Review Article

The anti-tumor potential of sinomenine: a narrative review

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Background and Objective: Currently, chemotherapy is the main treatment for most tumors. However, drug resistance and many adverse reactions associated with chemotherapy greatly limit its use. Therefore, an increasing number of researchers have shifted the research focus the anti-tumor activity of traditional Chinese medicine. The objective of this article is to review the anti-tumor mechanism of sinomenine and its derivatives to provide a reference for further study and clinical transformation.

Methods: In this study, we searched for relevant articles on the anti-tumor mechanism of *Sinomenium* using databases such as PubMed and Medline.

Key Content and Findings: Sinomenine is a monomer alkaloid component extracted from the rhizome of *Sinomenium acuturn*. A number of basic studies have proven that sinomenine and its derivatives show significant anti-tumor activity in breast cancer, lung cancer, liver cancer, stomach cancer, ovarian cancer, osteosarcoma and other tumors. They can induce apoptosis and autophagic death of tumor cells, inhibit proliferation, migration and invasion of tumor cells, increase the sensitivity of tumor cells to radiotherapy and chemotherapy, and reverse the drug resistance through various molecular mechanisms. In addition, sinomenine can effectively relieve osteolysis and bone pain in tumor patients. At present, anti-tumor research on sinomenine remains in the basic experimental stage.

Conclusions: Sinomenine and its derivatives are rich in substances with high anti-tumor potential. This analysis provides a review of the anti-tumor effects and mechanisms of sinomenine, with the hope of further exploring the medical value of sinomenine in anti-tumor treatments.

Keywords: Sinomenine; tumor; pharmacological mechanism

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Introduction

Since the second half of the 20th century, the incidence and mortality rates of cancer have been increasing year by year. According to statistics, in 2019, cancer became the fourth leading cause of death among young people worldwide (1). In 2023, there will be about 1,958,310 new cases of cancer worldwide and about 609,820 deaths occur in the United States (2). In recent years, Chinese herbal medicine has been playing an important role in the treatment of malignant tumors. Sinomenine has attracted the attention of scholars again because of its anti-tumor activity. *Sinomenium acutum* was used to treat rheumatic diseases more than 1,000 years ago. In the early 20th century, Japanese scholars isolated its main active ingredient from plant ivy (3). Its molecular formula is $C_{19}H_{23}NO_4$. Since sinomenine was discovered, scholars across the world have confirmed the cytotoxic effect of sinomenine on a variety of cancer cells *in vitro* and *in vivo*. It has been found to have many functions, such as anti-inflammatory, analgesic, immunomodulation, anti-tumor and drug addiction effects (4). Researchers have suggested

Table 1 Methodology of the search for the review

Items	Specification
Date of search	May 20th 2022–May 20th 2023
Databases and other sources searched	Medline and PubMed databases
Search terms used	"Sinomenine" AND "Tumor" OR "Pharmacological mechanism"
Time frame	1976–2023
Inclusion and exclusion criteria	Restricted to articles published in English; without predefined restriction as to the study type
Selection process	Conducted by the author of this study: Jun Zhu

that sinomenine is an effective chemoprophylaxis agent for cancer. However, sinomenine has the disadvantages of unstable physicochemical properties, poor water solubility, short half-life and low bioavailability, which limits its activity against cancer. Therefore, nanocarriers and molecular modification (such as sinomenine hydrochloride, sinomenine ester derivatives, chlorine-containing derivatives and YL064) is considered an effective method to solve these problems (5). Sinomenine has been successfully loaded into transmitter to enhance its bioactivity and bioavailability (6). Compared with sinomenine, Exo-SIN, a mixture of sinomenine and exosomes constructed by Wang *et al.*, showed significantly stronger cytotoxicity in HepG2 cells and significantly inhibited cell cycle arrest and apoptosis of hepatoma cells (7). Moreover, sinomenine also reduces osteolysis and bone pain in cancer patients. This review summarizes the molecular mechanism and potential value of sinomenine in the treatment of malignant tumors from the above aspects to provide a reference for the clinical transformation of sinomenine. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-267/rc).

Methods

A literature search was conducted in Medline and PubMed databases using the keywords "Sinomenine" AND "Tumor" OR "Pharmacological mechanism". The secondary references cited in articles obtained from the Medline and PubMed search were also retrieved. Methodology of the search is summarized in the *Table 1*.

