Application and research progress of cordycepin in the treatment of tumours (Review)

RU HE[1] and WENCE ZHOU[1,2]

[1]The Second Clinical Medical College, Lanzhou University, Lanzhou, Gansu 730000, P.R. China;
[2]Department of General Surgery, Lanzhou University Second Hospital, Lanzhou University, Lanzhou, Gansu 730000, P.R. China

Received March 28, 2024; Accepted June 20, 2024

DOI: 10.3892/mmr.2024.13285

Abstract. Cordycepin is a nucleoside molecule found in *Cordyceps sinensis* and can be obtained through chemical synthesis and biotransformation. Cordycepin has been extensively studied and has been shown to have antitumour activity. This activity includes effects on the autophagy process and inhibition of the MAPK/ERK and Hedgehog pathways. Ultimately, the inhibitory effect of cordycepin on tumour cells is due to the interplay of these effects. Cordycepin was shown to enhance the therapeutic effects of radiotherapy. There is increasing evidence indicating that cordycepin plays an anticancer role in the treatment of various cancers. The present review aims to provide a clear understanding of the antitumour mechanisms of cordycepin and discuss its present application in the treatment of tumours. This information can be an important theoretical basis and provide clinical guidance for the further development of cordycepin as an antitumour drug.

Contents

Correspondence to: Professor Wence Zhou, The Second Clinical Medical College, Lanzhou University, 199 Donggang West Road, Lanzhou, Gansu 730000, P.R. China
E-mail: zhouwc129@163.com

Key words: cordycepin, tumour, chemotherapy, apoptosis, cell cycle

1. Introduction

Cancer is a major global concern, causing millions of deaths each year and imposing a significant economic burden to society. In 2012, 8.2 million individuals died of cancer worldwide, and in 2020, >600,000 individuals in the United States succumbed to cancer (1). The disease is complex, involving tumour cells and a large number of noncancerous cells within the extracellular matrix. Any cell type can potentially transform into a tumour cell, which exhibits characteristics such as continuous self-proliferation, immune evasion, metabolic abnormalities, metastasis and invasion, and stimulation of angiogenesis (2). As healthcare technology advances, human life expectancy and the elderly population have increased, cancer deaths have also increased (3). Most cancers occur in individuals >60 years, making cancer a major public health issue that will increase in severity in the future (4). In China, rapid economic development, improved living standards, an aging population and lifestyle changes have led to a rapid rise in cancer morbidity and mortality (5). However, early diagnosis and effective treatment of malignant tumours remain challenging, and the overall survival rate of patients with malignant tumours is still low. For instance, pancreatic ductal adenocarcinoma (PDAC) is the third-leading cause of cancer-related mortality with a 5-year survival rate of <12% (6,7). Therefore, there is a need for further exploration of novel biomarkers and therapeutic targets to improve cancer diagnosis, treatment and prognosis. Recently, Traditional Chinese Medicine research has shed light on its potential in cancer treatment, particularly in inhibiting cancer progression (8). *Cordyceps sinensis* is a valuable medicinal compound widely used in north-western China that has garnered attention for its potential in cancer treatment (9). Further investigation into the function and mechanism of action of Cordyceps may lead to new opportunities for cancer treatment.

2. Introduction to cordycepin

Cordyceps sinensis is an entomopathogenic fungus belonging to the Ascomycetes family that is distributed mainly in China, Nepal, Tibet and the Himalayas region of India at an altitude of ~14,000 ft (10). It has been a commonly used drug in Traditional Chinese Medicine for the past 300 years (11). Cordyceps is considered to be one of the largest fungal genera

and contains ~500 species, such as *Cordyceps sinensis*, *Cordyceps sobolifera*, *Cordyceps cicadicola*, *Cordyceps liangshanesis*, *Cordyceps ophioglossoides* and *Cordyceps militaris* (12). Cordyceps are difficult to harvest and are unevenly distributed, but they are rich in natural bioactive components, such as proteins, fats, carbohydrates, polysaccharides, cordycepin, phenolic compounds, cordycepin and adenosine (11). Additionally, they have strong biological activity, and nutritional and medicinal value (13). Cordycepin is the main active ingredient in *Cordyceps sinensis*; it is a nucleoside molecule with a structure similar to adenosine but lacks the 3'-hydroxyl group in the ribose molecule (14). Its chemical structure is 3'-deoxyadenosine, which consists of a purine molecule and a ribose molecule (15). The determination of the chemical structure of cordycepin has enabled its chemical synthesis. In 1976, the biosynthetic pathway of cordycepin in *C. militaris* was studied using adenosine and ribose. The results showed that cordycepin is directly biosynthesized by converting adenosine to 3'-deoxyadenosine without hydrolysing the N-nucleotide bond (16). The results also showed that adenine or adenosine, precursors of cordycepin, could lead to an increase in cordycepin in *C. militaris* (16). However, due to the lack of genome sequence information, the biosynthetic pathway of this fungus took much longer to be elucidated. In 2011, whole-genome sequencing was performed for *C. militaris* and it was found that most of the genes related to *C. militaris* are also required for adenine and adenosine metabolism (17). They constructed the biosynthetic pathway of deoxyadenosine based on the existing purine and adenosine metabolic pathways (18). Adenosine is synthesized by three-step enzymatic reactions using inosine monophosphate and then phosphorylated by nucleoside/nucleotide kinases to adenosine-3'-monophosphate. Cordycepin is ultimately synthesized through distribution reactions using 3'-adenosine monophosphate as the precursor, which includes oxidoreductase/dehydrogenase and metal-dependent phosphohydrolase (19). In addition, some studies produced cordycepin from lipo-glucose (20,21).

A recent study examined the molecular interaction between cordycepin and the spike protein of SARS-CoV-2 and showed that cordycepin can inhibit virus entry and replication in the host, demonstrating its therapeutic potential against this disease (22). An increasing number of studies on the potential application of cordycepin in medicine have focused on its stable and effective production (19-21). However, the production of cordycepin is challenging due to various disadvantages, such as low yield, cost issues and poor extraction processes (23). Therefore, more effective strategies for cordycepin production need to be developed.

