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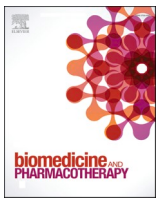

Review

Natural products as glycolytic inhibitors for cervical cancer treatment: A comprehensive review

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ABSTRACT

Cervical cancer, a prevalent gynaecological malignancy, presents challenges in late-stage treatment efficacy. Aerobic glycolysis, a prominent metabolic trait in cervical cancer, emerges as a promising target for novel drug discovery. Natural products, originating from traditional medicine, represent a significant therapeutic avenue and primary source for new drug development. This review explores the regulatory mechanisms of glycolysis in cervical cancer and summarises natural compounds that inhibit aerobic glycolysis as a therapeutic strategy. The glycolytic phenotype in cervical cancer is regulated by classical molecules such as HIF-1, HPV virulence factors and specificity protein 1, which facilitate the Warburg effect in cervical cancer. Various natural products, such as artemisinin, shikonin and kaempferol, exert inhibitory effects by downregulating key glycolytic enzymes through signalling pathways such as PI3K/AKT/HIF-1α and JAK2/STAT3. Despite challenges related to drug metabolism and toxicity, these natural compounds provide novel insights and promising avenues for cervical cancer treatment.

Abbreviations: ATP, Adenosine Triphosphate; AMPK, Adenosine monophosphate-activated protein kinase; AKT, activate protein kinase; AR-A, Artematrolide; ARS, Artemisinin; AP2α, activating protein 2 alpha; ALDOA, aldolase A; 1, 3-BPG, 1,3-bisphosphoglyceric acid; Bax, BCL2-Associated X; CC, Cervical cancer; CIN, cervical intraepithelial neoplasia; CSCC, cervical squamous cell carcinoma; I3C, Indole-3-carbinol; Cyclin D1, cell cycle protein D1; DNAJC8, DnaJ heat shock protein family member C8; 2-DG, 2-Deoxy-D-glucose; DHA, DIM, Dihydroartemisinindiindolylmethane; ENO1, increase α-enolase; ERK, extracellular signal-regulated kinase; FX11, [3-dihydroxy-6-methyl-7-phenylmethyl-4-propylnaphthalene-1-car boxylic acid]; G3P, glyceraldehyde-3-phosphate; GLUT, Glucose transporter; G6P, glucose 6-phosphate; HIF, Hypoxia-inducible factor; F-2, 6-BP, fructose-2,6-bisphosphate; FRA1, FOS related antigen-1; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; G3PD, glyceraldehyde 3-phosphate; HK2, Hexokinase 2; HPV, Human papilloma virus; HIV, Human Immunodeficiency Virus; ISCC, invasive squamous cell carcinoma; IGF1R, insulin-like growth factor 1 receptor; LDHA, Lactate dehydrogenase A; LPS, Lipopolysaccharide; LKB1, Liver kinase B1; MTOR, mammalian target of rapamycin; MDM2, murine double minute 2; Myo1b, Myosin 1b; MCT4, monocarboxylic acid transporter 4; M6A, N6-methyladenosine; Lnc-TDRG1, long noncoding -testis developmental related gene 1; MEK, mitogen-activated protein kinase; MED, Mycoepoxydiene; MMP-2, matrix metalloproteinases 2; MMP-9, matrix metalloproteinases 9; NTB, nitensidine B; OGDC, oxoglutarate dehydrogenase complex; PDH, pyruvate dehydrogenase; PDK1, pyruvate dehydrogenase1; PFK1, phosphofructokinase 1; PI3k, Phosphatidylinositol 3-kinase; Pak4, p21-activated kinase 4; POU2F2, POU class 2 homeobox 2; PDHA1, pyruvate dehydrogenase E1 subunit alpha; P-gp, P-glycoprotein; PYR, pyruvate; PDC, pyruvate dehydrogenase complex; PPP, pentose phosphate pathway; PFK1, Phosphofructokinase-1; PK, Pyruvate kinase; PEP, phosphoenolpyruvate; PKM, pyruvate kinase; PSB-P2, Patrinia scabra Bunge polysaccharide; PGLS, 6-phosphogluconolactonase; R13, Raddeanoside 13; RACK1, receptor for activated Ckinase 1; ShRNA, small hairpin RNAs; STAT, α Signal transducer and activator of transcription; STIP1, stress-induced phosphoprotein 1; Sp1, specificity protein 1; STAT5A, Signal Transducer And Activator Of Transcription 5A; SEMA4C, 3'-untranslated region Semaphorin 4C; TMBIM6, transmembrane BAX inhibitor motif containing 6; TIG1, tazarotene-induced gene 1; TCA, tricarboxylic acid; TIGAR, TP53-induced glycolysis and apoptosis-regulator; SiHa, Human Cervical Squamous Cell Carcinoma cells; SchB, Schisandrin B; TIIA, Tanshinone IIA; 20S-GRh2, 20S-Ginsenoside Rh2; UcA1, urothelial cancer associated 1; VDAC1, voltage-dependent anion channel 1.

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1. Introduction

Cervical cancer (CC) ranks among the most prevalent gynaecological malignancies globally, ranking fourth in incidence among female malignancies and even ranking first in some developing countries [1]. Human papillomavirus (HPV) infection underlies approximately 95% of all new CC cases [2]. Additionally, factors such as Human Immunodeficiency Virus (HIV) infection, prolonged contraceptive use and poor sexual behaviour contribute to CC occurrence [3,4]. Screening for high-risk HPV infection remains a cornerstone in many countries for CC incidence control [5]. While early-stage CC is primarily managed through surgery with high success rates, a considerable number of patients with CC present at locally advanced or advanced stages, necessitating radiotherapy and chemotherapy. However, locally advanced and advanced CC exhibit a high recurrence rate and metastatic rate, and radiotherapy and chemotherapy often result in severe toxicities and drug resistance [6,7], along with high rates of recurrence and metastasis, urging the search for more effective and less toxic treatment methods to improve treatment outcomes in patients with CC.

Tumour cells exhibit unique metabolic adaptations to sustain rapid proliferation. Even under aerobic conditions, tumour cells preferentially obtain energy through glycolysis, a phenomenon known as the Warburg effect. Notably, the Adenosine triphosphate (ATP) production rate of glycolysis is approximately 100 times faster than oxidative phosphorylation. This heightened glycolytic activity of tumour cells not only provides rapid ATP production but also furnishes intermediates crucial for biomacromolecular synthesis, meeting the heightened metabolic demands of proliferating tumour cells [8,9]. Moreover, elevated glycolysis produces large amounts of lactic acid, which promotes the acidification of the tumour microenvironment and changes in the extracellular matrix, leading to tumour cell immunosuppression and drug resistance and promoting tumour cell invasion and metastasis [10–12].

Inhibiting tumour glucose metabolism offers a strategy to deplete energy reserves in tumour cells, impeding their proliferation. Glycolysis inhibitors such as 2-Deoxy-D-glucosecan act on glycolysis and the Wingless-type (Wnt)/ β catenin signalling pathway, inhibiting the progression of CC. Additionally, 2-DG simultaneously targets glycolysis and Wnt-catenin signalling to inhibit CC progression [13]. Furthermore, Hexokinase 2 (HK2) inhibitors, small hairpin RNAs (shRNA) and/or metformin can induce cell apoptosis, inhibit cancer cell growth, impede cancer cells' energy source and, ultimately, inhibit CC development by inhibiting HPV16e7 oncoprotein-induced glycolysis. They can also increase the sensitivity of CC cells to radiotherapy [14]. Similarly, lactate dehydrogenase A (LDHA) inhibitor FX11(3-dihydroxy-6-methyl-7-(phenylmethyl)-4-propylnaphthalene-1-carboxylic acid) can significantly inhibit the transplantation progress of human lymphoma and pancreatic cancer by inhibiting LDHA [15]. Therefore, it can modulate the Warburg effect of tumour cells by interfering with the glycolysis pathway, Thus, impeding the occurrence and development of CC by cutting off its energy source provides a novel strategy for the treatment of CC.