In this study, 34 studies on the anti-tumor mechanism of sinomenine were included by searching the databases of PubMed and Web of Science. It was concluded that sinomenine and its derivatives played an anti-tumor role mainly by promoting apoptosis and autophagy, inhibiting proliferation, migration and invasion, and enhancing sensitivity to chemoradiotherapy (*Table 2*).

Sinomenine inhibits tumor cell proliferation

PI3K/AKT signalling pathway

Mutations and aberrant activation of the PI3K/AKT signalling pathway affect the proliferation, autophagy, migration, invasion and metabolism of cancer cells (41). Recently, AKT has been widely studied as a therapeutic target in cancer, and the AKT inhibitor capivasertib has been recognized as an effective targeting drug for tumors and has been approved for clinical use. Duan *et al.* reported that the proliferative capacity of HeLa cells decreased with increasing sinomenine concentration (8). In addition, researchers found that sinomenine inhibited the activation of p-PI3K and p-AKT and the expression of Ki67 and PCNA in a dose-dependent manner in breast cancer, renal cell carcinoma and cholangiocarcinoma. Moreover, activation of the PI3K/AKT pathway attenuated the inhibition of tumor cell proliferation (16,25). For example, Chen *et al.* showed that sinomenine hydrochloride inhibited the proliferation of mantle cell lymphoma by inhibiting the phosphorylation level of the AKT/mTOR/P70S6K pathway (36). In addition, Liu *et al.* demonstrated that hexokinase II (HK2) was highly expressed in non-small cell lung cancer tissues and cell lines, while sinomenine reduced the expression levels of HK2, p-AKT and its downstream kinase S6 (18). Moreover, after AKT knockdown, the expression level of HK2, glycolysis and proliferation ability of cells were inhibited, while overexpression of AKT reversed the above changes. This study showed that sinomenine could inhibit ovarian cancer cell proliferation by reducing the activity of p-AKT and its downstream kinase S6, thereby

Table 2 Anti-tumor effect and mechanism of sinomenine and its derivatives

Cancers	Real modules (animal/cell)	Possible mechanisms	References
Cervical cancer	Hela BALB/c nude mice	Inhibited Trx/TrxR and glutathione/glutaraldehyde toxin systems to promote oxidative stress, deplete mercaptan content, and active caspase-3	(8)
Breast cancer	MCF-7, MDA-MB-231; BALB/c nude mice	Inhibited cell stemness mediated by the Wnt/β-catenin pathway and inhibit the expression of CD44, MMP7, Cyclin D1, MET, MYC and JUN	(9)
Breast cancer	MDA-MB-231	Increased miR-340-5p and suppresses the SIAH2/HIF-1α pathway, thereby inhibiting epithelial-mesenchymal transition	(10)
Glioblastoma	U87, U251; BALB/c nude mice	Increased p53/p21 and Aurora A/PLK1/CDC25C pathway and the expression of p-CDC2 and CCNB1. Inhibited PI3K/AKT/mTOR and upregulate of AMPK/mTOR signaling pathway	(11)
Bladder cancer	T24, SW78	Inhibited the level of lncRNA-HEIH and up-regulated the expression of Bax, caspase-3	(12)
Hepatocellular carcinoma	HepG2	Exo-sinomenine showed a significantly stronger inhibitory effect in HepG 2 cells	(7)
Hepatocellular carcinoma	HepG2; Sprague Dawley rat	Sinomenine and 5-FU exhibited a synergistic inhibitory effect on HepG 2 cells	(13)
Lung cancer	A549; C57BL/6 mice	Inhibited the expression of p-ERK1/2, α7-nAChR, SP-1, TTF-1, and increase the expression of EGR1	(14)
Ovarian cancer	HeyA8-MDR	Inhibited P-CDK1 (Thr161) and P-H3 (Ser 10), downregulated CDK1, PLK1 and BUB1, and inhibited G2/M transition	(15)
Breast cancer	MDA-MB-231, MCF-71	Inhibited the activation of PI3K/Akt/mTOR signaling pathway and inhibited the express of MMP-2 and MMP-9	(16)
Lung cancer	A549, H1299	Inhibited the expression of miR-21, MMP-2, MMP-9, EMMPRIN/CD147, and Vimentin, increase the express of RECK, TIMP-1/-2 and E-cadherin	(17)
Non-small cell lung cancer	HCC827, H460, H23, H1650, H1299, H1975; female athymic nude mice	Inhibited AKT, kinase S6, and thus inhibited HK2-mediated glycolysis, and increase the expression of cleaved-caspase-3, cleaved-PARP, increase the expression of Cytochrome C and Bax	(18)
Ovarian cancer	HOEpiC, A2780, Caov3, Hey, OVCAR3, SKOV3	Down-regulated HOST2, Cyclin D1, CDK4, CDK6, Bcl-2, and Bax caspase-3 was up-regulated to induce G0/G1 stagnation	(19)
Breast cancer	MDA-MB-231, MCF-7	Increased the expression of miR-29/PDCD4, thereby blocking the JNK and MEK/ERK pathways. Increased the expression of caspase-3/-9, p16. Inhibited the expression of PCNA, Cyclin D1, and CDK4	(20)
Breast cancer	BALB/c nude mice	Regulated IL-8/CXCR1 and c-Fos/NFATc1 signaling to inhibit osteolysis in breast cancer	(21)
Cervical cancer	HeLa; female BALB/c nude mice	Suppressed the expression of Ku80 and Rad51 and enhanced radiotherapy sensitivity	(22)
Breast cancer	MDA-MB-231; BALB/C male nude mice	Inhibited NF-κB/SHh signaling pathway and inhibited the expression of Cyclin D1, Bcl-2, MMP-2 and IL-11	(23)
Breast cancer	Virgin female Sprague Dawley rats	Inhibited the microglial JAK2/STAT3 signaling pathway and neuronal CAMKII/CREB cascade in the rat model to alleviate cancer-induced bone pain	(24)
Renal carcinoma	Human renal cell adenocarcinoma	Inhibited PI3K/AKT/mTOR signaling pathway to promoted autophagy and inhibited the expression of Ki-67 and PCNA	(25)
Renal carcinoma	Clear cell renal cell carcinoma	Inhibited the expression of TGF-β, Snail1, Twist and Smad signaling pathways and then inhibit epithelial-mesenchymal transition	(26)

