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Antitumor Effect of Ginsenosides: A Systematic Review

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Abstract

Tumor is a serious disease that threatens human health and has a high mortality. Chemotherapy is the most commonly used treatment, but it has a lot of side effects due to its toxicity. It has been found that ginsenosides exert an effective antitumor role. Ginsenosides are a class of triterpenoid saponins primarily found in the plant genus Panax. Many monomer components are studied, the most often investigated are Rg3, and Rh2, etc. Reports have shown that ginsenosides can inhibit tumor cells by suppressing proliferation and metastasis, and promoting apoptosis. In addition, ginsenosides can enhance sensitivity to conventional chemotherapeutic drugs. In this review, the recent articles about anti-tumor of ginsenosides were reviewed to promote the further development of anti-tumor therapy.

Keywords

Ginsenosides, Autophagy, Apoptosis, Proliferation, Metastasis

1. Introduction

Tumor is a life-threatening disease that affects human health, and both the incidence and mortality are very high [1]. At present, that surgery, radiotherapy and chemotherapy are the most commonly used ways of treatment for tumor. However, conventional chemotherapy has a lot of side effects due to its toxicity, and natural products with low side effects drugs are expected as alternative choice for tumor treatment [2]. Ginseng is derived from the root or rhizome of *P. ginseng*

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C.A. Meyer, which has become one of the most commonly used alternative herbal medicines all over the world, and it has been widely and extensively used in China for medicinal purposes for thousands of years due to its rich content of saponins [3]. Ginsenosides are a class of triterpenoid saponins primarily found in the plant genus Panax, which has a wide variety of biological effects including cardio-protector, neuro-protector, anti-cancer, vasodilating, antioxidant, anti-diabetic activities and hepatoprotective effects [4]. Ginsenosides include many monomer components, such as Rg3, Rh2, Rh4, Rg2, Rg5, etc. The mechanisms of anti-tumor effects of ginsenosides are discussed in detail in this review. Ginsenosides can inhibit tumor cells by suppressing proliferation and metastasis, and promoting apoptosis. In addition, ginsenosides can enhance sensitivity to conventional chemotherapeutic drugs, summarized in **Table 1**.

2. Anti-Proliferation

Proliferation plays an important role in the occurrence and development of tumor. Recent studies showed that ginsenoside can inhibit tumor by inhibiting cell proliferation.

2.1. Ginsenoside Rg3

Ham *et al.* [5] showed that Rg3 up-regulated tumor-related genes through alteration of epigenetic methylation levels, thereby inhibiting the growth of breast cancer cells. Rg3 down-regulated hypermethylated TRMT1L, PSMC6 and NOX4, and up-regulated methylated ST3GAL4, RNLS and KDM5A. Yang *et al.* [6] found that ginsenoside Rg3 inhibited the proliferation of colorectal cancer SW-480 cells by down-regulating the transcriptional activity of C/EBP beta NF-kappaB. Sun *et al.* [7] found that ginsenoside Rg3 inhibited the proliferation of Lewis lung cancer (LLC) cells by reducing ROS and down-regulating the expression of cyclin and cyclin dependent kinase. Shan *et al.* [8] showed that ginsenoside Rg3 can inhibit malignant melanoma by inducing G0/G1 cell cycle arrest, reducing histone deacetylase 3 (HDAC3) and up-regulating p53 acetylation. In a further study, Shan *et al.* [9] pointed out that ginsenoside Rg3 prevented the growth of melanoma through deactivation of EGFR/MAPK pathway mediated by decreased FUT4/LeY expression. In pancreatic cancer, ginsenoside Rg3 enhanced erotinib-induced apoptosis by increased the expression levels of caspase-3, 9 and cleaved PARP, and reduced the expression levels of p-EGFR, p-PI3K, and p-AKT. Therefore, ginsenoside Rg3 could enhance the role of erotinib on proliferation suppression and apoptosis induction via down-regulating the EGFR/PI3K/AKT pathway [10].

2.2. Ginsenoside Rh2

Li *et al.* [11] found that ginsenoside Rh2 induced cell cycle arrest by down-regulated cyclin dependent kinase 4 and cyclin D, and significantly reduced the level of phosphorylated AKT. Therefore, ginsenoside Rh2 inhibited proliferation of

Table 1. The anti-tumor effects and mechanisms of ginsenosides.

