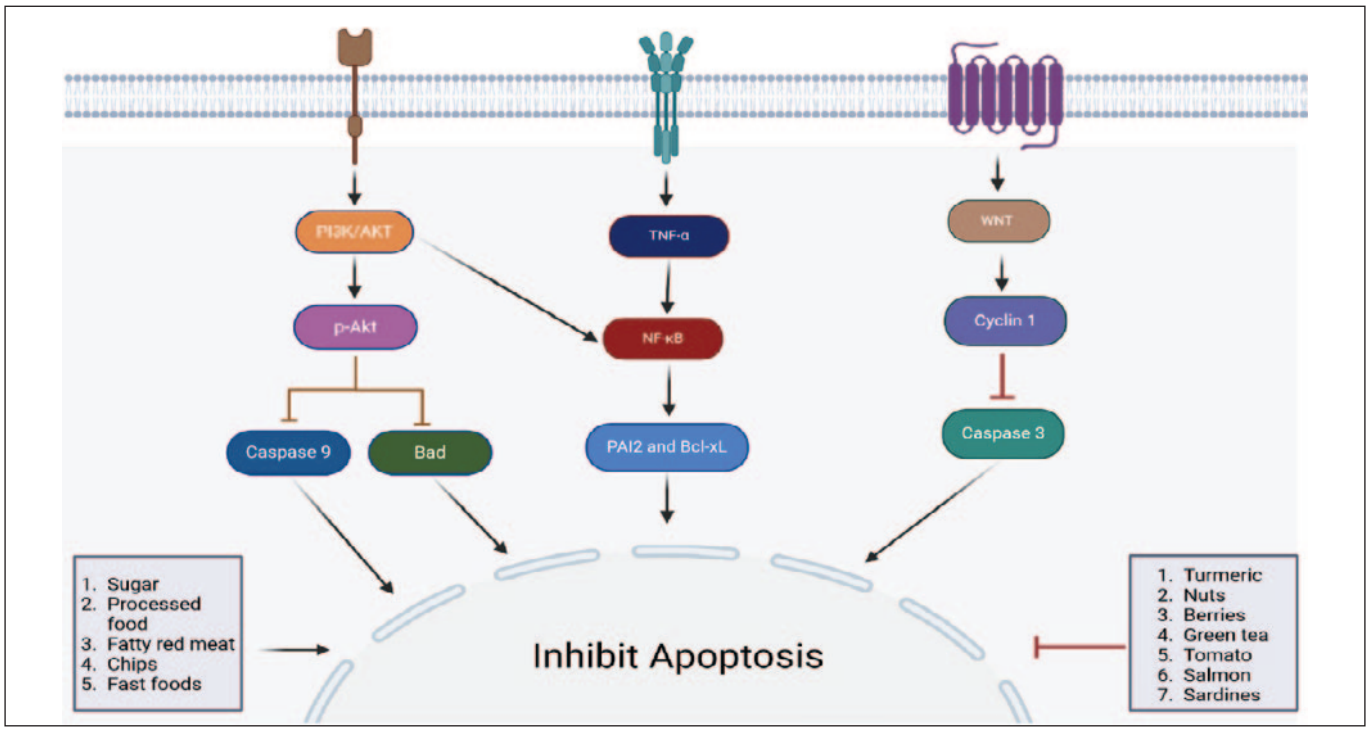

Figure 3. Mechanism of PI3K/AKT/mTOR, NF-κB, Wnt/β-catenin in inhibiting apoptosis and several example of foods that inhibit and trigger apoptosis

