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Review Article

Anticancer potentials of sinomenine from *Sinomenium acutum*: A mini-review

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Abstract

Sinomenine, an important isoquinoline from Sinomenium acutum (Menispermaceae), is currently considered as a reliable drug for treating various malignant cancers including breast cancer, colon cancer, lung cancer, liver cancer, gastric cancer, osteosarcoma cervical cancer, and esophageal cancer. The pharmacological mechanisms are probably related to induction of apoptosis and cell cycle arrest. This paper was aimed at reviewing the anticancer potential of sinomenine, which is expected to be beneficial in developing this compound as a candidate drug for cancer therapy.

Keywords: *Sinomenine, Anticancer, Sinomenium acutum, Traditional Chinese Medicine*

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INTRODUCTION

Sinomenium acutum (Menispermaceae), also called *Qing-feng-teng* in Chinese and first recorded in *Compendium of Materia medica*, has been successfully used for hundreds of years as a traditional Chinese medicine for rheumatism and neuralgia, and with low side effect [1,2]. Sinomenine (SIN, Figure 1), an isoquinoline, is the most important active constituent of this plant, and is currently considered as a reliable drug for treating rheumatoid arthritis (RA) in clinics [3,4]. Furthermore, increasing evidence has demonstrated that cancer has become the leading cause of disease-related death in recent years. Malignant tumors are among the diseases that endanger human life and cause death. Due to the increasing number of new cases every year, cancer also imposes a heavy burden on society and medical care.

Chemotherapy predominates in the treatment of cancer, but it has the disadvantages of toxic side effects and drug resistance. Therefore, research emphasis is shifting more and more to the anticancer effects of Chinese herbal medicine. Interestingly, studies have reported that besides its anti-RA, anti-inflammatory, analgesic, sedative and immunosuppressive effects [1], SIN has promising anticancer potential against various cancers (Table 1, Table 2 and Table 3) [5-7]. Consequently, this paper was aimed at reviewing the anticancer effects of SIN and its potential molecular mechanisms, based on available

literature, so as to provide information which might be beneficial for drug development and clinic applications of the SIN for treating cancers.

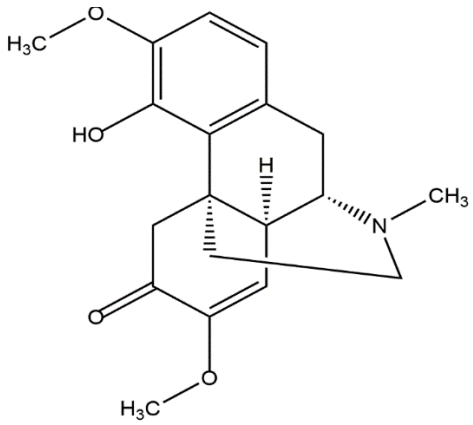

Figure 1: Chemical structure of sinomenine

ANTICANCER POTENTIALS OF SIN

Breast cancer

Breast cancer, a common malignant cancer of the mammary gland epithelial tissues with an increasing incidence in recent years, is a predominant cause of cancer related death in women [8,9]. Nowadays, some interesting investigations have indicated that SIN exerts anticancer potential on breast cancer *in vivo* and *in vitro*.

In 2015, a study by Song *et al* revealed that SIN at concentrations ranging from 0.25 to 1 mM, suppressed the invasion and migration of MDAMB-231 and 4T1 breast cancer cell lines *in vitro* in a dose-dependent manner. The possible molecular mechanisms were related to suppression of NF-kB activation via regulation of the IL4/miR-324-5p/CUEDC2 axis [10]. Furthermore, another study in 2017 reported that sinomenine hydrochloride (SH) inhibited the proliferation, migration and invasion of two breast cancer cell lines (MDAMB-231 and 4T1 breast cancer cell lines) *in vitro* [11]. By using orthotopic mouse model of 4T1 and MDA-MB-231 cell lines, it was shown that SH inhibited breast cancer metastasis by suppressing epithelial-mesenchymal transition (EMT) and cancer stem cell (CSC) properties via attenuation of inflammatory reactions, without obvious hepatotoxicity and renal toxicity [11]. In another study, Li *et al* reported that SH inhibited tumor growth by induction of apoptosis in human breast cancer cell lines (MDA-MB-231 and MCF-7 cells) *in vitro* without showing significant toxicity [12]. Moreover, it was reported that the potential mechanism involved might be closely related to up-regulation of MAPKs via ROS-dependent and -independent pathways [12]. Besides, Zhang *et al* reported that SH suppressed the proliferation and migration of human umbilical vein endothelial cells (HUVEC), and SH at dose of 100mg/kg inhibited the progression and metastasis of tumor in 4T1 murine breast cancer model and 168FARNcell 4T1 murine breast cancer model [13]. The inhibitory effect was attributed to the restoration of the balance between pro-angiogenic factor (bFGF) and anti-angiogenic factor (PF4), resulting in the normalization of blood vessels [13].