Anti-tumor function	Cancer types	ginsenosides	cells or tissues	Mechanisms	Ref.
anti-proliferation	breast cancer	Rg3	breast cancer cells	up-regulated tumor-related genes through alteration of epigenetic methylation levels down-regulated hypermethylated TRMT1L, PSMC6 and NOX4, up-regulated methylated ST3GAL4, RNLS and KDM5A	[5]
	colorectal cancer	Rg3	SW-480 cells	down-regulating the transcriptional activity of C/EBP beta NF-kappaB	[6]
	Lewis lung cancer	Rg3	lung cancer cells	reducing ROS and down-regulating the expression of cyclin and cyclin dependent kinase	[7]
	malignant melanoma	Rg3	malignant melanoma cells	inducing G0/G1 cell cycle arrest, reducing histone deacetylase 3 (HDAC3) and up-regulating p53 acetylation	[8]
	melanoma	Rg3	melanoma cells	deactivation of EGFR/MAPK pathway mediated by decreased FUT4/LeY expression	[9]
	pancreatic cancer	Rg3	pancreatic cancer cells	increased the expression levels of caspase-3, 9 and cleaved PARP, down-regulating the EGFR/PI3K/AKT pathway, reduced the expression levels of p-EGFR, p-PI3K, and p-AKT	[10]
	glioma	Rh2	human A172 glioma cell	regulating CDK4/CyclinD complex and AKT, down-regulated CDK4 and cyclin D, reduced the level of phosphorylated AKT	[11]
	lung cancer	Rh2	H1299 cells	induced ROS mediated endoplasmic reticulum stress-dependent apoptosis, and up-regulated the expression of activated transcription factor 4 (ATF4), CCAAT/enhanced binding protein homologous protein (CHOP), and caspase-4	[12]
	prostate cancer	Rh2	prostate cancer cells	inhibiting microrna-4295, activates the cell cycle inhibitor p21 (CDKN1A)	[14]
	colorectal cancer	Rp1	colorectal cancer LoVo cells	up-regulate apolipoprotein apo-a1	[15]
	breast cancer	Rp1	breast cancer cells	inhibit the Akt/mTOR/P70S6 kinase signaling pathway.	[16]
Pro-apoptosis	lung cancer	Rg3	Lewis lung cancer (LLC) cells	regulating apoptosis-related proteins, such as Bcl-2, Bax, PARP-1, and lysed caspase-3	[7]
	lung cancer	Rg3	non-small cell lung cancer (NSCLC) cells	up-regulated the pro-apoptotic protein Bax, down-regulated the anti-apoptotic protein Bcl-2, thereby activating caspase-3.	[17]
	gastric cancer	Rg3	gastric cancer cells	up-regulated the expression of SP1, activated caspase 3, 8, 9 and PARP, down-regulated HSF1	[18]
	human osteosarcoma	Rg3	osteosarcoma cell lines	reduced the protein expression of Bcl2, repressed PI3K/AKT/mTOR signaling pathway and increased the expression of lysed caspase3	[19]
	ovrian cancer	Rg3	HO-8910 cells	suppression of the PI3K/Akt pathway, reducing the expression of caspase-3 and caspase-9	[20]
	breast cancer	Rh4	McF-7 cells	down-regulating Bcl-2, up-regulating Bax, and activating caspase-8, -3 and PARP	[21]
	colorectal cancer	Rh4	colorectal cancer cells	activating the ROS/JNK/p53 pathway	[22]

