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Unveiling Gambogenic Acid as a Promising Antitumor Compound: A Review

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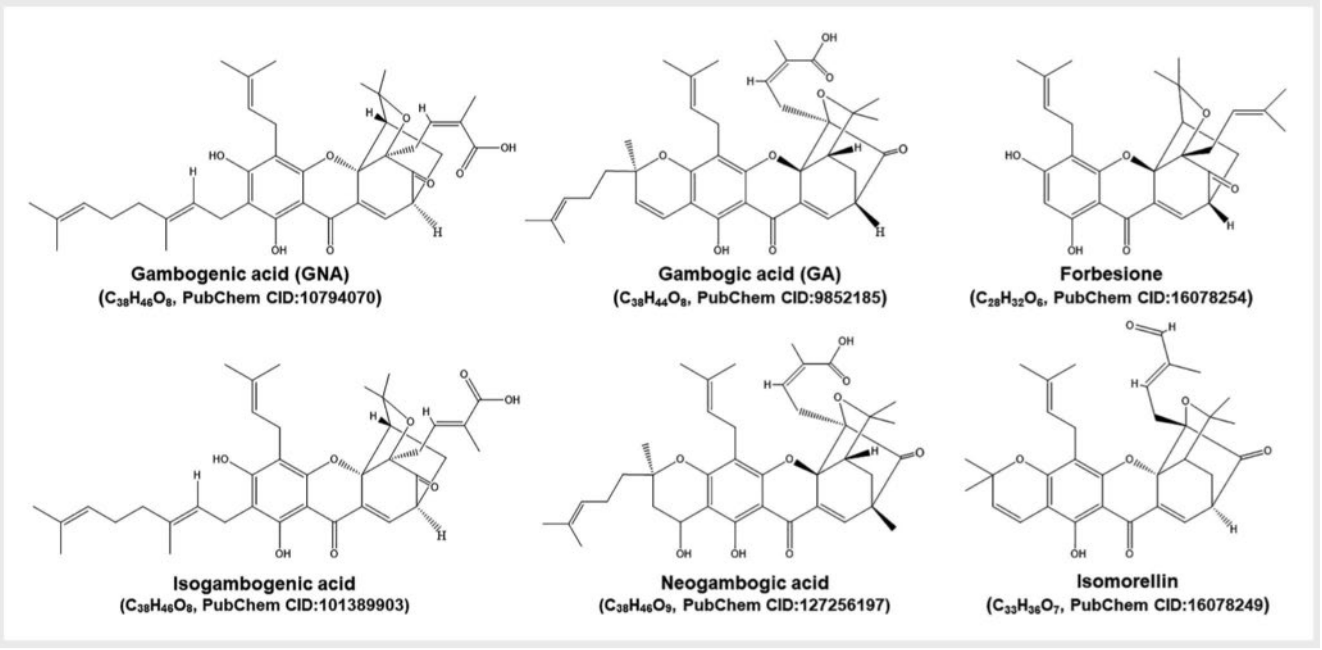
ABSTRACT

Gambogenic acid is a derivative of gambogic acid, a polyprenylated xanthone isolated from *Garcinia hanburyi*. Compared with the more widely studied gambogic acid, gambogenic acid has demonstrated advantages such as a more potent antitumor effect and less systemic toxicity than gambogic acid according to early investigations. Therefore, the present review summarizes the effectiveness and mechanisms of gambogenic acid in different cancers and highlights the mechanisms of action. In addition, drug delivery systems to improve the bioavailability of gambogenic acid and its pharmacokinetic profile are included. Gambogenic acid has been applied to treat a wide range of cancers, such as lung, liver, colorectal, breast, gastric, bladder, and prostate cancers. Gambogenic acid exerts its antitumor effects as a novel class of enhancer of zeste homolog 2 inhibitors. It prevents cancer cell proliferation by inducing apoptosis, ferroptosis, and necroptosis and controlling the cell cycle as well as autophagy. Gambogenic acid also hinders tumor cell invasion and metastasis by downregulating metastasis-related proteins. Moreover, gambogenic acid increases the sensitivity of cancer cells to chemotherapy and has shown effects on multidrug resistance in malignancy. This review adds insights for the prevention and treatment of cancers using gambogenic acid.

Introduction

Cancer continues to be the primary cause of mortality worldwide [1], with staggering numbers reported in the "Global Cancer Statistics 2020'' report; approximately 19.3 million new cancer cases and nearly 10.0 million cancer-related deaths were recorded in 2020 alone [2]. Furthermore, it is projected that the global cancer burden will increase to 28.4 million cases by 2040 [2]. These statistics highlight the urgent need for comprehensive efforts in cancer prevention, diagnosis, and treatment to alleviate the global burden of this devastating disease. Over the years, several treatment modalities, such as surgery, radiotherapy, chemotherapy, and immunotherapy, have been developed for cancer. However, these approaches often come with side effects and have limitations in tackling tumor recurrence and metastasis. In recent decades, there has been a notable increase in the use of natural products with diverse bioactivities to combat different types of cancer. Natural products are recognized as potentially safer alter-



▶ **Fig. 1** Structure diagrams of some caged xanthones with antitumor activity. The chemical structures of compounds were derived from PubChem (https://pubchem.ncbi. nlm.nih.gov/).

natives to traditional drug therapy, given the lower propensity for adverse effects [3,4].

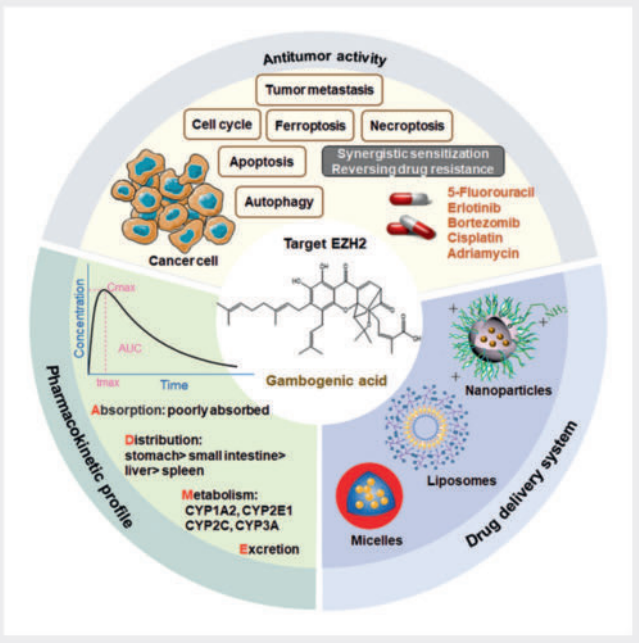
Garcinia hanburyi Hook. f., a plant belonging to the Guttiferae family, is a small tree distributed throughout India, Cambodia, Thailand, and the southern part of China [5]. Its resin, named gamboge, has been historically utilized in traditional folk medicine to address various conditions. Its applications include the treatment of chronic dermatitis, hemorrhoids, bedsores, and tapeworm infections [6]. In recent years, this resin has garnered heightened attention due to its broad spectrum of biological and pharmacological properties. These properties encompass cytotoxic [7–9], antiproliferative [10–12], antitumor [13,14], antiangiogenesis [15], anti-HIV-1 [16,17], antibacterial [18], and anti-inflammatory effects [19]. Gamboge contains a diverse array of bioactive components, primarily caged xanthones. To date, over 40 different caged xanthones have been identified and explored for their potential medicinal applications [20] (▶ **Fig. 1**). Gambogic acid (GA; $C_{38}H_{44}O_8$) has been claimed to be the major constituent of gamboge [21]. It has shown immense potential as a candidate broad-spectrum anticancer drug [22–25]. In 2014, GA was approved by the Chinese Food and Drug Administration for a phase II clinical trial in lung cancer and other solid tumor therapies [26], but this clinical trial has been terminated.

