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EDITED BY

Debasish Bandyopadhyay,
The University of Texas Rio Grande Valley,
United States

REVIEWED BY

Kulbhushan Thakur,
University of Delhi, India
Ziad Joha,
Sivas Cumhuriyet University, Türkiye

*CORRESPONDENCE

Binyan Lin,
✉ kl089@anjucm.edu.cn
Qin Zhu,
✉ 815024@anjucm.edu.cn

[†]These authors have contributed equally to
this work

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Antitumor effects and mechanisms of traditional Chinese medicine gamboge: A review

Yanqing Zhou^{1,2†}, Jialing Chen^{1†}, Qin Zhu^{3*} and Binyan Lin^{1*}

¹School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, China, ²School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, China, ³Experiment Center of Science and Technology, Nanjing University of Chinese Medicine, Nanjing, China

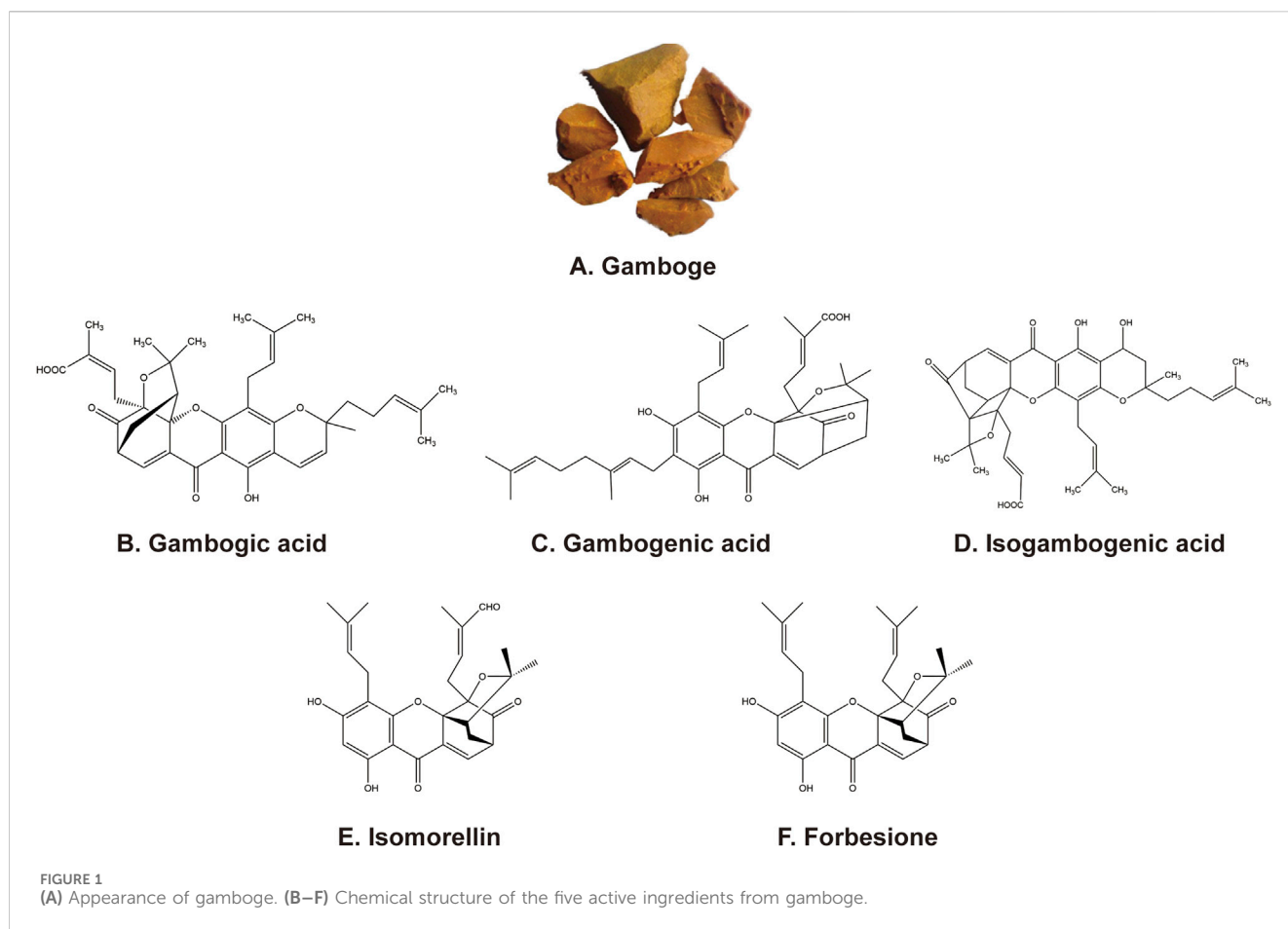
Traditional Chinese medicine (TCM) gamboge is a dried resin obtained from *Garcinia hanburyi* Hook f. For over 500 years, TCM gamboge has been used to treat scrofula, carbuncle, jaundice, furuncle, and other chronic and stubborn diseases. An increasing amount of evidence has proven the significant anticancer properties of the main active ingredients from gamboge in recent years. The ingredients of gamboge, such as gambogic acid (GA) and gambogenic acid (GNA), can inhibit tumor growth through various processes, including apoptosis induction, cell cycle arrest, tumor cell invasion and migration inhibition, and autophagy regulation. In this review, we elaborate on the role of the main active ingredients of gamboge in treating cancers. It would be enlightening to provide the possible therapeutic applications of gamboge in the clinic.

KEYWORDS

gamboge, antitumor, gambogic acid, gambogenic acid, traditional Chinese medicine

1 Introduction

Cancer is one of the leading causes of death worldwide, with a high incidence and mortality rate. As estimated by the American Cancer Society, there are 1,958,310 new cancer cases, and 609,820 cancer deaths are anticipated to occur in the United States in 2023 (Siegel et al., 2023). Surgery, radiotherapy, conventional chemotherapy, hormone therapy, immunotherapy, and targeted therapies are the main clinical treatment ways for cancer treatment. Additional therapy methods are also explored and applied. However, drug-related toxicities such as hair loss; heart, kidney, or nerve toxicity; infertility; and drug resistance caused additional challenges (Haque et al., 2021). Therefore, it is urgent to find an effective but low-toxicity drug. Many traditional Chinese medicines (TCMs) have been recorded in Chinese antiquarian books for their effectiveness in treating canker sores and erysipelas. These diseases represent inflammation or cancer in contemporary medical science. Moreover, a variety of TCMs (Wang Y. et al., 2020), including *Rhodiola rosea* (Loo et al., 2010; Rong et al., 2020), *Astragalus membranaceus* (Auyeung et al., 2016), *Coptis chinensis* Franch (Iizuka et al., 2000; Liu L. et al., 2020), *Garcinia hanburyi* Hook f. (Hahnvajjanawong et al., 2010; Anantachoke et al., 2012; Yang et al., 2013), and *Tripterygium wilfordii* (Yu et al., 2020), have been proven to treat different types of cancers. Natural compounds are characterized by their multiple targets and low toxicity (Luo et al., 2019). Meanwhile, new targets can be found based on natural products.



Therefore, natural compounds from TCMs should receive increased attention for cancer treatment.

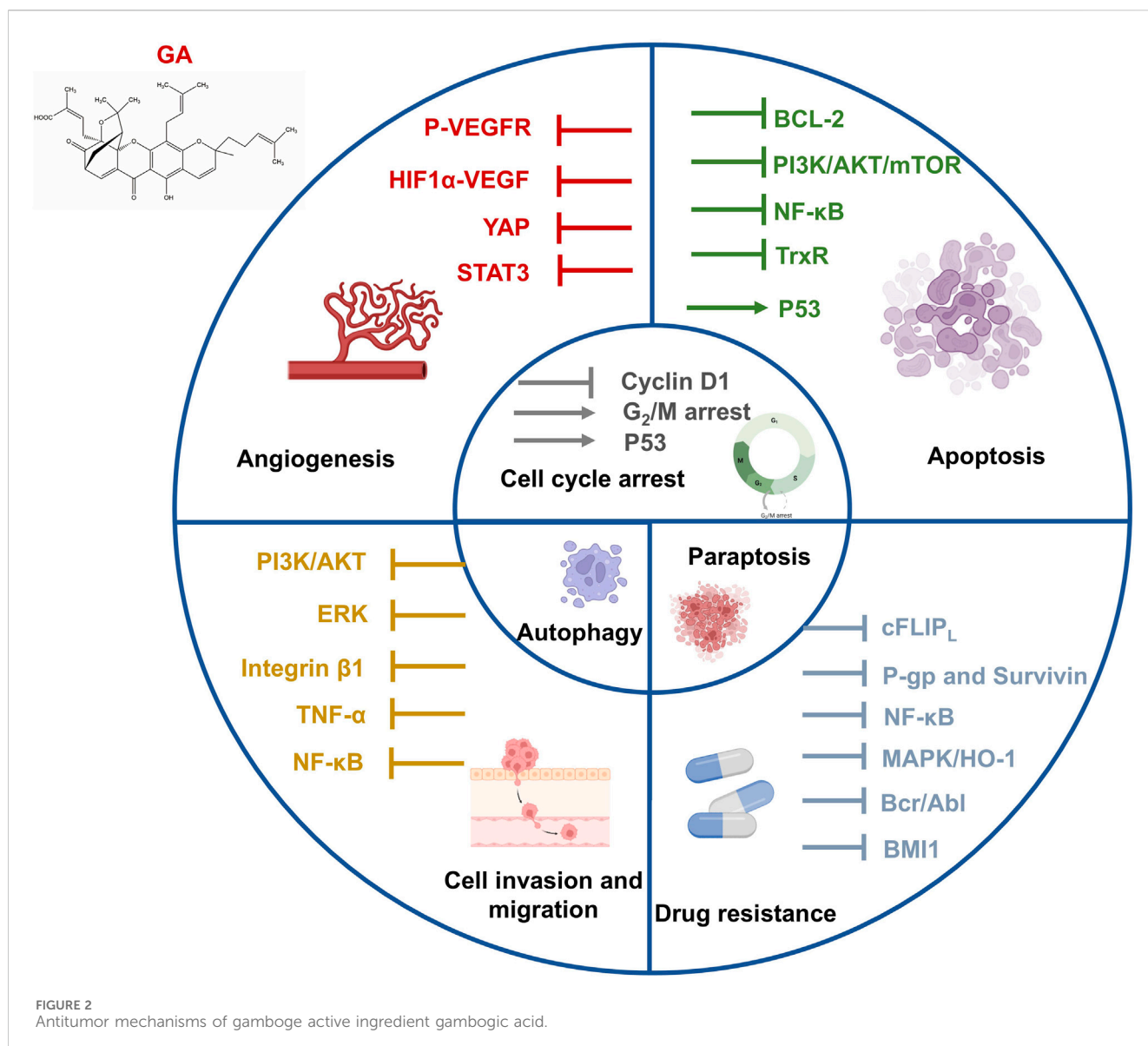
The main sources of natural compounds are terrestrial plants, marine macro-organisms, and micro-organisms from the sea and land, characterized by their wide range of sources, structural diversity, and low toxicity. Natural compounds have been demonstrated to have a broad potential curative value for the therapy of various cancers, including lung cancer (Oh et al., 2019; Zhao et al., 2022), liver cancer (Anwanwan et al., 2020; Zheng et al., 2021), stomach cancer (Chen et al., 2020b), breast cancer (Küpele Akkol et al., 2022; Malla et al., 2022), and colorectal cancer (Rejhová et al., 2018; Sanchez-Martin et al., 2022). Anticancer drugs such as paclitaxel, vincristine, and doxorubicin (DOX) are derived from natural organisms. Natural compounds usually affect multiple molecular targets, such as transcription factors, cytokines, chemokines, adhesion molecules, growth factor receptors, and inflammatory enzymes (Haque et al., 2021). Moreover, natural compounds have been proven to improve patient survival rates by increasing cancer cell sensitivity and reducing or reversing resistance to chemotherapy drugs (Rejhová et al., 2018; Maleki Dana et al., 2022; Sanchez-Martin et al., 2022). Therefore, the role of natural compounds in cancer therapy cannot be ignored.

Chinese medicine gamboge (Figure 1A) is a reddish yellow/orange-yellow colloidal resin secreted by *Garcinia hanburyi* Hook f., mainly from China, Cambodia, Thailand, Vietnam, India, and other tropical regions. Since ancient times, gamboge has been used to treat

scrofula, carbuncle, and boils, which modern medicine considers to be inflammation or cancer. Several caged xanthones are isolated from gamboge have been reported to have antitumor activities (Gold-Smith et al., 2016; Zhao et al., 2022). The main active ingredients from gamboge include gambogic acid (GA) (Figure 1B), gambogenic acid (GNA) (Figure 1C), isogambogenic acid (iso-GNA) (Figure 1D), isomorellin (Figure 1E), and forbesione (Figure 1F). Multiple reports validated that these components inhibit tumor cells in different pathways (Hahnvanawong et al., 2010; Anantachoke et al., 2012; Yang et al., 2013). In this review, we aim to summarize the antitumor research process of the main active xanthone ingredients from Chinese medicine gamboge and to improve the progress of these compounds in preclinical studies.