Colon cancer

Colon cancer is one of the most common cancers. At present, its incidence and mortality are ranked third in both male and female patients worldwide [8]. Postoperative metastasis and multi drug-resistant (MDR) caused by chemotherapy are the bottlenecks of the treatment. Some studies have shown that SIN may be an auxiliary drug in the treatment of colon cancer. It has been reported that *in vivo* and *in vitro*, the inhibitory effect of SIN combined with the first-line chemotherapy drug 5-fluorouracil (5-FU) on the growth of LoVo cells in colorectal cancer were significantly better than that of SIN or 5-FU when used alone [14]. There were no significant increases in side effects of chemotherapy in the study [14]. At the same time, SIN treatment up-regulated the expressions of Bax, whereas Bcl-2 was down-regulated, resulting in decline in the anti-apoptotic/pro-apoptotic (Bcl-2/Bax) protein ratio, and finally apoptosis. Thus, it can be said that SIN exhibits anticancer effects by controlling the permeability of mitochondrial membrane. Further studies [15] have found that SIN inhibited the survival of the human colon adenocarcinoma cell line SW1116 by inducingcell cycle arrest (mainly in G1 phase) and regulating the expression of cyclooxygenase-2 (COX-2). Consequently, COX-2 may be an important target for SIN in the treatment of colon cancer.

Studies using a multidrug-resistant Caco-2 (MDR-CaCO-2) cell model established with increasing concentrations of doxorubicin found that the expressions of COX-2 and MDR1 mRNA (MDR-1 genes) in the cells were enhanced, and the P-glycoprotein (P-gp) in the cells (MDR1 gene-encoding) was elevated, while the NF-κB signaling pathway was activated. It has been reported that SIN reduced the expressions of COX-2, MDR1 and P-gp through the NF-κB

signaling pathway, thus enhancing the sensitivity of MDR-CaCO-2 cells to doxorubicin, which is undoubtedly a new strategy for effectively reversing drug resistance of cancer cells [16].

Lung cancer

Currently, SIN is often reported in the treatment of lung cancer. Lung cancer is a malignant tumor that originates from bronchial mucosa or glands. Although the incidence in some developed countries has decreased in recent years, it still accounts for the highest mortality rate in the world [8,17,18]. The pharmacological effects of SIN on the treatment of lung cancer are mainly manifested in inhibition cell proliferation and induction apoptosis. Previous studies also found that SIN induced apoptosis and inhibited the proliferation of non-small cell lung adenocarcinoma NCI -H460 cells in a time- and dose-dependent manner *in vitro* [19]. The mitochondrial membrane potential of the cells also decreased with the increase in SIN concentration, indicating that SIN may induce apoptosis in NCI-H460 cells by activating the mitochondrial pathway.

Previous studies found that SIN may inhibit the proliferation of human lung cancer cell line A549 cells in a dose-dependent fashion *in vitro*, probably due to the inhibition of the expression of alpha 7 nicotinic acetylcholine receptor (α7nAChR) and n-nitrosomorpholine (NNK) (nicotine metabolite), thereby increasing the proportion of early apoptotic cells and reducing the proliferation of nicotine [20]. Furthermore, it has been reported that SIN exerted cytotoxic effects on A549 cells, and reduced the protein expressions of Janus kinase 2 (JAK2), signal transducer, activator of transcription 3 (STAT3), and EMT marker [21]. This demonstrates that it may restrain the invasion of lung cancer by regulating STAT 3 signaling pathway and interfering EMT [21].

