

Gambogic Acid as a Candidate for Cancer Therapy: A Review

This article was published in the following Dove Press journal:
International Journal of Nanomedicine

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Abstract: Gambogic acid (GA), a kind of dry resin secreted by the *Garcinia hanburyi* tree, is a natural active ingredient with various biological activities, such as anti-cancer, anti-inflammatory, antioxidant, anti-bacterial effects, etc. An increasing amount of evidence indicates that GA has obvious anti-cancer effects via various molecular mechanisms, including the induction of apoptosis, autophagy, cell cycle arrest and the inhibition of invasion, metastasis, angiogenesis. In order to improve the efficacy in cancer treatment, nanometer drug delivery systems have been employed to load GA and form micelles, nanoparticles, nanofibers, and so on. In this review, we aim to offer a summary of chemical structure and properties, anti-cancer activities, drug delivery systems and combination therapy of GA, which might provide a reference to promote the development and clinical application of GA.

Keywords: gambogic acid, anti-cancer activities, drug delivery systems, combination therapy

Introduction

Cancer has a highly growing incidence and mortality, which is a major public health problem worldwide. GLOBOCAN 2018 estimated 18.1 million new cases and 9.6 million cancer deaths in 2018 by investigating 36 cancers in 185 countries.¹ Chemotherapy is a type of malignant cancer treatment that extensively uses drugs to kill cancer cells. Herbal medicines are gifts from nature, exhibiting broad spectrum therapeutic potentials for a long time, especially in the field of anti-cancer activity. Plenty of active ingredients exist in the plants and have the great potential to develop into therapeutic drugs for cancer therapy, prolonging survival time, reducing side effects and improving the quality of life for cancer patients.² Drugs containing the xanthone structure have had a lot of attention due to the potential in inhibiting tumor growth. Xanthone compounds, as one kind of natural product, were originally isolated from plants and microorganisms, which have anti-tumor, anti-hypertensive, anti-thrombotic and other biological activities.³

Gambogic acid (GA), a naturally occurring prenylated xanthone moiety, is the most important member of the xanthone family that is investigated for its pharmaceutical consequentiality.⁴ GA, secreted as a dry resin by the *Garcinia hanburyi* tree, possesses several anticancer activities that have been documented, such as apoptosis, autophagy, cell cycle arrest and the inhibition of invasion, metastasis, and angiogenesis (Figure 1). GA could inhibit various cancer cell's growth, including breast cancer, pancreatic cancer, prostate cancer, lung cancer, osteosarcoma, etc., which might be related with modulating the signaling pathways of c-Jun

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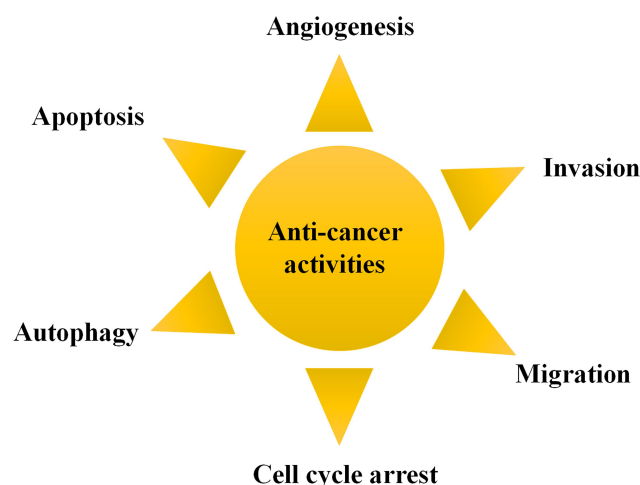


Figure 1 Anti-cancer activities of GA.

N-terminal kinase-1 (JNK-1), protein kinase B (AKT)/mammalian target of rapamycin (mTOR), AKT/ forkhead box protein O1(FOXO1)/BIM, nuclear factor kappa-B (NF- κ B) and so on. Although GA has been approved by the China Food and Drug Administration (CFDA) for Phase II clinical trials by intravenous injection in solid tumor therapy,^{5,6} there are still some problems needing to be solved for the purpose of accelerating the clinical applications. GA is mainly extracted from some plants but in low yield, and its complex chemical structure makes it difficult to synthesize. Moreover, the rigid structure and the poor water solubility of GA leads to the limitation of pharmacokinetic properties.⁷ Therefore, how to utilize the new technology to overcome the drawbacks of GA in order to enhance the applications is particularly important. The new drug delivery system based on nanotechnology could usefully encapsulate GA to overcome the poor water solubility and enhance the therapeutic effects in cancer therapy. This review aims to summarize the physical and chemical properties, structure-activity relationship, anticancer activities, the underlying molecular mechanisms, nano-drug delivery systems, as well as combination therapy of GA, to improve the developing speed of the preclinical study in the future.

Chemical Structures and Properties of Gambogic Acid

GA ($C_{38}H_{44}O_8$, MW: 628.75, [Figure 2](#)), the major active component accompanied by a caged polyprenylated xanthone derived from *Garcinia hanburyi*, is a kind of brownish-to-orange resin, which is mainly found in South China, Vietnam, Cambodia and Thailand.⁸ The boiling

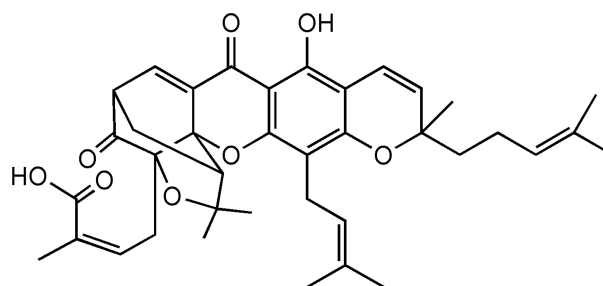


Figure 2 Structure of Gambogic acid.

