Supplementary Material

List of Abbreviations

Annexin V-PE	Annexin V-phycoerythrin
7-AAD	7-amino-actinomycin D
C1	Compound 1 (in this study *Trametes robiniophila* Murr, Huaier)
C2	Compound 2 (in this study Ershiwuwei Songshi Wan)
C3	Compound 3 (in this study Qiwei Honghua Shusheng Wan)
C_{12}FDG	5-Dodecanoylaminofluorescein di-β-D-galactopyranoside
CCA	Cholangiocarcinoma
CCK-8	Cell counting kit – 8
CVSA	Crystal violet staining assay
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethyl sulfoxide
FACS	Fluorescence-activated cell sorting (flow cytometry analysis)
FBS	Fetal bovine serum
5-FU	5-Fluorouracil
HCC	Hepatocellular carcinoma
iCCA	Intrahepatic cholangiocarcinoma
LC-MS/MS	Liquid chromatography mass spectrometry
MEM NEAA	Minimum essential medium non-essential amino acids
MQ	Milli-Q
NaCl	Sodium chloride
N.A.	Not applicable
OD	Optical density
PBS	Phosphate buffered saline
PLC	Primary liver cancer
SA-β-Gal	Senescence-associated β-galactosidase assay

SASP	Senescence-associated secretory phenotype
SEM	Standard error of the mean
PLC	Primary liver cancer
TACE	Transarterial chemoembolization
TCM	Traditional Chinese Medicine
TTM	Traditional Tibetan Medicine

Supplementary Tables

Supplementary Table 1 | List of all species contained in the formulations of C1, C2 and C3.

C1: Huaier Link to the purchaser: www.gaitianli.com.cn	
Ingredient	**Content in formulation**
Trametes robiniophila Murr	100%

C2: Ershiwuwei Songshi Wan Link to the purchaser: www.glzy.cn		
No.	**Ingredient**	**Content in formulation (g)**
1	Turquoise (mineral)	20
2	Pearl	10
3	Corals	40
4	Asparagaceae: *Dracaena cinnabari* Balf. f.	20
5	Combretaceae: *Terminalia chebula* Retz.	50
6	Combretaceae: Scrap iron of *Terminalia chebula* Retz.	100
7	Phyllanthaceae: *Phyllanthus emblica* L.	50
8	Sciuridae: *Trogopterus xanthipes* (Minlne Eduards)	40
9	Santalaceae: *Santalum album* L.	40
10	Fabaceae: *Dalbergia odorifera* T. C. Chen	40
11	Aristolochiaceae: *Aristolochia debilis* Siebold & Zucc.	50

12	Acanthaceae: *Justicia adhatoda* L.	50
13	Bovidae: *Bos taurus domesticus* Gmelin	5
14	Asteraceae: *Dolomiaea costus* (Falc.) Kasana & A. K. Pandey	60
15	Papaveraceae: *Meconopsis cambrica* Vig.	50
16	Ranunculaceae: *Aconitum naviculare* (Brühl) Stapf	40
17	Myristicaceae: *Myristica fragrans* Gronov	20
18	Myrtaceae: *Syzygium aromaticum* (L.) Merr. & L. M. Perry	25
19	Saxifragaceae*: Saxifraga umbellulata* var. *pectinata* (C. Marquand & Airy Shaw) J. T. Pan	50
20	Combretaceae: *Terminalia bellirica* (Gaertn.) Roxb.	5
21	Poaceae*: Bambusa testilis* McClure	35
22	Iridaceae: *Crocus sativus* L.	5
23	Malvaceae: *Bombax ceiba* L.	35
24	Moschidae: *Moschus* Flerov	0.25
25	Travertine (limestone)	35
C3: Qiwei Honghua Shusheng Wan Link to the purchaser: www.glzy.cn		
No.	**Ingredient**	**Content in formulation (g)**
1	Asteraceae: *Carthamus tinctorius* L.	112.5
2	*Poaceae: Bambusa testilis* McClure	75
3	Gentianaceae: *Swertia bimaculata* (Siebold & Zucc.) Hook. f. & Thomson ex C. B. Clarke	75
4	Combretaceae: *Terminalia chebula* Retz.	100
5	Ephedraceae: *Ephedra sinica* Stapf	75
6	Aristolochiaceae: *Aristolochia debilis* Siebold & Zucc.	75
7	Papaveraceae: *Meconopsis cambrica* Vig.	75

Supplementary Table 2 | The concentrations of TCM, TTM and standard therapeutics used in this study.

