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SUPPORTING INFORMATION

Terpenoids from the medicinal mushroom *Antrodia camphorata*: Chemistry and medicinal potential

Yi Kuang, Bin Li, Zilong Wang, Xue Qiao*, Min Ye*

[a] State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, 38 Xueyuan Road, Beijing 100191, China

* Corresponding authors. Fax: (+86)-10-8280-2024; Tel: (+86)-10-8280-1516; e-mail: qiaoxue@bjmu.edu.cn (X. Qiao) or yemin@bjmu.edu.cn (M. Ye).

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Table S1 Clinical trials of *A. camphorata* and antroquinonol

NCT Number	Study Title	Status	Interventions	Conditions	Phase	Population	Start
NCT01007656	A multiple-dose research study on safety evaluation of the GD *Antrodia camphorata* in 30 healthy adult subjects	Completed	Dietary supplement: GD *Antrodia camphorata*	Healthy	Not applicable	31, 20 to 40 years old	2009
NCT01287286	Cancers treated with combination of *Antrodia cinnamomea* and chemotherapy	Unknown status	Dietary supplement: AC-Can	Neoplasm; Functional gastrointestinal disorder	Phase 2/3	64, 18 to 80 years old	2010
NCT02532699	Anti-hypertensive effect of mycelia of *Antrodia cinnamomea*	Completed	Dietary supplement: AC mycelia	Hypertension	Not applicable	41, 20 to 80 years old	2011
NCT02347228	Evaluate safety, tolerability, pk, preliminary clinical activity of OB318 in patients with advanced solid malignancies	Unknown status	Drug: OB318 capsule	Advanced solid malignancies	Phase 1	20, 20 years and older	2017
NCT01134016	Determine MTD and to evaluate pk, safety/tolerability and efficacy profiles of hocena® in NSCLC subjects	Completed	Antroquinonol	Non-small cell lung cancer	Phase 1	13, 20 Years and older	2010
NCT02047344	Efficacy, safety and pharmacokinetics study of antroquinonol to treat NSCLC	Completed	Antroquinonol	Non-small cell lung cancer stage IV	Phase 2	31, 18 years and older	2013
NCT02719028	Trial of antroquinonol in patients with hypercholesterolemia and hyperlipidemia	Completed	Antroquinonol	Hyperlipidemias	Phase 2	120, 30 to 75 years old	2016
NCT03310632	Determine function of antroquinonol in combination with SOC in first line metastatic pancreatic cancer	Recruiting	Antroquinonol	Pancreatic neoplasm	Phase 1/2	52, 18 years and older	2017
NCT03622463	A trial of antroquinonol in patients with atopic dermatitis	Completed	Antroquinonol	Atopic dermatitis	Phase 2	14, 20 to 65 years old	2018
NCT03625102	A randomized, double-blind trial of antroquinonol in patients with chronic hepatitis B	Recruiting	Antroquinonol	HBV	Phase 2	60, 20 to 75 years old	2018
NCT04112147	A randomized, placebo-controlled trial of antroquinonol in patients with chronic hepatitis B	Recruiting	Antroquinonol capsule 100mg, 200 mg	Chronic hepatitis B	Phase 2	60, 20 to 75 years old	2018
NCT04110873	A phase II, placebo-controlled trial evaluating the efficacy of antroquinonol in patients with atopic dermatitis	Terminated	Antroquinonol capsule 50mg, 100 mg	Atopic dermatitis	Phase 2	14, 20 to 65 years old	2018
NCT03823352	Evaluate efficacy and safety/tolerability profiles of antroquinonol in acute myeloid leukemia (AML) adult patients	Recruiting	Antroquinonol	Leukemia, myeloid, acute	Phase 2	12, 18 to 70 years old	2019

Clinical trial information is from https://clinicaltrials.gov.

