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Review Article

Recent Research on Bioactive Xanthones from Natural Medicine: *Garcinia hanburyi*

Buyun Jia,[1] Shanshan Li,[1] Xuerui Hu,[1] Guangyu Zhu,[1,2] and Weidong Chen[1,3]

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Abstract. *Garcinia hanburyi*, a tropical plant found in south Asia, has a special long history in the development of both medicine and art. This review mainly focuses on the pharmacy research of the bioactive compounds from the plant in recent years. Preparative and analysis separation methods were introduced. Moreover, the chemical structure of the isolated compounds was included. The studies of biological activities of the caged xanthones from the plant, including antitumor, anti-HIV-1, antibacterial, and neurotrophic activities, were reviewed in detail. Furthermore, the mechanisms of its antitumor activity were also reviewed. As mentioned above, some of the xanthones from *G. hanburyi* can be promising drug candidates, which is worth studying. However, we still need much evidence to prove their efficacy and safety. So, further research is critical for the future application of xanthones from *G. hanburyi*.

KEYWORDS: bioactive; *Garcinia hanburyi*; xanthones.

INTRODUCTION

Garcinia hanburyi, whose resin named gamboge is originally used as pigment and folk medicine, was found in the tropical rainforest of Thailand, southern China, Cambodia, and part of Malaysia. As a matter of fact, gamboge, a gold-colored resin, has a long and rich history in both the sciences and the arts. In recent years, a special group of xanthones, caged *Garcinia* xanthones, which have been identified as bioactive compounds with potent biological activities such as antitumor, anti-HIV-1, antibacterial, and anti-inflammatory, is naturally found from the resin, fruit, and other parts of the plant. The unique 4-oxa-tricyclo(4.3.1.$0^{3,7}$)dec-8-en-2-one scaffold (Fig. 1), which contains a highly substituted tetrahydrofuran ring with three quaternary carbons, is the main structural character which is critical for the biological activities (1).

The isolation and characterization of xanthones from the *Garcinia* plant were reviewed by Prof. Venka-taraman in 1973, but only nine caged xanthones were mentioned. Recently, over 40 different xanthones were isolated from *G. hanburyi*. Furthermore, multiple mechanisms of its cytotoxic activity have been reported, such as cell cycle arrest, apoptosis induction, telomerase inhibition, and anti-angiogenesis (2). Due to its diversity of bioactive ingredients and potent activities, a series of in-depth researches were conduct by researchers all over the world. The authors and his team have engaged in the study of xanthones from *G. hanburyi*, which is subsidized by the national key new drug discovery projects. Our work includes many aspects, such as isolation, formulation, and pharmacokinetics study. To make the direction of future study more clear, the author made the following conclusion of the recent research on these compounds.

EXTRACTION AND ISOLATION METHODS

The special class of caged xanthones from *G. hanburyi* can be isolated by different kinds of methods. The plant was usually extracted with certain kinds of organic solvents, and then the extract was loaded in the preparative chromatography for further isolation.

It was reported that three new compounds, along with six known compounds, were isolated from the EtOAc extract of gamboge using silica gel columns with different sizes and eluted with solvents of various proportions to give several fractions. Semipreparative high-performance liquid chromatography (HPLC) was used to give the purified compounds (Fig. 2). The isolated compounds are garcinolic acid (C1), 10α-ethoxy-9,10-dihydromorellic acid (C2), 10α-ethoxy-9,10-dihydrogambogenic acid (C3), deoxygaudichaudione A (C4), gambogenic acid (C5), desoxygambogenin (C6), hanburin (C7), gambogic acid (C8), and desoxymorellin (C9) (3).

Another new caged-tetraprenylated xanthone, hanburinone, together with four known caged-tetraprenylated xanthones, was isolated from the fresh fruits of *G. hanburyi* using column chromatography and preparative HPLC (Fig. 3). They are hanburinone (C1), isomoreollin B (C2), morellin (C3), moreollic acid (C4), and morellic acid (C5), respectively (4).

Gambogic acid and epigambogic acid were preparative isolated from *G. hanburyi* with a high-speed counter-current chromatographic system using *n*-hexane–methanol–water (5:4:1, *v*/*v*/*v*) as the two-phase solvent system. 18.4 mg

Buyun Jia and Shanshan Li contributed equally to this work.

[1] School of Pharmacy, Anhui University of Chinese Medicine, 001 Qianjiang Road, Hefei, 230012Anhui, China.
[2] Ma'anshan Central Hospital, 027 Hudong Road, Ma'anshan, 243000Anhui, China.
[3] To whom correspondence should be addressed. (e-mail: anzhongdong@126.com)

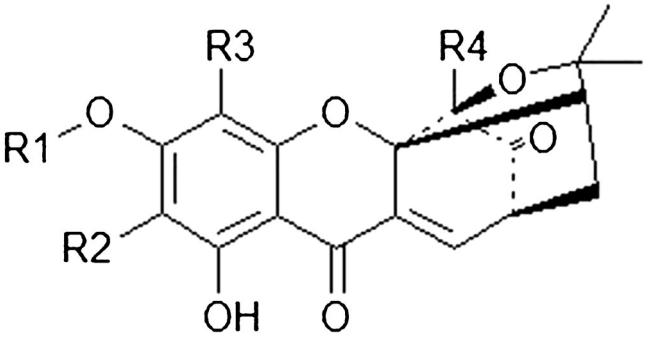


Fig. 1. The chemical skeleton of *Garcinia* xanthones

epigambogic acid and 28.2 mg gambogic acid were isolated from 50 mg of mixture compounds, whose purities were both above 97% (5). Besides, it was reported that another two polyprenylated xanthone epimers were separated from the resin of *G. hanburyi* using the preparative HPLC (Fig. 4) and identified as 30-hydroxygambogic acid (C1) and 30-hydroxyepigambogic acid (C2), respectively (6).

The author was occupied with the research of gambogenic acid and mainly in charge of the isolation of gambogenic acid and other active ingredients from the gamboge (Fig. 5). The equipment we used was a medium-pressure preparative chromatography loaded with ODS silica gel. It can provide a fast way to get the relatively pure gambogenic acid which is one of the compounds that draws great interests.

ANALYSIS OF THE BIOACTIVE INGREDIENTS

For the purpose of in-depth investigation of the chemical composition, advanced analytical equipments were used in the studies of the caged xanthones from *G. hanburyi*. Among them, high-performance liquid chromatography (HPLC), ultra performance liquid chromatography (UPLC), and ultra performance liquid chromatography/tandem mass spectrometry (UPLC/MS) were used frequently.

Forbesione, isomorellic acid, morellic acid, *R*-30-hydroxygambogic acid, *S*-30-hydroxygambogic acid, isogambogenic acid, isogambogenin, isomorellinol, and one likely new compound were effectively separated and identified using an ultra high-performance liquid chromatography/electrospray quadrupole time of flight tandem mass spectrometry (UHPLC-ESI–QTOF–MS/MS/MS) method proved to be efficient and rapid. Within 6 min, all the compounds were separated (7).

R-Isogambogic acid, *S*-isogambogic acid, *R*-gambogic acid, *S*-gambogic acid, forbesione, isomorellic acid, morellic acid, *R*-30-hydroxygambogic acid, *S*-30-hydroxygambogic acid, isogambogenic acid, gambogenic acid, and gambogellic acid were separated with an improved HPLC method validated to be precise, sensitive, and accurate (8).

It was reported that a group of caged xanthones were separated by a highly effective qualitative method in which an HPLC and multiple mass spectrometric scanning modes consisting of full scanning (FS), precursor ion scanning (PrecIS), product ion scanning (PIS), and selected reaction monitoring (SRM) were selected for the qualitative analysis. The isolated compounds were forbesionic acid, isoforbesionic acid, gaudichaudionol, isogaudichaudionol, gaudichaudione A, isogaudichaudione A, gaudichaudionic acid, isogaudichaudionic acid, morellin, isomorellin, desoxygambogenin, gambogeninol, forbesione, desoxygaudichaudione A, morellic acid, isomorellic acid, isogambogenin, gambogenic acid, isogambogenic acid, *S*/*R*-gambogic acid, *S*/*R*-isogambogic acid, *R*-30-hydroxyisogambogic acid, *S*-30-hydroxygambogic acid, and hanburin, respectively (9).