Cancer Type	Compounds				
	C1 (mg/ml)	**C2 (mg/ml)**	**C3 (mg/ml)**	**Sorafenib (μM)**	**Gemcitabine (μM)**
HCC	4 8 16	1 2 4	0.25 0.5 1	3.45 6.9 13.8 (human plasma concentration)	Not applicable (N.A.)
CCA	4 8 16	4 8 16	1 2 4	N.A.	0.025 0.05 0.1 50 (human plasma concentration)

Supplementary Table 3 | Individual metabolites detected in C1, C2 and C3. Table 3 is attached as a separate Excel file.

Supplementary Table 4 | Statistical analysis of all treatment groups of TCM, TTM and standard therapeutic agents in HCC and CCA representing *P* values. Table 4 is attached as a separate Excel file.

Supplementary Table 5 | Cancer studies describing inhibitory capacity of C1.

Constituent	Type of cancer	Investigated in human, *in vivo*, *in vitro*	Reference
Huaier *(Trametes robiniophila* Murr*)*	Breast cancer	MDA-MB-231, MCF7 Mouse study	(Wang et al., 2019)
	HCC	Patients	(Chen et al., 2018; J.Y.Lei, 2015; Wang et al., 2021)
		Rabbit study and HepG2 cells	(Ren et al., 2009)
			(Shan et al., 2017)

		Bel-7404, Bel-7402, SMMC-7721	
	Gastric cancer	Mouse study and MGC803, MKN74, AZ-521, MKN28 cells	(Shi et al., 2022)
	CCA	Patients Huh28 RBE, CCLP1, HuCCT1	(Feng et al., 2022) (Fu et al., 2019) (Ji et al., 2020)

Supplementary Table 6 | Cancer studies describing inhibitory capacity of individual constituents of C2.

Constituent	Type of cancer	Investigated cells/animals	Reference
Turquoise (mineral)	N.A.	N.A.	N.A.
Pearl	N.A.	N.A.	N.A.
Corals	Breast cancer	SKBR3, MDA-MB-231	(Huang et al., 2018)
	HCC	SK-HEP-1	(Ko et al., 2021)
Dracaena cinnabari Balf. f.	N.A.	N.A.	N.A.
§*Terminalia chebula* Retz.	Breast cancer	MCF-7, S115 (mouse)	(Saleem et al., 2002)
	Osteosarcoma	HOS-1	
	Prostate cancer	PC-3	
	Mammary gland adenocarcinoma Lung cancer	MCF-7 A-549	(Ravi Shankara et al., 2016)
	HCC	HepG2	(Achari et al., 2011)
Scrap iron of *Terminalia chebula* Retz.	N.A.	N.A.	N.A.
Phyllanthus emblica L.	Lung cancer HCC Cervical cancer Breast cancer Ovarian cancer Colorectal cancer	A-549 HepG2 HeLa MDA-MB-231 SK-OV3 SW620	(Ngamkitidechakul et al., 2010)