Natural products encompass a wide array of animal, plant, microbial and secondary metabolites, showcasing diverse biological activities. Traditionally used as primary treatments in various traditional medicinal systems, natural products also serve as vital resources for modern drug discovery [16]. Many natural products exhibit anticancer properties, such as Catharanthus alkaloids extracted from *Catharanthus roseus (L.) G. Don cv. Albus* plants, taxol extracted from the bark of *Taxus chinensis (Pilger) Rehd*, camptothecin extracted from *Camptotheca acuminata*, and have been utilised in treating CC, gastric cancer, lung cancer, breast cancer and other cancers [17–21]. Therefore, exploring natural compounds with anti-glycolysis activities holds promise in the development of novel CC therapies. This review aims to elucidate the glycolytic mechanism in CC cells and summarise natural products with potential anti-glycolysis properties, fostering the advancement and application of new anti-CC drugs.

2. Glycolysis in tumors

The glycolytic activity in tumor cells involves a cascade of biochemical processes. GLUT is the main carrier for glucose transport across the membrane into the cell [22]. HK2 phosphorylates glucose to yield glucose 6-phosphate (G6P), impacting tumor proliferation and migration significantly [10,23]. Phosphofructokinase-1 (PFK1) catalyses the conversion of fructose-6-phosphate into 1,6-fructose diphosphate, a pivotal rate-limiting step in the glycolysis pathway. Pyruvate kinase (PK) catalyses phosphoenolpyruvate (PEP) conversion to pyruvate, yielding Adenosine triphosphate (ATP), which is notably upregulated in CC cells [24]. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) catalyses the conversion of glyceraldehyde-3-phosphate (G3P) to 1,3-bisphosphoglyceric acid (1,3-BPG). Pyruvate, the end product of glycolysis, undergoes conversion to acetyl-CoA by pyruvate dehydrogenase (PDH) [9,10]. Subsequently, acetyl-CoA is transferred to the mitochondria, fuelling the tricarboxylic acid (TCA) cycle. Notably, LDH facilitates the reversible conversion of pyruvate and lactate. Under anoxic conditions, LDH drives pyruvate to lactate conversion, which is exported out of the cell through the monocarboxylic acid transporter 4 (MCT4) on the cell membrane surface, contributing to the acidification of the tumour microenvironment [25]. Moreover, LDHA is highly expressed in various tumour cells, including CC cells. In the presence of sufficient oxygen, extracellular lactate can enter cells, convert to pyruvate, catalyse into acetyl-CoA and enter the TCA cycle [9,11,26].

Multiple signalling pathways regulate aerobic glycolysis in tumour cells. Hypoxia-inducible factor (HIF)-1, notably its oxygen-sensitive subunit HIF-1 α, plays a pivotal role in mediating tumour cell responses to hypoxia. HIF-1 α also induces the overexpression of Glut1, assisting tumour cells in their shift from oxidative phosphorylation to glycolysis. Additionally, HIF-1 can directly upregulate the expression and activity of glycolytic enzymes such as HK2, pyruvate dehydrogenase1 (PDK1), 6-phosphofructokinase1 (PFK1) and LDH to bolster glycolysis rates [27–29]. The Myc oncogene family member c-Myc, highly expressed in various human tumours, orchestrates metabolic reprogramming in tumour tissues and is abnormally activated in most tumours. It promotes glycolysis by promoting GLUT expression and enhancing glycolytic enzyme activity, such as HK2, PKM2 and LDHA, further promoting pyruvate conversion to lactic acid [30,31]. As a tumour suppressor, p53 exerts inhibitory effects on glucose metabolism by downregulating GLUT1 and GLUT4 expression and reducing glucose uptake. Simultaneously, it also reduces the level of fructose-2, 6-bisphosphate (F-2,6-BP) by inducing the expression of TP53-induced glycolysis and apoptosis-regulator (TIGAR), thereby inhibiting the activity of PFK1 and reducing the rate of glycolysis [32,33]. Similarly, lipopolysaccharide (LPS) negatively regulates the FOS-related antigen-1 (FRA1)/murine double minute 2 (MDM2)/p53 pathway, promoting tumour cells growth and glycolysis [34]. Adenosine monophosphate-activated protein kinase (AMPK) enhances glucose uptake by upregulating GLUT1 and GLUT4 expression [35]. Phosphatidylinositol 3-kinase (PI3k) activates protein kinase B (AKT), promoting GLUT membrane translocation and HK2 expression, activating downstream molecules mammalian target of rapamycin (mTOR), and inducing HF1- α expression, thus fostering glycolysis [36,37].

3. Glycolysis in cervical cancer

Distinct glycolysis regulatory pathways are elucidated in CC. HPV16 E6/E7, a high-risk subtype of HPV, induces HIF-1 α overexpression in cervical squamous cell carcinoma (CSCC), intensifying glycolysis [38]. Increased levels of glucose metabolism enzymes PKM2 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in HPV16 AAE6-transduced keratinocytes enhance lactate and glucose production [39]. Liver kinase B1 (LKB1) inhibits c-Myc and HK-II, attenuating

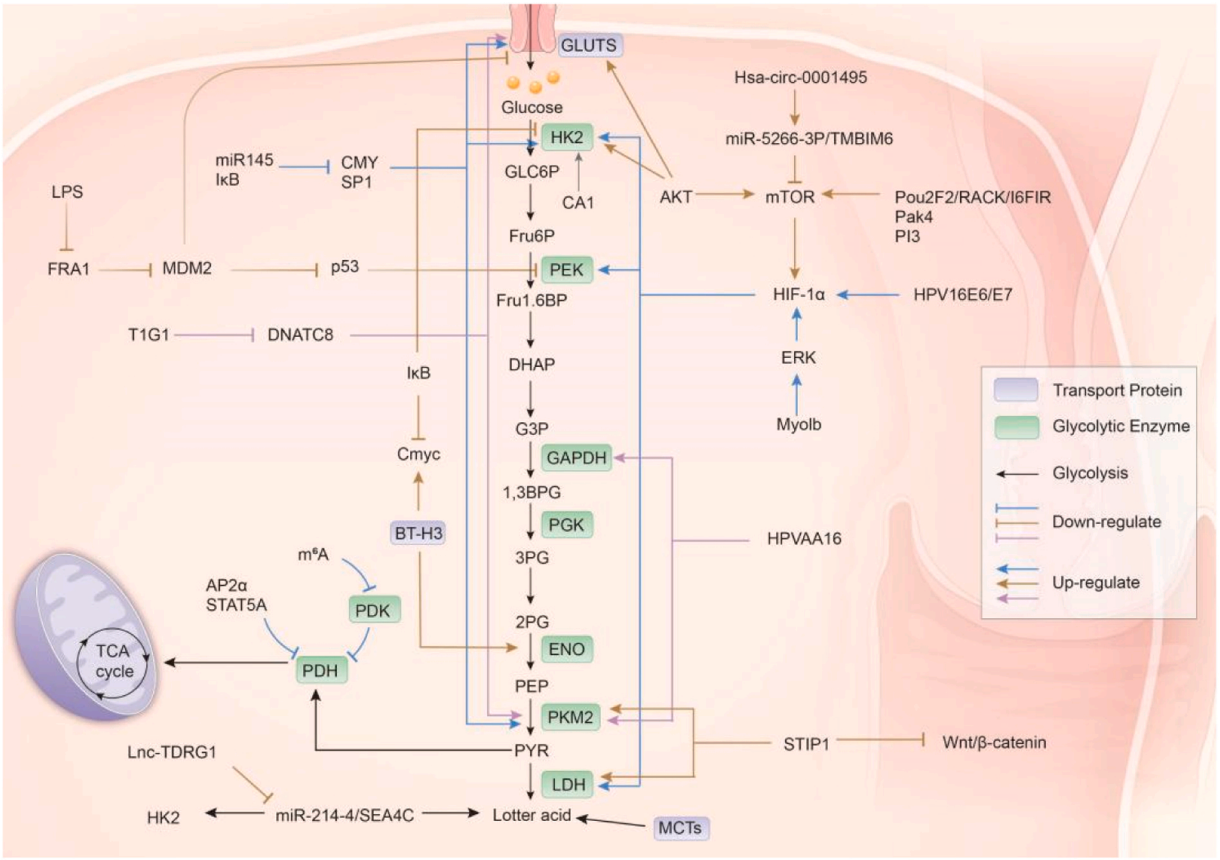

Fig. 1. Diagram of Glycolysis related mechanisms in cervical cancer.