point and flash point of GA is 808.9 °C and 251.4 °C, respectively. GA also possesses a maximum absorption wavelength of 365 nm as well as the unique xanthone skeleton.² The molecular structure of GA was elucidated in 1965 mainly via detailed nuclear magnetic resonance (NMR) analysis, and there were several synonyms, including guttic acid, guttatic acid, β -guttiiferin, 2-methyl-4-[(1R,3aS,5S,11R,14aS)-3a,4,5,7-tetrahydro-8-hydroxy-3,3,11-trimethyl-13-(3-methyl-2-buten-1-yl)-11-(4-methyl-3-penten-1-yl)-7,15-dioxo-1,5-methano-1H,3H,11 H-furo [3,4-g] pyrano [3,2-b] xanthen-1-yl]-2Z-botanical acid, etc.^{2,9} The studies reported that GA had been used in traditional Chinese medicine for hundreds of years and possessed diverse biological effects including anti-inflammatory, anti-oxidant, anti-viral, and anti-infectiousness, especially in the field of anti-cancer in recent years.^{10,11} The overall yield of GA isolated from available gamboge resin was approximately 5%. The method of purification was converting the crude gamboge resin extract into the pyridine salt, following the subsequent crystallization.¹² Besides, it was reported that GA was found to be stable in acetone, acetonitrile, chloroform and other acids, but unstable in methanol.⁵

Based on the activity relationship studies, the 9, 10 carbon double bond of α,β -unsaturated ketone moiety from GA plays an important role for its biological activity and various modifications can be performed in the 6-hydroxy and 3 α -carboxy group.¹³ The electrophilic α,β -unsaturated carbonyl group in the bioactive compounds could specifically react with protein thiols. In previous studies, GA could inhibit the activation of NF- κ B via modifying the 179Cys of IKK β , resulting in an anti-inflammatory effect via the decrease of COX-2, TNF α and iNOS.¹⁴ Furthermore, GA could also suppress the activation of thioredoxin (TRX-1/2) proteins by covalently binding to the active cysteine residues via Micheal addition reactions.¹⁵ These explorations on the

relationship between structure and activity of GA would provide a reference for the development of GA as a potent drug in clinics.

Anti-Cancer Mechanisms

Apoptosis

Figure 3 shows the anti-apoptotic pathway of GA in cancers. p53 is a crucial tumor suppressor gene mutated in most human cancers, which correlates with cell apoptosis, cell cycle arrest, metabolic adaptation and senescence.¹⁶ Both transcription-independent and transcription-dependent ways could target p53 to induce apoptosis, including inhibition of p53-MDM2 interaction, targeting p53 family protein, elimination of mutant p53, restoring mutated p53 and so on.¹⁷ Initially, GA was considered as an antagonist of bcl-2 family proteins in Hela cells.¹⁸ In human breast cancer cells (MCF-7), GA was found to inhibit bcl-2 expression by increased p53 resulting in cell apoptosis.¹⁹ Furthermore, GA increases p53 expression via down-regulating MDM2 in wild type p53 expressing human cancer cells (non-small cell lung H1299).²⁰ Interestingly, GA could enhance p21^{Waf1/CIP1} expression to induce cell apoptosis in human breast cancer cells (MCF-7) via suppressing MDM2 with or without p53 activation.²¹ It's reported that MDM2 activation was not the underlying cause for the stability of mutant p53 in cancer. GA could enhance the

degradation of mutant p53 in MDA-MB-435 cells (with p53 mutation) by chaperones-related (Hsp70 and Hsp90) ubiquitin-proteasome pathway. Hsp70 and Hsp90 could present mutant p53 to chaperone-associated ubiquitin ligase carboxy terminus of Hsp70-interacting protein (CHIP) to induce degradation by proteasome. GA promoted the interaction between mutant p53 and Hsp70, while inhibiting the formation of Hsp90/mutant p53 complex.²² Meanwhile, GA was considered as a natural product inhibitor of Hsp90.^{23,24} On the contrary, previous studies showed that GA functioned as an inhibitor of the ubiquitin-proteasome system (especially 20S proteasome) to induce cytotoxicity in melanoma cells.^{25–27} The influence of GA on the ubiquitin-proteasome system needs further investigation.

Mitochondria-dependent apoptosis (intrinsic apoptosis pathway) mainly involves activated caspase-3 through bcl-2 family members, while mitochondria-independent apoptosis (extrinsic apoptosis pathway) is related to death ligands and receptors.²⁸ In mitochondria-dependent apoptosis pathway, bcl-2 reduction is associated with the release of cytochrome c, leading to an apoptosis cascade reaction.²⁹ GA could induce an intrinsic apoptosis pathway by directly targeting the mitochondria with a rapid mitochondrial membrane depolarization and fragmentation, causing the release of cytochrome c, activation of caspase-3, 9 and cleaved