Asano et al. [27] isolated a polyprenylated xanthone from gamboge with a structure similar to GA, referred to as gambogenic acid (GNA; $C_{38}H_{46}O_8$). GNA shares structural similarity with GA but differs in the presence of a geranyl group and a hydroxyl group instead of the ether ring found in GA. Many studies have reported that GNA has multiple biological functions, such as anti-inflammation [28,29], anti-fibrosis [30], and antiangiogenesis [31]. Meanwhile, GNA has demonstrated a notable antitumor effect and serves as an inhibitor of enhancer of zeste homolog 2 (EZH2), employed in a study of diverse cancer types [32]. Compared with the more widely studied GA, GNA has shown several advantages in terms of its antitumor effect and systemic toxicity, as indicated by early investigations [27,33–37]. Nevertheless, to date, there has been no comprehensive review of the antitumor effect of GNA and its underlying mechanisms, as well as the drug delivery of GNA for cancer therapeutics. Therefore, this paper aims to systematically review the antitumor effects and mechanisms, pharmacokinetics, and nanotechnology-mediated delivery of GNA, with the goal of providing reference material for its application in antitumor research and promoting its further development and utilization (▶ **Fig. 2**). By searching PubMed, Web of Science, and ScienceDirect databases, covering the period from 1996 to 2023, this paper has retrieved a total of 104 articles using the main terms “gambogenic acid”, *“Garcinia hanburyi”*, “Guttiferae”, “gamboge”, “cancer”, “pharmacokinetic”, and their combinations. We evaluated both experimental papers and reviews that were deemed relevant and identified 55 articles that were considered to be useful and appropriate for analysis.

Therapeutic Activity of Gambogenic Acid in Cancer

In vitro studies

Numerous preclinical investigations have shown that GNA has an impact on a variety of human malignancies, including lung [38], breast [39], colorectal [36], cervical [40], gastric [41], bladder [42], prostate [43], epithelial cancers [32], hepatic carcinoma (HCC) [44], melanoma [45], multiple myeloma [33], nasopharyn-



▶ **Fig. 2** A schematic representation of the antitumor activity, pharmacokinetics, nanotechnology-mediated delivery of GNA.

geal carcinoma [46], glioblastomas [47], osteosarcoma [48], and leukemia [49] (▶ **Table 1**). GNA suppressed the cell growth of cancer cell lines but also showed low toxicity toward normal cells [36, 50].

Moreover, several recent studies have indicated that GNA exhibits significant synergistic effects when combined with different therapeutic agents, including 5-fluorouracil (5-FU) [51], erlotinib [52], and bortezomib (BTZ) [33], against various types of cancer cells. GNA could also overcome chemotherapeutic medication resistance in HCC [53], non-small cell lung cancer (NSCLC) [52], and breast cancer [54].

In vivo studies

Various studies have confirmed that GNA has antitumor potential *in vivo*. GNA can counteract tumor growth *in vivo* in various tumor mouse models, such as lung cancer [37], breast cancer [55], and multiple myeloma [33] (▶ **Table 2**). These experiments mostly utilize xenograft models, among which the patient-derived tumor xenograft (PDX) model has emerged as the most trustworthy *in vivo* human cancer model due to its ability to preserve the features of the original patient tumor, such as gene expression profiles and treatment responses [56]. GNA increased the antitumor activity of erlotinib in a fibroblast growth factor receptor (FGFR)-expressing PDX xenograft model [52]. In addition, GNA significantly suppressed tumor growth and progression in the $APC^{min/+}$ mouse model [36] and the azoxymethane (AOM)/dextran sulfate sodium (DSS) mouse model [57]. GNA exerts antitumor effects with low toxicity in animal models. No apoptotic cell death was observed in tissues [37]. Between the vehicle- and GNA-treated groups, there were no appreciable variations in body weight or blood biochemical markers [alanine aminotransferase (ALT) and aspartate aminotransferase AST)] [36].

The antitumor mechanism of gambogenic acid in cancer

GNA blocks cancer development *in vitro* and *in vivo* by inhibiting the proliferation of tumor cells, activating cell cycle arrest, and inducing tumor cell death through different processes (apoptosis, autophagy, necrosis and ferroptosis). GNA also hinders tumor cell invasion and metastasis. Furthermore, GNA increases the sensitivity of cancer cells to chemotherapy and has shown effects on drug resistance in malignancy. We summarized the effectiveness and mechanisms of GNA in different cancers (▶ **Table 3** and **Fig. 3**).

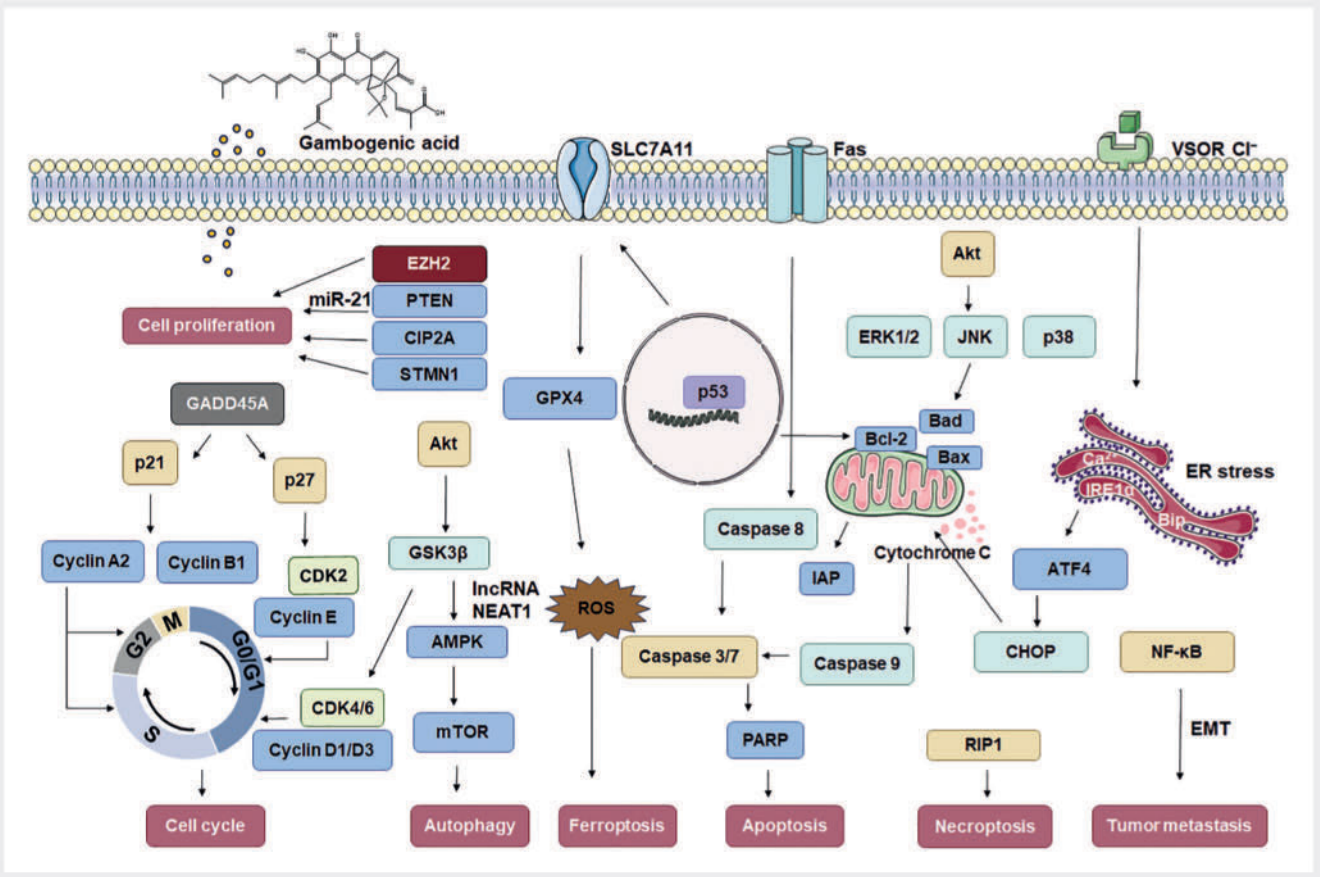
Gambogenic acid target-directed enhancer of zeste homolog 2