Table S2 Sesquiterpenoids, diterpenoids, and steroids **130-162** from *Antrodia camphorata*

No.	Compounds	Formula	MW	Source	References
130	Antrocin	$C_{15}H_{22}O_2$	234	F	1
131	1-Naphthalenecarboxaldehyde, 3,4,4*α*,5,6,7,8,8*α*-octa-hydro-2-(hydroxymethyl) -5,5,8*α*- trimethyl	$C_{15}H_{24}O_2$	236	F&M	2
132	Nerolidol	$C_{15}H_{26}O$	222	F&M	2
133	Cadinol	$C_{15}H_{26}O$	222	F&M	2
134	19-Hydroxylabda-8(17)-en-16,15-olide	$C_{20}H_{32}O_3$	320	F	3
135	3*β*,19-Dihydroxy-labda-8(17),11*E*-dien-16,15-olide	$C_{20}H_{30}O_4$	334	F	3
136	13-*epi*-3*β*,19-Dihydroxy-labda-8(17),11*E*-dien-16,15-olide	$C_{20}H_{30}O_4$	334	F	3
137	19-Hydroxy-labda-8(17),13-dien-16,15-olide	$C_{20}H_{30}O_3$	318	F	3
138	14-Deoxy-11,12-didehydroandrographolide	$C_{20}H_{28}O_4$	332	F	3
139	14-Deoxyandrographolide	$C_{20}H_{30}O_4$	334	F	3
140	Pinusolidic acid	$C_{20}H_{28}O_4$	332	F	3
141	Ergosterol	$C_{28}H_{44}O$	396	F, M & B	4
142	*β*-Sitosterol	$C_{29}H_{50}O$	414	F	5
143	Ergosta-4,6,8(14),22-tetra-en-3-one	$C_{28}H_{40}O$	392	F	6
144	*β*-Sitostenone	$C_{29}H_{48}O$	412	F	6
145	Stigmasterol	$C_{29}H_{48}O$	412	F	6
146	*epi*-Friedelinol	$C_{30}H_{52}O$	428	F	6
147	Ergosterol peroxide	$C_{28}H_{44}O_3$	428	B	7
148	Ergostatrien-3β-ol (antrosterol)	$C_{28}H_{44}O$	396	B	7
149	Camphoratin I	$C_{28}H_{44}O_2$	412	F	8
150	Ergosterol D	$C_{29}H_{46}O$	410	F	8
151	Cerevisterol	$C_{28}H_{46}O_3$	430	M	9
152	(14*α*,22*E*)-14-Hydroxyergosta-7,22-diene-3,6-dione	$C_{28}H_{42}O_3$	426	F&M	10
153	Camphosterol A	$C_{21}H_{32}O_3$	332	F&M	10
154	Citreoanthrasteroid B	$C_{28}H_{40}O$	392	F&M	11
155	1(10→6)*abeo*-Ergosta-5,7,9,22-tetraen-3α-ol	$C_{28}H_{42}O$	394	F&M	11
156	Dankasterone A	$C_{28}H_{42}O_3$	426	F&M	11
157	Dankasterone B	$C_{28}H_{40}O_3$	424	F&M	11
158	Herbarulide	$C_{28}H_{40}O_3$	424	F&M	2
159	Ergosta-7,22-diene-3,6-dione	$C_{28}H_{44}O_2$	412	F&M	2
160	Calvasterol B	$C_{28}H_{40}O_4$	440	D	12
161	Dankasterone A	$C_{27}H_{38}O_3$	410	D	12
162	Antcamphin M	$C_{28}H_{44}O_2$	412	D	12

F, fruiting body; M, mycelium; B, culture broth; D, dish culture.

Note: Some of the steroids like **148** and **162** may be classified into triterpenoids in other publications, as they could be considered as ergostanes without a C-4 methyl group. The molecular formula for **162** in literature [12] was wrong ($C_{28}H_{46}O_2$), and should be corrected.

Table S3 Terpenoids biosynthetic genes from *A. camphorata*[13-17]