Table 2 *(continued)*

Table 2 *(continued)*

Cancers	Real modules (animal/cell)	Possible mechanisms	References
Breast cancer	MDA-MB-231, RAW246.7, 4T1; female BALB/c nude mice	Inhibited the expression of IL-6, MMP9, CD44, and Sox-2; increased the expression of TIMP-1, TIMP-2, and inhibited epithelial-mesenchymal transition	(27)
Hepatocellular carcinoma	HepG2, Hep3B	Arrested hepatocellular carcinoma cell cycle at G0/G1 phase, induces cell death and growth inhibition through AMPK/STAT3 signaling pathway	(28)
Multiple myeloma	Multiple myeloma cells	YL064 may prevent the interaction of STAT3 with phosphorylated tyrosine residues on cytoplasmic receptor kinases through targeting the SH 2 domain of STAT3	(29)
Hepatocellular carcinoma	SK-Hep1, Hepa1-6p1	Inhibited ERK1/2/MMP2/9 signaling pathway and inhibit the growth and invasion of oncocytes	(30)
Colon cancer	LoVo	Sinomenine enhanced the inhibitory effect of 5-FU on the proliferation and apoptosis of colon cancer cells, and did not increase the side effects of chemotherapy	(31)
Gastric cancer	MKN-28, SGC-709, BGC823, HGC-27; male BALB/c-nu/nu mice	Sinomenine reduced thymidylate synthase mRNA accumulation and enhances the 5-FU-mediated mitochondrial apoptosis pathway	(32)
Hepatic carcinoma	Hep3B, SMMC7721, HepG2, and so on; male BALB/c athymic nude mice	Increased survivin, p21, cytochrome C and increase the release of Omi/HtrA2 from mitochondria into cytoplasm to induce apoptosis	(33)
Esophagus cancer	Eca109 and EC9706; BALB/c nude mice	Induced G2/M arrest, promoting radiation-induced apoptosis and inhibited DNA double-strand break repair	(34)
Glioblastoma	U87, U251	Promoted p53 expression and its acetylation, reduced sirtuin 1 expression, and induced G0/G1 cell cycle arrest and apoptosis	(35)
Mantle cell lymphoma	Jeko-1	Inhibited Akt/mTOR/P70S6K pathway and promote cell apoptosis	(36)
Osteosarcoma	Human osteosarcoma cells, U2OS	Inhibited CXCR4-STAT3 pathway and osteoclastgenesis mediated bone destruction and inhibit invasion and metastasis	(37)
Esophagus cancer	Eca-109	Promoted the progression of mitochondrial apoptosis induced by 5-FU, and the drug combination does not increase the side effects of chemotherapy	(38)
Myeloma	U266, MM1.S, BMSCs HS-5, Hela	Suppressed the nuclear translocation of STAT3 between its target gene Cyclin D1 and Mcl-1	(39)
Thyroid cancer	HTori-3, BCPAP, TPC-1	Enhanced the sensitivity of radiotherapy. Inhibited the ratio of Bcl-2 to Bax, and increase the expression of Fas, p21, p-ATM, p-Chk1, p-Chk2 and p53	(40)