EZH2 serves as the enzymatic component within polycomb repressive complex 2 (PRC2), which is responsible for methylating lysine 27 on histone H3. This methylation event ultimately aids in the process of transcriptional silencing, where gene expression is suppressed [58]. Dysregulation of EZH2 causes alterations in gene expression and functions, thereby promoting cancer development. Numerous studies have revealed that both overexpression and mutation of EZH2 have been detected in a wide array of human cancers, spanning from breast cancer, prostate cancer, endometrial cancer, melanoma, bladder cancer, colon cancer, liver cancer, and lung cancer to lymphoma [59]. Elevated levels of EZH2 have been associated with increased tumor cell proliferation, migration, and angiogenesis within tumor tissue. These effects contribute to further deterioration of the tumor tissue, leading to poor prognosis and shorter survival times for patients [60]. Therefore, EZH2 is regarded as a critical oncogene and a potential drug target for various human malignant tumors. Research on antitumor drugs directed at this target has garnered significant attention. From 2012 onwards, numerous EZH2 inhibitors have progressed into clinical trials, reflecting the growing interest in developing therapeutics targeting EZH2 [61, 62].

Wang et al. [32] documented that GNA and its derivatives serve as a novel category of EZH2 inhibitors, functioning through direct and covalent binding with EZH2. This process effectively disrupts the PRC2 complex, thus inhibiting its methyltransferase activity. Additionally, GNA demonstrates superior antitumor effects by not only inhibiting EZH2 enzymatic activity but also facilitating its ubiquitination-mediated degradation, thereby fully suppressing its oncogenic functions.

Gambogenic acid induces cell cycle arrest in cancer cells

The cell cycle plays a crucial role in regulating cell growth, proliferation, and survival. When prompted by extracellular signals, cyclin D is one of the primary proteins to be expressed, which then binds to cyclin-dependent kinases (CDKs) to activate the downstream cascade reaction [63]. GNA markedly arrested the cell cycle at the G0/G1 phase in lung cancer [38], nasopharyngeal carcinoma [46], choroidal melanoma [34], and glioblastoma multiforme cells [47]. Yu et al. [38] showed that GNA is a cyclin D1 inhibitor and induces G1 arrest via glycogen synthase kinase-3beta



▶ **Fig. 3** Mechanisms underlying the antitumor effect of GNA. GNA serves as an inhibitor of EZH2, effectively suppressing tumor cell proliferation through regulating various proteins such as PTEN, CIP2A, and STMN1. Through the activation of p21/p27, GNA modulates downstream cell cycle regulatory proteins like CDK2 and cyclins A2/B1/E, leading to cell cycle arrest. Another mechanism involves GNA inducing cell cycle arrest by inhibiting Akt, thereby impacting CDK4/6 and cyclin D1/D3 through downstream GSK3*β*. GNA's inhibition of Akt also triggers autophagy in tumor cells via the AMPK-mTOR pathway and facilitates mitochondrial apoptosis by modulating the expression of Bcl-2 family proteins. In some tumor cells, GNA also prompts apoptosis through ER stress. Furthermore, GNA activates caspase-8 through Fas, initiating cell apoptosis. In alternative antitumor mechanisms, GNA induces cell ferroptosis via the p53/SLC7A11/GPX4 signaling pathway and induces cell necrosis by activating RIP1, as well as hinders tumor cell migration through the NF-*κ*B-mediated EMT pathway.

(GSK3*β*)-dependent cyclin D1 degradation in the lung cancer cell lines H1975 and H460. GNA arrested the cell cycle at the G1 phase in the cisplatin-resistant lung cancer cell line A549/Cis through the downregulation of cyclin D1, cyclin D3, CDK4, and CDK6 and the upregulation of p21, p53, and growth arrest and DNA damage-inducible *α* (GADD45A) [64]. Meanwhile, GNA arrested A549 cells in the G0/G1 phase and downregulated the expression of cyclin D1 and cyclooxygenase (COX)-2 at the mRNA level [35]. In glioblastoma multiforme, GNA efficiently arrested U251 cells at the G0/G1 phase by specifically repressing the expression of cyclin D1, cyclin E, CDK2, and CDK4 and increasing the expression of p21 and p27 [47].

In addition, GNA could induce G2/M phase arrest in myeloma MM.1S cells [33]. GNA induced G2/M phase arrest in prostate cancer cells through the downregulation of cyclin A2 and cyclin B1 expression levels and the enhancement of p27 expression [43]. GNA also inhibited cell cycle progression in lung cancer and prostate cancer cell lines by inducing arrest at the S phase [37, 43].

Gambogenic acid induces apoptosis in cancer cells

Apoptosis was confirmed to be a crucial pathway in the chemotherapeutic approach to antitumor therapy. Multiple studies have indicated that GNA can hinder proliferation by inducing apoptosis in breast cancer [54], lung cancer [37], colorectal cancer (CRC) [36], bladder cancer [42], prostate cancer [43], gastric cancer [41], HCC [41, 65, 66], multiple myeloma [33], nasopharyngeal carcinoma [46], and glioblastoma multiforme [47]. Among them, most reports are on GNA-induced apoptosis in lung cancer cells. GNA facilitated the apoptosis of lung cancer cells in a dose- and time-dependent manner, a process associated with the modulation of proteins involved in apoptosis pathways in A549 [35, 41, 51, 67, 68], H446, and H1688 cells [37]. Caspase-3, -7, -8, and -9, Bcl-2 associated X (Bax), and cytochrome c were upregulated, while the B-cell lymphoma 2 (Bcl-2) protein was downregulated. The hallmark of apoptosis, poly(ADP-ribose) polymerase (PARP), which is associated with DNA repair, and p53 proteins were significantly increased by GNA treatment in lung cancer cell lines [37]. GNA was also able to significantly increase the activation of cas-

▶ **Table 1** Antitumor effect of GNA *in vitro*.