Gene	Function, expression pattern, or proposed function	Accession/contig name
AcCyp51	Lanosterol 14α-demethylase	EU149948
AcOSC	2,3-Oxidosqualene cyclase for lanosterol	KJ094413
pks63787	polyketide synthase / orsellinic acid synthase	KT460194
ac-1	specifically expressed in natural basidiomes, and clustered with CYP64 family	HM044136
ac-2	specifically expressed in natural basidiomes	HM044137
ac-3	probably be assigned as new CYP families; similar to ac-1	HM044138
ac-4		HM044139
ac-5	similar to ac-1	HM044140
ac-6	close to the CYP5150 family, probably participates in lignin modification or xenobiotic degradation	HM044141
ac-7	similar to ac-6	HM044142
ac-8	probably be assigned as new CYP families	HM044143
ac-9	a member of the CYP61 family. CYP61 is known to be a C-22 sterol desaturase that participates in the later ergosterol biosynthesis pathway	HM044144
ac-10	may be a member of the CYP63 family. CYP63 family genes show transcriptional induction with alkanes and their derivatives	HM044145
Ac-mvd	mevalonate pyrophosphate decarboxylase	KR364808
AcTPS1	generate one unknown terpenoid and δ-cadinol	M_Fcontig14619
AcTPS2	generate farnesol with FPP	M_Fcontig13346
AcTPS3	generate multiple monoterpene with GPP and EE α-farnesol with FPP	M_Fcontig26676
AcTPS4	generate multiple products when using GPP and FPP as substrate	M_Fcontig40411
AcTPS5	generate geraniol with GPP, T-cadinol and several minor sesquiterpenoid products with FPP as substrate	M_Fcontig40579
AcTPS6	generate linear terpenoid products	M_Fcontig28068
AcTPS7	generate linalool with GPP and nerolidol with FPP	M_Fcontig36944
AcTPS9	generate multiple products when using GPP and FPP as substrate	M_Fcontig47706
AcTPS10	generate mostly linear form terpenoids (geraniol and farnesol)	M_Fcontig62520
AcTPS11	generate geraniol when using GPP as substrate	M_Fcontig44443

Table S4 The antitumor activities of *A. camphorata* and its terpenoids

Drugs	Model	Efficacy	Mechanism	References
Methanol extract of dish cultured fruiting bodies	A small cell lung cancer patient	Surviving for 32 months without relapse (5 g/d up to 10 g/d for six months)	Through multiple signaling pathways: immunomodulatory, anti-angiogenic, anti-metastatic, anti-proliferative, and pro-apoptotic effects	18
Methanol extract	HepG2 and PLC/PRF/5 cells *in vitro*	IC_{50} 42.57 μg/mL, 47.1 μg/mL	Through induction of Fas/Fas ligand pathway and mitochondrial pathway, and inhibition of NF-κB signaling pathway	19
Ethanol extract	A549 cells *in vitro*; LLC cell xenografted male C57BL/6J mice	IC_{50} 170 μg/mL Inhibition of tumor size 30%, 58% (250, 500 mg/kg, p.o., for 2 weeks)	By suppressing the growth-promoting proteins, Akt, ERK1/2, cyclin D1, and cyclin E, and activating growth-suppressing proteins, p-AMPK, p21 and p27	20
Ethanol extract	T47D cells *in vitro*; T47D cell xenograft male Balb/c nude mice	IC_{50} 50 μg/mL; Inhibition of tumor size 73% (1 mg/kg, i.p., three times per week for 87 days)	Through cell cycle arrest and induction of autophagy mediated by ER stress and HDACs inhibition	21
Ethanol extract of fruiting bodies	T24 cells *in vitro*	Inhibition 61.56% (150 μg/mL)	By suppressing the expression of the active form of MMP-9	22
Ethanol extract of fruiting bodies	T47D cells *in vitro*; T47D cell xenograft female BALB/c nude mice	IC_{50} 52.7-141.9 μg/mL for different extracts; Tumor inhibition 89%, 81%, 90% (50 mg/kg, p.o., pretreated for 7 days before xenograft; 50, 100 mg/kg, p.o., every other day for 28 days)	Through modulation of protein expression of cell-cycle mediators, actin dynamics mediators, E-cadherin and β-catenin	23
Ethanol extract of fruiting bodies	WEHI-3 cells *in vitro*; WEHI-3 cell xenografted BALB/c mice	IC_{50} 15 μg/mL Inhibition of tumor size 30%, 52% (0.45, 0.9 g/kg, p.o., for 2 weeks)	Through reducing p-ERK1/2, p-Akt and MMP-9 and upregulating p21 and p27	24
Ethanol extract of fruiting bodies	CL1-0 cells *in vitro*	IC_{50} 16 μg/mL	Through the MAPK and PI3K/AKT signaling pathways	25
Ethanol extract of fruiting bodies	HCT116, HT29, SW480, Caco-2 and, Colo205 cells *in vitro*	IC_{50} 33.21-98.53 μg/mL	Through the CHOP/TRB3/Akt/mTOR pathway	26
Ethanol extract and ethyl acetate extract of fruiting bodies	BxPC-3 cells *in vitro*	IC_{50} 2.49 μg/mL, 2.36 μg/mL	By inhibiting migration and inducing mitochondria-mediated apoptosis	27
Methanol extract of mycelia	HL60 cells *in vitro*	Inhibition >90% (100 μg/mL for 72 h)	Through activating the ERK/CEBP-β signaling pathway	28
Water extract of fermented	MCF-7 cells *in vitro*	Inhibition >80% (150 μg/mL)	Through induction of apoptosis, by cytochrome C	29

