Progress in anticancer chemical constituents and pharmacological research of *Carpesium cernuum* L. (Review)

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Abstract. The present study aimed to systematically review the anticancer chemical constituents, pharmacological effects, and molecular targets of *Carpesium cernuum* L., clarify the molecular network of its anticancer mechanisms, summarize the research achievements and limitations and provide a scientific reference for its development and utilization, the research and development of novel anticancer drugs, and clinical applications. Through literature collation and experimental data integration, the chemical constituents of *C. cernuum* were classified and identified, and with the aid of *in vitro* cell experiments, partial *in vivo* animal experiments and molecular biology techniques, the anticancer effects of its extracts and active constituents as well as the key signaling pathways were investigated. Notably, all included evidence was strictly stratified by research type (crude extract/fraction/isolated monomer, *in vitro* cell model/*in vivo* animal model/network pharmacology prediction) to clarify the evidence level of each anticancer claim. A total of 109 compounds were isolated and identified from *C. cernuum*, among which 60 sesquiterpenoids were the major components. Its active constituents exhibited promising inhibitory effects in preclinical studies against multiple cancers including prostate cancer, pancreatic cancer, leukemia and breast cancer. Existing anticancer evidence was predominantly derived from *in vitro* cell-based assays, with a small number of *in vivo* animal validations and preliminary network pharmacology predictions; high-level clinical evidence is still vacant. By regulating signaling pathways such as phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR and Hippo, they exert multi-dimensional anticancer effects, including cell proliferation inhibition, apoptosis induction, and metastasis suppression. *In vitro* and partial *in vivo* preclinical evidence indicates that the active ingredients of *C. cernuum* exert potential inhibitory effects against various tumors such as prostate cancer and pancreatic cancer. By targeting key signaling pathways including PI3K/Akt/mTOR and Hippo, it achieves multi-modal anticancer effects such as proliferation inhibition and apoptosis induction, showing favorable preliminary biocompatibility in existing preclinical experiments. However, the current research has limitations including insufficient *in vivo* verification, uneven evidence quality, and lack of standardized dose-effect data, which restrict clinical transformation. Collectively, *C. cernuum* and its bio-active metabolites display pre-clinical antitumor potential, yet further pharmacological validation and translational investigations are required to evaluate clinical applicability

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1. Introduction

Cancer, a major global public health issue, accounted for 18.5 million new cases and 10.4 million deaths worldwide in 2023. It is projected to increase to 30.5 million new cases and 18.6

million deaths by 2050, and its high morbidity and mortality pose a severe threat to human health (1). Clinical treatment of various malignant tumors such as prostate cancer and leukemia is still confronted with plights including recurrent drug resistance, significant side effects and poor prognosis. Thus, the search for novel anticancer drugs with low toxicity, high efficacy, and wide availability has become a research hotspot in the medical and pharmaceutical fields (2). Natural products, by virtue of their advantages including structural diversity, broad biological activities and low toxicity and side effects, serve as an important source for the development of anticancer drugs (3). Furthermore, ethnic medicines embody the medicinal wisdom accumulated through long-term clinical practice and provide valuable clues for the discovery of novel anticancer drugs.

Carpesium cernuum L. is a perennial herbaceous plant belonging to the genus *Carpesium* of the Asteraceae family. It is distributed in many regions worldwide and mainly grows in wastelands, hillsides and ditch banks in China, with abundant resource reserves. As a commonly used traditional ethnic medicine of the Miao nationality, the entire plant is used for medicinal purposes. It is bitter and pungent in taste and in TCM possesses multiple effects including inducing diaphoresis, clearing heat and detoxifying and dissipating blood stasis. It is often used for the treatment of stranguria, inflammation and other diseases (4). Its medicinal value has been officially included in the Quality Standards for Chinese Medicinal Materials and Ethnic Medicinal Materials of Guizhou Province, and it serves as an important medicinal ingredient in prepared Miao medicinal formulas (5). Furthermore, there are folk records of its application in treating sore pain, dysentery and other diseases. The long-term medicinal practice has laid a solid foundation for its modern pharmacological research.

Modern pharmacological studies have confirmed that extracts of *C. cernuum* possess broad biological activities, among which the antitumor activity is particularly prominent and has become a research focus in recent years (6). Previous studies have shown that extracts of *C. cernuum* exert significant inhibitory effects on various tumor cells, including multiple cancer types such as prostate cancer, leukemia, hepatocellular carcinoma and breast cancer. Their anticancer effects are mainly reflected in inhibiting tumor cell proliferation, arresting the cell cycle, inducing cell apoptosis and autophagy and suppressing tumor cell migration and invasion, among other aspects (7). Further studies have revealed that its anticancer effects are closely associated with the regulation of key signaling pathways such as phosphatidylinositol 3-kinase-protein kinase b-mammalian target of rapamycin (PI3K/Akt/mTOR) and Hippo. These signaling pathways play a central role in tumor initiation, progression, and metastasis, thereby providing an important direction for the in-depth exploration of the anticancer mechanisms of *C. cernuum* (8).

The present study systematically summarized the research progress on the anticancer chemical constituents, pharmacological effects, and action targets of *C. cernuum*, combines the molecular network of its anticancer mechanisms. The present study strictly stratified existing anticancer evidence by research object (crude extract/active fraction/monomeric compound) and research model (*in vitro* cell assay/*in vivo* animal experiment/network pharmacology prediction) and further evaluated the reliability and limitations of each type of evidence. It aimed to provide scientific references for the further development and utilization of *C. cernuum*, the development of novel anticancer drugs and its clinical application, thereby promoting the research on this traditional medicinal plant toward a deeper and broader application-oriented direction in the field of anticancer research.

2. Search method

A standardized and transparent literature retrieval and screening framework was adopted in this narrative review to guarantee the comprehensiveness, accuracy and reproducibility of the included evidence. The detailed methodological procedures are presented below. i) Literature databases and search period: Relevant published studies were collected from PubMed (hpubmed.ncbi.nlm.nih.gov/), ScienceDirect (sciencedirect.com), Web of Science (webofscience.com/wos), and China National Knowledge Infrastructure (CNKI, https://www.cnki.net/), with a publication time range from January 2000 to August 2025. ii) Search terms: Boolean search strings were constructed based on core keywords: ('*Carpesium cernuum*' OR '*Carpesium cernuum* L.') and ('chemical constituent' OR 'sesquiterpenoid' OR 'natural product') and ('anticancer' OR 'antitumor' OR 'cancer cell') and ('pharmacology' OR 'mechanism' OR 'signaling pathway'). Corresponding synonyms and variant spellings were additionally supplemented to achieve maximal literature coverage. iii) Inclusion criteria: Original research articles and eligible reviews focusing on the chemical isolation, structural identification, anticancer pharmacological activities and molecular mechanisms of *C. cernuum* were enrolled. Studies with explicitly defined compound structures, molecular formulas, molecular weights and reproducible anticancer experimental data were prioritized for data tabulation and mechanistic discussion. All included studies were categorized into four evidence levels: Level 1 (*in vivo* animal experiments), Level 2 (*in vitro* cell assays of isolated monomeric compounds), Level 3 (*in vitro* cell assays of crude extracts/fractions) and Level 4 (network pharmacology/bioinformatics prediction without experimental verification). iv) Exclusion criteria: Letters, conference abstracts, case reports, duplicate publications, non-Chinese and non-English studies, as well as literature with incomplete experimental data or ambiguous compound information were excluded. v) Literature screening and data extraction: All retrieved records were initially screened by titles and abstracts, followed by rigorous full-text evaluation. Screening and data extraction were independently completed by two authors, and any inconsistencies were resolved through group discussion or consultation with a third author. Furthermore, the reference lists of eligible publications were manually screened to identify and supplement potential missing studies. vi) Data standardization for tables: All compound-related information in Tables I-IV, including compound name, classification, molecular formula and molecular weight, was uniformly verified and revised in accordance with authoritative spectral data and standard nominal mass calculation criteria. This process eliminated formulaic and numerical errors, ensuring consistent and reliable data accuracy throughout the manuscript.

Table I. Sesquiterpenes compounds from *Carpesium cernuum* L.

First author/s, year	Number	Chemical compound	Type	Molecular formula	Molecular weight	Plant part	Extract/ fraction	Biological relevance (anticancer activity)	(Refs.)
Liu *et al*, 2016	1	Cernuumolide A	Germacranolide	$C_{25}H_{38}O_{10}$	498	Whole plant	95% EtOH extract, EtOAc-soluble fraction	No significant cytotoxicity against A549, HCT116, MDA-MB-231, BEL-7404 in this assay	(9)
Liu *et al*, 2016	2	Cernuumolide B	Germacranolide	$C_{26}H_{40}O_{10}$	512	Whole plant	95% EtOH extract, EtOAc-soluble fraction	No significant cytotoxicity against A549, HCT116, MDA-MB-231, BEL-7404 in this assay	(9)
Liu *et al*, 2016	3	Cernuumolide C	Germacranolide	$C_{26}H_{38}O_{10}$	510	Whole plant	95% EtOH extract, EtOAc-soluble fraction	No significant cytotoxicity against A549, HCT116, MDA-MB-231, BEL-7404 in this assay	(9)
Liu *et al*, 2016	4	Cernuumolide D	Germacranolide	$C_{26}H_{40}O_{10}$	512	Whole plant	95% EtOH extract, EtOAc-soluble fraction	No significant cytotoxicity against A549, HCT116, MDA-MB-231, BEL-7404 in this assay	(9)
Liu *et al*, 2016	5	Cernuumolide E	Germacranolide	$C_{19}H_{28}O_{8}$	384	Whole plant	95% EtOH extract, EtOAc-soluble fraction	No significant cytotoxicity against A549, HCT116, MDA-MB-231, BEL-7404 in this assay	(9)
Liu *et al*, 2016	6	Cernuumolide F	Germacranolide	$C_{20}H_{28}O_{8}$	396	Whole plant	95% EtOH extract, EtOAc-soluble fraction	No significant cytotoxicity against A549, HCT116, MDA-MB-231, BEL-7404 in this assay	(9)
Liu *et al*, 2016	7	Cernuumolide G	Germacranolide	$C_{20}H_{28}O_{8}$	396	Whole plant	95% EtOH extract, EtOAc-soluble fraction	No significant cytotoxicity against A549, HCT116, MDA-MB-231, BEL-7404 in this assay	(9)
Liu *et al*, 2016	8	Cernuumolide H	Germacranolide	$C_{24}H_{34}O_{9}$	466	Whole plant	95% EtOH extract, EtOAc-soluble fraction	Moderate cytotoxicity toward A549, HCT116, MDA-MB-231, BEL-7404, IC_{50} values ranging from 0.87 μM to 2.02 μM	(9)
Liu *et al*, 2016	9	Cernuumolide I	Germacranolide	$C_{23}H_{34}O_{8}$	438	Whole plant	95% EtOH extract, EtOAc-soluble fraction	No significant cytotoxicity against A549, HCT116, MDA-MB-231, BEL-7404 in this assay	(9)
Liu *et al*, 2016	10	Cernuumolide J	Germacranolide	$C_{24}H_{34}O_{8}$	450	Whole plant	95% EtOH extract, EtOAc-soluble fraction	No significant cytotoxicity against A549, HCT116, MDA-MB-231, BEL-7404 in this assay	(9)

Table I. Continued.

First author/s, year	Number	Chemical compound	Type	Molecular formula	Molecular weight	Plant part	Extract/ fraction	Biological relevance (anticancer activity)	(Refs.)
Liu *et al*, 2016	11	(2*S*,4*S*,5*R*,6*S*, 8*R*,9*R*)-5,8-diangeloyloxy-4,9-dihydroxy-2,9-epoxygermacran-6,12-olide	Germacranolide	$C_{25}H_{34}O_9$	478	Whole plant	95% EtOH extract, EtOAc-soluble fraction	No significant cytotoxicity against A549, HCT116, MDA-MB-231, BEL-7404 in this assay	(9)
Liu *et al*, 2016	12	(2*R*,4*S*,5*R*,6*S*, 8*R*,9*S*,2'*S*)-8-angeloyloxy-4,9-dihydroxy-2,9-epoxy-5-(2-methylbutanoyloxy)germacran-6,12-olide	Germacranolide	$C_{25}H_{36}O_9$	480	Whole plant	95% EtOH extract, EtOAc-soluble fraction	No significant cytotoxicity against A549, HCT116, MDA-MB-231, BEL-7404 in this assay	(9)
Liu *et al*, 2016	13	(2*R**,4*S**,5*R**, 6*S**,8*R**,9*S**)-8-angeloyloxy-4,9-dihydroxy-2,9-epoxy-5-(2-methylpropanoyloxy) germacran-6,12-olide	Germacranolide	$C_{24}H_{34}O_9$	466	Whole plant	95% EtOH extract, EtOAc-soluble fraction	No significant cytotoxicity against A549, HCT116, MDA-MB-231, BEL-7404 in this assay	(9)
Yan *et al*, 2021	14	(4*R**,5*R**,6*S**, 8*R**,9*R**)-5-angeloyloxy-4,8-dihydroxy-9-(2-methylpropanoyloxy)-3-oxogermacran-6,12-olide	Germacranolide	$C_{24}H_{34}O_9$	466	Whole plant	95% EtOH extract, EtOAc-soluble fraction	Displayed moderate *in vitro* cytotoxicity against HEL, KG-1a and K562 human leukemia cell lines with reported IC_{50} values. It could trigger apoptosis in leukemia cells. No *in vivo* experiments were performed, and no cytotoxic evaluation on breast cancer or other solid tumor cell lines was described in this paper.	(58)

Table I. Continued.