Cancer	Cell type	Concentration range (μM)	IC_{50} values (μM)/ duration	Antitumor effect	Refs.
Breast cancer	MCF-7, MCF-7/ADR	0.06–31.73		Apoptosis	[54]
	MDA-MB-231	0.32–4.76	1.24/72 h	Apoptosis	[39]
	4 T1	0.78–310.00	7.57/24 h	Cytotoxicity	[55]
Lung cancer	H446	0.62–2.40	1.40/48 h	Apoptosis	[37]
	H1688	1.20–3.20	2.40/48 h		
	H1975, H460	0.50–10.00	~ 2.50/48 h	Autophagy	[38]
	HCC827		1.33/72 h	Proliferation inhibition	[52]
	HCC827/ER		1.51/72 h		
	H1650		0.91/72 h		
	A549	1.50–12.00		Autophagy	[74]
	A549	0.32–39.68		Cytotoxicity	[40]
	A549	0.32–32.00		Apoptosis	[67]
	A549	0.31–10.00	2.50/24 h		[35]
	A549		2.83/24 h	Apoptosis, necroptosis	[51]
	A549		8.07/24 h	Apoptosis	[41]
	A549		7.00/48 h	Autophagy	[38]
	A549	0.50–8.00	2.00/72 h	Apoptosis	[68]
	A549/Cis	0.50–6.00		Apoptosis	[64]
Hepatic carcinoma	HepG2	0.75–12.00	3.23/24 h, 2.62/ 48 h, 2.14/72 h	Apoptosis	[44]
	HepG2	0.50–4.00		Proliferation inhibition	[50]
	HepG2	0.32–32.00	10.27/24 h	Apoptosis	[95]
	HepG2	0.32–16.00	3.40/48 h	Proliferation inhibition	[53]
	HepG2	7.94–39.68	11.16/24 h	Cytotoxicity	[93]
	HepG2	0.51–16.43	15.70/24 h	Cytotoxicity	[92]
	HepG2		10.71/24 h	Apoptosis	[41]
	HepG2	0.78–15.50	7.43/24 h	Cytotoxicity	[94]
	HepG2	0.50–16.00	4.40/48 h	Cytotoxicity	[91]
	HepG2			Apoptosis	[66]
	HepG2	1.59–50.79	7.94–9.52/48 h	Apoptosis	[96]
	HepG2	1.00–8.00	3.90/48 h	Proliferation inhibition	[77]
	HepG2/ADR	0.32–16.00	7.19/48 h	Proliferation inhibition	[53]
	Hepa 1–6	0.16–5.08	1.27–1.59/48 h	Apoptosis	[96]
	BEL-7402/ADR	1.00–32.00		Apoptosis, autophagy	[70]
	Bel-7402	0.54–4.00		Proliferation inhibition	[50]
	SMMC-7721	1.00–16.00	10.68/24 h	Apoptosis	[65]

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▶ **Table 1** *Continued*

Cancer	Cell type	Concentration range (μM)	IC_{50} values (μM)/ duration	Antitumor effect	Refs.
Melanoma	A375	1.00–16.00	2.88/24 h	Ferroptosis, autophagy	[73]
	A2058	1.00–16.00	1.26/24 h		
	B16	0.50–8.00	2.09/24 h		
	B16F10	0.50–8.00	1.00/24 h		
	A375, A2058	1.00–16.00		Ferroptosis, metastasis inhibition	[45]
	B16, B16F10	0.10–4.00		Metastasis inhibition	[81]
	OCM-1	0.75–6.00		Proliferation and metastasis inhibition	[34]
Multiple myeloma	MM.1S		1.75/24 h, 0.90/ 48 h, 0.84/72 h	Apoptosis	[33]
	U266	0.10–1.60		Apoptosis, proliferation inhibition	[78]
Colorectal cancer	HCT116	0.50–3.00	1.88/24 h, 1.48/48 h	Apoptosis, proliferation inhibition	[36]
	SW620	0.50–3.00	2.83/24 h, 1.81/48 h		
	DLD-1	0.50–3.00	1.97/24 h, 1.55/48 h		
	HCT116	0.50–5.00		Apoptosis	[57]
	HCT116, HT29	0.50–5.00		Ferroptosis, proliferation inhibition	[77]
Bladder cancer	BIU-87, T24, J82	0.75–3.00		Apoptosis, metastasis inhibition	[42]
Prostate cancer	PC3, DU145	2.00–12.00		Apoptosis, autophagy	[43]
Nasopharyngeal carcinoma	CNE-1	0.25–8.00	1.87/72 h	Apoptosis	[46]
	CNE-2Z	0.25–8.00	2.25/24 h, 1.33/48 h	Apoptosis	[72]
Glioblastoma multiforme	U251	0.75–6.00		Apoptosis, metastasis inhibition	[47]
Epithelial cancer	HN-6			Proliferation inhibition	[32]
Gastric cancer	SGC-7901		16.15/24 h	Apoptosis	[41]
Cervical cancer	HeLa	0.10–1.59		Cytotoxicity	[40]
	HeLa	1.50–12.00		Autophagy	[74]
Leukemia	K562		3.83/44 h	Cytotoxicity	[49]
	K562/ADR		4.78/44 h		
Osteosarcoma	143B	0.25–8.00	1.18/24 h	Apoptosis, ferroptosis, metastasis inhibition	[48]
	HOS	0.25–8.00	1.10/24 h		

▶ **Table 2** Antitumor effect of GNA *in vivo*.