culture broth			translocation, caspase 3 activation, PARP degradation, and dysregulation of Bcl-2 and Bax	
The lyophilized broth from a fermented culture	HL-60 cells *in vitro*; HL-60 cell xenograft BALB/*c-nu* mice	IC_{50} 50.1 μg/mL; Inhibition of tumor size 57%, 96% (80, 120 mg/kg, i.p., for 3 weeks)	Through inducing G1 cell cycle arrest and apoptosis, by reducing cyclin D1, CDK4, cyclin E, CDK2, cyclin A, and p-Rb	30
Antrocin (**130**)	MDA-MB-231 cells *in vitro*	IC_{50} 0.6 μM	As an Akt/mTOR dual inhibitor	31
Antrocin (**130**)	H441 and H1975 cells *in vitro*; H441-L2G cell xenograft female NOD/SCID mice	IC_{50} 0.75 μM, 0.83 μM; Survival rate increased from 20% to 100% (5 and 10 mg/kg, i.p., for 4 weeks)	Through constitutive inhibition of JAK2/STAT3 pathway	32
Antrocin (**130**)	5637 and T24 cells *in vitro*	IC_{50} 78.4, 48.1 μg/mL	Through FAK-paxillin and ERK-c-Fos-MMP2 signaling pathways, upregulating Bax, Fas, and DR5	33
Antrocin (**130**)	MCF7 and MDA-MB-231 cells *in vitro*; MDA-MB-231 cell xenograft female NOD/SCID mice	IC_{50} ~100 μM; Inhibition of tumor size ~50% (30 mg/kg, i.p., 5 times/ week for 5 weeks)	Through downregulation of β-catenin/Notch1/Akt signaling	34
Antroquinonol (**104**)	HepG2, HepG2.2.15, Mahlavu, PLC/PRF/5, SK-Hep1 cells *in vitro*	IC_{50} 0.22-10.07 μM	Through activating AMPK pathway and inhibiting mTOR translational pathway, leading to G1 cell-cycle arrest and cell apoptosis	35
Antroquinonol (**104**)	HCT15 and LoVo cells *in vitro*	IC_{50} 34.8 μM, 17.9 μM	Through PI3K/AKT/β-catenin signaling	36
Antroquinonol (**104**)	A549 and PC-3 cells *in vitro*	IC_{50} 5.7 μM, 13.5 μM		37
Antroquinonol V, W (**122**,**123**)	A549 cells *in vitro*	IC_{50} 8.2 μM, 7.1 μM		37
Antroquinonol D (**108**)	MCF7, T47D, MDA-MB-231 cells *in vitro*	IC_{50} 8.01, 3.57, 25.08 μM	By inducing DNA demethylation and inhibiting cell growth and migration potential	38
4-Acetylantroquinonol B (**106**)	HepG2 cells *in vitro*	IC_{50} 0.1 μg/mL	Via affecting p53, p21 and p27 proteins	39
4-Acetylantroquinonol B (**106**)	DLD-1, HCT-116, SW480, RKO and HT-29 cells *in vitro*; DLD1 xenograft nude mice	IC_{50} 11.3-39.2 μM; Tumor inhibition rate 50% (2.5 mg/kg, i.p., for 6 weeks)	Through oncogenic and stem cell maintenance signal pathways, regulating Lgr5/Wnt/β-catenin and JAK-STAT pathways	40
4-Acetylantroquinonol B (**106**)	HuH-7 and HepG2 cells *in vitro*; HepG2 and HuH-7 cell xenograft male NOD SCID mice	IC_{50} 0.57 μg/mL, 0.365 μg/mL Tumor inhibition rate, >50% (2 mg/kg, i.p., for 22 and 18 days)	By inducing cell cycle arrest and blocking the PI3K/Akt/mTOR and ERK pathways	41
4-Acetylantroquinonol B (**106**)	U87MG and DBTRG-05MG cells *in vitro*; U87MG cell xenograft female	IC_{50} 9.2μM, 12.5 μM; Tumor inhibition rate 46.9%, 36.2% (5 mg/kg, i.p. or p.o., thrice weekly for 4 weeks)	Through disruption of the β-Catenin/TCF-1/STAT3 signaling axis	42

