Drug Design, Development and Therapy

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REVIEW

Caged Polyprenylated Xanthones in *Garcinia hanburyi* and the Biological Activities of Them

Ruixi He, Buyun Jia, Daiyin Peng, Weidong Chen

School of Pharmacy, Anhui University of Chinese Medicine, Hefei, People's Republic of China

Correspondence: Ruixi He, School of Pharmacy, Anhui University of Chinese Medicine, No. 350 Longzihu Road, Xinzhan District, Hefei, 230012, People's Republic of China, Tel +8613637080511, Fax +8655168129099, Email heruixi@ahtcm.edu.cn

Abstract: The previous phytochemical analyses of *Garcinia hanburyi* revealed that the main structural characteristic associated with its biological activity is the caged polyprenylated xanthones with a unique 4-oxatricyclo [4.3.1.$0^{3,7}$] dec-2-one scaffold, which contains a highly substituted tetrahydrofuran ring with three quaternary carbons. Based on the progress in research of the chemical constituents, pharmacological effects and modification methods of the caged polyprenylated xanthones, this paper presents a preliminary predictive analysis of their drug-like properties based on the absorption, distribution, metabolism, excretion and toxicity (ADME/T) properties. It was found out that these compounds have very similar pharmacokinetic properties because they possess the same caged xanthone structure, the 9,10-double bond in a,b-unsaturated ketones are critical for the antitumor activity. The author believes that there is an urgent need to seek new breakthroughs in the study of these caged polyprenylated xanthones. Thus, the research on the route of administration, therapeutic effect, structural modification and development of such active ingredients is of great interest. It is hoped that this paper will provide ideas for researchers to develop and utilize the active ingredients derived from natural products.

Keywords: caged polyprenylated xanthones, pharmacological effects, antitumor, modification, ADME/T properties

Introduction

Garcinia hanburyi is widely distributed in the tropical rainforests of Southeast Asia. Gamboge is the dried resin exuded from the stems of *Garcinia hanburyi* that can be used as a pigment and has also been used for a long time as a folk medicine.[1] In China, people are increasingly concerned about the safety of toxic herbs. *Garcinia hanburyi* is regulated as a toxic drug for medical use, and it requires special modification for clinical use. The previous phytochemical analyses of *Garcinia hanburyi* revealed that the main structural characteristic associated with its biological activity is the caged polyprenylated xanthones with a specialized 4-oxatricyclo [4.3.1.$0^{3,7}$] dec-2-one scaffold,[2–9] which contains a highly substituted tetrahydrofuran ring.[10] We have compiled the relevant literature and found out that more than 50 different xanthones have now been extracted from gamboge. The available evidence suggests that gamboge has anticancer properties, with gambogenic acid (GNA) and gambogic acid (GA) being the main components responsible for these activities. They have been demonstrated to exert cytotoxic activities through a variety of mechanisms.[11–14] Among them, GA has been applied to treat a wide range of cancers, such as breast, liver, gastric, lung, colon, and skin cancers. Its therapeutic effects have been well established,[15] and it has been shown to exert anticancer effects through apoptosis induction, cell cycle arrest, telomerase and angiogenesis inhibition.[16,17] In recent years, increasing evidence has demonstrated that GNA exhibits higher antitumor activity and lower toxicity compared to GA, and the extraction process is simple and less costly.[18–21] Despite these advantages, GNA has not been approved for clinical application mainly due to its poor aqueous solubility and low bioavailability.[22] With the aim of overcoming these limitations, researchers have carried out various studies such as on the technology nanocarrier drug delivery, to improve the bioavailability of GNA.

Due to the diversity and potent activities of caged polyprenylated xanthones extracted from *Garcinia hanburyi*, a series of in-depth studies have been conducted by researchers all over the world. Our team has conducted study on

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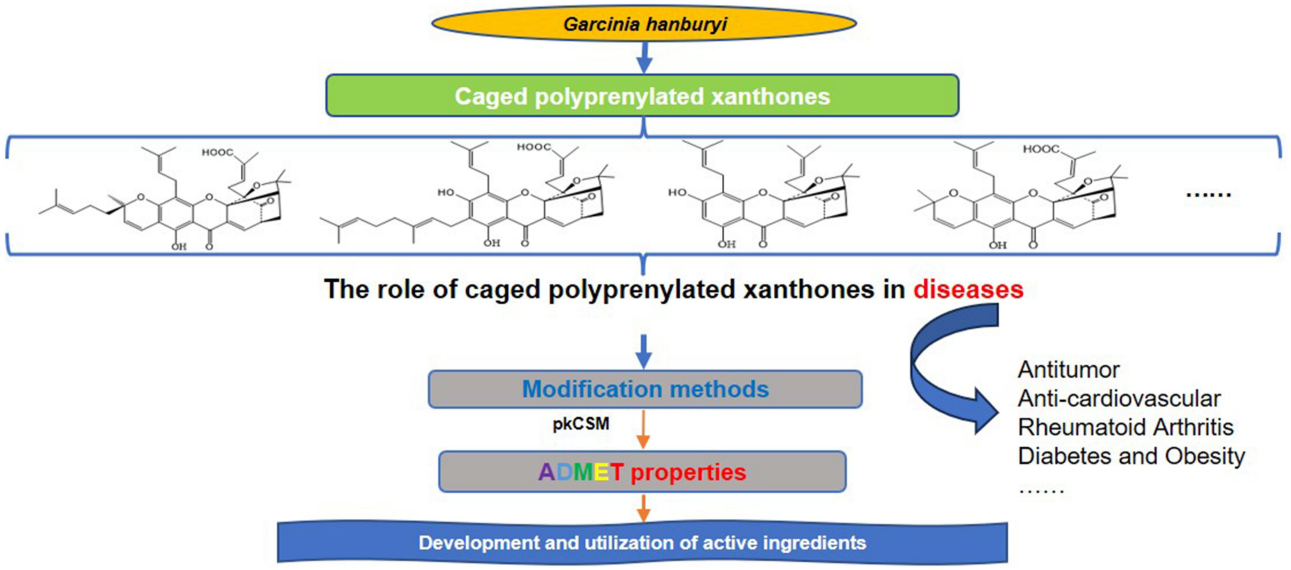
Graphical Abstract

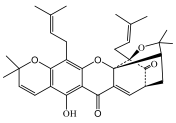
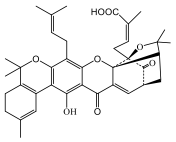
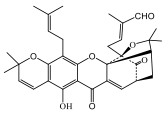
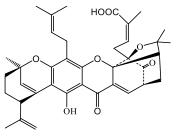
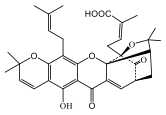
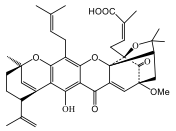
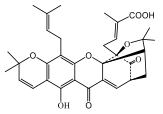
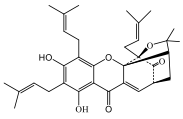
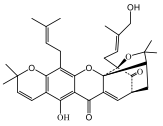
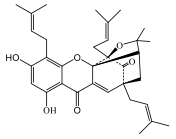
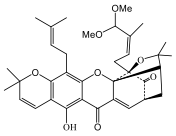
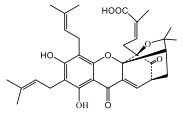
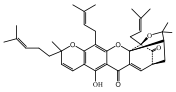
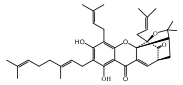
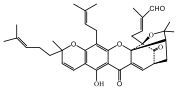
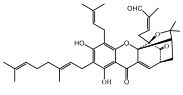


these bioactive ingredients. Our work covers many aspects, including compound isolation, pharmacokinetics, and formulation. In our previous studies, several highly fascinating methods were found to improve the therapeutic efficacy of GNA, including the use of solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs),[23] liquid crystal dispersions,[24] PEGylated liposomes, PEGylated nonionic surfactant vesicles,[25] and folic acid-modified nonionic surfactant vesicles.[26] More than 50 different types of caged polyprenylated xanthones have been extracted from *Garcinia hanburyi*, but researchers have mostly focused more on GNA and GA. However, the basic properties of the other ingredients, particularly their absorption, distribution, metabolism, excretion and toxicity (ADME/T) properties, all of which are the key factors affecting the efficacy of drugs in vivo, are unclear. However, in the development of new drugs, the evaluation of the physicochemical properties, such as ADME/T properties, is limited by a number of factors, such as the high economic cost and the long time required. Therefore, these properties are usually considered at the stage of clinical research. According to statistics, 40% of drug candidates are eliminated from further development due to poor bioavailability, pharmacokinetic properties or toxicity.[27] Based on a collection of reliable experimental data as reported, a computer program was developed to effectively predict the ADME/T properties of bioactive ingredients.[28] Compared with the traditional experiments in vivo, computer programs can process multiple active ingredients in batches and predict their ADME/T properties by simply providing the structure of the compound, thus making this process more efficient and less costly.[29] PkCSM software is a distance-based graphical feature that can be used to predict and optimize the pharmacokinetic properties and toxicity of small molecules. It consists of 30 predictors divided into five major classes: absorption (7 predictors), distribution (4 predictors), metabolism (7 predictors), excretion (2 predictors), and toxicity (10 predictors).[30] To start forecasting, only with the SMILES code of the compound, it enables easy and rapid early stage assessment of compounds. Under the pkCSM program, the ADME/T properties of 51 caged polyprenylated xanthones derived from *Garcinia hanburyi* were predicted and summarized. It is hoped that this will promote the development and utilization of natural products.