2 Gambogic acid

GA, one of the principal active ingredients in gamboge, is a caged xanthone compound with various bioactivities. GA prevents the development of tumors by inducing apoptosis, regulating cell autophagy, blocking the cell cycle, restricting cell metastasis, and impeding angiogenesis. Antitumor effects of GA in different types of cancer, including lung, breast, liver, pancreatic, and colorectal cancers, have been illustrated through *in vitro/in vivo* experiments (Hatami et al., 2020a; Liu Y. et al., 2020). Here, we



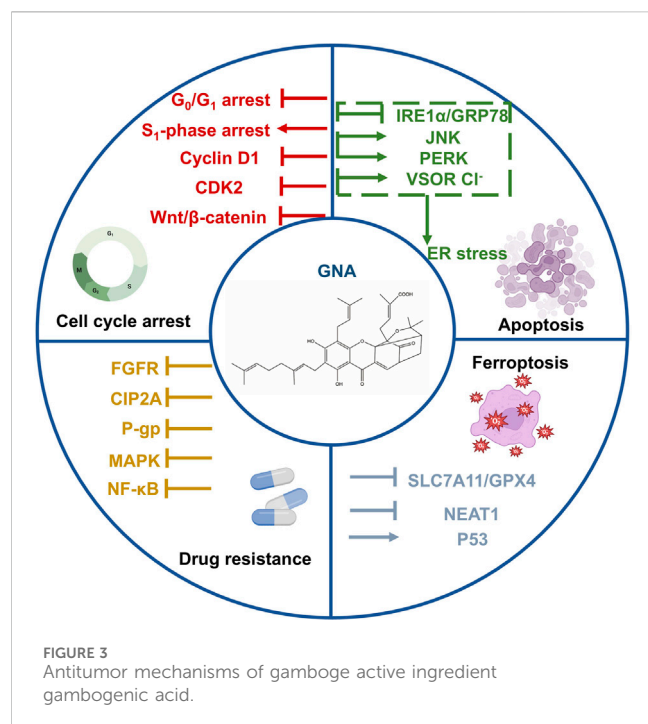
summarize the antitumor effects of GA from multiple mechanisms and applications (Figure 2).

2.1 Antitumor mechanisms of GA

2.1.1 Apoptosis

Apoptosis is recognized as a programmed cell death that occurs through both intrinsic (mitochondrial pathway) and extrinsic (death receptor pathway) processes. Apoptosis can be triggered by cellular stress, genetic damage, and the binding of ligands to death receptors (Pistrutto et al., 2016). Mitochondrial outer membrane permeabilization (MOMP) is a key step during cell apoptosis. The proapoptotic members of the B-cell lymphoma (BCL)-2 family proteins such as BAK induce or promote MOMP, whereas the antiapoptotic BCL-2 proteins interrupt MOMP occurrence (Gupta et al., 2009). The intrinsic apoptotic pathway is activated by intracellular signals (including imbalanced

homeostasis, intense oxidative stress, and DNA damage) to activate the cell death program (Lemke et al., 2014). GA is known as an antagonist of antiapoptotic BCL-2 family proteins (Zhai et al., 2008). GA antagonized BCL-2 family proteins, activated BAX/BAK, and promoted the release of apoptotic proteins such as cytochrome c and AIF into the cytoplasm, leading to the formation of apoptosomes and activation of caspases (O'Neill et al., 2016; Singh et al., 2019; Popgeorgiev et al., 2020). The transferrin receptor (TfR) is a target for cancer immunotherapy and also a target protein of GA. The attachment of GA and TfR triggered the apoptosis of tumor cells probably through the mitochondrial pathway (Kasibhatla et al., 2005; Ortiz-Sánchez et al., 2009). Excess reactive oxygen species (ROS) production induces an intrinsic apoptosis pathway in tumor cells (Zou et al., 2017). GA combined with thioredoxin reductase (TrxR) induced the imbalance of antioxidant defense, leading to the accumulation of intracellular ROS, which resulted in intracellular thiol depletion and oxidative stress that killed tumor cells (Duan et al., 2014).



The extrinsic apoptotic pathway depends on activating tumor necrosis factor (TNF) family death receptors by immune cells or receptor-activating drugs (Pollak et al., 2021). The PI3K/Akt/mTOR pathway is one of the most commonly triggered pathways in cancer cells, which plays various roles in normal physiological and carcinogenic processes, including cell proliferation, survival, and differentiation (Beck et al., 2014). The engagement of E-cadherin enhances the activation of DR4 and DR5 proapoptotic receptors, thereby promoting the progression of apoptosis (Singh and Lim, 2022). GA upregulated the expression of E-cadherin while blocking the mTOR signaling pathway to inhibit cell proliferation (Li X. et al., 2019).

P53, a key tumor suppressor, is one of the most frequently mutated proteins in cancer which suppresses the growth of tumors by triggering cell cycle arrest, cellular senescence, apoptosis, and genetic damage repair (Zhao and Sanyal, 2022). The murine double minute 2 (MDM2) gene encodes a p53 negative regulator. GA enhanced the expression of p53 by downregulating the transcription of MDM2, which inhibited the combination of MDM2 and p53, leading to the apoptosis of tumor cells (Gu et al., 2008).

Aberrant activation of NF-κB is related to various cellular processes in cancer, including cell proliferation, metastasis, angiogenesis, chemotherapy, and radiotherapy (Aggarwal and Sung, 2011). GA blocked the NF-κB signaling by targeting G protein-coupled receptor 108 (GPR108) in pancreatic and colorectal cancers (Lyu et al., 2022). GA triggered apoptosis in Burkitt's lymphoma Raji cells by upregulating death-inducer obliterator 1 (DIO-1) and downregulating NF-κB and Bcl-xL (Yang and Chen, 2013). In addition, GA downregulated the expression of cellular FADD-like inhibitory protein (cFLIP) L and induced apoptosis in renal carcinoma Caki cells, probably through the inhibition of the NF-κB pathway (Jang et al., 2016). Table 1 shows IC₅₀ of GA in a variety of cancer cell lines *in vitro*.

2.1.2 Cell cycle arrest

Cell cycle arrest is a well-known anticancer mechanism. GA reduced the level of cyclin D1 protein while increasing p53 expression to induce G₁ phase arrest in human colorectal cancer cells *in vitro* (Wen et al., 2015). GA treatment induced G₂/M phase arrest in human nasopharyngeal carcinoma (NPC) CNE-2 and 5-8F cells (Ren et al., 2022). In addition, Feng et al. found that GA can suppress the growth of human cervical carcinoma HeLa cells by increasing the amount of the G₂/M phase (Feng et al., 2016).

2.1.3 Cell invasion and migration

Tumor cell invasion and migration are labels of cancer development that allow tumor cells to escape from normal developmental regulation (Geho et al., 2005). Cell adhesion to the extracellular matrix (ECM) is critical in the cancer metastasis cascade. GA inhibited the migration and adhesion of malignant melanoma cells via suppressing the PI3K/Akt and ERK signaling pathways *in vitro* (Li C. Y. et al., 2019). GA suppressed integrin β1 and the membrane lipid raft-associated integrin signaling pathway to inhibit breast tumor cell adhesion *in vitro* (Li et al., 2011). Moreover, GA may restrain TNF-α-induced migration and invasion by blocking PI3K/Akt and NF-κB signaling pathways in human prostate cancer PC3 cells (Lü et al., 2012).

2.1.4 Angiogenesis

Angiogenesis is a well-known hallmark of cancer that provides necessary oxygen and nutrients for tumor growth. The most common angiogenesis inducer is vascular endothelial growth factor (VEGF)-A (Hanahan and Weinberg, 2000). The activation of vascular endothelial growth factor receptor 2 (VEGFR2) by the VEGF is the primary factor driving tumor angiogenesis (Vimalraj, 2022). GA inhibited the tube formation of human umbilical vein endothelial cells (HUVECs) and reduced the level of phospho-VEGFR2 in melanoma cells *in vitro* (Li C. Y. et al., 2019). GA can reduce HIF-1α/VEGF expression *in vivo* to suppress tumor angiogenesis, suggesting that GA might be a new potential drug to treat human multiple myeloma (Wang F. et al., 2014). In addition, GA restricted VEGF-induced angiogenesis by diminishing the YAP nuclear expression in a dose-dependent manner *in vitro/in vivo*, leading to the inactivation of downstream STAT3 in HUVECs (Wan et al., 2019).

2.1.5 Autophagy

Autophagy is a double-edged sword in regulating the tumor growth. It is widely accepted that autophagy suppresses tumor initiation, but evidence suggested that autophagy processes in established tumors are required to support uncontrolled cell growth for tumor maintenance. In breast cancer, loss of *BECN1*, an autophagy-associated gene, results in tumor-prone conditions (Liang et al., 1999). On the other hand, some tumor tissues exhibit high levels of LC3 puncta and lipidated LC3, supporting the role of autophagy in maintaining pancreatic cancer development (Fujii et al., 2008). P53 mutation was detected in the vast majority of malignancies, which may lead to an increase in the oncogenic activity (Duffy et al., 2017). Mutant p53 inhibits autophagy by blocking AMPK and activating the AKT/mTOR pathway through overexpression of growth factor receptors (Khromova et al., 2009; Cordani et al., 2016). Autophagy induction can deplete mutant

TABLE 1 IC₅₀ of active ingredients in gamboge for different types of cancer cell lines.

Compound	Type of cancer	Cell	IC ₅₀	Treatment time (h)	Reference
Gambogic acid	Melanoma	A375	2.86 μ M 2.15 μ M 1.55 μ M	24 48 72	Li et al. (2019a)
		B16-F10	2.61 μ M 1.89 μ M 1.26 μ M	24 48 72	
	Chronic myeloid leukemia	KBM5	0.32 μ M	48	Shi et al. (2014)
		KBM5-T315I	0.35 μ M	48	
		K562	0.40 μ M	48	
	Breast cancer	MDA-MB 453	1.5 μ M	24	Seo et al. (2019)
		MDA-MB 468	2.35 μ M	24	
		MDA-MB 435S	1.33 μ M	24	
		MCF7-ER α -Y537S	1.81 \pm 0.21 μ M	96	Liu et al. (2021)
		MCF-7	1 μ M	48	Wang et al. (2015)
		MCF-7	4.11 μ M	48	Gu et al. (2008)
	Non-small-cell lung cancer	A549	3.56 \pm 0.36 μ M	48	Wang et al. (2014b)
		NCI-H460	4.05 \pm 0.51 μ M	48	
		NCI-H1299	1.12 \pm 0.31 μ M	48	
	Colorectal cancer	HCT-15P	1.08 μ M	48	Wen et al. (2015)
		HCT-15R	0.87 μ M	48	
		HCT116	1.1 μ M 0.6 μ M 0.5 μ M	12 24 36	Zhang et al. (2014)
		HCT116	1.24 μ M	48	Gu et al. (2008)
	Pancreatic cancer	PANC-1	7.198 μ M 3.780 μ M 0.977 μ M	12 24 48	Xia et al. (2017)
		BxPC-3	2.692 μ M 0.362 μ M 0.778 μ M	12 24 48	
		MIA PaCa-2	4.520 μ M 2.721 μ M 1.635 μ M	12 24 48	
		SW1990	8.204 μ M 3.055 μ M 0.795 μ M	12 24 48	
	Cervical carcinoma	HeLa	4.17 \pm 0.30 μ M 2.19 \pm 0.11 μ M 1.59 \pm 0.05 μ M	24 48 72	Feng et al. (2016)
		HeLa	3.53 μ M	48	Gu et al. (2008)
	Cholangiocarcinoma	KKU-100	3.22 \pm 0.17 μ M 2.83 \pm 0.18 μ M 2.47 \pm 0.03 μ M	—	Hahnvajjanawong et al. (2012)
		KKU-M156	1.96 \pm 0.01 μ M 1.30 \pm 0.15 μ M 0.76 \pm 0.14 μ M	—	
	Hepatoma	HepG2	3.8 μ M	48	Gu et al. (2008)

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TABLE 1 (Continued) IC₅₀ of active ingredients in gamboge for different types of cancer cell lines.

Compound	Type of cancer	Cell	IC ₅₀	Treatment time (h)	Reference
	Cervical carcinoma	HeLa	4.17 ± 0.30 μM 2.19 ± 0.11 μM 1.59 ± 0.05 μM	24 48 72	Feng et al. (2016)
		HeLa	3.53 μM	48	Gu et al. (2008)
	Cholangiocarcinoma	KKU-100	3.22 ± 0.17 μM 2.83 ± 0.18 μM 2.47 ± 0.03 μM	—	Hahnvanawong et al. (2012)
		KKU-M156	1.96 ± 0.01 μM 1.30 ± 0.15 μM 0.76 ± 0.14 μM	—	
	Hepatoma	HepG2	3.8 μM	48	Gu et al. (2008)
Gambogenic acid	Hepatoma	HepG2	3.23 μM 2.62 μM 2.14 μM	24 48 72	Yan et al. (2012)
		HepG2	2.141 μM	48	Xu et al. (2019a)
		HepG2/ADR	4.532 μM	48	
		HepG2	4.4 ± 0.12 μM	48	Yuan et al. (2016)
		HepG2	10.71 μM	24	Tang et al. (2018)
		SMMC-7721	4.25 ± 0.14 μM	48	Luo et al. (2015)
		NCI-H446	1.4 μM	—	Huang et al. (2019)
		NCI-H1688	2.4 μM	—	
	Colorectal cancer	HCT116	1.88 μM 1.48 μM	24 48	Zhao et al. (2020)
		SW620	2.83 μM 1.81 μM	24 48	
		DLD-1	1.97 μM 1.55 μM	24 48	
		SW480	8.159 μM	24	Li et al. (2022a)
		HCT116	8.172 μM	24	
	Nasopharyngeal carcinoma	CNE-2Z	2.25 μM 1.33 μM	24 48	Su et al. (2019)
		CNE-1	1.87 μM	72	Yan et al. (2011)
	Melanoma	A375	2.875 μM	24	Wang et al. (2022b)
		A2058	1.263 μM	24	
		B16	2.085 μM	24	
		B16F10	0.9959 μM	24	
	Non-small-cell lung cancer	HCC827	1.51 μM	72	Xu et al. (2018)
		HCC827ER	1.328 μM	72	
		H1650	0.909 μM	72	
		A549	7 μM	48	Yu et al. (2012)
		HCC827	1–2 μM	—	
		NCI-H1975	2–3 μM	—	
		A549	8.07 μM	24	Tang et al. (2018)

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TABLE 1 (Continued) IC₅₀ of active ingredients in gamboge for different types of cancer cell lines.