First author/s, year	Number	Chemical compound	Type	Molecular formula	Molecular weight	Plant part	Extract/ fraction	Biological relevance (anticancer activity)	(Refs.)
Dong, 2024	15	4β-8α-dihydroxy-5β-isobutyryloxy-9β-3-methylbutyryloxy-3-oxo-germacran-7β, 12α-olide	Germacranolide	$C_{24}H_{36}O_9$	468	Whole plant	Plant crude extract	Antitumor/cytotoxic activity against multiple human tumor cell lines; antibacterial activity against bacteria and phytopathogenic fungi; anti-inflammatory activity via suppressing inflammatory mediators and related signalling pathways; anti-HSV-1 antiviral activity; anti-plasmodial (antimalarial) activity against Plasmodium falciparum D10 strain.	(10)
Yan *et al*, 2018	16	Carpescernolide A	Germacranolide	$C_{16}H_{22}O_6$	310	Whole plant	95% EtOH extract, EtOAc-soluble fraction	Exhibited moderate *in-vitro* cytotoxic activity against SMMC-7721 human hepatocellular carcinoma cells. No cytotoxic assessment on breast cancer, leukemia and other solid tumour cell lines; no *in vivo* animal experiments were performed in this paper.	(11)
Yan *et al*, 2018	17	Carpescernolide B	Germacranolide	$C_{20}H_{26}O_7$	378	Whole plant	95% EtOH extract, EtOAc-soluble fraction	No anticancer bio assay data publicly available in published literature	(11)
Baruah *et al*, 1980	18	ineupatolide	Germacranolide	$C_{25}H_{36}O_9$	480	Aerial parts	Ethanol extract, chloroform-soluble fraction	No anticancer bio-assay was performed in this original isolation paper	(12)
Yan *et al*, 2021	19	Carpescernolide C	Germacranolide	$C_{19}H_{26}O_7$	366	Whole plant	95% EtOH extract, EtOAc-soluble fraction	Moderate cytotoxicity against human leukemia HEL, KG-1a and K562 cells, IC_{50} ranging from 1.59-5.47 μmol·l^{-1}	(13)
Yan *et al*, 2021	20	Carpescernolide D	Germacranolide	$C_{20}H_{28}O_7$	380	Whole plant	95% EtOH extract, EtOAc-soluble fraction	Moderate cytotoxicity against human leukemia HEL, KG-1a and K562 cells, IC_{50} ranging from 1.59-5.47 μmol·l^{-1}	(13)

Table I. Continued.

First author/s, year	Number	Chemical compound	Type	Molecular formula	Molecular weight	Plant part	Extract/ fraction	Biological relevance (anticancer activity)	(Refs.)
Yan *et al*, 2021	21	Carpescernolide E	Germacranolide	$C_{23}H_{34}O_8$	438	Whole plant	95% EtOH extract, EtOAc-soluble fraction	Moderate cytotoxicity against human leukemia HEL, KG-1a and K562 cells, IC_{50} ranging from 1.59-5.47 $\mu mol \cdot l^{-1}$	(13)
Wu *et al*, 2017	22	Ineupatolide E	Germacranolide	$C_{20}H_{26}O_7$	378	Whole plant	95% ethanol extract, petroleum ether fraction	Showed moderate *in vitro* cytotoxicity against A431, A549, BGC-823, HL-60, HT-29 and MCF-7 human tumour cell lines, with IC_{50} values provided.	(14)
Kłeczek *et al*, 2021; Maruyama *et al*, 1990	23	Divaricin B	Germacranolide	$C_{24}H_{34}O_9$	466	Aerial parts	Ethanol extract, chloroform-soluble fraction	Exhibited *in vitro* cytotoxicity against DU145 and PC3 human prostate cancer cells and A375 melanoma cells. It also exerted anti-inflammatory activity by suppressing LPS-induced release of proinflammatory cytokines (IL-1β, IL-8, TNF-α, CCL2) in human neutrophils. No *in vivo* animal experiments were performed	(15, 59)
Cheng *et al*, 2013	24	4*E*-9*β*-hydroxy-7*α*,10*α*H-germacra-4,11(13)-dien-12,6*α*-olide	Germacranolide	$C_{15}H_{22}O_3$	250	Whole plant	95% ethanol extract; EtOAc-soluble fraction	It exhibited moderate inhibitory activity against LPS-induced NO production in RAW 264.7 macrophages (anti-inflammatory assay)	(16)
Zhang *et al*, 2016	25	Incaspitolide A	Germacranolide	$C_{23}H_{34}O_8$	438	Whole plant	95% ethanol extract, petroleum ether fraction	Showed *in vitro* cytotoxicity against HeLa, SMMC-7721 and MCF-7 cancer cells with IC_{50} values reported in the paper. No *in vivo* animal experiments were performed.	(17)
Mossa *et al*, 1997	26	4α,5α-epoxy-10α,14H-1-epi-inuviscolide	Guaianolide	$C_{15}H_{20}O_3$	248	Aerial parts	CH_2Cl_2 extract	N/A	(18)

Table I. Continued.

First author/s, year	Number	Chemical compound	Type	Molecular formula	Molecular weight	Plant part	Extract/ fraction	Biological relevance (anticancer activity)	(Refs.)
Mossa *et al*, 1997	27	1-epi-inuviscolide	Guaianolide	$C_{15}H_{20}O_3$	248	Aerial parts	Dichloromethane extract	N/A	(18)
Liu *et al*, 2010	28	4β,10β-dihydroxy-1αH,5αH-guai-11 (13)-en-12,8α-olide	Guaianolide	$C_{15}H_{22}O_4$	266	Whole plant	95% ethanol extract; EtOAc-soluble fraction	N/A	(56)
Dong, 2024	29	4α,10α-dihydroxy-1βH,5βH-guaian-11(13)-en-12,8α-olide	Guaianolide	$C_{15}H_{22}O_4$	266	Whole plant	Plant crude extract	Antibacterial activity against bacterial strains and phytopathogenic fungi; cytotoxic/antitumor potential against several human cancer cell lines; anti-inflammatory activity by inhibition of inflammatory mediators and related signaling pathways.	(10)
Li *et al*, 2011	30	4β,10β-dihydroxy-1αH,5αH,11αH-guaian-12,8β-olide	Guaianolide	$C_{15}H_{24}O_4$	268	Whole plant	95% ethanol extract; EtOAc-soluble fraction	This compound showed antiproliferative activity against MCF-7 human breast cancer cells in MTT assay. Some related sesquiterpene lactones could induce MCF-7 cell apoptosis.	(65)
Liu *et al*, 2010	31	6β-hydroxy-8α-ethoxyeremophil-7(11)-en-12,8β-olide	Eremophilane	$C_{17}H_{26}O_4$	294	Whole plant	95% ethanol extract;EtOAc-soluble fraction	N/A	(56)
Aguiar *et al*, 2010	32	caryolane-1,9β-diol	Tricyclododecane	$C_{15}H_{26}O_2$	238	Ripe fruit peel	Ethanol extract of ripe fruit peel	N/A	(61)
Perera *et al*, 2019	33	confertin	Pseudoguaiane	$C_{15}H_{20}O_3$	248	Twigs and leaves	Ethyl-acetate extract	Confertin showed phytotoxic activity inhibiting the growth of Lactuca sativa and Azolla stolonifera, and antifungal activity against plant-pathogenic fungi; no anticancer or *in vivo* assays were performed.	(60)

Table I. Continued.

First author/s, year	Number	Chemical compound	Type	Molecular formula	Molecular weight	Plant part	Extract/ fraction	Biological relevance (anticancer activity)	(Refs.)
Mossa *et al*, 1997	34	8-epi-confertin	Pseudoguaiane	$C_{15}H_{20}O_3$	248	Aerial parts	Dichloromethane extract	N/A	(18)
Gao *et al*, 2007	35	Ivalin	Eudesmanolide	$C_{15}H_{20}O_3$	248	Seeds	Chloroform extract	Ivalin exhibited significant *in-vitro* cytotoxic activity against HL-60 human leukemia cells; no *in-vivo* experiments were performed	(19)
Kulyyasov *et al*, 1996	36	Isoalantolactone	Eudesmanolide	$C_{15}H_{20}O_2$	232	N/A	N/A	N/A	(63)
Liu *et al*, 2014	37	4(15)-β-epoxyiso-telekin	Eudesmanolide	$C_{15}H_{20}O_2$	232	Whole plant	95% ethanol extract; EtOAc-soluble fraction	N/A	(64)
Kulyyasov *et al*, 1996	38	alantolactone	Eudesmanolide	$C_{15}H_{20}O_2$	232	N/A	N/A	N/A	(63)
Zhao *et al*, 2014	39	11(13)-dihydro alantolactone	Eudesmanolide	$C_{15}H_{22}O_2$	234	Roots	Ethanol extract	N/A	(62)
Yang *et al*, 2001	40	13-Hydroxy-5,7 (11)-eudesmadien-12,8-olide	Eudesmanolide	$C_{15}H_{20}O_3$	248	Roots	Mixed solvent EtOAc-MeOH-AcOH	N/A	(20)
Yang *et al*, 2002	41	2α-Hydroxy-eudesman-4(15)-en-12,8β-olide	Eudesmanolide	$C_{15}H_{22}O_3$	250	Aerial parts	EtOAc fraction of 70% ethanol extract	N/A	(21)
Lee *et al*, 2002	42	telekin	Eudesmanolide	$C_{15}H_{20}O_3$	248	Aerial parts	EtOAc-soluble fraction of 70% ethanol extract	Telekin exhibited potent *in-vitro* cytotoxic activity against multiple tumour cell lines (L1210, A549, SK-OV-3, SK-MEL-2, XF-498, HCT-15) with ED_{50} <10 μM, comparable to cisplatin; no *in vivo* experiments were performed	(50)
Wang *et al*, 2009	43	11(13)-dihydro-telekin	Eudesmanolide	$C_{15}H_{22}O_3$	250	Whole plant	EtOAc-soluble fraction of ethanol extract	N/A	(22)

Table I. Continued.

First author/s, year	Number	Chemical compound	Type	Molecular formula	Molecular weight	Plant part	Extract/ fraction	Biological relevance (anticancer activity)	(Refs.)
Yang *et al*, 2002	44	2α-hydroxy-5αH-eudesman-4(15), 11(13)-dien-8β, 12-olide	Eudesmanolide	$C_{15}H_{20}O_3$	248	Aerial parts	95% ethanol extract; EtOAc-soluble fraction	N/A	(21)
Yang *et al*, 2002	45	2α-O-β-D-gluco-pyranosyl-5α, 11αH-eudesma-4 (15)-en-12,8β-olide	Eudesmanolide	$C_{17}H_{24}O_5$	308	Aerial parts	95% ethanol extract; n-BuOH-soluble fraction	N/A	(51)
Yang *et al*, 2002	46	2α,5α-dihydroxy-11αH-eudesman-4(15)-en-12,8β-olide	Eudesmanolide	$C_{15}H_{22}O_4$	266	Seeds	95% ethanol extract; EtOAc-soluble fraction	It exhibited appreciable cytotoxic activity against SMMC-7721 human hepatoma cells in this study.	(23)
Holub *et al*, 1972	47	Carabrone	Carabranolide	$C_{15}H_{20}O_3$	248	Whole plant	Petroleum ether extract	N/A	(24)
Feng *et al*, 2012	48	Carabrol	Carabranolide	$C_{15}H_{22}O_3$	250	N/A	N/A	Carabrol showed moderate *in vitro* antifungal activity against Colletotrichum lagenarium using spore germination assay.	(52)
Cheng, 2020	49	4H-xanthalongia	Xantanolide	$C_{15}H_{20}O_3$	248	Flower buds	Volatile oil obtained by super-critical CO_2 extraction	N/A	(25)
Cheng, 2020	50	Xanthalongia	Xantanolide	$C_{15}H_{22}O_3$	250	Flower buds	Volatile oil obtained by super-critical CO_2 extraction	N/A	(25)
Chen *et al*, 2008	51	(3S,5*R*,6*S*,7*E*)-5,6-epoxy-3-hydroxy-7-mega-stigmene-9-one	Sesquiterpenes without lactone	$C_{15}H_{22}O_3$	250	Aerial parts	95% ethanol extract; purified by column chromatography.	This megastigmane was tested or *in vitro* cytotoxicity against fSGC-7901 (human gastric cancer) and HL-60 (human leukemia) cell lines.	(26)

Table I. Continued.

First author/s, year	Number	Chemical compound	Type	Molecular formula	Molecular weight	Plant part	Extract/ fraction	Biological relevance (anticancer activity)	(Refs.)
Häusler and Montag, 1989	52	S-(+)-dehydrovomifoliol	Sesquiterpenes without lactone	$C_{13}H_{18}O_3$	222	N/A	Extract of honey	N/A	(53)
Feng *et al*, 2023	53	2,9-epoxy-5,9-dihydroxy-8-angeloyloxy-11-methoxymethyl-4(15)-germacraen-6,12-lide	Germacraenlide	$C_{22}H_{30}O_7$	406	Whole plant	ethyl acetate fraction of ethanol extract	Assayed *in vitro* anti-leukemia activity against K562 and HEL human leukemia cell lines by MTT assay. This compound showed weak cytotoxic effect	(27)
Malarz *et al*, 2025	54	8α-angeloyloxy-4β-hydroxy-5β-(3-methylbutyryloxy)-9-oxo-germacran-6α,12-olide	Germacranolide	$C_{25}H_{38}O_9$	466	Aerial parts	Chloroform extract	N/A	(39)
Malarz *et al*, 2025	55	9β-angeloyloxy-4β,8α-dihydroxy-5β-(3-methylbutyryloxy)-3-oxo-germacran-6α,12-olide	Germacranolide	$C_{25}H_{38}O_8$	466	Whole plant	Chloroform extract	N/A	(39)
Malarz *et al*, 2025	56	Incaspitolide D	Germacranolide	$C_{23}H_{34}O_9$	454	Aerial parts	Chloroform extract	N/A	(39)
Dong, 2024	57	4β,8α-dihydroxy-5*β*-isobutyryloxy-9β-(3-methylbutyryloxy)-3-oxo-germacran-7*β*,12-olide	Germacranolide	$C_{25}H_{36}O_8$	464	Whole plant	Plant crude extract	Exhibited cytotoxic/antitumor effects on multiple human tumor cell lines; possessed antibacterial activity against bacteria and phytopathogenic fungi; exerted anti-inflammatory effects *via* suppressing inflammatory mediators and relevant signaling pathways; showed anti-HSV-1 antiviral and anti-plasmodial (antimalarial) activities.	(10)

Table I. Continued.