glycolysis and counteracting HPV-induced metabolic reprogramming, thereby inhibiting the carcinogenic activity of HPV [40]. Stress-induced phosphoprotein 1 (STIP1) positively correlates with PKM2 and LDHA levels, with its high expression serving as a marker for CC. However, the downregulation of STIP1 can reduce the expression levels of PKM2 and LDHA and hinder the Wnt/β-catenin signalling pathway, thereby reducing glycolysis and inhibiting CC progression [41]. Specificity protein 1 (Sp1), highly expressed in human CSCC and cervical adenocarcinoma tissues, upregulates GLUT1, HK2, LDHA and PKM2 protein levels, augmenting aerobic glycolysis, and promoting CC proliferation, migration and invasion [42]. B7-H3 is a type I transmembrane glycoprotein, and its expression level is positively correlated with the differentiation and clinical stage of CC. B7-H3 can increase α-enolase (ENO1) expression and promote LDHA expression by promoting c-Myc, thereby promoting glycolysis in HeLa cells [43]. P21-activated kinase 4 (Pak4) is highly expressed in HeLa cells and can enhance HIF-1α expression via Akt-mTOR pathway activation [44]. Myosin 1b (Myo1b) stimulates HIF-1α expression via the extracellular signal-regulated kinase (ERK)/HIF-1α signalling pathway, promoting CC migration, invasion and glycolysis [45]. POU class 2 homeobox 2 (POU2F2) activates receptors for activated C kinase 1 (RACK1) transcription, stimulating AKT/mTOR signalling by interacting with insulin-like growth factor 1 receptor (IGF1R), and glycolysis in CC [46]. Activating protein 2 alpha (AP2α) emerges as a potential transcription factor for pyruvate dehydrogenase E1 subunit alpha (PDHA1), binding to its promoter and suppressing PDHA1 expression, thus promoting CC malignant progression [47]. In HeLa cells, Signal Transducer And Activator Of Transcription 5 A (STAT5A) exacerbates the Warburg effect by inhibiting PDH activity [48]. DnaJ heat shock protein family member C8 (DNAJC8) in HeLa cells binds to PKM2, enhancing its nuclear accumulation, and subsequently upregulating Glut1 expression to promote glucose metabolism. Tazarotene-induced gene 1 (TIG1) interacts with DNAJC8 to hinder DNAJC8-mediated PKM2 translocation, thereby inhibiting glycolysis in HeLa cells [49]. In HeLa cells, the 5′-untranslated region (5′-UTR) and 3′-untranslated region (3′-UTR) regions of pyruvate dehydrogenase kinase 4 (PDK4) exhibit significant enrichment in N6-methyladenosine (m6A). Notably, m6A can reduce glycolysis in CC by inhibiting PDK4 [50]. P-glycoprotein (P-gp) is elevated during the growth of human cervical carcinoma cell line KB-3–1 tumour spheroids, and the decrease in pyruvate can downregulate P-gp expression through cell redox-related mechanisms. Urothelial cancer associated 1 (UcA1) enhances CC radioresistance by activating the HK2/glycolysis pathway [51].

miR-145 negatively regulates metabolic reprogramming-related genes, targeting the 3′-UTR of Myc to inhibit aerobic glycolysis, thus impeding CC proliferation and metastasis [52]. miR-214–5p/ Semaphorin 4 C (SEMA4C) axis increases HK2 expression and lactic acid production. Long noncoding-testis developmental-related gene 1 (Lnc-TDRG1) is highly expressed in CC tissues and cells and is upregulated under hypoxia. Lnc-TDRG1 targets and negatively regulates the miR-214–5p/SEMA4C axis, inhibiting CC invasion and glycolysis [53]. circCDKN2B-AS1 (a circular RNA) stabilises HK2 mRNA by interacting with IMP3, promoting aerobic glycolysis in CSCC and enhancing the malignant phenotype of CC *in vitro* and *in vivo*. circ_ 0001495 (has-Circular RNAs 0001495) and transmembrane BCL2-Associated X (Bax) inhibitor motif containing 6 (TMBIM6) promote CC migration, proliferation and glycolysis. Furthermore, hsa_ circ_ 0001495 can target and positively regulate TMBIM6 expression by adsorbing miR-526b-3p, which can phosphorylate mTOR in CC cells, thereby inhibiting CC progression [54]. In summary, CC exhibits high glycolytic flux characteristics, with numerous pathways directly or indirectly influencing its occurrence and development through glycolysis. Therefore, targeting

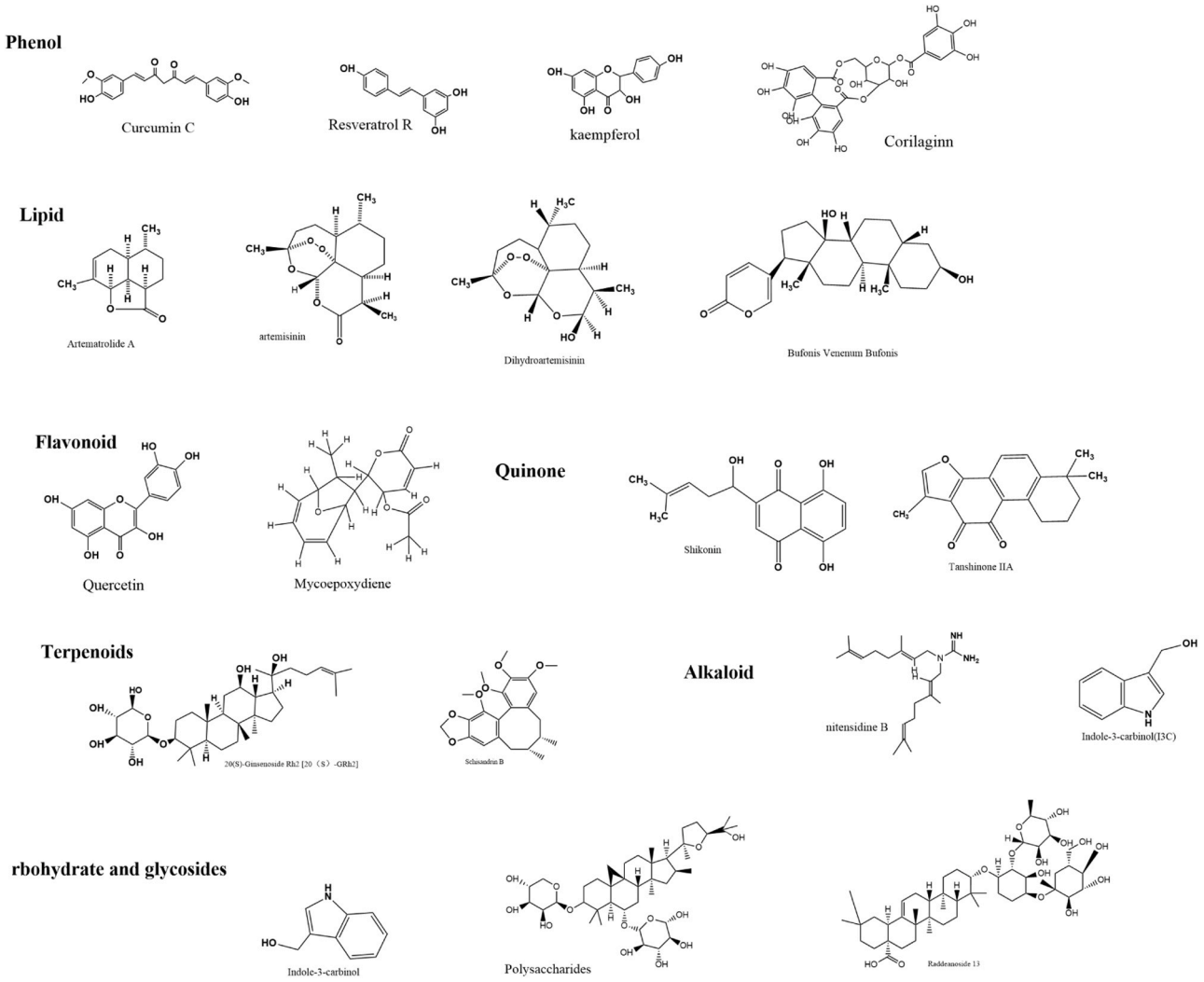

Fig. 2. Structural formulae of the Natural Products.

glycolytic metabolism represents a promising avenue for CC treatment Figs. 1–3.