Some of the epimers which are difficult to separate using the common column exist in *G. hanburyi*. So, the ion-pair HPLC is needed in the separation works of these kinds of caged *Garcinia* xanthones. For example, three pairs of epimers, including isogambogic acid, epiisogambogic acid, 30-hydroxygambogic acid, 30-hydroxyepigambogic acid, gambogic acid, and epigambogic acid, were analytical separated from the resin of *G. hanburyi* using a rapid ion-pair HPLC method. The separation was performed on a narrow bore C_8 column with isocratic elution using a mixture of methanol–ACN–40 mM KH_2PO_4 buffer (37.5:37.5:25 *v*/*v*/*v*, containing 0.1% tetradecyltrimethylammonium bromide). This method provided a specific and fast solution for the determination of the epimers, which is crucial for the quality control of gamboge (10).

An analytical method was developed for the determination of gambogic acid in human plasma using a high-performance liquid chromatography–atmospheric pressure chemical ionization–mass spectrometry (HPLC–APCI–MS) method, which was worked in the selected ion monitoring (SIM) mode with target ions at $(M-H)^-$ *m*/*z* 627.4 for gambogic acid and $(M-H)^-$ *m*/*z* 455.4 for the I.S. The method can be applied to monitoring of gambogic acid in the future clinical treatment (11).

Currently known *Garcinia* xanthones are listed in Table I.

MODIFICATION OF XANTHONES

Shortages of these compounds, such as poor water solubility, short half-life, and vessel irritation, need to be overcome. Therefore, various modification methods were used to make these compounds more suitable therapeutic drugs for clinical applications.

Due to the poor water solubility, the application of gambogic acid was limited. Therefore, water-soluble gambogic acid PEGylated prodrugs were prepared and investigated both *in vitro* and *in vivo*. The result showed that the solubility of gambogic acid was dramatically enhanced. Moreover, an *in vivo* study suggested that the half-life ($t_{1/2}$) of PEGylated gambogic acid in plasma ranged from 1.26 to 6.12 h, which is much longer then that of gambogic acid itself. The stability of the gambogic acid PEGylated prodrugs was significantly improved with increasing molecular weight of PEG (12).

An oxidative analog of gambogic acid was synthesized, and the newly synthesized analog of gambogic acid showed potential antitumor activity by inducing apoptosis in HepG2 cells (13).

Two new products which were different from reported *Garcinia* natural products were got by treated gambogic acid with methanol in acidic condition under microwave irradiation. Both of the two modified compounds could dramatically inhibit the growth of various cancer cell lines such as HepG2, BGC-803, and SGC-7901 (14).

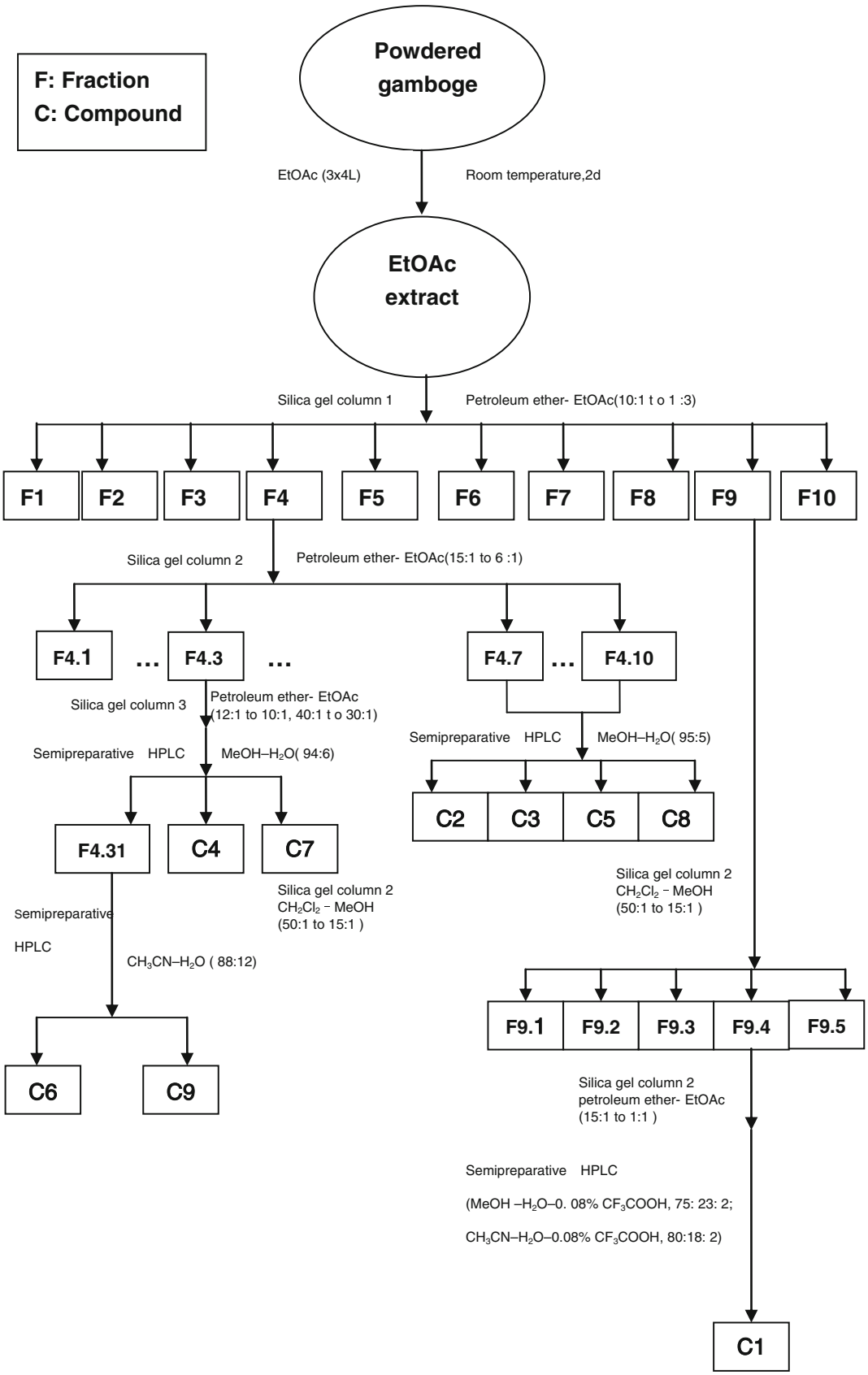


Fig. 2. Isolation method of nine compounds from gamboge

Thirteen novel compounds were obtained by modification of gambogic acid *via* a base-catalyzed diene intramolecular annelation, and their inhibitory activity on HT-29, Bel-7402, BGC-823, and A549 cell lines were evaluated *in vitro*. Among