First author/s, year	Number	Chemical compound	Type	Molecular formula	Molecular weight	Plant part	Extract/ fraction	Biological relevance (anticancer activity)	(Refs.)
Zhang *et al*, 2018	58	5β-angeloyloxy-4*β*,8α-dihydroxy-9*β*-isobutyryloxy-3-oxo-germacran-7*β*,12-olide	Germacranolide	$C_{24}H_{34}O_9$	466	Seeds	N/A	Cytotoxic activity against HL-60 human leukemia cells; belongs to active germacranolide series 26-34; α,β-unsaturated lactone is key pharmacophore.	(54)
Zhang *et al*, 2018	59	Divarolide E	Terpenoid lactone	$C_{74}H_{34}O_{10}$	482	Whole plant	95% ethanol extract	Evaluated for *in-vitro* cytotoxicity against HeLa (human cervical cancer) and HepG2 (human hepatocellular carcinoma) cell lines by MTT assay. divarolide E exhibited potent cytotoxic activity, and its activity was superior to the positive control cis-platin.	(54)
Feng *et al*, 2023	60	Cardivin D	Germacranolide	$C_{23}H_{34}O_9$	454	Whole plant	Ethyl acetate fraction of ethanol extract	Tested for *in vitro* anti-leukemia cytotoxicity against K562 and HEL human leukemia cell lines via MTT assay. It displayed potent activity, with IC_{50} values of 2.27±0.46 μmol·l^{-1} (K562) and 1.84±0.14 μmol·l^{-1} (HEL).	(27)

Table II. Diterpenoid compounds in *Carpesium cernuum* L.

First author/s, year	Number	Chemical compound	Type	Molecular formula	Molecular weight	(Refs.)
Feng *et al*, 2022	61	(5Z)-6-[(acetyloxy) methyl]-2-oxo-2,10,14-trimethylhexadeca-5,13-diene-11α-ol	Diterpenoids	$C_{22}H_{36}O_4$	364	(28)
Feng *et al*, 2022	62	(2E,10E)-1,12-dihydroxy-18-acetoxy-3,7,15-trimethylhexadeca-2,10,14-triene	Diterpenoids	$C_{22}H_{38}O_4$	366	(28)
Feng *et al*, 2022	63	(2E,6Z,10E,12R)-7-[(acetyloxy) methyl]-3,11,15-trimethylhexadeca-2,6,10,14-tetraene-1,12-diol	Diterpenoids	$C_{22}H_{38}O_4$	366	(28)
Feng *et al*, 2022	64	(2E,6Z,11S,12R)-3,7,11,15-tetramethylhexadeca-2,6,14-triene-7-[(acetyloxy) methyl]-1,12,19-triol	Diterpenoids	$C_{23}H_{40}O_5$	396	(28)
Feng *et al*, 2022	65	Plauonotol	Diterpenoids	$C_{20}H_{34}O_2$	306	(28)
Feng *et al*, 2023	66	(5Z)-2-oxo-2,10,14-trimethylhexadeca-5,13-diene-11α,18-diol	Miscellaneous compounds	$C_{19}H_{34}O_3$	310	(29)
Feng *et al*, 2023	67	(2E,10E)-7-[(acetyloxy)methyl]-3,11,15-trimethylhexadeca-2,10,14-triene-1,12α-diol	Miscellaneous compounds	$C_{22}H38O_4$	367	(29)
Feng *et al*, 2023	68	(2E,6Z)-3,11,15-trimethylhexadeca-2,6,14-triene-1,12α,19-triol	Miscellaneous compounds	$C_{19}H_{34}O_3$	310	(29)
Dang *et al*, 2019	69	Incaspitolide D	Terpenoid lactone	$C_{23}H_{34}O_9$	455	(57)

Table III. Flavonoid compounds in *Carpesium cernuum* L.

First author/s, year	Number	Chemical compound name	Type	Molecular formula	Molecular weigh	(Refs.)
Batterham and Highet,1964	70	3,4',5,7-tetrahydroxyflavanonol	Flavonoids	$C_{15}H_{12}O_6$	288	(30)
Agrawal *et al,* 2024	71	isoquercetin	Flavonoids	$C_{21}H_{20}O_{12}$	464	(31)
Beninger and Hosfield, 1999	72	3-β-D-glucopyranosyl-3,4',5,7-tetrahydroxyflavonol	Flavonoids	$C_{17}H_{12}O_9$	360	(32)

3. Chemical constituents and pharmacological studies of *C. cernuum*

Chemical constituents in C. cernuum. A total of 109 compounds have been isolated and identified from *C. cernuum*, mainly including sesquiterpenoids, diterpenoids, flavonoids, and other classes of compounds. Among these, sesquiterpenoids are considered to be the major bioactive constituents of *C. cernuum* The chemical compound name, compound type, molecular formula and molecular weight were included in Tables I-IV based on related references respectively (9-75).

Sesquiterpenoids. A total of 60 sesquiterpenoids have been isolated and identified from *C. cernuum* (Table I) and their detailed structural types shown in Figs. 1 (compounds 1-30) and 2 (compounds 31-60).

Diterpenoids. A total of nine diterpenoids have been isolated and identified from *C. cernuum*, with their detailed names and information listed in Table II and their detailed structural types shown in Fig. 3 (compounds 61-69).

Flavonoids. A total of three flavonoids have been isolated and identified from *C. cernuum*, with their detailed names and information listed in Table III and their detailed structural types shown in Fig. 4 (compounds 70-72).

Table IV. Other types of compounds in *Carpesium cernuum* L.

First author/s, year	Number	Chemical compound name	Type	Molecular formula	Molecular weight, Da	(Refs.)
Yang *et al*, 2002	73	4-hydroxy-acetophenone	Aromatic	$C_8H_8O_2$	136	(21)
Yang *et al*, 2002	74	2-hydro xy-4-methoxyacetophenone	Aromatic	$C_9H_{10}O_3$	166	(21)
Dhavale *et al*, 1997	75	2,4-dimethoxy(acetophenone)	Aromatic	$C_{10}H_{12}O_4$	196	(66)
Yang *et al*, 2001	76	3-methyl-8-acetoxy-9,10-diisobutyryloxy-p-cymene	Aromatic	$C_{21}H_{30}O_6$	378	(33)
Ma *et al*, 2008	77	eupatriol-9-O-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside	Glycoside	$C_{21}H_{32}O_{12}$	499	(34)
Yan *et al*, 2018	78	carpescernolides A	Glycoside	$C_{26}H_{34}O_{12}$	561	(55)
Yan *et al*, 2018	79	carpescernolides B	Glycoside	$C_{26}H_{34}O_{12}$	561	(55)
Greea *et al*, 1990	80	stigmast-5-en-3β-ol-7-one	Sterols	$C_{29}H_{48}O_2$	428	(35)
Feng *et al*, 2023	81	β-sitosterol	Sterols	$C_{29}H_{50}O$	414	(27)
Meagher *et al*, 1999	82	pinoresinol	Lignans	$C_{20}H_{22}O_6$	358	(36)
Lyu and Park, 2010	83	tortoside A	lignans	$C_{24}H_{28}O_{10}$	476	(37)
Seo *et al*, 2018	84	Ursolic acid	Triterpenes	$C_{30}H_{48}O_3$	456	(38)
Zhou *et al*, 2017	85	aurantiamide acetate modified dipeptide	Phenol	$C_{27}H_{28}N_2O_4$	444	(49)
Flourat *et al*, 2021	86	p-hydroxycinnamic acid	Phenol	$C_9H_8O_3$	164	(40)
Teng *et al*, 2005	87	Caffeic acid	Phenol	$C_9H_8O_4$	180	(41)
Teng *et al*, 2005	88	3,4-dihydroxybenzoic acid	Phenol	$C_7H_6O_4$	154	(41)
Zhou *et al*, 2021	89	2,4-dihydroxy-6-methoxyacetophenone	Phenol	$C_9H_{10}O_4$	182	(42)
Teng *et al*, 2005	90	citrusin C	Phenol	$C_{12}H_{14}O_4$	222	(41)
Healy *et al*, 2003	91	Indole-3-carboxylic acid	Indole acid	$C_9H_7NO_2$	161	(43)
Cai *et al*, 2022	92	7-hydroxycoumarin	Coumarins	$C_9H_7O_3$	162	(44)
Nghiem *et al*, 2017	93	succinic acid	Miscellaneous compounds	$C_4H_6O_4$	118	(45)
Mondul *et al*, 2014	94	1-stearoyl glycerate	Miscellaneous compounds	$C_{25}H_{50}O_4$	414	(46)
Moghaddam *et al*, 2010	95	loliolid	Compounds	$C_{11}H_{16}O_3$	196	(47)
Zhang *et al*, 2026	96	paeonol	Miscellaneous compounds	$C_9H_{10}O_3$	166	(48)
Malarz *et al*, 2025	97	8-hydroxy-9,10-diisobutyryloxythymol	Phenol	$C_{18}H_{26}O_6$	338	(39)
Ren *et al*, 2014	98	8-hydroxy-9-isobutyryloxy-10-(2-methylbutyryloxy)-thymol	Phenol	$C_{22}H_{34}O_7$	410	(67)
Malarz *et al*, 2025	99	8,9-dihydroxy-10-isobutyryloxythymol	Terpenoids	$C_{14}H_{22}O_5$	270	(39)
Stojakowska *et al*, 2005	100	8,9-epoxy-10-isobutyryloxythymol isobutyrate	Phenol	$C_{22}H_{32}O_5$	376	(68)
Malarz *et al*, 2025	101	5-CQA	Caffeoylquinic acids,CQAs	$C_{33}H_{18}O_{15}$	665	(39)
Li *et al*, 2005	102	3,4-di-o-caffeoylquinic acid	Polyphenolic ester derivatives	$C_{33}H_{28}O_{15}$	665	(69)
Shen *et al*, 2010	103	1,5-Di-o-caffeoylquinic acid	Polyphenolic ester derivatives	$C_{25}H_{24}O_{12}$	516	(70)

Table IV. Continued.

First author/s, year	Number	Chemical compound name	Type	Molecular formula	Molecular weight, Da	(Refs.)
Kim *et al*, 2005	104	3,5-di-o-caffeoylquinic acid	Polyphenolic ester derivatives	$C_{25}H_{24}O_{12}$	516	(71)
Miyamae *et al*, 2012	105	4,5-di-o-caffeoylquinic acid	Polyphenolic ester derivatives	$C_{25}H_{24}O_{12}$	516	(72)
Malarz *et al*, 2025	106	3-hydroxy-3,6-dimethyl-2,3-dihydrobenzofuran-2-yl isobutyrate	Benzofuran-derived ester compounds	$C_{14}H_{18}O_3$	234	(39)
Bakrim *et al*, 2022	107	Stigmasterol	Phytosterol derivatives	$C_{29}H_{48}O$	412	(73)
Kumar *et al*, 2021	108	Syringaldehyde	Phenolic aldehyde derivatives	$C_9H1_0O_4$	182	(74)
Ribeiro *et al*, 2011	109	β-carotene	Sterols	$C_{31}H_{52}O_3$	472	(75)

Other classes of compounds. A total of 37 other classes of compounds have been isolated and identified from *C. cernuum*, with their detailed names and information listed in Table IV and their detailed structural types shown in Fig. 5 (compounds 73-92) and Fig. 6 (compounds 93-109).

Anticancer pharmacological effects of C. cernuum. To clarify the evidence quality of existing anticancer research, this subsection systematically re-analyzes the anticancer effects of *C. cernuum* by distinguishing research materials (crude extract/fraction/monomer) and experimental models (cell/animal). Overall, current anticancer evidence is dominated by *in vitro* cell experiments, with limited *in vivo* validation and no clinical data, and the research depth varies significantly across different cancer types. Consistent with existing preclinical findings, *C. cernuum* and its active constituents exhibit tentative anticancer activity in *in vitro* and partial *in vivo* models, which merits further systematic verification.

Anti-prostate cancer effects. As an important component of traditional Miao medicine, the anti-prostate cancer pharmacological effects of *C. cernuum* have been fully verified by *in vitro* experiments and have demonstrated promising preclinical anticancer potential (2). Notably, existing anti-prostate cancer evidence for *C. cernuum* is derived from two types of research materials: Aqueous crude extract (Level 3 evidence) and purified monomeric sesquiterpenoids (ineupatolide, incaspitolide A, Level 2 evidence), with all validations based on *in vitro* PC3 and DU-145 cell models; no *in vivo* animal experiments have been reported. Modern pharmacological studies have shown that the anti-prostate cancer activity of *C. cernuum* is mainly achieved through its extracts and bioactive constituents *via* multiple pathways, including inhibiting cell proliferation, inducing cell apoptosis, and suppressing migration and invasion. Moreover, its mechanism is closely associated with the regulation of key signaling pathways (4). The aqueous extract of *C. cernuum* (AECC) significantly inhibits the proliferation of prostate cancer PC3 cells in a concentration- and time-dependent manner, with a progressive decrease in cell survival rate (statistically significant vs. control group). AECC induces late apoptosis of PC3 cells, as confirmed by Hoechst 33258 staining and flow cytometry, which is associated with regulating apoptosis-related proteins: It upregulates the mRNA and protein levels of cysteine-aspartic acid protease (caspase)-3 and Bcl-2-associated X protein (Bax), while downregulating B-cell lymphoma/leukemia (Bcl-2) expression (76).

Regarding the migration and invasion abilities of tumor cells, Transwell assay showed that AECC significantly reduced the number of migrated and invaded PC3 cells. This effect is associated with the inhibition of the β-catenin signaling pathway (2), which can downregulate the mRNA and protein expression of β-catenin and its downstream targets, including matrix metalloproteinases (MMPs) 7 and myelocytomatosis virus oncogene (c-Myc).

Taken together, *C. cernuum* exerts anti-prostate cancer effects through a multi-targeted and multi-mechanistic mode of action. However, the lack of *in vivo* animal model verification greatly weakens the reliability of existing conclusions and the effective concentration range of crude extracts and monomers *in vitro* cannot be directly converted for *in vivo* application, indicating that its actual *in vivo* efficacy and clinical translational value remain to be further validated.

Anti-pancreatic cancer effects. Anti-pancreatic cancer research of *C. cernuum* is highly specific, with all valid evidence derived from the purified monomer carabrone (carabrane-type sesquiterpenoid, Level 2 *in vitro* cell evidence), and no relevant activity evaluation of crude extracts or fractions has been reported. No *in vivo* animal experiments or clinical studies are available.