Cancer	Animal model type	Dose (mg/kg)	Route	Duration	Antitumor effect	Molecular mechanism	Refs.
Breast cancer	4 T1 xenograft	24.0	i. g.	23 days	Tumor growth and weight ↓		[55]
	MDA-MB-231 xenograft	4.0, 8.0, 12.0		16 days	Tumor growth and weight ↓		[39]
Lung cancer	NCI-H446 xenograft	4.0, 12.0	i. v.	14 days	Tumor growth and weight ↓	Apoptosis ↑	[37]
	A549 xenograft	7.5, 30.0	i. g.	14 days	Tumor growth and weight ↓		[85]
	A549 xenograft	1.5	i. p.	14 days	Tumor growth and weight ↓		
	A549 xenograft	16.0	i. v.		Tumor growth and weight ↓	LC3-II/I ↑, p62 ↑	[74]
	HCC827/ER xenograft	10.0	i. p.	27 days	Tumor growth and weight ↓	FGFR signaling pathway ↓	[52]
	PDX model	7.5	i. p.	22 days			
	A549 xenograft	8.0, 16.0, 32.0	i. p.	2 weeks	Tumor growth ↓	Apoptosis ↑	[35]
Melanoma	B16F10 xenograft	2.0, 4.0, 8.0	i. p.	18 days	Tumor growth and weight ↓		[73]
	B16F10 xenograft	2.0, 4.0, 8.0	i. p.	22 days	Tumor growth and weight ↓, pulmonary metastasis ↓	EMT ↓	[81]
Multiple myeloma	MM.1S xenograft	2.0	i. v.	2 weeks	Tumor growth and weight ↓	Apoptosis ↑	[33]
	U266 xenograft	5.0	i. v.	14 days	Tumor growth and weight ↓	microRNA-21/PTEN ↓	[78]
Colorectal cancer	HCT116 xenograft	1.0, 2.0	i. p.	21 days	Tumor growth ↓	IRE1α/JNK ↑, Noxa-induced apoptosis ↑	[36]
	HCT116 xenograft	4.0	i. p.	21 days	Tumor growth and weight ↓		[77]
	$APC^{min/+}$ model	1.0, 2.0	i. p.	2 months	Number and size of intestinal polyps ↓		[36]
	AOM/DSS mouse model				Colon length ↑	BiP ↑, CHOP ↑	[57]
Prostate cancer	PC3 xenograft	4.0	i. p.	25 days	Tumor growth and weight ↓	PCNA ↓, PARP ↑, LC3 ↑, p-IRE1 ↑, p-JNK ↑, Nrf2 ↑	[43]
Hepatic carcinoma	Hepa1-6 xenograft	4.0	i. v.	12 days	Tumor growth and weight ↓		[96]
Osteosarcoma	143B xenograft	30.0, 60.0	i. g.	3 weeks	Tumor growth ↓	GPX4 ↓, caspase-3 ↑	[48]

AOM, azoxymethane; APC, adenomatous polyposis coli; BiP, immunoglobulin heavy chain-binding protein; CHOP, C/EBP-homologous protein; DSS, dextran sulfate sodium; FGFR, fibroblast growth factor receptor; GPX4, glutathione peroxidase 4; IRE1, inositol-requiring enzyme 1; JNK, c-Jun N-terminal kinase; Nrf2, nuclear factor E2-related factor 2; PARP, poly(ADP-ribose) polymerase; PCNA, proliferating cell nuclear antigen; PDX, patient-derived xenograft; PTEN, phosphatase and tensin homolog

▶ **Table 3** Molecular mechanisms underlying antitumor activities of GNA.

Effect	Cancer type	Molecular mechanism	Refs.
G0/G1 phase arrest	Lung cancer	cyclin D1, D3 ↓, CDK 4, 6 ↓, COX-2 ↓, GSK3β ↓, p21 ↑, p27 ↑, GADD45A ↑, p53 ↑	[35, 38, 64]
	Glioblastoma multiforme	cyclin D1, E ↓, CDK 2, 4 ↓, p21 ↑, p27 ↑, GSK3β ↓, Akt ↓	[47]
	Choroidal melanoma	cyclin D1, E ↓, CDK 2 ↓	[34]
	Nasopharyngeal carcinoma		[46]
G2/M phase arrest	Prostate cancer	cyclin A2, B1 ↓, p27 ↑	[43]
	Multiple myeloma		[33]
S phase arrest	Lung cancer	p53 ↑	[37]
	Prostate cancer	cyclin A2, B1 ↓, p27 ↑	[43]
Apoptosis	Lung cancer	caspase-3, -7, -8, -9 ↑, PARP ↑, cytochrome c ↑, Bax ↑, Bcl-2 ↓, p53 ↑, p38 ↓, MAPK ↓	[35, 37, 41, 51, 64, 67, 68]
	Hepatic carcinoma	caspase-3, -9 ↑, Bax ↑, Bcl-2 ↓, ROS ↑, p-p38 ↑, p-ERK1/2 ↓	[41, 44, 65, 66, 70]
	Breast cancer	caspase-3, -8, -9 ↑, Fas ↑, Bax ↑, Bcl-2 ↓	[39, 54]
	Multiple myeloma	caspase-3 ↑, PARP ↑, p53 ↑, Bax ↑, Bcl-2 ↓	[33, 78]
	Colorectal cancer	caspase-3, -8, -9 ↑, PARP ↑, ROS/IRE1α/JNK ↑, Aurora A ↓	[36, 57]
	Nasopharyngeal carcinoma	caspase-9 ↑, cytochrome c ↑, Ca^{2+} ↑, Bax ↑, Bad ↑, Bcl-2 ↓, Akt ↓, VSOR·Cl^- channels ↑	[46, 72]
	Glioblastoma multiforme	caspase-3 ↑, Akt ↓	[47]
	Gastric cancer	caspase-3, -9 ↑, Bax ↑, Bcl-2 ↓	[41]
	Osteosarcoma	caspase-3, -9 ↑, Bax ↑, Bcl-2 ↓, p53 ↑	[48]
	Prostate cancer	PARP ↑, Bax ↑, Bcl-2 ↓, JNK/c-JUN ↑, ROS ↑	[43]
	Bladder cancer	cIAP2 ↓, XIAP ↓, Survivin ↓	[42]
Ferroptosis	Melanoma	SLC7A11/GPX4 ↓, lncRNA NEAT1 ↓	[45, 73]
	Osteosarcoma	SLC7A11/GPX4 ↓	[48]
	Colorectal cancer	Target the miR-1291/FOXA2 and AMPKα/SLC7A11/GPX4 axis	[77]
Necroptosis	Lung cancer	RIP1 ↑	[51]
Autophagy	Lung cancer	LC3-II/I ↑, p62 ↑, Beclin1 ↑, Akt/mTOR ↓, GSK3β ↓	[38, 74]
	Hepatic carcinoma	LC3-II/I ↑, p62 ↑, Beclin1 ↑	[70]
	Melanoma	AMPK/mTOR ↓, lncRNA NEAT1 ↓	[73]
	Prostate cancer	JNK/c-JUN ↑, p62 ↑	[43]
Proliferation inhibition	Hepatic carcinoma	CIP2A ↓, STMN1 ↓	[50, 77]
	Multiple myeloma	microRNA-21/PTEN ↓	[78]
	Colorectal cancer	c-Myc ↓, PCNA ↓	[36]
	Choroidal melanoma	PI3K/Akt ↓	[34]
Metastasis inhibition	Melanoma	EMT ↓	[34, 45]
	Melanoma	EMT ↓, lncRNA MEG3 ↑	[81]
	Bladder cancer	NF-κB ↓	[42]
	Glioblastoma multiforme		[47]
	Osteosarcoma		[48]
Synergistic effect	Lung cancer (Erlotinib)	FGFR signaling pathway ↓	[52]
	Lung cancer (5-Fluorouracil)	ROS-mitochondria pathway ↑	[51]
	Multiple myeloma (Bortezomib)	apoptosis ↑	[33]