Continued

	colorectal cancer	Rh2	HCT116 and SW480 cells	induce the caspase-mediated apoptosis, activated the p53 pathway, increasing the level of pro-apoptotic protein Bax and reducing the level of anti-apoptotic protein Bcl-2	[23]
	prostate cancer	Rh2	DU145 cells	up-regulating the expression of PPAR-delta and p-STAT3, induction OF ROS/superoxide	[25]
autophagy	breast cancer	Rg3	breast cancer cells	decreased P62 levels, increased generation of LC3-II cleaved from LC3-I	[29]
	ovarian cancer	Rg3	SKOV3 cells	increasing the levels of LC3-II, Atg5, and Atg7	[28]
	colorectal cancer	Rh4	colorectal cancer cells	activating ROS/JNK/p53 pathway, increased the Beclin 1 levels, increase the expression of Atg-7 and LC3-II, promote the autophagy	[22]
	breast cancer	Rg2	MCF-7 cells	Increased p53 levels by transcriptional activation of GR, activated TSC1 and TSC2, phosphorylated AMPK, inhibited the mTOR pathway, and increased autophagy	[32]
	breast cancer	Rg5	breast cancer cells	inhibiting P13K/AKT/mTOR pathway, decreased P62 levels, increased Atg5, Atg7, Atg12, accelerated the LC3-I to LC3-II transformation	[33]
	non-small-cell cancer	CK	non-small-cell cancer cells	induced generation of LC3-II cleaved from LC3-I, and decreased the P62 levels	[34]
Anti-metasis	breast cancer	Rg3	MDA-MB-231 cells	inhibits CXCR4 expression and	[37]
	ovarian cancer	Rg3	SKOV3 cells	down-regulating the expression of VEGF mRNA and protein, reducing microvascular density and blocking angiogenesis	[38]
	ovarian cancer	Rg3	SKOV3 cells	reduction of MMP-9 expression, promote the invasion	[39]
	breast cancer	Rd	4T1 cells	decreasing miR-18a-mediated Smad2 expression, decaying migration	[56]
	hepatocellr cancer	Rd	HepG2 cells	down-regulating the expression of MMP-1, MMP-2, and MMP-7 by inhibiting ERK and MAPK signaling pathways	[57]
	melanoma cancer	Rp1	B16F10 Cells	down-regulating the expression of beta1-integrin (CD29), inhibiting the formation of blood vessels	[63]
	glioblastoma multiforme	Rh2	U251 cells	inhibit AKT mediated MMP13 activation	[58]
	colerectal cancer	20(S)-Rh2	CRC cells	down-regulatingIL-6-induced signal transducer, STAT3, MMPs (MMP-1, -2, and -9)	[60]
	colorectal cancer	20(S)-Rg3	SW280 and SW620 cells	inhibited the expression of fatty acid synthetase and histone H4	[10]
	colerectal cancer	Rb2	HT29 and SW620 cells	down-regulating stemness and Epithelial-mesenchymal transition (EMT)-related genes via the EGFR/SOX2 signaling axis	[61]
	malignant gliomas	Rh1	U87MG and U373MG cells	inhibited mRNA expressions and promoter activity, down-regulating the expression of MMP-1, -3, and -9	[59]
Inhibiting EMT	lung cancer	20(R)-Rg3	A549 cells	suppressing the expression of E-cadherin and vimentin by inhibiting TGF-ß1 activation	[46]
	liver cancer	Rg1	HepG2 cells	increased the expression of E-cadherin and inhibited the expression of the mesenchymal phenotype marker vimentin by inhibiting TGF-β1	[54]

Continued

	ovarian cancer	Rg1	SKOV3 cells	recovered the expression of E-cadherin and attenuated expression of vimentin by regulating NF-κB pathway	[55]
	ovarian cancer	Rb1	SKOV3 and 3AO cells	by down-regulating the expression of miR-25, E-cadherin transcriptional activator EP300 is overexpressed, thus increasing E-cadherin level	[62]
	breast cancer	CK	MCF-7 cells	decreasing N-cadherin and vimentin, and increase level of E-cadherin through inhibition the activation of PI3K/Akt pathway	[66] [67]
Chemotherapy sensibilization	lung cancer	Rg3	hypoxic lung cancer cell	blocking of NF-κB mediated EMT and stemness, reduced the toxicity induced by cisplatin	[70] [71] [72]
	lung cancer	Rg3	lung cancer cells	attenuated cisplatin resistance and increased chemosensitivity by down-regulating PD-L1 and resuming immune	[10]
	colon cancer	Rg3	colon cancer cells	enhanced the sensitivity of cisplatin by reducing the basal level of nuclear factor erythroid 2-related factor2-mediated heme oxygenase-1/NAD(P)H quinone oxidoreductase-1	[13]
	pancreatic cancer	Rg3	pancreatic cancer cells	enhances the anti-proliferative activity of erlotinib by downregulation of EGFR/PI3K/Akt signaling pathway By downregulation of EGFR/PI3K/Akt signaling pathway	[75]
	hepatocellar cancer	Rg3	hepatocellular carcinoma cells	sensitize TRAIL-induced cell death CHOP-mediated DR5 upregulation	[59]
	ovarian cancer	Rb1	ovarian cancer cells	promote sensitivity of cisplatin and paclitaxel by suppressing the Wnt/β-catenin signaling and EMT	[76]
	lung cancer	Rd	lung cancer cells	significant sensitization was achieved by inhibiting NRF2	[79]
	esophageal cancer	Ro	esophageal cancer cells	delayed DNA repair and the accumulation of DNA damage by potentiating 5-Fu cytotoxicity via delaying CHEK1 (checkpoint kinase 1) degradation and downregulating DNA replication process	[28]

human A172 glioma cell by regulating CDK4/CyclinD complex and AKT. In lung cancer H1299 cells, Ge *et al.* [12] found that ginsenoside Rh2 induced ROS mediated endoplasmic reticulum stress-dependent apoptosis, and up-regulated the expression of activated transcription factor 4 (ATF4), CCAAT/enhanced binding protein homologous protein (CHOP), and caspase-4, thereby inhibiting cell proliferation. Yong *et al.* [13] proved that ginsenoside Rh2 significantly inhibited the proliferation of nasopharyngeal carcinoma CSCs *in vitro*, promoted apoptosis, and reduced the expression of IL-6. Gao *et al.* [14] indicated that ginsenoside Rh2 inhibited the growth of prostate cancer cells by inhibiting microrna-4295, which activates the cell cycle inhibitor p21 (CDKN1A).