Carabrone, a sesquiterpenoid isolated from *C. cernuum*, has previously been demonstrated to possess multiple antitumor activities, including anti-hepatocellular carcinoma and anti-breast cancer effects. The present review

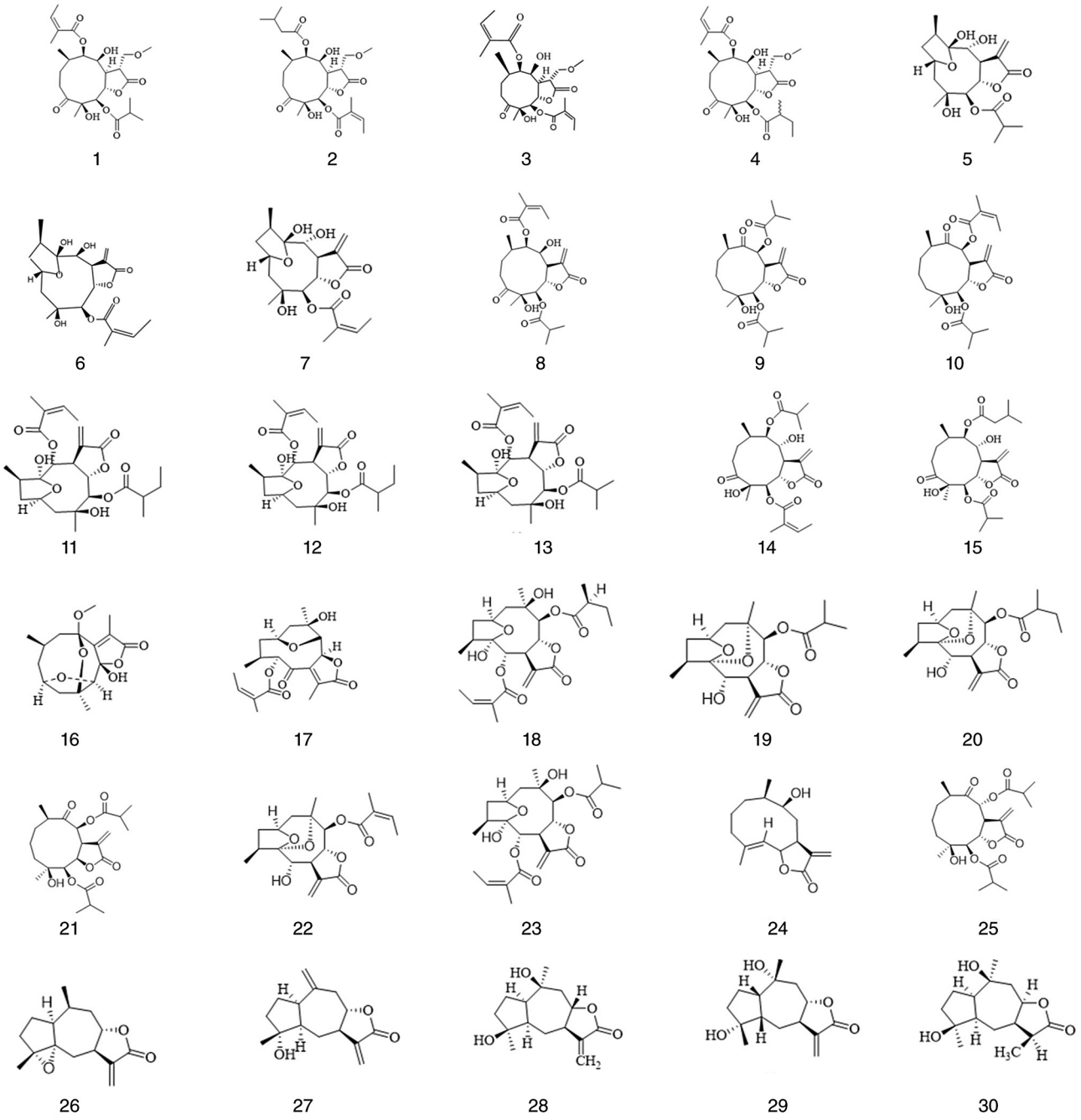


Figure 1. Sesquiterpenes compounds from *Carpesium cernuum* L. (1-30); see Table I for key.

further revealed its potential anti-pancreatic cancer activity in preclinical cell models (77). Cell proliferation inhibition assay showed that carabrone exerted inhibitory effects on the proliferation of multiple pancreatic cancer cell lines in a dose-dependent manner, among which it exhibited the most prominent inhibitory effect on human pancreatic ductal adenocarcinoma SW1990 cells (78). It can effectively impair the colony proliferation capacity of pancreatic cancer cells. Furthermore, colony formation assay demonstrated that it exerted a significant inhibitory effect on cell colony formation, with its potency comparable to that of paclitaxel, a clinically commonly used anti-cancer drug, thereby exhibiting favorable antiproliferative activity (77,79). Immunofluorescence confirmed that this compound downregulated the protein expression of MMP2 and MMP9, which are closely associated with tumor migration (80). This undermines the molecular basis for tumor cell invasion, thereby reducing the metastatic potential of pancreatic cancer cells and providing experimental support for inhibiting pancreatic cancer metastasis.

Taken together, carabrone derived from *C. cernuum* exerts anti-pancreatic cancer activity through a multi-targeted and multi-pathway mode of action. It exhibits clear *in vitro* inhibitory effects, and as a natural plant-derived compound, it possesses favorable biocompatibility in cell-level experiments. Nevertheless, the single-cell-model limitation and absence of *in vivo* verification restrict its further pharmacological evaluation and drug development.

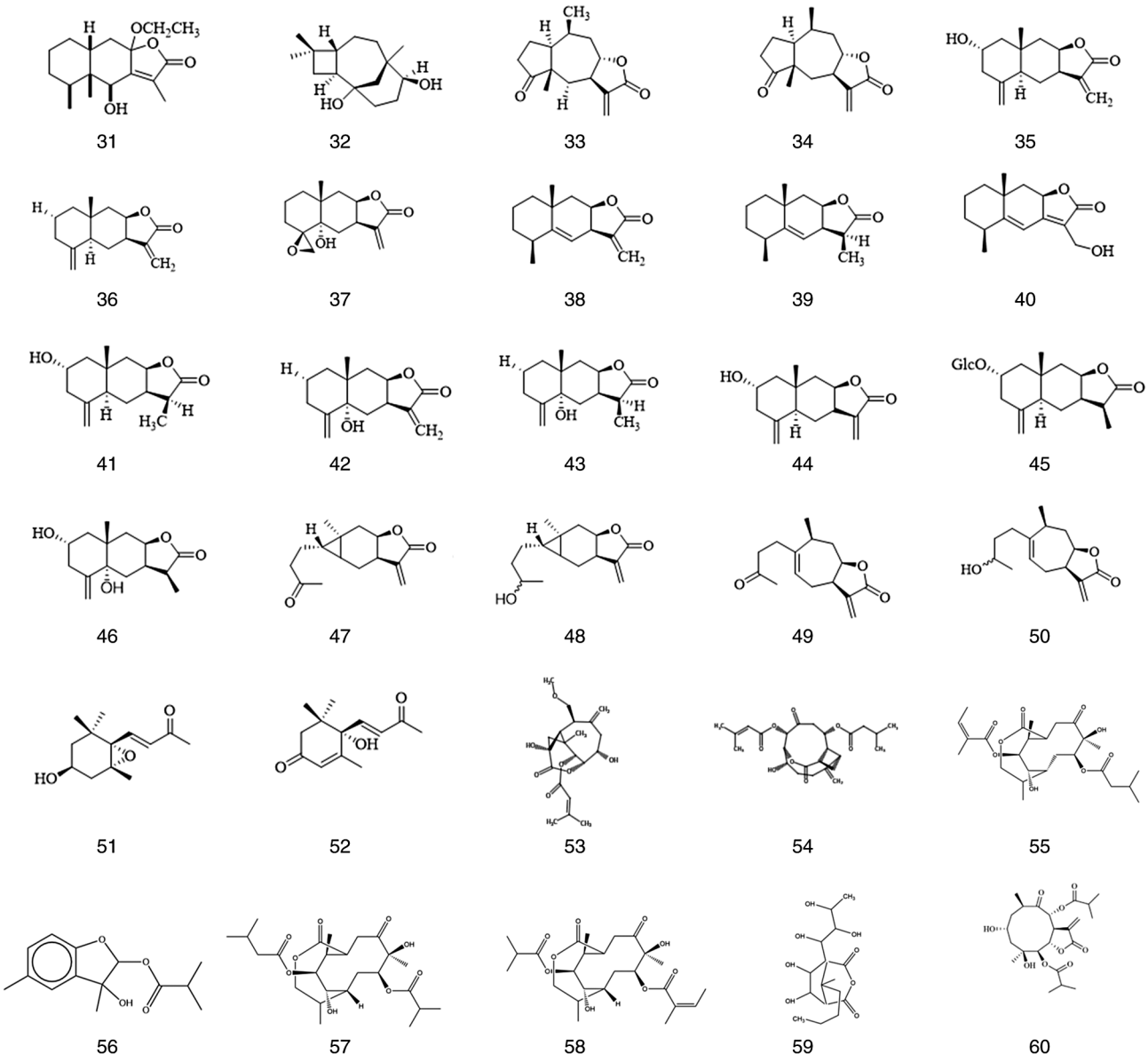


Figure 2. Sesquiterpenes compounds from *Carpesium cernuum* L. (31-60); see Table I for key.

Antileukemic effects. Anti-leukemia evidence of *C. cernuum* includes two levels: ethanol crude extract (Level 3 evidence, K562 cell model) and purified monomer cernuumolide J [Level 2 evidence, human erythroleukemia (HEL) cell model], all based on *in vitro* cell experiments without *in vivo* validation.

Numerous modern experiments have verified that *C. cernuum*, its extracts and bioactive components exert potential pharmacological activities against leukemia in *in vitro* models. The underlying mechanisms mainly include inducing apoptosis, suppressing proliferation and modulating relevant signaling pathways in leukemia cells (81). The ethanol extract of *C. cernuum* exerts a significant inhibitory effect on human chronic myeloid leukemia (CML) K562 cells. Yan *et al* (13) demonstrated that within a certain concentration range, this ethanol extract inhibited the proliferation of K562 cells in a dose-dependent manner. Furthermore, Hoechst 33258 staining revealed that K562 cells treated with this extract exhibited typical apoptotic morphological characteristics, including chromatin condensation and nuclear fragmentation. Moreover, flow cytometry analysis showed that the apoptotic rate of K562 cells increased significantly with the elevation of extract concentration. Mechanistic studies have confirmed that this ethanol extract of *C. cernuum* can downregulate Bcl-2 expression, upregulate Bax expression and activate the caspase-3 signaling pathway, thereby initiating the apoptotic program of leukemia cells (82). Wei *et al* (81) demonstrated that cernuumolide J, an extract of *C. cernuum*, exerted a significant inhibitory effect on human erythroleukemia (HEL) cells. Its core mechanism involves regulating the JAK2/STAT3 and the mitogen-activated protein kinase (MAPK) signaling pathway. On the one hand, it induces HEL cell cycle arrest at the G_2/M phase to inhibit their abnormal proliferation. On the other hand, it triggers the apoptotic program via decreased mitochondrial membrane potential ($\Delta\Psi m$), thereby reducing the viability of tumor cells.

Taken together, *C. cernuum* and its bioactive constituents exert anti-leukemic effects through multiple pathways. Current studies only confirm *in vitro* anti-leukemic activity and the

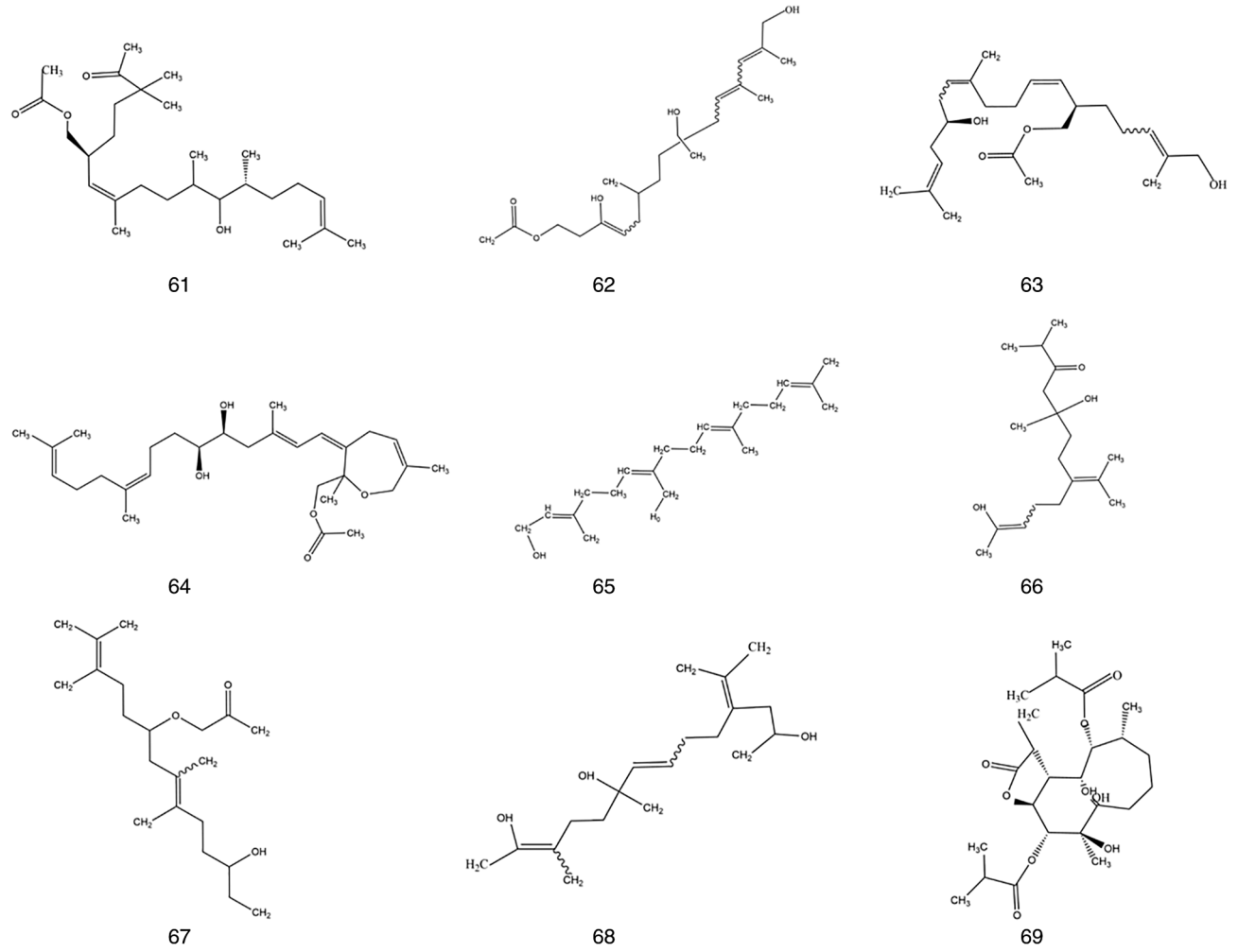


Figure 3. Diterpenoid compounds from *Carpesium cernuum* L. (61-69); see Table II for key.