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▶ **Table 3** *Continued*

Effect	Cancer type	Molecular mechanism	Refs.
Reversal drug resistance	Lung cancer (Erlotinib)	FGFR signaling pathway ↓	[52]
	Lung cancer (Cisplatin)	apoptosis ↑	[64]
	Liver cancer (Adriamycin)	P-gp ↓ , MAPK ↓ , NF-κB ↓	[53]
	Breast cancer (Adriamycin)	PTEN/PI3K/Akt ↓	[54]
	Hepatic carcinoma (Adriamycin)	basal autophagy ↓	[70]

AMPK, AMP-activated protein kinase; Bad, Bcl-2-associated death; Bax, Bcl-2 associated X; Bcl-2, B-cell lymphoma 2; CDKs, cyclin-dependent kinases; cIAP2, cellular inhibitor of apoptosis 2; CIP2A, cancerous inhibitor of protein phosphatase 2A; COX, cyclooxygenase; EMT, epithelial-to-mesenchymal transition; ERK1/2, extracellular signal-regulated kinase 1/2; FGFR, fibroblast growth factor receptor; FOXA2, forkhead box protein A2; GADD45A, growth arrest and DNA damage-inducible α; GPX4, glutathione peroxidase 4; GSK3β, glycogen synthase kinase-3beta; IRE1, inositol-requiring enzyme 1; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEG3, maternally expressed gene 3; mTOR, mammalian target of rapamycin; NEAT1, nuclear-enriched abundant transcript 1; NF-κB, nuclear transcription factor-kappa B; PARP, poly(ADP-ribose) polymerase; PCNA, proliferating cell nuclear antigen; P-gp, P-glycoprotein; PI3K, the phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; RIP1, receptor-interacting protein 1; ROS, reactive oxygen species; STMN1, stathmin 1; VSOR · Cl^-, volume-sensitive outwardly rectifying chloride; XIAP, X-linked inhibitor of apoptosis

pase-3 and caspase-7 in addition to the cleavage of PARP, in the cisplatin-resistant NSCLC cell line A549/Cis [64].

Apoptosis encompasses three pathways: (1) the death receptor or extrinsic pathway, (2) the mitochondrial or intrinsic pathway, and (3) the endoplasmic reticulum pathway. The mitochondrial apoptotic pathway serves as a significant cellular death pathway, involving death receptors initiating apoptosis from the cell surface, Bcl-2 family members acting as the guardians of the mitochondrial pathway, and caspases-3, -7, and − 9 as the executor enzymes [69]. Many studies have reported that GNA induces mitochondria-dependent apoptosis in various cancers, such as HCC [41, 70], osteosarcoma [48], multiple myeloma [33], nasopharyngeal carcinoma [46], breast cancer [54], gastric cancer [41], CRC [36], prostate cancer [43], and lung cancer [41, 51]. The p38 mitogen-activated protein kinase (MAPK) cascade inhibits apoptosis. GNA induced mitochondria-dependent apoptosis via the extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 MAPK pathways in human hepatoma HepG2 cells and lung cancer A549 cells [44, 68]. Yan et al. [46] stated that GNA induces apoptosis through mitochondrial oxidative stress, and its molecular mechanisms are linked to the generation of ROS, intracellular calcium overload, and inactivation of the Akt signaling pathway in nasopharyngeal carcinoma CNE-1 cells. Noxa, a proapoptotic member of the Bcl-2 protein family, induces Bax-mediated mitochondrial dysfunction through indirect inhibition of other Bcl-2 family members. GNA induced Noxa-mediated apoptosis by inducing reactive oxygen species (ROS) generation and c-Jun N-terminal kinase (JNK) activation in CRC both *in vitro* and *in vivo* [36]. Zhou et al. [39] confirmed that GNA could effectively suppress breast cancer MDA-MB-231 cell growth by mediating apoptosis not only through the mitochondrial pathway but also through the Fas/FasL death receptor pathway *in vitro* and *in vivo*.

ROS overproduction induces the accumulation of misfolded proteins in the endoplasmic reticulum (ER), subsequently leading to ER stress [71]. GNA increased the expression of the ER stress-associated proteins p-IRE1, immunoglobulin heavy chain-binding protein (BiP), and C/EBP-homologous protein (CHOP) in prostate cancer cells [43]. GNA triggers ER stress-mediated apoptosis through the ROS/inositol-requiring enzyme 1 (IRE1α)/c-Jun JNK signaling pathway in CRC [36] and triggers apoptosis via BiP, activating transcription factor 4 (ATF4), and CHOP in nasopharyngeal carcinoma [72]. Liu et al. [57] showed that GNA inhibited CRC proliferation by activating ER stress *in vitro* and *in vivo* and triggered ER stress by regulating Aurora A. GNA can activate volume-sensitive outwardly rectifying chloride (VSOR · Cl^-) channels, leading to ER stress, inducing apoptosis, and inhibiting proliferation in CNE-2Z cells [72].

Moreover, GNA treatment significantly inhibited the expression of antiapoptotic proteins, including cellular inhibitor of apoptosis 2 (cIAP2), X-linked inhibitor of apoptosis (XIAP), and survivin, in bladder cancer cells [42]. The proapoptotic effect of GNA on U251 glioblastoma cells was shown to be mediated through inactivation of the Akt pathway [47]. Furthermore, GNA-mediated inactivation of EZH2 led to elevated expression of the proapoptotic protein Bim, which is a well-characterized EZH2 downstream transcriptional target [32].

Gambogenic acid induces autophagy in cancers

Autophagy, a self-degradation mechanism, plays a critical role in maintaining cellular homeostasis during stress and exhibits complex, dual roles in both tumorigenesis and cancer development. On the one hand, GNA induces "autophagic cell death", which is also known as type II programmed cell death, in lung cancer [38], prostate cancer [43], and melanoma [73]. GNA induces autophagy in lung cancer cells, possibly due to activation of GSK3β and inactivation of the Akt/mammalian target of rapamycin (mTOR) signaling pathway [38]. GNA autophagy in melanoma cells could be induced by inhibiting the activation of AMP-activated protein kinase (AMPK) by long non-coding RNA (lncRNA) nuclear-enriched abundant transcript 1 (NEAT1), indirectly inhibiting the phosphorylation of downstream mTOR proteins [73]. GNA induces apoptosis and autophagy through ROS-mediated ER stress via the JNK signaling pathway in prostate cancer cells [43].

On the other hand, the levels of autophagy in tumor cells can influence cellular resistance. Inhibition of autophagy can reverse drug resistance in cancer cells, potentially increasing the effectiveness of chemotherapy. GNA inhibits protective autophagy in BEL-7402/ADR HCC cells [70]. Furthermore, GNA has the ability to impede the fusion of autophagosomes with lysosomes by inhibiting lysosomal acidification. This dysfunctional autophagy contributes to the pro-death role in GNA-mediated lung cancer cell death [74].

Gambogenic acid induces necroptosis and ferroptosis in cancers

Necroptosis, a form of programmed cell death, differs from apoptosis in that it does not engage key apoptosis regulators, such as Bcl-2 family members. In this pathway, receptor interacting protein 1 (RIP1) is a specific target associated with necroptosis [75]. The combination of GNA and 5-FU induced cell death in A549 cells by activating caspase-independent necroptosis [51].