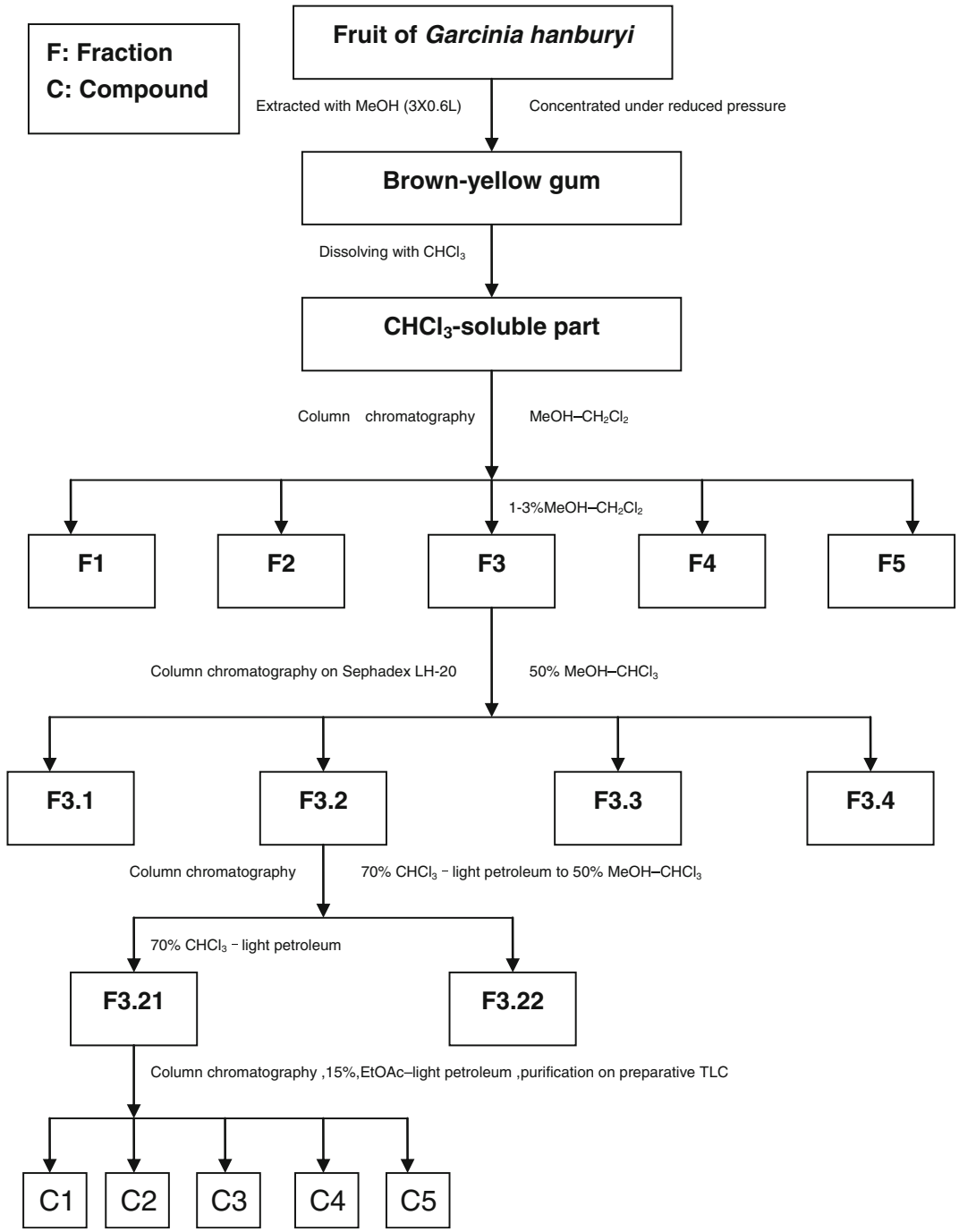


Fig. 3. Isolation method of five compounds from the fruit of *Garcinia hanburyi*

these compounds, (38, 40)-epoxy-33-chlorogambogellic acid was found to be a BGC-823 cell apoptosis inducer which showed strong effects in inducing apoptosis (15).

In another study carried out by the expert from China Pharmaceutical University, 11 oxidized derivatives of gambogic acid were synthesized. Some of them showed dramatic inhibitory effects on A549, Bel-7402, BGC-823, HT-29, and SKOV 3 cell lines. Among them, 9-hydroxy-6-methoxy-gambogic acid methyl ester may act as a potential lead compound for the development of novel anticancer drugs. The result also suggests that modification of the compound on certain structures can improve its antitumor effect (16).

Gambogic acid-loaded micelles were prepared using chitosan derivatives, whose physical properties and stability were also evaluated. The result suggested that the solubility and stability were both improved dramatically by the delivery system (17).

Gambogic acid-loaded poloxamer 407/TPGS mixed micelles were prepared as a drug delivery system *via* a thin film hydration method. Physicochemical properties, cellular accumulation, and cytotoxicity of the drug delivery system were investigated. The result showed that the gambogic acid-loaded poloxamer 407/TPGS mixed micelles have a good entrapment efficiency, stability, and stronger cytotoxic activity compared with gambogic acid solution (18).

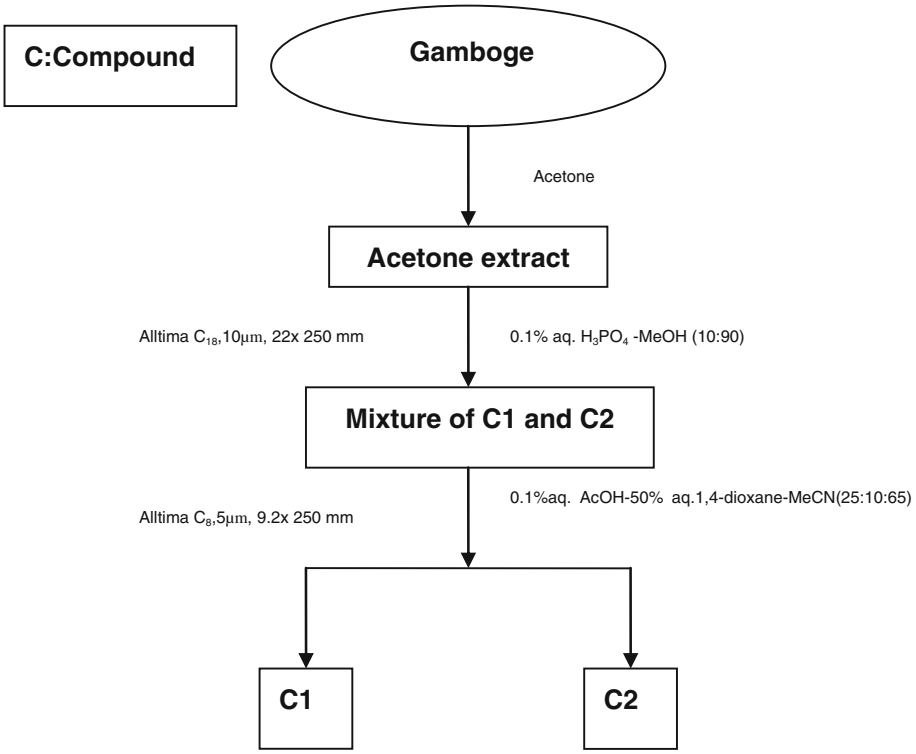


Fig. 4. Isolation method of two compounds from gamboge

Gambogic acid-loaded OACS (*N*-octyl-*N*-arginine-chitosan) micelles were prepared using a dialysis method. The solubility and the absorption of gambogic acid were dramatically enhanced, which suggested that OACS micelles as an oral drug delivery system may have potential application values (19).

Gambogic acid-lactoferrin nanoparticles were successfully prepared through the nanoparticle albumin-bound (NAB) technology for the oral delivery. Gambogic acid-lactoferrin nanoparticles showed a better stability and a slow-release behavior. Moreover, it also proved to have a higher inhibitory