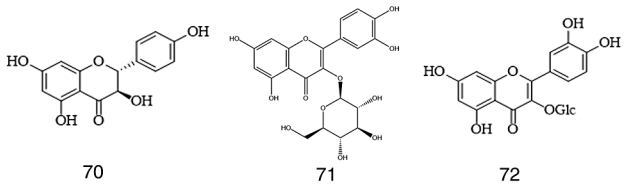


Figure 4. Flavonoid compounds from *Carpesium cernuum* L. (70-72); see Table III for key.

in vivo efficacy, toxicity and pharmacokinetic characteristics remain unclear, which limits the comprehensive evaluation of its anti-leukemic application potential (83,84).

Anti-breast cancer effects. Anti-breast cancer evidence is mainly derived from ethyl acetate active fraction of *C. cernuum* 95% ethanol extract (Level 3 evidence), verified by MDA-MB-231 and MCF7 breast cancer cell models; no single active monomer has been confirmed for targeted anti-breast cancer activity, and no *in vivo* experiments have been conducted.

The pharmacological effects of *C. cernuum* against breast cancer have been clearly confirmed by modern pharmacological studies, providing important evidence for the development of new antitumor drugs. The extracts of this plant and its monomeric components exhibit significant inhibitory activity against breast cancer cells. Feng *et al* (28) isolated and identified compounds from the ethyl acetate fraction of the 95% ethanol extract of *C. cernuum*, which exhibited potent cytotoxic activity against human triple-negative breast cancer (TNBC) MDA-MB-231 cells with an IC_{50} value of 6.80 μmol/l. Dang *et al* (57) further confirmed that the extract of *C. cernuum* (CCE) exhibited the most significant antiproliferative activity against MDA-MB-231 cells and was also effective against hormone-dependent human breast cancer (MCF7) cells. Its mechanism is associated with inhibiting DNA synthesis, downregulating the expression of key cell proliferation genes, namely epidermal growth factor receptor (EGFR) and cyclin-dependent kinase 2 (CDK2), and simultaneously blocking the activation of phosphorylated (p-) EGFR induced by epidermal growth factor (EGF).

In terms of anti-breast cancer metastasis, *C. cernuum* exerts significant inhibitory effects on TNBC metastasis by regulating cell adhesion pathways and metastasis-related genes. Transcriptomic analysis indicated that the active sesquiterpene lactones from *C. cernuum* significantly enriched the cell adhesion molecules (CAMs) pathway (57), upregulated the tumor metastasis suppressor gene tissue inhibitor of metalloproteinase-1 (TIMP1), and downregulated pro-metastatic genes such as MMP9, cluster of differentiation 44 (CD44)

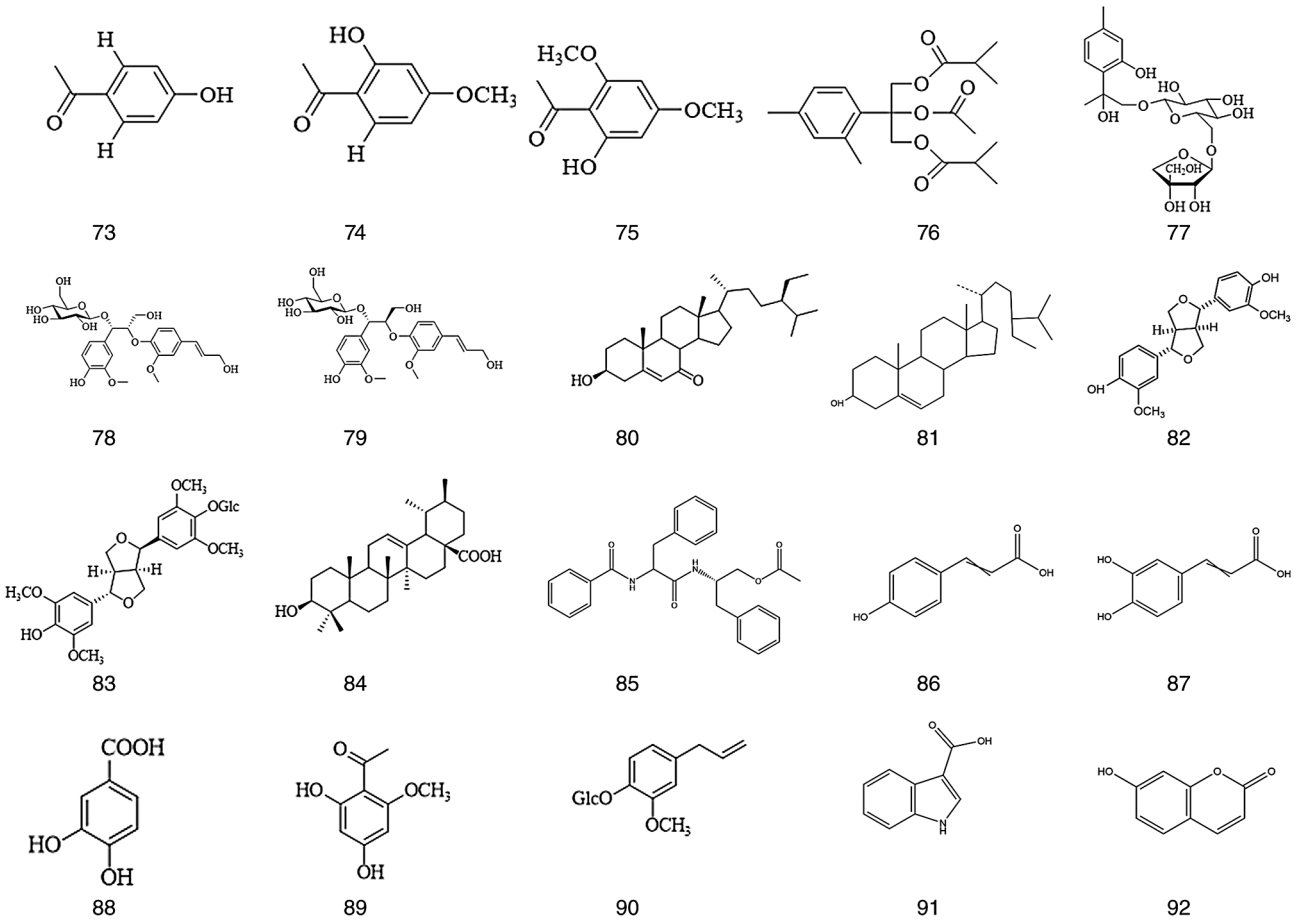


Figure 5. Other types of compounds from *Carpesium cernuum* L. (73-92); see Table IV for key.

and collagen type IV α 2 chain (COL4A2). By balancing the MMP9/TIMP1 signaling axis, the active constituents of *C. cernuum* inhibit extracellular matrix (ECM) degradation (57), thereby markedly suppressing the migration and invasion capacities of MDA-MB-231 cells (57). The core bioactive components of *C. cernuum* are sesquiterpene lactones, which recapitulate the anti-metastatic performance of the botanical extract and constitute the material basis for its anti-breast cancer activity.

In addition, previous studies have confirmed that sesquiterpenoid monomers from *C. cernuum* may block cancer cell proliferation by inhibiting associated signaling pathways. Combined with their dual inhibitory effects on the proliferation and metastasis of breast cancer cells, as well as definite molecular targets, this suggests that *C. cernuum* extracts and sesquiterpene lactone components have preliminary potential for development into anti-breast cancer drug candidates, especially for TNBC metastasis intervention, providing a novel candidate direction for clinical breast cancer treatment (Table V).

4. Analysis of action targets of C. cernuum

Regulation of the PI3K/Akt/mTOR signaling axis by C. cernuum. The core anti-prostate cancer bioactive constituents of *C. cernuum* are ineupatolide and incaspitolide A, both of which are germacrane-type sesquiterpenes. Their core mechanism lies in the targeted regulation of the PI3K/Akt/mTOR signaling axis, exerting antitumor effects through multi-node inhibition. The PI3K/Akt/mTOR signaling axis is a key pathway regulating cell proliferation, cell cycle, apoptosis and autophagy (85) and the bioactive constituents of *C. cernuum* exert their effects by directly acting on the core molecules of this pathway. First, ineupatolide and incaspitolide A can specifically bind to the catalytic subunit of PI3K, downregulate the phosphorylation level of PI3K (p-PI3K), block its ability to convert phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3), and further inhibit the phosphorylation and activation of downstream Akt (p-Akt), forming a key block at the upstream of the pathway (86). Following the inhibition of Akt phosphorylation, its ability to activate downstream mTOR is attenuated, resulting in a significant decrease in the level of phosphorylated mTOR (p-mTOR). As the core kinase of the pathway, inhibition of mTOR activity directly affects its downstream substrates. On the one hand, they downregulate the phosphorylation of ribosomal protein S6 kinase 70 kDa polypeptide 1 and proline-rich Akt substrate of 40 kDa, thereby inhibiting ribosome biogenesis and the transcription of cell proliferation-related genes (87). On the other hand, they downregulate the protein expression of sequestosome 1, a protein primarily functioning as an autophagic adaptor rather than a nucleolar-specific protein, promote the conversion of microtubule-associated protein 1A/1B-light chain 3-I

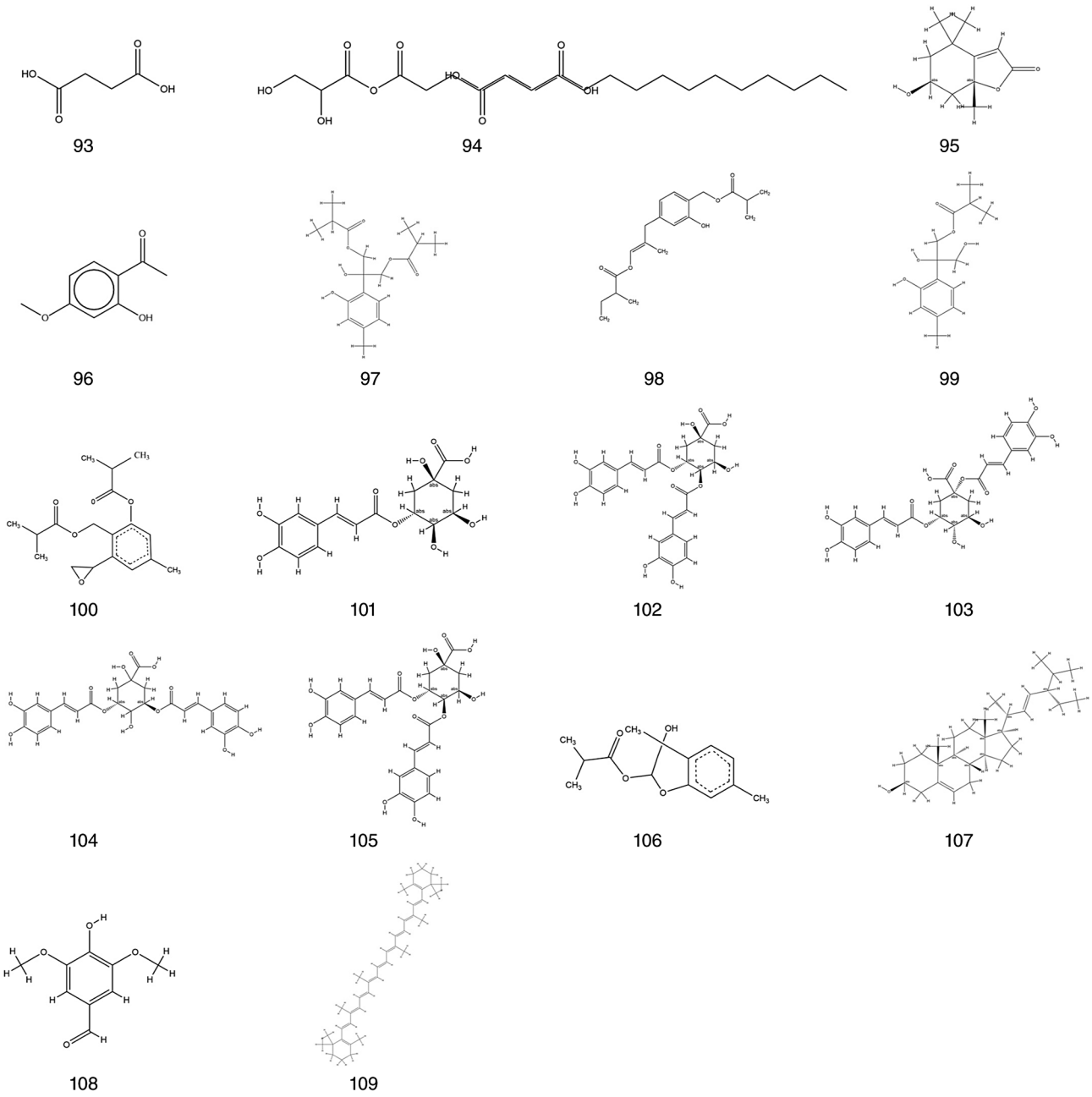


Figure 6. Other types of compounds from *Carpesium cernuum* L. (93-109); see Table IV for key.