In further studies on the molecular mechanism of SIN-induced apoptosis in lung cancer cells, it was suggested that the activation of the two signal pathways of PI3K/Akt and MEK/ERK antagonized the apoptosis-inducing effect of SIN on 3 human lung cancer cell lines (NCL-H460, NCI-H 226 and NCI-H 522 cells)[22]. When the activation of two signal pathways is suppressed, SIN can synergistically enhance apoptosis induced by inhibitors. The synergistic effect of Akt and ERK pathway is an important route for SIN to induce apoptosis in multiple lung cancer cell lines. Thus, SIN is expected to be an effective drug for the treatment of lung cancer.

Liver cancer

In recent years, the therapeutic potential of SIN for liver cancer has also been demonstrated. Liver cancer is a malignant tumor that originates in hepatocytes or intrahepatic bile duct cells. In recent decades, the incidence of liver cancer has increased steadily [8]. The survival time after diagnosis is usually less than 6 months, and only 5 - 9 % of the patients survive more than 5 years [23]. It has been found that SH (0.5-4.0 mM) not only inhibited the proliferation of human liver cancer cell SMMC-7721 *in vitro*, but also induced apoptosis, as was evident through MTT and Hoechst33258 staining [24]. At the same time, it increased the protein expression levels of death receptor DR4 and DR5 in a concentration-dependent manner, suggesting that exogenous apoptosis may be one of the mechanisms involved in the anticancer action of SH.

Previous investigations have revealed that the SIN inhibition and apoptosis induction on human hepatoma cell SMMC-7721 may be related to the inhibition of the transcription factor C/EBP β, and the expressions of inflammatory factors such as TNF-α and IL-1β, which may further damage the micro-environmental role of tumor inflammation [25]. Since C/EBP β is a downstream transcription factor of RAS signaling pathway and COX-2 has been shown to be closely related to cancer pathogenesis, it can be speculated that SIN may inhibit the downstream target molecule COX-2 through the RAS signaling pathway to regulate the expressions of inflammatory factors such as TNF-α and IL-1β, and then play an anticancer role by destroying the microenvironment of swelling and inflammation. However, there are no experimental evidence linking liver cancer cells, RAS signaling pathway and COX-2. The mechanism remains to be further verified.

Gastric cancer

Gastric cancer is also one of the common digestive system cancers. Every year around the world, about 990,000 people are diagnosed with gastric cancers, and about 738,000 affected people die, more than half of them in developing countries [26,27]. Some studies have suggested that SIN may be a chemotherapeutic adjunct to gastric cancer [28].

Some researchers have investigated the effect of combined use of SIN + 5 FU on gastric cancer. The results showed that when combined using the half effective doses of the two drugs (20 M

SIN + 50 mg/ L 5 FU) to cultivate the human gastric cancer cell line MKN-28, the inhibitory effect was significantly higher than that obtained using the single complete effective dose of one drug (40 M SIN or 100 mg/L 5 FU) [28]. These observations were also confirmed *in vivo* using MKN-28 xenograft mouse model. It was suggested that SIN and 5-Fu exerted synergistic effect on the inhibition of the proliferation of gastric cancer cells through a mechanism involving SIN-assisted, 5-FU-induced release of cytochrome c from the mitochondria to cytoplasm through the mitochondrial pathway, and activation of the caspase-3 and caspase-9. This would enhance the apoptotic effect of 5-Fu on the cells. In addition, SIN also significantly inhibited the expression of thymidylate synthase (TS) mRNA (key gene of 5-Fu metabolism). These results indicate that SIN combined with 5-FU is expected to improve chemo-sensitivity of gastric cancer cells.

Osteosarcoma

Osteosarcoma occurs predominantly in children and adolescents, and its incidence accounts for approximately 3 - 4 % of all childhood tumors [29,30]. The disease is a malignant bone tumor characterized by vascular invasion and local soft tissue infiltration. It is characteristically of high malignancy, early distant metastasis and high local recurrence [31]. Previous researchers have studied the effect of SIN on the treatment of osteosarcoma using human osteosarcoma (OS) cell lines HOS and U2OS, and found that SIN restrained the expressions of RANKL, VEGF, MMP-2 and MMP-9 via the CXCR4-STAT3 signaling pathway [32]. This reduced the bone destruction and osteolysis mediated by RANKL in osteosarcoma, and also decreased the formation of neovascularization associated with VEGF and the degradation of extracellular matrix (ECM) by the cancer cells [32].