	Lung cancer HCC	A-549 HepG2	(Pinmai et al., 2008)
	Colorectal cancer	Colo205	(Guo et al., 2017)
Trogopterus xanthipes (Minlne Eduards)	N.A.	N.A.	N.A.
Santalum album L.	Bladder cancer	J82	(Dozmorov et al., 2014)
	Skin cancer	A431	(Kaur et al., 2005)
	Prostate cancer	PC-3	(Bommareddy et al., 2012)
Dalbergia odorifera T.C. Chen	Cervical cancer	C-33A, SiHa	(Yang et al., 2018)
§*Aristolochia debilis* Siebold & Zuccarini	N.A.	N.A.	N.A.
Justicia adhatoda L.	T-cell lymphoma	Mouse study	(V., 2019)
	Cervical cancer	HeLa	(Pandiyan et al., 2019; Sudevan et al., 2019)
Bos taurus domesticus Gmelin	HCC	SMMC-7721	(Dimin et al., 2022; Zhang et al., 2021)
Dolomiaea costus (Falc.) Kasana & A. K. Pandey	N.A.	N.A.	N.A.
§*Meconopsis cambrica* Vig.	Lymphocytic leukemia	L1210	(Fan et al., 2015b)
	Leukemia	K562	(Fan et al., 2015a)
Aconitum naviculare (Brühl) Stapf	N.A.	N.A.	N.A.
Myristica fragrans Gronov	Sarcoma	Mouse study	(Thuong et al., 2014)
	Oral epidermal carcinoma	Oral epidermal carcinoma KB cells	(Rengasamy, 2018)
Syzygium aromaticum (L.) Merr. & L. M. Perry	Colon carcinoma	Human colon carcinoma cells	(Yassin, 2020)
Saxifraga umbellulata var. pectinata (C. Marquand & Airy Shaw) J. T. Pan	N.A.	N.A.	N.A.
Terminalia bellirica (Gaertn.) Roxb.	Breast ductal carcinoma Colorectal cancer Colon cancer Breast cancer Ductal carcinoma Prostatic cancer	BT-474 Colo-205 HAT-29 MCF-7 ZR-75-1 LnCap	(Shi Li, 2018)
§*Bambusa testilis* McClure	Breast cancer	Rat study	(Lin et al., 2008)
Crocus sativus L.	HCC	Rat study	(Amin et al., 2011)
	HCC Cervical cancer	HepG2 HeLa	(Tavakkol-Afshari et al., 2008)

Bombax ceiba L.	Mammary gland carcinoma	Rat study	(Mahmoud, 2020)
	Leukemia	HL-60	(Sharma et al., 2020)
Moschus Flerov	Lung cancer	Eplc-32M1, GLC-82, XLA-07, XL-JT, A549, NCIH-460, 801-D, NCIH-446	(Xu and Cao, 2016)
	Mammary carcinoma	MDA-MB-231	
	Esophageal carcinoma	TE-1	
	Gastric carcinoma	HSC, NCI-N87SGC-7901	
	Colorectal carcinoma	HT-29, Caco-2SW480	
	HCC	Huh7, HepG2,	
	Acute myelogenous leukemia	HL-60	
	B cell lymphoma	Daudi	
Travertine (limestone)	N.A.	N.A.	N.A.

§These compounds are also represented in C3.

Supplementary Table 7 | Cancer studies describing inhibitory capacity of individual constituents of C3.

Constituent	Type of cancer	Investigated cells/animals	Reference
Carthamus tinctorius L.	Colorectal cancer	HCT116, SW480 LoVo, HT-29	(Park, 2016)
	Breast cancer	MDA-MB-231 MCF-7	
	HCC	HepG2, Hep3B	(Sharula and Wu, 2017)
§§*Bambusa testilis* McClure	Breast cancer	Rat study	(Lin et al., 2008)
Swertia bimaculata (Siebold & Zucc.) Hook. f. & Thomson ex C.B. Clarke	N.A.	N.A.	N.A.
§§*Terminalia chebula* Retz.	Breast cancer Osteosarcoma Prostate cancer	MCF-7, S115, HOS-1 PC-3	(Saleem et al., 2002)

	Mammary gland adenocarcinoma Lung cancer	MCF-7 A-549	(Ravi Shankara et al., 2016)
	HCC	HepG2	(Achari et al., 2011)
Ephedra sinica Stapf	Lung cancer	H1993	(Hyuga et al., 2020)
§§*Aristolochia debilis* Siebold & Zucc.	N.A.	N.A.	N.A.
§§*Meconopsis cambrica* Vig.	Lymphocytic leukemia	L1210	(Fan et al., 2015b)
	Leukemia	K562	(Fan et al., 2015a)

§§These compounds are also represented in C2.