Compound	Type of cancer	Cell	IC ₅₀	Treatment time (h)	Reference
	Breast cancer	4T1	7.57 μ M	24	Wang et al. (2021)
	Gastric cancer	SGC-7901	16.15 μ M	24	Tang et al. (2018)
Isogambogenic acid	Glioma	U251 U-87MG	3–4 μ M	24	Zhao et al. (2017)
	Cervical carcinoma	HeLa	6.35 μ M	—	Yang et al. (2013)
	Non-small-cell lung cancer	A549	12.69 μ M	—	
	Colorectal cancer	HCT-116	11.74 μ M	—	
	Hepatoma	HepG-2	6.35 μ M	—	
Isomorellin	Cholangiocarcinoma	KKU-100	3.46 \pm 0.19 μ M 3.78 \pm 0.02 μ M 4.01 \pm 0.01 μ M	24 48 72	Hahnvajjanawong et al. (2021)
		KKU-100	6.2 \pm 0.13 μ M 5.1 \pm 0.11 μ M 3.5 \pm 0.25 μ M	24 48 72	Hahnvajjanawong et al. (2012)
		KKU-M156	1.9 \pm 0.22 μ M 1.7 \pm 0.14 μ M 1.5 \pm 0.14 μ M	24 48 72	
		KKU-100	3.34 \pm 0.12 μ M	72	Hahnvajjanawong et al. (2014)
		KKU-M139	2.71 \pm 0.10 μ M	72	
		KKU-M156	2.26 \pm 0.05 μ M	72	
Forbesione	Cholangiocarcinoma	Ham-1	3.34 \pm 0.31 μ M	72	Boueroy et al. (2017)
		KKU-100	3.53 \pm 0.05 μ M	72	Hahnvajjanawong et al. (2014)
		KKU-M139	2.29 \pm 0.04 μ M	72	
		KKU-M156	2.63 \pm 0.05 μ M	72	
Ethanol extract of gamboge	Colon cancer	SW480-GFP	0.54 μ g/mL 0.36 μ g/mL 0.24 μ g/mL	24 48 72	Wang et al. (2018b)
		Ham-1	3.34 \pm 0.31 μ M	72	Boueroy et al. (2017)
		KKU-100	3.53 \pm 0.05 μ M	72	Hahnvajjanawong et al. (2014)

p53 protein to interfere with cancer development (Choudhury et al., 2013). GA promoted mtp53 degradation and tumor cell death by inducing autophagy (Foggetti et al., 2017). Similarly, inhibiting GA-induced autophagy in pancreatic cancer cells can enhance its proapoptotic function (Wang et al., 2019). Suppression of GA-induced cytoprotective autophagy promotes apoptosis in colorectal cancer (CRC) cells. Evidence showed that GA-induced autophagy might be involved in tumor growth suppression *in vivo*. The result revealed a new perspective on GA in CRC treatment, which may be necessary in combination with autophagy inhibitors (Zhang et al., 2014).

2.1.6 Drug resistance

Resistance to chemotherapeutic agents is a primary obstacle in cancer treatment. Numerous studies have confirmed that GA has the capacity to reduce drug resistance in tumor cells, making them more susceptible to chemotherapeutic drugs. GA can sensitize TNF-related apoptosis-inducing ligand (TRAIL)-mediated renal

carcinoma Caki cell apoptosis via downregulating cFLIP_L (Jang et al., 2016), and it also sensitizes TRAIL-resistant breast cancer cells to TRAIL-induced apoptosis (Wang S. et al., 2018). P-glycoprotein (P-gp) and survivin expression were related to cancer multidrug resistance (Deng et al., 2021). GA elevated the susceptibility of DOX in drug-resistant breast cancer MCF-7/ADR cells by downregulating P-gp and survivin (Wang et al., 2015). GA also inhibited the NF- κ B and MAPK/HO-1 pathways to enhance apoptosis triggered by cisplatin (CDDP) in non-small-cell lung cancer (NSCLC) (Wang L. H. et al., 2014). The activation of Bcr-Abl tyrosine kinase has been regarded as a characteristic of chronic myeloid leukemia (CML). GA deregulated the expression of Bcr-Abl and induced apoptosis in primary imatinib-resistant monocytes from patients (Shi et al., 2014). Glioma stem cells (GSCs) are strongly associated with high drug resistance in glioblastoma (GBM) (Boyd et al., 2021). Biotin-GA directly targeted the ring finger structural domain of B-cell-specific Moloney leukemia virus insert site 1 (BMI1), inducing BMI1 degradation and inhibiting the

self-renewal capability of GSCs. Meanwhile, combining GA with temozolomide (TMZ) showed superior anti-GBM ability (Sun et al., 2024).

2.1.7 Paraptosis

Paraptosis is a non-apoptotic cell death characterized by the lack of caspase inhibitor effects, cytoplasmic vacuolization, and mitochondrial swelling (Sperandio et al., 2000). Seo et al. (2019) observed that GA-induced cell death was accompanied by vacuolation and showed morphological and biochemical characteristics of paraptosis in breast cancer cells.

As mentioned above, multiple pieces of evidence have confirmed the antitumor effect of GA in a variety of cancers by inducing apoptosis and non-apoptosis cell death, arresting the cell cycle, inhibiting migration and invasion, angiogenesis, regulating autophagy, and reducing cellular drug resistance. Thus, GA might be the ideal agent for cancer therapy.

2.2 Nanoscale drug delivery system

GA has shown potent antitumor activity with clinical significance. However, its clinical application is limited due to its poor aqueous solubility, instability, low bioavailability, and severe systemic toxicity. Different types of nanoscale drug delivery systems, such as micelles, nanoparticles, and liposomes, have been applied to solve these challenges (Liu Y. et al., 2020).

In recent years, polymeric micelles have been used widely in preclinical studies. GA encapsulated by a multiple environment-sensitive prodrug self-assembled micelles based on chitosan graftomer increased the release and distribution in tumor tissue significantly compared to free GA, resulting in improved GA tumor-targeting ability (Du et al., 2021). Cai et al. (2014) prepared micelles formed by condensation of low-molecular-weight monomethoxy-poly (ethylene glycol) (mPEG)-2000 with GA, which showed 2.7×10^5 times higher aqueous solubility than that of GA and decreased the poisonous side effect of GA effectively. Redox/pH dual-responsive and magnetic targeted hybrid multifunctional complex micelles (SPEG/HA/CSO-SS-HEX/Fe₃O₄/GA) were developed as a drug delivery system for GA to improve triple-negative breast cancer (TNBC) therapeutic efficacy. The tumor suppression rate *in vivo* of SPEG/HA/CSO-SS-HEX/Fe₃O₄/GA was 84.1%, which was 2.19 times higher than that of GA (Sang et al., 2018). Treating with free GA and GA-loaded PEG-pHis-PLGA/TPGS micelle system resulted in a significant decrease in P-gp in MCF-7/ADR cells, but the mixed micelle was better. The result suggested that the micelle system may be a viable strategy for GA to overcome clinical drug resistance in breast cancer (Wang et al., 2015).

Wang et al. prepared GA-loaded nanobubble-microbubble complexes (GA/PLGA-CMB) that could be used to open the blood-brain barrier noninvasively and reversibly under the action of focused ultrasound (FUS). GA/PLGA-CMB also supported GA to be distributed uniformly throughout tumor tissue for targeted glioma therapy (Wang F. et al., 2022). Both GA-loaded biomimetic nanoparticles (RBCm-GA/PLGA NPs) and GA could induce S phase arrest in CRC SW480 cells *in vitro*, but the RBCm-GA/PLGA group markedly reduced the tumor volume and relative tumor volume *in vivo* compared with the GA group (Zhang et al., 2017).

The liposome delivery system is widely used in tumor treatment, and liposomes have been the most successful drug delivery carriers among the nanoparticles studied (Natarajan et al., 2014). The repression of Bcl-2 was 1.23-fold higher after treatment with positively charged PEGylated liposomal formulation of GA (GAL) *in vitro* than that with free GA (Doddapaneni et al., 2016). Dang et al. (2021) prepared CB5005N-GA-liposome using the thin film hydration method, which showed a nearly three times higher percentage of tumor growth inhibition in breast cancer cells *in vivo* than that of GA-Sol.

The introduction of GA (GPgWSC) copolymer by polyethylenimine (PEI)-grafted water-soluble chitosan (WSC) achieved target specificity via targeting tumor cells overexpressing TfR (Park et al., 2022).

2.3 Applications in cancers

2.3.1 Breast cancer

Breast cancer is one of the most common cancers and the most frequent malignancies in women. Current therapeutic options include surgery, chemotherapy, radiotherapy, adjuvant treatment, and target therapy (Harbeck and Gnant, 2017; Li et al., 2022b). However, poor prognosis, drug resistance, and high relapse risk of breast cancer indicate that it is essential to seek a novel drug to treat breast cancer. GA has shown its ability to increase the apoptosis rate significantly via combination with other antitumor agents. Optimized protein-fragment complementation assay revealed that GA acts as an antagonist of estrogen receptor alpha (ERα) Y537S. GA directly targeted ERα Y537S and inhibited MDA-MB-231 cells with the ERα Y537S mutant, inducing MCF7 cell apoptosis combined with CDK4/6 inhibitor abemaciclib (Liu et al., 2021). MCF-7/ADR cells showed an increase in the sub-G₁ phase (23.15%) and apoptosis rate (19.7%) after 48 h GA (1 μM) treatment. The accumulation of the sub-G₁ phase increased to 41.95%, and the number of apoptotic nuclei and annexin V-PI-positive cells increased to 38.6% after being treated with DOX and GA concurrently, possibly resulting from sensitizing MCF-7/ADR cells to DOX by inhibiting P-gp and survivin (Wang et al., 2015). In addition, treatment with TRAIL (25 ng/mL) and GA (0.25 μM) induced 14.7% and 13.8% apoptosis, respectively, in MCF-7 cells. However, concurrent TRAIL and GA treatment increased the apoptosis rate to 51.8%, which was associated with enhanced sensitivity of MCF-7 cells to TRAIL by GA (Wang S. et al., 2018).

2.3.2 Non-small-cell lung cancer

Lung cancer is still a leading cause of cancer death, accounting for 23% of all cancer deaths. NSCLC accounts for 40%–45% of all cases of lung cancer (Desai et al., 2023). Liver kinase B1 (LKB1) is a tumor inhibitor that mediates cellular functions and is one of the most frequently mutated genes in NSCLC (Shukuya et al., 2019). GA exhibited stronger inhibitory effects in cells with wild-type LKB1 than that with mutated LKB1 cells. GA upregulated the level of p-AMPK by enhancing the binding of E-cadherin to LKB1 while suppressing the Akt/mTOR signaling pathway (Li X. et al., 2019). Gemcitabine (Gem) is considered a first-line option for NSCLC patients (Wu et al., 2014). However, the therapeutic effect of Gem is hampered by drug resistance (Olaussen and Postel-Vinay,

2016). GA reduced Gem resistance and promoted Gem antitumor potential *in vitro/in vivo*. The IC₅₀ of Gem was reduced to 4.4, 2.2, and 0.63 nM by treatment with 100, 200, and 400 nM GA concurrently in A549 cells. A similar trend was observed in H1299 cells. The GA + Gem group showed minimal proliferating cell nuclear antigen (PCNA) marker staining (27%) compared to control (95%), GA (86%), and Gem (42%) treatments *in vivo*, indicating that tumor cell proliferation was suppressed by the GA + Gem group. These results confirmed the synergistic action of the GA and Gem combination in NSCLC (Hatami et al., 2020b). GA increased the accumulation of ROS via inhibiting CDDP-induced upregulation of HO-1. The tumor inhibition rate *in vivo* was 69.3% by treatment with GA and CDDP concurrently, whereas those treated with GA and CDDP alone were 29.0% and 57.2%, respectively, suggesting that the combination of GA and CDDP may provide a potential regimen to treat NSCLC (Wang L. H. et al., 2014).

2.3.3 Colorectal cancer

CRC is the fourth most deadly cancer all over the world. It is the women's second most common cancer and the men's third (Dekker et al., 2019). After treatment with GA for 48 h, the level of proapoptotic proteins increased significantly in HT-29 cells. Moreover, the tumor volume in the tumor xenograft mouse model was decreased in a dose- and time-dependent manner after treatment with GA (Huang et al., 2015). Wen et al. (2015) indicated that GA activated the c-Jun N-terminal kinase (JNK) signaling pathway and induced apoptosis in both 5-fluorouracil (5-FU)-sensitive and 5-FU-resistant cells, suggesting that GA had the potential to combat 5-FU resistance in CRC. The IC₅₀ value of GA in HCT116 cells was 1.1, 0.6, and 0.5 μ M for 12, 24, and 36 h, respectively. In addition, GA induced protective autophagy, thereby restricting its antitumor effects via increasing 5-LOX-regulated ROS levels (Zhang et al., 2014).