	NOD/SCID mice			
Ergone (Ergosta-4,6,8(14),22-tetraen-3-one, **143**)	HNSCCs *in vitro*; HNSCCs xenografted NCR nude mice	Reduce cancer initiating cells subpopulation without cytotoxicity (20 μg/mL); Tumor inhibition >70% (20 mg/kg, i.p., on days 13, 15 and 20)	Through inducing differentiation and reducing tumorigenicity of cancer initiating cells	43
Dehydroeburicoic acid (**83**)	HL-60 cells *in vitro*; HL-60 cell xenograft female immunodeficient athymic mice	IC_{50} 3.39 μg/mL Tumor inhibition >50% (10 mg/kg, p.o., every other day for 5 weeks)	Through apoptotic and DNA damaging	44
Dehydroeburicoic acid (**83**)	U87MG cells *in vitro*	IC_{50} 25.7 μM	Through mitochondrial dysfunction and calpain activation	45
Antcin K (**18**/**19**)	Hep3B cells *in vitro*	Inhibiting Matrigel attaching without cytotoxicity (10 μM)	Through suppression of integrin-mediated adhesion, migration and invasion	46
Antcin B (**3**/**4**)	HepG2, Hep3B, and Huh7 cells *in vitro*	IC_{50} 39.4, 50.6, 45.3 μM	By inducing the NADPH oxidase-provoked oxidative stress and apoptosis	47
Methyl antcinate B (**21**)	HepG2, Hep3B, and Huh7 cells *in vitro*	IC_{50} 25.8, 70.3, 29.8 μM	By inducing the NADPH oxidase-provoked oxidative stress and apoptosis	47
Antcin H (**14**/**15**)	Epstein-Barr virus-infected Raji and LCL cells *in vitro*; Raji cell xenograft NOD-SCID mice	IC_{50} 19.25 μM, 9.37 μM; Tumor inhibition >40% (20 mg/kg, intratumorally, every 2 days for 24 days)	As a pan-JAK inhibitor	48
Antcin H (**14**/**15**)	786-0 cells *in vitro*	IC_{50} 170 μM	Through inactivation of FAK-ERK-C/EBP-β/c-Fos-MMP-7 pathways	49
Methyl antcinate A (**20**)	Huh7, HepG2, and Hep3B cells *in vitro*	IC_{50} 52.2, 78.0, and 30.2 μM	Through activation of the ROS-dependent cofilin- and Bax-triggered mitochondrial pathway	50
Antcin B (**3**/**4**), antcin H (**14**/**15**), methyl antcinate B (**21**)	HT-29, HCT-116, SW-480, Huh7, HepG2, Hep3B, MDA-MB-231, MCF-7 cells *in vitro*	IC_{50} 22.3-75.0 μM	Through the cleavage of poly(ADP-ribose) polymerase, pro-caspase-3 and Bcl-2	51

Note: Human liver cancer cell lines HepG2, Hep3B, PLC/PRF/5, SK-Hep1, Mahlavu, HuH-7; human lung cancer cell lines A549, H1975, H441, CL1-0; murine Lewis lung carcinoma cell line LLC1; human bladder cancer cell lines T24 and 5637; human breast cancer cell line MCF-7, MDA-MB-231, T47D; human ovarian cancer lines SKOV-3 and A2780; human pancreatic cancer cell line BxPC-3; human promyelocytic leukemia cell line HL60; murine leukemia cell line WEHI-3; human primary B lymphocytes, Raji and LCL; human colon cancer cell lines HCT15, LoVo, DLD-1, HCT-116, SW480, RKO, HT-29, COLO-205, Caco-2; head and neck squamous cell carcinoma cell line HNSCCs; human glioblastoma cell lines U87MG, DBTRG-05MG; human renal carcinoma cell line 786-0.