Chemical Structures of the Xanthones in *Garcinia hanburyi*

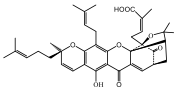
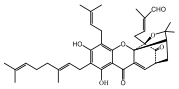
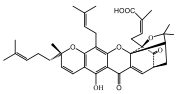
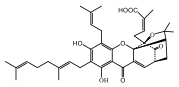
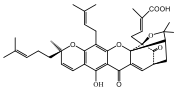
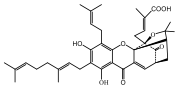
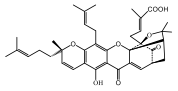
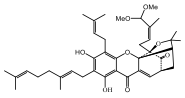
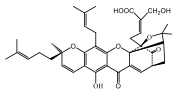
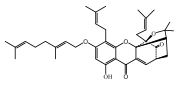
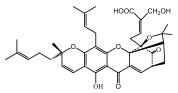
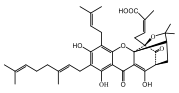
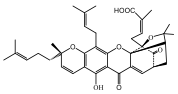
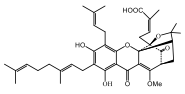
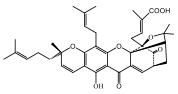
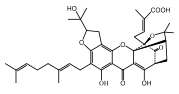
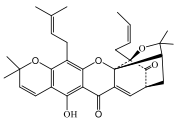
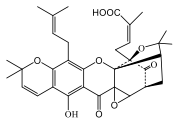
To predict and compare the ADME/T properties of the caged polyprenylated xanthones derived from *Garcinia hanburyi* more comprehensively, we summarized 51 of them that had been isolated to date. The caged polyprenylated xanthones currently known derived from *Garcinia hanburyi* are listed in Table 1. As typical caged polyprenylated xanthones in

Table 1 Chemical Structures of the Caged Polyprenylated Xanthones Derived from *Garcinia hanburyi*

No.	Chemical structure	Name	Reference(s)	No.	Chemical structure	Name	Reference(s)
1		Desoxymorellin	[9,10]	27		Gambogefic acid	[10]
2		Isomorellin	[10,31]	28		Gambogellic acid	[10]
3		Morellic acid	[3,10,32,33]	29		7-Methoxygambogellic acid	[10]
4		Isomorellic acid	[10,32,33]	30		Desoxygaudichaudione A	[9,10]
5		Isomorellinol	[10,32]	31		Hanburin	[9,10,31]
6		Morellin dimethyl acetal	[10]	32		Gaudichaudic acid	[10,31]
7		Gambogin	[10]	33		Desoxygambogenin	[9,10,31]
8		Gambogic aldehyde	[10]	34		Gambogenin	[10]

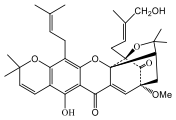
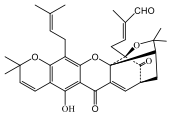
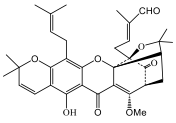
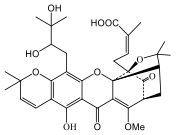
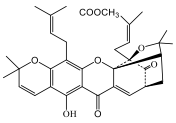
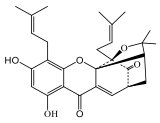
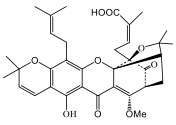
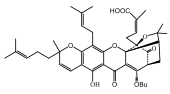
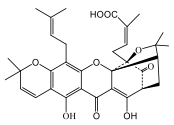
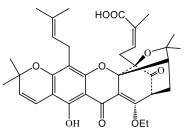
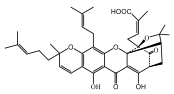
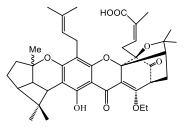
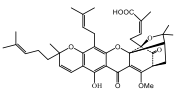
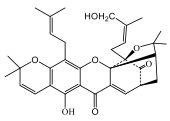
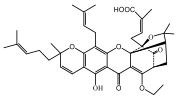
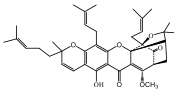
(*Continued*)

Table 1 (Continued).

No.	Chemical structure	Name	Reference(s)	No.	Chemical structure	Name	Reference(s)
9		Gambogic acid	[9,10,33]	35		Isogambogenin	[10,32]
10		Epigambogic acid	[10]	36		Gambogenic acid	[9,10,33]
11		Isogambogic acid	[10,33]	37		Isogambogenic acid	[10,31–33]
12		Epiisogambogic acid	[10]	38		Gambogenin dimethyl acetal	[10]
13		30-Hydroxygambogic acid	[10]	39		3-O-Geranylforbesione	[10]
14		30-Hydroxyepigambogic acid	[10]	40		8,8a-Dihydro -8-hydroxygambogenic acid	[10]
15		7-Methoxygambogic acid	[10]	41		10-Methoxygambogenic acid	[10]
16		7-Methoxyepigambogic acid	[10]	42		Gambogenific acid	[10]
17		7-Methyoxydesoxymorellin	[10]	43		8,8a-Epoxymorellic acid	[10]

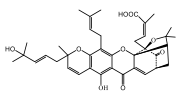
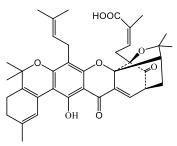
(*Continued*)

Table 1 (Continued).

No.	Chemical structure	Name	Reference(s)	No.	Chemical structure	Name	Reference(s)
18		7-Methoxyisomorellin	[10]	44		Dihydroisomorellin	[10]
19		Isomoreollin B	[3,10]	45		Hanburinone	[10]
20		Methyl-8,8a-dihydromorellate	[10]	46		Forbesione	[10,33]
21		Moreollic acid	[3,10]	47		10α-Butoxygambogic acid	[1]
22		8,8a-Dihydro -8-hydroxymorellic acid	[10]	48		10α-ethoxy-9,10- dihydrogambogenic acid	[1]
23		8,8a-Dihydro -8-hydroxygambogic acid	[10]	49		Gambogic acid C or epigambogic acid C	[1]
24		Gambogic acid A or 10- methoxygambogic acid	[10]	50		Morellinol	[34]
25		Gambogic acid B or 10- ethoxygambogic acid	[10]	51		10-Methoxygambogin	[34]

(*Continued*)

Table 1 (Continued).

No.	Chemical structure	Name	Reference(s)	No.	Chemical structure	Name	Reference(s)
26		Oxygambogic acid	[10]	27		Gambogefic acid	[10]

Garcinia hanburyi, GA (Compound 9) and GNA (Compound 36) are of great interest for their proliferation inhibitory effects on a variety of tumor cells.

The Role of Caged Polyprenylated Xanthones in Diseases

Antitumor

In recent years, in vitro and in vivo experiments have shown that the caged polyprenylated xanthones extracted from *Garcinia hanburyi* exhibits anti-tumor effects, the anti-tumor effects of GA and GNA are mainly achieved through induction of apoptosis, cell cycle arrest and inhibition of tumor cell invasion and migration, and the compounds of gambogefic acid, 7-methoxygambogellic acid, 7-methoxygambogic acid, 7-methoxyepigambogic acid, 8,8a-dihydro -8-hydroxymorellic acid, 8,8a-dihydro-8-hydroxygambogenic acid, oxygambogic acid, gambogenific acid, 7-methoxyi-somorellinol, 8,8a-dihydro-8-hydroxygambogic acid also have inhibitory effects on cancer cells.[4]

Induction of Apoptosis

It was demonstrated that GA induces apoptosis in non-small cell lung cancer (NSCLC) A549 cells by upregulating the expression of pro-apoptotic genes BAX and PUMA and downregulating the expression of anti-apoptotic gene BCL-2 through transcription factor P53.[35] In addition, GA can increase the sensitivity of MCF-7 to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and promoted TRAIL-induced apoptosis in breast cancer cells by enhancing the activity of caspase-3 and caspase-8.[36] GA can also induce apoptosis in glioblastoma by increasing the levels of the pro-apoptotic proteins BAX and apoptosis-inducing factor (AIF), and this is a non-caspase-related apoptotic pathway.[37,38] The Janus kinase-signal transducers and activators of transcription (JAK-STAT) signaling pathway are closely related to tumor cell apoptosis, and it was shown that GA could induce apoptosis of esophageal cancer cells by inhibiting the JAK-STAT signaling pathway.[39] The mechanism of GNA-induced apoptosis in tumor cells has also received considerable attention in recent years, studies have shown that GNA can induce apoptosis in breast cancer cells through the mitochondrial pathway, it can also induce apoptosis by inhibiting the expression of the anti-apoptotic protein BCL-2 and activating apoptosis-related proteins.[40,41]

Blocking the Cell Cycle

Cell cycle factor is an important target for tumor treatment. Several studies show that caged polyprenylated xanthones in *Garcinia hanburyi* can block the tumor cell cycle. GNA can induce apoptosis by downregulating the expression of cyclin-dependent kinases (CDKs) that arrest the cell cycle in the G1 phase and subsequently activate caspases.[42] GA can induce mRNA expression of genes related to cell cycle arrest, thereby causing cells to arrest in the G0/G1 phase.[43]

Inhibit the Invasion and Metastasis of Tumor Cells

Invasion and metastasis of tumor cells are the main reasons for the poor prognosis of patients. Experimental results have shown that GA can reduce the invasion of breast cancer cells and colon cancer cells, follow-up mechanistic studies revealed that this may be related to the c-Jun N-terminal kinase (JNK) signaling pathway, which increases the secretion of matrix metalloproteinases (MMPs) in cancer cells, disrupts the extracellular matrix, decreases intercellular adhesion,

and thus promotes invasion and metastasis of cancer cells.[44] GNA and isomorellin were found to attenuate the migration and invasion of tumor cells by inhibiting the NF-κB pathway.[45,46]