Supplementary Figure Legends

Supplementary Figure 1 | A detailed description of the 25 components of the TTM C2 used in the study. 25 components of C2 comprise of the following: 1) Turquoise; 2) Pearl; 3) Corals; 4) *Dracaena cinnabari* Balf. f.; 5) *Terminalia chebula* Retz.; 6) Scrap iron of *Terminalia chebula* Retz.; 7) *Phyllanthus emblica* L.; 8) *Trogopterus xanthipes* (Minlne Eduards); 9) *Santalum album* L.; 10) *Dalbergia odorifera* T.C. Chen; 11) *Aristolochia debilis* Siebold & Zuccarini; 12) *Justicia adhatoda* L.; 13) *Bos taurus domesticus* Gmelin; 14) *Dolomiaea costus* (Falc.) Kasana & A. K. Pandey; 15) *Meconopsis cambrica* Vig.; 16) *Aconitum naviculare* (Brühl) Stapf; 17) *Myristica* fragrans Gronov; 18) *Syzygium aromaticum* (L.) Merr. & L.M.Perry; 19) *Saxifraga umbellulata var. pectinata* (C. Marquand & Airy Shaw) J.T. Pan; 20) *Terminalia bellirica* (Gaertn.) Roxb.; 21) *Bambusae concertio silicea*; 22) *Crocus sativus* L.; 23) *Bombax ceiba* L.; 24) *Moschus* Flerov; 25) Travertine (limestone). The flower symbol represents a plant-origin.

Supplementary Figure 2 | A detailed description of the seven components of the TTM C3 used in this study. The seven components comprise: 1) *Carthamus tinctorius* L.; 2) *Bambusa testilis* McClure; 3) *Swertia bimaculata* (Siebold & Zucc.) Hook. F. & Thomson ex C. B. Clarke; 4) *Terminalia chebula* Retz.; 5) *Ephedra sinica* Stapf; 6) *Aristolochia debilis* Siebold & Zucc; 7) *Meconopsis cambrica* Vig. The flower symbol represents a plant-origin.

Supplementary Figure 3 | Analysis of C1, C2 and C3 components by **LC-MS/MS**. The powders C1, C2 and C3 were extracted in water and analyzed by ultrahigh-performance liquid chromatography coupled to a quadrupol time-of-flight mass spectrometry in positive mode. The figure shows the base peak chromatograms for C1 to C3 and a blank sample (top to bottom).

Supplementary Figure 4 | C1 possessed inhibitory capacity towards HCC cell line as confirmed by CVSA analysis using ImageJ. Cell viability analysis performed **(A)** 24 h and **(B)** 48 h post-incubation. Values represent mean ± standard error of the mean (Petriv et al.). Significance levels were depicted as: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ and $****p < 0.0001$. Detailed *P* values for all groups are displayed in **Supplementary Table 4**.

Supplementary Figure 5 | C2 in combination with sorafenib possessed an inhibitory capacity towards the HCC cell line in CVSA analysis, whereas C2 monotherapy was completely inefficient. CVSA readouts were performed **(A)** 24 h and **(B)** 48 h after incubation to test the inhibitory capacity of C2 at

concentrations 1, 2, 4 mg/ml as a monotherapy or in combination with sorafenib (3.45 µM and 6.9 µM). Sorafenib dose of 13.8 µM (plasma concentration, as reported for the clinic (Fucile et al., 2015)), has been used as a positive control. DMSO and DMEM were used as negative controls, as a carrier for sorafenib and C2, respectively.

Supplementary Figure 6 | C2 possessed inhibitory capacity towards HCC cell line as confirmed by CVSA analysis using ImageJ. Cell viability analysis performed **(A)** 24 h and **(B)** 48 h post-incubation. Values represent mean ± SEM. Significance levels were depicted as: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ and ****$p < 0.0001$. Detailed *P* values for all groups are displayed in **Supplementary Table 4**.

Supplementary Figure 7 | C3 in combination with sorafenib inhibited the growth of the HCC cell line, as shown by CVSA analysis. CVSA has been performed **(A)** 24 h and **(B)** 48 h after incubation, to test the inhibitory capacity of C3 at concentrations 0.25, 0.5 and 1 mg/ml as monotherapy or in combination with sorafenib (3.45 µM and 6.9 µM). DMSO and DMEM were used as negative controls, as a carrier for sorafenib and C3, respectively.

Supplementary Figure 8 | C3 possessed inhibitory capacity towards HCC cell line as confirmed by CVSA analysis using ImageJ. Cell viability analysis performed **(A)** 24 h and **(B)** 48 h post-incubation. Values represent mean ± SEM. Significance levels were depicted as: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ and ****$p < 0.0001$. Detailed *P* values for all groups are displayed in **Supplementary Table 4**.