Other cancers

Studies have reported that SIN induced apoptosis in cancer cells in common malignancies such as cervical cancer and esophageal cancer. At doses of 0.625 - 2.5mmol/L, SIN inhibited the proliferation of human cervical cancer Hela cells [33]. This inhibition was achieved by blocking the expression of AKT signal transduction protein, promoting the formation of Caspase-3, and inducing apoptosis Hela cells. A previous study observed that SIN inhibited the proliferation of EC109 in the esophageal cancer cell line, and the expressions of COX-2 and survivin proteins in the cells were significantly weakened by SIN [34]. Therefore, it may be speculated that SIN may inhibit the expression of COX-2 and reduce the expression of survivin protein, thus promoting apoptosis.

CONCLUDING REMARKS

Cancer is a disease of immense concern in medical research [35]. In the past decade, the incidence of most cancers has continued to rise due to environmental pollution, aging population, and bad living habits. Among them, the rising trends in breast cancer, lung cancer and other cancers are particularly significant. Although there have been remarkable improvements in early diagnosis and treatment, the five-year survival for cancer patients is still not encouraging [8,36]. Thus, research has focused on the discovery of more effective and safer therapeutic drugs. Plants and their metabolites are the treasure-house of drug sources. Indeed, about 40 % of drugs or pharmaceutical raw materials are derived from plants [37,38]. Therefore, more and more researchers have turned their attention to a wide variety of medicinal plants with great potential.

The compound SIN is derived from the natural medicinal plant *Sinomenium acutum*. A large number of studies have shown that SIN is a potent anticancer principle from Traditional Chinese Medicine (TCM) [1-5]. It acts on different cancer types through multiple links, multiple pathways, and multiple targets. Studies have shown that SIN induces apoptosis in various cancers such as breast cancer, lung cancer, colon cancer, and gastric cancer. Moreover, SIN has fewer toxic and side effects and high safety. When combined with chemotherapy drugs, the side effects of SIN on colon cancer cells are not significantly increased, and the combined treatment effectively reverses drug resistance of cancer cells. Thus, its clinical application value is great. It is believed that with the deepening of research on the anticancer mechanism of SIN, it is likely to become a candidate drug for clinical treatment of cancers. However, more research works should be devoted to elucidating the exact mechanism(s) involved in the anticancer properties of SIN, as well as its toxicities and druggability.

Table 1: Anti-cancer effects of sinomenine

Cancer type	Effective dose /concentration	Animal/cell study	Possible mechanisms	References
Breast cancer	0.25-1mM	Murine breast cancer cell lines 4T1; human breast cancer cell lines MDA-MB-231	Inhibiting invasion and migration of breast cancer cells by suppressing NF-kB activation mediated by IL-4/miR-324-5p/CUEDC2 axis	[10]
	0.25-0.5mM 75-150mg/kg	Murine breast cancer cell lines 4T1; human breast cancer cell lines MDA-MB-231; murine macrophage cell lines RAW246.7; orthotopicmouse model of 4T1; mouse breast cancer model of MDA-MB- 231-luc	Inhibiting breast cancer metastasis by suppressing EMT and CSC through anti-inflammatory effects	[11]
	0.25-1mM 75-150mg/kg	Human breast cancer cell lines of MDA-MB-231, MCF-7,SK-BR-3,ZR-75-30,BT474andT47D; Normal human breast epithelial cellline of MCF-10A; Human breast cancer xenograftsathymic mouse model	Inducing breast cancer cell death through ROS-dependent and -independent pathways with an upregulation of MAPKs	[12]
	31.25-1000mM 100mg/kg	Human umbilical vein endothelial cell; 4T1 murine breast cancer model and 168FARN cell murine breast cancer model	Inducing normalization of blood vessels by restoring the balance between pro-angiogenic factors (bFGF) and anti-angiogenic factors (PF4)	*[13]*
Colon cancer	200-3200mM 25 mg/kg	Colon carcinoma cell linesLoVo cell; Xenograft tumor xenograft model	Decreasing the antiapoptotic/proapoptotic (Bcl-2/Bax) protein ratio via mitochondrial pathway to induce apoptosis in colon cancer cells	*[14]*
	4-16μM 25-100mg/kg	Human colon carcinoma cell line SW1116; Model of SW1116 tumor xenograft growth in athymic nude mice	Inhibiting the growth of colon cancer cells by inducing G1 phase cell cycle arrest and regulating the expression of COX-2	*[15]*
	500mM	Multidrug-resistant Caco-2 (MDR-Caco-2) cell line	Downregulating the expression of COX-2, MDR1 and p-gp through NF-κB signaling pathway and reversing p-gp-mediated tumor resistance	[16]