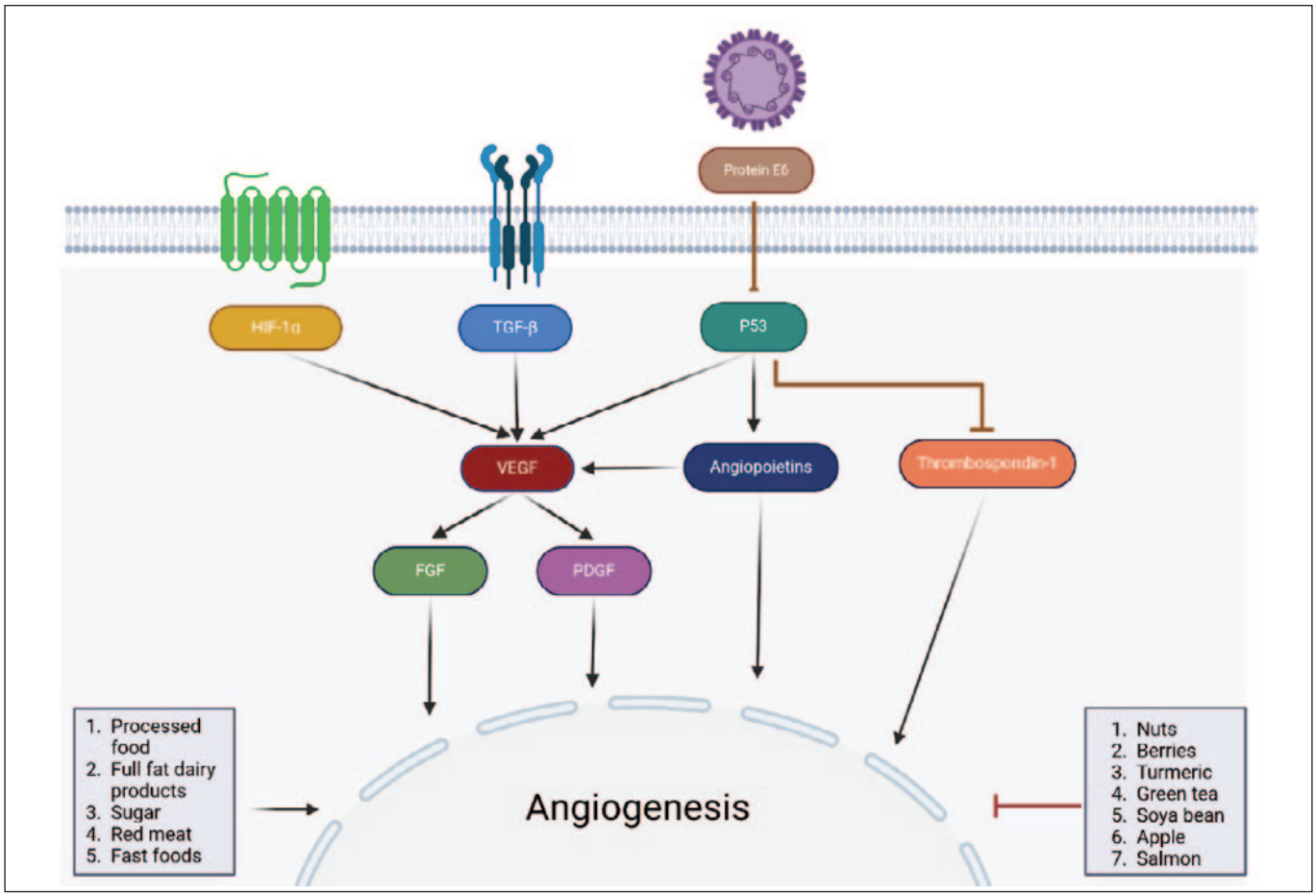

Figure 4. Mechanism of angiogenesis caused by HIF-1 alpha, TGF-β, P53 and several example of foods that inhibit and trigger angiogenesis

VEGF production is the body's response to acidosis, hypoxia, and mechanical stress. Increased angiogenesis correlates with premalignant lesions in cervical cancer. Microvessel density increases as the degree of CIN (Cervical Intraepithelial Neoplasia) increases[34].

VEGF activation is influenced by several factors, such as cytokines (TGF-β), hormones (estrogen), growth factors, and hypoxia (HIF-1 alpha). The binding between VEGF and its receptor (VEGFR2) forms an interaction that regulates the formation of DLL4. Then, DLL4 binds to the notch receptor and releases the Notch Intracellular Domain (NICD). This series of interactions activates the expression of VEGFR 1[35].

HIF-1α controls how cells adapt to low oxygen levels and activate numerous genes linked to various cellular functions, including energy metabolism, angiogenesis, cell growth, specialization, and survival[15].

Invasion and metastasis

Based on the involvement of the oncologic pathway in triggering invasion and metastasis, there are 8 oncologic pathways involved, as shown in Fig 5, namely: 1) HIF - 1A; 2) BMP4/Hippo /YAP1/TAZ; 3) PI3K/AKT/mTOR; 4) NF-kB; 5) FOXM1/WNT/β-catenin; and 6) ERK/c-Myc; The oncology pathway was described in the 10 articles included[7,8,10–12,15,18,22,23,25].