3. *In vivo* and *in vitro* antitumour effects of cordycepin

Numerous studies have shown that cordycepin can penetrate cells and be converted to the phosphoric form, competitively inhibiting the synthesis and metabolism of DNA and RNA, post-transcriptionally processing heterogeneous nuclear RNA, activating adenylate cyclase, inhibiting macrophage lineage and chemotaxis, and specifically promoting protein synthesis (24-26). Additionally, cordycepin has antitumour effects on some cell lines, enhances cell differentiation, inhibits the growth and metastasis of tumour cells during cell cycle arrest, and induces apoptosis in cancer cells and inhibits angiogenesis (27,28). Cordycepin can also regulate cell function through adenosine receptors, death receptors or epidermal growth factor receptors, inhibit tumour proliferation, migration, invasion and the cell cycle, and regulate chemotherapy resistance of gastric cancer, liver cancer, kidney cancer, bladder cancer and testicular cancer cells (29).

The latest research shows that cordycepin may participate in antitumour mechanisms through mitogen-activated protein kinase, NF-κB, caspase, serine/threonine kinase (Akt) and JNK-MAPK pathways (28). In addition, it was reported that cordycepin can activate the caspase cascade and increase intracellular reactive oxygen species (ROS) levels, thereby eliminating human tongue cancer cells, testicular tumour cells and human OEC-M1 oral cancer cells (30). The aforementioned results indicate that cordycepin can activate different cell signalling pathways and play a role in tumour progression. Cordycepin also induced a systemic antitumour immune response in a subcutaneous tumour model in colon cancer mice and inhibited tumour growth (31). In addition, cordycepin promoted the antitumour function of immune cells by upregulating the immune response and downregulating immunosuppression in the tumour microenvironment and resetting the immune cell phenotype (30).

Previous studies have shown that cordycepin has tumour treatment efficacy both *in vitro* and *in vivo*. Table I summarizes the studies on the antitumour effects of cordycepin on various tumour diseases.

4. Cordycepin inhibits tumour growth through various pathways

Direct antitumour effect. Cordycepin may affect tumour cells through a variety of mechanisms, including promoting tumour cell apoptosis, inhibiting tumour cell proliferation, invasion and metastasis, and regulating the expression of tumour-related genes. Additionally, in animal models, cordycepin also inhibited tumour growth (28). Fig. 1 shows a diagram of the antitumour mechanism of cordycepin.

Signalling pathway inhibition

MAPK/ERK signalling pathway. The MAPK/ERK pathway plays an important role in cancer development. This pathway is involved in biological processes such as cell proliferation, survival, differentiation and metastasis (32). Abnormal MAPK/ERK pathway activation is closely associated with the development and progression of various cancers (33), such as lung cancer, stomach cancer, ovarian cancer (34-36). Therefore, this pathway has become an important target for cancer treatment. Currently, several inhibitors of the MAPK/ERK pathway have been developed and used to treat several cancers (37). These inhibitors can reduce the proliferation and metastasis of cancer cells by inhibiting the MAPK/ERK pathway, thereby achieving therapeutic effects (38). In a study on oral cancer, it showed that the small molecule inhibitor OTX008 induced the MAPK signaling pathway early (39).

The study by Zhou *et al* (40) explored the anticancer potential and mechanism of cordycepin in nasopharyngeal carcinoma. RNA sequencing (RNA-seq) combined with *in vitro* experiments revealed that the expression levels of

Table I. Summary of antitumour mechanism of cordycepin on various tumour diseases.

Tumour type	Cell lines	Tumour xenograft model	Effects and related pathways	(Refs.)
Nasopharyngeal carcinoma	C666-1	-	Activation of MAPK/ERK and β-catenin signalling pathways	(40)
Oesophageal cancer	ECA109, TE-1	Four- to six-week-old male nude mice	Influence on cell proliferation, apoptosis and cell cycle arrest via MEK/ERK pathway	(41)
	HK, K180, K70, ECA109	Four-week-old female nude mice	Induction of activation of AMPK and inhibition of AKT signalling pathway enhances chemoresistance to cisplatin in cancer cells	(106)
Pancreatic cancer	BxPC-3, AsPC-1	Female BALB/cA nu/nu mice	Induction of apoptosis and blockade of FGFR/Ras/ERK signalling causing cell cycle arrest	(42)
Bladder cancer	T24	-	Activation of exogenous and endogenous apoptotic pathways and ROS-dependent inactivation of PI3K/AKT signalling	(50)
	T24	-	Inhibition of Est-1-dependent MDR1 transcription enhances cisplatin sensitivity in cancer cells	(104)
Testicular cancer	MA-10	-	Activation of AKT and MAPK pathways, upregulation of ERK and JNK and downregulation of p38	(51)
	MA-10	-	Inhibition of ERK1/2, Rb/E2FR1, cell cycle pathway and FGFR1-4 protein expression inhibits tumour growth	(81)
	MA-10	Male 5- to 7-week-old C57BL/6 mice	Cell cycle arrest, cysteine asparaginase pathway and endoplasmic reticulum stress enhance radiosensitivity and induce apoptosis in cancer cells	(101)
	MA-10	Male 4 to 5-week-old C57BL/6 mice	Induction of cancer cell death via ROS accumulation and DNA damage in combination with radiotherapy	(102)
Cholangiocarcinoma	HuCCT1, QBC939, RBE	Four-week-old BALB/c nude female mice	Reprogramming lipid metabolism to inhibit metastasis and EMT via ERO1A/mTOR/SREBP1	(52)
	KKU-213A, KKU-100, KKU-055	-	Increased TRAILR expression enhances cancer cell sensitivity to NK-92 cells	(84)
Lung cancer	A549	BALB/c nude mice	Activation of AMPK and inhibition of AKT signalling pathway reverses cisplatin resistance in non-small cell lung cancer	(59)
	H1957, PC9,	Nude mice	Activation of AMPK signalling pathway inhibits progression of drug-resistant non-small cell lung cancer	(60)
	A549, PC9	-	Down-regulation of VEGF/PI3K/AKT signalling pathway in combination with apatinib synergistically inhibits cancer cell growth	(109)
Ovarian cancer	A2780, OVCAR3	4-week-old BALB/c nude mice	Through ENT1-mediated transport, induction of AMPK signalling and cellular autophagy	(61)
	SKOV-3, OVCAR3	-	Induction of autophagy and apoptosis through Dickkopf-related protein 1/β-catenin signalling	(75)

Table I. Continued.