Inhibit Angiogenesis

It was revealed that GNA could significantly reduce p-PI3K, p-AKT, and vascular endothelial growth factor (VEGF) expression, further experiments showed that GNA inhibits angiogenesis through the PTENPI3K/AKT/VEGF/eNOS pathway.[47] In addition, it was also demonstrated that morellic acid, gambogenin and isogambogenic acid showed comparable antiangiogenic activities with less toxicities than GA.[48]

Induction of Cellular Autophagy

In recent years, autophagy has received extensive attention in numerous researches of antitumor drugs. GA could induce significant upregulation the expression of autophagy-related factors ATG7, BECLIN-1 and LC3-II in acute lymphoid leukemia cells, while inhibiting Wnt/β-catenin signaling, thus further inhibiting cell growth.[49] It was observed that glioma cells treated with GNA showed increased expression of autophagic proteins and increased secretion of autophagic vesicles, suggesting that GNA can induce autophagy in tumor cells, thereby inhibiting tumor growth.[50]

Other Mechanism Studies

The accumulation of reactive oxygen species (ROS) has an important impact on the development of tumors. It was suggested that GA can induce the accumulation of ROS in tumor cells, which may be related to the ability of GA to inhibit cytosolic thioredoxin (TRX-1) and mitochondrial thioredoxin (TRX2) distributed in the cytoplasm and mitochondrion, which play a key role in maintaining ROS homeostasis.[51–53] Recent studies have observed that GA kills cancer cells by inducing a vacuolization-associated cell death, and this phenomenon may be associated with GA-induced proteasomal inhibition leads to the endoplasmic reticulum (ER) dilation and ER stress in treated cancer cells.[54]

Anti-Cardiovascular Diseases

Currently, cardiovascular disease (CVD) is a great threat to human health. Previous studies have shown that the inflammation and risk of cardiovascular diseases have a strong consistent relationship, and this result has been proven by clinical trials and epidemiological studies.[55] Studies have concluded that the activated pro-inflammatory cytokines, oxidative stress and inflammation and C-reactive protein (CRP) are key mechanisms in the development of CVD.[56] Fu et al[57] evaluated the role of neoglycyrrhetinic acid in sepsis-associated myocardial injury, and they discovered that GNA exerts anti-apoptotic, anti-fibrotic and anti-inflammatory effects in septic mice through inactivation of the MAPK/NF-κB pathway. Studies have shown that GA can inhibit cardiac hypertrophy and fibrosis induced by pressure or isoprenaline infusion by inhibiting the NF-κB pathways and proteasome, indicating that GA therapy may a new strategy for the treatment of cardiac hypertrophy and fibrosis.[58]

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, systemic disease characterized by inflammatory synovitis. It is characterized by polyarticular, symmetric, aggressive joint inflammation of the small joints of the hands and feet, often accompanied by extra-articular organ involvement and positive serum rheumatoid factor, which can lead to deformities of the joints. There is no specific treatment for rheumatoid arthritis. The aim of treatment is to maintain joint mobility and coordinated function, and different therapies are used at different stages of the disease. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to relieve pain and inflammation in the acute phase of RA. Early findings suggest that the ethyl acetate extract of gamboge appears to have a mechanism of action similar to NSAIDs rather than to steroids.[59] Subsequent studies have demonstrated that GA is one of the NSAIDs that inhibit the development of RA by suppressing the levels of inflammatory molecules and cytokines.[60] Wu et al[61] revealed that the anti-inflammatory effect of GA in RA rats was mediated by modulation of the PI3K/Akt/mTOR signaling pathway.

Diabetes and Obesity

AMP-activated protein kinase (AMPK), an AMP-dependent protein kinase, is a key factor in the regulation of biological energy metabolism and also a key factor in the study of metabolism-related diseases, such as type 2 diabetes and obesity.[62,63] Genetic and pharmacological studies have shown that AMPK is essential for the body to maintain glucose homeostasis. Zhao et al[63] demonstrated for the first time that GA activates the AMPK signaling pathway by directly interacting with AMPK. Protein tyrosine phosphatase 1B (PTP1B) is involved in maintaining the balance of tyrosine protein phosphorylation and negatively regulates insulin signaling.[34] The active compounds extracted from *Garcinia hanburyi* such as GA, moreollic acid, morellic acid, 10-methoxygambogenic acid, GNA, GA, morellinol, 10-methoxygambogin and desoxymorellin, were identified to be PTP1B inhibitors, they inhibit PTP1B in dose-dependent manner, the binding sites of GA and morellinol with PTP1B were studied, and it was revealed that the inhibitory activities are highly correlated with the caged motif and prenyl group in A ring.

Other Diseases

Recent research has shown that GNA ameliorates cardiac injury and dysfunction in LPS-induced septic mice by inhibiting cardiac apoptosis, fibrosis and inflammation through downregulation of p-JNK and p-NF-κB.[57] In a recent work, binding affinities of xanthone compounds which including morellic acid, gambogellic acid, GNA, moreollic acid with SARS-CoV-2 main protease (Mpro) were predicted using the molecular docking technique, the results showed that morellic acid has a high-binding affinity towards SARS-CoV-2 Mpro, and this suggests that MA is a promising candidate for anti-COVID-19; however, this requires further detailed in vivo experimental estimation and clinical evaluation.[64]

Pharmacokinetic Studies and Countermeasures for Improving the Drug-Like Properties of Caged Polyprenylated Xanthones

To effectively utilize the curative effects of caged polyprenylated xanthones in clinic, an in vivo pharmacokinetic study of the drug is essential. In previous studies, GA was administered via intravenous injection; however, GA has an extremely short half-life in plasma.[17,65] Administering GA intravenously to patients to treat tumors leads to side effects such as cardiotoxicity, liver damage and phlebitis.[66] For these reasons, GA was not evaluated in Phase III clinical trials as an intravenous antitumor agent. In addition, the previous study found that, GA is poorly absorbed after gastrointestinal administration in rats and has low bioavailability in vivo; studies have shown that, after oral administration, GA is toxic to various rat organs.[67,68] In view of the above-mentioned drawbacks, the clinical applications of GA administered via intravenous injection and orally are limited. Actually, many active ingredients of TCM with antitumor activity have strong hydrophobicity, and the conventional solubilization techniques cannot meet the needs of the development of insoluble drugs. To address these challenges, multiple studies have been conducted to refine the pharmacokinetic and pharmacodynamic performance of GA, chemical structure modifications, combination therapy and different types of nanoscale drug delivery systems (Table 2) and have been employed to modify or encapsulate GA while avoiding vascular irritation and organ toxicity in vivo. Rational medicinal modifications on GA will improve its physicochemical properties and drug-like characters. The chemical structural of GA is shown in Figure 1. Previous structure modifications of GA mainly focused on the 9,10-double carbon bond of a,b-unsaturated ketone, 6-hydroxyl group, isopentenyl groups and the 30-carboxyl group. It was found that the 9,10-double bond in a,b-unsaturated ketones is essential for the apoptosis-inducing activity, and the replacement of the acidic carboxyl group with ester and amide does not have much effect on the activity, it is also suggests that the hydrophilic face of GA may not have much relevance for its binding to biological targets. With the development of nano drug delivery systems, more and more elaborate and complex drug delivery systems are being designed, researchers have conducted studies on various nano-delivery systems of GA, including passive targeting, active targeting, tumor microenvironment response and bionic targeting, for example, the aqueous solubility of GA can be improved by chemical conjugation to a water-soluble polymer such as polyethylene glycol (PEG),[69] Moreover, in order to control the release of GA, enhance its accumulation at tumor sites, and reduce side effects, multifunctional nanoparticles of GA with pH-sensitive and redox-responsive sensitivities as well as receptor-targeted responses were developed. However, more attention should be paid to the in vivo degradation and systemic

Table 2 GA Modifications

No.	Modification Method	Specific Form(s)	Indication	Status	Cell(s)	Reference
1	Chemical structure modification	The derivatives of GA with aliphatic amino moieties at C(39)	Antitumor	In vitro	T47D, HCT116 and SNU398 cells	[81]
2	Chemical structure modification	The derivatives of GA with modification of the 30-carboxy and 6-hydroxy group. The derivatives of GA without the 9,10 carbon–carbon double bond in the a,b-unsaturated ketone	Antitumor	In vitro	T47D, ZR751 and DLD-1 cells	[82]
3	Chemical structure modification	Modified the carbon–carbon double bond at C-32/33 or C-37/38 and of the methyl groups at C-39/C-35	Antitumor	In vitro	HT-29, Bel-7402, BGC-823, A549, and SKOV 3 cells	[83]
4	Chemical structure modification	The carbon-carbon double bonds of C-32/33 and C-38/40 and the methyl group of C-34 were converted to epoxy group and hydroxymethyl group	Antitumor	In vitro	Bel-7402, HT-29, and BGC-823 cells	[84]
5	Chemical structure modification	Two GA derivatives with neo-type A ring systems were generated during microwave irradiation in acidic condition	Antitumor	In vitro	HepG2, BGC-803, SGC-7901 and MCF-7 cells.	[85]
6	Chemical structure modification	GA analogues that address potential key structural features after A and B rings were completely cut from the core structure	Antitumor	In vitro	HepG2 cells	[86]
7	Chemical structure modification	Modified C(39) of GA by introducing aliphatic amino, aromatic amino, alkoxy, and halogen moieties in this position	Antitumor	In vitro	A549, BGC-823, U251, HepG2, and MB-231 cells	[87]
8	Chemical structure modification	Aliphatic amino moieties at C(39)	Antitumor	In vitro	A549, BGC823, U251, HepG2, and MDA-MB -231 cells	[87]
9	Chemical structure modification	Chemical modification at C(34) by introducing of hydrophilic aliphatic amines	Lung cancer	In vitro	A549 cells	[88]
10	Drug delivery system	GA-loaded poloxamer 407/TPGS mixed micelles	Breast and multidrug-resistant cancer	In vitro	NCI/ADR-RES cells	[89]
11	Drug delivery system	GA-lactoferrin nanoparticles	Antitumor	In vitro	HepG2 cells	[90]
12	Drug delivery system	GA-mPEG2000 micelles	Antitumor	In vitro	B16F10 and C26 cells	[91]
13	Drug delivery system	N-Octyl-N-arginine-chitosan (OACS) micelles for GA		In situ intestinal perfusion		[92]
14	Drug delivery system	GA-Ps	Liver cancer	In vivo	H22 cells	[93]

(*Continued*)

Table 2 (Continued).