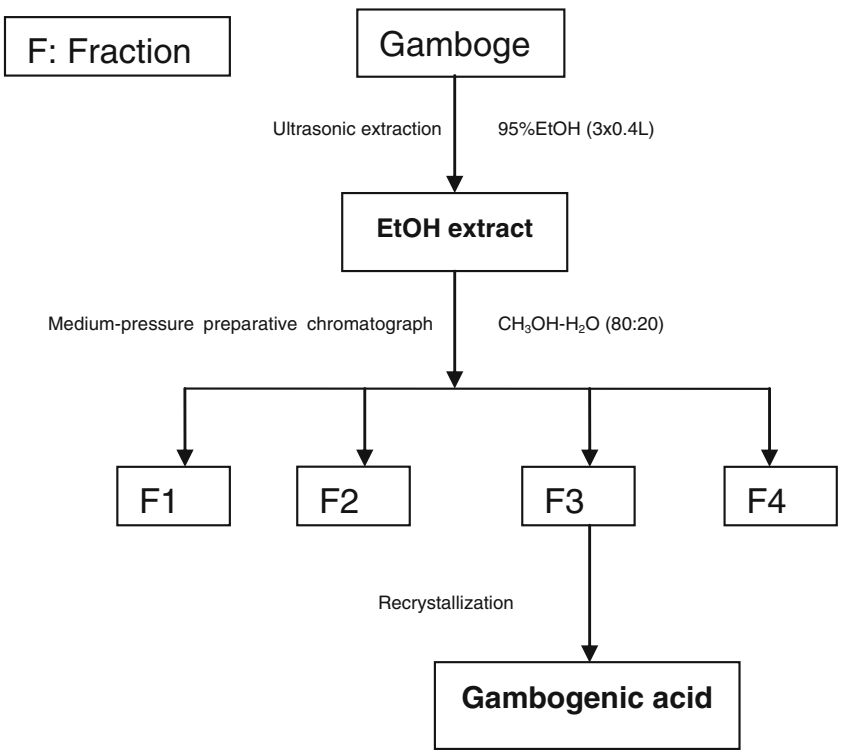


Fig. 5. Isolation method of gambogenic acid

Table I. Chemical Structure of the Active Ingredients from *Garcinia hanburyi*

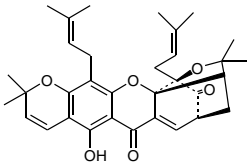
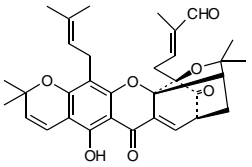
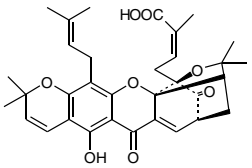
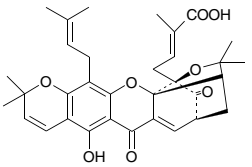
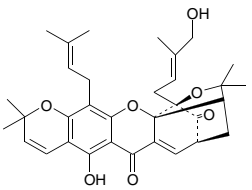
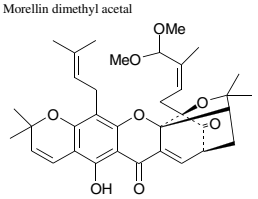
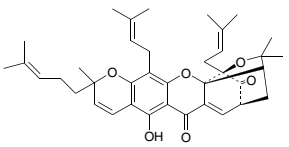
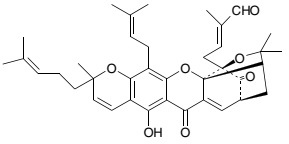
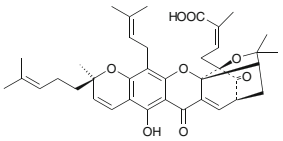
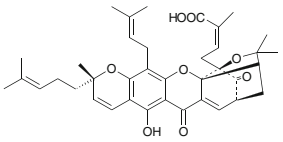
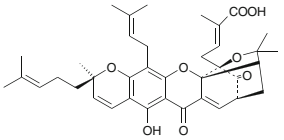
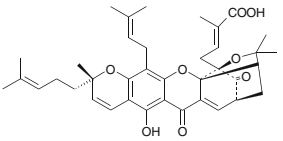
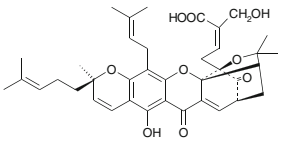
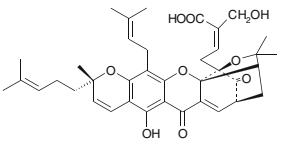
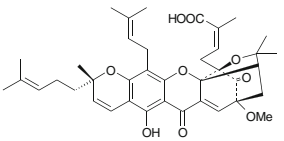
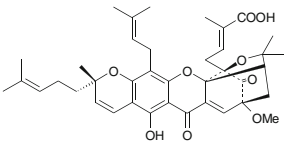
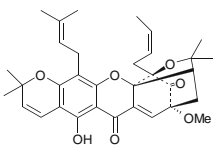
No.	Name and chemical structure	Sources	References
1	Desoxymorellin 	Resin Fruit	(1, 3)
2	Isomorellin 	Resin Fruit	(1, 9)
3	Morellic acid 	Resin Fruit	(1, 4, 7, 8)
4	Isomorellic acid 	Resin	(1, 7, 8)
5	Isomorellinol 	Resin Fruit	(1, 7)
6	Morellin dimethyl acetal 	Resin	(1)
7	Gambogin 	Resin	(1)
8	Gambogic aldehyde 	Resin	(1)
9	Gambogic acid 	Whole plant	(1, 3, 5, 8)
10	Epigambogic acid 	Resin	(1, 5, 10)
11	Isogambogic acid 	Resin	(1, 8, 10)
12	Epiisogambogic acid 	Resin	(1, 10)
13	30-Hydroxygambogic acid 	Resin	(1, 6-10)
14	30-Hydroxyepigambogic acid 	Resin	(1, 6)
15	7-Methoxygambogic acid 	Resin	(1)
16	7-Methoxyepigambogic acid 	Resin	(1)
17	7-Methyoxydesoxymorellin 	Resin	(1)

Table I. (continued)

18	7-Methoxyisomorellinol	Resin	(1)
19	Isomoreollin B	Resin Fruit	(1, 4)
20	Methyl 8,8a-dihydromorellate	Resin	(1)
21	Moreollic acid	Resin Fruit	(1, 4)
22	8,8a-Dihydro-8-hydroxymorellic acid	Resin	(1)
23	8,8a-Dihydro-8-hydroxygambogic acid	Resin	(1)
24	Gambogoic acid A or 10-methoxygambogic acid	Resin	(1)
25	Gambogoic acid B or 10-ethoxygambogic acid	Resin	(1)
26	Oxygambogic acid	Resin	(1)
27	Gambogefic acid	Resin	(1)

Table I. (continued)

28	Gambogellic acid	Resin	(1, 8)
29	7-Methoxygambogellic acid	Resin	(1)
30	Desoxygaudichaudione A	Resin Fruit	(1, 3)
31	Hanburin	Resin	(1, 3, 9)
32	Gaudichaudic acid	Resin	(1, 9)
33	Desoxygambogenin	Resin Fruit	(1, 3, 9)
34	Gambogenin	Resin	(1)
35	Isogambogenin	Resin	(1, 7)
36	Gambogenic acid	Resin	(1, 3) (8, 9)
37	Isogambogenic acid	Resin	(1, 7, 8, 9)

Table I. (continued)

38	Gambogenin dimethyl acetal	Resin	(1)
39	3- *O*-geranylforbesione	Resin	(1)
40	8,8a-Dihydro8-hydroxygambogenic acid	Resin	(1)
41	10-Methoxygambogenic acid	Resin	(1)
42	Gambogenific acid	Resin	(1)
43	8,8a-Epoxymorellic acid	Fruit	(1)
44	Dihydroisomorellin	Fruit	(1)
45	Hanburinone	Fruit	(1, 4)
46	Forbesione	Fruit	(1, 7, 8)

Table I. (continued)

rate against S180 tumor mice after oral administration which is 1.39 times higher than that of intravenous injection of arginine solution of gambogic acid (20).

Gambogic acid was successfully connected with the magnetic nanoparticle (MNP)-Fe_3O_4 by mechanical absorption polymerization to prepare gambogic acid-MNP-Fe_3O_4 as a drug delivery system. The combination of gambogic acid and MNP-Fe_3O_4 dramatically improved the water solubility and the anticancer activity of gambogic acid against Capan-1 pancreatic cancer cells, which made a further step approach the clinical application of gambogic acid (21). The effects caused by gambogic acid-MNP-Fe_3O_4 on the growth of Panc-1 pancreatic cancer cells were also tested. Gambogic acid-MNP-Fe_3O_4 can dramatically inhibit cancer cell proliferation and prevent cells from migrating which was partly because gambogic acid-MNP-Fe_3O_4 suppressed the expression of ETS1, along with its downstream target genes for u-PA, cyclin D1, and VEGF (22).

The result of the in-depth investigations indicated that these kinds of modified compounds and *Garcinia* xanthone-loaded drug delivery systems can improve the solubility, bioactivity, and stability of the compounds. Furthermore, the *in vivo* study suggested that a longer half-life, larger area under concentration–time curve (AUC), and relatively smaller side effect were found compared with the pure compound.