Table 2: Anti-cancer effects of sinomenine (*contd*)

Cancer type	Effective dose /concentration	Animal/cell study	Possible mechanisms	References
Lung cancer	80-240 μg/mL	Non-small cell lung adenocarcinoma cell line NCI -H460	Inducing apoptosis of NCI-H460 cells through activation of mitochondrial pathway	*[19]*
	0.1-4 mM	Human lung cancer cell line A549	Reducing the proliferation of nicotine by inhibiting the expression of NNK and α7nAChR	*[20]*
	0.25-2.0 mM	Human lung cancer cell line A549	Inhibiting invasion of lung cancer cells by interfering EMT by regulating STAT 3 signaling pathway	*[21]*
	200 μg/mL	Human lung cancer cells NCI-H460,NCI-H 226 and NCI-H 522	Inducing apoptosis of multiple lung cancer cell lines through both Akt and ERK pathways	*[22]*
Liver cancer	0.5-4.0 mM	Human hepatocellular carcinoma cell line SMMC-7721	Upregulating the protein expression level of death receptor DR4 and DR5 and inhibiting proliferation of liver cancer cells through exogenous apoptosis	*[24]*
	0.5-4.0 mM	Human hepatocellular carcinoma cell line SMMC-7721	*Regulating the expression of inflammatory factors such as TNF-α and IL-1β through the RAS pathway (including its downstream transcription factor C/EBPβ), and then exerting anti-cancer effects by destroying the tumor inflammatory microenvironment*	[25]
Gastric cancer	20-80μM 20 mg/kg5-Fu+10 mg/kg SIN	Human gastric cancer cell line MKN-28,SGC-709,BGC-823 and HGC-27; MKN-28 xenograft mouse model	Downregulating the expression of TSmRNA and enhancing the sensitivity of gastric cancer cells to 5-Fu by increasing 5-Fu-induced apoptosis through mitochondrial pathway	[28]

Table 3: Anti-cancer effects of sinomenine (*contd*)

Cancer type	Effective dose /concentration	Animal/cell study	Possible mechanisms	References
Gastric cancer	20-80μM 20 mg/kg5-Fu+10 mg/kg SIN	Human gastric cancer cell line MKN-28,SGC-709,BGC-823 and HGC-27; MKN-28 xenograft mouse model	Downregulating the expression of TSmRNA and enhancing the sensitivity of gastric cancer cells to 5-Fu by increasing 5-Fu-induced apoptosis through mitochondrial pathway	[28]
Osteosarcoma	400μM 150mg/kg	Human osteosarcoma cell lines HOS and U2OS ;HUVEC; Mouse osteosarcoma model of HOS-Luc	Inhibiting the expression of RANKL, VEGF, MMP-2, and MMP-9 through CXCR4-STAT3 signaling pathway, thus reducing RANKL-mediated bone destruction and osteolysis in osteosarcoma, and VEGF-related neovascularization	*[32]*
Others cancers	0.625-2.5mM	Human cervical cancer cell Hela	Promoting the formation of Caspase-3 and inducing apoptosis of Hela cells by inhibiting the expression of AKT signal transduction protein	[33]
	0.2-0.4mM	Esophageal cancer cell line EC109	Inhibiting the expression of COX-2 and reducing the expression of Survivin protein, thus promoting apoptosis	[34]