Tumour type	Cell lines	Tumour xenograft model	Effects and related pathways	(Refs.)
Breast cancer	MAD-MB-231, MAD- MB-468, MCF-7	-	Induction of apoptosis and inhibition of metastasis in breast cancer cells by inhibiting the hedgehog pathway	(65)
	-	BALB/c nude mice	Modulation of the hedgehog pathway inhibits growth and metastasis of xenograft tumours in nude mice	(66)
	BT549	Female BALB/c mice	Regulation of EMT-TFs SLUG, TWIST1, SNAIL1 and ZEB1 inhibits cancer cell migration and invasion	(27)
	MCF-7, MAD-MB-231	-	Increased Nrf2-related ROS sensitise cancer cells to radiation	(87)
Leukaemia	AC133-MUTZ-2	-	Induction of leukaemia cell death through re-expression of WIF and down-regulation of MYC	(71)
	U937	-	Regulation of the MAPK pathway enhances thermotherapy-induced apoptosis and cell cycle arrest	(80)
Oral squamous cell carcinoma	HSC-4	-	Attenuation of cancer cell migration and invasion through autophagy-dependent FAK/AKT and MMP2/MMP9 inhibition	(74)
	SAS, OC-3	Nude mice	Induces DNA damage repair and enhances radiosensitivity	(103)
Colorectal cancer	HCT116	-	Inducing Bax-dependent apoptosis	(76)
	CT26, SW480, CCD841, CoN	6-8weeks old BALB/c nude mice	Inhibition of the expression of the phagocytic immune checkpoint CD47 enhances anti-tumour immunity	(84)
	MC38, CT26	-	Enhancement of CD8+ T cell mediated anti-tumour immunity	(31)
	MC38, CT26	C57BL/6J mice	Significant enhancement of tumour suppression by combination therapy with anti-CD47 antibody	(86)
	HCT-116, Caco-2	-	Inhibition of MYC expression suppresses cancer cell proliferation	(92)
	HT-29	-	Cordycepin-coated liposomes effectively increase apoptosis and inhibit growth of cancer cells	(99)
Tongue cancer	CAL-27	Male nude BALB/c mice	Induces apoptosis	(104)
Retinoblastoma	-	Nude mice	Regulation of c-Myc/cell cycle protein D1 pathway inhibits cancer cell proliferation, migration invasion and lung metastasis	(78)
Cervical cancer-	-	-	Downregulation of CDK-2 interferes with the cell cycle and increases ROS to increase apoptosis	(82)
	-	C57BL/6J mice	Lactobacillus plantarum CQPC02 prevents obesity in mice through PPAR-α signalling pathway	(88)
Liver cancer	HUVECs, HCAECs, HPAECs	C57BL/6 and BALB/c nude mice	Regulation of adhesion spot kinase and p53 inhibits endothelial cell proliferation, migration, angiogenesis and tumour growth	(89)
	HepG2, Huh7	-	Downregulation of CXCR4 expression inhibits migration and invasion of hepatocellular carcinoma cells	(90)
Stomach cancer	MGC-803, HGC-27	-	Inhibition of lipid metabolism through AMPK and MAPK activation inhibits cancer cell proliferation and migration	(91)

Table I. Continued.

Tumour type	Cell lines	Tumour xenograft model	Effects and related pathways	(Refs.)
Uveal melanoma	92.1, Omm1, Mel202, Omm2.3, Omm2.5, MP46, MM28	Female nude mice	Inhibition of heat shock protein 90 function targets tumour growth in an adenosine deamination-dependent manner	(93)
Choriocarcinoma	JAR	-	Disruption of centrosome homeostasis inhibits cancer cell growth	(94)
Endometrial cancer	Ishikawa	-	Induction of apoptosis in cancer cells	(98)
Osteosarcoma	U2OS, SAOS2, MNNGHOS, 143B, MG63, SJSA1	Female BALB/c nude mice (4-5 weeks old)	Activation of AMPK and inhibition of the AKT signalling pathway enhances the chemosensitivity of cancer cells to cisplatin	(105)
Glioblastoma	LN-299	-	Down-regulation of MYC improves the sensitivity of cancer cells to temozolomide	(107)
	LN-229, U251, T98G	-	Modulation of EMT in combination with doxorubicin inhibits cell migration and invasion	(108)

MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase kinase; AMPK, AMP-activated protein kinase; AKT, serine/threonine kinase; FGFR, fibroblast growth factor receptor; Ras, rat sarcoma; PI3K, phosphoinositide 3-kinase; MDR1, multidrug resistance protein 1; JNK, c-Jun N-terminal kinase; ROS, reactive oxygen species; EMT, epithelial-mesenchymal transition; ERO1A, endoplasmic reticulum oxidoreductase 1α; mTOR, mechanistic target of rapamycin; SREBP1, SRE binding transcription factor 1; TRAILR, tumour necrosis factor-related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor; ENT1, equilibrative nucleoside transporter 1; HUVECs, human umbilical vein endothelial cells; HCAECs, human coronary artery endothelial cells; HPAECs, human pulmonary artery endothelial cells; EMT-TFs SLUG, EMT-transcription factors SLUG; TWIST1, Twist family bHLH transcription factor 1; SNAIL1, snail family transcriptional repressor 1; ZEB1, zinc finger E-box binding homeobox 1; Nrf2, NFE2 like bZIP transcription factor 2; WIF, WNT inhibitory factor; MYC, MYC proto-oncogene; MMP, matrix metalloproteinase; PPAR-α, peroxisome proliferator activated receptor α; CXCR4, C-X-C motif chemokine receptor 4.

ERK1/2, phosphorylated ERK1/2 and β-catenin were significantly decreased after cordycepin treatment. This suggests that cordycepin may be a novel drug candidate for nasopharyngeal cancer treatment. In addition, in oesophageal cancer, cordycepin induces chromatin condensation, activates the caspase cascade, induces apoptotic signalling, regulates Bcl-2 family members to increase cell apoptosis and alters cyclin-dependent kinases 1 and 2. The expression of cyclin B1 led to G_2/M phase arrest (41). A mechanistic study revealed that inactivation of the ERK pathway was involved in the antitumour effect of cordycepin and the same result was also observed *in vivo* (41). Moreover, cordycepin was confirmed to activate caspase-3, caspase-9 and cytochrome C to induce apoptosis, activate the checkpoint kinase 2 pathway and downregulate cyclin A2 and cyclin-dependent kinase 2 (CDK2) phosphorylation-related genes, S-phase arrest and DNA damage (42). Furthermore, the same study showed that cordycepin blocks the MAPK pathway by inhibiting the expression of Ras and the phosphorylation of ERK, and the blockade of the Ras/ERK pathway with fibroblast growth factor receptor 2 effectively inhibited the growth of pancreatic cancer cells (42).