2.3. Other Ginsenosides

Ginsenoside Rp1 is a new ginsenoside derived from ginsenoside Rk1. Kim *et al.* [15] found that ginsenoside Rp1 can up-regulate apolipoprotein apo-a1 in colorectal cancer LoVo cells, strongly inhibiting cell proliferation and promoting cell apoptosis. Zhang *et al.* [16] found that ginsenoside Rd can inhibit the prolifera-

tion and induce apoptosis of breast cancer cells, and inhibit the Akt/mTOR/P70S6 kinase signaling pathway.

3. Pro-Apoptosis

Apoptosis refers to the spontaneous and orderly death of cells controlled by genes to maintain the stability of the internal environment. Different from cell necrosis, cell apoptosis is not a passive process, but an active process, which involves the activation, expression and regulation of a series of genes. It is not a phenomenon of self-injury under pathological conditions, but a death process that actively strives for better adaptation to the living environment. With the development of scientific research, it has been found that inadequate apoptosis plays a key role in the occurrence and development of tumor cells.

3.1. Ginsenoside Rg3

Sun *et al.* [7] found Rg3 induced apoptosis of Lewis lung cancer (LLC) cells by regulating apoptosis-related proteins, such as Bcl-2, Bax, PARP-1, and lysed caspase-3. Dai *et al.* [17] demonstrated that the combined use of ginsenoside Rg3 and gefitinib can up-regulated the pro-apoptotic protein Bax and down-regulated the anti-apoptotic protein Bcl-2, thereby activating caspase-3 and promoting the apoptosis of non-small cell lung cancer (NSCLC) cells. Aziz F.'s *et al.* [18] pointed out that ginsenoside Rg3 up-regulated the expression of specific protein 1 (SP1) and down-regulated heat shock factor 1 (HSF1) to inhibit the expression of brown alginase transferase IV (FUT4), and activated caspase-3, -8, -9 and PARP to promote the apoptosis of gastric cancer cells. Li *et al.* [19] found that ginsenoside Rg3 reduced the protein expression of Bcl2 and repressed PI3K/AKT/mTOR signaling pathway in human osteosarcoma cell lines (mg-63, u-2os and saos-2), and increased the expression of lysed caspase3. Therefore, Rg3 induced apoptosis of human osteosarcoma cell lines. In addition, ginsenoside 20(S) -Rg3 can also induce apoptosis of ovarian cancer HO-8910 cells through suppression of the PI3K/Akt pathway. Concordantly, Wang *et al.* [20] found that 20(S)-ginsenoside Rg3 reduced the activity of ovarian cancer HO-8910 cells in dose- and time-dependent manners, and induced apoptosis. Apoptosis induction was due to down-regulation of phosphatidylinositol 3-kinase (PI3K)/Akt family protein and apoptosis-inhibiting protein (IAP) family protein, and up-regulation of the expression of caspase-3 and caspase-9.

3.2. Ginsenoside Rh4

Duan *et al.* [21] found that ginsenoside Rh4 can promote apoptosis of breast cancer McF-7 cells by down-regulating Bcl-2, up-regulating Bax, and activating caspase-8, -3 and PARP. Another study indicated that Rh4 increased the accumulation of reactive oxygen species (ROS), thereby activating the JNK-p53 pathway [22]. Reactive oxygen scavenging agents, JNK and p53 inhibitors can significantly reduce Rh4-induced apoptosis, suggesting that Rh4 can trigger

apoptosis by activating the ROS/JNK/p53 pathway in colorectal cancer cells.

3.3. Ginsenoside Rh2

Li *et al.* [23] confirmed that in colorectal cancer HCT116 and SW480 cells, ginsenoside Rh2 can induce the caspase-mediated apoptosis of colorectal cancer cells. Rh2 activated the p53 pathway, significantly increasing the level of pro-apoptotic protein Bax and reducing the level of anti-apoptotic protein Bcl-2. It was reported that ginsenoside Rh2 inhibited the proliferation of gastric cancer SGC-7901 Side Population cells in a dose-dependent manner. Rh2 arrested cells at G1/G0 phase, followed by stimulation of apoptosis through up-regulation of Bax and down-regulation of Bcl-2 [24]. Wu *et al.* [25] found that ginsenoside Rh2 induced apoptosis of prostate cancer DU145 cells by up-regulating the expression of PPAR-delta, which was related to the up-regulation of p-STAT3 and induction OF ROS/ superoxide.