No.	Modification Method	Specific Form(s)	Indication	Status	Cell(s)	Reference
15	Drug delivery system and combination therapy	GA-loaded HRA nanoparticles	Breast cancer	In vitro and in vivo	MCF-7 cells	[94]
16	Drug delivery system	GA-TiO_2 nanocomposites	Liver cancer	In vitro	HepG2 cells	[95]
17	Drug delivery system and combination therapy	BTZ-GA-loaded MNP-Fe_3O_4	Multiple myeloma	In vitro and in vivo	RPMI-8226 cells	[96]
18	Drug delivery system	PEGylated liposomal formulation of GA (GAL)	Breast cancer	In vitro and in vivo	MDA-MB-231, Hep G2 and MIA PaCa-2 cells	[97]
19	Combination therapy	GA+Fe_3O_4 -MNP	Liver cancer	In vitro	SMMC-7721 cells	[98]
20	Drug delivery system	GA-loaded cp-rHDL nanoparticles	Antitumor	In vitro and in vivo	HepG2 and HT1080 cells	[99]
21	Drug delivery system	GA-loaded F68-LA nanospheres	Ovarian cancer	In vitro	A2780 cells	[100]
22	Drug delivery system	GA/RACC-loaded glycol chitosan nanoparticles	Osteosarcoma	In vitro	MG63 cells	[101]
23	Drug delivery system	GA-loaded long-circulating liposomes		In vivo pharmacokinetics		[102]
24	Drug delivery system	GA-loaded FA-Arg-PEUU nanoparticles	Antitumor	In vitro	HeLa and A549 cells	[103]
25	Drug delivery system	GA-HSA nanoparticles	Lung cancer	In vivo	A549 cells	[104]
26	Drug delivery system and combination therapy	DTX/GA PLGA nanoparticles	Lung cancer	In vitro and in vivo	MCF-7 and MCF-7/Adr cells	[105]
27	Drug delivery system	PLGA-GA nanosystem		In vitro and ex vivo transport	Caco-2 cells	[106]
28	Drug delivery system	GA and LMWH loaded nanosystem	Malignant glioma	In vitro and in vivo	U87MG cells and HUVECs	[107]
29	Drug delivery system	RBCm-GA/PLGA nanoparticles	Colorectal cancer	In vitro and in vivo	SW480, MKN45 and AGS cells	[108]
30	Drug delivery system	GA-loaded PEG-PCL nanoparticles	Gastric cancer	In vitro and in vivo	MKN45 cells	[109]
31	Drug delivery system	F68-LA/GA nanospheres	Ovarian cancer	In vitro	A2780 cells	[100]

(*Continued*)

Table 2 (Continued).

No.	Modification Method	Specific Form(s)	Indication	Status	Cell(s)	Reference
32	Drug delivery system	GA-LMWH micelles	Liver cancer	In vitro and in vivo	H22 cells	[110]
33	Drug delivery system and combination therapy	pTRAIL and GA coloaded HA-coated PEI-PLGA NPs	Breast cancer	In vitro and in vivo	MCF-7, MDA-MB-231 and 4T1 cells	[111]
34	Drug delivery system	GA-loaded PEG-PCL (GA-PP) micelles	Lung cancer	In vitro	A549 cells	[112]
35	Drug delivery system	GA-loaded HA(CD)-4Phe4 nanocomplex	Breast cancer	In vitro	MDA-MB-435/MDR cells	[113]
36	Drug delivery system	GA-loaded OACS micelles		In vivo pharmacokinetics and biodistribution study		[114]
37	Drug delivery system and combination therapy	GA-conjugated PAAs/DTX-shRNA micelles	Breast cancer	In vitro and in vivo	MCF-7 cells	[115]
38	Targeted drug delivery system	GA-loaded magnetic nanoparticles	Mesenchymal epidermolysis bullosa carcinoma	In vivo	VX-2 cells	[116]
39	Drug delivery system	GA-loaded FA-Arg-PEUU nanoparticles	Antitumor	In vitro	HeLa and HCT116 cells	[103]
40	Drug delivery system	GA-HSA nanoparticles	Lung cancer	In vivo	A549 cells	[104]
41	Targeted drug delivery system	GA-loaded Mn-ICG@pHis-PEG NCPs	Breast cancer	In vitro and in vivo	4T1 cells	[117]
42	Drug delivery system	GA-loaded precision polymer nanosystem		In vivo pharmacokinetics and biodistribution		[118]
43	Drug delivery system	GA-encapsulated MPEG-PCL micelles	Breast cancer	In vitro and in vivo	MCF-7 cells	[119]
44	Drug delivery system	GA-NLC-cRGD, GA-NLC-RGE, GA-NLC-cRGD/RGE	Breast cancer	In vitro and in vivo	MDA-MB-231 cells	[120]
45	Targeted drug delivery system	(sPEG/HA/CSO)-SS-Hex/Fe3O4/GA	Breast cancer	In vitro and in vivo	4T1 cells	[121]
46	Structural modification	GA-CPP conjugate	Bladder cancer	In vitro	EJ bladder cancer cells	[122]
47	Drug delivery system	HA-PRM-GA micelles	Lung cancer	In vitro	A549 cells	[123]

(*Continued*)

Table 2 (Continued).

No.	Modification Method	Specific Form(s)	Indication	Status	Cell(s)	Reference
48	Drug delivery system	GA-encapsulated oil-in-water nanoemulsion	Acute myeloid leukemia	In vitro and in vivo	HL-60, Jurkat, MV4-11 and L929 cells	[124]
49	Drug delivery system	GA-loaded liposomes	Melanoma	In vitro and in vivo	B16F10 and EMT6 cells	[17]
50	Drug delivery system	iE–RBCm–GA/PLGA NPs	Colorectal cancer	In vitro and in vivo	Caco-2, HT-29 and SW480 cells	[125]
51	Sequential and site-specific drug delivery	LbL fabrication of GA and TRAIL codelivered BSA nanoparticles	Antitumor	In vitro and in vivo	A549 and MCF-7 cells	[126]
52	Drug delivery system	Hydrophilic, positively charged lung-targeting GA-loaded particles	Lung cancer	In vitro and in vivo	LL/2 cells	[127]
53	Targeted drug delivery system	GA-loaded BzPGA-HA-C6-ATRA core–shell nanoparticles	Antitumor	In vitro and in vivo	B16F10, HepG2, A549 and L929 cells	[128]
54	Drug delivery system	HA(HECS-ss-OA)/GA nanoparticles	Lung cancer	In vitro and in vivo	A549 cells	[129]
55	Dual sensitive drug delivery system	mPEG-VC-SS-GA NPs	Liver cancer	In vitro	HepG2 cells	[130]
56	Targeted drug delivery system	Fe_3O_4@NH_2-b-CD MNPs	Antitumor	In vitro cytotoxicity and in vivo pharmacokinetics	HepG2 and HL-60 cells	[131]
57	Drug delivery system	PLGA–GA nanosystem		In vivo safety assessment		[132]
58	Drug delivery system	c(RGD) peptides modified with GA-NLC	Breast cancer	In vitro and in vivo	4T1 cells	[133]
59	Drug delivery system	GA-Cy7 NPs	Hypoxic cancer	In vitro and in vivo	PC3 cells	[134]
60	Drug delivery system	GA-encapsulated BSA nanoparticles	Antitumor	In vitro and in vivo	HepG2 cells	[135]
61	Topical drug delivery	GA and AZ-PG combination	Melanoma	In vitro and in vivo	B16F10 cells	[70]
62	Drug delivery system for synergistic anticancer therapy	GA and retinoic acid co-encapsulated liposomes	Breast cancer	In vitro and in vivo	4T1 cells	[136]
63	Drug delivery system and synergistic anticancer therapy	Hydrogels packaging GA NPs and iRGD	Antitumor	In vitro and in vivo	MKN45 cells	[137]

(*Continued*)

Table 2 (Continued).