4. Natural products that inhibit cervical cancer through glycolysis

Many basic in vivo and ex vivo studies have shown that a large number of natural products have a variety of anticancer activities and also attenuate the adverse effects produced by radiotherapy.This study systematically searched Web of Science, PubMed, Science Direct, SciFinder, SpringerLink, Embase and EBSCO databases from their inception to February 2024 to comprehensively retrieve articles related to the topic. The selected literature encompassed three primary subject headings and associated free words: 1) 'Cervix Cancer' and its synonyms, including 'Uterine Cervical Neoplasms', 'Uterine CCs' and 'Cervical Neoplasms'; 2) 'Glycolysis' and its synonyms, including 'Embden-Meyerhof pathway' and 'Warburg effect'. Articles containing terms like 'HIF-1', 'GLUT', 'HK2' and 'LDH' were also incorporated to broaden the search scope; 3) 'Natural products' and its synonyms, including 'plant bioactive compounds', 'herbs', 'organisms', 'plant sources', 'phytochemistry', 'medicinal plants' and 'plant nutrients'. The following natural products that inhibit cervical cancer by affecting glycolysis-related enzymes or genes were screened and we categorized the compounds according to their molecular structure.

4.1. Phenol

4.1.1. Curcumin

Curcumin, a polyphenolic compound extracted from the rhizome of *Curcuma longa*, exhibits diverse therapeutic effects, including antioxidant, anti-inflammatory, analgesic and anticancer effects [55–57]. The IC50 value of curcumin treatment on HeLa cells for 96 hours was measured at 23.86 μM. Treatment with 20 μM curcumin led to decreased intracellular lactate levels and glucose concentrations, increased pyruvate levels, apoptosis activation and HeLa cell migration inhibition. These findings suggest that curcumin inhibits the glycolysis pathway in HeLa cells, consequently inhibiting the migration and growth of CC cells [58].

4.1.2. Resveratrol

Resveratrol, a polyphenol compound found in various plants such as *Vitis vinifera*, *Arachis hypogaea* and *Vaccinium*, exhibits diverse biological activities, including antioxidant, anti-inflammatory, cardiovascular protection, anticancer, neuroprotective and anti-ageing effects [59]. The IC50 value of resveratrol on HeLa cells for 96 hours was recorded at 43.36 μM. Treatment with 20 μM resveratrol resulted in reduced intracellular glucose concentration and lactate levels, increased pyruvate levels and inhibited HeLa cell migration and growth. This suggests that resveratrol can inhibit the Warburg effect in HeLa cells, thereby inhibiting the migration and growth of CC cells [58].

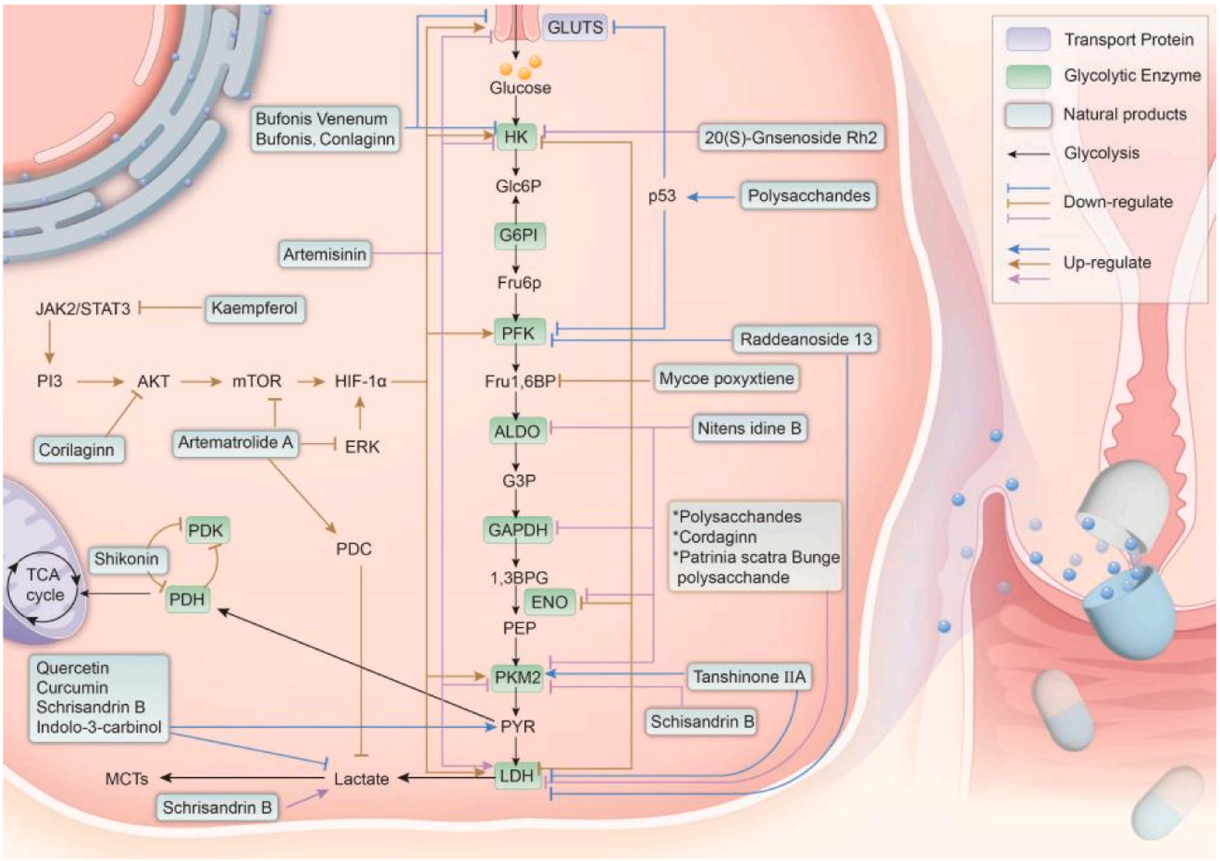

Fig. 3. Natural Products targeting the glycolysis in cervical cancer.

4.1.3. *Kaempferol*

Kaempferol, a polyphenol widely distributed in fruits and vegetables such as *Fragaria* and *Brassica oleracea var. acephala*[60], exhibits various pharmacological functions, including anti-inflammatory, antioxidant and anticancer effects [61]. Treatment of HeLa cells with 100 μmol/L kaempferol for 24 hours significantly inhibited cell proliferation rate, adhesion number, lactate content and glucose consumption level. Additionally, it downregulated the expression of p-JAK2 and p-STAT3 proteins, indicating that kaempferol inhibits the malignant behaviour of HeLa cells by blocking the JAK2/STAT3 signalling pathway [62].