(LC3-I) to LC3-II, enhance autophagolysosome formation, and thereby induce autophagic cell death of tumor cells. Inhibition of this signaling axis triggers downstream cascade regulation: at the cell cycle level, it downregulates the protein expression of cyclin-dependent kinase 1 (CDK1), CDK2 and cyclin A2 (CCNA2), upregulates P53 expression, and arrests prostate cancer cells at the S phase or G_2/M phase. At the apoptotic level, it inhibits the anti-apoptotic effects of X-linked inhibitor of apoptosis protein and Bcl-2, promotes the expression of Bax, cleaved-caspase-3 (activated/cleaved form), and cleaved-PARP, thereby initiating the mitochondria-dependent apoptotic pathway (88). At the migration and invasion level, by inhibiting PI3K-Akt-mediated MMPs activity, it reduces the migration and invasion abilities of human prostate cancer cell lines PC-3 and human prostate cancer cell line DU-145 (89).

This pathway has been validated by network pharmacology, transcriptomics and *in vitro* and *in vivo* experiments. Notably, all pathway verification data are derived from *in vitro* cell models, and the *in vivo* regulatory effect of the PI3K/Akt/mTOR axis remains to be confirmed. The bioactive constituents regulate the phosphorylation levels of various nodes in the signaling axis in a dose-dependent manner, forming a complete regulatory chain: PI3K-Akt inhibition, mTOR inactivation, proliferation inhibition + apoptosis induction + autophagy activation, which provides clear molecular mechanism support for *C. cernuum* potential candidate for anti-prostate cancer preclinical research (Fig. 7).

Regulation of the Hippo signaling pathway by the bioactive constituent carabrone. Carabrone is a carabrane-type

Table V. Standardized summary table of anticancer evidence.

Tested material	Cancer type	Experimental model	Concentration/dose	Main anticancer outcomes	Proposed mechanism	Evidence level	(Refs.)
Ineupatolide, incaspitolide A (purified monomers)	Prostate cancer	*In vitro* PC3 cell line	No exact single-molecule $IC_{5□}$ reported	Suppresses prostate cancer cell proliferation and metastasis; induces cell cycle arrest and autophagic apoptosis	Inhibits PI3K-Akt-mTOR signaling axis, regulates cell cycle and apoptosis-related proteins	Level 2 (monomer, *in vitro*)	(86,100)
Carabrone (purified monomer)	Pancreatic cancer	*In vitro* SW1990 cell line	Dose-dependent intervention	Inhibits pancreatic cancer cell proliferation and colony formation; suppresses cell migration and invasion	Regulates Hippo signaling pathway; induces G2 cell cycle arrest, ROS accumulation and ferroptosis; downregulates MMP2/MMP9	Level 2 (monomer, *in vitro*)	(77)
Ethanol crude extract of *Carpesium cernuum* L.	Prostate cancer; breast cancer	*In vitro* PC3 cell line; *in vitro* MDA-MB-231, MCF7 cell lines	Concentration and time-dependent intervention; dose-dependent intervention	Inhibits PC3 cell proliferation, migration and invasion; induces late apoptosis; inhibits breast cancer cell proliferation and metastasis; suppresses ECM degradation	Upregulates bax/caspase-3, downregulates Bcl-2; inhibits β-catenin/MMP-7/c-Myc pathway; regulates MMP9/TIMP1 axis and CAMs pathway	Level 3 (crude extract, *in vitro*)	(57,76)
Cernuumolide J (purified monomer)	Leukemia	*In vitro* HEL cells	Dose-dependent intervention	Suppresses HEL cell proliferation; induces G2/M cell cycle arrest and apoptosis	Dual regulation of MAPK (ERK/JNK/p38) and JAK2/STAT3 pathways; activates ROS-mitochondria-caspase axis	Level 2 (monomer, *in vitro*)	(81)

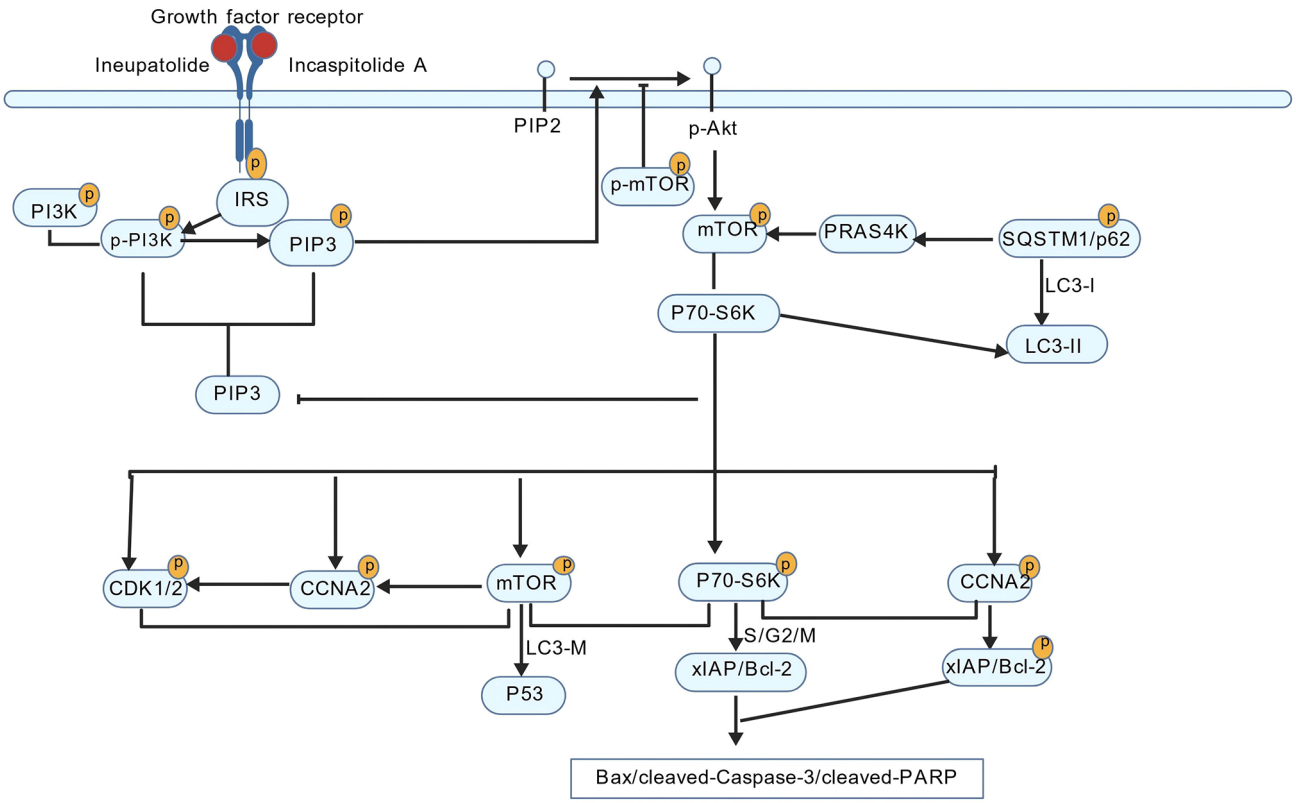


Figure 7. Ineupatolide and incaspitolide A modulate the PI3K/Akt/mTOR signaling axis. p-PI3K, phosphorylated phosphatidylinositol 3-kinase; IRS, insulin receptor substrate; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PRAS4K, proline-rich Akt substrate of 40 kDa; SQSTM1/p62, sequestosome 1; LC3-I/II/M, microtubule-associated protein light chain 3-I/II/modified; P70-S6K, 70 kDa ribosomal protein S6 kinase; CDK1/2, cyclin-dependent kinase 1/2; CCNA2, cyclin A2; p53, tumor protein p53; xIAP, X-linked inhibitor of apoptosis protein.

sesquiterpenoid isolated from *C. cernuum*, a plant belonging to the genus *Carpesium*. It exhibits potent *in vitro* anti-pancreatic cancer activity and its mechanism of action is closely associated with the precise regulation of the Hippo signaling pathway.

The Hippo signaling pathway is a key pathway regulating cell proliferation, migration and apoptosis and its aberrant activation or silencing is closely associated with tumor initiation and progression (90). Previous studies have shown that carabrone exerts its effects through the bidirectional regulation of core molecules in the Hippo signaling pathway. On the one hand, it specifically upregulates the expression of casein kinase 1ε (CSNK1E). On the other hand, it significantly downregulates the expression of WW domain-containing transcription regulator 1 (WWTR1). These two molecules are precisely co-involved in the regulation of cell proliferation, forming a synergistic regulatory network that directly inhibits the proliferation and colony-forming ability of pancreatic cancer cells, thereby activating the antitumor effects of the Hippo signaling pathway (77).

Mediated by the Hippo signaling pathway, carabrone can also impair the cell migration potential: Activation of the pathway by carabrone inhibits the binding of core effector molecules Yes-associated protein/transcriptional co-activator with PDZ-binding motif (YAP/TAZ) to TEA domain transcription factors, thereby reducing the expression and phosphorylation modification of migration-related protein MMP2. Given the bidirectional regulatory relationship between MMP2 and MMP9, the inhibition of MMP2 activity further downregulates the function of MMP9, ultimately resulting in a significant inhibition of pancreatic cancer cell migration (77).

Meanwhile, activation of this pathway can induce G_2 phase cell cycle arrest in pancreatic cancer cells *via* the core component MOB kinase activator 1 (MOB1) and this arrest is accompanied by the phosphorylation modification of cell cycle-related proteins, which effectively prevents cells from entering the mitotic phase (91). Simultaneously, regulation of this pathway promotes an increase in reactive oxygen species (ROS) levels and triggers a decrease in $\Delta\Psi m$ an abnormality that is one of the key characteristics of ferroptosis. Ultimately, building on apoptosis, the pathway further forms crosstalk and synergy with the ferroptosis pathway, thereby enhancing its antitumor efficacy.

In summary, carabrone activates the Hippo signaling pathway by upregulating CSNK1E and downregulating WWTR1, thereby inhibiting the malignant progression of pancreatic cancer cells through multiple aspects including cell proliferation, migration, cell cycle regulation and cell death. All mechanistic conclusions are limited to the *in vitro* SW1990 cell model and the universality and *in vivo* applicability of the Hippo pathway regulation need verification. Elucidation of this mechanism not only reveals the core molecular targets of carabrone against pancreatic cancer but also provides important theoretical support for the development of anti-pancreatic cancer drugs derived from natural products that target the

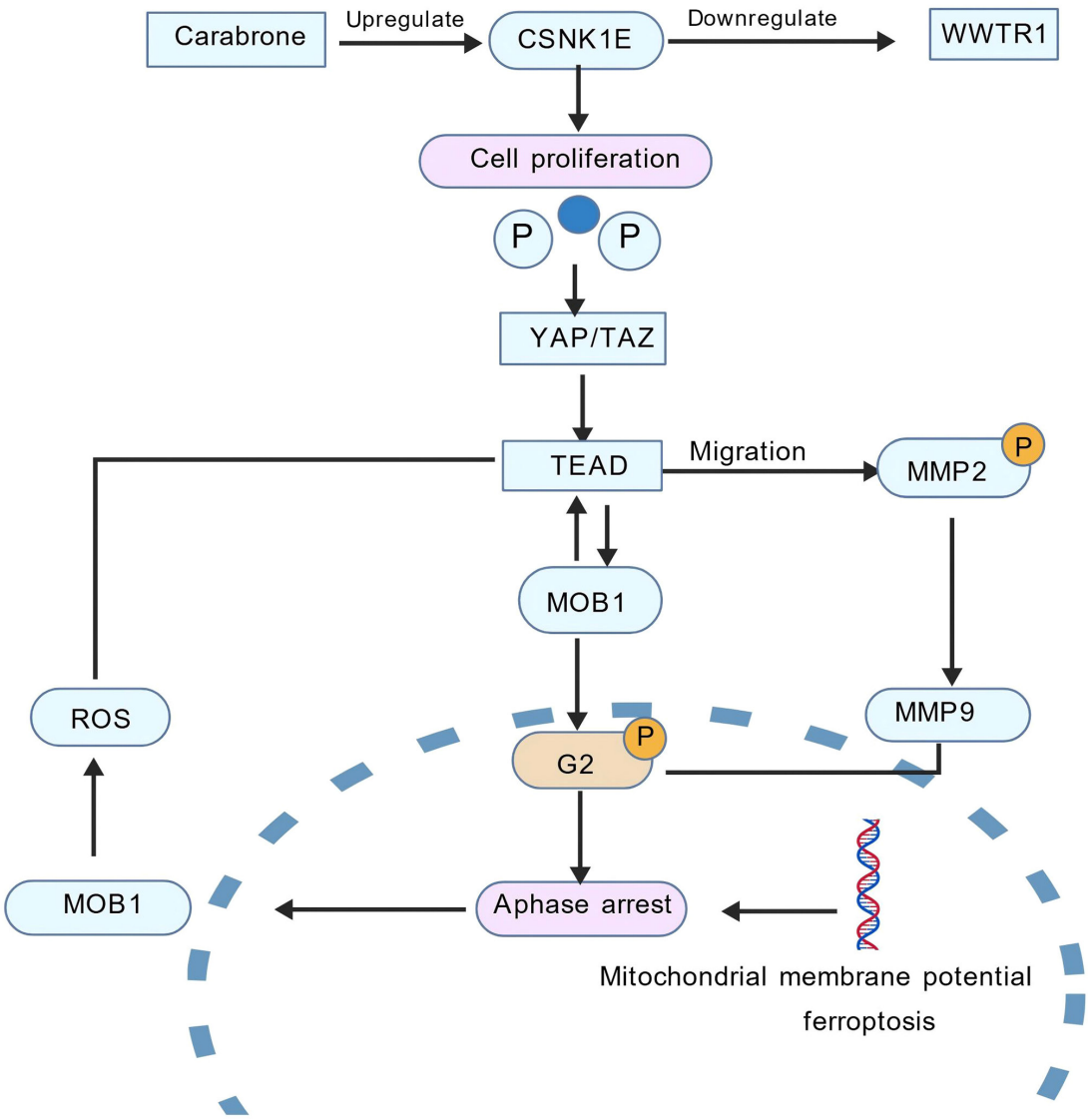


Figure 8. The regulatory effect of the active component carabrone on the Hippo signaling pathway. CSNK1E, casein kinase 1 ε; WWTR1, WW domain-containing transcription regulator 1; YAP, yes-associated protein; TAZ, transcriptional co-activator with PDZ-binding motif; TEAD, TEA domain transcription factor; MOB1, MOB kinase activator 1; ROS, reactive oxygen species.