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

REFERENCES

1. *Zhao XX, Peng C, Zhang H, Qin LP. Sinomenium acutum: A review of chemistry, pharmacology, pharmacokinetics, and clinical use. Pharm Biol 2012; 50: 1053-1061.*
2. *Zhang MF, Zhao Y, Jiang KY, Han L, Lu XY, Wang X, Zuo L, Meng SN. Comparative pharmacokinetics study of sinomenine in rats after oral administration of sinomenine monomer and Sinomenium acutum extract. Molecules 2014; 19: 12065-12077.*
3. *Xu M, Liu L, Qi C, Deng B, Cai X. Sinomenine versus NSAIDs for the treatment of rheumatoid arthritis: A systematic review andmeta-analysis. Planta Med 2008; 74: 1423-1429.*
4. *Wei HH, Zhao XX, Cheng L, Li SS, Song YL, Han TF, Ju DH, Hao BH. Progress and the prospect of sinomenine to treat rheumatoid arthritis. Chin J Tradit Chin Med Pharm 2013; 28: 3001-3005.*
5. *Qin F, Cai H. Research progress on pharmacological effects of sinomenine. Res Prac Chin Med 2016; 30: 81-86.*
6. *Zhu SL, Chen DZ, Li Y, Lin HW, Duan YG. Progress in the study of sinomenine. J Jishou Unv 2011; 32: 95-100.*
7. *Zhang H, Ren Y, Tang X, Wang K, Liu Y, Zhang L, Li X, Liu P, Zhao C, He J. Vascular normalization induced by sinomenine hydrochloride results in suppressed mammary tumor growth and metastasis. Sci Rep 2015; 5: 8888.*
8. *Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66: 7-30.*
9. *Bai L, Yang HH, Hu Y, Shukla A, Ha NH, Doran A, Faraji F, Goldberger N, Lee MP, Keane T, Hunter KW. An integrated genome-wide systems genetics screen for breast cancer metastasis susceptibility genes. PLoS Genet 2016; 12: e1005989.*
10. *Song L, Liu D, Zhao Y, He J, Kang H, Dai Z, Wang X, Zhang S, Zan Y. Sinomenine inhibits breast cancer cell invasion and migration by suppressing NF-κB activation mediated by IL-4/miR-324-5p/CUEDC2 axis. Biochem Biophys Res Commun 2015; 464: 705-710.*
11. *Li X, Li P, Liu C, Ren Y, Tang X, Wang K, He J. Sinomenine hydrochloride inhibits breast cancer metastasis by attenuating inflammation-related epithelial mesenchymal transition and cancer stemness. Oncotarget 2017; 8: 13560-13574.*
12. *Li X, Wang K, Ren Y, Zhang L, Tang XJ, Zhang HM, Zhao CQ, Liu PJ, Zhang JM, He JJ. MAPK signaling mediates sinomenine hydrochloride induced human breast cancer cell death via both reactive oxygen species-dependent and -independent pathways: an in vitro and in vivo study. Cell Death Dis 2014; 5: e1356.*
13. *Zhang H, Ren Y, Tang X, Wang K, Liu Y, Zhang L, Li X, Liu P, Zhao C, He J. Vascular normalization induced by sinomenine hydrochloride results in suppressed mammary tumor growth and metastasis. Sci Rep 2015; 5: 8888.*
14. *Zhang JX, Yang ZR, Wu DD, Song J, Guo XF, Wang J, Wei GD. Suppressive effect of sinomenine combined with 5-fluorouracil on colon carcinoma cell growth. Asian Pac J Cancer Prev 2014; 15: 6737-6743.*
15. *Yang HB, Yin PH, Shi Z, Ma YC, Zhao CG, Zheng JP, Chen T. Sinomenine, a COX-2 inhibitor, induces cell cycle arrest and inhibits growth of human colon carcinoma cells in vitro and in vivo. Oncol Lett 2016; 11: 411-418.*
16. *Liu Z, Duan ZJ, Chang JY, Zhang ZF, Chu R, Li YL, Dai KH, Mo GQ, Chang QY. Sinomenine sensitizes multi-drug-resistant colon cancer cells (Caco-2) to doxorubicin by down-regulation of MDR-1 expression. PLoS One 2014; 9: e98560.*
17. *Dubey AK, Gupta U, Jain S. Epidemiology of lung cancer and approaches for its prediction: A systematic review and analysis. Chin J Cancer 2016; 35: 71.*
18. *Peng W, Wu JG, Jiang YB, Liu YJ, Sun T, Wu N, Wu CJ. Antitumor activity of 4-O-(2"-O-acetyl-6"-O-p-coumaroyl-β-D-glucopyranosyl)-p-coumaricacid against lung cancers via mitochondrial-mediated apoptosis. Chem Biol Intera 2015, 233: 8-13.*
19. *Jiang TS, Li H, Zhai SP, Mao QS. The primary research on sinomenine induced apoptosis of lung cancer NCI-H460 cells by the mitochondrial signaling pathway. J Mod Oncol 2016; 24:703-706.*
20. *Xie BB, Yi L, Dong Y, Bai SS, Wang Q, Wang PX. Effect of Sinomenine on lung cancer cell A549 proliferation and alpha 7 nicotinic acetylcholine receptor expression. Trad Chin Drug Res Clin Pharmacol2015; 26: 164-169.*
21. *Jiang SL, Gao YB, Hou W, Liu R, Qi X, Xu X, Li J, Bao YJ, Zheng HJ, Hua BJ. Sinomenine inhibits A549 human lung cancer cell invasion by mediating the STAT3 signaling pathway. Oncol Lett 2016; 12: 1380-1386.*
22. *Zhou LP, Luan H, Liu QP, Jiang TS, Liang HY, Dong XH, Shang H. Activation of PI3K/Akt and ERK signaling pathways antagonized sinomenine-induced lung cancer cell apoptosis. Mol Med Rep 2012; 5: 1256-1260.*