IN VIVO STUDIES

Pharmacokinetics Studies

The plasma pharmacokinetics, tissue distribution, and excretion of gambogic acid, a promising antitumor drug candidate, were studied after i.v. administration in SD rats at the doses of 1, 2, and 4 rng/kg. The elimination half-life ($t_{1/2}$) values of gambogic acid were 14.9, 15.7, and 16.1 min, respectively. The mean AUC values were 54.2, 96.1, and 182.4 μg·min/mL, and most of the gambogic acid seemed to be excreted into the bile within 16 h of administration. It was found that the short half-life of gambogic acid may be due to its rapid tissue distribution. After i.v. administration, the highest drug concentration was found in the liver. So, the high liver uptake of gambogic acid may result in its high ratio of bile extraction (23).

A pharmacokinetics study of gambogic acid injection in six beagle dogs was conducted using a LC–MS/MS method. The result suggested that the method established by the researchers is suitable for the *in vivo* analysis. However, the drug concentration–time curve showed that gambogic acid has a short half-life, so it has to depend on some formulation method to overcome the shortage (24).

A validated HPLC method was established to study the pharmacokinetics behavior of gambogic acid in dog plasma after i.v. 0.5, 1, and 2 mg/kg gambogic acid to 12 beagle dogs. The result indicated that $t_{1/2}$ and CL_t did not change dramatically with doses. The $t_{1/2}$ values were determined to be 57.9, 59.2, and 60.9 min, respectively. The CL_t values ranged from 7.5 to 8.5 mL/kg/min, respectively. However, the AUC increased with increasing doses. The AUC values were calculated to be 49.5, 116.6, and 150.9 μg·min/mL, respectively.

Additionally, the result of dose range studies exhibited that the pharmacokinetics of gambogic acid in beagle dogs was linear (25).

The metabolism of gambogic acid was investigated *in vivo* in rat bile using high-performance liquid chromatography (HPLC), HPLC/nuclear magnetic resonance, and HPLC/ion trap electrospray ionization–mass spectrometry. Four main metabolites were identified, and in the process of metabolism, gambogic acid was first oxidized by oxidase and then combined with glucuronide. There are several olefinic bonds in the chemical structure of gambogic acid. However, the 9,10-olefinic bond was the most likely to be oxidized among them since it was not only in the α,β-unsaturated ketone structure system but also in a unique rigid bridged ring system (26).

The metabolism of gambogic acid was studied in rats. A rare intestinal metabolic pathway which involves Michael addition of the sulfite ion to the 9,10 carbon–carbon double bond of α, β-unsaturated ketone was found to have a relationship with the process of the metabolism of gambogic acid. Moreover, it was also reported that gambogic acid might be metabolized by various routes, including mono oxidation, hydration, glucosidation, glucuronidation, and glutathionylation in the liver of rats (27).

The pharmacokinetics study in SD rats of gambogenic acid solution and gambogenic acid-loaded solid lipid nanoparticles (GNA–SLNs) was carried out by the senior author, and the result indicated that the GNA–SLNs showed a better performance than the gambogenic acid solution, which has a relatively long half-life and improved safety. The AUC value of GNA–SLNs was 3.11 times larger than that of gambogenic acid solution, and the $t_{1/2}$ was 1.29 times longer than that of gambogenic acid solution. Moreover, the higher level of safety was confirmed by hemocompatibility test and vascular irritation test. The result of both tests indicated that the GNA–SLNs may have a relatively small side effect compared with gambogenic acid solution (28).

The short half-life of gambogic acid is probably caused by the metabolic inhibition effect induced by CYP1A2 which is major rat CYP involved in the metabolism process of gambogic acid. Therefore, inhibition of the related metabolic pathway can lower the formation rate of metabolites and increase the concentration of gambogic acid, suggesting pharmaceutical modifications and metabolic interactions of gambogic acid with other therapeutic agents may help this process (29).

Pharmacological Studies

It was reported that for the purpose of proving the antitumor effects of gambogic acid against glioblastoma *in vivo*, rats which were injected C6 glioma cells were treated with gambogic acid or a vehicle for 2 weeks starting 24 h after glioma cell injection. The gambogic acid-treated rats showed a significant reduction of tumor volume after 14 days of treatment compared with vehicle-treated rats. It was found that gambogic acid might be able to enter the blood–brain barrier and affect the central nervous system. The results of cytotoxicity test indicated that gambogic acid can inhibit the growth of C6 glioma cells in a concentration-dependent manner and the IC_{50} value was determined to be 1.2 mmol/L. In addition, gambogic acid can upregulate the expression of Bax and pro-caspase-3 and downregulate the expression of Bcl-2, which indicated that gambogic acid might induce cell apoptosis *in vivo* (30).

Gambogic acid also showed dramatic anti-metastasis activity on the growth of artificial metastases *in vivo* in C57BL/6 mice injected with B16-F10 melanoma tumor cells by suppressing α4 integrin expression. Further results suggested that gambogic acid could inhibit the adhesion and migration of B16-F10 cells. Therefore, it might be a promising anti-metastasis drug (31).

Gambogic acid dramatically inhibited the lung metastases and xenograft tumor growth in athymic BALB/c nude mice infecting MDA-MB-231 human breast carcinoma cells. The inhibition effect might have a relationship with the fact that treatment with gambogic acid induced apoptosis and accumulated the amount of reactive oxygen species (ROS) in MDA-MB-231 cells. In addition, gambogic acid could induce activation of caspase-3, caspase-8, and caspase-9,as well as an increasing ratio of Bax/Bcl-2. Moreover, the translocation of apoptotic inducing factor (AIF) and the release of cytochrome c (Cyt c) from mitochondria were also found, suggesting that gambogic acid induced apoptosis through the accumulation of ROS and the mitochondrial apoptotic pathway. Gambogic acid also inhibited cell proliferation *via* blocking the Akt/mTOR pathway (32).

General gambogic acid was tested for its antitumor activity against human hepatoma SMMC-7721 cells in nude mice. The result showed that the growth of SMMC-7721 tumor in nude mice was significantly inhibited after i.v. injection of general gambogic acid 2, 4, and 8 mg/kg. The result also indicated that gambogic acid could significantly inhibit the activity of telomerase which is one of the crucial enzymes for the replication of RNA and a kind of ribo-nucleoprotein in SMMC-7721 (33).

Besides the strong cytotoxicity, the *in vivo* antitumor activity might also have a relationship with the inhibition effect on angiogenesis of gambogic acid. It is reported that gambogic acid can reduce the vascular endothelial growth factor (VEGF)-induced human umbilical vein endothelial cells (HUVEC) proliferation, mobility, and tube formation. The microvessel counts (MVCs) test which is conducted *in vivo* indicated that the mean intratumoral microvessel densities of gambogic acid-treated rats were dramatically reduced compared with the control group (30). The results of the *in vivo* experiment indicated that gambogic acid is able to dramatically inhibit angiogenesis by inhibiting vascular endothelial growth factor-triggered tyrosine phosphorylation of KDR/Flk-1 (34). It was also found that gambogic acid inhibited the activity of vascular endothelial growth factor receptor 2 and its downstream protein kinases, such as focal adhesion kinase, c-Src, and AKT, which give rise to inhibition of angiogenesis and antitumor activity (35). Moreover, the anti-angiogenic effects also proved to have a relationship with the inhibition of the PHD2–VHL–HIF-1α pathway induced by gambogic acid (36).

Toxicity Studies

The toxicity of gambogic acid was tested using beagle dogs and albino mice as experimental animals, and the result indicated that the LD_{50} of gambogic acid was 45–96 mg/kg. Moreover, the chronic toxicity studies showed that the toxicity targets in the model animals were the kidney and liver. It is reported that after gambogic acid i.v. administration, the most significant levels were observed in the liver, which was also in good agreement with the results of the above toxicological investigations. The study of the toxicity set a foundation for clinical applications of gambogic acid (23, 37).

The chronic toxicity of gambogic acid was tested in rats. The results of the studies suggested that the damage on the kidney and liver can be caused by treating with a high dose (120 mg/kg) of gambogic acid for a long time. A safe dose was developed to be 60 mg/kg after administration to rats for 13 weeks at a frequency of a single administration every other day (38).