Hippo signaling pathway and possesses potential clinical translational value (Fig. 8).

Regulation of the Wnt/β-catenin) signaling pathway by the crude extract of C. cernuum. The crude extract of *C. cernuum* enhances GSK-3β activity to exert bidirectional regulation on key genes of the Wnt/β-catenin signaling pathway and the core regulatory complex adenomatous polyposis coli/axis inhibition protein (APC/Axin), thereby forming a molecular network that synergistically antagonizes prostatic hyperplasia. As core negative regulators of the Wnt signaling pathway, APC and Axin can form a stable complex to promote the phosphorylation and degradation of β-catenin, thereby maintaining pathway homeostasis (92). Meanwhile, the crude extract interferes with the function of this complex, laying the foundation for subsequent gene regulation.

Crude extract of *C. cernuum* promotes the expression of the pathway inhibitor secreted frizzled-related protein 2 (SFRP2) as well as apoptosis-related genes, including β-catenin and c-Myc. Mechanistically, the crude extract of *C. cernuum* inhibits the degradative activity of the APC/Axin complex, reduces the phosphorylation-mediated loss of β-catenin, resulting in its moderate accumulation in the cytoplasm. Meanwhile, as a Wnt ligand-competing binding protein, secreted SFRP2 may blocks the interaction between Wnt ligands and the receptor frizzled class receptor 2 (FZD2), directly inhibiting the aberrant activation of the pathway. This forms synergy with the regulation of the APC/Axin complex (93). Notably, the upregulation of β-catenin here does not mediate a pro-proliferative effect but rather synergizes with c-Myc to initiate the apoptotic program. This is consistent with apoptotic characteristics such as the formation of apoptotic bodies and DNA fragmentation observed in cellular morphological studies, further indicating that β-catenin can switch to the apoptotic regulatory pathway to exert its function following the inhibition of the APC/Axin complex.

In terms of gene downregulation, the crude extract of *C. cernuum* can significantly inhibit the expression of

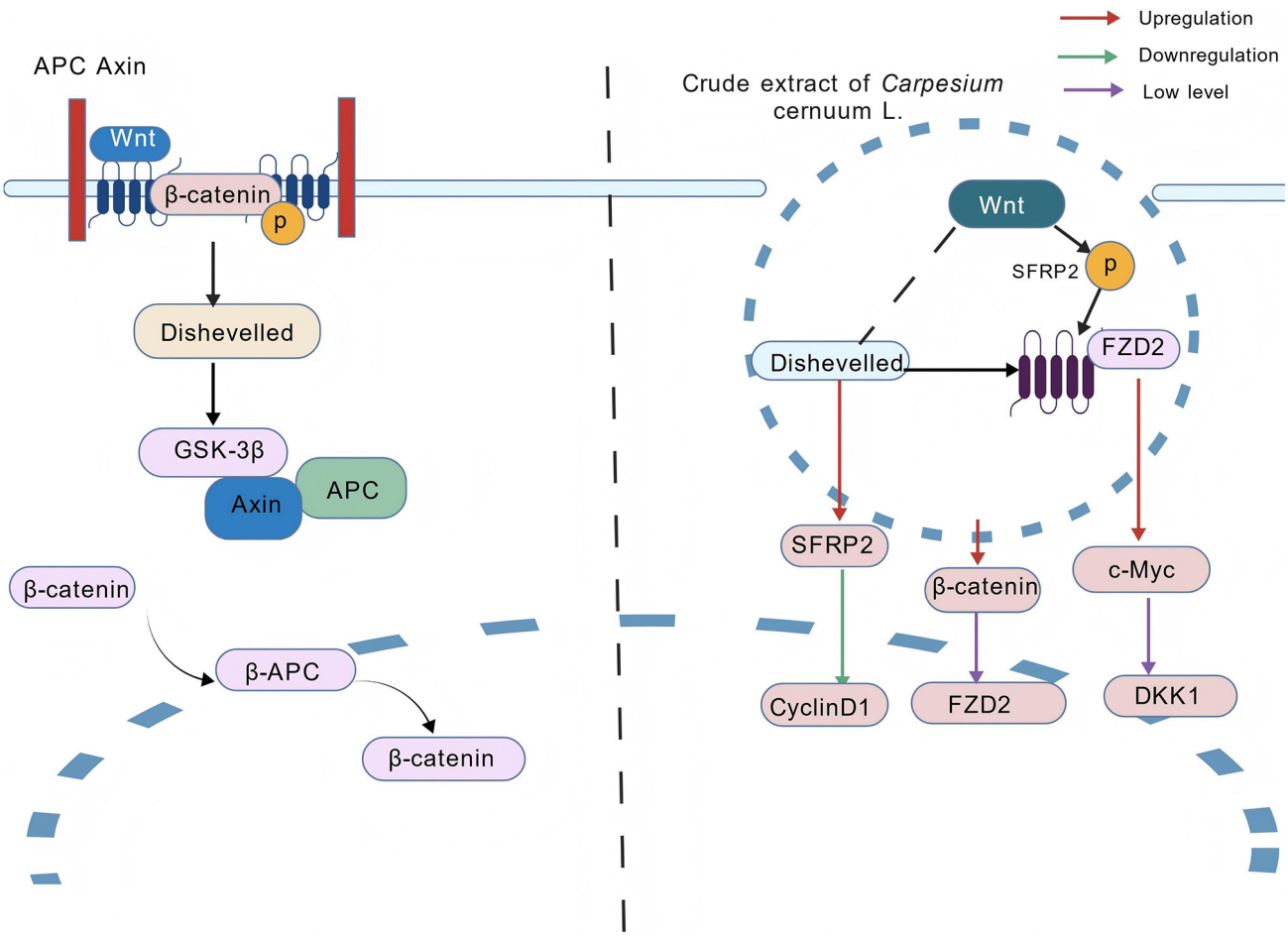


Figure 9. Regulatory effects of the crude extract of *Carpesium cernuum* L. on the Wnt/β-catenin signaling pathway. APC, adenomatous polyposis coli; Axin, axis inhibition protein; GSK-3β, glycogen synthase kinase-3 beta; SFRP2, secreted frizzled-related protein 2; FZD2, frizzled class receptor 2; c-Myc, cellular myelocytomatosis oncogene; CyclinD1, cyclin D1; DKK1, dickkopf WNT signaling pathway inhibitor 1.

Cyclin D1, a pro-proliferative target gene downstream of the Wnt/β-catenin signaling pathway (7,94). As a key molecule in cell cycle regulation, Cyclin D1 is indirectly regulated by the APC/Axin-β-catenin pathway. The crude extract of *C. cernuum* indirectly blocks the transcriptional activation of Cyclin D1 by regulating the function of this complex, thereby effectively blocking the cell cycle progression and inhibiting the aberrant proliferation of prostatic hyperplasia cells. Meanwhile, although the expression of FZD2, an upstream receptor of the pathway, and dickkopf-related protein 1 (DKK1), a signal transduction molecule, exhibits slight fluctuations, it remains consistently at a low level. This further weakens the pro-proliferative signal input of the pathway and forms a synergy with the APC/Axin-mediated regulation of β-catenin, thereby synergistically enhancing the anti-proliferative effect (81) (Fig. 9).

Regulation of the mitogen-activated protein kinases (MAPKs) signaling pathway by Cernuumolide J, a bioactive constituent isolated from *C. cernuum*. Cernuumolide J exerts anti-proliferative and pro-apoptotic effects on leukemia cells by targeting and regulating the MAPKs signaling pathway, with the core mechanisms as follows:

The three major subfamilies of the MAPKs pathway, extracellular signal-regulated kinase (ERK), c-Jun N-terminal Kinase (JNK), and p38 MAPK, are the key targets of cernuumolide J, with significant selectivity in its regulation: Cernuumolide J can significantly downregulate the phosphorylation level of ERK (p-ERK), block the pro-proliferative signaling mediated by ERK, and thereby impair the survival advantage of leukemia cells. Meanwhile, it specifically activates the phosphorylation of JNK and p38 MAPK (p-JNK and p-p38), initiating cascade reactions that lead to pro-apoptosis and cell cycle arrest (81).

In downstream effects, the activated JNK/p38 pathway exerts its functions through multiple core mechanisms: First, it regulates key cell cycle molecules and promotes the upregulation of DNA damage-related protein checkpoint kinase 2, tumor suppressor protein p53, and cell cycle inhibitor p21. Simultaneously, it inhibits the activity of the oncoprotein c-Myc, cell cycle driver protein Cyclin B1, CDK1 and phosphorylated cell division cycle 2 (p-CDC2), leading to the accumulation of DNA damage in HEL cells, arresting them at the G_2/M phase and blocking their aberrant proliferation. Second, it induces the release of intracellular ROS, decreases the $\Delta\Psi m$ and impairs mitochondrial homeostasis, thereby activating the cysteine-dependent aspartate-specific protease (caspase) apoptotic pathway, upregulating the protein expression of cleaved caspase-3, cleaved caspase-9 and cleaved poly (ADP-ribose) polymerase (cleaved-PARP) and initiating programmed cell death (81,95).

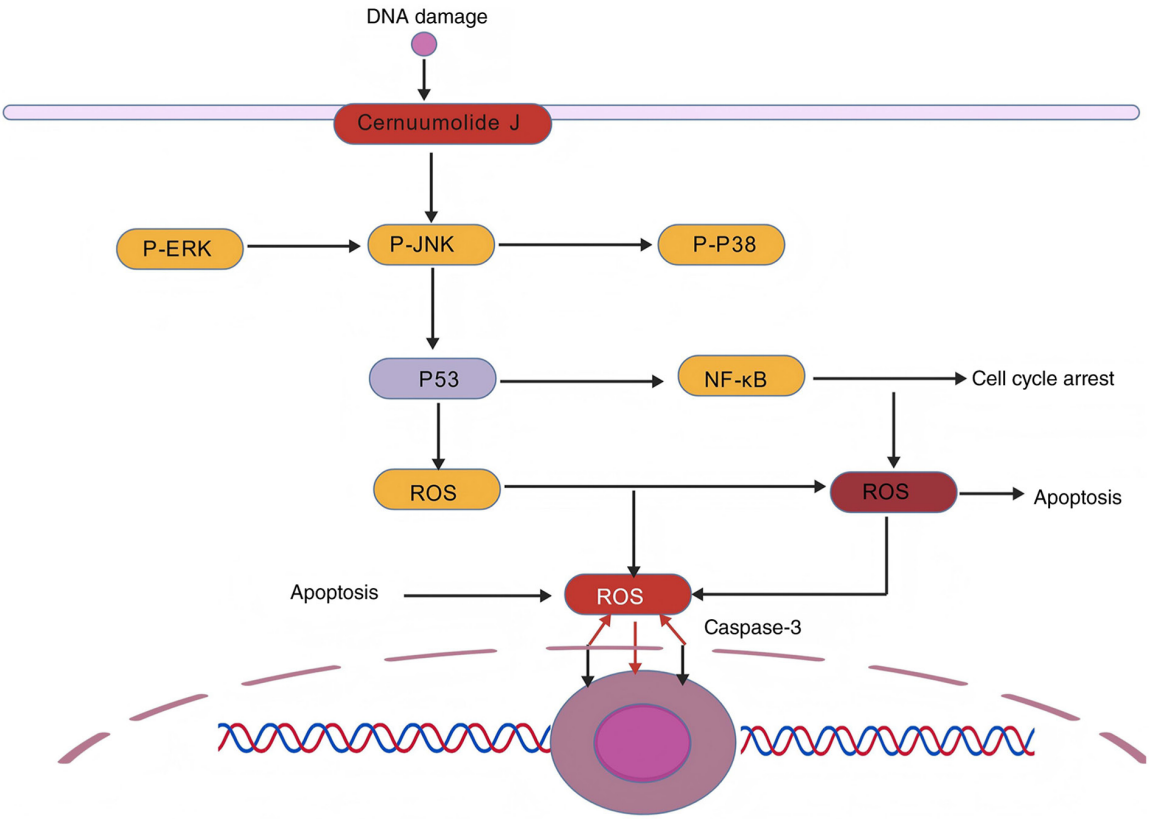


Figure 10. Regulation of the MAPK signaling pathway by cernuumolide J, a bioactive constituent isolated from *Carpesium cernuum* L. p-p38, phosphorylated p38 mitogen-activated protein kinase; p53, tumor protein p53; NF-κB, nuclear factor-kappa B; ROS, reactive oxygen species; Caspase-3, cysteinyl aspartate specific proteinase-3; DNA, deoxyribonucleic acid.

Furthermore, the regulation of the MAPKs pathway by cernuumolide J exerts a synergistic effect with the inhibition of the JAK2/STAT3 pathway. Additionally, its apoptosis-inducing effect can be significantly reversed by the pan-caspase inhibitor z-val-ala-asp (OMe)-fmk (Z-VAD-FMK), confirming that the caspase-dependent apoptotic pathway is a key executive component downstream of the MAPK signaling pathway (81). Taken together, cernuumolide J adopts a dual regulatory mode of inhibiting ERK-mediated pro-proliferation and activating JNK/p38-mediated pro-apoptosis/cell cycle arrest, orchestrates the ROS-ΔΨm-caspase axis and the cell cycle regulatory network, thereby providing core mechanistic support for its potential as a novel anti-leukemia drug candidate worthy of further exploration (Fig. 10). This mechanism is only validated in HEL leukemia cell model, and whether it is universal in other leukemia cell lines or *in vivo* needs further exploration.