Ferroptosis, a mode of regulated necrosis that is dependent on iron, has emerged as a novel form of cell death. The three core features of ferroptosis include sufficient polyunsaturated fatty acid phospholipid oxidation, the concentration of active iron, and the loss of lipid peroxidation [76]. GNA induced ferroptosis in osteosarcoma cells [48] and transforming growth factor beta (TGF-β)1-stimulated melanoma cells via the p53/SLC7A11/glutathione peroxidase 4 (GPX4) signaling pathway [45]. Furthermore, GNA downregulated lncRNA NEAT1, which can weaken the direct binding of SLC7A11, indirectly leading to inhibition of GPX4 activity and subsequent ferroptosis in melanoma cells [73]. In addition, GNA inhibited proliferation and ferroptosis by targeting the microRNA-1291 (miR-1291)/FOXA2 and AMPKα/SLC7A11/GPX4 axis in CRC [77].

Other pathways by which gambogenic acid inhibits the proliferation of cancer cells

By using a proteomics approach, Wang et al. [78] identified that stathmin 1 (STMN1) might be a major molecular target by which GNA inhibits HCC cell proliferation. Meanwhile, GNA was identified as a cancerous inhibitor of protein phosphatase 2A (CIP2A) inhibitor that interferes with the ubiquitination and destabilization of CIP2A and showed potent antiproliferative activity and enhanced the effect of chemotherapeutic agents against HCC by suppressing the CIP2A-Akt pathway [50]. Li et al. [34] reported that GNA may inhibit choroidal melanoma cell growth via inhibition of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway.

In addition, microRNA-21 (miR-21) has been found to be overexpressed in multiple myeloma patients and associated with the occurrence and development of multiple myeloma. GNA inhibited tumor proliferation in hypoxic multiple myeloma cells by regulating the miR-21/phosphatase and tensin homolog (PTEN) pathway [79].

Gambogenic acid inhibits the metastasis of cancer cells

Extensive invasion and migration into surrounding tissue are hallmark characteristics of cancer, making these lesions resistant to definitive surgical treatment. The wound healing assay showed that the addition of nondeath-inducing concentrations of GNA significantly reduced the migration ability of U251 glioblastoma cells [47]. Transwell invasion assays showed that GNA decreased the invasive ability of osteosarcoma 143B and HOS cells [48]. GNA could remarkably impede the migration and invasion abilities of bladder cancer cells by inhibiting the nuclear transcription factor-kappa B (NF-κB) signal transduction pathway [42].

Epithelial-to-mesenchymal transition (EMT) denotes the process through which polar epithelial cells transform into stromal cells with migratory capacity, and it represents a crucial mechanism associated with the invasive and migratory capabilities of tumor cells [80]. GNA inhibits invasion, metastasis, and EMT in OCM-1 choroidal melanoma cells and TGF-β1-treated A375 melanoma cells [34, 45]. GNA could also improve EMT by upregulating the expression of lncRNA MEG3, thereby inhibiting melanoma metastasis *in vitro* and *in vivo* [81].

Gambogenic acid shows synergistic effects in cancers

Combination therapy is a pharmaceutical regimen involving the use of multiple drugs to treat a disease, aiming to achieve higher response rates than a single treatment. 5-FU is a widely used chemotherapeutic drug for various cancer treatments. GNA combined with 5-FU induced cell death caused by apoptotic and necroptotic mechanisms via the ROS-mitochondrial pathway in A549 cells [51]. Erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, was approved by the FDA as a first-line treatment for metastatic NSCLC patients with EGFR mutations. GNA enhances the antitumor activity of erlotinib through the FGFR signaling pathway [52]. BTZ is one of the most widely used agents in the current therapy for multiple myeloma. BTZ and GNA combination treatment resulted in a strong synergistic action against the MM.1S cell line *in vitro* and *in vivo* [33].

Gambogenic acid reverses the effect on drug resistance in cancers

Drug resistance is a major obstacle in chemotherapy. GNA has been revealed to have a potent inhibitory effect on cell growth in the cisplatin-resistant NSCLC cell line A549/Cis by blocking the cell cycle and inducing apoptosis [64]. In addition, GNA treatment increased the chemosensitivity of breast cancer cells to adriamycin (ADR) by suppressing the PTEN/PI3K/Akt pathway, which led to apoptosis in MCF-7/ADR-resistant cells [54]. GNA may enhance ADR sensitivity and promote ADR-induced apoptosis by inhibiting basal autophagy levels in BEL-7402/ADR HCC cells [70]. Studies have shown that GNA can reverse the multidrug resistance of HepG2/ADR cells by inhibiting the expression of P-glycoprotein (P-gp), which may result from the inhibition of the NF-κB and MAPK pathways [53]. GNA efficiently overcomes erlotinib resistance in NSCLC *in vitro* and *in vivo* by inhibiting the FGFR signaling pathway [52].

Pharmacokinetic study of gambogenic acid

It is well known that the bioavailability of drugs can vary with different administration methods, and GNA is not an exception. The area under the plasma concentration-time (AUC) values after oral administration are very low compared with those after intravenous injection administration of GNA [82, 83]. GNA and GA were found to have poor absorption, and their pharmacokinetic parameters were similar, suggesting that minor changes in the positions of the substituent groups of the alkyl side chain do not sig-

▶ **Table 4** Drug delivery systems of GNA.

Delivery systems	Labels	Cancer type	Cancer cell	IC_{50} values	Refs.
Nanoparticles	GNA-PDA-FA SA NPs	Breast cancer	4 T1	2.58 μM	[55]
	GNA-Zein-PDA NPs	Hepatic carcinoma	HepG2	1.59 μg/mL	[92]
	GNA-Zein-NPs				[90]
	FA-GNA-MNPs	Cervical cancer	HeLa		[40]
	GNA-SLNs				[86]
	CRNP-GNA	Hepatic carcinoma	HepG2, Hepa 1–6		[96]
Nanostructured lipid carrier	GNA-PEG-NLC				[87]
Nanosuspensions	GNA-NS	Hepatic carcinoma	HepG2	2.22 μM	[91]
Cubs	GNA-Cubs	Hepatic carcinoma	SMMC-7721	4.25 μM	[65]
Nonionic surfactant vesicles	FA-GNA-NISVs	Lung cancer	A549		[67]
	PEG-GNA-NISVs				[89]
Micelles	GNA-PAA-b-PCL micelles	Hepatic carcinoma	HepG2	5.04 μg/mL	[93]
	GNA-mPEGPCL/mPEG-PLA mixed micelles	Hepatic carcinoma	HepG2		[66]
	GNA-PLC micelles	Hepatic carcinoma	HepG2	4.53 μM	[94]
Liposomes	GNA-PEG-LPs	Hepatic carcinoma	HepG2	5.16 μM	[41]
	GNA-PEG-LPs	Gastric cancer	SGC-7901	7.66 μM	[41]
	GNA-PEG-LPs	Lung cancer	A549	4.83 μM	[41]
	GNA-PEI/siRNA-liposome	Hepatic carcinoma	HepG2	3.28 μg/mL	[95]
	PEG-GNA-L				[88]

nificantly impact the *in vivo* distribution of the compounds [82]. Moreover, the maximum plasma concentration (C_{max}) of GNA increased significantly after processing, which showed a processing influence on the absorption of GNA [84].