downregulating glycolysis mediated by HK2. Deng *et al.* also demonstrated that sinomenine inhibits renal cancer cell proliferation by promoting the inhibition of PI3K/AKT/mTOR signalling pathway by reactive oxygen species (25). In conclusion, sinomenine and its derivatives can inhibit tumor proliferation by regulating AKT-related signalling pathways.

Stemness of tumor cells

Cancer stem cells with the abilities of self-renewal, proliferation and differentiation play an important role in the survival, proliferation, metastasis and recurrence of tumors. Because cancer stem cells can be dormant for a long time, they are not sensitive to radiotherapy and chemotherapy, which seriously affects the anti-tumor effect. Thus, targeted cancer stem cell therapy may be an emerging strategy for anti-tumor development. CD44/CD24 is currently a well-recognized stem cell marker in breast cancer. Li *et al.* team showed that in breast cancer, sinomenine hydrochloride could inhibit the activity of

Wnt/β-catenin signalling pathway by downregulating the expression of WNT10B, thus inhibiting the percentage of CD44/CD24 in MDA-MB-231 and MCF-7 cell lines and inhibiting the expression of breast cancer stem cell-related genes (including *JUN*, *MET*, *MYC*, *INHBB*, *CHCR4*, *HMGA2* and *TGFB2*) (9). This study demonstrated that sinomenine hydrochloride can inhibit the stemness of breast cancer stem cells *in vivo* and *in vitro* by negatively regulating WNT10B expression. In conclusion, sinomenine and its derivatives can inhibit tumor proliferation by inhibiting the stemness of cancer cells.

Cell cycle

Cell cycle regulation contains three checkpoints, namely G1/S, G2/M and the mitotic spindle checkpoint. Dysregulation of the cell cycle causes normal cells to enter a state of uncontrolled growth and transform into tumor cells. Meanwhile, the tumor cells also depend on the cell cycle for their proliferation. Cyclins and cyclin-dependent kinases (CDK) are important positive regulators of the cell cycle. A variety of compounds targeting CDK have recently been developed to inhibit the activity of CDK by blocking the cell cycle to inhibit tumor cell proliferation. Qu *et al.* suggested that the expression of cell cycle regulators such as CDK 1, PLK 1, and BUB 1 and the phosphorylation of histone H3 were significantly reduced in ovarian cancer after the sinomenine treatment (15). Moreover, the G2/M transition in ovarian cancer cells was inhibited, thereby inhibiting mitosis. Among them, histone H3 is closely associated with chromosome condensation during mitosis. In addition, Xu *et al.* have shown that sinomenine hydrochloride inhibited ovarian cancer cell growth by reducing the expression of long non-coding RNA-HOST 2, thus downregulating Cyclin D1, CDK 4 and CDK 6 to induce cell G0/G1 phase arrest (19). In myeloma, YL064, a derivative of sinomenine, inhibited of myeloma cell proliferation by inhibiting the nuclear translocation of STAT3 and the expression of its target gene Cyclin D1 (39). In conclusion, sinomenine and its derivatives can significantly inhibit the proliferation of a variety of tumor cells by blocking the cell cycle.