4.1.4. *Corilaginn*

Corilagin, a natural ellagic tannin, isolated from *Caesalpinia coriaria (Jacq.) W*, possesses various protective activities, including anti-tumour, antibacterial, antioxidant and liver protection properties [63]. Corilagin significantly inhibited the proliferation, migration and invasion of U14 cells, while promoting apoptosis. The IC50 values at 24 h and 48 h were 391.0 μ mol/L and 394.5 μ mol/L, respectively. Corilagin at a dose of 15 mg/kg also exhibited significant anti-tumour effects in U14 tumour-bearing mice, with no significant toxicity. Mechanistic studies revealed that Corilagin downregulates the expression of GLUT1, HK2 and LDH1 genes through the AKT/HIF signalling pathway, thereby inhibiting glycolysis. Moreover, Corilagin induces tumour apoptosis through various pathways, including caspase3/9, Bcl-2, AKT/FOXO3/Bim and JNK/p38 MAPK. Additionally, it induces autophagy in tumours by regulating the expression of Ulk1, Beclin-1 and Atg12 [64].

4.2. *Lipid*

4.2.1. *Artemisinin(ARS)*

ARS, belonging to the family of sesquiterpene lactones, is primarily sourced from *Artemisia annua*. ARS exhibits a broad spectrum of antitumour activities, including anti-angiogenesis, apoptosis promotion, cell cycle blockade and cell invasion and migration inhibition [65,66]. The IC50 values of ARS in HeLa cells and CasKi cells for 48 h were 144.35 and 142.904 μmol/L, respectively. Treatment of HeLa and CasKi cells for 48 h with ARS at a concentration of 20–300 μmol/L significantly inhibited the growth and proliferative activity of HeLa cells, suppressed the expression of glycolysis-related enzymes, such as HK1, HK2, GLUT1, GLUT3, LDHB and PKM2, and downregulated the expression of silent information regulator 2 (SIRT2). Notably, SIRT2 is a member of the sirtuin family, which affects cellular metabolism by targeting various enzymes involved in glycolysis. ARS achieves its anti-CC effects by downregulating SIRT2 expression and inhibiting glycolysis in CC cells [67].

4.2.2. *Artematrolide A (AR-A)*

AR-A, isolated from *Artemisia atrovirens*, is a guaiacolide dimer. *In vitro* experiments demonstrated significant inhibition of cell viability, proliferation, migration and invasion of HeLa and Human CSCC cells (SiHa), inducing the apoptosis of CC cells. The IC50 values of AR-A for HeLa S3 cells were 5. 7 and 5.1 μM at 24 and 48 hours, respectively, while for SiHa cells, they were 10.1 and 5.4 μM at 24 and 48 hours. AR-A phosphorylated CC cells and the IC50 values of AR-A for CC cells were 10.1 and 5.4 μM at 24 and 48 hours. M. AR-A phosphorylates mitogen-activated protein kinase kinase (MEK) and ERK in CC cells, inhibits mTOR phosphorylation and HIF-1α expression, increases pyruvate dehydrogenase complex (PDC) and oxoglutarate dehydrogenase complex (OGDC) activity, thereby promoting pyruvate oxidative decarboxylation, reducing lactate production, increasing ATP production, promoting metabolic switch from aerobic glycolysis to mitochondrial respiration, inducing G2/M cell cycle arrest and apoptosis and inhibiting CC cell proliferation [68].

Table 1
Natural Products targeting the glycolysis for cervical cancer therapy. (↑ increase, ↓ decrease).

Compound	Source	Experimental model				Efficacy	Mechanism	Reference
		in vitro	Experimental dosage	in vivo	Experimental dosage			
Raddeanoside 13	Pulsatilla chinensis (Bunge) Regel	HeLa	5UM (24 h)	-	-	Significantly inhibited the glucose metabolism of cervical cancer cells, inhibited the proliferation of hela cells, block the G0/G1 phase of the cell cycle, Induce apoptosis and autophagy in cells.	↓ATP、PFK PYR、lactic acid，	[96]
Corilaginn	Euryale ferox	U14	0、200、400、600、800、1000μmol/L (24 and 48 h)	Cervical ancer U14 cells Subcutaneous transplantation tumor mice model	15 mg/kg 15d Administer the next day	Significantly inhibit the proliferation, migration, and invasion of U14 cells, and induce apoptosis in tumor tissues	↑Bim、CASPASE9，AKT/FOXO3/Bim、MAPK ↓AKT/HIF、Ulk1，Glut1、Hk2、Ldha、AKT/mTOR	[64]
kaempferol	dried roots of Neocheiropteris palmatopedata、the leaf extract of Siraitiagrosvenori	HeLa	40μM (24h)	-	-	It can significantly inhibit cell proliferation rate, adhesion number, lactate content, and glucose consumption level	↓p-JAK2 、p-STAT3	[62]
Artematrolide	atrovirens	HeLa S3，SiHa	2.5–10 μM (3–48 h)	-	-	Inhibiting cell glycolysis, proliferation, migration, invasion, and promoting apoptosis	↑ROS/ERK/mTOR ↓ LDH	[68]
Shikonin	Lithospermum erythrorhizon	HeLa	1、2、 4 mM (24 h)	HeLa cell xenograft mice	1 mg/ kg/ d 15d	Significantly inhibit the growth of tumor in mice	↓PDK1、lactic acid ↑PDH	[78]
Bufonis Venenum Bufonis	Venenum Bufonis	ME180 C33A	0.1 μmol/L (48 h)	-	-	Reduce the glycolysis level of cells and inhibit the proliferation of ME180 and C33A cells	↓GLUT1、HK2	[73]
Patrinia scabra Bunge polysaccharide	Patrinia scabra Bunge	-	-	U14 cell transfected mice	(40、80 mg/kg) 1time/d，14d	Significantly reduce tumor weight in mice and promote cell apoptosis	↓LDH、	[98]
polysaccharides	Patrinia heterophylla Bunge	-	-	U15 cell transfected mice	30 mg /kg/ d 14d	Significantly reduce tumor weight and promote cell apoptosis	↓LDH	[99]
Tanshinone IIA	alvia miltiorrhiza	Siha	0.5、1、2、4、8、16 mg/L (24 h)	-	-	Inhibit cell malignant proliferation, migration, invasion, and promote cell apoptosis	↓glucose、lactic acid Bcl-x1,MMP-2 ↑PKM2，STAT3	[82]
Mycoepoxydiene	Diaporthe sp. HLY-1	HeLa	20 μM (24 h)	-	-	Inhibiting cell growth	↓HK2、PFKM、ALDOA、TPI、ENO1、PGLS、LDHA、G6PD	[76]
nitensidine B	Pterogyne nitens	SiHa	30 μM、60 μM、120.0 μM (24 h)	-	-	Inhibit cell proliferation and induce cell apoptosis	↓ALDOA、G3PD、PKM、ENO1	[93]
artemisinin,	Artemisia annua	HeLa CasKi	20–300 μmol/L-1 (48 h)	-	-	Inhibits cell growth and proliferation activity	↓HK1、HK2、GLUT1、GLUT3、LDHB、PKM2 SIRT2	[67]
20(S)-Ginsenoside Rh2	Panax ginseng	HeLa	35、45 μM (24 h)	-	-	Promote apoptosis and inhibit mitochondrial oxidative phosphorylation and glycolysis	↓HK2 ↑VDAC1	[90]
Dihydroartemisinin	Artemisia annua	HeLa	40 μM、80 μM、160.0 μM、	-	-	Inhibits cellular glucose uptake and lactate	↑Bax、Caspase- ↓Bcl-2、PI3K、AKT、HIF1α	[69]

(*continued on next page*)

Table 1 (*continued*)

Compound	Source	Experimental model				Efficacy	Mechanism	Reference
		in vitro	Experimental dosage	in vivo	Experimental dosage			
			320 μM、480 μM/L（24 h）			production, promotes cell apoptosis		
Schisandrin B	Schisandra chinensis	HeLa	25 μM/L、50 μM/L、100.0 μM/L（48 h）	-	-	Inhibiting cell proliferation and migration	↓PKM2、STAT3、BCL-xl、MMP-9、Cyclin D1	[69]
Curcumin Quercetin	Curcuma longa Allium cepa Asparagus officinalis Lactuca sativa	HeLa	20 μM(24 h)	-	-	inhibit cell migration and growth	↓glucose、lactic acid 、PYR	[58]
Indole-3-carbinol Ellagic acid	Brassica cretica Punica granatum Diospyros rhombifolia Rubus idaeus Rubus mesogaeus							

4.2.3. Dihydroartemisinin (DHA)

DHA is a major derivative of *artemisinin*. Compared with ARS, DHA exhibits significant anti-tumour effects alongside its high antimalarial activity, rapid metabolism rate and good water solubility. Treatment of HeLa cells with 40–480 μM/L DHA for 24 h significantly inhibited glucose uptake and lactic acid production in HeLa cells and promoted cell apoptosis. Moreover, the expression of Bax and caspase-3 proteins increased, whereas that of Bcl-2, PI3K, AKT and HIF1α decreased in HeLa cells. This suggests that DHA may inhibit glycolysis by blocking the PI3K/AKT/HIF1α signalling pathway, thereby promoting the apoptosis of CC cells [69].