Supplementary Figure 9 | C3 demonstrated an inhibitory effect on the HCC cell line both as a monotherapy and in combination with sorafenib in CCK-8 analysis and induced cellular senescence. CCK-8 analysis was performed on **(Martinez-Velez et al.)** C2- or **(C-D)** C3-treated HCC cells. OD_{450} was detected **(A-C)** 24 h and **(B-D)** 48 h after incubation with compounds. Values represent mean ± SEM. Significance levels were depicted as: *$p < 0.05$, **$p < 0.01$ and ****$p < 0.0001$. **(E)** SA-β-Gal assay was performed 48 h post-incubation in C3-treated group. Senescent cells stained in blue are depicted with the white arrows.

Supplementary Figure 10 | FACS analysis performed 48 h after incubation revealed the induction of late apoptosis in HCC cells treated with C2 combined with sorafenib. FACS analysis to detect **(A)** early, **(B)** late apoptosis and **(C)** necroptosis was performed and results are shown as frequencies in percent. The grey line represents the values for the control group (DMEM).

Supplementary Figure 11 | FACS analysis performed 48 h after the incubation with C3 alone or in combination with sorafenib confirmed the induction of late apoptosis in HCC cells. FACS analysis to detect **(A)** early, **(B)** late apoptosis and **(C)** necroptosis was performed and results are shown as frequencies in percent. The grey line represents the values for the DMEM control group.

Supplementary Figure 12 | C1 showed no impact on CCA cell line growth in CVSA after 24 h of incubation. CVSA has been performed to test the inhibitory capacity of C1 alone or in combination with sorafenib 24 h post-incubation. Carriers (DMEM for C1, NaCl for gemcitabine) were used as negative controls. Gemcitabine was applied at different concentrations increasing from 0.025, 0.05, 0.1 to 50 µM (human plasma concentration (Fujiwara et al., 2015)), which was applied as a positive control.

Supplementary Figure 13 | C1 shows no impact on CCA cell line growth in CVSA after 48 h of incubation. CVSA has been performed to test the inhibitory capacity of C1 alone or in combination with sorafenib 48 h post-incubation as described in **Supplementary Figure 12**.

Supplementary Figure 14 | C1 possessed inhibitory capacity towards CCA cell line as confirmed by CVSA analysis using ImageJ. Cell viability analysis performed **(A)** 24 h and **(B)** 48 h post-incubation. Values represent mean ± SEM. Significance levels were depicted as: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ and $****p < 0.0001$. Detailed *P* values for all groups are displayed in **Supplementary Table 4**.

Supplementary Figure 15 | C2 possessed inhibitory capacity towards CCA cell line as confirmed by CVSA analysis using ImageJ. Cell viability analysis performed **(A)** 24 h and **(B)** 48 h post-incubation. Values represent mean ± SEM. Significance levels were depicted as: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ and $****p < 0.0001$. Detailed *P* values for all groups are displayed in **Supplementary Table 4**.

Supplementary Figure 16 | C3 possessed inhibitory capacity towards CCA cell line as confirmed by CVSA analysis using ImageJ. Cell viability analysis performed **(A)** 24 h and **(B)** 48 h post-incubation. Values represent mean ± SEM. Significance levels were depicted as: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ and $****p < 0.0001$. Detailed *P* values for all groups are displayed in **Supplementary Table 4**.

Supplementary Figure 17 | C1 and C3 induced a stronger cellular senescence response than gemcitabine as detected by SA-β-Gal assay and FACS analysis. **(A)** SA-β-gal assay was performed to detect senescent cells in C1-treated CCA cells 48 h post-incubation. **(B)** Gating strategy to detect $C_{12}FDG^{+}$ senescent, early and late apoptotic, and necroptotic cells. Cells were gated using forward- and side scatter characteristics and duplicates were omitted. Thereafter $C_{12}FDG^{+}$ (FDG^{+}) senescent cells were detected and three different populations based on 7-AAD and Annexin V-PE staining were detected among FDG^{-} cells. **(C-D)** Detection of FDG^{+} senescent CCA cells treated with **(C)** C1, **(D)** C2 and **(E)** C3. The grey line represents the values for the control group DMEM.

Supplementary Figure 18 | C1 induced mostly necroptosis and late apoptosis in CCA cells as shown by FACS analysis. FACS analysis to detect **(A)** early, **(B)** late apoptosis and **(C)** necroptosis was performed and shown as frequencies in percent. The grey line represents the values for the DMEM control group.

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