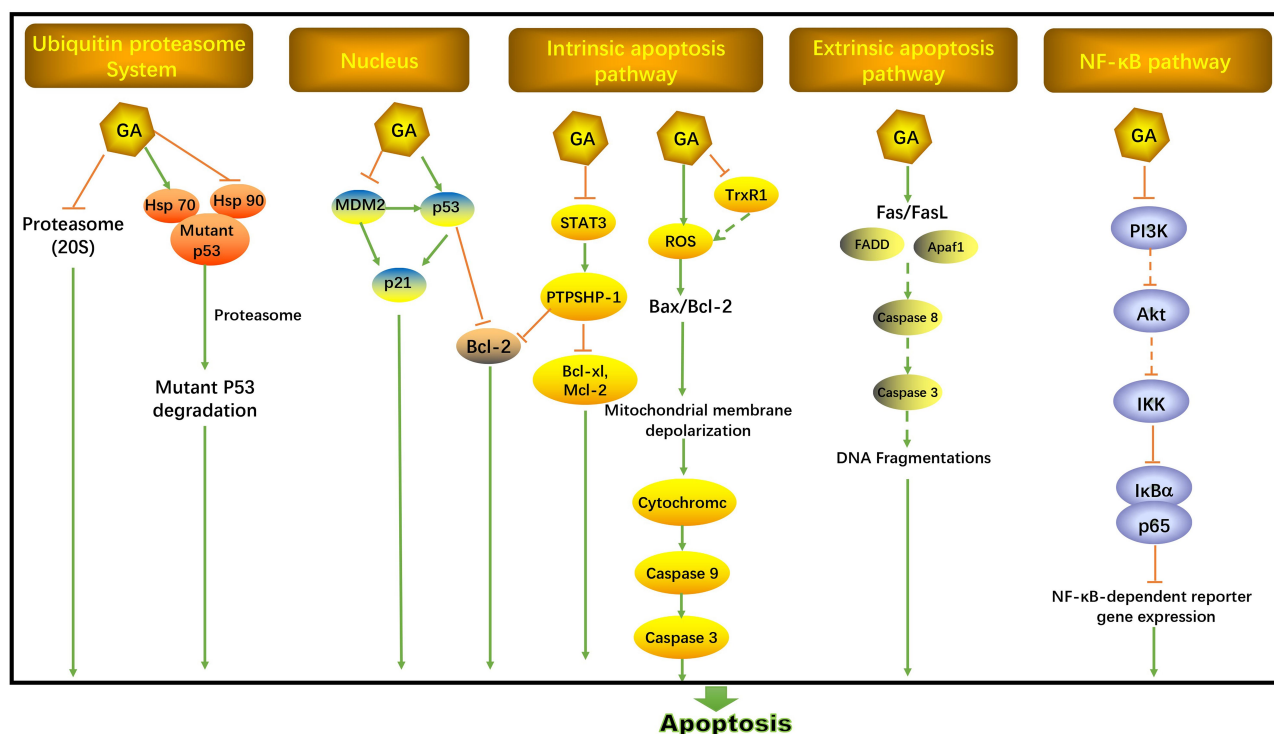


Figure 3 Anti-apoptosis activities of GA.

PARP and increased ratio of bax/bcl-2. GA-induced reactive oxygen species (ROS) may be the cause of the collapse of mitochondrial transmembrane potential, which could also down-regulate SIRT1 in multiple myeloma and enhance the phosphorylation of c-Jun-N-terminal protein kinase (JNK) and p38 in hepatoma SMMC-7721 cells.^{30–38} GA may also interact with the thioredoxin reductase 1 (TrxR1) to elicit oxidative stress leading to ROS accumulation in hepatocellular carcinoma.³⁹ Extrinsic apoptosis pathway was also induced by GA with increased death receptor (Fas, FasL, Fas-associated protein with death domain (FADD) and Apaf-1) and deoxyribonucleic acid (DNA) fragmentation.^{35,36,40} Interestingly, GA was found to bind to the transferrin receptor and might induce a special signal resulting in rapid apoptosis in cancer.^{40–42}

Furthermore, GA could inhibit NF- κ B pathway through suppressing I κ B α and p65 phosphorylation resulting in abrogated NF- κ B-dependent reporter gene expression.^{24,42,43} AKT and PI3K may be also involved in GA-induced apoptosis relating to the NF- κ B pathway.^{44,45} GA also suppressed the signal transducer and activator of transcription (STAT3) phosphorylation to induce cell apoptosis through activating protein tyrosine phosphatase SHP-1, which down-regulated the expression of STAT3-associated antiapoptotic proteins (bcl-xl, bcl-2 and Mcl-2) in myeloma cells.⁴⁶ For prostate cancer with phosphate and tension homology (PTEN) and p53 genes deletion, GA induced cell apoptosis via suppression of mitogen-activated protein kinases (MAPK) pathway and c-fos.⁴⁷ With the higher expression of miR-21 in multiple myeloma, GA induced cell apoptosis and proliferation through the regulation of the AKT/FOXO1/BIM signaling pathway.⁴⁸ Notch signaling pathway was also involved in GA-induced apoptosis with reduction of bcl-2 and PI3K in non-small cell lung cancer.⁴⁹

In addition, GA-associated targets in apoptosis have been found in various types of cancers, including TR3 in cervical cancer,⁵⁰ hERG and steroid receptor coactivator-3 (SRC-3) in leukemia,^{51,52} BRD4 in anaplastic thyroid cancer,⁵³ DDIT3, DUSP1, DUSP5, GADD45B, TOP2A, TOP2B, TOP3A and ALDOA in pancreatic cancer.⁸ GA could also enhance epidermal growth factor receptor (EGFR) degradation and inhibit AKT/mTOR complex 1 (mTORC1) via up-regulating AMP-activated protein kinase (AMPK)-dependent-leucine-rich repeats and immunoglobulin-like domains 1 (LRIG1) in glioma cells.⁵⁴ Surprisingly, GA was able to induce cell apoptosis by activating T lymphocyte in H22 transplanted mice.⁵⁵

Cell Cycle Arrest

The cell cycle arrest is one of the anti-cancer mechanisms, which is associated with the cell cycle process and cellular growth after the GA treatment (Figure 4). Several related researches revealed that GA distinctly influenced different cell phases on diverse types of cancer cell lines. GA could obviously induce G2/M or G0/G1 arrest in various cancer cell lines, such as MCF-7 cells, K562 cells, U2OS cells, and so on. Among them, G2/M arrest was induced by GA via decreasing the levels of phospho-cdc2 (Thr 161) and cdc25B in MG63 cells.⁵⁶ Besides, Chen et al demonstrated that G2/M arrest in MCF-7 cells was induced by GA depolymerization of microtubules.¹⁰ GA could induce the G0/G1 phase cell cycle arrest and apoptosis in human chronic myelogenous leukemia cell line K562 cells via downregulating the expression of SRC-3 and inhibiting the Akt pathway.¹¹ Similarly, GA treatment induced the G0/G1 phase arrest in U2OS cells was associated with a decrease in phospho-GSgsk3- β (Ser9) and the expression of cyclin D1.⁵⁶