4.2.4. Bufonis venenum bufonis

Bufonis Venenum Bufonis, a primary active ingredient of the traditional Chinese medicine *Venenum Bufonis*, is a toad toxin lactone compound extracted from the *parotid venom glands* and skin of the *toad Bufonis Venenum*. It exhibits both toxicological and pharmacological effects [70,71], including anti-tumour effects [72]. *In vitro* experiments demonstrated that treatment with 0.1 μmol/L Buis Venenum Bufonis for 48 h significantly downregulated the expression of GLUT1 and HK2, consequently reducing glycolysis levels and inhibiting proliferation of ME180 and C33A CC cells [73].

4.3. Flavonoid

4.3.1. Quercetin

Quercetin, a major flavonoid found in various fruits and vegetables such as *Allium cepa*, *Asparagus officinalis L*, and red leaf *lettu Lactuca sativa L*[74]., exhibits anti-tumour effects. The IC50 value of quercetin on HeLa cells for 96 hours was recorded at 26.41 μM. Treatment with 20 μM quercetin for 24 hours inhibited migration, induced apoptosis, reduced intracellular glucose concentration and lactate levels and increased pyruvate levels in HeLa cells. This suggests that quercetin inhibits the Warburg effect in HeLa cells, thereby inhibiting the migration and growth of CC cells and exerting anticancer effects [58].

4.3.2. Mycoepoxydiene(MED)

MED, a natural product isolated from the marine fungus *Diaporthe sp.*, inhibits the growth of various cancer cells. The fungal polyketide isolated from HLY-1 can inhibit the growth of various types of cancer cells. MED can induce apoptosis in HeLa cells, arrest the cell cycle in the G2/M phase and mediate cytoskeleton rearrangement [75]. Treatment of HeLa cells with 20 μ MED for 24 hours inhibited cell proliferation and reduced the expression levels of enzymes involved in glycolysis and the pentose phosphate pathway(PPP), such as HK2, PFKM, aldolase A (ALDOA), triosephosphate isomerase (TPI), ENO1, PGLS (6-phosphogluconolactonase). MED also inhibited the activity of LDHA and G6PD enzymes in HeLa cells, suggesting the inhibition of glycolysis and the PPP as mechanisms for suppressing HeLa cell growth [76].

4.4. Quinone

4.4.1. Shikonin

Shikonin, derived from the dried root of *Lithospermum erythrorhizon*, possesses diverse biological activities, such as anti-inflammatory, antiviral, anti-tumour and wound healing promotion. Notably, it also induces the apoptosis of many tumour cells, exerting a strong anticancer activity [77]. *In vitro* experiments demonstrated that treatment with shikonin (1, 2 and 4 mM) inhibited PDK1, activated PDH, disrupted the Warburg effect, induced aerobic metabolism, promoted apoptosis, and reduced glucose consumption and lactic acid production in HeLa cells. *In vivo* experiments with HeLa cell xenograft mice showed inhibition of tumour growth following oral treatment with shikonin, indicating its potential as an anti-CC agent [78].

4.4.2. Tanshinone IIA (TIIA)

Salvia miltiorrhiza Bge is the dried rhizome of *Salvia miltiorrhiza*. Tanshinone IIA (TIIA) is a diterpene quinone extracted from the dried root of *Salvia miltiorrhiza* and is the most studied biologically active lipophilic constituent of *Salvia miltiorrhiza* in cardiovascular medicine. It also possesses certain anti-tumour properties [79–81]. Treatment of SiHa cells with 0.5–16 mg/L TanIIA for 24 h dose-dependently inhibited the malignant proliferation, migration and invasion of SiHa cells, along with the promotion of apoptosis. TanIIA reduced the glucose uptake and lactic acid production of SiHa cells, decreased the protein expression level of Bcl-x1 and MMP-2 and upregulated the protein expression of PKM2 and STAT3. These findings suggest that TanIIA inhibits PKM2 activation, interferes with glucose metabolism and exerts anticancer effects [82].

4.5. Terpenoids

4.5.1. 20(S)-Ginsenoside Rh2 (20(S)-GRh2)

(20(S)-GRh2) is a type of dammarane triterpenoid compound, mainly derived from *Panax ginseng C. A. Mey*[83,84]. 20(S)-GRh2 is a rare ginsenoside with anti-inflammatory, antioxidant, anti-glycemic and anti-tumour activities [85–89]. Treatment with 20(S)-GRh2 for 24 hours upregulated voltage-dependent anion channel 1 (VDAC1) expression, inhibited HK2 expression, promoted HK2 separation from the mitochondria, promoted mitochondrial-dependent apoptosis and inhibited

mitochondrial oxidative phosphorylation and glycolysis in HeLa cells [90].

4.5.2. Schisandrin B (SchB)

SchB, sourced from the berries of *Schisandra chinensis*, is an active dibenzo-cycloheptene that possesses anti-inflammatory, antioxidant and multiple drug resistance-suppressing effects [91]. Treatment of SiHa cells with SchB for 48 hours significantly inhibited cell proliferation and migration; reduced PKM2, STAT3, matrix metalloproteinases 2 (MMP-2), matrix metalloproteinases 9 (MMP-9) and cell cycle protein D1 (Cyclin D1) level; inhibited glucose metabolism and lactate production. SchB may directly affect the phosphorylation of STAT3 by downregulating the level of PKM2 in the glycolysis pathway, thereby weakening the migration ability of cells and exerting an anticancer effect [92].

4.6. Alkaloid

4.6.1. Nitrendipine B (NTB)

NTB is a guanidinic alkaloid isolated from the leaves of *Pterogyne nitens Tul*, a plant in the Fabaceae family. Its IC50 value for SiHa cells was measured at 40.98 μ M. NTB inhibits the protein expression of glycolysis-related enzymes in SiHa cells, namely ALDOA (aldolase A), G3PD (glyceraldehyde 3-phosphate), PKM (pyruvate kinase) and ENO1, thereby inhibiting the proliferation of SiHa cells and inducing apoptosis [93].

4.6.2. Indole-3-carbinol (I3C)

I3C is a glucosinolate decomposition product found in cruciferous vegetables such as *Brassica oleracea* and *Brassica cretica*. It exhibits anticancer, anti-inflammatory, anti-fungal and antibacterial effects [94]. The IC50 value of I3C on HeLa cells for 96 hours was recorded as 52.09 μM. Treatment with 20 μM I3C for 24 hours inhibited the migration of HeLa cells and induced their cytotoxicity. The decrease in intracellular glucose concentration and lactate levels, along with the increase in pyruvate levels, indicate that I3C can inhibit the Warburg effect in HeLa cells, thereby inhibiting the migration and growth of CC cells and exerting anticancer effects [58].