3.4. Ginsenoside F2

Ginsenoside F2 is the potential bioactive metabolite of main ginsenosides. Mao [26] indicated that Ginsenoside F2 induced ROS accumulation, decreased mitochondrial transmembrane potential (MTP), stimulated the release of cytochrome c, and induced caspase-dependent apoptosis. The regulation of ASK-1/JNK pathway also contributed to apoptosis. Results suggested that Ginsenoside F2 induced apoptosis by inducing ROS accumulation and activating ASK-1/JNK signaling pathway.

4. Ginsenoside Inhibits Tumor Cells by Autophagy

Autophagy is an intracellular degradation pathway that transports damaged, deformed, aging or dysfunctional proteins and organelles in cells to lysosomes for digestion and degradation, so as to realize the metabolic needs of cells and the renewal of organelles. It has been found that autophagy plays a very important role in the genesis and development of tumors, which gradually attracts people's wide attention. Recent studies show that ginsenoside can inhibit tumor cells through autophagy.

4.1. Ginsenoside Rg3

The effect of ginsenosides on autophagy is controversial. Reportedly, ginsenoside 20(S)-Rg3 (a type of Rg3 ginsenosides stereo isomer) inhibited autophagic flux by suppression of late-stage autophagosome maturation or degradation and eventually induced apoptosis in cervical cancer cells [5]. However, Zhang Y *et al.* [27] found that that ginsenoside Rg3 induced autophagy so as to inhibit breast cancer tumor growth in tumor-bearing mice, and its mechanism was associated with P13K/AKT/mTOR pathway, Rg3 decreased P62 levels, increased generation of LC3-II cleaved from LC3-I. Zheng *et al.* [28] showed that 20 (S)-ginsenosides Rg3 induced autophagy in ovarian cancer SKOV3 cells by increasing the levels of

LC3-II, Atg5, and Atg7.

4.2. Ginsenoside Rh2, Rh4

Lv *et al.* [29] found that smith-4 can inhibit the phosphorylation of AKT/mTOR and reduce the activity of AKT/mTOR pathway to promote autophagy, while ginsenoside Rh2 can enhance this autophagy activity *in vivo* and *in vitro* to enhance the anti-melanoma efficacy of smith-4. Liu *et al.* [30] found that ginsenoside Rh2 promoted autophagy and apoptosis of K562 cells. Rh2 ginsenosides reduced the expression of HDAC6, promoted acetylation of Hsp90, and increased the expression of LC3-I, LC3-II, Beclin 1. Sarkar *et al.* [31] showed that increasing the acetylation of Hsp90 and decreasing the expression of Hsp90 would both cause autophagy and apoptosis of cells.

Wu *et al.* [22] *et al.* investigated the role of ginsenoside Rh4 in colorectal cancer cells (Caco 2, HCT116 cell) on growth inhibition, and they found that Rh4 promoted autophagy of colorectal cancer cells by activating ROS/JNK/p53 pathway. Rh4 promoted intracellular reactive oxygen species (ROS), which led to JNK phosphorylation and further promotes the p53 phosphorylation. Phosphorylated p53 increased the Beclin 1 levels, which can further increase the expression of Atg-7 and LC3-Ⅱ so as to promote the autophagy, optimization inhibition of colon cancer cells growth.

4.3. Ginsenoside Rg2, Rg5

Chung *et al.* [32] found that in breast cancer MCF-7 cells, Rg2 can bind to glucocorticoid receptor (GR) as a glucocorticoid-like cellular mechanism. Rg2 increased p53 levels by transcriptional activation of GR, which activated the tuberous sclerosis complex 1 (TSC1) and TSC2, then phosphorylated AMPK and subsequently inhibited the mTOR pathway, and increased autophagy. Rg2 increased the levels of p-p53, p-AMPK, Atg-7, and LC3-II, while decreased the levels of p62.

Liu *et al.* [33] proved that ginsenoside Rg5 had a strong anti-tumor effect in human breast cancer cells. Rg5 promoted autophagy by inhibiting P13K/AKT/mTOR pathway, which decreased P62 levels, increased by Atg5, Atg7, Atg12, and accelerated the LC3-I to LC3-II transformation to promote autophagy.

CK, the metabolite of ginsenoside, can increase the phosphorylation level of AMPK and reduce the phosphorylation level of mTOR, thereby promoting autophagy and promoting apoptosis. Chen *et al.* [34] found that CK treatment up-regulated the expression of Beclin 1 in non-small-cell cancer cells, induced generation of LC3-II cleaved from LC3-I, and decreased the P62 levels.

5. Anti-Metastasis

Tumor metastasis is the outcome of combined action of many factors, such as transfer signals, extracellular matrix, adhesion molecules, and hyaluronic acid receptor family, as well as genes related to angiogenesis [35].