The general pharmacological toxicity of gambogic acid, a new anticancer agent, on the dog cardiovascular and respiratory systems and the mouse central nervous system (CNS) was investigated. The results indicated that gambogic acid did not lead to any toxic symptoms on blood pressure, respiratory frequency, and heart rate (HR) while a high dose of gambogic acid exhibited slight side effects on the mouse CNS. The above results were also partly because gambogic acid might be able to enter the blood–brain barrier. (30, 39).

IN VITRO STUDIES

Cytotoxic Activity

Caged xanthones isolated from *G. hanburyi* showed cytotoxic activities against many cell lines such as human lung carcinoma cells (A549), Henrietta Lacks cervical carcinoma tumor cells (HeLa), human hepatoma (SMMC-7221), human leukemia K562 (K562/S), doxorubicin-resistant K562 (K562/R), human colon carcinoma cells (HCT116), human breast carcinoma cells (SK-BR-3), human hepatocellular carcinoma cells (HepG2), human liver cancer cells (Hep3B), human liver cancer cells (Huh7), and human euroblastoma cells (SH-SY5Y).

Garcinolic acid, acid deoxygaudichaudione A, gambogenic acid 10α-ethoxy-9,10-dihydromorellic acid, 10α-ethoxy-9,10-dihydrogambogenic desoxygambogenin, hanburin, gambogic acid, and desoxymorellin showed high inhibitory effects on human lung carcinoma cells (A549), human colon carcinoma cells (HCT116), human breast carcinoma cells (SK-BR-3), and human hepatocellular carcinoma cells (HepG2) with the IC_{50} values which were all below 10 μM (2).

Gaudichaudic acid, isogambogenic acid, deoxygaudichaudione A, gambogoic acid A, gambogenic acid, desoxygambogenin, isomorellic acid, morellic acid, desoxymorellin, and isomorellinol which were found from the resin of *G. hanburyi* exhibited significant cytotoxicities against human leukemia K562 (K562/S) and doxorubicin-resistant K562 (K562/R) cell lines with the IC_{50} value range of 0.11–3.04 μg/mL (40). Moreover, 30-hydroxygambogic acid and its (2*S*)-epimer 30-hydroxyepigambogic acid were tested for their cytotoxicities against the above two cell lines and the result indicated that 30-hydroxyepigambogic acid showed reduced activities compared with 30-hydroxygambogic acid (5).

Isomorellin, isomorellinol, forbesione, and gambogic acid were tested against KKU-100 and KKU-M156. The result indicated that the inhibition effect on both cell lines was found and growth inhibition induced by these compounds might be due to apoptosis (41).

It was reported that gambogic acid, a highly concerning compound from *G. hanburyi*, inhibited the growth of human liver cancer cells (Hep3B and Huh7) and human neuroblastoma cell (SH-SY5Y) viability with IC_{50} values of 1.8, 2.2, and 1.28 μM, respectively (42, 43).

Gambogenic acid and its microbial transformation product 16,17-dihydroxygambogenic acid were evaluated for their cytotoxicity against human cervical carcinoma cells (HeLa), but only modest activity was shown from both of the compounds (44).

Another research reported that gambospiroene methyl, 8,8a-dihydromorellate, 3-*O*-geranylforbesion, 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-methoxyisomorellinol 8,8a-dihydro-8-hydroxygambogic acid, and 8,8a-dihydro-8-hydroxygambogic acid were also tested for their cytotoxic effect against HeLa cells. All compounds displayed potent cytotoxicity except methyl 8,8a-dihydromorellate (45).

KKU-10 0 and KKU-M156 CCA cells were dramatically inhibited by isomorellin which is a caged xanthone isolated from *G. hanburyi* with IC_{50} values of 6.2±0.13, 5.1±0.11, and 3.5±0.25 μM at 24, 48, and 72 h (46).

It was found that the efficiency of cell growth inhibition increased dramatically when the concentration of gambogic acid was increased. A liner regression of the data allowed the calculation of the IC_{50} of gambogic acid for human hepatoma SMMC-7721, which is 1.2 μM with 48 h exposure (47).

Different apoptotic induction of gambogic acid on human hepatoma SMMC-7721 cells and human normal embryo hepatic L02 cells was compared by observing morphological changes, detecting growth inhibition, and the expressions of the relative apoptotic proteins, which indicated that gambogic acid could selectively induce apoptosis of human hepatoma SMMC-7721 cells, while had a relatively small effect on human normal embryo hepatic L02 cells (48).

Gambogic acid was also tested for its inhibitory effect against Jurkat T cells. And the result showed that gambogic acid has a significant inhibition effect on Jurkat T cells with the IC_{50} values of 1.51±0.09 (24 h), 0.98±0.13 (48 h), and 0.67±0.12 μmol/L (72 h). Gambogic acid can also induce apoptosis in Jurkat cells (49).

Table II summarizes some of the results of cytotoxic tests of *G.* xanthones.

Anti-HIV Activity

Recently, the anti-HIV activity of the caged xanthones from *G. hanburyi* was also mentioned in some of the researches. For example, 2-acetoxyalphitolic acid and 3-acetox yalphitolic acid,

Table II. Cytotoxic Activity of *Garcinia* Xanthones

No.	Compound	Cell lines	IC_{50} (μg/mL)	Reference
1	Deoxygaudichaudione A	A549	3.12 (72 h)	(3)
		HCT116	0.78 (72 h)	(3)
		SK-BR-3	2.49 (72 h)	(3)
		HepG2	2.75 (72 h)	(3)
		K562/ADR	3.04 (44 h)	(13)
		K562/S	1.74 (44 h)	(13)
2	Desoxygambogenin	A549	3.12 (72 h)	(3)
		HCT116	4.02 (72 h)	(3)
		SK-BR-3	2.80 (72 h)	(3)
		HepG2	4.99 (72 h)	(3)
		K562/ADR	2.43 (44 h)	(13)
		K562/S	0.91 (44 h)	(13)
3	Desoxymorellin	A549	1.42 (72 h)	(3)
		HCT116	0.28 (72 h)	(3)
		SK-BR-3	0.61 (72 h)	(3)
		HepG2	0.85 (72 h)	(3)
		K562/ADR	1.53 (44 h)	(40)
		K562/S	0.64 (44 h)	(40)
4	Gambogenic acid	A549	3.14 (72 h)	(3)
		HCT116	3.50 (72 h)	(3)
		SK-BR-3	1.66 (72 h)	(3)
		HepG2	1.80 (72 h)	(3)
		K562/ADR	3.90 (48 h)	(50)
		K562/S	3.01 (44 h)	(40)
		CICC 2445	2.41 (44 h)	(40)
			1.22[a]	(44)
5	Gambogic acid	A549	1.20 (72 h)	(3)
		HCT116	0.50 (72 h)	(3)
		SK-BR-3	1.16 (72 h)	(3)
		HepG2	1.02 (72 h)	(3)
		Hep3B	1.80 (24 h)	(42)
		Huh7	2.20 (24 h)	(42)
		SH-SY5Y	1.28 (6 h)	(43)
		MGC-803	0.96 (48 h)	(51)
		SPC-A1	1.74 (24 h)	(52)
		BGC-823	1.01 (48 h)	(52)
		T47D	0.81 (72 h)	(52)
		ZR751	2.30 (24 h)	(53, 54)
		HL60	1.41 (48 h)	(53)
		Jurkat	1,02 (72 h)	(53)
		Calu1	0.63[a]	(55)
		MES	0.40[a]	(55)
		MES ADR	0.115[a]	(55)
		K562/S	0.624 (72 h)	(56)
		K562/ADR	0.168[a]	(55)
		MCF7	0.55[a]	(55)
		MDA-MB-468	0.30[a]	(55)
		SGC-7901	1.00[a]	(55)
		U937	0.28 (2 days)	(57)
			10.78 (44 h)	(58)
			0.24 (4 days)	(58)
			0.33 (5 days)	(58)
			2.0 (48 h)	(59)
			1.019 (24 h)	(60)
6	Gambogoic acid A	K562/ADR	1.65 (44 h)	(40)
		K562/S	1.38 (44 h)	(40)
7	Gaudichaudic acid	K562/ADR	0.61 (44 h)	(40)
		K562/S	0.41 (44 h)	(40)
8	Isogambogic acid	K562/ADR	2.86 (44 h)	(40)
		K562/S	2.10 (44 h)	(40)
9	Isomorellic acid	K562/ADR	1.86 (44 h)	(40)
		K562/S	0.91 (44 h)	(40)
10	Morellic acid	K562/ADR	2.29 (44 h)	(40)
		K562/S	1.48 (44 h)	(40)