Non-coding RNA

Non-coding RNAs is involved in all stages of tumor initiation, development and metastasis, and they are constantly being discovered as disease markers and targets for tumor treatment. Among them, miRNA can promote the deadenylation and degradation of the target mRNA to regulate the protein expression level. In addition, lncRNAs act as ceRNAs to absorb miRNAs to regulate the expression of related genes. It can also cooperate with transcription factors to activate related genes, or directly bind to the protein to prevent its degradation, promoting protein function. Among them, miR-29 has the dual role of tumor suppressor and procancer and has been recognized to play a key role in cancer pathogenesis. More than 85% of miR-29-related studies have shown that it suppresses multiple cancer-related targets to exert anti-tumor effects (42). Gao *et al.* showed that sinomenine hydrochloride could block the JNK and MEK/ERK pathways by upregulating miR-29/PDCD4 expression to inhibit the proliferation of breast cancer cells (20). LncRNA-HEIH is carcinogenic in various cancers. Xu *et al.* found that lncRNA-HEIH was upregulated in bladder cancer cell lines (T24,5637, HT-1197, TCCSUP and SW 780) (12). However, sinomenine can downregulate the expression of lncRNA-HEIH, and knockdown of lncRNA-HEIH reversed the inhibition of proliferation in bladder cancer cells. Overall, sinomenine and its derivatives can inhibit tumor cell proliferation by regulating the expression of non-coding RNAs and theirs target genes.

Sinomenine induces tumor cell apoptosis

p21 leads to CDK2/cyclin-E activation and ribosome phosphorylation

As an effective inhibitor of CDK, p21 can not only block the cell cycle and inhibit cell proliferation, but also promote cell apoptosis. p53 can not only induce the expression of p21 but also form a complex with p21 to play an anti-tumor role. For example, p53 and p21 can form a complex with Bcl-2 family proteins to release Bax proteins and promote the apoptosis of tumor cells (43). In glioblastoma, SW33, a sinomenine derivative, causes G2/M arrest and cell apoptosis by regulating p53/p21 signaling pathway and the activity of the CCNB1/CDC2 complex, inducing cell apoptosis (11). As a key regulator of the cell cycle and cell apoptosis, Survivin is only expressed in tumor and embryonic tissues. Survivin could inhibit the activity of Caspasc-3 and Caspasc-7 either directly or indirectly through p21. Survivin can also bind to the cell cycle regulator CDK 4 to accelerate the G1/S phase conversion and release p21, causing it to bind and inhibit caspase-3 activity, thus preventing mitochondria from releasing

cytochrome C to inhibit apoptosis (44). In Lu *et al.*'s study, sinomenine hydrochloride downregulated Survivin to upregulated p21 expression levels and promoted the release of cytochrome c and Omi/HtrA 2 from mitochondria into the cytosol, promoting mitochondrial apoptosis in hepatocellular carcinoma cells (33).

MAPK signalling pathway

As a tumor suppressor, MAPK has four main subfamilies: ERK 1/2, p38 MAPK, JNK, and ERK 5. Among them, the JNK and p38 signalling pathways regulate cell apoptosis by targeting various genes (including Bcl-2, Bax and cyclin D1). Sinomenine can have chemopreventive properties by altering the level of oxidative stress in tumors. In Gao *et al.*'s study, sinomenine upregulates PDCD4 expression by mediating miR-29; PDCD4 obstructs the JNK and MEK/ERK pathways in MDA-MB-231 cells (20). However, the ERK signalling pathway is a double-edged sword in tumors. On the one hand, its inhibitors BPI-27336, HH2710, and HMPL-295S1 have been used clinically as anti-tumor drugs. On the other hand, the ERK 1/2 kinase has similar proapoptotic functions, namely, the activation of the ERK signalling pathway can also lead to the apoptosis of tumor cells. In addition, α7 nicotinic acetylcholine receptor (α7 nAChR) was first identified as a neuromodulator, and its overexpression was later proven to be closely related to the proliferation, and apoptosis, specifically, invasion of cancer cells (45). α7 nAChR and its major upstream regulator ERK 1/2 are also involved in the anti-tumor mechanism of sinomenine. In lung cancer, sinomenine can promote apoptosis in lung cancer cells by inhibiting ERK 1/2 phosphorylation and mediating α7 nAChR levels. Moreover, sinomenine not only downregulated the positive regulators of α7 nAChR—SP 1 and TTF-1—but also upregulated its negative regulator—Egr-1 (14).