PI3K/AKT/mTOR signalling pathway. Under normal conditions, the phosphatidylinositol 3-kinase (PI3K/AKT/mTOR) signalling pathway regulates cell proliferation and survival through a series of signal transduction and phosphorylation cascades (43). As an initiation factor of the pathway, PI3K is activated under the signal stimulation of molecules, including growth factors and cytokines, to catalyse the conversion of phosphatidylinositol diphosphate into phosphatidylinositol triphosphate (PIP3) (44). PIP3 activates AKT, which affects downstream activity, including that of FOXO transcription factors and mTOR proteins, to regulate cell proliferation and activity (45). In ovarian, stomach and breast cancer, abnormal activation of the PI3K/AKT/mTOR signalling pathway may be due to PIK3CA mutations such as deletion of the phosphatase and tensin homolog gene, overexpression of AKT and an increase in mTOR activity (46-48). Abnormally activated PI3K/AKT/mTOR signalling promotes the abnormal proliferation, survival and metastasis of cancer cells (49).

In a concentration-dependent manner, treatment of bladder cancer cells with cordycepin significantly reduced the survival rate of the cells and activated exogenous and endogenous cell apoptosis pathways, increased the caspase effect and resulted in polymerase cleavage (50). By increasing the ratio of Bax/Bcl-2, disrupting the integrity of mitochondria and promoting the release of cytochrome C, mechanistic study showed that cordycepin induces cell apoptosis by activating exogenous and endogenous apoptotic pathways and ROS-dependent inactivation of the PI3K/AKT

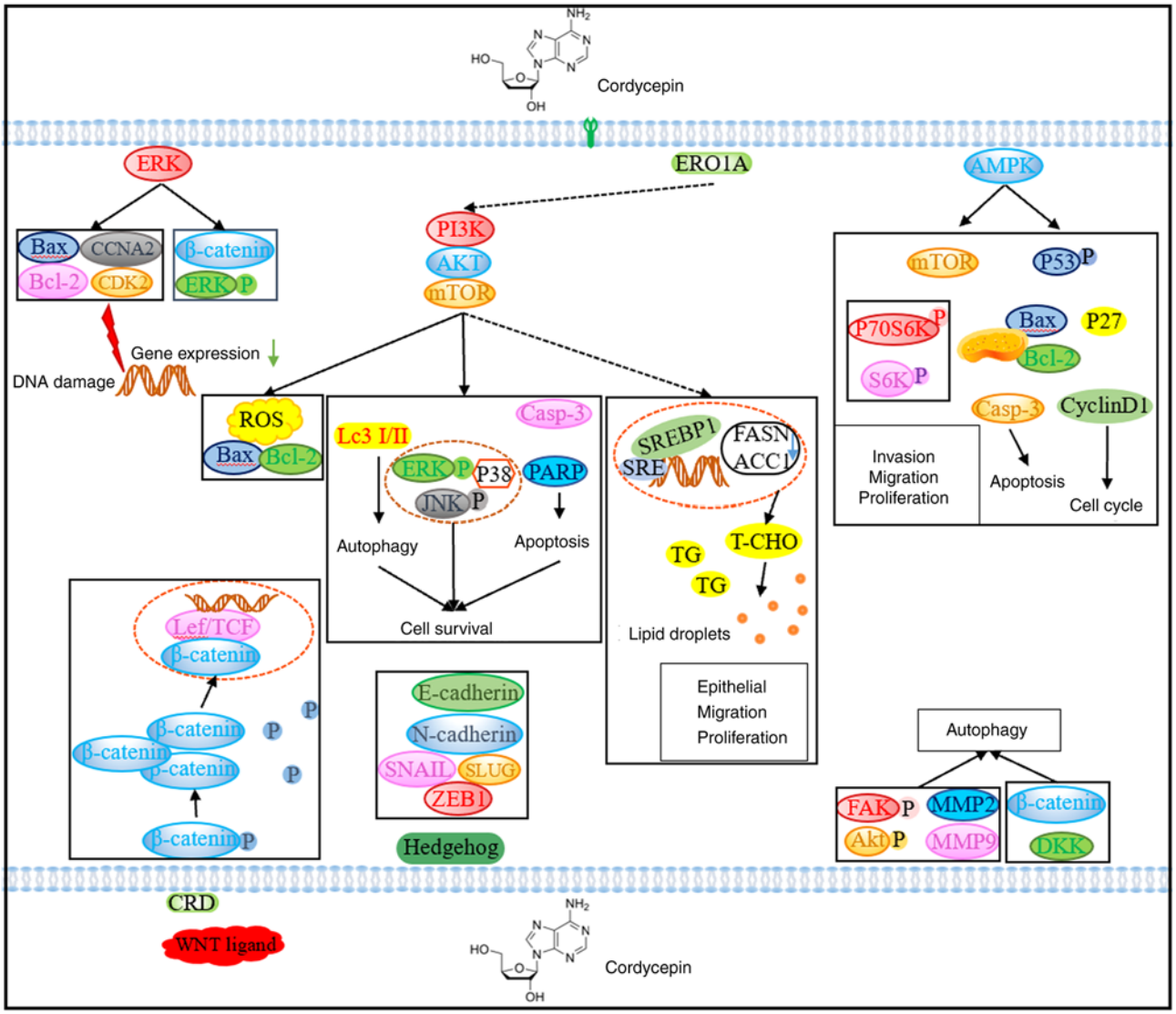

Figure 1. Schematic diagram of the antitumour mechanism of cordyceps. Cordycepin affects tumour growth and proliferation through various signalling pathways such as ERK, PI3K, AMPK, Hedgehog, ROS and autophagy, and exerts antitumour effects in cancer. ERO1A, endoplasmic reticulum oxidoreductase 1α; CCNA2, cyclin A2; CDK2, cyclin-dependent kinase 2; ROS, reactive oxygen species; Casp-3, caspase 3; PARP, poly(ADP-ribose) polymerase; S6K, ribosomal protein s6 kinase; P70S6K, p70 ribosomal S6 protein kinase; DKK, Dickkopf; FAK, protein tyrosine kinase 2; MMP, matrix metalloproteinase; T-CHO, total cholesterol; TG, triglyceride; SRE, sterol regulatory element; SREBP1, SRE binding transcription factor 1; FASN, fatty acid synthase; ACC1, acetyl-CoA carboxylase alpha; LeF, anthrax toxin lethal factor; CRD, Retinitis pigmentosa GTPase regulator; TCF, expressed protein.