5.1. Ginsenoside Rg3

It has been found that Chemokine CXC receptor 4 (CXCR4) plays an important role in metastasis by acting on the chemokine ligand CXCL12. [36] Chen *et al.* [37] demonstrated that ginsenoside Rg3 inhibited CXCR4 expression and CXCL12 (CXCR4 ligand) induced chemotaxis in cultured MDA-MB-231 cell, a highly metastatic cell line of breast cancer, thus inhibiting cancer cell migration. Pan *et al.* [38] found that ginsenoside Rg3 can inhibit the growth and metastasis of ovarian cancer cells by down-regulating the expression of VEGF mRNA and protein, reducing microvascular density and blocking angiogenesis. XU *et al.* [39] found that ginsenoside Rg3 can significantly inhibit the metastasis of ovarian cancer. The inhibitory effect was partly due to reduction of MMP-9 expression, which promoted the ovarian cancer SKOV3 cells to invade.

Lee *et al.* [40] investigated the effects of ginsenoside 20(S)-Rg(3) in colorectal cancer SW620 cells, and found that ginsenoside 20(S)-Rg(3) inhibited the expression of fatty acid synthetase and histone H4, thus inhibiting the metastasis of SW620 cells.

The epithelial-mesenchymal transition (EMT) is a physiological and pathological phenomenon, characterized by the loss of typical epithelial characteristics and the acquisition of mesenchymal traits. [41] Studies have revealed that EMT contributes to cancer progression, invasion and migration in various types of cancer [42] [43]. In the process of EMT, the expression of E-cadherin, a membrane protein mediating the tight junction between epithelial cells, is downregulated, and the expression of connexin between mesenchymal cells, such as N-cadherin and vimentin, is upregulated. [44] Tian *et al.* [45] found that Rg3 significantly up-regulated the mRNA levels of the E-cadherin, and down-regulated the mRNA levels of Snail, N-cadherin and Vimentin in NSCLC cells (A549, H1299 and H358 cells), thereby effectively preventing EMT process in dose- and time-dependent manners. Kim *et al.* [46] found that 20(R)-Rg3 inhibited the EMT by suppressing E-cadherin and vimentin expression in TGF-ß1-activated lung cancer A549 cells. Ting *et al.* [47] found that ginsenoside 20(S)-Rg3 potently blocked hypoxia-induced EMT of ovarian cancer cells *in vitro* and *in vivo*. They confirmed that 20(S)-Rg3 reduced the expression of hypoxia-inducible factor 1a (HIF-1a) by activating the ubiquitin-proteasome pathway to promote HIF-1a degradation. Decreased HIF-1a suppressed Snail transcription, leading to up-regulation of E-cadherin (the epithelial cell-specific marker) and down-regulation of vimentin (the mesenchymal cell-specific marker) under hypoxic conditions.

5.2. Ginsenoside Rg1

Transforming growth factor (TGF)-β1 was found to be the main inducer of ETM [48] [49]. Ginsenoside Rg1, is one active and abundant components in ginseng, which has exerts anticancer properties [50] [51] [52] [53]. Yu *et al.* [54] found that TGF-β1 could induce the expression of vimentin and decrease the

expression of E-cadherin, which could make human liver cancer HepG2 cells behave as mesenchymal phenotype and significantly enhance the invasion and migration of cells. When treated with ginsenoside Rg1, Rg1 increased the expression of E-cadherin and inhibited the expression of the mesenchymal phenotype marker vimentin, showing a typical epithelial morphology. Therefore, ginsenoside Rg1 inhibited the invasion and migration of hepatocellular carcinoma HepG2 cells *in vitro* by inhibiting EMT. Concordantly, Dan *et al.* [55] found that treatment with ginsenoside Rg1 for 48 h in ovarian cancer cell SKOV3, the EMT morphology change induced by hypoxia was partially reversed. Rg1 recovered the expression of E-cadherin and attenuated expression of vimentin by regulating NF-KB pathway.

5.3. Ginsenoside Rd

Ginsenoside Rd is a kind of procyanidins found in ginseng ginseng saponin. Wang *et al.* [56] found that Rd treatment increased expression of Smad2 by down-regulating microRNA (miR)-18a in cultured 4T1 cells and in tumors grown from inoculated 4T1 cells. Smad2, a direct target of miR-18a, significantly induced attenuation of migration in 4T1 cells.

Yoon *et al.* [57] showed that ginsengside inhibited migration and invasion of human hepatocellular cancer HepG2 cells by inhibiting ERK and MAPK signaling pathways, which reduced the expression of MMP-1, MMP-2 and MMP-7.