Table II. (continued)

No.	Compound	Cell lines	IC_{50} (μg/mL)	Reference
11	Garcinolic acid	A549	2.84 (72 h)	(3)
		HCT116	1.77 (72 h)	(3)
		SK-BR-3	1.92 (72 h)	(3)
		HepG2	1.83 (72 h)	(3)
12	10α-Ethoxy-9,10-dihydromorellic acid	A549	4.86 (72 h)	(3)
		HCT116	1.68 (72 h)	(3)
		SK-BR-3	2.16 (72 h)	(3)
		HepG2	2.07 (72 h)	(3)
13	10α-Ethoxy-9,10-dihydrogambogenic acid	A549	9.19 (72 h)	(3)
		HCT116	3.63 (72 h)	(3)
		SK-BR-3	9.22 (72 h)	(3)
		HepG2	6.65 (72 h)	(3)
14	Hanburin	A549	5.94 (72 h)	(3)
		HCT116	4.25 (72 h)	(3)
		SK-BR-3	3.18 (72 h)	(3)
		HepG2	2.92 (72 h)	(3)
15	30-Hydroxygambogic acid	K562/R	2.89[a]	(6)
		K562/S	1.27[a]	(6)
16	30-Hydroxyepigambogic acid	K562/R	4.49[a]	(6)
		K562/S	3.61[a]	(6)
17	16,17-Dihydroxygambogenic acid	CICC 2445	4.25[a]	(44)

[a] Not mentioned

along with betulinic acid, and betulin, which were isolated from the leaves and twigs of *G. hanburyi* were reported to show anti-HIV-1 activity with the IC_{50} values of 15.9, 19.8, 27.2, and 11.6 μg/mL, respectively (61)

Moreover, 7-methoxydesoxymorellin, 2-isoprenylforbesione and 8,8a-epoxymorellic acid, desoxymorellin, isomorellin, isomorellinol, gambogic acid, desoxygambogenin, hanburin, and forbesione were tested for their anti-HIV-1 activity. However, only desoxygambogenin and dihydroisomorellin showed significant anti-HIV-1 activity (62).

Neurotrophic Activity

Gambogic acid which proved to be a selective agonist for TrkA receptor showed a strongly neurotrophic activity by selectively binding to TrkA, inducing its tyrosine phosphorylation, provoking neurite outgrowth in PC12 cells, eliciting PI3-kinase/Akt and MAPK activation, and preventing neuronal cell death (63).

Antibacterial Activity

Caged xanthones which were isolated from *G. hanburyi* were evaluated for the antibacterial activity against several kinds of bacteria. Among those, the antibacterial activity of hanburinone, isomoreollin B, morellin, moreollic acid, and morellic acid was tested against MRSA. As a result, moreollic acid and morellic acid displayed significant antibacterial activity with a MIC value of 25 μg/mL while hanburinone, isomoreollin B, and morellin exhibited a relatively modest activity with an equal MIC value of 200 μg/mL (4).

MOLECULAR MECHANISM STUDIES

It was reported that instead of dealing with the tumor cell directly, these compounds work through a series of biochemical reactions. Among the compounds isolated from *G. hanburyi*, gambogic acid and gambogenic acid attracted much more interests than the other ones and their potential mechanisms were also well documented in past decades.

Inhibition of Proliferation and Induction of Apoptosis-Related Mechanisms

The effects of gambogic acid on the growth and apoptosis of osteosarcoma cells were observed *in vitro*. The result indicated that the inhibition effect of gambogic acid against osteosarcoma cells was found to have a relationship with apoptosis and cell cycle arrest induced by gambogic acid (64). Also, gambogic acid was reported to have an inhibition effect on the catalytic activity of human topoisomerase IIα which can reduce the gambogic acid-induced apoptosis and restore cell proliferation and the phosphorylation of c-Jun upon gambogic acid treatment (65). It is reported that gambogenic acid induced A549 cell apoptosis, inhibited the expression of cyclooxygenase (COX-2) and cyclin D1 in messenger RNA (mRNA) level, and arrested the cells to G0/G1 phase *in vitro*. These results might indicate that gambogenic inhibits cancer cell growth through cell cycle arrest and apoptosis induction (66). Gambogic acid activates T lymphocytes to induce tumor cell apoptosis. The cDNA microarray analysis revealed that most of the genes that were affected by gambogic acid treatment were immune-related genes (67). Growth inhibition induces the G0/G1 phase cell cycle arrest, and apoptosis could be caused by gambogic acid in human chronic myelogenous leukemia cell line K562 cells. Moreover,

gambogic acid might show its strong antitumor effects through the interruption of SRC-3 (68). Gambogic acid showed both growth arrest and apoptosis induction effects on Jurkat cells by significantly suppressing the expression of nucleophosmin, which indicated the fact that nucleophosmin and some nucleoporins might serve as new targets of gambogic acid (69). Gambogic acid inhibited tumor cell proliferation by blocking STAT3 activation which associated with proliferation, metastasis, and survival of cancer cells (70). The result of the *in vitro* research on K562 cells suggests that gambogic acid showed its anti-leukemia effects partially by suppressing the expression level of hERG channel in K562 cells, indicating that gambogic acid can be a promising antitumor agent against leukemia with a mechanism of inhibiting the hERG channel (71).

Among the various signal pathways, the p53 pathway was one of the most important pathways, which is related with apoptosis of cancer cells. Gambogic acid induced apoptosis of tumor cells that expressed wild-type p53 by suppressing MDM2 at both protein and mRNA levels (72). It was confirmed that gambogic acid enhances the p53 protein level through inhibition of MDM2 in p53 wild-type tumor cells. Further study revealed that gambogic acid reduced MDM2 expression in a time-dependent and concentration-dependent way and the inhibition effects were displayed at both posttranslational and transcriptional levels. Moreover, the cytotoxicity, apoptosis, and G2/M cell cycle arrest induced by gambogic acid were found in both p53 wild-type and p53 null tumor cells (73). Gambogic acid was also proved to be a potential inhibitor of the p53-MDM2 interaction via a gene reporter assay in human tumor cells (74). By investigating the relationship between p53 activation and its posttranslational modifications in the human tumor cell lines HepG2 and A549 in response to gambogic acid or adriamycin treatment, it was found that DNA damage response mediated by ATR-Chk1 which is induced by gambogic acid treatment played an important role in p53/p21$^{Waf/CIP1}$ activation and downstream G2/M arrest (75). It is reported that gambogic acid inhibited cell growth by downregulating the p21$^{waf1/cip1}$ expression with small interfering RNA which blocked gambogic acid-induced cell differentiation and growth inhibition (76). Additional targets that contribute to its cytotoxic mechanism were reported to be the suppression effect on anti-apoptotic Bcl-2 family proteins induced by gambogic acid, which is indicated by experiments using separated mitochondria in which recombinant purified Bcl-2 family proteins inhibit SMAC release *in vitro* (77). Gambogic acid can inhibit the growth of A375 cells in a dose-dependent manner and induce their apoptosis, by increasing the Bax/Bcl-2 ratio and caspase-3 activity (78). It was reported that gambogic acid induced apoptosis in human MCL JeKo-1 cells via regulating the ratio of Bcl-2/Bax and activating caspase-3, caspase-8, and caspase-9 through the mitochondrial pathway (79). Gambogic acid can decrease XIAP expression levels and the ratio of Bcl-2/Bax, which results in inducing HeLa cell apoptosis. During the research, it was also found that gambogic acid seems to bind to the N-terminal ATP-binding domain of Hsp90, which results in the inhibition of heat shock protein 90 (Hsp90) (80). Moreover, human breast cancer cells MCF-7 apoptosis was induced by gambogic acid reducing Bcl-2 expression through p53 (81).