No.	Modification Method	Specific Form(s)	Indication	Status	Cell(s)	Reference
64	Structural modification and drug delivery system	GA prodrug and chitosan nanoparticles	Orthotopic bladder cancer	In vitro	MB49 cells	[138]
65	Drug delivery system and combination therapy	HA-NI shells with MnO2 NPs as oxygen modulators and γ-PFGA as the cores to deliver GA and Ce6	Breast cancer	In vitro and in vivo	4T1 cells	[139]
66	Click chemistry platform and drug delivery system	NPs with mPEG-GA conjugates	Antiarthritis	In vitro and in vivo anti-inflammatory activity	RAW 264.7 cells	[140]
67	Drug delivery system	GA-loaded ROS-responsive amino acid-based poly(ester amide) nanoparticles	Antitumor	In vitro	PC3 and HeLa cells	[141]
68	Drug delivery system and synergistic anticancer therapy	PLGA nanoparticles coloaded with GA, HP and CpG ODN	Liver cancer	In vitro and in vivo	HepG2 and H22 cells	[142]
69	Drug delivery system and synergistic anticancer therapy	PDA–SNO–GA–HA–DOX nanocomplex	Antitumor	In vitro and in vivo	HaCaT and HN6 cells	[143]
70	Drug delivery system and combination therapy	P2Ns-GA-CsA	Systemic lupus erythematosus	In vitro and in vivo		[144]
71	Drug delivery system and synergistic anticancer therapy	GA/PTX NLCs	Breast cancer	In vitro and in vivo	4T1, MCF-7, MCF-7/ADR, and MDA-MB -231 cells	[145]
72	Drug delivery system and combination therapy	PLGA-GA_2-CUR nanoparticles	Ocular inflammation	In vivo		[146]
73	Drug delivery system and synergistic anticancer therapy	GA-loaded FA-Arg-PEUU NPs	Breast cancer	In vitro and in vivo	TNBC and HCC1806 cells	[147]
74	Drug delivery system and molecular docking	^{93}Zr-CS-GA multifunctional liposomes	Breast cancer	In vivo	MDA-MB-231 cells	[148]
75	Drug delivery system and synergistic anticancer therapy	HMCS-PEG-GA nanosystem	Antitumor	In vitro	HepG2 cells	[149]

(*Continued*)

Table 2 (Continued).

No.	Modification Method	Specific Form(s)	Indication	Status	Cell(s)	Reference
76	Drug delivery system and synergistic anticancer therapy	GA-loaded BZ (GBZ) nanoparticles	Hepatocellular carcinoma	In vitro and in vivo	Huh7 cells	[150]
77	Drug delivery system and combination therapy	GA porous lipid/PLGA microbubbles	Human glioma	In vitro	U251 human glioma cells	[151]
78	Topical and transdermal therapeutic system	GA b+ EN-US	Cutaneous melanoma	In vitro penetration and in vivo antitumor effect	B16F10 cells	[71]
79	Drug delivery system	GA-loaded prodrug nanomicelles sensitive to multiple environments	Antitumor	In vitro and in vivo	MCF-7, HepG2, LO2, and HeLa cells	[152]
80	Targeted drug delivery system	Copolymer of PEI-grafted WSC and GA	Antitumor	In vitro and in vivo	PC-3, MCF-7, LoVo and HCT116 cells	[153]
81	Targeted drug delivery system	CB5005N-GA-liposomes	Breast cancer	In vitro and in vivo	4T1 and MDA-MB-231 cells	[154]
82	Oral tumor-targeting delivery system	GNA@PDA-FA SA NPs	Antitumor	In vitro and in vivo	4T1 cells	[78]
83	Drug delivery system and combination therapy	cFA/dNP2-GA/PTX NLCs	Breast cancer	In vitro and in vivo	4T1 cells	[155]
84	Drug delivery system and combination therapy	GA@PEG-TK-ICG polymeric micelles	Breast cancer	In vitro and in vivo	4T1 cells	[156]
85	Codelivery system and combination therapy	Carrier-free codelivered nanoassembly of GA and DiR	Breast cancer	In vitro and in vivo	4T1 cells	[157]
86	Chemical tools and combination therapy	COF-GA nanoagents	Breast cancer	In vitro and in vivo	4T1 cells	[158]
87	Chemical tools and combination therapy	DOX/Cypate/ GA@Rb1 NPs	Breast cancer	In vitro	MCF-7 and 4T1 cells	[159]
88	Drug delivery system and combination therapy	GA-PB@MONs@LA nanoplatform	Breast cancer	In vitro and in vivo	4T1 cells	[160]

(*Continued*)

Table 2 (Continued).

No.	Modification Method	Specific Form(s)	Indication	Status	Cell(s)	Reference
89	Drug delivery system and combination therapy	PPMD@GA/si NPs	Breast cancer	In vitro and in vivo	4T1 cells	[161]
90	Codelivery system	G–G@HTA NPs	Lung cancer	In vitro and in vivo	NSCLC, A549, and H1299 cells	[162]
91	Drug delivery system and combination therapy	NIR-II thermosensitive liposomes containing DTBZ and GA	Antitumor	In vitro and in vivo	B16F10 and NIH-3T3 cells	[163]
92	Click chemistry and drug delivery system	mPEG–GA conjugate NPs	Antitumor	In vitro and in vivo	CT-26 cells	[69]

toxicity of excipients used in these preparations, especially administered via intravenous injection. To date, no related oral or intravenous preparations of GA that have successfully passed clinical trials for market approval. In recent years, people have continued to explore new routes to deliver GA with improved bioavailability and reduced toxicity to serve as a breakthrough in tumor treatment. In addition to intravenous and oral administration, recent attention has been focused on improving the effectiveness of GNA through local delivery. Previously, researchers demonstrated that localized administration of GA with the help of chemical penetration enhancers could be a safe and effective therapy for the treatment of melanoma.[70] In their follow-up study, compared with chemical penetration enhancers, ultrasound, and intravenous injection, GA exhibited the strongest antimelanoma activity with combined chemical penetration enhancers and ultrasound administration, as chemical penetration enhancers can increase the cavitation effect of US.[71]

GNA is another major active ingredient extracted from the resin of gamboge, exhibits broader antitumor activity and less systemic toxicity than GA.[72] To date, in vivo pharmacokinetic results in rats have shown that GNA is as poorly absorbed as GA after intragastric administration of *Garcinia hanburyi* extract. Additionally, the pharmacokinetic data of these two structurally similar xanthones are comparable, which means that slight changes in the position of the substituent on the alkyl side chain do not appreciably affect the in vivo pharmacokinetic properties of the compound.[65,67,73–75] With the aim of overcoming the in vivo pharmacokinetic shortcomings of GNA for cancer therapy, recent studies have been trying to modify GNA with the aid of nanocarriers to improve its bioavailability and reduce its toxicity (Table 3). In 2013, our group prepared GNA-SLNs and compared the pharmacokinetic characteristics in rats after intraperitoneal injection of GNA solution and GNA-SLNs.[76] Additionally, colloidal delivery systems were successfully fabricated for the targeted delivery of GNA. As demonstrated by the pharmacokinetic assay, after being encapsulated by

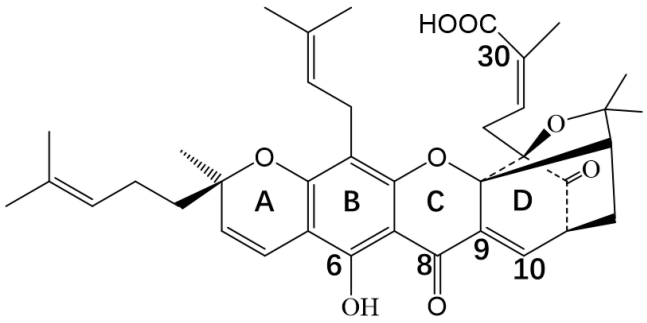


Figure 1 The chemical structure of GA.

Table 3 GNA Modifications

No.	Modification Method	Specific Form	Indication	Status	Cancer Cell(s)	Reference
1	Drug delivery system	GNA SLNs	Antitumor	In vivo safety		[76]
2	Drug delivery system	PEG-GNA NISVs		In vivo pharmacokinetics		[25]
3	Drug delivery system	FA-GNA MNPs	Lung cancer	In vitro cytotoxicity	A549 cells	[164]
4	Drug delivery system	GNA nanosuspensions	Antitumor	In vitro cytotoxicity and in vivo pharmacokinetics	HepG2 cells	[165]
5	Drug delivery system	GNA-loaded cubosomes	Antitumor	In vitro cytotoxicity and in vivo pharmacokinetics	SMMC-7721 cells	[24]
6	Drug delivery system	Monodispersed ceria nanoparticles (CNPs) covered with GNA	Breast cancer	In vitro cytotoxicity	MCF-7 cells	[166]
7	Drug delivery system	GNA-PEG NLCs		In vitro release and in vivo pharmacokinetics		[23]
8	Drug delivery system	GNA nanoliposomes		In vivo pharmacokinetics		[167]
9	Drug delivery system	GNA-PEG liposomes	Antitumor	In vitro and in vivo	A549, SGC-7901, HepG2, and LLC cells	[168]
10	Drug delivery system	GNA-PLC micelles	Antitumor	In vitro cytotoxicity and in vivo pharmacokinetics	HepG2 cells	[169]
11	Drug delivery system	GNA-PEI/siRNA liposomes	Antitumor	In vitro cytotoxicity	HepG2 cells	[170]
12	Drug delivery system	GNA-loaded zein nanoparticles		In vivo pharmacokinetics and tissue distribution		[171]
13	Drug delivery system	GNA-loaded mPEG-PLA/mPEG-PCL mixed micelles	Antitumor	In vitro cytotoxicity	HepG2 cells	[172]
14	Drug delivery system	FA-GNA NISVs	Lung cancer	In vitro cytotoxicity and in vivo pharmacokinetics	A549 cells	[26]
15	Drug delivery system	GNA@Zein-PDA NPs	Antitumor	In vitro cytotoxicity and in vivo pharmacokinetics	HepG2 cells	[173]
16	Oral drug delivery system	GNA@PDA-FA SA NPs	Breast cancer	In vitro and in vivo	4T1 cells	[78]

the nano-delivery system, the residence time of GNA in the blood circulation was prolonged; in addition, the antitumor ability of the encapsulated GNA was significantly enhanced. In conclusion, the results of this study suggest that the nano-delivery system can potentially be used to deliver GNA. Notably, intravenous administration increases vascular damage and causes recurrent pain due to the vascular irritability of GA. As an attractive alternative, oral administration offers the following advantages, for instance, various dosage forms are available, relatively low production costs, ease of production and good patient compliance.[77] Researchers have also designed oral dosage forms of GNA, such as, polydopamine nanoparticles were prepared for encapsulating and stabilizing GNA coated with sodium alginate after the modification of

folic acid to achieve antitumor effect after oral administration and to improve the water solubility, bioavailability and tumor targeting of GNA.[78] Our subject group also successfully isolated and extracted another component of *Garcinia hanburyi*, morellic acid (MA) (Compound 3, Table 1), which has also shown a good antitumor effect. As predicted, MA also has unfavorable pharmacokinetics; therefore, our group prepared MA NLCs to conquer this problem.[79] However, the feasibility of producing this nano-delivery system, as well as the in vivo degradation and systemic toxicity of the excipients, need to be further investigated.