5.4. Ginsenoside Rh2, Rh1

Guan *et al.* [58] found that Rh2 reduced the invasiveness of glioblastoma cells in a dose-dependent manner by inhibiting AKT mediated MMP13 activation, assessed by wound healing test and Transwell assay. Jung *et al.* [59] showed that Rh1 inhibited the mRNA expressions of MMP-1, -3 and -9 in human malignant gliomas cells (U87MG and U373MG). Rh1 also inhibits promoter activity of MMP-1, -3, and -9. Further studies showed that Rh1 played an important role in inhibiting MAPK and PI3K/Akt signaling pathways and downstream transcription factors. Han *et al.* [60] found that ginsenoside 20(S)-Rh2 effectively inhibited the phosphorylation of signal transducers and transcriptional activator 3 (STAT3), as well as the expression of matrix metalloproteinases (MMPs), including MMP-1, -2, and -9, thereby inhibiting the metastasis of colorectal cancer cells.

5.5. Ginsenoside Rb2, Rb1, Rp1

Phi *et al.* [61] found that ginsenoside Rb2 inhibited CSC properties and EMT of HT29 SW620 cells, thereby inhibiting the transfer of CRC cells *in vivo*, which was achieved by inhibiting EGFR and its downstream signal pathways, SOX2 and Snail. Liu *et al.* [62] demonstrated that Rb1 downregulated the expression of miR-25, resulting in overexpression of E-cadherin transcriptional activator EP300, thus increasing E-cadherin level and inhibiting the hypoxia-induced

EMT process in ovarian cancer SKOV3 and 3AO cells. Ginsenoside Rp1, a new type of ginseng saponin, was showed to play an anticancer role by inhibiting the adhesion of tumor cells and the formation of blood vessels, and by strongly inhibiting the cell activity and metastasis process. Park *et al.* proved that Rp1 inhibited human umbilical vein endothelial cells (HUVECs) tube formed, blocked HCT15 and A549 cell viability, and strongly inhibited the pulmonary metastasis of B16-F10 melanoma cells [63].

5.6. Ginsenoside Compound K (CK)

CK (20-O-*β*-d-glucopyranosyl-20(S)-protopanaxadiol) is an active metabolite that are synthesized by intestinal bacteria after oral administration of ginsenosides Rb1, Rb2, Rc and Rd. [64] It was found that CK increased the level of epithelial marker molecule Ecadherin, and reduced the level of mesenchymal markers N-cadherin and vimentin in MCF-7 cells, indicating that CK inhibited the EMT process in MCF-7 cells [65]. The activation of PI3K/Akt signalling pathway may promote the occurrence of EMT in most tumour cells [66] [67]. Studies showed that CK inhibited the EMT in MCF-7 cells, which may be due to inhibition the activation of PI3K/Akt pathway [68], since it was clarified that CK could inhibit EMT by reducing the level of p-AKT [65]. Peng *et al.* [69] found that CK decreased N-cadherin and increased E-cadherin in liver cancer HepG2 cells, indicating that CK inhibited the EMT process. Suppression of ERK and Akt signaling pathways was involved in this pharmacologic action.

6. Sensitization to Chemotherapeutic Drugs

Chemotherapy has been the mainstay of cancer treatment for the past several decades. As a result of the heterogeneity of the tumor cell population, the sensitivity of the different clones of the same cell related to the drug is different, and it is easy to produce the drug resistance to the chemotherapeutic agent. Therefore, it has become a new strategy of tumor chemotherapy to seek low toxic chemotherapeutic sensitizers to enhance the cytotoxicity of antineoplastic drugs or to change the resistance of tumor cells to chemotherapy in the future.

6.1. Ginsenoside Rg3

Wang *et al.* [70] [71] reported that ginsenoside Rg3 sensitized hypoxic lung cancer cells to cisplatin via blocking of NF-*κ*B mediated EMT and stemness [72], and Rg3 also reduced the toxicity induced by cisplatin. Lee *et al.* [73] found that Rg3 enhanced the sensitivity of colon cancer cells to cisplatin by reducing the basal level of nuclear factor erythroid 2-related factor2-mediated heme oxygenase-1/NAD(P)H quinone oxidoreductase-1, and prevented normal tissue damage by scavenging cisplatin-induced intracellular ROS. Jiang *et al.* [10] showed that Rg3 attenuated cisplatin resistance and increased chemosensitivity in lung cancer by down-regulating PD-L1 and resuming immune. Tang *et al.* [74] found that Rg3 could strengthen the cytotoxicity of 5-Fluorouracil and oxalip-

latin against orthotopic xenografts *in vivo* in colorectal cancer by downregulating the levels of B7-H1 and B7-H3, predictors of adverse clinical outcomes in CRC. Jiang *et al.* [75] found Ginsenoside Rg3 enhances the anti-proliferative activity of erlotinib in pancreatic cancer cell lines by downregulation of EGFR/PI3K/Akt signaling pathway. Lee [59] *et al.* found that ginsendoside Rg3 sensitize TRAIL-induced cell death by via CHOP-mediated DR5 upregulation in human hepatocellular carcinoma cells.