23. Boyle P, Levin B. World Cancer Report 2008. Lyon: IARC Press 2008; pp 55-56.
24. Zhang J, Lu GF, Ren MD, Lu XL, Cao RQ, Yan HL, Wang X, He SX. Sinomenine hydrochloride inducing apoptosis of hepatocellular carcinoma SMMC-7721 cells and its effect on expressions of DR4 and DR5. Chin J Gastroenterol Hepatol 2016; 25: 873-876.
25. Cao RQ, Lu XL, Ren MD, Zhang J, Lu GF, Zhang D, Zhao Y, Yan HL, He SX. Sinomenine hydrochloride induces the apoptosis of hepatocellular carcinoma SMMC-7721 cells and its effect on expression levels of IL-1β, TNF-α and C/EBPβ. J Xi'an Jiaotong Univ 2017; 38: 290-294.
26. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008:GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-2917.
27. Sitarz R, Skierucha M, Mielko J, Offerhaus GJA, Maciejewski R, Polkowski WP. Gastric cancer: Epidemiology, prevention, classification, and treatment. Cancer Manag Res 2018; 10: 239-248.
28. Liao F, Yang ZR, Lu XH, Guo XF, Dong WG. Sinomenine sensitizes gastric cancercells to 5-fluorouracil in vitro and in vivo. Oncol Lett 2013; 6: 1604-1610.
29. Clark JC, Dass CR, Choong PF. A review of clinical and molecular prognostic factors in osteosarcoma. J Cancer Res Clin Oncol 2008; 134: 281-297.
30. Kansara M, Thomas DM. Molecular pathogenesis of osteosarcoma. DNA Cell Biol 2007; 26: 1-18.
31. Moore DD, Luu HH. Osteosarcoma. Orthopaedic Oncol 2014; 162: 65-92.
32. Xie T, Ren HY, Lin HQ, Mao JP, Zhu T, Wang SD, Ye ZM. Sinomenine prevents metastasis of human osteosarcoma cells via S phase arrest and suppression of tumor-related neovascularization and osteolysis through the CXCR4-STAT3 pathway. Int J Oncol 2016; 48:2098-2112.
33. Tang SQ. Study on PI3K/Akt signal transduction pathway of sinomenine inhibiting proliferation and inducing apoptosis in Hela cells. Chengdu: Chengdu University of Traditional Chinese Medicine Master's Thesis, 2009.
34. Zhang ZD, Jiang C, Yan YH. Effect of sinomenine on proliferation and apoptosis of EC109 cell through COX-2 pathway.ChinWestMedRes2012; 4:241-243,247.
35. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66: 115-132.
36. Di J, Rutherford S, Chu C.Review of the cervical cancer burden and population-based cervical cancer screening in China. Asian Pac J Cancer Prev 2015; 16: 7401-7407.
37. Peng W, Shen H, Lin B, Han P, Li CH, Zhang QY, Ye BZ, Rahman K, Xin HL, Qin LP, Han T. Docking study and antiosteoporosis effects of a dibenzylbutanelignan isolated from Litseacubeba targeting Cathepsin K and MEK1. Med Chem Res 2018; 27: 2062-2070.
38. Newman DJ, Cragg GM. Natural products as sources of new drugs from 1981 to 2014. J Nat Prod 2016; 79: 629-661.