signalling pathway in human bladder cancer T24 cells (50). In another study, cluster analysis of mRNA expression profiling and western blot analysis was performed on cordycepin-treated testicular cancer cells. The results showed that cordycepin regulates the FOXO/P15/P27, PERK-eIF2α and IRE1-XBP1UPR pathways. This study also found that activation of the AKT and MAPK pathways may lead to cancer cell resistance to cordycepin (51). In addition, cordycepin has a strong hypolipidemic effect. Therefore, it has been found that cordycepin-mediated endoplasmic reticulum oxidoreductase 1α/mTOR/SRE binding transcription factor 1 axis inhibits lipid metabolism and transfer in CCA cells *in vivo* and *in vitro*. After treating CCA cells with simvastatin and exogenous cholesterol, the same results were obtained, further confirming that cordycepin inhibits CCA migration through the regulation of lipid metabolism (52). These data indicate that cordycepin could be used as a novel drug for the clinical treatment of CCA and may improve the prognosis of patients with CCA.

AMPK signalling pathway. In cells, the AMP-activated protein kinase (AMPK) signalling pathway inhibits the growth and proliferation of cancer cells while inducing apoptosis (53). It also inhibits the synthesis and secretion of vascular endothelial growth factor (VEGF) to prevent angiogenesis, thereby inhibiting tumour growth and metastasis (54). In addition, activation of the AMPK pathway can also inhibit autophagy in cancer cells, thereby reducing the growth rate of tumour cells (55). In terms of metabolism, activation of the AMPK pathway can promote the metabolism of glucose and fat, thereby reducing blood glucose and blood lipid levels while increasing intracellular ATP production (56). The AMPK pathway has been confirmed to be associated with the development of cancer (57). Since tumour cells usually depend on

glycolysis to generate energy, activation of the AMPK pathway is considered to interfere with the metabolism of cancer cells (58). In conclusion, the AMPK signalling pathway plays an important role in cancer.

In a study on non-small cell lung cancer (NSCLC) cells, compared with cisplatin alone, cordycepin significantly inhibited the effect of cisplatin on cell proliferation and the promotion of cell apoptosis. Moreover, reversing cisplatin resistance in NSCLC through the AMPK and AKT signalling pathways could lead to the development of a potential treatment strategy for overcoming cisplatin resistance in patients with NSCLC (59). In another NSCLC study, cells with EGFR mutations were more sensitive to cordycepin treatment than the control cells (60). In ovarian cancer, cordycepin was found to activate AMPK signalling to transduce downstream target proteins to induce autophagy-dependent cell death (61). Based on the aforementioned results, the present authors considered that cordycepin alone or in combination with currently available targeted therapies might be an additional option for the treatment of lung cancer, especially for patients with EGFR-mutant lung cancer.

Hedgehog (Hh) signalling pathway. The Hh pathway is composed mainly of the Hh ligand, the intracellular protein patched (Ptch) and the signal transduction protein GLI family zinc finger (GLI). In the inactive state, Hh ligands bind to the Ptch protein on the cell surface. When Hh signalling is activated, the Hh ligand is released to dissociate from the Ptch protein (62,63). Persistent activation of the Hh signalling pathway is associated with the development of a variety of tumours, such as skin, brain and pancreatic cancer (64). Therefore, studying the Hh pathway is highly important for understanding the underlying mechanisms of cancers and identifying new therapeutic targets.

For the first time, Liu *et al* (65) studied the function of the Hh pathway in the effect of cordycepin on human breast cancer cells and the results showed that cell apoptosis induced by cordycepin led to an increase in the p53-upregulated modulator of apoptosis, Cytochrome C, Fas cell surface death receptor, death receptors 4/5 and caspase-3 and also led to the inhibition of Bcl-2, X-linked inhibitor of apoptosis protein and PDGFR-α. It also inhibits the expression of the Hh pathway and the transcriptional activity of GLI (65). The blockage of cordycepin-mediated cell apoptosis, epithelial-mesenchymal transition (EMT) and the Notch pathway after GIL knockout plays an important role in the effect of cordycepin on breast cancer. Further *in vivo* studies revealed that cordycepin reduced the volume and weight of xenograft tumours, affected proliferation, apoptosis and EMT, and affected the expression of matrix metalloproteinase-related proteins in cancer cells but had no side effects (65). Analysis of RNA-seq data showed that the Hh pathway was the most enriched in breast cancer tissues, and by analysing Hh pathway markers and assessing changes in expression in xenografts, the Hh pathway was shown to play an important role in the anti-breast cancer effect of cordycepin (66).

Wnt signalling pathway. The Wnt signalling pathway completes signal transduction through the extracellular Wnt protein and intracellular receptors, ligands and transcription regulators (67). The specific cascades involved include the Wnt/β-catenin, the canonical Wnt signalling, the Wnt-planar cell polarity and the Wnt-Ca^{2+} signalling pathways (68). In tumours, abnormal activation of the Wnt signalling pathway is common, as activation of the Wnt signalling pathway maintains stem cell properties and promotes tumour development (69). Therefore, the Wnt signalling pathway is an important target in tumour treatment.

Wnt/β-catenin signalling is required for the development and maintenance of leukaemia stem cells (LSCs) in acute myeloid leukaemia (AML) (70). Cordycepin downregulates the expression of the Wnt target genes MYC and prominin-1 (key factors for the maintenance of stem cells) through Wnt inhibitory factor 1 and Dickkopf-1 (Dkk1). These results provide new insights into the involvement of cordycepin-mediated molecular circuits in pharmacological inhibition and enhanced targeting (71). Wnt/β-catenin and its regulatory complex in AML treated with cordycepin can potentially target LSCs by reducing cell viability and stimulating LSC apoptosis, which supports the potential use of cordycepin as an adjuvant in the treatment of AML (70). Therefore, cordycepin may be effective in the treatment of AML.