5. Discussion

As a perennial herbaceous plant belonging to the genus *Carpesium* of the family *Asteraceae* (60), *C. cernuum* occupies an important position in the traditional medicine systems of ethnic minorities such as the Miao nation (4,96). Its traditional efficacies of heat-clearing, detoxification, detumescence and analgesia have been validated by long-term folk medicinal application, which provides solid traditional empirical basis for modern pharmacological mechanism research (13). With the growing attention paid to natural products in the field of novel anticancer drug development, *C. cernuum* has gradually emerged as a research focus in this area owing to its unique chemical composition and preliminarily reported anti-tumor activity. For decades, natural products have been regarded as an important origin for anticancer drug development due to their inherent merits in structure, biocompatibility and safety profile (97). *C. cernuum* harbors diverse bioactive constituents, which lay a solid material foundation for further exploring its potential anticancer potential (60). Currently, anticancer research on *C. cernuum* has achieved phased progress in aspects such as chemical constituent identification, pharmacological activity verification and molecular mechanism elucidation. Notably, existing evidence presents prominent hierarchical limitations and uneven research depth across studies: All available anticancer outcomes are exclusively supported by *in vitro* cell-based experiments, while high-level *in vivo* animal validation and clinical evidence remain absent; the reliability of research findings varies substantially across different cancer types, and the material basis and molecular mechanisms underlying several observed bioactivities remain incompletely clarified.

The anticancer potential of *C. cernuum* is derived from its complex and diverse chemical composition system, among which sesquiterpenoids play a crucial role. As secondary metabolites formed through the long-term evolution of plants, the chemical constituents of *C. cernuum* encompass multiple categories such as sesquiterpenoids, diterpenoids, flavonoids, aromatic compounds and sterols (60). These substances (plant sterols) can yield 5,7-dienal sterols, which can be converted into bioactive secosteroidal products upon exposure to UVB

irradiation (98). It is also reported that secosteroids can affect circadian rhythm (99). Such a diverse composition endows it with the inherent advantage of 'multi-component synergistic effect'. Among these constituents, sesquiterpenoids are widely recognized as core bioactive compounds with anticancer-related carriers, exhibiting rich structural diversity including germacrane-type, carabrane-type, guaiiane-type and other diverse backbone structures. Different structural types of sesquiterpenoids participate in the anti-tumor process through their respective targets. Unlike the single structural feature of chemically synthesized anticancer drugs, the structural diversity of sesquiterpenoids from *C. cernuum* derived sesquiterpenoids enables potential interactions with multiple biological targets in tumor cells (100), which may help alleviate the tumor drug resistance commonly induced by single-target therapeutic agents. This characteristic is highly consistent with the 'multi-target, multi-pathway' anticancer mode of action of natural products (101). Furthermore, although flavonoids, diterpenoids and phenolic acids are present in relatively low amounts, they are not superfluous. Instead, they may further enhance the overall anticancer effect through mechanisms such as regulating the tumor microenvironment, improving the bioavailability of core bioactive constituents, or synergistically regulating signaling pathways (60). Such a multi-component coordinated and synergistic chemical system is an important characteristic that distinguishes *C. cernuum* from single chemical drugs and also provides important theoretical basis for subsequent evaluation of its potential value as a compound anticancer preparation candidate (102). In terms of anticancer pharmacological effects, *C. cernuum* and its bioactive constituents exhibit preliminary evidence of broad-spectrum antitumor inhibitory activity in preclinical cell models, exerting significant regulatory effects on various clinically common malignant tumors. Its mechanism spans multiple key links in tumor initiation and progression. For prostate cancer, *C. cernuum* extract achieves multi-dimensional regulation of tumor cell proliferation, apoptosis, migration and invasion by regulating key signaling pathways. It not only inhibits the aberrant proliferation of tumor cells but also initiates the apoptotic program, while reducing the metastatic potential of tumor cells, thereby forming a comprehensive anti-tumor effect at the cellular level (90). In pancreatic cancer treatment research, specific sesquiterpenoid components from *C. cernuum* exhibit prominent anti-tumor activity *in vitro* assays. They can not only effectively inhibit the proliferation capacity of pancreatic cancer cell populations but also disrupt the molecular basis of cancer cell invasion by downregulating the expression of tumor migration-related MMPs, thereby providing a research direction for inhibiting the metastasis and spread of pancreatic cancer (77). For leukemia, the extracts and bioactive constituents of *C. cernuum* mainly exert their effects through mechanisms such as activating apoptotic signaling pathways and inducing cell cycle arrest. They can induce typical apoptotic morphological characteristics in leukemia cells while inhibiting their aberrant proliferation, thereby representing a candidate for further preclinical investigation for leukemia treatment (13). In breast cancer research, the extracts and monomeric constituents of *C. cernuum* exhibit inhibitory activity against different subtypes of breast cancer cells. They show particular potential in inhibiting the metastasis of triple-negative breast cancer, with the underlying mechanisms involving the regulation of cell adhesion pathways and the balancing of metastasis-related gene expression, thereby suppressing extracellular matrix degradation mediated by MMPs and reducing the migratory and invasive capacities of tumor cells (28). Notably, as a naturally derived medicinal plant, the bioactive constituents of *C. cernuum* exert potent anticancer effects with acceptable *in vitro* biocompatibility. This advantage enables it to potentially exert a chemosensitizing effect when combined with chemotherapeutic drugs, reducing the dosage of chemical agents and alleviating the toxic side effects on normal tissues, thereby providing a novel possibility for the optimization of clinical chemotherapeutic regimens (103).

Despite progress achieved in anticancer research on *C. cernuum*, it still faces numerous academic challenges and technical bottlenecks in the transition from basic research to clinical application. These issues not only restrict the translation efficiency but also point out the direction for subsequent research (104). First, the isolation, purification and large-scale acquisition of bioactive constituents constitute the primary current technical challenge. Most core bioactive constituents in *C. cernuum* are present in trace amounts and some exhibit complex structures and similar polarities. Traditional isolation and purification methods are cumbersome and inefficient, making it difficult to achieve large-scale preparation of high-purity monomers. This insufficient sample availability restricts the implementation of subsequent *in vivo* pharmacodynamic verification, pharmacokinetic profiling and systematic preclinical safety evaluation, greatly hindering in-depth translational research (105). Second, the extreme scarcity of standardized *in vivo* experimental evidence is the core limitation restricting the reliability and translational value of existing conclusions (106). Most existing studies have focused on *in vitro* cell experiments. Although these studies have clarified the anticancer activity and partial molecular mechanisms, there are significant differences between the *in vitro* environment and the complex physiological and pathological conditions *in vivo*. Key factors such as the regulatory role of the tumor microenvironment, the influence of drug-metabolizing enzymes and the interaction of immune cells have not been fully considered (107). Currently, *in vivo* studies on *C. cernuum* remain relatively limited, lacking systematic animal model validation for different tumor types. Furthermore, pharmacokinetic profiles and long-term toxicological data of *C. cernuum* remain severely lacking (105). Such data are indispensable prerequisites for advancing clinical research and their scarcity greatly hinders the translational progress of this medicinal plant from basic laboratory studies to clinical application.

In terms of research on the mechanism of action, the existing achievements still have insufficient depth and breadth. Current research mostly focuses on the regulation of a specific signaling pathway by a single bioactive constituent. Although the roles of some key molecules have been clarified, as a multi-component complex, the overall anticancer effect of *C. cernuum* is more likely derived from the synergistic regulation of multiple signaling pathways by multiple constituents. Currently, the synergistic or antagonistic interactions between different types of constituents, the cross-regulatory networks

among structural analogues of the same compound class, and their collective contribution to anticancer bioactivity have not been systematically elucidated (108). Furthermore, as an important factor affecting tumor initiation and progression (109), whether the bioactive constituents of *C. cernuum* exert their effects through pathways such as regulating the functions of cancer-associated fibroblasts and immune cells, or inhibiting tumor angiogenesis, remains under initial research. This also limits the comprehensive understanding of its anticancer mechanism. Meanwhile, numerous obstacles in the clinical translation process cannot be ignored. To date, there are no clinical research reports on *C. cernuum* related preparations for tumor treatment and key issues such as their safety, efficacy, optimal dosage and administration route in humans remain unclear. Since factors such as the growth environment, harvesting time and processing methods of *C. cernuum* all affect its chemical composition and content, the lack of unified quality control standards will make it difficult to guarantee the pharmacodynamic stability of different batches of products, which is also a common key academic issue in the development of natural drugs. In addition, as a wild medicinal plant, long-term overharvesting of *C. cernuum* may lead to the depletion of natural resources. Meanwhile, the immaturity of artificial cultivation technology makes it difficult to meet the demand for large-scale development, and the issue of resource sustainability also requires adequate attention (28).

To address the aforementioned issues, future anticancer research on *C. cernuum* should adhere to the philosophy of interdisciplinary integration (110), conducting systematic research from multiple dimensions including technological innovation, mechanism refinement, clinical translation and resource protection. In terms of the technology for the isolation and preparation of bioactive constituents, modern and efficient separation technologies should be actively introduced and separation process parameters optimized to improve the separation efficiency and purity of bioactive constituents. Meanwhile, exploring the application of biosynthesis technology, by constructing engineered strains *via* genetic engineering approaches, can achieve large-scale production of core bioactive constituents, fundamentally addressing the issue of insufficient raw material supply. In terms of pharmacological and toxicological research, it is necessary to strengthen the systematicness and comprehensiveness of *in vivo* experiments, establish orthotopic transplantation models or patient-derived xenograft models for various tumors to more realistically simulate the clinical tumor growth characteristics (111) and comprehensively evaluate the *in vivo* anticancer efficacy of *C. cernuum* extracts and bioactive monomers. Meanwhile, systematic pharmacokinetic studies should be conducted to clarify the rules of absorption, distribution, metabolism, and excretion *in vivo*, thereby providing a scientific basis for the design of clinical administration regimens (112). Furthermore, long-term toxicological experiments should focus on the impacts on vital organs such as the liver, kidneys and hematopoietic system to verify its safety and toxicological characteristics, so as to support its potential clinical application.

Tumor progression represents systemic homeostasis disruption and multi-component natural products are well-suited to modulate these intricate interconnected regulatory networks (113). In terms of mechanism-of-action research, it is essential to break through the research paradigm of single constituent and single pathway. Multi-omics technologies such as network pharmacology, transcriptomics and proteomics should be adopted to dissect the interaction network between multiple constituents of *C. cernuum* and multiple targets in tumor cells, thereby clarifying the synergistic regulatory mechanisms of different constituents (114). Meanwhile, it is necessary to further explore its regulatory role in the tumor microenvironment, analyze the interactions between bioactive constituents and immune cells or vascular endothelial cells and provide theoretical support for the development of novel preparations with both direct anti-tumor and immunomodulatory functions (115). In addition, the application of artificial intelligence (AI) technology in this field is particularly essential (116). AI technologies including big data mining, target prediction, molecular simulation and intelligent screening can rapidly clarify the constituents and action mechanisms of natural products, efficiently integrate multi-omics data, optimize clinical medication regimens and medicinal material quality evaluation (117). It can comprehensively promote pharmacological research, clinical transformation and resource management of medicinal plants, and accelerate and improve the research and development of natural anti-tumor drugs (118).

In terms of clinical translation, the scientific pathway of 'preclinical research-clinical trials' should be followed. First, the preparation process should be optimized to develop dosage forms suitable for clinical application and improve the bioavailability of bioactive constituents. Phase I, II and III clinical trials will be sequentially conducted to clarify its safety and efficacy in cancer patients, explore its combination therapy regimens with chemotherapeutic agents, targeted drugs, or immune checkpoint inhibitors and assess its possible clinical therapeutic value. In terms of quality control and resource protection, a multi-index component-based quality evaluation system should be established and modern analytical techniques should be employed for the quantitative analysis of core bioactive components to ensure the stability and uniformity of product quality. Meanwhile, the resource investigation and protection of *C. cernuum* should be strengthened, a germplasm resource bank should be established and the conditions for artificial cultivation should be optimized to realize the sustainable utilization of its resources.

To summarize, as a traditional medicinal plant, *C. cernuum* possesses abundant chemical components and *in vitro*-observed anticancer activity, thereby providing a valuable natural resource for exploring potential novel anticancer drugs. Existing studies have initially confirmed its definite effects in inhibiting the proliferation, metastasis of various tumor cells and inducing their apoptosis. Furthermore, its multi-component and multi-target mode of action, coupled with the advantage of *in vitro* biocompatibility, endows it with certain research potential for further investigation. However, issues such as the difficulty in the large-scale acquisition of bioactive components, the scarcity of *in vivo* data, insufficient in-depth studies on its mechanisms, the lag in clinical translation and the insufficiency of resource sustainability still need to be addressed through multidisciplinary collaborative innovation. In the future, through the innovation of technical methods, the expansion of research depth, and the advancement of translational

application, it is expected to clarify whether *C. cernuum* can progress from basic research to clinical application, thereby potentially offering a new natural drug option for tumor therapy and also offering a referable research paradigm for the modernized development of traditional medicinal plants.

6. Conclusion

The present study systematically summarized the traditional applications, chemical components, anticancer pharmacological effects, and action targets of *C. cernuum* It has been demonstrated that *C. cernuum* abounds in sesquiterpenoids, flavonoids, phenolic acids, and other bioactive components, among which sesquiterpenoids are the core anticancer bioactive components. Additionally, it contains diterpenoids and other auxiliary bioactive components, which collectively form the material basis for its broad-spectrum anticancer activity. Its bioactive components have been shown to exhibit significant inhibitory effects on various tumor cells, including prostate cancer, pancreatic cancer, leukemia and breast cancer. They can not only achieve multi-dimensional anticancer effects such as cell cycle arrest, apoptosis induction, autophagy activation, and metastasis inhibition by regulating key signaling pathways including the PI3K/Akt/mTOR signaling axis and Hippo signaling pathway, but some components can also synergistically enhance the efficacy of clinical drugs. Moreover, they exhibit low toxicity and side effects, thus possessing great potential for development as novel anticancer drugs or chemosensitizers.

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Availability of data and materials

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Authors' contributions

JXM, MQL and HMW wrote the manuscript and created the figures. JXM, QH and YL performed literature screening and critically revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethical approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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