The HIF-1α pathway plays a key role in cervical cancer invasion and metastasis through an adaptive response to hypoxic conditions, regulating genes that support typical tumor behaviors such as angiogenesis and metabolic reprogramming[36]. The BMP4/Hippo/YAP1/TAZ pathway stimulates metastasis by regulating YAP and TAZ activity and related gene expression. When the Hippo pathway is inactive, YAP and TAZ enter the cell nucleus, stimulating the expression of genes that support cancer cell proliferation and resistance to apoptosis[36]. The PI3K/AKT/mTOR pathway play a central role in the growth and proliferation of cervical cancer cells[37]. It promotes metastasis by regulating the EMT phenotype, which allows cancer cells to move and spread to surrounding tissues[36].

The NF-κB promotes metastasis by induction of various target genes; there are c-Myc, VEGF, IL-6, IL-8, Bcl-2, Bcl-XL,

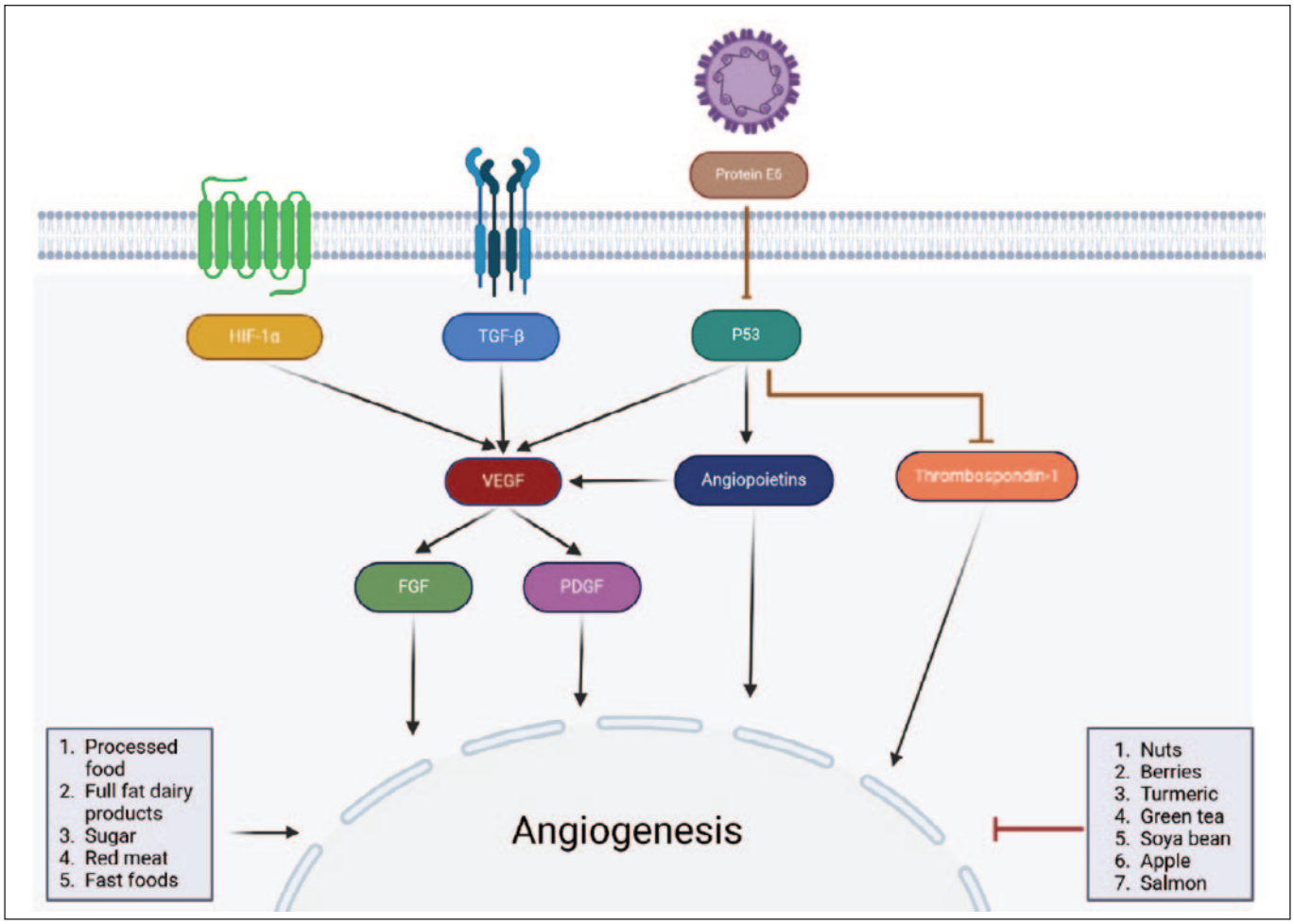

Figure 5. Mechanisms involving HIF-1α, RAS, and WNT trigger several pathways leading to the expression of EMT, which in turn promotes invasion and metastasis. Additionally, several nutrients have been found to inhibit these processes

CyclinD1 and IκB-α[38]. The FOXM1/WNT/β-catenin pathway stimulates metastasis by regulating cell growth and cell mobility. FOXM1 promotes cervical cancer cell proliferation, while the WNT/β-catenin pathway enhances invasiveness by affecting cell mobility and the ability of cells to penetrate surrounding tissue[36]. The ERK/c-Myc promotes metastasis by transcribing specific target genes and thereby contributes to the malignant progression of cancer[23].

Diet and oncological pathway

Nutritional status plays an important role in the development of cervical cancer, where poor nutrition inhibits the immune response to HPV, potentially leading to cancer development[39]. HPV infection is a high risk in women who consume a Western diet that includes processed meats, salty foods, chips, red meat, and instant foods. On the other hand, women who consume a Mediterranean diet that includes vegetables, fruits, milk, and cereals have the potential to lower cancer risk and inflammation. There is a reported 60% reduction in the risk of HPV infection when consuming a Mediterranean diet[40].