In recent years, studies have shown that water processing could alter the bioavailability of five caged xanthones in *Garcinia hanburyi*, which could attenuate toxicity and increase their effects.[80] Apart from the abovementioned studies, very few pharmacokinetic studies of other caged xanthones have been reported.

Interpretation of the Prediction Model

Physical and Chemical Properties

The pkCSM prediction results of physical and chemical properties (Table 4) show that the molecular weights of these caged polyprenylated xanthones are all greater than 500 with the exception of forbesione (Compound 46), the number of hydrogen bond acceptors is less than 10, the number of hydrogen bond donors is less than 5, and the logP values are between 5.0 and 8.5. The above parameters partially conform to the rule of Lipinski,[174] and among these parameters, their drug-like properties are mainly limited by their larger molecular weight and higher lipid solubility.

Table 4 Predicted Physical and Chemical Properties for the Caged Polyprenylated Xanthones in *Garcinia hanburyi* Provided by pkCSM

No.	Molecular Weight	LogP	Rotatable Bonds	Acceptors	Donors
1	530.661	6.4481	4	6	1
2	544.644	5.6271	5	7	1
3	560.643	5.5128	5	7	2
4	560.643	5.5128	5	7	2
5	546.66	5.4205	5	7	2
6	590.713	6.0471	7	8	1
7	598.78	8.1746	7	6	1
8	612.763	7.3539	8	7	1
9	628.762	7.2393	8	7	2
10	628.762	7.2393	8	7	2
11	628.762	7.2393	8	7	2
12	628.762	7.2393	8	7	2
13	644.761	6.2117	9	8	3
14	644.761	6.2117	9	8	3
15	658.788	7.0083	9	8	2
16	658.788	7.0083	9	8	2
17	546.66	5.827	5	7	1
18	576.686	5.1859	6	8	2

(*Continued*)

Table 4 (Continued).

No.	Molecular Weight	LogP	Rotatable Bonds	Acceptors	Donors
19	574.67	5.6012	6	8	1
20	574.67	5.6012	6	8	1
21	590.669	5.4869	6	8	2
22	576.642	5.3985	5	8	3
23	644.761	7.125	8	8	3
24	658.788	7.2134	9	8	2
25	672.815	7.6035	10	8	2
26	644.761	6.2101	8	8	3
27	626.746	6.9933	5	7	2
28	626.746	6.8492	6	7	2
29	656.772	6.1682	7	8	2
30	532.677	6.4782	6	6	2
31	532.677	6.696	6	6	2
32	562.659	5.5429	7	7	3
33	600.796	8.2047	9	6	2
34	614.779	7.3837	10	7	2
35	614.779	7.3837	10	7	2
36	630.778	7.2694	10	7	3
37	630.778	7.2694	10	7	3
38	660.848	7.8037	12	8	2
39	600.796	8.3354	10	6	1
40	646.777	7.1551	10	8	4
41	660.804	7.2435	11	8	3
42	662.776	6.0152	9	9	4
43	576.642	4.724	5	8	2
44	544.644	5.6271	5	7	1
45	624.683	3.6525	7	10	4
46	464.588	4.9695	4	6	2
47	700.869	8.3837	12	8	2
48	604.696	5.877	7	8	2
49	672.815	6.9935	7	8	2
50	546.66	5.4205	5	7	2
51	628.806	8.1487	8	7	1

Absorption

The absorption parameter (Table 5) results show that these caged polyprenylated xanthones have poor water solubility, and lipid-soluble drugs are not absorbed as well as those that are water-soluble, especially after administration via the gastrointestinal tract.[175] Additionally, these compounds have different degrees of Caco-2 cell permeability. In the pkCSM

Table 5 Predicted Absorption Properties for the Caged Polyprenylated Xanthones in *Garcinia hanburyi* Provided by pkCSM

No.	Absorption						
	Water Solubility (Log mol/L)	**Caco2 Permeability (Log Papp in 10^{-6} cm/s)**	**Intestinal Absorption (Human) (% Absorbed)**	**Skin Permeability (Log Kp)**	**P-Glycoprotein Substrate (Yes/No)**	**P-GlycoproteinI Inhibitor (Yes/No)**	**P-GlycoproteinII Inhibitor (Yes/No)**
1	−4.892	1.405	95.565	−2.829	No	Yes	Yes
2	−4.792	1.54	100	−2.762	No	Yes	Yes
3	−4.14	1.335	81.218	−2.734	Yes	No	Yes
4	−4.14	1.335	81.218	−2.734	Yes	No	Yes
5	−4.685	1.489	100	−2.817	Yes	Yes	Yes
6	−4.21	1.277	100	−2.749	No	Yes	Yes
7	−4.298	1.686	97.634	−2.734	Yes	Yes	Yes
8	−4.239	1.21	100	−2.735	Yes	Yes	Yes
9	3.835	1.065	98.839	−2.735	Yes	No	Yes
10	−3.835	1.065	98.839	−2.735	Yes	No	Yes
11	−3.835	1.065	98.839	−2.735	Yes	No	Yes
12	−3.835	1.065	98.839	−2.735	Yes	No	Yes
13	−3.28	−0.041	89.992	−2.735	Yes	No	No
14	−3.28	−0.041	89.992	−2.735	Yes	No	No
15	−4.464	0.763	98.935	−2.735	Yes	No	Yes
16	−4.464	0.763	98.935	−2.735	Yes	No	Yes
17	−4.88	0.969	98.516	−2.845	No	Yes	Yes
18	−4.674	0.918	100	−2.817	Yes	Yes	Yes
19	−3.885	0.894	100	−2.735	Yes	Yes	Yes
20	−4.171	1.284	100	−2.754	No	Yes	Yes
21	−3.542	0.69	82.287	−2.735	Yes	No	Yes
22	−3.805	0.032	70.71	−2.735	Yes	No	Yes
23	−3.441	0.136	88.414	−2.735	Yes	No	Yes
24	−3.401	0.707	85.855	−2.735	Yes	No	Yes
25	−3.386	0.707	86.613	−2.735	Yes	No	Yes
26	−4.034	−0.01	75.41	−2.735	Yes	No	Yes

(*Continued*)

Table 5 (Continued).

No.	Absorption						
	Water Solubility (Log mol/L)	Caco2 Permeability (Log Papp in 10^{-6} cm/s)	Intestinal Absorption (Human) (% Absorbed)	Skin Permeability (Log Kp)	P-Glycoprotein Substrate (Yes/No)	P-GlycoproteinI Inhibitor (Yes/No)	P-GlycoproteinII Inhibitor (Yes/No)
27	−3.88	1.338	89.438	−2.735	Yes	No	Yes
28	−3.914	1.41	88.719	−2.735	Yes	No	Yes
29	−3.796	0.742	100	−2.735	Yes	No	Yes
30	−4.432	1.218	100	−2.736	Yes	Yes	Yes
31	−4.5	1.348	100	−2.752	Yes	Yes	Yes
32	−3.894	0.829	71.535	−2.735	Yes	No	Yes
33	−4.481	1.339	100	−2.721	Yes	Yes	Yes
34	−4.388	1.154	100	−2.731	Yes	Yes	Yes
35	−4.388	1.154	100	−2.731	Yes	Yes	Yes
36	−3.852	0.949	74.491	−2.735	Yes	No	Yes
37	−3.852	0.949	74.491	−2.735	Yes	No	Yes
38	−3.81	1.118	98.002	−2.73	Yes	Yes	Yes
39	−4.39	1.582	96.309	−2.733	Yes	Yes	Yes
40	−3.493	−0.132	65.765	−2.735	Yes	No	Yes
41	−3.256	−0.066	76.201	−2.735	Yes	No	Yes
42	−3.541	−0.143	67.485	−2.735	Yes	No	No
43	−3.708	1.274	76.851	−2.735	Yes	No	No
44	−4.792	1.54	100	−2.762	No	Yes	Yes
45	−3.34	−0.051	69.628	−2.735	Yes	No	No
46	−3.991	1.211	98.907	−2.821	Yes	Yes	Yes
47	−3.337	0.725	88.143	−2.735	Yes	No	Yes
48	−3.542	0.689	83.044	−2.735	Yes	No	Yes
49	−3.176	0.599	94.653	−2.735	Yes	No	Yes
50	−4.685	1.489	100	−2.817	Yes	Yes	Yes
51	−3.764	1.581	96.212	−2.732	Yes	Yes	Yes

predictive model, high Caco-2 permeability would give predicted values greater than 0.90. Thus, GA and GNA are predicted to have high Caco-2 permeability. The intestinal absorption rates of these compounds ranged from 65% to 100%, well above the low intestinal absorption threshold of 30%, and they are considered to be well absorbed. These compounds also have certain skin permeability (they are not easily absorbed through the skin if the value is greater than −2.5).[176] Notably, most of these compounds are substrates or inhibitors of p-glycoprotein (P-gp), suggesting that they may be excreted from cells by P-gp, which would lead to drug resistance.[177] As P-gp inhibitors, these compounds may

have significant pharmacokinetic implications for P-gp substrates, and may either be exploited for specific therapeutic advantages or result in contraindication.