Autophagy

GA provoked autophagy in NCI-H441 cells by up-regulating the Beclin 1 (initiation factor for autophagosome formation) and converting LC3 I to LC3 II (autophagosome marker).⁵⁷ Similarly, GA induced an apparent autophagy association with the up-regulated expressions of Atg5, Beclin 1 and LC3-II in glioblastoma multiforme (GBM) cells.⁵⁸ Besides, GA treatment in A549 cells induced autophagy through suppressing the Akt/mTOR signaling pathway with the remarkable reduction of the phosphorylation levels of Akt, mTOR, and S6.⁵⁹ Foggetti et al demonstrated that GA may induce mtp53 degradation through autophagy mechanism in human breast cancer cell line MDA-MB-231 and human colorectal adenoma cell line DLD1 carrying p53-S241F in expressing the p53-R280K and the p53-S241F proteins, respectively.⁶⁰ The autophagy of GA against colorectal cancer was regulated by 5-LOX-generated ROS accumulation, which might associate with the inhibition of Akt-mTOR pathways.⁶¹ In human bladder cancer cells T24 and UMUC3, GA triggered ROS mediated autophagy through activating the JNK pathway.⁶²

Migration and Invasion

The wound healing assay was performed to validate the effect of GA on the HT-29 colorectal cancer cell, which indicated that GA inhibits migration via blocking miR-21 activity.⁶³ Such researches revealed that GA suppressed

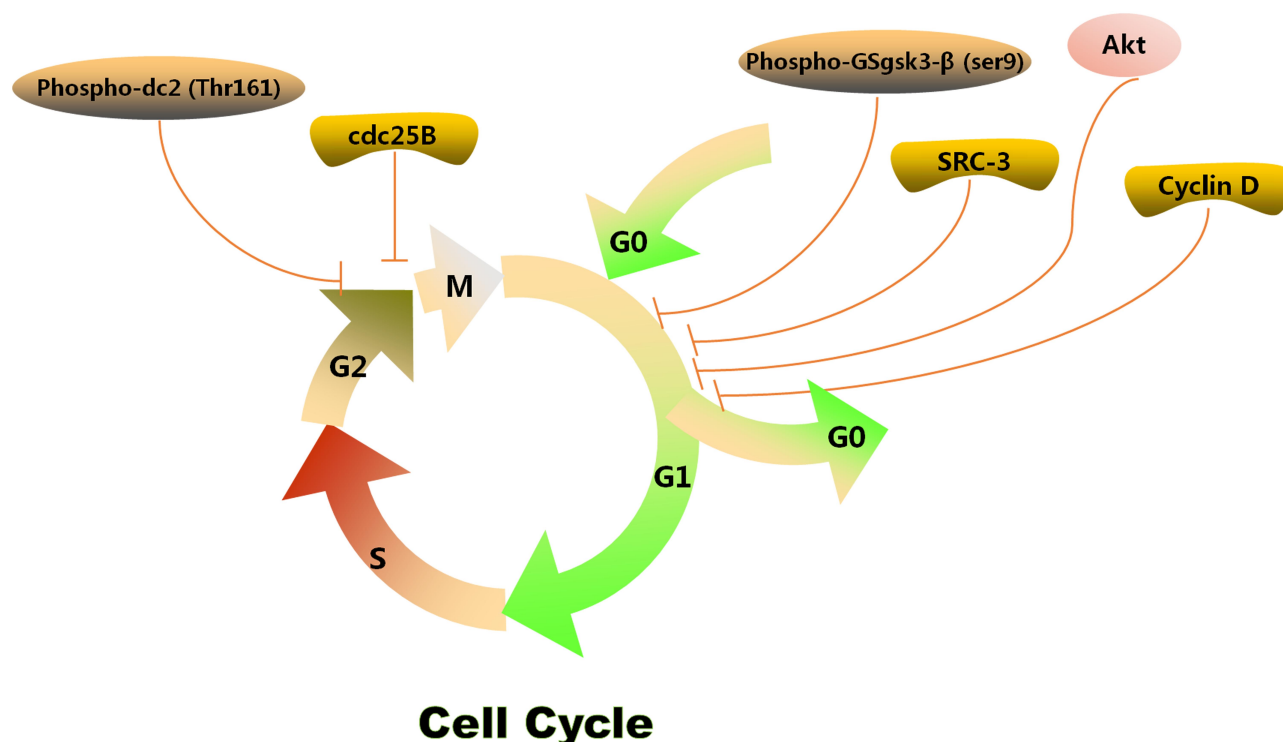


Figure 4 Cell cycle arrest mechanism of GA.

migration and invasion via activation of NF- κ B pathway or the inhibition of matrix metalloproteinase (MMP)-2 and MMP-9 in A549 cells.^{64,65} Moreover, GA also, dose-dependently, suppressed MDA-MB-231 human breast carcinoma cell invasion and metastasis via the inhibition of MMP-2 and MMP-9.^{31,66,67} The migration and invasion of SK-HEP1 cells treated by GA were evaluated, the results showed that GA down-regulated the expression of the integrin β 1/rho family GTPase signaling pathway and suppressed the expression of MMP-2, MMP-9, and NF- κ B.⁶⁸ Lu et al found that GA could inhibit TNF- α -induced migration and invasion, likely mediated by regulation of the PI3K/Akt and NF- κ B signaling pathways on human prostate cancer PC3 cells.⁶⁹ The down-regulation of MMP-9 and the up-regulation of TIMP-1 played an important role in inhibiting the invasion of osteosarcoma cells treated by GA.⁷⁰ Besides, GA could inhibit the adhesion and migration in down-regulation of the α 4 integrin expression on B16-F10 cells in vitro and in vivo.⁷¹