AKT signalling pathway

In addition to proliferation, several studies have demonstrated that AKT signalling is involved in the mechanism by which picoline promotes tumor cell apoptosis. Liu *et al.* showed that sinomenine can regulate Bcl-2, Bax and caspase-3 by downregulating of p-AKT in non-small cell lung cancer (18). Among them, overexpression of HK2 reduced the induction of mitochondrial apoptosis in non-small cell lung cancer cells. Moreover, HK2 expression was also decreased with AKT knockdown. That is, sinomenine can promote apoptosis in non-small cell lung cancer by inhibiting HK2 activation by p-AKT. Similarly, Deng *et al.* showed that sinomenine induced apoptosis in renal cancer cells through activation of the mitochondrial apoptotic pathway, while activation of the PI3K/AKT signalling pathway antagonized sinomenine-induced apoptosis in renal cancer cells (25). Similarly, Chen *et al.* showed that sinomenine hydrochloride could regulate the expression of Cyclin D1, BCL-2, BAX and caspase-3 through downregulation of p-AKT levels, thereby promoting apoptosis in mantle cell lymphoma cells (36).

The others

Similar to the mechanism by which sinomenine inhibits cell proliferation, sinomenine and its derivatives can also activate the mitochondrial apoptosis pathway in bladder cancer and hepatocellular carcinoma by downregulating lncRNA-HEIH and miR-29 (12,20). In addition, sinomenine can induce apoptosis of pancreatic cancer cells by inducing G0/G1 cell cycle arrest and apoptosis of malignant glioma and liver cancer cells (35). Among them, the AMPK/STAT3 signalling pathway mediated by the MARCH1 gene is also involved in the mechanism by which sinomenine promotes apoptosis in hepatoma cells (28).

Sinomenine induces tumor cell migration and invasion

miRNA

miRNAs are widely involved in the regulation of gene expression during tumor migration and invasion. In the development of tumors, miR-21 acts as a proto-oncogene, which negatively regulates the tumor suppressor genes *TPM1*, *PDCD4* and *MASPIN*. Several studies have shown that miR-324-5p has antitumor effects in some tumors, and the aberrant reduction in its expression is related to the proliferation, differentiation, metastasis and invasion of tumor cells (46,47). However, in another subset of tumors, miR-324-5p promoted tumor cell viability and invasion and migration (48). Zhang *et al.* showed that the expression of miR-324-5p was significantly downregulated in gallbladder cancer tissues and cells compared with normal gallbladder tissue, and the level of miR-324-5p was negatively correlated with the degree of tumor invasion and metastasis (47). Several studies have shown that sinomenine and its derivatives can upregulate E-cadherin,

TIMP-1/2, downregulate the expression levels of MMP2, MMP9, N-cadherin, vimentin, and EphA2, and inhibit the progression of epithelial epithelial-mesenchymal transition (EMT) and the migration and invasion of cancer cells (17,27). Song *et al.* showed that sinomenine could inhibit the SIAH2/HIF-1α axis by upregulating miR-324-5p, and that inhibition of miR-324-5p or overexpression of SIAH 2 counteracted the inhibition of EMT in breast cancer cells (10). Moreover, sinomenine downregulated miR-21, which promoted the expression of RECK, TIMP-1/-2 and E-cadherin, and decreased the expression of MMP2/MMP9 and Vimentin (17). In addition to inhibiting proliferation, sinomenine hydrochloride can also inhibit the migration and invasion of breast cancer cells by inhibiting the miR-29/PDCD4 axis (20).

TGF-β/Smad signalling pathway

EMT induced by TGF-β signalling is necessary for tumor metastasis, and its components are dysregulated in multiple tumors. Among them, in the classical TGF-β signalling pathway, receptor activation induces phosphorylation at the SMAD C-terminus, and phosphorylated SMADs form a complex with SMAD4 and promote SMAD4 translocation to bind to target gene promoters in the nucleus, controlling the transcription of hundreds of genes. Among them, SMAD1/7 plays a critical role in EMT progression induced by TGF-β. In the nonclassical TGF-β signalling pathway, TGF-β receptors are activated through other signalling pathways, such as the MAPK (ERK, p38 and JNK), AKT and Rho GTPase pathways, which are indirectly involved in cell EMT, proliferation, apoptosis and other cellular activities. Zhao *et al.* showed that sinomenine hydrochloride not only inhibited the TGF-β/Smad signaling pathway, and depleted p-Smad 2 and p-Smad 3, but also inhibited the EMT-related transcription factors Snail1 and Twist to inhibit EMT (26). Studies have also shown that sinomenine and its derivatives can inhibit the migration and invasion of cancer cells by inhibiting PI3K/Akt/mTOR activation and MAPK (ERK, p38 and JNK) signalling pathways (14,16,49).