JNK and p38 MAPkinase pathway also play a critical role in cell cycle. Microtubule depolymerization and microtubule cytoskeleton disruption can be caused by gambogic acid in human breast carcinoma MCF-7 cells. Gambogic acid can dramatically increase phosphorylation levels of p38 and c-Jun N-terminal kinase-1 (JNK-1). Therefore, gambogic acid depolymerized microtubules and increased the phosphorylation levels of p38 and JNK1, which result in G2/M cell cycle arrest and apoptosis in MCF-7 cells (82). It was reported that gambogenic acid induced apoptosis and was related with the Phospho-Erk1/2 and Phospho-p38 MAPK protein expression changes in HepG2 cells (83).

The effect of gambogic on the induction of reactive oxygen species (ROS) accumulation and induction of the mitochondrial signaling pathway was investigated in human hepatoma SMMC-7721 cells. The result indicated that the accumulation of reactive oxygen species (ROS) played an important role in the gambogoc acid-induced mitochondrial signaling pathway, which provided further evidence for the application of gambogic as a promising antitumor agent (84). Further investigation showed the molecular mechanism of ROS toxicity was that the gambogic acid inhibited the TRX-1 and TRx-2 proteins by covalent binding to the active cysteine residues in the functional domain through Michael addition reactions. Because TRX-1 and TRX-2 play critical roles in regulating the redox signaling of cancer cells, the present studies have explained the relationship between protein binding and cellular ROS accumulation triggered by gambogic acid (85). Gambogic acid can induce apoptosis in RPMI-8226 cells via ROS accumulation caused by activation of caspase-3, cleavage of PARP, and downregulation of SIRT1 (86).

Moreover, the posttranscriptional regulation effect of the telomerase hTERT induced by gambogic acid was investigated in human gastric carcinoma BGC-823 cells. The result indicated that gambogic acid represses telomerase activity not only by inhibiting hTERT transcriptional activity through c-Myc but also by posttranslational modification of hTERT through Akt (87). Gambogic acid can also induce U87 glioma cell apoptosis via degradation of the epidermal growth factor receptor and inhibition of its downstream Akt/mTORC1 (88).

Inhibition of Invasion and Metastasis-Related Mechanisms

The cytotoxic effect of gambogic acid was tested against human prostate cancer PC3 cells, whose result showed that gambogic acid inhibits TNF-α-induced invasion of PC3 cells through blocking PI3K/Akt and NF-κB signaling pathways (89). The effect on A549 and U251 cells was also tested, and the results showed that gambogic acid and its analogs inhibit the activity of IκB kinase-beta (IKKβ) by blocking the activation of the TNF-α/NF-κB pathway (90). It was reported that reduction of the expression of MMP-2 and MMP-9 was confirmed to be another mechanism of the inhibition activity for cancer metastasis induced by gambogic acid (91). The anti-invasive effect of gambogic acid was investigated in human breast carcinoma cells MDA-MB-231. The result suggests that this effect might be partly because gambogic acid can reduce the expressions of MMP-2 and MMP-9 in MDA-MB-231 (92). It is also reported that gambogic acid reduces the invasiveness

and metastasis of osteosarcoma cells via suppressing the expression of MMP-9 and upregulating the expression of TIMP-1 (93).

DRUG INTERACTIONS

An interesting research demonstrated that the inhibition of cell viability was dramatically increased when human leukemia K562 and murine hepatocarcinoma H22 cells were treated with the proteasome inhibitor MG262 at different doses and 0.4 μM of gambogic acid for 48 h, while using any of them alone could not achieve an identical effect. The result indicated that the combination of gambogic acid and the proteasome inhibitor may result in a synergistic inhibitory effect on the growth of cancer cells (94).

Another study on the inhibitory effects of 5-fluorouracil (5-FU) combined with gambogic acid on BGC-823 human gastric carcinoma cells indicated that the pro-apoptotic activity of the two-drug combination was much stronger than single use (95).

It is reported that gambogic acid can dramatically increase docetaxel sensitivity. The IC_{50} values of docetaxel against BGC-823 and BGC-823/Doc cells were 0.03 and 1.69 μM, respectively, indicating that BGC-823/Doc cells were 56.3 times more resistant to docetaxel than parental cells. Gambogic acid can decrease the IC_{50} of docetaxel to 4–14 times in BGC-823/Doc cells. It was found that gambogic acid at 0.3 μM was able to complete reverse docetaxel resistance in BGC-823/Doc cells (96).

The human transferrin receptor (hTfR) is a target for cancer immunotherapy because of its overexpression on the surface of cancer cells. Cytotoxicity was enhanced by combination use of gambogic acid and anti-hTfR IgG3-Av (97).

Proliferation was dramatically inhibited, and the apoptotic rate of Tca8113 cells was significantly improved by combined treatment with gambogic acid and celastrol or the dominant negative mutant SR-IκBα. Therefore, the combination of gambogic acid and celastrol may be a promising method for treating oral squamous cell carcinoma (98).

The inhibitory activity of gambogic acid combined with magnetic nanoparticle of Fe_3O_4 (Fe_3O_4-MNP) on U937 leukemia cells was evaluated, and the result showed that Fe_3O_4-MNP can promote gambogic acid-triggered apoptosis in U937 leukemia cells, and the combination of gambogic acid and Fe_3O_4-MNP may be a safer treatment for leukemia (99).

Gambogic acid could also inhibit proliferation of LOVO cells and induce apoptosis, which was significantly enhanced by combination use of magnetic nanoparticles containing Fe_3O_4 (100).

Gambogic acid treatment can cause the accumulation of monodansylcadaverine (MDC) in autophagic vacuoles, increase expressions of Beclin 1, Atg5, and LC3-II, and increase punctate fluorescent signals in glioblastoma cells pretransfected with GFP-tagged LC3 plasmid. Gambogic acid-induced growth inhibition and apoptotic cell death was enhanced by combination use of autophagy inhibitors and gambogic acid (101).

The effect of gambogic acid in combination with sunitinib (SU), a new multi-targeted oral medication on renal cancer indicated that the combination use of gambogic acid and SU can provide stronger antitumor efficacy compared to either drug alone, which may provide a new clinical treatment strategy for renal cell carcinoma (102).

The combination of gambogic acid and docetaxel can provide synergistic anti-proliferative effects in gastrointestinal cancer cells. Furthermore, gambogic acid dramatically inhibited the mRNA expression of docetaxel-related genes, including tau, β-tubulinIII, and survivin (103).

It was also found that when gambogic acid and methotrexate were used together, the proportion of cells surviving was lower than that of methotrexate treatment alone (104).

Gambogic acid can also enhance the antitumor activity of doxorubicin on the platinum-resistant human ovarian cancer cell line (SKOV-3) through ROS-induced apoptosis (105).

In another study, the interaction between gambogic acid and chemotherapeutic agents, 5-fluorouracil (5-FU), oxaliplatin (Oxa), and docetaxel (Doc), was investigated. It was found that gambogic acid had a synergistic effect on the cytotoxic activity of chemotherapeutic drugs against human gastric cancer BGC-823 cells and MKN-28 cells. The combination of gambogic acid and chemotherapeutic drugs could also induce apoptosis in a synergistic way. Moreover, gambogic acid was able to downregulate chemotherapeutic agent-associated genes (106).

CONCLUSION

The caged xanthones from *G. hanburyi* displayed many potent bioactivities, especially antitumor activity. Analytical and preparative isolation methods also developed along with the process of the research. However, the majority of recent research concentrated on cytotoxicity *in vitro* and its mechanism. The author thinks that more effort should be put on the research of the *in vivo* therapy effects and safety. In order to make a further step towards clinical application, we should pay more attention to the shortages of these compounds which hindered their clinical use. To overcome the shortcomings of these xanthones, formulation and structure modification method should be further investigated. Moreover, currently, gambogic acid and gambogenic acid were most studied, so other xanthones should also be concerned for the purpose of finding new drug candidates.

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