2.3.4 Pancreatic cancer

Pancreatic cancer is a deadly cancer that is predicted to be the second leading cause of cancer-related death before 2040 (Halbrook et al., 2023). GA promoted the accumulation of autophagosomes, inducing protective autophagy in both PANC-1 and BxPC-3 cells, which resulted from activating the autophagic promoter (Beclin-1) by inhibiting the Akt/mTOR pathway. However, concurrent treatment with GA and chloroquine (CQ) led to excessive accumulation of ROS, then triggered oxidative stress, resulting in apoptosis, and exhibited the strongest antitumor efficacy *in vivo* (Wang et al., 2019). The inhibition of the ERK/E2F1 signaling pathway by GA induced apoptosis in pancreatic cancer cell lines, reducing ribonucleotide reductase subunit-M2 (RRM2) expression. The tumor inhibition rate was 72.9% in the combined group (GA and Gem) compared to the control group, indicating that GA can promote the sensitivity of pancreatic cancer cells to Gem (Xia et al., 2017).

2.3.5 Gastric cancer

Gastric cancer (GC) has poor survival with limited treatment; therefore, GC remains a leading cause of cancer-related mortality worldwide. GA showed a concentration-dependent inhibition of GC cell growth accompanied by apoptosis, oxidative DNA damage,

and autophagy induction (Joha et al., 2023). MicroRNA (miRNA)-driven post-transcriptional gene silencing regulates biological processes, including cell proliferation, apoptosis, and development. GA induced ferroptosis in GC through the miR-1291/FOXA2 axis (Qian et al., 2025) and GA induced apoptosis via the circRNA_ASAP2/miR33a-5p/CDK7 axis (Lin et al., 2020). In addition, GA contributed to docetaxel resistance reversion in GC by inhibiting survivin (Wang et al., 2008). In conclusion, GA showed anti-GC effects through multiple processes.

2.3.6 Other cancers

GA exhibited IC₅₀ in human cervical carcinoma HeLa cells as 4.17 ± 0.30 , 2.19 ± 0.11 , and 1.59 ± 0.05 μ M for 24, 48, and 72 h treatment, respectively, and it exhibited a dose-dependent increase in the number of cells in the G2/M phase (Feng et al., 2016). GA induced G2/M phase arrest and apoptosis in CNE-2 and 5-8F cells. Moreover, GA inhibited the overexpression of CD47 stimulated by chemotherapy drugs and showed a synergistic effect with 5-FU (Ren et al., 2022).

2.4 Toxicity and clinical application

GA has demonstrated good antitumor efficacy in preclinical studies. Nevertheless, its side effects and poor hydrophilicity have limited its clinical application. Previous reports have shown the toxicology of GA. GA showed no serious CNS effects and caused no significant changes in spontaneous locomotor activity of mice (Zhao et al., 2010). However, GA has shown toxicity on pregnant rats and fetuses, and caused pectoral fin defect and lethal toxicity in zebrafish embryos in a dose-dependent manner (Zhao et al., 2010; Jiang et al., 2016). The LD₅₀ of GA in mice was 45.993 mg/kg. In the beagle dog model, when GA (8 mg/kg) was injected intraperitoneally, the typical toxicological responses mainly included hydrostomia, astasia, and anepithymia (Guo et al., 2006). Most of all, long-term use of a high dose of GA led to damage to the kidney and liver in Sprague-Dawley rats (Qi et al., 2008). The symptoms of adverse reactions following GA injection administration include abdominal pain, phlebitis, and nausea in the phase IIa study (Yihebal et al., 2013). The phase II clinical trial of GA approved for the treatment of NSCLC has been terminated probably due to the high toxicity of GA, especially liver toxicity. Therefore, additional manners should be explored to improve reverse reaction while retaining the antitumor activity of GA, for example, precision drug delivery and chemical structure modification. GA was conjugated with unsaturated long-chain oleyl alcohol (OA) and self-assembled into NPs in water to prepare GA-OA@TPGS/NPs. The GA-OA@TPGS/NPs showed excellent stability, prolonged circulation, more precise targeting of tumor cells, and most importantly, lower toxicity (Wang et al., 2024). In the previous study, a new delivery nanoparticle containing both tumor-penetrating peptide (internalizing RGD peptide, iRGD) and EGFR single-domain antibody (sdAb) was constructed, the anti-EGFR-iRGD recombinant protein was modified on the surface of red blood cell membrane-coated nanoparticle (RBCm-NP), and GA was loaded. The new iE-RBCm-GA/PLGA NPs enhanced the diffusion ability of GA into cancer cells *in vitro*, increased stability and biocompatibility, and reduced side effects *in vivo*

(Zhang et al., 2018). GA was loaded into a novel situ nanocomposite hydrogel vaccine system (Gel-NP@GA), along with a near-infrared (NIR) fluorescent dye, causing a sustained GA release to reduce toxicity reactions and enhance antitumor effects (Lei et al., 2025). The mesoporous polydopamine (MPDA) nanoparticles endowed with photothermal conversion capabilities could be used to deliver GA, and the GA-loaded GA@MPDA NPs significantly inhibited tumor growth and reduced the toxicity in vital organs (heart, liver, lung, spleen, and kidney) (Liu et al., 2024). Many studies have focused on the effect of chemical structure modification on the biological activity of GA, but little attention has been paid to the relationship between toxicity and chemical structure (Wang et al., 2009; Wang et al., 2011). We speculate that chemical modification may be a new avenue for the reduction in GA toxicity.

3 Gambogic acid

GNA is another active component from gamboge with a structure similar to GA. GNA has more substantial antitumor effects and lower systemic toxicity than GA and exerts antitumor activity through several mechanisms, including the induction of apoptosis and ferroptosis, and cell cycle arrest (Sun et al., 2018). Here, we elaborate on these mechanisms in detail (Figure 3).

3.1 Antitumor mechanisms of GNA

3.1.1 Apoptosis

GNA was found to increase the Bax/Bcl-2 ratio in a time-dependent manner and induce apoptosis through the mitochondrial pathway in human hepatoma HepG2 cells (Yan et al., 2012). GNA upregulated the expression of proapoptotic proteins and induced apoptosis in small-cell lung cancer (SCLC) cell lines (Huang et al., 2019). Endoplasmic reticulum (ER) stress exhibits a proapoptotic effect in tumor cells (Oakes, 2020; Albayrak et al., 2021). GNA induced ER stress by overproducing ROS, leading to the dissociation of inositol-requiring enzyme-1 α (IRE1 α) from glucose-regulated protein 78 (GRP78), which then activated JNK to trigger apoptosis in CRC cells (Zhao et al., 2020). GNA triggered ER stress through interaction with Aurora A in HCT116 cells, suppressing CRC. The phosphorylation of PERK and downstream PERK was observed in HCT116 cells. Therefore, the activation of ER stress may be mediated by promoting the PERK signaling pathway in addition to IRE1 α (Wang et al., 2021). Moreover, GNA activated volume-sensitive chloride (VSOR Cl⁻) channels to trigger ER stress and eventually induced apoptosis in human NPC CNE-2Z cells (Su et al., 2019).

3.1.2 Cell cycle arrest

In SCLC NCI-H446 cells, low doses of GNA blocked the cycle in the G₀/G₁ phase, whereas higher-dose concentrations induced S phase arrest (Huang et al., 2019). High concentrations of GNA significantly blocked the G₀/G₁ phase in CNE-1 cells (Yan et al., 2011). GNA induced G₁ phase arrest in lung cancer cells by promoting the degradation of GSK3 β -dependent cyclin D1 and

inhibiting CDK2 (Yu et al., 2012). Similarly, GNA reduced the level of cyclin D1 and blocked the G₀/G₁ cycle of CRC stem cells related to the Wnt/ β -catenin signaling pathway (Li et al., 2022a).

3.1.3 Ferroptosis

Ferroptosis is a novel cell-programmed death mediated by iron-dependent lipid peroxidation, characterized by the overload of iron, the accumulation of ROS, and lipid peroxidation (Wang M. et al., 2020; Wu et al., 2020). The inhibition of the cystine/glutamate antiporter (System xc⁻) is a disulfide-linked heterodimer composed of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2) (Dixon et al., 2012; Xu T. et al., 2019). GNA triggered ferroptosis in melanoma cells by decreasing lncRNA nuclear-enriched abundant transcript 1 (NEAT1) and downregulating levels of SLC7A11/glutathione peroxidase 4 (GPX4) (Wang M. et al., 2022). In addition, GNA activated the p53/SLC7A11/GPX4 signaling pathway, disrupted the oxidative stress balance, with increased ROS accumulation in TGF- β 1-induced treated melanoma cells, and then triggered ferroptosis (Wang M. et al., 2020).

3.1.4 Drug resistance

GNA potentiated the efficacy of erlotinib in inhibiting NSCLC cell proliferation by suppressing the fibroblast growth factor receptor (FGFR) signaling pathway. GNA and erlotinib synergistically inhibited HCC827 erlotinib-resistant (HCC827ER) xenograft growth *in vivo* (Xu et al., 2018). The overexpression of the cancerous inhibitor of protein phosphatase 2A (CIP2A) is related to resistance and tumor formation. GNA induced degradation of CIP2A and enhanced sensitivity to antitumor agents in hepatocellular carcinoma. However, the mechanisms of GNA to promote CIP2A degradation remain unclear and require further investigation (Yu et al., 2016). GNA potentiated the apoptotic effect of bortezomib in human myeloma MM.1S cells by regulating apoptosis-related proteins (Chen et al., 2017). In addition, GNA downregulated P-gp and P-gp-related proteins to reverse multidrug resistance in HepG2/ADR cells, probably by inhibiting the NF- κ B and MAPK pathways (Xu Q. et al., 2019).

3.1.5 Other mechanisms

GNA inhibited NF- κ B signaling by downregulating p65 expression and suppressing the metastasis of bladder cancer cells (Zhou et al., 2020). Mei et al. (2014) demonstrated that GNA blocked the degradation of p62, leading to aberrant autophagic degradation that plays a pro-death role in GNA-mediated cell death.

3.2 Nanoscale drug delivery system

Efforts have been made to investigate novel GNA delivery systems to overcome the problems of GNA, including poor water solubility, high vascular irritation, and low bioavailability. Wang et al. (2021) prepared functional polydopamine nanoparticles to encapsulate and stabilize GNA, improving the bioavailability and tumor-targeting action of raw GNA. The curve ($AUC_{0 \rightarrow \infty}$) of the plasma drug concentration–time of polydopamine-coating GNA-loaded Zein nanoparticles was approximately 3.48-fold higher than that of GNA *in vivo* (Zha et al., 2020). PEGylated liposomes as

delivery systems for GNA increased the local GNA concentration at the tumor site after tail vein injection and showed higher antitumor efficacy than GNA *in vitro/in vivo* (Tang et al., 2018). The relative bioavailability of GNA nanosuspensions prepared using the anti-solvent precipitation method was 263%, and it exhibited a longer $t_{1/2}$ than the GNA solution (Yuan et al., 2016). Luo et al. (2015) prepared glyceryl monoolein-bearing cubosomes for GNA that showed higher AUC and C_{max} obtaining long-circulating colloidal delivery systems after intraperitoneal administration.

3.3 Toxicity and clinical application

GNA is a derivative formed by opening the pyran ring of GA and exerts less systemic toxicity than GA. GNA showed no effect on body weight in mice (Xu et al., 2018; Chen et al., 2020a). In the SCLC xenograft mice, no apoptotic cell death was observed in the lung, liver, kidney, spleen, or heart tissues after GNA treatment (Xu et al., 2018). Meanwhile, GNA possessed a liver-protective effect by attenuating the acetaminophen (APAP)-induced liver injury, inflammation, and apoptosis (Ding et al., 2021). GNA has not been used in the clinic alone despite its significant antitumor activity and hypotonicity. GNA has stronger antitumor effects and lower systemic toxicity than GA, but research and applications are limited. It is expected that GNA will receive more attention to exploration in future studies.

4 Other active ingredients

4.1 Isogambogenic acid

Iso-GNA is an isomer compound of GNA. Iso-GNA induced apoptosis-independent autophagic cell death by inhibiting the Akt-mTOR signaling pathway and overcame drug resistance caused by apoptosis deficiency in NSCLC (Yang et al., 2015). Iso-GNA promoted autophagy and apoptosis in glioma cells by activating the AMPK/mTOR pathway (Zhao et al., 2017). Furthermore, iso-GNA exhibited HUVEC migration *in vitro* and had antiangiogenic activities with less toxicity than GA *in vivo* (Yang et al., 2013).

4.2 Isomorellin and forbesione

Isomorellin and forbesione are caged polyprenylated xanthenes isolated from gamboge. Isomorellin reduced cholangiocarcinoma (CCA) KLU-100 cell migration and invasion by downregulating FAK and inhibiting NF- κ B signaling translocation (Hahnvajjanawong et al., 2021). Moreover, isomorellin downregulated proteins that operate the G_0/G_1 phase, including cyclin D1, cyclin E, Cdk2, and Cdk4, and arrested the cell cycle in CCA cell lines (Hahnvajjanawong et al., 2012). Forbesione inhibited the growth of CCA cell lines *in vitro/in vivo* by triggering S phase arrest and apoptosis through multiple pathways (Boueroy et al., 2016). Additionally, forbesione was found to synergistically exhibit antitumor effects with 5-FU in Ham-1 cells through apoptosis induction (Boueroy et al., 2017). Isomorellin and forbesione induced apoptosis by regulating the expression of apoptosis-

related genes and proteins in CCA cell lines (Hahnvajjanawong et al., 2010). In addition, isomorellin/DOX and forbesione/DOX combinations showed synergistic effects on CCA cells, but the same drug combinations did not show synergistic properties in human liver Chang cells. The result indicated that isomorellin and forbesione enhanced the antitumor effects of DOX and selectively inhibited the growth of CCA cell lines (Hahnvajjanawong et al., 2014).