4.7. Carbohydrate and glycosides

4.7.1. Raddeanoside 13 (R13)

Pulsatilla chinensis (Bunge) Regel is a perennial herb in the genus *Anemone* of the family *Ranunculaceae*. It possesses anti-inflammatory and antibacterial effects [95]. R13 (Raddeanoside 13) is an active ingredient of Pulsatilla chinensis and exerts an anticancer effect. R13 can inhibit the activity of HeLa cells, block the cell cycle and induce apoptosis and autophagy. Additionally, R13 can inhibit glucose uptake, ATP production, PFK activity and pyruvate and lactic acid production in HeLa cells, thereby inhibiting glycolysis in CC [96].

4.7.2. Patrinia scabra Bunge polysaccharide (PSB-P2)

Patrinia scabra Bunge is a herb native to Asia. It is used to treat diseases, such as malaria, anthrax, typhoid fever and cancer [97]. PSB-P2 is an active substance in *Patrinia scabra Bunge*. Treatment of U14 cell-bearing mice with 40–80 mg/kg of PSB-P2 for 14 days significantly reduced tumour weight and LDH activity, promoted tumour cell apoptosis and blocked cell cycle G0/G1 phase [98].

4.7.3. Polysaccharides

Valerianaceae, a herbaceous plant native to Asia, is used in folk medicine to treat hematoma, typhoid fever, carbuncles and abnormal uterine bleeding [97]. It has strong toxicity against cancer cells. Polysaccharides are the main compounds in herbal medicine, Patrinia heterophylla. Treatment of U14 cell-transfected mice with 30 mg/kg/day of polysaccharides isolated from *Patrinia heterophylla* for 14 days significantly reduced tumour weight. Mechanistic studies demonstrated that polysaccharides can induce apoptosis by downregulating Bcl-2 expression and upregulating p53 and Bax expressions in tumour tissues, thereby arresting the cell cycle at the G0/G1 phase, reducing LDH levels and inhibiting tumour glycolysis [99].

5. Clinical applications and limitations

Many clinical trials of natural products in CC therapy have been completed or are underway, suggesting that natural products have a promising future in CC therapy. Curcumin has safety and pleiotropic properties [100–102]. A phase II clinical trial showed that topical application of curcumin or curcumin-containing creams could promoted the clearance of HPV,a high-risk factor for cervical carcinogenesis, without side effects [103]. However, another double-blind, randomized, placebo-controlled clinical trial of more than 2 years demonstrated that curcumin was not effective in improving the clinical response to radiotherapy for CC [104]. Several clinical trials to evaluate the safety and efficacy of curcumin in the treatment of CC are already underway ClinicalTrials.gov: NCT02554344; NCT04266275; NCT04294836; CT02944578). The most common side effects of curcumin in the clinic are gastrointestinal symptoms,and its low bioavailability limits its promotion as a clinical drug. 20 (S)-GRh2 is considered to be one of the ginsenosides with the most potent antitumor activity,and in a clinical trial, the simultaneous application of 20(S)-GRh2 with radiotherapy for the treatment of patients with intermediate and advanced stage cervical cancer significantly reduced the gastrointestinal reactions and myelosuppression, and other adverse reactions in the patients incidence of gastrointestinal reactions and myelosuppression [105]. This suggests that synchronous adjuvant treatment of cervical cancer with 20 (S)-GRh2 and radiotherapy is feasible. It indicates that synchronous adjuvant treatment of CC with 20(S)-GRh2 and radiotherapy is feasible. In clinical trials, artemisinin and its derivatives have demonstrated safe and effective tumor inhibition, and a large number of clinical trials have been conducted to explore the antitumor effects of artemisinin and its derivatives. There have been some clinical reports on artemisinin and its derivatives for the treatment of cervical precancerous lesions and HPV infection but there are no clinical reports on the use of artemisinin in the treatment of cervical cancer. A phase I clinical trial demonstrated that vaginally administered artesunate for the treatment of CIN2/3 was well tolerated and safe at clinically effective doses [106]. A clinical trial is underway to evaluate the dose, frequency, pharmacokinetics, and safety of vaginally AS and DHA for the treatment of CIN (ClinicalTrials.gov: NCT06263582). Several phase I clinical trials have demonstrated the safety and potential role of quercetin in cancer prevention and treatment, but the low bioavailability of quercetin limits its clinical use. A phase I clinical trial showed that the safe dose of quercetin can be up to 945 mg/m2 intravenously, and overdose can cause adverse reactions such as vomiting and hypertension [107].Basic experimental studies have found that quercetin intervention can inhibit the proliferation of CC cells and increase the sensitivity of CC cells to radiation [108]. In a clinical study [109] Quercetin cervical administration for 6 months effectively increased the number of HPV conversion rate in ASCUS patients, and another clinical study [110] further demonstrated its superiority to interferon in the treatment of HPV infection. However, no clinical application of quercetin in CC was found. There are many studies demonstrating the preventive effect of IC13 in a variety of cancers [111–113]. A phase II clinical trial showed that a 12-week oral treatment with I3C was effective in promoting CIN regression in patients with CIN [114]. A phase I clinical trial demonstrated that the production and uptake of diindolylmethane (DIM), the major circulating product produced by IC13, was optimal when I3C was administered orally at a dose of 1000 mg, and that I3C does not accumulate extensively in the body and its clearance is not enhanced by enzyme induction [115].

The use of natural products is promising and many drugs have entered preclinical and clinical trials. However, there is a discrepancy

between the dose of many natural products in in vitro experiments and the effective dose in vivo.The IC50 value of curcumin in in vitro experiments on HeLa cells was 23.86 μM, and the 1–2 h mean peak serum concentrations (Cmax) of 4000 mg, 6000 mg, and 8000 mg of curcumin in cancer patients in clinical studies were. 0.51 ± 0.11 μM, 0.63 ± 0.06 μM, and 1.77 ± 1.87 μM, respectively [116]. The IC50 values of artemisinin in HeLa and CasKi cells were 144.35 μmol/L and 142.904 μmol/L for 48 h in in vitro experiments, while the Tmax of artemisinin tablets 1000 mg in humans in clinical studies was (2. 15 ± 0. 91) h, and the Cmax was (466. 50 ± 120. 15) μg-L $^{-1}$[117]. In in vitro studies, resveratrol requires a level of at least 5 μmol/ml to achieve cancer chemopreventive effect, and its IC50 value in HeLa cells was 43.36 μM. The serum level of resveratrol after oral administration of 25 mg resveratrol in humans in clinical trials was 2 μM [118]. quercetin in in vitro experiments in HeLa cells had an IC50 value of 26.41 μM. The IC50 value of quercetin in HeLa cells in in vitro assay was 26.41 μM, while in clinical studies it is recommended to inject 1400 mg/m2 of quercetin intravenously weekly or every 3 weeks to achieve antitumor activity [107]. The IC50 value of I3C in in vitro assay in HeLa cells was 52.09 μM, and in clinical studies it is recommended that the daily dose of I3C for its therapeutic potential should be in the range of 200–400 mg/kg [120]. In conclusion, there are significant differences in the dosage of natural products in in vivo and in vitro experiments, and determining the EC50 of a drug is crucial for the clinical application of natural products. This requires extensive preclinical studies to determine the potency-dose relationship in animal studies Table 1.

The journey from discovery to clinical application poses numerous challenges for natural compounds. For example, while curcumin exerts anti-tumour activity in various cancers, including those of the digestive, respiratory, reproductive and urinary systems [119], its clinical trials are still in its infancy, often hindered by small sample sizes, short follow-up periods, and limited understanding of its mechanism of action. Moreover, the properties of curcumin also have certain drawbacks in application, such as poor stability, poor water solubility, easy degradation and low bioavailability, which pose difficulties for direct administration in clinical settings [120,121]. Despite progress in the research and development of various new drug delivery systems for curcumin, its clinical efficacy warrants further study, necessitating the need for more research into its function, mechanism and metabolism in the human body.Many natural compounds are limited to *in vitro* and animal studies, lacking clear mechanisms of action and presenting undesirable side effects. For example, while toadflax inhibits the proliferation of ME180 and C33A CC cells through the glycolytic pathway in *in vitro* experiments, its effects *in vivo* require further research [73]. Extensive high-quality clinical studies are needed to evaluate the efficacy, mechanism of action, constitutive relationship and clinical application of many natural compounds in vivo, which further aid in developing specific drug delivery modes, understanding adverse drug reactions and determining dosages, thereby enhancing their clinical efficacy. Currently, the research on the anti-CC of coriolagin is at the *in vitro* level, warranting the need for animal experimentation [63,64]. ARS, a relatively safe drug, has undergone pharmacokinetic and pharmacodynamic studies, but its application in tumours requires further preclinical and clinical studies to investigate its molecular and cellular mechanisms in tumours [66,67].