Distribution

In terms of distribution (Table 6), the steady-state volume of distribution (VDss) values of these xanthones are between −0.478 and 0.755, with those of GA and GNA being −0.154 and −0.478, respectively. The higher the VDss is, the more

Table 6 Predicted Distribution Properties for the Caged Polyprenylated Xanthones in *Garcinia hanburyi* Provided by pkCSM

No.	Distribution			
	VDss (Human) (Log L/kg)	Fraction Unbound (Human) (Fu)	BBB Permeability (Log BB)	CNS Permeability (Log PS)
1	0.336	0.047	−0.272	−2.296
2	0.272	0.054	−0.506	−2.539
3	0.012	0.103	−0.693	−2.678
4	0.012	0.103	−0.693	−2.678
5	0.282	0.064	−0.464	−2.609
6	0.72	0.016	−0.396	−2.542
7	0.189	0	0.144	−1.979
8	0.11	0	−0.073	−2.235
9	−0.154	0	−0.195	−2.391
10	−0.154	0	−0.195	−2.391
11	−0.154	0	−0.195	−2.391
12	−0.154	0	−0.195	−2.391
13	−0.243	0.04	−1.527	−2.751
14	−0.243	0.04	−1.527	−2.751
15	−0.236	0	−1.033	−2.736
16	−0.236	0	−1.033	−2.736
17	0.466	0	−0.573	−2.553
18	0.349	0	−0.738	−2.789
19	0.325	0.033	−0.258	−2.353
20	0.645	0.044	−0.363	−2.521
21	0.309	0.08	−0.428	−2.492
22	0.384	0.135	−1.372	−2.735
23	0.251	0.029	−1.522	−2.358
24	0.092	0.065	−0.291	−2.193
25	0.128	0.067	−0.298	−2.181

(*Continued*)

Table 6 (Continued).

No.	Distribution			
	VDss (Human) (Log L/kg)	Fraction Unbound (Human) (Fu)	BBB Permeability (Log BB)	CNS Permeability (Log PS)
26	−0.136	0.09	−1.354	−2.646
27	−0.084	0.07	−0.18	−2.312
28	−0.015	0.071	−0.195	−2.363
29	−0.009	0	−0.436	−2.567
30	0	0	0.236	−2.318
31	−0.219	0.034	0.198	−2.406
32	−0.169	0.051	−1.272	−2.7
33	−0.318	0	0.236	−2.191
34	−0.325	0	0.027	−2.433
35	−0.325	0	0.027	−2.433
36	−0.478	0.027	−1.35	−2.573
37	−0.478	0.027	−1.35	−2.573
38	0.255	0.006	−0.088	−2.298
39	0.071	0	0.052	−1.995
40	0.023	0.071	−1.529	−2.618
41	−0.085	0.088	−1.583	−2.244
42	0.348	0.068	−1.411	−2.856
43	0.321	0.143	−0.863	−2.859
44	0.272	0.054	−0.506	−2.539
45	0.755	0.149	−1.627	−3.056
46	0.193	0.088	0.172	−2.604
47	0.103	0.068	−0.309	−2.145
48	0.351	0.078	−0.435	−2.48
49	0.106	0.082	−0.196	−2.169
50	0.282	0.064	−0.464	−2.609
51	0.083	0.02	0.096	−1.811

a drug is distributed in tissue rather than plasma.[178] This means that the compound would be cleared quickly with a short retention time in vivo if the VDss value is less than −0.15. It can be seen from the unbound fraction[179,180] that most of these compounds bind to serum proteins. The VDss values and unbound fraction jointly predict that these caged polyprenylated xanthones have a short residence time, are eliminated quickly, and do not accumulate easily in vivo. The predicted values of blood–brain barrier (BBB) permeability (logBB) for these compounds are less than 0.3, which means that none of these compounds can easily cross the BBB. Notably, the logBB values for GNA and GA are less than

−1, which means that they are poorly distributed to the brain. The predicted extent of BBB permeability and central nervous system (CNS) permeability suggest that these compounds do not easily penetrate the BBB or enter the CNS, and therefore, they do not produce side effects on the brain.

Metabolism

In terms of metabolism (Table 7), cytochrome P450s (CYP450s) are an important class of enzymes involved in the metabolism of exogenous substances and mainly found in the liver. The two main isoforms responsible for drug metabolism are 2D6 and 3A4. Many drugs are deactivated by CYP450s; however, some are activated by these enzymes,

Table 7 Predicted Metabolism Properties for the Caged Polyprenylated Xanthones in *Garcinia hanburyi* Provided by pkCSM

No.	Metabolism						
	CYP2D6 Substrate (Yes/No)	**CYP3A4 Substrate (Yes/No)**	**CYP1A2 Inhibitor (Yes/No)**	**CYP2C19 Inhibitor (Yes/No)**	**CYP2C9 Inhibitor (Yes/No)**	**CYP2D6 Inhibitor (Yes/No)**	**CYP3A4 Inhibitor (Yes/No)**
1	No	Yes	No	No	No	No	Yes
2	No	Yes	No	No	No	No	Yes
3	No	Yes	No	No	No	No	No
4	No	Yes	No	No	No	No	No
5	No	Yes	No	No	No	No	Yes
6	No	Yes	No	No	No	No	Yes
7	No	Yes	No	No	No	No	Yes
8	No	Yes	No	No	No	No	Yes
9	No	Yes	No	No	No	No	No
10	No	Yes	No	No	No	No	No
11	No	Yes	No	No	No	No	No
12	No	Yes	No	No	No	No	No
13	No	Yes	No	No	No	No	No
14	No	Yes	No	No	No	No	No
15	No	Yes	No	No	No	No	No
16	No	Yes	No	No	No	No	No
17	No	Yes	No	No	No	No	Yes
18	No	Yes	No	No	No	No	Yes
19	No	Yes	No	No	No	No	Yes
20	No	Yes	No	No	No	No	Yes
21	No	Yes	No	No	No	No	No
22	No	Yes	No	No	No	No	No
23	No	Yes	No	No	No	No	No

(*Continued*)

Table 7 (Continued).

No.	Metabolism						
	CYP2D6 Substrate (Yes/No)	CYP3A4 Substrate (Yes/No)	CYP1A2 Inhibitor (Yes/No)	CYP2C19 Inhibitor (Yes/No)	CYP2C9 Inhibitor (Yes/No)	CYP2D6 Inhibitor (Yes/No)	CYP3A4 Inhibitor (Yes/No)
24	No	Yes	No	No	No	No	No
25	No	Yes	No	No	No	No	No
26	No	Yes	No	No	No	No	No
27	No	Yes	No	No	No	No	No
28	No	Yes	No	No	No	No	No
29	No	Yes	No	No	No	No	No
30	No	Yes	No	No	No	No	Yes
31	No	Yes	No	No	No	No	Yes
32	No	Yes	No	No	No	No	Yes
33	No	Yes	No	No	No	No	No
34	No	Yes	No	No	No	No	Yes
35	No	Yes	No	No	No	No	Yes
36	No	Yes	No	No	No	No	Yes
37	No	Yes	No	No	No	No	Yes
38	No	Yes	No	No	No	No	Yes
39	No	Yes	No	No	No	No	Yes
40	No	Yes	No	No	No	No	No
41	No	Yes	No	No	No	No	No
42	No	Yes	No	No	No	No	No
43	No	Yes	No	No	No	No	No
44	No	Yes	No	No	No	No	Yes
45	No	Yes	No	No	No	No	No
46	No	No	No	No	No	No	Yes
47	No	Yes	No	No	No	No	No
48	No	Yes	No	No	No	No	No
49	No	Yes	No	No	No	No	No
50	No	Yes	No	No	No	No	Yes
51	No	Yes	No	No	No	No	Yes

which may lead to excessive drug accumulation if the compound is a CYP450 inhibitor.[181] The prediction results indicated that these caged polyprenylated xanthones are substrates of CYP3A4 with the exception of forbesione (Compound 46), and some of them, including GNA, are also inhibitors of CYP3A4. This implies that when these

xanthones are co-administered with drugs that are CYP3A4 substrates, they will interfere with metabolism and may induce drug accumulation in vivo, leading to toxicity.

Excretion

The excretion section (Table 8) describes the total clearance of the caged polyprenylated xanthones and whether they are organic cation transporter 2 (OCT2) substrates. Total clearance is related to bioavailability, which is important when determining dosing rates so that steady-state concentrations can be achieved. OCT2 is a renal uptake transporter that plays important roles in the disposition and renal clearance of drugs and endogenous compounds.[182,183] From the predicted excretion data, these caged polyprenylated xanthones are not substrates of OCT2 and thus have a low risk of nephrotoxicity.