4.3 Extract of gamboge

The ethanolic extract of gamboge (EGG) upregulated E-cadherin expression to induce dose-dependent apoptosis in colon cancer cells. In addition, EGG reduced β -catenin to inhibit Wnt signaling, resulting in decreased cyclin D1 and matrix metalloproteinase (MMP)-7 (Wang W. et al., 2018).

5 Discussion

Natural products have evolved over a long period in nature, and TCMs have been used for thousands of years. Although there are many problems of active ingredients from TCMs, such as poor water solubility, poor stability, and low bioavailability, which limited the clinical application, preclinical research works showed that various active ingredients from TCMs have excellent antitumor abilities. Gamboge is a reddish yellow/orange-yellow colloidal resin secreted by *Garcinia hanburyi* Hook f., mainly from China, Cambodia, Thailand, Vietnam, India, and other tropical regions, and has been used to treat scrofula, carbuncle, and boils, which modern medicine considers to be inflammation or cancer. In this review, we summarized the anticancer effect and mechanism of the active ingredients from gamboge. GA prevents the development of tumors by inducing apoptosis, regulating cell autophagy, blocking the cell cycle, restricting cell metastasis, impeding angiogenesis, and reversing drug resistance. GNA has more substantial antitumor effects and less systemic toxicity than GA and exerts antitumor activity through several mechanisms, including the induction of apoptosis and ferroptosis, cell cycle arrest, and drug resistance reversion. Iso-GNA primarily induces autophagy and inhibits angiogenesis. Isomorellin can induce cell cycle arrest and suppress tumor cell migration. Forbesione promotes cancer cell apoptosis to inhibit tumor growth. Meanwhile, the side effect of gamboge limits the clinical application, especially GA. Previous studies have mentioned that a high dose of GA can impair kidney and liver function. GA also affected pregnant rats and fetuses in a dose-dependent manner. GNA/iso-GNA exerted lower toxicity *in vitro/in vivo* than GA, but the specific mechanisms remain unknown because of the lack of specialized toxicity tests of GNA/iso-GNA. GNA/iso-GNA differs from GA in terms of the structure on the open ring of its pyran. We presume that the poisonousness of GA is possibly due to the presence of its pyran ring. Therefore, the reverse effects might be improved by changing the chemical structure of GA. Moreover, almost no studies have elaborated on the toxicity of other components; the side effects of these compounds with excellent antitumor activity should be explored in the future.

The reverse effects of GA might have led to the failure of its clinical trials, and the clinical superiority assessment of GA was disrupted due to the rapid metabolism and short half-life (Wang et al., 2024). The clinical translation of GA is limited by these challenges. As a result, we suppose that more delivery systems or chemical modifications probably promote the development. Reducing the dose of administration, increasing dosing intervals, or combining with other chemotherapy drugs may decrease the toxicity of GA. Compared to GA, GNA showed less toxicity and even protective effects on the liver. GNA has a higher potential for clinical application.

When compared to other anticancer agents, the active ingredients of gamboge have a number of advantages over them. For example, the current approaches for treating GBM are surgery, radiotherapy, and chemotherapy using TMZ. However, the primary obstacle remained the emergence of TMZ resistance. In a previous study, GA caused stronger apoptosis in TMZ- and IR-resistant cells, and the combination of GA and TMZ or IR enhanced therapeutic efficacy (Sun et al., 2024). GA has been shown to be more cytotoxic than CDDP in NSCLC cell lines *in vitro*; GA also sensitized NSCLC cells to CDDP to inhibit tumor growth *in vivo* (Wang L. H. et al., 2014). Moreover, GNA exhibited potent inhibitory activities in CDDP-resistant NSCLC cells (Shen et al., 2020), and GNA potentiated the therapeutic efficacy of erlotinib on NSCLC (Xu et al., 2018). The application of gamboge may solve the challenges of drug resistance in the clinic and provide more therapeutic approaches for patients suffering from refractor and recurrent cancers.

6 Conclusion

In this review, we summarized the research on antitumor properties and mechanisms of gamboge's active xanthone ingredients. Evidence suggests that the active components of gamboge have various antitumor activities *in vitro* and *in vivo*, including triggering cell apoptosis, inducing cell cycle arrest, and inhibiting cell invasion and migration. Several novel drug delivery systems are listed simultaneously, such as GA-loaded micelles, nanoparticles, and GNA-encapsulated nanoparticles and liposomes. Moreover, the antitumor mechanisms of these compounds still need to be further explored to develop more antitumor agents. There was little development in exploring the structure of the xanthone moiety of gamboge ingredients. Therefore, the commonalities of xanthone moieties and the role of the structure in treating cancers need to be explored in the future. In conclusion,

the development of active ingredients from gamboge will attract more and more attention, especially in clinical applications.

Author contributions

YZ: Writing – original draft. JC: Writing – original draft. QZ: Writing – review and editing. BL: Writing – review and editing, Conceptualization, Supervision.

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Conflict of interest

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References

- Aggarwal, B. B., and Sung, B. (2011). NF- κ B in cancer: a matter of life and death. *Cancer Discov.* 1 (6), 469–471. doi:10.1158/2159-8290.CD-11-0260
- Albayrak, D., Doğanlar, O., Erdoğan, S., Meraklı, M., Doğan, A., Turker, P., et al. (2021). Naringin combined with NF- κ B inhibition and endoplasmic reticulum stress induces apoptotic cell death via oxidative stress and the PERK/eIF2 α /ATF4/CHOP Axis in HT29 colon cancer cells. *Biochem. Genet.* 59 (1), 159–184. doi:10.1007/s10528-020-09996-5
- Anantachoke, N., Tuchinda, P., Kuhakarn, C., Pohmakotr, M., and Reutrakul, V. (2012). Prenylated caged xanthones: chemistry and biology. *Pharm. Biol.* 50 (1), 78–91. doi:10.3109/13880209.2011.636176
- Anwanwan, D., Singh, S. K., Singh, S., Saikam, V., and Singh, R. (2020). Challenges in liver cancer and possible treatment approaches. *Biochim. Biophys. Acta Rev. Cancer* 1873 (1), 188314. doi:10.1016/j.bbcan.2019.188314
- Auyeung, K. K., Han, Q. B., and Ko, J. K. (2016). Astragalus membranaceus: a review of its protection against inflammation and gastrointestinal cancers. *Am. J. Chin. Med.* 44 (1), 1–22. doi:10.1142/s0192415x16500014
- Beck, J. T., Ismail, A., and Tolomeo, C. (2014). Targeting the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway: an emerging treatment strategy for squamous cell lung carcinoma. *Cancer Treat. Rev.* 40 (8), 980–989. doi:10.1016/j.ctrv.2014.06.006