Table S5 The hepatoprotective activities of *A. camphorata* and its terpenoids

Drugs	Model	Dose	References
Mycelia and fruiting bodies	Alcohol-induced acute liver damage in SD rats	0.5-1 g/kg, p.o., for 9 days	52
Water extract	CCl_4-induced chronic liver damage in ICR mice	250-1250 mg/kg, p.o., for 8 weeks	53
Methanol extract of fruiting bodies	Alcohol-induced acute liver damage in Kunming mice	0.3-1.2 g/kg, p.o., for 30 days	54
Ethanol extract of fruiting bodies	Chronic consumption of alcohol induced fatty liver in Wistar rats	0.025-0.1 g/kg, p.o., for 4 weeks	55
Ethanol extract of fruiting bodies	High-fat-diet induced hepatic steatosis in C57 mice	3 mg/kg, p.o., for 36 weeks	56
Ethanol extract of fruiting bodies	Irradiation-induced hepatitis in BNL/Luc cell xenografted Balb/c mice	20-100 μg/mouse, p.o., for 20 days	57
Water extract of fruiting bodies	Chronic consumption of alcohol induced liver fibrosis in Wistar rats	0.025 g/kg, p.o., for 4 weeks	58
Ethanol extract of mycelia	Alcohol-induced acute liver damage in ICR mice	250-1000 mg/kg, p.o., for 10 days	59
Ethanol extract of fermented culture broth	Alcohol-induced acute liver damage in SD rats	0.5-1.0 g/kg, p.o., for 10 days	60
Water extract of fermented culture broth	Alcohol-induced cytotoxicity on AML12 hepatocytes	500 μg/mL	61
Water extract of fermented culture broth	Alcohol-induced acute liver damage in SD rats	0.5-1.0 g/kg, p.o., for 10 days	62
Lyophilized fermented culture broth	CCl_4-induced acute liver damage in SD rats	250-500 mg/kg, p.o., for 5 days	63
Lyophilized fermented culture broth	Alcohol-induced acute liver injury in mice	75-675 mg/kg, p.o., for 2 weeks	64
Fermented culture	CCl_4-induced chronic liver fibrosis in Wistar rats	0.5-1.0 g/kg, p.o., for 3 weeks	65
Fermentation of AC in deep ocean water	TAA-induced liver damage and fibrosis in SD rats	126.44 mg/kg, p.o., for 8 weeks	66
Wheat-based solid-state fermented AC	CCl_4-induced chronic liver damage in SD rats	180, 540, 1080 mg/kg, p.o., for 8 weeks	67
Antroquinonol (**104**)	Alcohol-induced acute liver damage in ICR mice	5, 10, 20 μM, for 24 h	59
Antcin B (**3/4**)	Concanavalin A-induced hepatitis in BALB/c mice	5-20 mg/kg, i.p., 1 hour before, once	68
Antcin B (**3/4**)	CCl_4-induced acute liver damage in ICR mice	10, 50 mg/kg, p.o., for 7 days	69

Antcin K (**18/19**)	CCl_4-induced acute liver damage in ICR mice	10, 50 mg/kg, p.o., for 7 days	69
Antcin C (**5/6**)	AAPH induced HepG2 cell injury	5-200 μM, for 24 h	70
Antcin H (**14/15**)	APAP and galactosamine/TNF-α induced acute liver damage in Male C57BL/6NHsd mice	25, 50 mg/kg, i.p., once	71
Eburicoic acid (**77**)	CCl_4-induced acute liver damage in ICR mice	5, 10, 20 mg/kg, i.p., for 7 days	72
Dehydroeburicoic acid (**83**)	CCl_4-induced acute liver damage in ICR mice	5, 10, 20 mg/kg, i.p., for 7 days	72
Antrosterol (Ergostatrien-3*β*-ol, **148**)	CCl_4-induced acute liver damage in ICR mice	2.5, 5, 10 mg/kg, i.p., for 7 days	73
Antrosterol (Ergostatrien-3*β*-ol, **148**)	Chronic-alcohol induced liver damage in male C57BL/6J (*B6*) mice	1, 5, 10 mg/kg, p.o., for 4 weeks	74