Cell cycle and apoptosis regulation

Cell apoptosis. Cordycepin inhibits the growth of colorectal cancer (CRC) cells *in vitro* and may accelerate cancer cell apoptosis by inducing Bax translocation to the mitochondrial membrane (72). The same study also found that cordycepin-induced Bax translocation-induced cell apoptosis and reintroduction of Bax expression could restore the ability of cells to induce apoptosis. These results indicate that cordycepin may be a new agent for the treatment of Bax-deficient cancers (72). Cordycepin significantly inhibited the proliferation of tongue cancer cells in a dose-dependent manner and further induced the upregulation of Bax, caspase-3, caspase-9 and caspase-12 at the mRNA and protein levels while downregulating the increase in the level of the antiapoptotic gene Bcl-2. In addition, cordycepin effectively inhibited the growth of tongue cancer tumours in a mouse xenograft model (73). For the first time, Fong *et al* (74) confirmed the cytotoxic effect of cordycepin on endometrial cancer cells. The authors observed cell cycle arrest at the G_0/G_1 phase in cells treated with different concentrations of cordycepin, cisplatin or a combination of the two agents. In addition, the antitumour effect of the combination treatment was improved compared with that of a single compound, with fewer adverse drug reactions.

Cell cycle. A previous study showed that C-Myc is a downstream target of cordycepin and is positively associated with cell cycle pathways. In retinoblastoma (RB), cordycepin was found to inhibit the expression of cyclin D1 and overexpression of c-Myc could reverse this effect, thereby inhibiting the malignant biological behaviour of RB cells (75). In leukaemia, after hyperthermia and cordycepin combined treatment, the MAPK pathway significantly increased cell apoptosis, the level of matrix metalloproteinases also significantly decreased and ROS generation increased. Combination treatment also downregulates the expression of cyclin-dependent kinase 1 and cyclin B1 proteins and induces cell cycle arrest in the G_2/M phase (76). Cordycepin treatment inhibited the growth

of cervical cancer cells, increased apoptosis and interfered with the cell cycle, especially through prolongation of the S phase. After cordycepin treatment, the mRNA levels of the cell cyclins CDK2, Cyclin-A2 and Cyclin-E1 were downregulated, but the expression of apoptosis-related proteins did not significantly change. The aforementioned results indicate that cordycepin is effective at treating cervical cancer cells (77). Microarray analysis of cordycepin-treated MA-10 mouse stromal tumour cells revealed that cordycepin downregulated the expression levels of FGF9, FGF18, FGFR2 and FGFR3 in MA-10 cells. Moreover, the pathway prediction results showed that the inhibition of ERK1/2 and retinoblastoma protein/E2F transcription factor 1 pathways, the cell cycle pathway and the expression of the FGFR1-4 protein might inhibit the growth of FGF9-induced testicular tumours (78). In a mouse allograft model, the amount of FGF9-induced tumour growth in the cordycepin treatment group was significantly lower than that in the PBS treatment group (78). In summary, cordycepin could be used as a new anticancer drug for tumours and play a role in cancer treatment.

Autophagy regulation. Autophagy is an important biochemical process in cells. Its main function is to maintain cell homeostasis and vitality by decomposing and recycling damaged proteins, organelles and other cellular components (79). Autophagy mainly includes microautophagy, macroautophagy and chaperone-mediated autophagy, and among these processes, macroautophagy is the most extensively studied and understood (80). Autophagy has dual roles in tumours. In the early stage, autophagy may suppress tumour formation; after tumour progression to a certain stage, autophagy may switch to a role in promoting tumour survival and progression (81). Therefore, in tumour treatment, the regulatory and intervention strategies for autophagy need to be precisely adjusted according to the specific situation to achieve the best therapeutic effect.

In oral squamous cell carcinoma cells, the cordycepin-mediated inhibition of cancer cell migration and invasion was also altered when autophagy was inhibited by chloroquine, indicating that the migration and invasion inhibited by cordycepin may be mediated by autophagy (82). After cordycepin treatment, autophagy was induced, the fluorescence intensity of monodansylcadaverine fluorescence intensity (MDC)- and MDC-positive cells increased, and the expression level of the LC3 gene increased. Mechanistic study have shown that high doses of cordycepin inhibit cell death and invasion by inducing stress, while low doses inhibit invasion through autophagy-dependent focal adhesion kinase (FAK)/Akt/MMP2 and MMP9 pathways (82). Cordycepin can increase the level of Dkk1 and inhibit β-catenin signalling in human ovarian cancer cells. These results indicate that cordycepin may promote the cleavage of caspase-3 and inhibit the growth of ovarian cancer cells by coordinating autophagy and Dkk1/β-catenin signalling. Taken together, these data indicate that cordycepin may inhibit the growth of ovarian cancer cells through coordinated autophagy and Dkk1/β-catenin signalling (83). Cordycepin activates DNA-dependent protein kinase and ERK and triggers centrosome expansion to inhibit cell proliferation and destroy the cytoskeleton but does not affect the growth of normal placental cells (84). In addition, cordycepin treatment activated autophagy, and the inhibition of cordycepin-induced cell death by chloroquine prevented cordycepin-induced cell death, revealing the potential therapeutic effect of cordycepin.

Immune regulation. Cordycepin inhibited the growth and migration of and promoted the apoptosis of CRC cells in a dose-dependent manner, increased the infiltration of $CD4^+$ T cells, $CD8^+$ T cells, M1 macrophages and NK cells in the tumour immune microenvironment and inhibited the expression of trisodium phosphate in tumour cells (85). Reducing the binding of thrombospondin to CD47 allows more T cells to infiltrate tumours and inhibits the growth of CRC in a mouse tumour model (31). These results indicate that the adjuvant of cordycepin with other antitumour drugs can further enhance antitumour immunity and inhibit the growth of CRC and is a potential adjuvant drug for the immunotherapy of CRC. For the first time, Panwong *et al* (86) reported the ability of cordycepin to sensitize NK cells to toxicity in CCA cells. Compared with cordycepin or NK treatment alone, cordycepin treatment significantly increased the expression of the tumour necrosis factor-related apoptosis-inducing ligand receptor (TRAILR) in KKU-4A cells. The increased expression of the TRAILR may help cordycepin regulate immune activity. However, how cordycepin promotes NK cell activation remains unclear. These results indicate that cordycepin can be further developed as a substitute immunomodulatory drug in adoptive NK cell therapy.