- Boueroy, P., Hahnvanawong, C., Boonmars, T., Saensa-Ard, S., Anantachoke, N., Vaeteewoottacharn, K., et al. (2016). Antitumor effect of forbesione isolated from *Garcinia hanburyi* on cholangiocarcinoma *in vitro* and *in vivo*. *Oncol. Lett.* 12 (6), 4685–4698. doi:10.3892/ol.2016.5284
- Boueroy, P., Hahnvanawong, C., Boonmars, T., Saensa-ard, S., Wattanawongdon, W., Kongsanthia, C., et al. (2017). Synergistic effect of forbesione from *Garcinia hanburyi* in combination with 5-fluorouracil on cholangiocarcinoma. *Asian Pac J. Cancer Prev.* 18 (12), 3343–3351. doi:10.22034/apjcp.2017.18.12.3343
- Boyd, N. H., Tran, A. N., Bernstock, J. D., Etminan, T., Jones, A. B., Gillespie, G. Y., et al. (2021). Glioma stem cells and their roles within the hypoxic tumor microenvironment. *Theranostics* 11 (2), 665–683. doi:10.7150/thno.41692
- Cai, L., Qiu, N., Xiang, M., Tong, R., Yan, J., He, L., et al. (2014). Improving aqueous solubility and antitumor effects by nanosized gambogic acid-mPEG₂₀₀₀ micelles. *Int. J. Nanomedicine* 9, 243–255. doi:10.2147/ijn.S54050
- Chen, R., Zhang, H., Liu, P., Wu, X., and Chen, B. (2017). Gambogic acid synergistically potentiates bortezomib-induced apoptosis in multiple myeloma. *J. Cancer* 8 (5), 839–851. doi:10.7150/jca.17657
- Chen, X., Zhang, X., Cai, H., Yang, W., Lei, H., Xu, H., et al. (2020a). Targeting USP9x/SOX2 axis contributes to the anti-osteosarcoma effect of neogambogic acid. *Cancer Lett.* 469, 277–286. doi:10.1016/j.canlet.2019.10.015
- Chen, X., Zhao, Y., Luo, W., Chen, S., Lin, F., Zhang, X., et al. (2020b). Celastrol induces ROS-mediated apoptosis via directly targeting peroxiredoxin-2 in gastric cancer cells. *Theranostics* 10 (22), 10290–10308. doi:10.7150/thno.46728
- Choudhury, S., Kolukula, V. K., Preet, A., Albanese, C., and Avantaggiati, M. L. (2013). Dissecting the pathways that destabilize mutant p53: the proteasome or autophagy? *Cell Cycle* 12 (7), 1022–1029. doi:10.4161/cc.24128
- Cordani, M., Oppici, E., Dando, I., Butturini, E., Dalla Pozza, E., Nadal-Serrano, M., et al. (2016). Mutant p53 proteins counteract autophagic mechanism sensitizing cancer cells to mTOR inhibition. *Mol. Oncol.* 10 (7), 1008–1029. doi:10.1016/j.molonc.2016.04.001
- Dang, W., Guo, P., Song, X., Zhang, Y., Li, N., Yu, C., et al. (2021). Nuclear targeted peptide combined with gambogic acid for synergistic treatment of breast cancer. *Front. Chem.* 9, 821426. doi:10.3389/fchem.2021.821426
- Dekker, E., Tanis, P. J., Vleugels, J. L. A., Kasi, P. M., and Wallace, M. B. (2019). Colorectal cancer. *Lancet* 394 (10207), 1467–1480. doi:10.1016/s0140-6736(19)32319-0
- Deng, C., Hu, F., Zhao, Z., Zhou, Y., Liu, Y., Zhang, T., et al. (2021). The establishment of quantitatively regulating expression cassette with sgRNA targeting BIRC5 to elucidate the synergistic pathway of survivin with P-glycoprotein in cancer multidrug resistance. *Front. Cell Dev. Biol.* 9, 797005. doi:10.3389/fcell.2021.797005
- Desai, A. P., Adashek, J. J., Reuss, J. E., West, H. J., and Mansfield, A. S. (2023). Perioperative immune checkpoint inhibition in early-stage non-small cell lung cancer: a review. *JAMA Oncol.* 9 (1), 135–142. doi:10.1001/jamaoncol.2022.5389
- Ding, Z., Li, Y., Tang, Z., Song, X., Jing, F., Wu, H., et al. (2021). Role of gambogic acid in regulating PI3K/Akt/NF- κ B signaling pathways in rat model of acute hepatotoxicity. *Biosci. Biotechnol. Biochem.* 85 (3), 520–527. doi:10.1093/bbb/zbab039
- Dixon, S. J., Lemberg, K. M., Lamprecht, M. R., Skouta, R., Zaitsev, E. M., Gleason, C. E., et al. (2012). Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell* 149 (5), 1060–1072. doi:10.1016/j.cell.2012.03.042
- Doddapaneni, R., Patel, K., Owaid, I. H., and Singh, M. (2016). Tumor neovasculature-targeted cationic PEGylated liposomes of gambogic acid for the treatment of triple-negative breast cancer. *Drug Deliv.* 23 (4), 1232–1241. doi:10.3109/10717544.2015.1124472
- Du, Q., Lv, F., Huang, J., Tang, X., Zhao, Z., and Chen, J. (2021). A multiple environment-sensitive prodrug nanomicelle strategy based on chitosan graftomer for enhanced tumor therapy of gambogic acid. *Carbohydr. Polym.* 267, 118229. doi:10.1016/j.carbpol.2021.118229
- Duan, D., Zhang, B., Yao, J., Liu, Y., Sun, J., Ge, C., et al. (2014). Gambogic acid induces apoptosis in hepatocellular carcinoma SMMC-7721 cells by targeting cytosolic thioredoxin reductase. *Free Radic. Biol. Med.* 69, 15–25. doi:10.1016/j.freeradbiomed.2013.12.027
- Duffy, M. J., Synnott, N. C., and Crown, J. (2017). Mutant p53 as a target for cancer treatment. *Eur. J. Cancer* 83, 258–265. doi:10.1016/j.ejca.2017.06.023
- Feng, L., Cao, B., Liu, M., Zhang, D., Wu, W., Jiang, B., et al. (2016). Proteomic analysis revealed the important role of vimentin in human cervical carcinoma HeLa cells treated with gambogic acid. *Mol. Cell Proteomics* 15 (1), 26–44. doi:10.1074/mcp.M115.053272
- Foggetti, G., Ottaggio, L., Russo, D., Monti, P., Degan, P., Fronza, G., et al. (2017). Gambogic acid counteracts mutant p53 stability by inducing autophagy. *Biochim. Biophys. Acta Mol. Cell Res.* 1864 (2), 382–392. doi:10.1016/j.bbamcr.2016.11.023
- Fujii, S., Mitsunaga, S., Yamazaki, M., Hasebe, T., Ishii, G., Kojima, M., et al. (2008). Autophagy is activated in pancreatic cancer cells and correlates with poor patient outcome. *Cancer Sci.* 99 (9), 1813–1819. doi:10.1111/j.1349-7006.2008.00893.x
- Geho, D. H., Bandle, R. W., Clair, T., and Liotta, L. A. (2005). Physiological mechanisms of tumor-cell invasion and migration. *Physiol. (Bethesda)* 20, 194–200. doi:10.1152/physiol.00009.2005
- Gold-Smith, F., Fernandez, A., and Bishop, K. (2016). Mangiferin and cancer: mechanisms of action. *Nutrients* 8 (7), 396. doi:10.3390/nu8070396
- Gu, H., Wang, X., Rao, S., Wang, J., Zhao, J., Ren, F. L., et al. (2008). Gambogic acid mediates apoptosis as a p53 inducer through down-regulation of mdm2 in wild-type p53-expressing cancer cells. *Mol. Cancer Ther.* 7 (10), 3298–3305. doi:10.1158/1535-7163.Mct-08-0212
- Guo, Q., Qi, Q., You, Q., Gu, H., Zhao, L., and Wu, Z. (2006). Toxicological studies of gambogic acid and its potential targets in experimental animals. *Basic Clin. Pharmacol. Toxicol.* 99 (2), 178–184. doi:10.1111/j.1742-7843.2006.pto_485.x
- Gupta, S., Kass, G. E., Szegezdi, E., and Joseph, B. (2009). The mitochondrial death pathway: a promising therapeutic target in diseases. *J. Cell Mol. Med.* 13 (6), 1004–1033. doi:10.1111/j.1582-4934.2009.00697.x
- Hahnvanawong, C., Boonyanugomol, W., Nasomyon, T., Loilome, W., Namwat, N., Anantachoke, N., et al. (2010). Apoptotic activity of caged xanthenes from *Garcinia hanburyi* in cholangiocarcinoma cell lines. *World J. Gastroenterol.* 16 (18), 2235–2243. doi:10.3748/wjg.v16.i18.2235
- Hahnvanawong, C., Ketnimit, S., Pattanapanyasat, K., Anantachoke, N., Sripa, B., Pinnai, K., et al. (2012). Involvement of p53 and nuclear factor- κ B signaling pathway for the induction of G1-phase cell cycle arrest of cholangiocarcinoma cell lines by isomorellin. *Biol. Pharm. Bull.* 35 (11), 1914–1925. doi:10.1248/bpb.b12-00118
- Hahnvanawong, C., Sahakulboonyarak, T., Boonmars, T., Reutrakul, V., Kerdsin, A., and Boueroy, P. (2021). Inhibitory effect of isomorellin on cholangiocarcinoma cells via suppression of NF- κ B translocation, the phosphorylated p38 MAPK pathway and MMP-2 and uPA expression. *Exp. Ther. Med.* 21 (2), 151. doi:10.3892/etm.2020.9583
- Hahnvanawong, C., Wattanawongdon, W., Chomvarin, C., Anantachoke, N., Kanthawong, S., Sripa, B., et al. (2014). Synergistic effects of isomorellin and forbesione with doxorubicin on apoptosis induction in human cholangiocarcinoma cell lines. *Cancer Cell Int.* 14, 68. doi:10.1186/1475-2867-14-68
- Halbrook, C. J., Lyssiotis, C. A., Pasca di Magliano, M., and Maitra, A. (2023). Pancreatic cancer: advances and challenges. *Cell* 186 (8), 1729–1754. doi:10.1016/j.cell.2023.02.014
- Hanahan, D., and Weinberg, R. A. (2000). The hallmarks of cancer. *Cell* 100 (1), 57–70. doi:10.1016/s0092-8674(00)81683-9
- Haque, A., Brazeau, D., and Amin, A. R. (2021). Perspectives on natural compounds in chemoprevention and treatment of cancer: an update with new promising compounds. *Eur. J. Cancer* 149, 165–183. doi:10.1016/j.ejca.2021.03.009
- Harbeck, N., and Gnant, M. (2017). Breast cancer. *Lancet* 389 (10074), 1134–1150. doi:10.1016/s0140-6736(16)31891-8
- Hatami, E., Jaggi, M., Chauhan, S. C., and Yallapu, M. M. (2020a). Gambogic acid: a shining natural compound to nanomedicine for cancer therapeutics. *Biochim. Biophys. Acta Rev. Cancer* 1874 (1), 188381. doi:10.1016/j.bbcan.2020.188381
- Hatami, E., Nagesh, P. K. B., Jaggi, M., Chauhan, S. C., and Yallapu, M. M. (2020b). Gambogic acid potentiates gemcitabine induced anticancer activity in non-small cell lung cancer. *Eur. J. Pharmacol.* 888, 173486. doi:10.1016/j.ejphar.2020.173486
- Huang, G. M., Sun, Y., Ge, X., Wan, X., and Li, C. B. (2015). Gambogic acid induces apoptosis and inhibits colorectal tumor growth via mitochondrial pathways. *World J. Gastroenterol.* 21 (20), 6194–6205. doi:10.3748/wjg.v21.i20.6194
- Huang, T., Zhang, H., Wang, X., Xu, L., Jia, J., and Zhu, X. (2019). Gambogic acid inhibits the proliferation of small-cell lung cancer cells by arresting the cell cycle and inducing apoptosis. *Oncol. Rep.* 41 (3), 1700–1706. doi:10.3892/or.2018.6950
- Iizuka, N., Miyamoto, K., Okita, K., Tangoku, A., Hayashi, H., Yosino, S., et al. (2000). Inhibitory effect of Coptidis Rhizoma and berberine on the proliferation of human esophageal cancer cell lines. *Cancer Lett.* 148 (1), 19–25. doi:10.1016/s0304-3835(99)00264-5
- Jang, J. H., Kim, J. Y., Sung, E. G., Kim, E. A., and Lee, T. J. (2016). Gambogic acid induces apoptosis and sensitizes TRAIL-mediated apoptosis through downregulation of cFLIPL in renal carcinoma Caki cells. *Int. J. Oncol.* 48 (1), 376–384. doi:10.3892/ijo.2015.3249
- Jiang, L. L., Li, K., Lin, Q. H., Ren, J., He, Z. H., Li, H., et al. (2016). Gambogic acid causes fin developmental defect in zebrafish embryo partially via retinoic acid signaling. *Reprod. Toxicol.* 63, 161–168. doi:10.1016/j.reprotox.2016.06.004
- Joha, Z., Öztürk, A., Yulak, F., Karataş, Ö., and Ataseven, H. (2023). Mechanism of anticancer effect of gambogic acid on gastric signet ring cell carcinoma. *Med. Oncol.* 40 (9), 269. doi:10.1007/s12032-023-02149-9
- Kasibhatla, S., Jessen, K. A., Maliartchouk, S., Wang, J. Y., English, N. M., Drewe, J., et al. (2005). A role for transferrin receptor in triggering apoptosis when targeted with gambogic acid. *Proc. Natl. Acad. Sci. U. S. A.* 102 (34), 12095–12100. doi:10.1073/pnas.0406731102
- Khromova, N. V., Kopnin, P. B., Stepanova, E. V., Agapova, L. S., and Kopnin, B. P. (2009). p53 hot-spot mutants increase tumor vascularization via ROS-mediated activation of the HIF1/VEGF-A pathway. *Cancer Lett.* 276 (2), 143–151. doi:10.1016/j.canlet.2008.10.049
- Küpeli Akkol, E., Bardakci, H., Barak, T. H., Aschner, M., Şeker Karatoprak, G., Khan, H., et al. (2022). Herbal ingredients in the prevention of breast cancer: comprehensive

review of potential molecular targets and role of natural products. *Oxid. Med. Cell Longev.* 2022, 6044640. doi:10.1155/2022/6044640

Lei, D., Wang, W., Zhao, J., Zhou, Y., Chen, Y., Dai, J., et al. (2025). An injectable gambogic acid loaded nanocomposite hydrogel enhances antitumor effect by reshaping immunosuppressive tumor microenvironment. *Mater. Today Bio* 31, 101611. doi:10.1016/j.mtbio.2025.101611

Lemke, J., von Karstedt, S., Zinngrebe, J., and Walczak, H. (2014). Getting TRAIL back on track for cancer therapy. *Cell Death Differ.* 21 (9), 1350–1364. doi:10.1038/cdd.2014.81

Li, C., Lu, N., Qi, Q., Li, F., Ling, Y., Chen, Y., et al. (2011). Gambogic acid inhibits tumor cell adhesion by suppressing integrin $\beta 1$ and membrane lipid rafts-associated integrin signaling pathway. *Biochem. Pharmacol.* 82 (12), 1873–1883. doi:10.1016/j.bcp.2011.09.013

Li, C. Y., Wang, Q., Wang, X. M., Li, G. X., Shen, S., and Wei, X. L. (2019a). Gambogic acid exhibits anti-metastatic activity on malignant melanoma mainly through inhibition of PI3K/Akt and ERK signaling pathways. *Eur. J. Pharmacol.* 864, 172719. doi:10.1016/j.ejphar.2019.172719

Li, X., Tang, X., Su, J., Xu, G., Zhao, L., and Qi, Q. (2019b). Involvement of E-cadherin/AMPK/mTOR axis in LKB1-induced sensitivity of non-small cell lung cancer to gambogic acid. *Biochem. Pharmacol.* 169, 113635. doi:10.1016/j.bcp.2019.113635

Li, Y., Lu, Y., Wu, M., Wang, H., Gong, Y., and Gu, Y. (2022a). Neogambogic acid suppresses characteristics and growth of colorectal cancer stem cells by inhibition of DLK1 and Wnt/ β -catenin pathway. *Eur. J. Pharmacol.* 929, 175112. doi:10.1016/j.ejphar.2022.175112

Li, Y., Zhang, H., Merker, Y., Chen, L., Liu, N., Leonov, S., et al. (2022b). Recent advances in therapeutic strategies for triple-negative breast cancer. *J. Hematol. Oncol.* 15 (1), 121. doi:10.1186/s13045-022-01341-0

Liang, X. H., Jackson, S., Seaman, M., Brown, K., Kempkes, B., Hibshoosh, H., et al. (1999). Induction of autophagy and inhibition of tumorigenesis by beclin 1. *Nature* 402 (6762), 672–676. doi:10.1038/45257

Lin, D., Lin, X., He, T., and Xie, G. (2020). Gambogic acid inhibits the progression of gastric cancer via circRNA_ASAP2/miR-33a-5p/CDK7 Axis. *Cancer Manag. Res.* 12, 9221–9233. doi:10.2147/cmar.S269768

Liu, J., Liu, H., Huang, S., Peng, H., Li, J., Tu, K., et al. (2024). Multiple treatment of triple-negative breast cancer through gambogic acid-loaded mesoporous polydopamine. *Small* 20 (31), e2309583. doi:10.1002/sml.202309583

Liu, L., Li, J., and He, Y. (2020a). Multifunctional epiberberine mediates multi-therapeutic effects. *Fitoterapia* 147, 104771. doi:10.1016/j.fitote.2020.104771

Liu, X., Hu, Q., Wang, W., Ma, H., Pu, J., Cui, J., et al. (2021). A protein-fragment complementation assay reveals that celastrol and gambogic acid suppress ER α mutants in breast cancer. *Biochem. Pharmacol.* 188, 114583. doi:10.1016/j.bcp.2021.114583

Liu, Y., Chen, Y., Lin, L., and Li, H. (2020b). Gambogic acid as a candidate for cancer therapy: a review. *Int. J. Nanomedicine* 15, 10385–10399. doi:10.2147/ijn.S277645

Loo, W. T., Jin, L. J., Chow, L. W., Cheung, M. N., and Wang, M. (2010). Rhodiola alga improves chemotherapy-induced oral mucositis in breast cancer patients. *Expert Opin. Investig. Drugs* 19 (Suppl. 1), S91–S100. doi:10.1517/13543781003727057

Lü, L., Tang, D., Wang, L., Huang, L. Q., Jiang, G. S., Xiao, X. Y., et al. (2012). Gambogic acid inhibits TNF- α -induced invasion of human prostate cancer PC3 cells *in vitro* through PI3K/Akt and NF- κ B signaling pathways. *Acta Pharmacol. Sin.* 33 (4), 531–541. doi:10.1038/aps.2011.180

Luo, H., Vong, C. T., Chen, H., Gao, Y., Lyu, P., Qiu, L., et al. (2019). Naturally occurring anti-cancer compounds: shining from Chinese herbal medicine. *Chin. Med.* 14, 48. doi:10.1186/s13020-019-0270-9

Luo, Q., Lin, T., Zhang, C. Y., Zhu, T., Wang, L., Ji, Z., et al. (2015). A novel glyceryl monoolein-bearing cubosomes for gambogic acid: preparation, cytotoxicity and intracellular uptake. *Int. J. Pharm.* 493 (1–2), 30–39. doi:10.1016/j.ijpharm.2015.07.036

Lyu, S., Zhang, X., Tu, Z., Zhou, H., Ke, X., and Qu, Y. (2022). GPR108 is required for gambogic acid inhibiting NF- κ B signaling in cancer. *Pharmacol. Res.* 182, 106279. doi:10.1016/j.phrs.2022.106279

Maleki Dana, P., Sadoughi, F., Asemi, Z., and Yousefi, B. (2022). The role of polyphenols in overcoming cancer drug resistance: a comprehensive review. *Cell Mol. Biol. Lett.* 27 (1), 1. doi:10.1186/s11658-021-00301-9

Malla, R., Padmaraju, V., and Kundrapu, D. B. (2022). Tumor-associated macrophages: potential target of natural compounds for management of breast cancer. *Life Sci.* 301, 120572. doi:10.1016/j.lfs.2022.120572