Angiogenesis

Angiogenesis plays an important role in tumor growth and has been a promising strategy for the treatment of cancer.⁷² Hypoxia-inducible factor-1 α (HIF-1 α) plays a vital role in

tumor progression. GA induced tumor antiangiogenesis via the inhibition of HIF-1 α /VEGF in vivo, suggesting that GA may inhibit human multiple myeloma progression and angiogenesis.⁷³ Other research also found that GA had the ability to inhibit angiogenesis correlated with inhibiting prolyl hydroxylase-2 (PHD2)–von Hippel-Lindau gene (VHL)–HIF-1 α pathway.⁷⁴ Moreover, GA lead to the inhibition of angiogenesis by suppressing vascular endothelial growth factor receptor 2 (VEGFR 2) signaling.⁷⁵

Drug Resistance

Drug resistance is a crucial obstacle in chemotherapy that may lead to treatment failure and relapse in patients with cancer.⁷⁶ GA exhibits multi-target anti-cancer effects with few side effects, which shows the ability in reversing resistance to anti-cancer drugs in diverse cancer treatments. It was reported that GA could reverse oxaliplatin resistance in LoVo colorectal cancer cells through the approach of increasing intracellular platinum levels associated with the increase of hCTR1 levels and the decrease of ATP7A and ATP7B levels.⁷⁷ Moreover, GA reduced the resistance to gemcitabine mainly through inhibiting the extracellular signal-regulated kinase (ERK)/E2F1 signaling pathway accompanied with the reduction of the ribonucleotide reductase subunit-M2 (RRM2) protein and mRNA

expression.⁷⁸ Hypoxia-inducible factor (HIF)-1 played an important role in inducing resistance to cancer therapy, however, Zhao et al showed evidence that GA reversed hypoxia-induced resistance to cisplatin-mediated apoptosis independently of HIF-1 α in osteosarcoma cells.⁷⁹ GA distinctly sensitized doxorubicin (DOX)-resistant breast cancer cells through inhibiting P-glycoprotein and suppressing the survivin expression revealed by ROS-mediated activation of the p38 MAPK.⁸⁰ GA also reversed docetaxel resistance through down-regulation of survivin in BGC-823/Doc gastric cancer cell lines.⁸¹ Wang et al deemed that the combinational administration of gefitinib and GA had the ability to overcome gefitinib-resistant tumor growth caused by the EGFR T790M mutant lung cancer.⁸²

Nano-Scale Drug Delivery Systems

To achieve higher anticancer efficiency, nano-scale drug delivery systems have been used to deliver anticancer drugs based on the enhanced permeation and retention (EPR) effect.⁸³ Different types of nano-scale drug delivery systems have been applied to modify or encapsulate GA, such as micelles, nanoparticles, nano-spheres, etc., which have been listed in Table 1. Furthermore, multifunctional nanoparticles have been investigated for pH-sensitive, redox-sensitive, receptor targeting response, which may enhance drug release, improve drug accumulation in the tumor and reduce some side effects of GA. For example, hyaluronic acid (HA), folic acid (FA) and RGD are conjugated to the surfaces of the carriers for higher anticancer efficiency.^{84,85}

Micelles

Self-assembled polymeric micelles have received growing attention in the field of drug delivery systems in recent years owing to the ability of drug solubilization, sustained drug release and drug targeting.⁸⁶ Polymeric micelles consist of amphiphilic block copolymers, having a hydrophilic shell and a hydrophobic core, which can be used as a promising drug delivery system for the hydrophobic drugs.⁸⁷ Table 1 has listed the micelles encapsulated with GA.

Mixed micelles self-assembled from two or more dissimilar block copolymers provide a direct and convenient approach to increase micelle stability and drug-loading efficiency, superior to those of the individual components.⁸⁸ GA was encapsulated in the mixed micelles constituted of Poloxamer 407 and TPGS, which showed increased cellular uptake and in vitro cytotoxicity compared with free GA in MCF-7 breast cancer cells and in multidrug resistant NCI/ADR-RES cells.⁸⁹ N-octyl-N-arginine-chitosan micelles for

GA delivery might be the better target approach for getting less peripheral toxicity and higher targeting in liver and lung, which might be a promising formulation for GA to cure hepatic carcinoma or lung cancer in the future.⁹⁰ The GA-loaded mixed micelles made of poly(ethylene glycol)-poly(L-histidine)-poly(D,L-lactide-co-glycolide) (PEG-pHis-PLGA) and D- α -tocopheryl polyethylene glycol 1000 (TPGS) included several abilities of having pH-sensitive behavior, inhibiting P-gp expression and down-regulating of anti-apoptotic proteins, which increased the cell cytotoxicity of GA on both MCF-7 and MCF-7/ADR cells.⁹¹ Monomethylpoly(ethylene glycol)-poly(ϵ -caprolactone)-poly(trimethylene carbonate) (MPEG-P(CL-ran-TMC)) was used to encapsulate GA, which showed superior antitumor efficacy and a better apoptosis induced effect in AsPC-1 cells compared to free GA.⁹² N-octyl-N-arginine-chitosan (OACS) micelles prepared by the dialysis method were utilized for GA oral delivery, which increased solubility by 2320 times and several folds of absorption compared with GA.⁹³

Besides, GA was encapsulated into the novel redox/pH dual-responsive and HA-decorated multifunctional magnetic complex micelles possessing excellent bioavailability, controllable release and multi-functionality, which could be an effective and promising strategy for the treatment of triple negative breast cancer.⁹⁴ Ke et al applied lecithin/solutol HS15 via the film-dispersion method to prepare the multi-layer micelle employing protamine (PRM) and HA to deliver GA (HA-PRM-GA-M) for cancer treatment of inhibiting drug resistance. The results suggested that HA-PRM-GA-M showed the significant antitumor efficacy and tumor growth inhibitory effects without obvious histological abnormalities or hematological toxicity in the liver and kidney.⁹⁵ Low molecular weight heparin (LMWH) with the function of antiangiogenesis effects showed favorable hydrophilicity and few side effects, which was grafted with GA to form the micelles in aqueous solution. This simultaneous combination of anti-angiogenesis drugs and chemotherapeutics achieved the aim of improving the anticancer efficacy by tumor-targeted delivery against hepatocellular carcinoma.⁹⁶ Triphenylphosphonium (TPP), a mitochondriotropic molecule, was designed to target mitochondria by the reason of penetrating the mitochondrial intermembrane potential barrier. TPP was conjugated to micelles for delivering GA to overcome the shortages of GA and target the mitochondria, reaching the target of pro-apoptotic effect of lung cancer via mitochondrial signaling pathway with promoting the activities of caspase 3/7 and 9 as well as inducing the loss of MMP and the release of cytochrome c.⁹⁷