In a previous study, combination treatment with cordycepin and an anti-CD47 antibody significantly inhibited tumour growth and prolonged the survival of tumour-bearing mice. The flow cytometry results showed that when cordycepin was used in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocker, the proportion of M1 and M2 macrophages was decreased, the presence of tumour-infiltrating $CD8^+$ T cells was significantly increased, and the proportion of M2 macrophages was decreased (27). Reducing the number of Foxp3 Tregs in the tumour microenvironment significantly inhibited tumour growth and prolonged the survival of tumour-bearing mice (27). In summary, the results of this study indicate that the combination of cordycepin and a CTLA-4 blockade can change the effector and exhaustion states of $CD8^+$ T cells, thereby enhancing $CD8^+$ T cell-mediated antitumour immunity in the tumor microenvironment (TME). According to the results of another single-cell RNA-seq study, the combination of cordycepin and a CD47 antibody could reactivate macrophages, reverse polarization, increase the proportion of M1 macrophages, decrease the proportion of M2 macrophages, regulate the proportion of $CD8^+$ T cells, and prolong the progression-free survival of patients with malignant tumours (87). In summary, these results prove that the use of cordycepin may enhance the function of immune cells, which is valuable for the treatment of various types of cancer.

Other. A study on triple-negative breast cancer showed that cordycepin can inhibit the expression of twist-related protein 1 and snail homolog 2 to inhibit the EMT signalling pathway. IT was also reported that combination therapy with cordycepin and thymoquinone had synergistic effects on the inhibition of

tumour metastasis (88). Cordycepin significantly decreased FAK expression and induced p53 and p21 expression in endothelial cell (EC) to impair angiogenesis and tumour growth and reduce hepatocellular carcinoma (HCC) tumour growth in a xenograft model. The present authors further examined the number of ECs in the tumour area in tumour-bearing mice. However, due to severe necrosis in the tumour area, the number of ECs or blood vessels could not be quantified (89). In another HCC study, cordycepin significantly inhibited IκBα phosphorylation, limited the nuclear translocation of P65 and activated tissue transcription factors, resulting in the downregulation of CXCR4 expression and the inhibition of migration and invasion in HCC cells. JSH-23 (an NF-κB pathway inhibitor) can inhibit the migration of liver cancer cells and was found to exert a synergistic effect when combined with cordycepin (90). These findings indicate that cordycepin can be used as a potential adjuvant in cancer treatment and may prevent HCC metastasis when it is used in combination with other therapeutic compounds.

Cordycepin activates the AMPK and MAPK signalling pathways, inhibits lipid metabolism and EMT processes, and significantly inhibits the proliferation, colony formation and migration of gastric cancer cells (91). Cancer cell proliferation is inhibited by downregulating MYC mRNA and protein expression and upregulating miR-2a in CRC cells. Furthermore, MYC overexpression inhibited the expression of miR-26a, while miR-26a expression was restored after cordycepin treatment. These results indicated that the inhibition of CRC cell proliferation by cordycepin might be mediated by the MYC/miR-26a pathway (92).

Cordycepin can slow the migration, growth and clonality of uveal melanoma and other invasive malignant tumours with low adenosine deaminase (ADA) levels, indicating that ADA may be a predictive biomarker of the cordycepin response and that tumours that are resistant to monotherapy may be sensitive to combination therapy. The present authors also found that cordycepin inhibited heat shock protein 90, thereby destroying its function and leading to the degradation of client proteins such as hypoxia-inducible factor, protein kinase B, extracellular signal-regulated kinase and EGFR, resulting in the activation of proteins in oncogenic signalling pathways, and reported a new mechanism of action of cordycepin (93). However, only *in vivo* studies were performed and the effect of cordycepin on the growth of orthotopic xenografts in other types of tumours needs to be evaluated.

Based on a combination of theoretical and experimental studies, the design and preparation of cordycepin-encapsulating liposomes were performed. Molecular dynamics simulations and free energy calculations showed that the phosphatidylcholine lipid environment was conducive to the adsorption of cordycepin. Cordycepin passively permeates into the PC lipid bilayer without causing damage to the membrane and tightly binds to the polar group of lipids by flipping its deoxyribose sugar toward the centre of the bilayer. In an *in vitro* study of colon cancer cell lines, cordycepin-encapsulated liposomes enhanced the anticancer activity of cordycepin (94). The study indicated that cordycepin-encapsulated liposomes may be effective drug candidates for the treatment of CRC.

5. Cordycepin in combination with chemotherapies and radiotherapy

In combination with radiotherapy. Radiation therapy uses radiation energy to damage the DNA of cancer cells, prevent their ability to proliferate and divide, and shrink or even eliminate tumours, and can be used to treat breast cancer, lung cancer, lymphoma, head and neck cancer and other tumor (95-98). A study showed that in mouse stromal tumour cells, the combination of cordycepin and radiotherapy has synergistic effects on the inhibition of cancer cell viability by activating exogenous and endogenous caspase pathways, cell cycle arrest and endoplasmic reticulum stress. Moreover, in animal experiments, it also reduced the tumour mass of stromal tumours (99). Subsequently, after combination treatment, ROS accumulated, heme oxygenase-1 protein levels decreased in mouse mesenchymal tumour cells and DNA damage-related signalling pathways were activated, including the ataxia-telangiectasia mutation induced by double-strand and single-strand breaks/checkpoint kinase 2 (Chk2), ataxia-telangiectasia mutations and Rad3 related (ATR)/Chk1 signaling axes were identified. The tumour volume, size and weight were reduced, and high expression of γ-H2AX was observed in *in vivo* tumour tissues after combination therapy (100). Network pharmacology analysis revealed the systemic mechanism underlying the inhibitory effect of cordycepin on the proliferation of breast cancer cells. Several studies showed that after radiation exposure, breast cancer cells cultured with cordycepin increased the levels of intracellular ROS and γ-H2AX lesions. However, the expression levels of nuclear factor erythrocyte 2-related factors and a series of downstream genes were downregulated after cordycepin treatment, sensitizing breast cancer cells to radiation through the Nrf2/HO-1/ROS axis. In addition, cordycepin promoted G_2/M arrest and apoptosis in breast cancer cells, thereby inhibiting cell proliferation *in vitro* and *in vivo* after radiation. Therefore, these study results indicate that cordycepin may be used as a radiosensitizer during clinical breast cancer radiotherapy (101,102). Another study showed that cordycepin can repair DNA damage in oral squamous cell carcinoma cells through Chk1 phosphorylation and prolong radiotherapy-induced G_2/M phase arrest. According to *in vivo* experiments, the growth inhibitory effect of the combination of cordycepin and radiotherapy on xenografts was greater than that of radiotherapy alone, and no excessive toxicity was observed (103). However, the clinical application of cordycepin in enhancing radiosensitivity needs further verification.