Mei, W., Dong, C., Hui, C., Bin, L., Fenggen, Y., Jingjing, S., et al. (2014). Gambogic acid kills lung cancer cells through aberrant autophagy. *PLoS One* 9 (1), e83604. doi:10.1371/journal.pone.0083604

Natarajan, J. V., Nugraha, C., Ng, X. W., and Venkatraman, S. (2014). Sustained-release from nanocarriers: a review. *J. Control Release* 193, 122–138. doi:10.1016/j.jconrel.2014.05.029

Oakes, S. A. (2020). Endoplasmic reticulum stress signaling in cancer cells. *Am. J. Pathol.* 190 (5), 934–946. doi:10.1016/j.ajpath.2020.01.010

Oh, H. N., Lee, M. H., Kim, E., Yoon, G., Chae, J. I., and Shim, J. H. (2019). Licochalcone B inhibits growth and induces apoptosis of human non-small-cell lung cancer cells by dual targeting of EGFR and MET. *Phytomedicine* 63, 153014. doi:10.1016/j.phymed.2019.153014

Olaussen, K. A., and Postel-Vinay, S. (2016). Predictors of chemotherapy efficacy in non-small-cell lung cancer: a challenging landscape. *Ann. Oncol.* 27 (11), 2004–2016. doi:10.1093/annonc/mdw321

O'Neill, K. L., Huang, K., Zhang, J., Chen, Y., and Luo, X. (2016). Inactivation of prosurvival Bcl-2 proteins activates Bax/Bak through the outer mitochondrial membrane. *Genes Dev.* 30 (8), 973–988. doi:10.1101/gad.276725.115

Ortiz-Sánchez, E., Daniels, T. R., Helguera, G., Martínez-Maza, O., Bonavida, B., and Penichet, M. L. (2009). Enhanced cytotoxicity of an anti-transferrin receptor IgG3-avidin fusion protein in combination with gambogic acid against human malignant hematopoietic cells: functional relevance of iron, the receptor, and reactive oxygen species. *Leukemia* 23 (1), 59–70. doi:10.1038/leu.2008.270

Park, S. C., Heo, H., and Jang, M. K. (2022). Polyethylenimine grafted-chitosan based Gambogic acid copolymers for targeting cancer cells overexpressing transferrin receptors. *Carbohydr. Polym.* 277, 118755. doi:10.1016/j.carbpol.2021.118755

Pistritto, G., Trisciuglio, D., Ceci, C., Garufi, A., and D'Orazi, G. (2016). Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies. *Aging (Albany NY)* 8 (4), 603–619. doi:10.18632/aging.100934

Pollak, N., Lindner, A., Imig, D., Kuritz, K., Fritze, J. S., Decker, L., et al. (2021). Cell cycle progression and transmittic apoptosis resistance promote escape from extrinsic apoptosis. *J. Cell Sci.* 134 (24), jcs258966. doi:10.1242/jcs.258966

Popgeorgiev, N., Sa, J. D., Jabbour, L., Banjara, S., Nguyen, T. T. M., Akhavan, E. S. A., et al. (2020). Ancient and conserved functional interplay between Bcl-2 family proteins in the mitochondrial pathway of apoptosis. *Sci. Adv.* 6 (40), eabc4149. doi:10.1126/sciadv.abc4149

Qi, Q., You, Q., Gu, H., Zhao, L., Liu, W., Lu, N., et al. (2008). Studies on the toxicity of gambogic acid in rats. *J. Ethnopharmacol.* 117 (3), 433–438. doi:10.1016/j.jep.2008.02.027

Qian, C. M., Yang, L., Wang, Y. Y., Wang, Z. L., Xu, Z. H., Xu, M. D., et al. (2025). Gambogic acid induces ferroptosis via miR-1291/FOXA2 Axis in gastric cancer. *Am. J. Chin. Med.* 53 (3), 951–971. doi:10.1142/s0192415x25500363

Rejhová, A., Opatková, A., Čumová, A., Sliva, D., and Vodička, P. (2018). Natural compounds and combination therapy in colorectal cancer treatment. *Eur. J. Med. Chem.* 144, 582–594. doi:10.1016/j.ejmech.2017.12.039

Ren, T., Bai, X. Y., Yang, M. Z., Xu, N., Guo, X. Z., Qin, L. J., et al. (2022). Gambogic acid suppresses nasopharyngeal carcinoma via rewiring molecular network of cancer malignancy and immunosurveillance. *Biomed. Pharmacother.* 150, 113012. doi:10.1016/j.biopha.2022.113012

Rong, L., Li, Z., Leng, X., Li, H., Ma, Y., Chen, Y., et al. (2020). Salidroside induces apoptosis and protective autophagy in human gastric cancer AGS cells through the PI3K/Akt/mTOR pathway. *Biomed. Pharmacother.* 122, 109726. doi:10.1016/j.biopha.2019.109726

Sanchez-Martin, V., Plaza-Calonge, M. D. C., Soriano-Lerma, A., Ortiz-Gonzalez, M., Linde-Rodriguez, A., Perez-Carrasco, V., et al. (2022). Gallic acid: a natural phenolic compound exerting antitumoral activities in colorectal cancer via interaction with G-quadruplexes. *Cancers (Basel)* 14 (11), 2648. doi:10.3390/cancers14112648

Sang, M. M., Liu, F. L., Wang, Y., Luo, R. J., Huan, X. X., Han, L. F., et al. (2018). A novel redox/pH dual-responsive and hyaluronic acid-decorated multifunctional magnetic complex micelle for targeted gambogic acid delivery for the treatment of triple negative breast cancer. *Drug Deliv.* 25 (1), 1846–1857. doi:10.1080/10717544.2018.1486472

Seo, M. J., Lee, D. M., Kim, I. Y., Lee, D., Choi, M. K., Lee, J. Y., et al. (2019). Gambogic acid triggers vacuolization-associated cell death in cancer cells via disruption of thiol proteostasis. *Cell Death Dis.* 10 (3), 187. doi:10.1038/s41419-019-1360-4

Shen, D., Wang, Y., Niu, H., and Liu, C. (2020). Gambogic acid exerts anticancer effects in cisplatin-resistant non-small cell lung cancer cells. *Mol. Med. Rep.* 21 (3), 1267–1275. doi:10.3892/mmr.2020.10909

Shi, X., Chen, X., Li, X., Lan, X., Zhao, C., Liu, S., et al. (2014). Gambogic acid induces apoptosis in imatinib-resistant chronic myeloid leukemia cells via inducing proteasome inhibition and caspase-dependent Bcr-Abl downregulation. *Clin. Cancer Res.* 20 (1), 151–163. doi:10.1158/1078-0432.Ccr-13-1063

Shukuya, T., Yamada, T., Koenig, M. J., Xu, J., Okimoto, T., Li, F., et al. (2019). The effect of LKB1 activity on the sensitivity to PI3K/mTOR inhibition in non-small cell lung cancer. *J. Thorac. Oncol.* 14 (6), 1061–1076. doi:10.1016/j.jtho.2019.02.019

Siegel, R. L., Miller, K. D., Wagle, N. S., and Jemal, A. (2023). Cancer statistics, 2023. *CA Cancer J. Clin.* 73 (1), 17–48. doi:10.3322/caac.21763

Singh, P., and Lim, B. (2022). Targeting apoptosis in cancer. *Curr. Oncol. Rep.* 24 (3), 273–284. doi:10.1007/s11912-022-01199-y

Singh, R., Letai, A., and Sarosiek, K. (2019). Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins. *Nat. Rev. Mol. Cell Biol.* 20 (3), 175–193. doi:10.1038/s41580-018-0089-8