STAT3 and NF-κB signaling pathway

Chronic inflammation is a trigger for tumor proliferation and migration, while STAT3 and NF-κB are the focus of inflammation and cancer research. The two interact at multiple levels to activate the transcription of their common downstream target genes and promote tumor development and progression. Wang *et al.* showed that the sinomenine derivative YL064, a novel STAT3 inhibitor with promising anti-myeloma activity, may prevent the interaction of STAT3 with phosphorylated tyrosine residues on cytoplasmic receptor kinases by targeting the SH2 domain of STAT3 (29). Song *et al.* showed that sinomenine could inhibit the migration and invasion capacity of breast cancer cells by inhibiting NF-κB activation and NF-κB-mediated activation of the SHh signalling pathway (23,50).

Sinomenine induces tumor cell autophagy

Autophagy is an intracellular degradation mechanism that is a double-edged sword for tumors. On the one hand, autophagy can provide energy for cancer cells in nutrient deficient conditions for a long time and improve their tolerance in stress environments such as starvation, hypoxia, and chemoradiotherapy. On the other hand, autophagy can protect normal cells and maintain homeostasis against malignant changes, and excessive autophagy can also induce autophagic death in tumors. The mechanism of autophagy regulation in cancer involves signalling pathways such as the PI3K/AKT/mTOR, MAPK/mTOR, and AMPK/mTOR pathways and autophagy-related proteins (LC3B, ATG, Beclin-1, and P62) (51). The study suggested that treatment with the sinomenine ester derivative SW33 and sinomenine hydrochloride increased the number of phagosomes and phagolysosomes in U87 and U251 and SF767 cells, the transition of LC3BI to membrane-bound LC3BII, and increased the levels of ATG5 and Becline1. Moreover, the PI3K/AKT/mTOR, AMPK/mTOR and JNK signalling pathways are all involved in the mechanism by which sinomenine and its derivatives promote autophagy in glioblastoma cells (11).

Sinomenine enhances sensitivity to chemotherapy or radiotherapy, reverses drug resistance, and alleviates tumor complications

Although radiotherapy and chemotherapy have become two powerful tools in the treatment of many cancers, after a long period of treatment, the tumor may be tolerant to chemotherapy and radiotherapy, and the adverse reactions of radiotherapy and chemotherapy negatively affect the cooperation of patients. This situation is undoubtedly a huge challenge for clinicians. Therefore, the enhancement of chemoradiotherapy sensitivity and the reversal of drug resistance have become a research focus in recent years.

Sinomenin enhances chemosensitivity

5-Fluorouracil (5-FU) has a wide anti-cancer spectrum, and mainly serves as the preferred chemotherapeutic agent for digestive system tumors. Cisplatin, as a first-line anticancer drug, is mostly used in the treatment of various solid tumors, such as ovarian cancer, prostate cancer, testicular cancer, lung cancer, thyroid cancer and osteosarcoma. However, its severe side effects and drug resistance hinder its clinical application. At present, it has been found that sinomenine and its derivatives can not only enhance the sensitivity of liver cancer (13), colon cancer (31), gastric cancer (32), and oesophageal cancer (38) to 5-FU, but also enhance the sensitivity of gastric cancer (52) to cisplatin and the sensitivity of breast cancer to tamoxifen. First, sinomenine could enhance the sensitivity of MCF-7 cells to TAM in breast cancer by inhibiting the hyperactivation of the PI3K/AKT/mTOR signalling pathway, and then reverse the resistance of MCF-7 cells to tamoxifen. Second, sinomenine can further enhance the sensitivity of tumor cells to 5-FU and cisplatin through the induction of apoptosis and growth inhibition (32,52). For example, sinomenine can sensitize human gastric cancer cells to cisplatin through downregulation of the PI3K/AKT/Wnt signalling pathway. Moreover, Duan *et al.*'s study showed that sinomenine suppresses the Trx/TrxR system, and the high expression of TrxR is closely related to chemoresistance (8). Moreover, it is noteworthy that sinomenine does not increase chemotherapeutic side effects when enhancing tumor cell sensitivity to 5-FU (31).