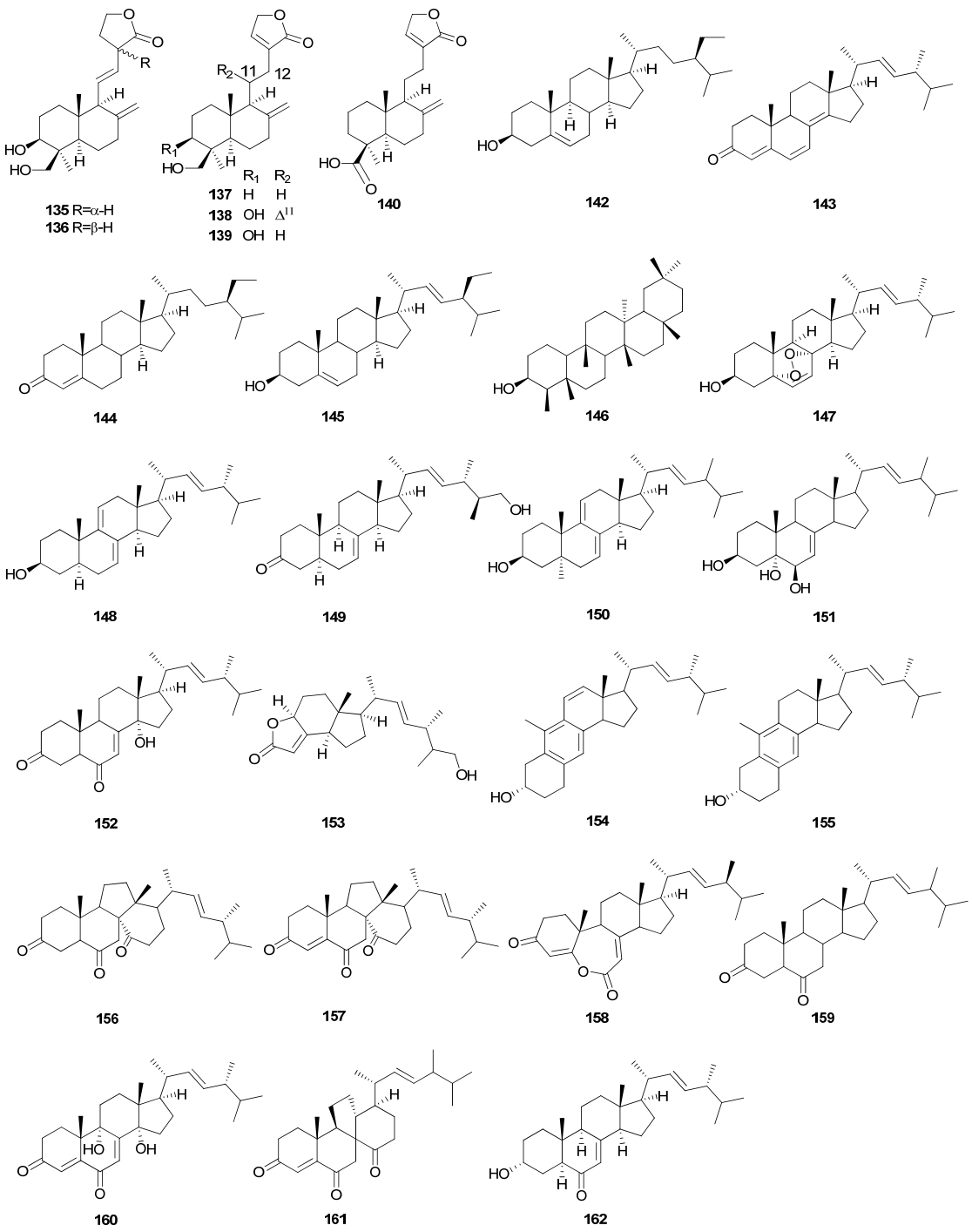

Fig. S1. Structures of diterpenoids and steroids **135-162**.

Note: The structures for **135** and **136** may be interchangeable. The literature did not fully determine the stereo-configuration.[3]

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