- Sperandio, S., de Belle, I., and Bredesen, D. E. (2000). An alternative, nonapoptotic form of programmed cell death. *Proc. Natl. Acad. Sci. U. S. A.* 97 (26), 14376–14381. doi:10.1073/pnas.97.26.14376
- Su, J., Xu, T., Jiang, G., Hou, M., Liang, M., Cheng, H., et al. (2019). Gambogic acid triggers apoptosis in human nasopharyngeal carcinoma CNE-2Z cells by activating volume-sensitive outwardly rectifying chloride channel. *Fitoterapia* 133, 150–158. doi:10.1016/j.fitote.2019.01.002
- Sun, T., Lin, B., Sun, Q., Zhang, X., Wang, T., Yang, J., et al. (2024). Gambogic acid impairs the maintenance and therapeutic resistance of glioma stem cells by targeting B-cell-specific Moloney leukemia virus insert site 1. *Phytomedicine* 135, 156070. doi:10.1016/j.phymed.2024.156070
- Sun, R., Zhang, H. M., and Chen, B. A. (2018). Anticancer activity and underlying mechanism of neogambogic acid. *Chin. J. Nat. Med.* 16 (9), 641–643. doi:10.1016/s1875-5364(18)30103-1
- Tang, X., Sun, J., Ge, T., Zhang, K., Gui, Q., Zhang, S., et al. (2018). PEGylated liposomes as delivery systems for Gambogic acid: characterization and *in vitro/in vivo* evaluation. *Colloids Surf. B Biointerfaces* 172, 26–36. doi:10.1016/j.colsurfb.2018.08.022
- Vimalraj, S. (2022). A concise review of VEGF, PDGF, FGF, Notch, angiopoietin, and HGF signalling in tumor angiogenesis with a focus on alternative approaches and future directions. *Int. J. Biol. Macromol.* 221, 1428–1438. doi:10.1016/j.ijbiomac.2022.09.129
- Wan, L., Zhang, Q., Wang, S., Gao, Y., Chen, X., Zhao, Y., et al. (2019). Gambogic acid impairs tumor angiogenesis by targeting YAP/STAT3 signaling axis. *Phytother. Res.* 33 (5), 1579–1591. doi:10.1002/ptr.6350
- Wang, B., Yuan, T., Zha, L., Liu, Y., Chen, W., Zhang, C., et al. (2021). Oral delivery of gambogic acid by functional polydopamine nanoparticles for targeted tumor therapy. *Mol. Pharm.* 18 (3), 1470–1479. doi:10.1021/acs.molpharmaceut.1c00030
- Wang, F., Dong, L., Liang, S., Wei, X., Wang, Y., Chang, L., et al. (2022a). Ultrasound-triggered drug delivery for glioma therapy through gambogic acid-loaded nanobubble-microbubble complexes. *Biomed. Pharmacother.* 150, 113042. doi:10.1016/j.biopha.2022.113042
- Wang, F., Zhang, W., Guo, L., Bao, W., Jin, N., Liu, R., et al. (2014a). Gambogic acid suppresses hypoxia-induced hypoxia-inducible factor-1 α /vascular endothelial growth factor expression via inhibiting phosphatidylinositol 3-kinase/Akt/mammalian target protein of rapamycin pathway in multiple myeloma cells. *Cancer Sci.* 105 (8), 1063–1070. doi:10.1111/cas.12458
- Wang, H., Zhao, Z., Lei, S., Li, S., Xiang, Z., Wang, X., et al. (2019). Gambogic acid induces autophagy and combines synergistically with chloroquine to suppress pancreatic cancer by increasing the accumulation of reactive oxygen species. *Cancer Cell Int.* 19, 7. doi:10.1186/s12935-018-0705-x
- Wang, J., Zhao, L., Hu, Y., Guo, Q., Zhang, L., Wang, X., et al. (2009). Studies on chemical structure modification and biology of a natural product, gambogic acid (I): synthesis and biological evaluation of oxidized analogues of gambogic acid. *Eur. J. Med. Chem.* 44 (6), 2611–2620. doi:10.1016/j.ejmech.2008.09.034
- Wang, L. H., Li, Y., Yang, S. N., Wang, F. Y., Hou, Y., Cui, W., et al. (2014b). Gambogic acid synergistically potentiates cisplatin-induced apoptosis in non-small-cell lung cancer through suppressing NF- κ B and MAPK/HO-1 signalling. *Br. J. Cancer* 110 (2), 341–352. doi:10.1038/bjc.2013.752
- Wang, W., Li, Y., Chen, Y., Chen, H., Zhu, P., Xu, M., et al. (2018b). Ethanolic extract of traditional Chinese medicine (TCM) Gamboge inhibits colon cancer via the wnt/ β -catenin signaling pathway in an orthotopic mouse model. *Anticancer Res.* 38 (4), 1917–1925. doi:10.21873/anticancer.12429
- Wang, M., Cheng, H., Wu, H., Liu, C., Li, S., Li, B., et al. (2022b). Gambogic acid antagonizes the expression and effects of long non-coding RNA NEAT1 and triggers autophagy and ferroptosis in melanoma. *Biomed. Pharmacother.* 154, 113636. doi:10.1016/j.biopha.2022.113636
- Wang, M., Li, S., Wang, Y., Cheng, H., Su, J., and Li, Q. (2020a). Gambogic acid induces ferroptosis in melanoma cells undergoing epithelial-to-mesenchymal transition. *Toxicol. Appl. Pharmacol.* 401, 115110. doi:10.1016/j.taap.2020.115110
- Wang, R., Xiao, Y., Zhang, Z., Huang, X., Zhu, W., Ma, X., et al. (2024). Simplified gambogic acid prodrug nanoparticles to improve efficiency and reduce toxicity for clinical translation potential. *Adv. Healthc. Mater.* 13 (31), e2401950. doi:10.1002/adhm.202401950
- Wang, S., Xu, Y., Li, C., Tao, H., Wang, A., Sun, C., et al. (2018a). Gambogic acid sensitizes breast cancer cells to TRAIL-induced apoptosis by promoting the crosstalk of extrinsic and intrinsic apoptotic signalings. *Food Chem. Toxicol.* 119, 334–341. doi:10.1016/j.fct.2018.02.037
- Wang, S., Yang, Y., Wang, Y., and Chen, M. (2015). Gambogic acid-loaded pH-sensitive mixed micelles for overcoming breast cancer resistance. *Int. J. Pharm.* 495 (2), 840–848. doi:10.1016/j.ijpharm.2015.09.041
- Wang, T., Wei, J., Qian, X., Ding, Y., Yu, L., and Liu, B. (2008). Gambogic acid, a potent inhibitor of survivin, reverses docetaxel resistance in gastric cancer cells. *Cancer Lett.* 262 (2), 214–222. doi:10.1016/j.canlet.2007.12.004
- Wang, X., Lu, N., Yang, Q., Gong, D., Lin, C., Zhang, S., et al. (2011). Studies on chemical modification and biology of a natural product, gambogic acid (III): determination of the essential pharmacophore for biological activity. *Eur. J. Med. Chem.* 46 (4), 1280–1290. doi:10.1016/j.ejmech.2011.01.051
- Wang, Y., Zhang, Q., Chen, Y., Liang, C. L., Liu, H., Qiu, F., et al. (2020b). Antitumor effects of immunity-enhancing traditional Chinese medicine. *Biomed. Pharmacother.* 121, 109570. doi:10.1016/j.biopha.2019.109570
- Wen, C., Huang, L., Chen, J., Lin, M., Li, W., Lu, B., et al. (2015). Gambogic acid inhibits growth, induces apoptosis, and overcomes drug resistance in human colorectal cancer cells. *Int. J. Oncol.* 47 (5), 1663–1671. doi:10.3892/ijo.2015.3166
- Wu, Y., Zhang, S., Gong, X., Tam, S., Xiao, D., Liu, S., et al. (2020). The epigenetic regulators and metabolic changes in ferroptosis-associated cancer progression. *Mol. Cancer* 19 (1), 39. doi:10.1186/s12943-020-01157-x
- Wu, Y. L., Zhou, C., Hu, C. P., Feng, J., Lu, S., Huang, Y., et al. (2014). Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol.* 15 (2), 213–222. doi:10.1016/s1470-2045(13)70604-1
- Xia, G., Wang, H., Song, Z., Meng, Q., Huang, X., and Huang, X. (2017). Gambogic acid sensitizes gemcitabine efficacy in pancreatic cancer by reducing the expression of ribonucleotide reductase subunit-M2 (RRM2). *J. Exp. Clin. Cancer Res.* 36 (1), 107. doi:10.1186/s13046-017-0579-0
- Xu, L., Meng, X., Xu, N., Fu, W., Tan, H., Zhang, L., et al. (2018). Gambogic acid inhibits fibroblast growth factor receptor signaling pathway in erlotinib-resistant non-small-cell lung cancer and suppresses patient-derived xenograft growth. *Cell Death Dis.* 9 (3), 262. doi:10.1038/s41419-018-0314-6
- Xu, Q., Guo, J., and Chen, W. (2019a). Gambogic acid reverses P-glycoprotein mediated multidrug resistance in HepG2/Adr cells and its underlying mechanism. *Biochem. Biophys. Res. Commun.* 508 (3), 882–888. doi:10.1016/j.bbrc.2018.12.028
- Xu, T., Ding, W., Ji, X., Ao, X., Liu, Y., Yu, W., et al. (2019b). Molecular mechanisms of ferroptosis and its role in cancer therapy. *J. Cell Mol. Med.* 23 (8), 4900–4912. doi:10.1111/jcmm.14511
- Yan, F., Wang, M., Chen, H., Su, J., Wang, X., Wang, F., et al. (2011). Gambogic acid mediated apoptosis through the mitochondrial oxidative stress and inactivation of Akt signaling pathway in human nasopharyngeal carcinoma CNE-1 cells. *Eur. J. Pharmacol.* 652 (1–3), 23–32. doi:10.1016/j.ejphar.2010.11.018
- Yan, F., Wang, M., Li, J., Cheng, H., Su, J., Wang, X., et al. (2012). Gambogic acid induced mitochondrial-dependent apoptosis and referred to phospho-Erk1/2 and phospho-p38 MAPK in human hepatoma HepG2 cells. *Environ. Toxicol. Pharmacol.* 33 (2), 181–190. doi:10.1016/j.etap.2011.12.006
- Yang, J., He, S., Li, S., Zhang, R., Peng, A., and Chen, L. (2013). *In vitro* and *in vivo* antiangiogenic activity of caged polypropylenated xanthones isolated from *Garcinia hanburyi* Hook. f. *Molecules* 18 (12), 15305–15313. doi:10.3390/molecules181215305
- Yang, J., Zhou, Y., Cheng, X., Fan, Y., He, S., Li, S., et al. (2015). Isogambogic acid induces apoptosis-independent autophagic cell death in human non-small-cell lung carcinoma cells. *Sci. Rep.* 5, 7697. doi:10.1038/srep07697
- Yang, L. J., and Chen, Y. (2013). New targets for the antitumor activity of gambogic acid in hematologic malignancies. *Acta Pharmacol. Sin.* 34 (2), 191–198. doi:10.1038/aps.2012.163
- Yihebal, C., Xiao-Kai, Z., Hao, Y. U., Guang-Ru, X., Zhen-Zhong, W., Wei, X., et al. (2013). An open-labeled, randomized, multicenter phase IIa study of gambogic acid injection for advanced malignant tumors. *Chin Med J (Engl)* (9), 5.
- Yu, D., Liu, Y., Zhou, Y., Ruiz-Rodado, V., Larion, M., Xu, G., et al. (2020). Triptolide suppresses IDH1-mutated malignancy via Nrf2-driven glutathione metabolism. *Proc. Natl. Acad. Sci. U. S. A.* 117 (18), 9964–9972. doi:10.1073/pnas.1913631117
- Yu, X. J., Han, Q. B., Wen, Z. S., Ma, L., Gao, J., and Zhou, G. B. (2012). Gambogic acid induces G1 arrest via GSK3 β -dependent cyclin D1 degradation and triggers autophagy in lung cancer cells. *Cancer Lett.* 322 (2), 185–194. doi:10.1016/j.canlet.2012.03.004
- Yu, X. J., Zhao, Q., Wang, X. B., Zhang, J. X., and Wang, X. B. (2016). Gambogic acid induces proteasomal degradation of CIP2A and sensitizes hepatocellular carcinoma to anticancer agents. *Oncol. Rep.* 36 (6), 3611–3618. doi:10.3892/or.2016.5188
- Yuan, H., Li, X., Zhang, C., Pan, W., Liang, Y., Chen, Y., et al. (2016). Nanosuspensions as delivery system for gambogic acid: characterization and *in vitro/in vivo* evaluation. *Drug Deliv.* 23 (8), 2772–2779. doi:10.3109/10717544.2015.1077294
- Zha, L., Qian, J., Wang, B., Liu, H., Zhang, C., Dong, Q., et al. (2020). *In vitro/in vivo* evaluation of pH-sensitive Gambogic acid loaded Zein nanoparticles with polydopamine coating. *Int. J. Pharm.* 587, 119665. doi:10.1016/j.ijpharm.2020.119665
- Zhai, D., Jin, C., Shiau, C. W., Kitada, S., Satterthwait, A. C., and Reed, J. C. (2008). Gambogic acid is an antagonist of antiapoptotic Bcl-2 family proteins. *Mol. Cancer Ther.* 7 (6), 1639–1646. doi:10.1158/1535-7163.Mct-07-2373
- Zhang, H., Lei, Y., Yuan, P., Li, L., Luo, C., Gao, R., et al. (2014). ROS-mediated autophagy induced by dysregulation of lipid metabolism plays a protective role in colorectal cancer cells treated with gambogic acid. *PLoS One* 9 (5), e96418. doi:10.1371/journal.pone.0096418
- Zhang, Z., Qian, H., Huang, J., Sha, H., Zhang, H., Yu, L., et al. (2018). Anti-EGFR-iRGD recombinant protein modified biomimetic nanoparticles loaded with gambogic

- acid to enhance targeting and antitumor ability in colorectal cancer treatment. *Int. J. Nanomedicine* 13, 4961–4975. doi:10.2147/IJN.S170148
- Zhang, Z., Qian, H., Yang, M., Li, R., Hu, J., Li, L., et al. (2017). Gambogic acid-loaded biomimetic nanoparticles in colorectal cancer treatment. *Int. J. Nanomedicine* 12, 1593–1605. doi:10.2147/ijn.S127256
- Zhao, L., and Sanyal, S. (2022). p53 isoforms as cancer biomarkers and therapeutic targets. *Cancers (Basel)* 14 (13), 3145. doi:10.3390/cancers14133145
- Zhao, L., Zhen, C., Wu, Z., Hu, R., Zhou, C., and Guo, Q. (2010). General pharmacological properties, developmental toxicity, and analgesic activity of gambogic acid, a novel natural anticancer agent. *Drug Chem. Toxicol.* 33 (1), 88–96. doi:10.3109/01480540903173534
- Zhao, Q., Zhong, J., Bi, Y., Liu, Y., Liu, Y., Guo, J., et al. (2020). Gambogenic acid induces Noxa-mediated apoptosis in colorectal cancer through ROS-dependent activation of IRE1 α /JNK. *Phytomedicine* 78, 153306. doi:10.1016/j.phymed.2020.153306
- Zhao, W., Peng, F., Shu, M., Liu, H., Hou, X., Wang, X., et al. (2017). Isogambogenic acid inhibits the growth of glioma through activation of the AMPK-mTOR pathway. *Cell Physiol. Biochem.* 44 (4), 1381–1395. doi:10.1159/000485535
- Zhao, Y., Zhang, X., Li, Y., Li, Y., Zhang, H., Song, Z., et al. (2022). A natural xanthone suppresses lung cancer growth and metastasis by targeting STAT3 and FAK signaling pathways. *Phytomedicine* 102, 154118. doi:10.1016/j.phymed.2022.154118
- Zheng, Y., Zhang, W., Xu, L., Zhou, H., Yuan, M., and Xu, H. (2021). Recent progress in understanding the action of natural compounds at novel therapeutic drug targets for the treatment of liver cancer. *Front. Oncol.* 11, 795548. doi:10.3389/fonc.2021.795548
- Zhou, S., Zhao, N., and Wang, J. (2020). Gambogenic acid suppresses bladder cancer cells growth and metastasis by regulating NF- κ B signaling. *Chem. Biol. Drug Des.* 96 (5), 1272–1279. doi:10.1111/cbdd.13737
- Zou, Z., Chang, H., Li, H., and Wang, S. (2017). Induction of reactive oxygen species: an emerging approach for cancer therapy. *Apoptosis* 22 (11), 1321–1335. doi:10.1007/s10495-017-1424-9

Glossary

5-FU	5-fluorouracil	OA	oleyl alcohol
APAP	attenuating the acetaminophen	PCNA	proliferating cell nuclear antigen
BMI1	B-cell-specific Moloney leukemia virus insert site 1	PEI	polyethylenimine
CCA	cholangiocarcinoma	RBCm-GA/PLGA NPs	GA-loaded biomimetic nanoparticles
CDDP	cisplatin	RBCm-NP	red blood cell membrane-coated nanoparticle
CFDA	China Food and Drug Administration	ROS	reactive oxygen species
cFLIP	cellular FADD-like apoptosis regulator	RRM2	ribonucleotide reductase subunit-M2
CIP2A	cancerous inhibitor of protein phosphatase 2A	SCLC	small-cell lung cancer
CML	chronic myeloid leukemia	sdAb	single-domain antibody
CQ	chloroquine	SLC3A2	solute carrier family 3 member 2
CRC	colorectal cancer	SLC7A11	solute carrier family 7 member 11
DIO-1	death-inducer obliterator	SPEG/HA/CSO-SS-HEX/Fe₃O₄/GA	redox/pH dual-responsive and magnetic targeted hybrid multifunctional complex micelles
DOX	doxorubicin	System xc⁻	the cystine/glutamate antiporter
EGG	ethanolic extract of gamboge	TCM	traditional Chinese medicine
ER	endoplasmic reticulum	TfR	transferrin receptor
ERα	estrogen receptor alpha	TNBC	triple-negative breast cancer
FGFR	fibroblast growth factor receptor	TNF	tumor necrosis factor
FUS	focused ultrasound	TRAIL	TNF-related apoptosis-inducing ligand
GA/PLGA-CMB	GA-loaded nanobubble-microbubble complexes	TrxR	thioredoxin reductase
GA	gambogic acid	VEGF	vascular endothelial growth factor-A
GAL	liposomal formulation of GA	VEGFR2	vascular endothelial growth factor receptor 2
GBM	glioblastoma	VSOR Cl⁻	volume-sensitive chloride
Gem	gemcitabine	WSC	water-soluble chitosan
GNA	gambogenic acid		
GPR108	G protein-coupled receptor 108		
GPX4	glutathione peroxidase 4		
GRP78	glucose-regulated protein 78		
GSCs	glioma stem cells		
HCC827ER	HCC827 erlotinib-resistant		
HUVECs	human umbilical vein endothelial cells		
IRE1α	inositol-requiring enzyme-1 α		
iRGD	internalizing RGD peptide		
iso-GNA	isogambogenic acid		
JNK	C-Jun N-terminal kinase		
LKB1	liver kinase B1		
MDM2	murine double minute 2		
MM	multiple myeloma		
MMP	matrix metalloproteinase		
mPEG	monomethoxy-poly(ethylene glycol)		
NEAT1	nuclear-enriched abundant transcript 1		
NPC	nasopharyngeal carcinoma		
NSCLC	non-small-cell lung cancer		