Specific nutrients like beta-carotene, lutein, zeaxanthin, and vitamins C and E in fruits and vegetables exhibit properties that combat HPV and inflammation (Medina, 2020). Vitamin A (retinol) plays a role in protein inhibition and basal mucosal cell replication. Vitamin D can reduce the incidence of CIN 1. Patients who took vitamin D for 6 months at a dose of 50,000 IU showed a reduction in oxidative stress (NO). Consumption of vitamin A, vitamin D, and papaya is effective in reducing the risk of CIN, CIN 2, and CIN 3[41].

Quercetin is a member of flavonoids and has a relationship with invading several signaling pathways in cervical cancer, including influencing the expression of JAK / STAT, PI3K, MAPK < WNT, apoptosis, and cell cycle inhibition. Quercetin also has the ability to inhibit the E6 protein in HPV, resulting in an increase in p53 protein levels to induce apoptosis. Quercetin, PUFA, Sulforaphane, and polyphenols play a role in the prevention of cervical cancer at the invasive stage[42].

The nutritional status of cervical cancer patients is essential, given the prevalence of overweight and obesity, as well as malnutrition and sarcopenia. Tailored nutritional management is necessary to address these factors[39].

Strength and limitation

This study describes and provides information related to the mechanism of oncology signaling pathways that play a role in tumorigenesis in cervical cancer. This information in this study can be an insight and also a consideration regarding the mechanism of target therapy in cervical cancer. In addition, this study discusses diet and nutrition that correlate at each stage of cervical cancer. The limitation of this study is that study it is based more on nutritional patterns, not on measuring food consumption intake. Hence, it cannot see the relationship between the nutritional value of food intake and the development of each stage of cervical cancer.

CONCLUSION

According to the defining characteristics of cancer, cervical cancer can be caused by oncologic pathways with different various mechanisms. This review highlights that the PI3K/AKT and Hif 1-alpha pathways are predominantly implicated in tumorigenesis, primarily contributing to increased proliferation, invasion, and metastasis.

Several other oncologic pathways, namely: P53, (TNF)-mediated, FOXM1/WNT/β-catenin, EGFR, VEGF, Nf-kB, Her-2, Histone 3, ERCC1, JAK/STAT, TGF-β, ErbB, BMP4/Hippo/YAP1/TAZ, and ERK/c-Myc pathway. Nutrition in the form of a Western diet that includes processed meats, salty foods, chips, red meat, and instant foods also affects the hyperactivation of oncologic pathways, thereby increasing the risk of cervical cancer.

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