Sinomenine enhances radiotherapy sensitivity

Radiotherapy occurs through the use of ionizing radiation with high-energy rays, changing the cell structure and directly or indirectly acting on the DNA, causing the breakage and cross-linking of DNA molecules, resulting in cell death. During radiotherapy, some cells continued to survive after DNA repair, and anaerobic cells and cells in early G1 have poor sensitivity to radiation, while oxygen-rich cells and cells in G2/M phase are the most sensitive to radiation. Zhang *et al.* have demonstrated in a mouse xenograft model of cervical cancer that sinomenine hydrochloride prevents DNA repair by inhibiting the expression of the DNA damage response factors Ku80 and Rad 51 to enhance the sensitivity of cervical cancer to radiotherapy (22). In oesophageal cancer, sinomenine hydrochloride can increase radiation sensitivity in ESCC cells by inducing G2/M phase arrest, promoting radiation-induced apoptosis and inhibiting the DNA double strand break (DSB) repair pathway (34). Zhao *et al.* suggests that sinomenine hydrochloride may be a potential sensitizer for papillary thyroid cancer after total thyroidectomy, which is related to the downregulation of Bcl-2 and Bax protein expression and the upregulation of Fas, p21, p-ATM, p-Chk 1, p-Chk 2, and p53 protein expression (40).

Sinomenine relieves tumor complications

Bone metastases often occur in various cancers to advanced stages, such as lung cancer, breast cancer, and prostate cancer. Bone metastasis can lead to a variety of bone complications, such as osteolysis, fracture, hypercalcaemia and bone pain, which can seriously reduce the quality of life of patients and increase patient mortality. Among them, bone pain is one of the most common and severe types of cancer pain. Currently, radiotherapy is the treatment of choice for patients with such tumors, but many patients need a combination of analgesic drugs to provide effective pain relief. Among them, the osteoclasts treatment is considered the most effective strategy to alleviate bone destruction caused by cancer cell bone metastasis and reduce bone-related events (such as pain and fractures) and thus improving the quality of life of patients (53). Sinomenine is widely used in the treatment of rheumatoid arthritis because of its anti-inflammatory and analgesic effects and few side effects. In addition, sinomenine can be used to treat osteolysis caused by rheumatoid arthritis. It has been demonstrated that sinomenine suppresses osteoclast genesis and osteolysis induced by human nuclear factor-activated factor receptor ligand and lipopolysaccharide (54). Subsequently, it was been demonstrated that sinomenine could inhibit osteoclast formation and osteolytic injury in breast cancer cells by reducing IL-8 and c-Fos/NFATc1 (21).

Conclusions

This review has the following improvement from the review by Gao *et al.* published in 2019 (55). First, nanocarriers and molecular modifications are considered to be effective methods for the development and utilization of sinomenine. Therefore, in addition to sinomenine, our review also described the anti-tumor effects of derivatives of sinomenine. And suggested that it is still necessary to improve the water solubility and bioavailability of sinomenine by using new technologies and new processes, such as drug synthesis, genetic modification or structural

modification and optimization of natural active ingredients. Second, this review provides a more detailed explanation of the anti-tumor mechanism of sinomenine and its derivatives and describes the study of alleviating tumor complications. Third, this review enriches the literature on the anti-tumor mechanism of sinomenine and its derivatives and adds to the understanding of the antitumor potential of sinomenine and its derivatives. Finally, this review collects and summarizes the relevant literature in the form of tables to facilitate reference by researchers in the field. Sinomenine is widely used in the treatment of rheumatism and joint pain because of its anti-inflammatory and analgesic effects, ability to remove wind dampness and ability to connect meridians. With the deepening of the study of its pharmacological properties, its anti-tumor value has been continuously explored. Moreover, the derivatives and nanocarriers of sinomenine resolve the problems of poor water solubility and low bioavailability. It is still necessary to improve the water solubility and bioavailability of sinomenine by using new technologies and new processes, such as drug synthesis, genetic modification or structural modification and optimization of natural active ingredients. Several studies of sinomenine have proven that sinomenine and its derivatives can not only promote tumor cell apoptosis and autophagy, and inhibit the proliferation, metastasis and invasion of tumor cells, but also enhance the chemo- and chemotherapy sensitivity of tumor cells and reverse the anti-tumor effect without increasing side effects (8,9,13,25). The anti-tumor mechanism of sinomenine is complex and plays a role in various pathways. Despite many studies, the main specific mechanism and targets of sinomenine anti-tumor, activity still need to be further explored through network pharmacology, and molecular docking combined with *in vivo* and *in vitro* experiments to lay a solid theoretical foundation for the clinical transformation of sinomenine and its derivatives as anti-tumor drugs. In conclusion, sinomenine and its derivatives have high anti-tumor potential and need to be further studied to promote their clinical development.

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Footnote

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