Table I Drug Delivery Systems of GA

Delivery Systems	Abbrev	Status	Functional Moiety	Types of Cancer	Cancer Cells	References
Micelles	GA-OACS micelles	In vitro and in vivo		Hepatic carcinoma	HepG2 cells	[90]
	GA encapsulated MPEG-P (CLran-TMC) micelles	In vitro and in vivo		Pancreatic cancer	AsPC-I cells	[92]
	sPEG/HA/CSO-SS-Hex /Fe ₃ O ₄ /GA micelles	In vitro and in vivo	CD44-target moiety: HA; redox-responsive moiety: disulfide linker; magnetic target moiety: Fe ₃ O ₄	Breast cancer	4T1 cells	[94]
	HA-GA@Ce6 micelles	In vitro and in vivo	CD44-target moiety: HA; ROS responsive moiety: Ce6	Breast cancer	4T1 cells	[99]
	HA-PRM-GA-M	In vitro and in vivo	CD44-target moiety: HA	Lung adenocarcinoma	A549 cells	[95]
	PAG/DTX-shRNA micelles	In vitro and in vivo		Breast cancer	MCF-7 cells	[121]
	GA-LMWH micelles	In vivo		Hepatic cancer	H ₂₂ cells	[96]
	GA-PEG-PCL micelles	In vitro		Lung cancer	A549 cells	[97]
	PEG-pHis-PLGA/TPGS micelles	In vitro	pH sensitive moiety: poly (L-histidine) (pHis)	Breast cancer	MCF-7 cells; MCF-7/Adr cells	[91]
	GA-PEG ^{5k} CA ₄ -L-VE ₄ micelles	In vitro and in vivo		Colon cancer	HT-29 and HCT116	[122]
	Poloxamer 407/TPGS mixed micelles	In vitro		Breast cancer	MCF-7 cells; NCI/ADR-RES cells	[89]
Nanoparticles	GA-Cy7-NP	In vitro and in vivo	Hypoxia target moiety: near-infrared dye (Cy7)	Prostate cancer	PC3 cells	[105]
	iE-RBCm-GA/PLGA NPs	In vitro and in vivo	EGFR-target moiety: bispecific recombinant protein anti-EGFR-iRGD	Colon cancer	Caco-2 cells; SW480 cells	[106]
	GA and TRAIL co-loaded BSA NPs	In vitro and in vivo		Breast cancer; Lung cancer	MCF-7 cells; A549 cells	[123]
	GA-loaded PEG-PCL NPs	In vitro and in vivo		Gastric cancer	MKN-45 cells	[107]
	CS/PLGA-GA NPs	In vitro and in vivo		Lewis lung carcinoma	LL/2 cells	[124]
	LyP-I-LMWH-Qu (PLQ)/GA NPs	In vitro and in vivo	p32 target moiety: LyP-I	Breast cancer	MCF-7 cells	[125]
	RBCm-GA/PLGA NPs	In vitro and in vivo		Colorectal cancer; Gastric cancer	SW480 cells; MKN45 cells; AGS cells	[108]
	GA-HAS NPs	in vivo		Lung cancer	A549 cells	[112]
	GA/pTRAIL-HA/PPNPs	In vitro and in vivo	CD44-target moiety: HA	Breast cancer	MCF-7 cells; MDA-MB-231 cells	[109]

(Continued)

Table I (Continued).

Delivery Systems	Abbrev	Status	Functional Moiety	Types of Cancer	Cancer Cells	References
	GA-loaded FA-Arg-PEUU NPs	In vitro	Folate receptor- target moiety: folic acid (FA)	Lung cancer	A549 cells; Hela cells	[110]
	DTX/GA PLGA NPs	In vitro and in vivo		Breast cancer	MCF-7 cells; MCF-7/Adr cells	[126]
	GA/RACC loaded NPs	In vitro		Osteosarcoma cancer	MG63 cells	[127]
	cRHG NPs	In vitro and in vivo	$\alpha\beta 3$ integrin target moiety: cyclic arginine-glycine-asparagine-tyrosine-lysine (c(RGDyK))	Breast cancer; glioblastoma	MCF-7 cells; U87MG cells	[128]
	GA-HRA NPs	In vitro and in vivo		Breast cancer; nasopharyngeal cancer	MCF-7 cells; KB31 cells	[129]
	GA-MNP-Fe ₃ O ₄ NPs	In vitro		Pancreatic cancer; leukemia	Panc-1 cells; Capan-1 cells; K562 cells	[101–103]
Nano-spheres	F68-LA/GA nano-spheres	In vitro		Ovarian cancer	A2780 cells	[113]
Nanofibers	Mn-ICG@pHis-PEG/GA nanofibers	In vitro and in vivo	Magnetic target moiety: Fe ₃ O ₄	Breast cancer	4T1 cells	[115]
Nanorods	GNR/TiO ₂ nanorods	In vitro	Folate receptor- target moiety: folic acid (FA)	Glioblastoma	U-87 MG cells	[117]
Nanocomplex	HA(CD)-4Phe4 nanocomplex	In vitro	pH sensitive moiety: poly (L-histidine) (pHis)	Melanoma cells	MDA-MB-435/MDR cells	[118]
Quantum dots	CdTe QDs	In vitro		Hepatic carcinoma	HepG2 cells	[120]
Liposomes	GA liposomes	In vitro and in vivo	CD44-target moiety: HA	Breast cancer	MDA-MB-231 cells	[130]