6. Discussions and prospectives

6.1. The toxic side effects of natural compounds

Natural products are increasingly recognised as potential sources of anticancer drugs. However, many natural compounds exhibit both pharmacological benefits and toxicological risks, which could pose adverse effects on human health. Throughout drug development, many candidate compounds are often eliminated due to their toxic effects and adverse reactions. For example, while toad venom has been clinically used in China for years, its side effects on ion channels can cause fatal arrhythmia, limiting its widespread clinical application [72]. Studies have suggested that ARS may have teratogenic and embryotoxic effects, with exposure during pregnancy potentially causing embryo loss. Furthermore, its combination with temozolomide in patients with glioblastoma multiforme can induce liver toxicity [122]. The median lethal dose of Pulsatilla extract in mice is 175.5 g/kg, suggesting caution in its clinical use [123].

Therefore, the research and development of natural compounds targeting glycolysis in anti-CC must address their biological toxicity to identify low-toxicity, highly effective drugs. Xu Ying et al.[124]. proposed a novel albumin polymer hybrid that can target the delivery of bufalin, enhancing its anti-tumour effect *in vivo*, while reducing its hemolytic and cardiotoxic effects. Recently, the development of micro-nano drug delivery systems can achieve targeted delivery of multiple active ingredients, enhancing drug efficacy and reducing drug toxicity. For example, hybrid nanoparticles loaded with paclitaxel and baicalin can target and specifically release active ingredients at the target site, thereby reducing the toxic effects of free paclitaxel [125,126]. Additionally, co-crystal structures formed by two or more active ingredients through intermolecular forces such as hydrogen bonding can also achieve synergistic and attenuated effects. For example, the preparation of theophylline-quercetin co-crystal through a liquid milling method achieves the co-delivery of theophylline and quercetin, achieving beneficial effects in improving the bioavailability of quercetin, reducing the hepatotoxicity of theophylline and increasing the synergistic therapeutic effect of the two drugs [127–129].

6.2. The bioavailability of natural compounds

Many natural compounds have been demonstrated to inhibit the growth of CC cells *in vitro* and *in vivo* through the glycolytic pathway; however, poor solubility, low bioavailability and poor stability impeded their development and application in clinical settings. Resveratrol exerts therapeutic effects on cancers such as colon cancer and hepatocellular carcinoma and also has been reported to be effective when combined with other anticancer therapies, including immunotherapy. However, the drawbacks of resveratrol, such as poor water solubility, low chemical stability, low bioavailability and short biological half-life, limit its clinical utility [130–132]. Quercetin can regulate multiple targets and signalling pathways and possesses anticancer, anti-ageing, antiviral, anti-inflammatory and hypoglycaemic effects, which have promising applications, but its low solubility and bioavailability affect its clinical application [58,133,134]. Similarly, shikonin exerts potent anti-tumour activity against a variety of tumour cells, but its poor solubility and high toxicity hinder its development as a clinical anticancer drug [134–136]. ASR, as a low-toxicity and highly potent natural compound, has many clinical applications but is limited by poor bioavailability and low solubility in water or oil [66,137].

To address these challenges, semi-synthetic derivative drugs have been developed, such as incorporating naturally occurring pyruvate dehydrogenase (PDH) cofactor a-lipoic acid into shikonin, designing a dual inhibitor of mitosis (tubulin) and glycolysis (PDK), which exhibits better PDK1 inhibitory activity and cytotoxicity compared to shikonin [78].

Moreover, advancements in micro- and nano-delivery systems have enabled the precise delivery of multiple active ingredients in traditional Chinese medicine, offering opportunities to enhance the bioavailability of natural products. For example, nanotechnology has been applied to develop new dosage forms of resveratrol against cancer, such as nanoparticles, to improve solubility, oral bioavailability and stability, thereby enhancing its clinical efficiency [130,131]. Additionally, novel drug delivery systems like ginsenoside liposomes have been developed. Using this system, paclitaxel was loaded into the liposome for targeted synchronous delivery of the drug in gastric cancer treatment. The ginsenoside not only exerts its inherent anticancer effect but also synergises

with paclitaxel [138]. Additionally, the construction of self-assembled micelles using drugs with amphiphilic moieties, many of which are glycosides, has been successfully applied to the delivery of difficult-to-solubilise drugs such as baicalin and resveratrol [139,140].

7. Conclusion

CC remains one of the most prevalent malignant tumours affecting women, with a 5-year survival rate of approximately 15% for advanced patients [141]. Notably, CC cells exhibit typical cancer metabolic characteristics, including high glycolytic flux and lactic acid accumulation. Compared with normal cervical cells, CC cells display elevated expression levels of various glycolytic enzymes, such as GLUTI, PKM2 and LDHA, and classical cancer signalling molecules, such as HIF-1α, C-myc and PI3K, underscoring the significance of glycolytic regulatory pathways in CC pathogenesis, such as STIP1, HPV16 E6/E7, Sp1, B7-H3 and miR-145. Key glycolytic oncogenic signalling pathways, such as Akt and HIF-related pathways, play pivotal roles in regulating the malignant behaviours of CC cells, including growth, metastasis and angiogenesis.

Among the natural compounds screened, SchB, ARS, ARS-A, toadflax, MED, NTB and 20(S)-GRh2 have shown promise in inhibiting the glycolytic pathway by directly targeting key enzymes in the glycolytic pathway. Others such as curcumin, resveratrol, R13, kaempferol, quercetin, indole-3-methanol, comfreyin and Tan IIA regulate glucose uptake or consumption, along with lactate and pyruvate production, to inhibit glycolysis, Furthermore, compounds like Corilagin indirectly inhibits glycolysis by regulating the AKT/HIF signalling pathway to downregulate the expression of GLUT1, HK2 and LDH1 genes. Notably, PSB-P2 can upregulate p53 while decreasing the level of LDH to inhibit tumour glycolysis. While these natural compounds hold the potential to hinder CC development by targeting glycolysis, challenges remain in terms of drug toxicity, bioavailability and clinical translation. Moreover, due to the variety and complexity of natural drugs, relatively few varieties have been researched, and further studies on the composition of many kinds of natural drugs are still needed. Additionally, the clinical application of natural drugs demonstrates that the combination of synthetic drugs with natural compounds can enhance their pharmacological activities. Thus, exploring natural compounds, either singly or in combination, for the treatment of CC, particularly targeting glycolysis, holds significant promise for future therapeutic interventions.

Ethics statement

This paper does not conduct research on humans or animals.

CRediT authorship contribution statement

Yurong Tan: Visualization. **Jiao Liu:** Software, Data curation. **Mingya Zhu:** Visualization, Conceptualization. **Qun Liu:** Writing – review & editing, Writing – original draft. **Xiuhan Chen:** Writing – original draft. **Delin Li:** Visualization, Conceptualization. **Yijie Zhou:** Visualization, Software, Data curation. **Qiaozhi Yin:** Writing – review & editing. **Tiane Zhang:** Writing – review & editing, Project administration.

Declaration of Competing Interest

I am authorized on behalf of all the authors of this article to confirm that no author has any conflict of interest to disclose, all authors have approved the version submitted for publication, the work in this article is original and has not been published previously and the article is not under consideration by any other journal.

Data availability

No data was used for the research described in the article.

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