6.2. Ginsenoside Rb1, Rh2, Rp1, Rd, Ro

Deng *et al.* [76] proved that ginsenoside Rb1 exerted strong cytotoxicity to tumor stem cells. Rb1 and its metabolites can effectively inhibit the growth of ovarian cancer stem cells, promoting cells more sensitive to clinical-related doses of chemotherapeutic drugs, such as cisplatin and paclitaxel. The mechanism is that by suppressing the Wnt/β-catenin signaling and EMT. Studies delivered by Nakata indicated that ginsenoside Rh2 combined with cisplatin can enhance the therapeutic effect in ovarian cancer, since Rh2 sensitized ovarian cancer cell to cisplatin *in vitro* and *in vivo* [77]. The membrane transporter MDR-1, located on the lipid rafts of the plasma membrane, and increased MDR-1 activity is an important contributor to multidrug resistance. Yun *et al.* [78] found that ginsenoside Rp1 repressed MDR-1 activity by redistributing lipid rafts, which reversed resistance to anti-tumor drugs, including doxorubicin. Chian found that GS-Rd significantly sensitized A549/DDP cells to therapeutic drugs by inhibiting NRF2 which could develop multidrug resistance [79]. Zheng K *et al.* [28] found that ginsenoside Ro potentiates 5-Fu cytotoxicity via delaying CHEK1 (checkpoint kinase 1) degradation and downregulating DNA replication process, resulting in the delayed DNA repair and the accumulation of DNA damage.

7. Conclusions

Malignant tumors are in the forefront of mortality and morbidity in malignant diseases, which seriously affects the health of people. Therefore, it is very important to explore the effective treatment for malignant tumors. At present, surgery and radiotherapy combined with chemotherapy are mainly used in clinic, the main chemotherapeutic drugs are cisplatin, paclitaxel and so on. However, multi-drug resistance, toxic reactions and adverse reactions greatly limit its clinical efficacy. Therefore, there is a need to explore more ideal drugs for the treatment of tumors.

To sum up, a large number of feasibility trials have shown that ginsenosides can not only interfere with cancer by targeting several molecules and pathways involved in cancer development, but also do little harm to normal cells in the body. Moreover, when these plant extracts are used in combination with chemotherapeutic drugs, it is observed a stronger anti-cancer effect and less toxic than using chemotherapy alone. More importantly, it can reverse the multi-drug resistance of chemotherapeutic drugs. The antitumor effects of ginsenosides and signal pathways are shown in **Figure 1**, including anti-proliferation, pro-apoptosis,

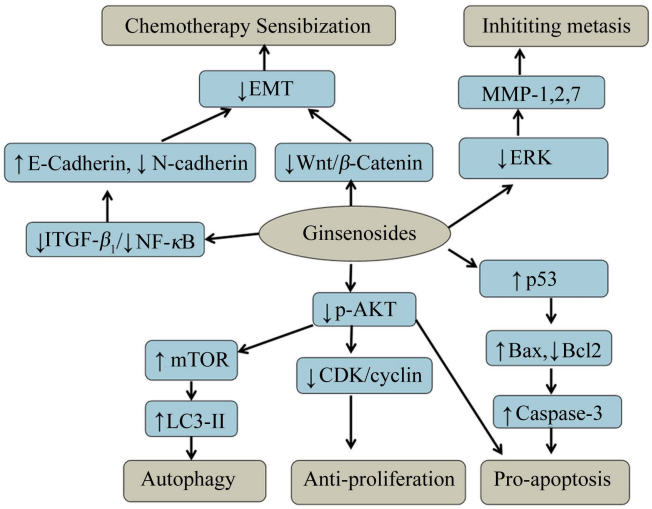

Figure 1. This figure shows the antitumor effects of ginsenosides and signal pathways.

anti-metasis, and chemotherapy sensibilization. Therefore, it is of great significance to further study the pharmacological effects of total ginsenosides and their monomers. It can be predicted that with the study of the deep human system of ginsenosides, many aspects of their biological effects will gradually be revealed. The combination of ginsenoside and chemotherapeutic drugs may be a more ideal strategy for the treatment of tumors in clinical studies in future.

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Authors' Contributions

Jing Wu, Shuaishuai Niu, and Li Guan initiated the topic and wrote the manuscript. Ying Xiang revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declared that there was no conflict of interests.

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