Photodynamic therapy (PDT) as a noninvasive therapeutic approach for cancer treatment relies on photosensitizers to generate cytotoxic ROS resulting in the tumor cells apoptosis, which exhibited significant advantages of selective cytotoxicity to tumor cells and few side effects on normal tissues.⁹⁸ Liang et al prepared an amphipathic prodrug of GA-grafted HA to encapsulate the photosensitizer chlorin e6 (Ce6) forming amphipathic nanomicelles (HA-GA@Ce6), which showed stronger cell uptake in 4T1 tumor cells and superior anti-tumor efficacy by reducing intracellular antioxidant levels.⁹⁹

Nanoparticles

Magnetic Fe₃O₄ nanoparticles (MNP Fe₃O₄), a promising candidate owning biocompatible and superparamagnetic properties, have been widely studied as targeted drug

delivery systems with satisfactory stability and low toxicity in the field of cancer therapy.¹⁰⁰ Wang et al constructed the GA-loaded MNP-Fe₃O₄ by mechanical absorption polymerization, which demonstrated a remarkable potential in inducing apoptosis on Capan-1 pancreatic cancer cells. Besides, the findings showed that the synergistic anti-cancer effects might associate with the mechanisms of reducing protein expression of Bcl-2 and enhancing proapoptotic gene products of Bax, caspase 9 and caspase 3.¹⁰¹ In addition, MNP-Fe₃O₄ was also considered as a promising drug carrier for GA in suppressing ETS1-mediated cell proliferation and migration on to Panc-1 pancreatic cancer cells.¹⁰² Chen et al discovered that MNP-Fe₃O₄ dramatically enhanced apoptosis induction and cytotoxicity of GA in K562 cells, accompanied with the regulation of caspase-3, bax, bcl-2, NF- κ B, and survivin.¹⁰³ MNP-Fe₃O₄ conjugated with GA to

enhance the chemotherapeutic efficiency in Capan-1 pancreatic cancer cells via regulating the apoptosis pathway related gene products, including Bax, Bcl-2, caspase 9, and caspase 3.¹⁰¹ Furthermore, the combination therapy of MNP-Fe₃O₄ and GA was also evidenced in LOVO human colon cancer cells by the regulation of the PI3K/Akt/Bad pathway.¹⁰⁴

Hypoxia-targeting near-infrared dye (Cy7) moiety was conjugated to GA, which could self-assemble into the novel “mosaic-type” nanoparticles with surfactin in the aqueous solution for selective drug release targeting hypoxic cancer cells in order to decrease nonspecific accumulation in the liver and improve antitumor efficacy.¹⁰⁵ The anti-EGFR-iRGD recombinant protein was modified on the surface of red blood cell membrane-coated nanoparticles (RBCm-NPs) that loaded the potential anti-tumor drug GA to improve antitumor efficiency with the reduction of the side effects of GA and ensuring the safety in colorectal cancer models.¹⁰⁶ Zhang et al also evidenced that GA-loaded polyethylene glycol (PEG)-polycaprolactone (PCL) nanoparticles exhibited superior antitumor activity compared with free GA in gastric cancer using nanoparticles to encapsulate drugs.¹⁰⁷ The nanoparticles that combined poly(lactic-co-glycolic acid) (PLGA) with RBCm were utilized to deliver GA, which exhibited a certain antitumor efficacy and notable tumor inhibition with relatively lower toxicity compared with free GA in colorectal cancer treatment.¹⁰⁸ Wang et al constructed the HA-coated CD44-targeted nanoparticles to co-deliver GA and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in triple negative breast cancer treatment, showing the augmented pro-apoptotic effects in vitro and tumor suppression in vivo.¹⁰⁹ Folate receptor (FR) was overexpressed on poorly differentiated and more aggressive tumors, bound with FA and to transport them via the nonclassical endocytic way. FA decorated arginine-based poly(ester urea urethane) (FA-Arg-PEUUs) conjugates were utilized to deliver GA, resulting in the higher cytotoxicity, apoptosis percentage, mitochondrial membrane potential disruption and DNA fragmentation compared to free drug on cancer cells.¹¹⁰

RBCm was introduced into synthetic biomimetic nanocarriers, which could evade the mononuclear phagocyte response to prolong systemic circulation and reduce the uptake of reticuloendothelial system.¹¹¹ Zhang et al established the RBCm-GA/PLGA drug delivery systems with good biocompatibility and drug solubilizing capacity, providing the significant reduction in tumor volume size in vivo for colorectal cancer treatment.¹⁰⁸ Moreover,

human serum albumin (HSA) with low toxicity was designed to bring into the nanoparticles that helped with improving drug solubility, increasing retention in the tumor interstitium and improving the anticancer efficacy in delivering GA.¹¹²

Nano-Spheres

F68 was conjugated with linoleic acids (LA) to form nanospheres with a hydrophobic core in order to incorporate GA. Fang et al showed further evidence that the pluronic F68-linoleic acid nano-spheres induced enhanced higher cytotoxicity and apoptosis against ovarian cancer A2780 cells, which were considered as a potential delivery system for GA in the field of ovarian cancer treatment.¹¹³

Nanofibers and Nanorods

Photothermal therapy (PTT) is one kind of cancer therapy that has attracted tremendous attention, which works through generating hyperthermia under near-infrared (NIR) light to ablate tumors.¹¹⁴ Yang et al fabricated novel PEGylated one-dimensional nanoscale coordination polymers (1D-NCPs) to load GA to enhance tumor destruction efficacy by low-temperature PTT, showing the tumor-specific pH responsiveness and theranostic functionalities of GA nanoparticles accompanied by a unique perspective to kill cancer.¹¹⁵

Gold nanorods (GNRs) as one kind of gold nanostructure, have been extensively studied by researchers owing to the unique plasmonic properties, which could penetrate deeply into tissues and were deemed as a candidate agent for in vivo imaging and therapy.¹¹⁶ Titanium dioxide (TiO₂)-coated GNR (GNR/TiO₂) nanostructures were constructed as a carrier for GA, induced a higher intracellular drug content and superior cytotoxicity under 808 nm NIR laser irradiation due to the synergistic PPT and chemotherapy.¹¹⁷