Toxicity

In terms of toxicity (Table 9), these caged polyprenylated xanthones are not hERG inhibitors and therefore have no cardiotoxicity, were predicted to be negative in the AMES test and skin sensitivity test, and thus have no mutagenicity

Table 8 Predicted Excretion Properties for the Caged Polyprenylated Xanthones in *Garcinia hanburyi* Provided by pkCSM

No.	Excretion	
	Total Clearance (log mL/min/kg)	Renal OCT2 Substrate (Yes/No)
1	−0.344	No
2	−0.281	No
3	−0.38	No
4	−0.38	No
5	−0.282	No
6	−0.213	No
7	−0.373	No
8	−0.315	No
9	−0.41	No
10	−0.41	No
11	−0.41	No
12	−0.41	No
13	−0.347	No
14	−0.347	No
15	−0.386	No
16	−0.386	No
17	−0.209	No
18	−0.258	No
19	−0.27	No
20	−0.294	No

(*Continued*)

Table 8 (Continued).

No.	Excretion	
	Total Clearance (log mL/min/kg)	Renal OCT2 Substrate (Yes/No)
21	−0.369	No
22	−0.445	No
23	−0.479	No
24	−0.394	No
25	−0.365	No
26	−0.494	No
27	−0.661	No
28	−0.589	No
29	−0.573	No
30	0.029	No
31	−0.004	No
32	−0.007	No
33	−0.149	No
34	−0.086	No
35	−0.086	No
36	−0.185	No
37	−0.185	No
38	−0.008	No
39	−0.063	No
40	−0.254	No
41	−0.004	No
42	−0.435	No
43	−0.461	No
44	−0.281	No
45	−0.398	No
46	0.121	No
47	−0.355	No
48	−0.34	No
49	−0.765	No
50	−0.282	No
51	−0.356	No

Table 9 Predicted Toxicity for the Caged Polyprenylated Xanthones in *Garcinia hanburyi* Provided by pkCSM

No.	Toxicity									
	AMES Toxicity (Yes/No)	**Max. Tolerated Dose (Human) (Log mg/kg/day)**	**hERGI Inhibitor (Yes/No)**	**hERGII Inhibitor (Yes/No)**	**Oral Rat Acute Toxicity (LD50) (mol/kg)**	**Oral Rat Chronic Toxicity (LOAEL) (log mg/kg bw/day)**	**Hepatotoxicity (Yes/No)**	**Skin Sensitisation (Yes/No)**	***T.pyriformis* Toxicity (Log μg/L)**	**Minnow Toxicity (Log mM)**
1	No	−0.059	No	No	2.746	2.058	No	No	0.286	−0.723
2	No	−0.166	No	No	2.366	2.362	No	No	0.285	−0.205
3	No	0.275	No	No	3.465	1.865	No	No	0.285	0.215
4	No	0.275	No	No	3.465	1.865	No	No	0.285	0.215
5	No	−0.302	No	No	2.826	1.658	No	No	0.285	0.063
6	No	−0.284	No	No	3.432	1.991	No	No	0.285	−2.24
7	No	0.259	No	No	2.921	1.84	No	No	0.285	−2.08
8	No	0.141	No	No	2.613	1.737	No	No	0.285	−1.679
9	No	0.001	No	No	3.598	1.662	No	No	0.285	−0.794
10	No	0.001	No	No	3.598	1.662	No	No	0.285	−0.794
11	No	0.001	No	No	3.598	1.662	No	No	0.285	−0.794
12	No	0.001	No	No	3.598	1.662	No	No	0.285	−0.794
13	No	−0.364	No	No	3.187	1.845	No	No	0.285	0.603
14	No	−0.364	No	No	3.187	1.845	No	No	0.285	0.603
15	No	−0.049	No	No	3.488	1.794	No	No	0.285	−2.747
16	No	−0.049	No	No	3.488	1.794	No	No	0.285	−2.747
17	No	−0.273	No	No	3.009	1.951	No	No	0.286	−1.146
18	No	−0.524	No	No	3.591	1.573	No	No	0.285	0.789
19	No	−0.224	No	No	2.764	1.688	No	No	0.285	−0.276
20	No	−0.261	No	No	3.455	2.054	No	No	0.285	−2.021
21	No	0.031	No	No	3.526	1.831	No	No	0.285	0.242

(*Continued*)

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Table 9 (Continued).

No.	Toxicity									
	AMES Toxicity (Yes/No)	**Max. Tolerated Dose (Human) (Log mg/kg/day)**	**hERGI Inhibitor (Yes/No)**	**hERGII Inhibitor (Yes/No)**	**Oral Rat Acute Toxicity (LD50) (mol/kg)**	**Oral Rat Chronic Toxicity (LOAEL) (log mg/kg bw/day)**	**Hepatotoxicity (Yes/No)**	**Skin Sensitisation (Yes/No)**	***T.pyriformis* Toxicity (Log μg/L)**	**Minnow Toxicity (Log mM)**
22	No	0.153	No	No	3.596	1.922	No	No	0.285	0.502
23	No	0.066	No	No	3.474	1.688	No	No	0.285	−0.53
24	No	0.107	No	No	3.269	1.79	No	No	0.285	−1.501
25	No	0.104	No	No	3.268	1.75	No	No	0.285	−1.666
26	No	0.079	No	No	3.493	1.917	No	No	0.285	−0.155
27	No	0.23	No	No	3.4	1.796	No	No	0.285	−0.742
28	No	0.159	No	No	3.43	1.81	No	No	0.285	−0.762
29	No	−0.158	No	No	3.53	1.669	No	No	0.285	−1.279
30	No	−0.411	No	No	3.213	1.35	No	No	0.286	−0.82
31	No	−0.204	No	No	2.64	1.449	No	No	0.285	−0.917
32	No	−0.092	No	No	3.543	1.837	No	No	0.285	0.118
33	No	−0.032	No	No	3.297	1.375	No	No	0.285	−1.767
34	No	−0.126	No	No	2.688	1.615	No	No	0.285	−1.249
35	No	−0.126	No	No	2.688	1.615	No	No	0.285	−1.249
36	No	0.013	No	No	3.432	1.862	No	No	0.285	−0.829
37	No	0.013	No	No	3.432	1.862	No	No	0.285	−0.829
38	No	0	No	No	4.23	1.829	No	No	0.285	−4.795
39	No	0.194	No	No	2.725	1.767	No	No	0.285	−2.493
40	No	0.142	No	No	3.181	1.975	No	No	0.285	−0.373
41	No	0.225	No	No	3.167	1.675	No	No	0.285	−1.886
42	No	−0.028	No	No	3.366	2.018	No	No	0.285	0.614

43	No	0.169	No	No	2.802	1.956	No	No	0.285	0.929
44	No	−0.166	No	No	2.366	2.362	No	No	0.285	−0.205
45	No	0.096	No	No	3.516	2.018	No	No	0.285	4.02
46	No	−0.518	No	No	2.559	1.494	No	No	0.286	0.068
47	No	0.123	No	No	3.178	1.795	No	No	0.285	−2.153
48	No	0.021	No	No	3.534	1.79	No	No	0.285	0.076
49	No	0.178	No	No	3.201	1.684	No	No	0.285	−0.83
50	No	−0.302	No	No	2.826	1.658	No	No	0.285	0.063
51	No	0.156	No	No	3.265	1.718	No	No	0.285	−2.635

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and do not irritate the skin; however, these compounds have certain *Tetrahymena pyriformis* and minnow toxicity. *T. pyriformis* is a protozoan bacterium with nutritional requirements, subcellular organelles and biochemical pathways similar to those of mammalian cells.[184] This organism is commonly used to predict drug toxicity, and a predicted value greater than −0.5 is considered toxic. The value of minnow toxicity represents the concentration of a molecule that is necessary to cause the death of 50% of flathead minnows. This predicted value was below −0.3 for all of the caged polyprenylated xanthones, indicating that they may have aquatic toxicity.

Conclusion

In recent years, a lot of researches have been conducted on the pharmacological effects and formulation of caged polyprenylated xanthones in *Garcinia hanburyi*, with plenty of results achieved. However, the pharmacological study of the caged polyprenylated xanthones is still not deep enough, and there is no systematic research conducted on the quality standards and in vivo processes of active ingredients in *Garcinia hanburyi*. Based on the progress in research of the chemical constituents, pharmacological effects and modification methods of the caged polyprenylated xanthones, this paper presents a preliminary predictive analysis of their drug-like properties based on the ADME/T properties. These compounds have disadvantageous physical and chemical properties, including a large molecular weight, poor water solubility and low bioavailability in vivo, which is an obstacle to developing new drugs through the use of active ingredients contained in natural products. For the caged xanthones in *Garcinia hanburyi*, the author believes that subsequent studies could be carried out by considering the following points. (1) The new dosage forms and routes of administration. Currently, these compounds are mainly considered for injectable formulations. For example, based on the predicted results, these compounds have a certain degree of skin permeability, and it might be worth considering the possibility of dermal delivery. (2) The focus on researches for other indications. In addition to their use in cancer treatment, the caged xanthones can be studied and developed for other indications. Notably, gamboge has been used in traditional medicine as a potent purgative and to treat infected wounds. (3) The chemical modifications based on streamlined structure. Previous studies have shown that the 9,10-double bond in a,b-unsaturated ketones is essential for the antitumor activity and the acidic carboxyl group of GA without much effect on apoptosis-inducing activity. In terms of drug-likeness, the large molecular weights of these caged xanthones cause certain difficulties in both formulation studies and industrialization, and attempts can be made to simplify their structures while retaining the pharmacophores in the research and development of these ingredients. (4) The systematic studies on other caged xanthones. In addition to GA and GNA, we can also fully compare and explore the properties of other caged xanthones in *Garcinia hanburyi*, such as forbesione, which has been found to have a therapeutic effect on cholangiocarcinoma.[185–187]

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Disclosure

The authors report no conflicts of interest in this work.

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