Cordycepin in combination with chemotherapy. Treatment with cordycepin or cisplatin alone failed to induce cell death in bladder cancer cells, but these two drugs in combination induced mitochondrial membrane depolarization, decreased the expression of antiapoptotic proteins and increased the expression of proapoptotic proteins. A high expression level of multidrug resistance protein 1 (MDR1) in bladder cancer results in cisplatin resistance. After cordycepin treatment, the inhibition of MDR1 promoter activity reduces MDR1 expression and induces resensitization of cancer cells to cisplatin (104). The combination of cordycepin and cisplatin enhances the sensitivity of osteosarcoma cells to cisplatin, increases apoptosis and inhibits the growth

and invasion of osteosarcoma cells by activating AMPK and inhibiting the AKT/mTOR signalling pathway (105). RNA-seq analysis revealed 72 genes whose expression was significantly different from that of the other genes and in which different signalling pathways may be regulated by cordycepin; in addition, the expression levels of ERK1/2, phosphorylated ERK1/2 and β-catenin were significantly downregulated (40). A relevant study confirmed that cordycepin enhances the chemosensitivity of oesophageal cancer cells to cisplatin through the activation of AMPK and the inhibition of the AKT signalling pathway, and *in vivo* and *in vitro* experiments demonstrated the synergistic effects of these two drugs (106). In clinical practice, combination therapy comprising cordycepin and cisplatin may be a potential treatment method for improving the treatment of oesophageal cancer (106). In addition, sensitization to other chemotherapeutic drugs was also found when other chemotherapeutic drugs were used in combination. Cordycepin combined with temozolomide inhibits EMT and regulates the proliferation, migration and apoptosis of glioblastoma cells (107). Cordycepin combined with doxorubicin regulates the EMT of tumour cells to inhibit cell invasion and migration, and this synergistic effect was proven through network pharmacology and *in vitro* experiments (108). Cordycepin and apatinib inhibited the VEGF/PI3K/AKT pathway, reduced cell proliferation, inhibited cell migration and invasion, altered the cell cycle to increase cell apoptosis, and exerted synergistic anticancer effects (109).

Therefore, cordycepin may be a novel drug candidate for cancer treatment and a candidate for combination therapy with other drugs, but the clinical feasibility of combination treatment still needs to be comprehensively evaluated in future studies, which could provide potential insights for anticancer drug design targets.

6. Advantages and challenges associated with cordycepin

Cordycepin is a natural medicinal ingredient extracted from *Cordyceps sinensis* that is widely used in health products and pharmaceuticals and has good safety and biological activity (11). Cordycepin has a variety of advantages in disease treatment, including the following: i) An immunomodulatory effect, whereby cordycepin can increase the activity of immune cells and promote the production and function of immune cells, thereby helping the body resist the invasion of diseases and pathogens (110); ii) an antioxidant effect that can neutralize free radicals, reduce oxidative damage to cells and delay the cell aging process; iii) an anti-inflammatory effect, which includes a reduction in the release of inflammatory mediators and tissue damage caused by inflammation, and inhibition of the occurrence and development of inflammation (111,112); iv) an antitumour effect, whereby cordycepin inhibits the growth and spread of tumour cells, induces tumour cell apoptosis and reduces tumour malignancy (113); and v) an improvement in the efficacy of radiotherapy and chemotherapy, whereby cordycepin can enhance the efficacy of chemotherapeutic drugs, reduce the side effects of chemotherapy, reduce the side effects of radiotherapy, enhance radiosensitivity, promote the repair of damaged tissues, improve the effect of radiotherapy and enhance the efficacy of patients, can reduce the recovery time after chemotherapy and improve the quality of life (114).

Long-term cordycepin use may cause chronic toxicity to organs such as the liver and kidney. when the intake of cordycepin exceeds the metabolic capacity of the human body, the surplus may accumulate in the liver, inducing a hepatotoxic response (115,116). In addition, cordycepin has poor stability and low solubility in water, which results in the loss of biological activity. Cordycepin is a bioactive compound extracted from *Cordyceps sinensis*. As a natural antibiotic, cordycepin has a variety of pharmacological effects. It was shown that cordycepin is rapidly deaminated by ADA, thereby shortening the half-life of the drug and reducing its bioavailability (117,118).

In conclusion, there are several problems associated with the medicinal use of cordycepin, which may differ among different cancer types and individuals. However, if managed according to the specific conditions of the patient, its pharmacological effects and functions can also achieve maximum efficacy, bringing additional benefits to the treatment of human diseases.

7. Discussion and future perspectives

Due to the clinical success of artemisinin, several researchers have focused on natural extracts (119). Artemisinin has been widely studied in the treatment of malaria and cancer (120,121). An increasing number of researchers are studying the safety and long-term use of natural extracts, as well as exploring the molecular mechanisms of their activities in various pathways. As an active component of cordyceps, cordycepin has been used in the fields of traditional Chinese medicine and health care products (11,13). The main mechanism of action of cordycepin is to fight cancer by regulating the human immune system and exerting antioxidative effects, which stimulate the immune system to enhance its ability to clear cancer cells and limit the growth and spread of tumours by inhibiting the formation and spread of the tumour microvasculature (110). Cordycepin also has antioxidant effects and can reduce oxidative damage caused by free radicals, protect the liver, lungs and other vital organs, and improve the anticancer ability of the body (111,112). The anticancer effect of cordycepin has been confirmed in several experimental studies. For instance, previous studies showed that cordycepin has the potential to prevent and treat various cancer types, such as colon (31,85,92,94), liver (90), breast (65,88,101) and prostate cancers (53). However, cordycepin cannot completely replace traditional tumour treatment methods and it still needs to be combined with other treatment methods, such as surgery, radiotherapy and chemotherapy, to increase the therapeutic effect. With the development of precision medicine, cordycepin may become a part of individualized drug treatment. The analysis of genomic information, genetic variation and tumour characteristics of patients could allow identification of which patients will respond best to cordycepin treatment and provide additional individualized treatment options. Nevertheless, more research and clinical trials are needed to ensure its safety and efficacy.

Acknowledgements

Not applicable.

Funding

The present study was supported by The National Natural Science Foundation of China (grant no. 82260555) and Gansu Provincial Science and Technology Major Project (grant no. 22ZD6FA021-4).

Availability of data and materials

Not applicable.

Authors' contributions

RH wrote and revised the manuscript; and WZ reviewed and edited the project. Both authors read and approved the final version of the manuscript. Data authentication not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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