Nanocomplex

The biodegradable inclusion complex was developed by β -cyclodextrin grafted HA(HA(CD)) and phenylalanine based poly(ester amide)s (4Phe4), which were enabled to target the overexpressed CD44 receptors on tumor cells and loaded with the hydrophobic GA to improve the therapeutic effect. The results evidenced that the HA(CD)-4Phe4 nanocomplex significantly induced apoptotic cell death and effectively inhibited tumor metastasis via suppressing the MMP activities in MDA-MB-435/MDR cells.¹¹⁸

Quantum Dots

Quantum dots (QDs) have been applied in the fields of biological and clinical applications, including labeling, targeted drug delivery, imaging and photodynamic therapy.¹¹⁹ The novel fluorescent nanocomposites based on GA and cadmium–tellurium (CdTe) quantum dots (CdTe QDs) were prepared, which induced G2/M phase arrest and apoptosis in HepG2 cells as well as remarkably reduced side effects of GA on normal cells/tissues given the pH sensitive mechanism.¹²⁰

Combination Therapy

The combination therapy of GA and cisplatin showed the synergistic effects of suppression of tumorigenesis in human osteosarcoma treatment via inducing the cell cycle arrest and promoting mitochondria-independent cell apoptosis.¹³¹ The combined application of GA and docetaxel also showed a synergistic anti-tumor effect in gastrointestinal cancer cells, possibly related to the suppression of mRNA expression, including β -tubulin III, tau and surviving.¹³² Wang et al made similar findings of the synergistic effect of 5-fluorouracil and GA on BGC-823 human gastric carcinoma, with the underlying mechanism of the gene expressions of thymidine synthetase (TS), dihydropyrimidine dehydrogenase (DPD) and orotate phosphoribosyltransferase (OPRT) regulated by GA, which played a vital role in the 5-FU metabolic procession.¹³³

Nanoparticles possess many excellent properties that have been widely investigated as drug delivery carriers. GA and retinoic acid chloroalcone (RACC) were simultaneously loaded in glycol chitosan nanoparticles for combination cancer chemotherapy against osteosarcoma cancer cells, which induced a higher apoptosis rate of MG63 cancer cells with 28%.¹²⁷ Besides, the folate-modified carboxymethyl-chitosan/polyethylenimine/bovine serum albumin based nanoparticles were used to co-deliver GA and TRAIL, which embodied the combined tumor therapy by regulating both intrinsic and extrinsic apoptotic pathways.¹²³ The amphiphilic conjugate constructed by HA and all-trans retinoic acid (ATRA) was applied to entrapped GA for reducing tumor volume and side effects also via the combination therapy strategy.¹²⁹ The combination of drugs and gene therapy for the treatment of cancer presents great potential advantages due to the reduction of side effects, the synergistic/combined antitumor effects and the ability of overcoming drug resistance. GA was

conjugated with poly(amido amine)s (PAAs) through amide bonds to establish a novel redox-sensitive system for co-delivering docetaxel and MMP-9 shRNA, which could rapidly trigger and simultaneously release the docetaxel (DTX), GA and MMP-9 shRNA in response to cytoplasmic reducing reagents resulting in greater anti-tumor efficacy.¹²¹ Moreover, Zhou et al synthesized cysteamine-modified cadmium tellurium (Cys-CdTe) quantum dots to load daunorubicin (DNR) and GA to reduce the side effects and multidrug resistance (MDR) generated from DNR chemotherapy of malignant lymphoma, which could down-regulate the expression of P-glycoprotein on Raji/DNR cells resulting in minimizing MDR.¹³⁴ It was reported that GA and DTX could simultaneously release from PLGA nanoparticles, showing the synergistic antitumor effect attributed to the reversion of multidrug resistance of MCF-7/ADR cells to DTX and inducing cell apoptosis through downregulating the expression of P-gp.¹²⁶

The combination therapy of chemotherapeutic drug and antiangiogenesis agent was designed to inhibit tumor proliferation and invasion while establishing a dual-targeted and multifunctional polymeric nanosystem. Dahmani et al synthesized an amphiphilic α (RGDyK)-functionalized conjugate consisting of LMWH and GA, which could target both tumor cells and angiogenic vasculature, accompanied with increasing accumulation of drugs within the tumor site.¹²⁸

Conclusion

In this review, the evidence given above supports that GA has great potential in multiple cancer treatments. We discussed and summarized GA in many ways, including the chemical properties, underlying molecular mechanisms, anti-cancer activities, drug resistance, combinational influence, and novel drug delivery systems based on nanotechnology. Numerous facts were well proven, that GA had various anti-cancer properties both in vitro and in vivo, including triggering apoptosis, inducing autophagy and cell cycle arrest, inhibiting invasion, metastasis and angiogenesis, and so forth. Multiple novel drug delivery systems of GA including micelles, nanoparticles, nanofibers, and nanorods, have been developed with the purpose of increasing the solubility, prolonging circulation, triggering drug release via responsive manner, reducing side effects and enhancing the drug therapeutic effect. Despite the novel techniques utilized in GA being studied in treating cancer, there was little development in the clinical application of GA and new formulations because of the complicated process to produce them and the lack of clinical trials of these GA formulations during

the pharmaceutical research. The structure of the xanthone moiety in GA still needs to be explored in the future and utilized to develop more active derivatives in treating diseases. Meanwhile, it is vital that more chances to explore and find more unknown properties of GA are pursued in the future. In sum, it is expected that more and more attention can be paid to the development of GA in multiple aspects, especially in the field of clinical application, which will lead to a breakthrough and better treatments in future.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (81803743), the Basic Research Foundation of the China Academy of Chinese Medical Sciences (ZZ13-YQ-041), and the National Major Scientific and Technological Special Project for "Significant New Drugs Development" (2019ZX09301160, 2019ZX09721001-005-002).

Disclosure

The authors report no conflicts of interest in this work.

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