Regarding tissue distribution after oral administration, GNA was distributed widely and rapidly in rats and was mainly distributed in the stomach, small intestine, and liver and less distributed in spleen tissues [85]. The cytochrome P450 (CYP450) superfamily is usually considered the most important phase I drug-metabolizing enzyme system. GNA increased the activity of liver CYP1A2, CYP2E1, CYP2C, and CYP3A [86, 87]. Therefore, when GNA is administered with other drugs, potential drug-drug interactions mediated by CYP1A2, CYP2E1, CYP2C, and CYP3A induction should be taken into consideration.

Drug delivery system of gambogenic acid in cancers

GNA can inhibit the initiation and progression of many cancers. However, its poor aqueous solubility, short elimination half-life, low bioavailability, and excessive irritation to blood vessels by intravenous administration could reduce its antitumor activities. Therefore, various strategies have been developed to improve GNA bioavailability and enhance its antitumor activities (▶ **Table 4**). These techniques mainly include diverse novel drug delivery systems such as solid lipid nanoparticles [88], long circulation lipid nanoparticles [89], PEGylated liposomes [90], PEGylated niosomes [91], and zein nanoparticles [92].

Many researchers have developed GNA-loaded drug delivery systems for the treatment of liver cancer. Luo et al. [65] prepared GNA-loaded cubosomes (GNA-Cubs), which showed higher *in vitro* cytotoxicity and higher cellular uptake against HCC SMMC-7721 cells. Yuan et al. [93] developed GNA nanosuspensions (GNA-NS) with PVPK30 and PEG2000 as stabilizers. Compared to GNA solution, GNA-NS exerted a much slower *in vitro* dissolution rate and enhanced cytotoxicity in HCC HepG2 cells. Tang et al. [41] prepared GNA-loaded PEGylated liposomes (GNA-PEG-LPs), which showed enhanced cytotoxicity against lung cancer (A549), gastric cancer (SGC-7901), and HCC (HepG2) cells and induced apoptosis via the mitochondrial pathway *in vitro* and *in vivo*. Cheng et al. [92] illustrated that GNA-loaded zein nanoparticles (GNA-Zein-NPs) showed hepatic targeting properties. Zha et al. [94] further proposed polydopamine (PDA)-coated GNA-loaded zein nanoparticles (GNA-Zein-PDA NPs), which had higher inhibitory activity on HepG2 cells. Compared with the above nanocarriers, polymeric micelles have great potential for the solubilization of poorly water-soluble drugs. Liu et al. [95] reported GNA-loaded polymeric micelles based on pH-responsive copolymers, which delivered the highest drug loading efficiency (DLE) and drug loading capacity (DLC) value, enhancing both the cytotoxicity and cel-

lular uptake against HepG2 cells. Lin et al. [66] demonstrated that GNA-loaded mixed polymeric micelles (GNA-MMs) featured a small size and high entrapment efficiency and maintained the cytotoxicity of GNA on HepG2 cells. Wang et al. [96] presented GNA-phospholipid complex (GNA-PLC) micelles. GNA has a higher cytotoxic effect on HepG2 cells after forming GNA-PLC micelles.

Preliminary studies have indicated that liver cancer cells express high levels of vascular endothelial growth factor (VEGF), a key component that fosters the proliferation of vascular endothelial cells. Yu et al. [97] developed a lipopolyplex delivery system composed of anionic liposomes and polyethylenimine complexes to codeliver GNA and VEGF siRNA to HepG2 cells. VEGF-siRNA could mediate VEGF silencing through a lipopolyplex delivery system. The combination of the two drugs increased cell sensitivity and further promoted cell apoptosis. Du et al. [98] demonstrated that GNA was an anti-vascular agent with dual pathways of antiangiogenesis and vascular disruption and reported charge-reversible nanoparticles of GNA for self-augmented accumulation and antitumor efficacy by inducing a positive feedback loop between enhanced tumor vascular permeability and improved accumulation of GNA in tumors.

In addition, Wang et al. [55] encapsulated and stabilized GNA in polydopamine nanoparticles (PDA-NPs), which further modified the surface of the particles with folic acid (FA) and finally coated it with sodium alginate (SA) to form GNA@PDA-FA SA NPs, where FA was used as an active targeting ligand due to its high specific binding with folate receptors, making it easily taken up by 4 T1 cells, while SA was used to prevent the modified nanoparticles from being degraded by the gastric fluid when taken orally. Compared with GNA, GNA@PDA-FA SA NPs exhibited a higher anti-breast cancer therapeutic effect *in vivo* and *in vitro*. Huang et al. [40] synthesized GNA-loaded FA-armed magnetic and superparamagnetic nanoparticles (MNPs), which exhibited substantial inhibitory effects in folate receptor-expressing HeLa cancer cells. Lin et al. [67] developed FA-modified nonionic surfactant vesicles (NISVs, niosomes) as carrier systems for the targeted delivery of GNA. The FA-GNA-NISVs prolonged the residence time of GNA in blood circulation, increased accumulation in the lung, and enhanced cytotoxicity against A549 cells by inducing apoptosis.

Conclusion and Further Directions

Bioactive compounds derived from natural sources are acknowledged for their potential in preventing various human diseases, including cancer. One such compound, GNA, a derivative of GA extracted from *G. hanburyi*, has demonstrated promising antitumor activity in lung, liver, colorectal, breast, gastric, bladder, and prostate cancers. Research has highlighted its ability to induce apoptosis, necroptosis, ferroptosis, and autophagy as well as cell cycle arrest and inhibition of metastasis across multiple cancer cell lines. GNA has also shown promise in increasing the sensitivity of tumor cells to chemotherapy and in reversing chemotherapy resistance.

However, it should be noted that Pesonen et al. [99] cautioned against the potential negative impact of GNA on cancer therapies due to its ability to induce a strong heat shock response. Furthermore, the information regarding the effects and potential applications of GNA mentioned earlier is primarily based on animal and *in vitro* experiments, while clinical study is lacking. Therefore, to promote its development for acceptable clinical application, future research should consider focusing primarily on the following aspects: (1) carrying out in-depth research on its antitumor molecular targets and mechanism, (2) performing more *in vivo* experiments to clarify its safety, (3) expanding the clinical use of GNA through chemical structure modification and combination with other drugs, and (4) conducting more investigations on the drug delivery system of GNA to improve its oral bioavailability. Overall, this study provides a comprehensive review of the antitumor effects and mechanisms, pharmacokinetic properties, and nanotechnology-mediated delivery of GNA and thus serves as a valuable resource for researchers exploring the potential of GNA as a promising candidate for treating various types of cancers.

Contributors' Statement

Data collection and analysis: L. Mi, Z. C. Xing, and Y. J. Zhang, T. He; design of the study: L. Mi, Z. H. Li, and W. S. Wu; drafting the manuscript: L. Mi, Z. C. Xing, Y. J. Zhang, T. He, A. P. Su, and T. Wei; critical revision of the manuscript: L. Mi, Z. H. Li, and W. S. Wu.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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