THE ROLE OF CANCER CELL LINES IN MODERN ONCOLOGY RESEARCH

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Abstract: Cancer cell lines are pivotal tools in cancer research, providing invaluable insights into tumor biology, drug development, and treatment response. Derived from human tumors, these immortalized cell lines allow for the study of cancer mechanisms in a controlled laboratory environment. This article reviews the characteristics, types, and applications of various cancer cell lines, including their role in screening potential therapeutic agents and understanding cancer cell behavior. While they offer significant advantages in research, including reproducibility and ease of manipulation, limitations such as genetic drift and a lack of tumor microenvironment simulation must be acknowledged. This review underscores the importance of cancer cell lines in advancing cancer research and highlights the need for complementary approaches to fully understand the complexities of cancer.

Keywords: Cancer, cell lines, A375, A431, A498, A549, **A2780,** B16-F1, BE(2)-C, BT-20, BxPC-3 (BxPC3), Caco-2 [Caco2]

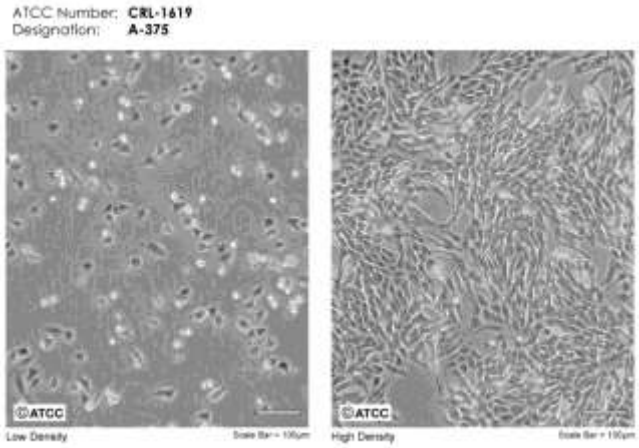
Introduction: Cancer cell lines are derived from human tumors and are widely used in laboratory settings to study cancer mechanisms and test new therapies. They have become crucial in the development of targeted treatments and in the exploration of cancer biology. This section provides an overview of the significance of cancer cell lines, their history, and their impact on modern cancer research.

Methods: A systematic literature review was conducted using databases such as PubMed and Scopus, focusing on studies published in the last decade. Keywords included "cancer cell lines," "tumor models," and specific cancer types. Inclusion criteria comprised peer-reviewed articles and significant experimental studies, while non-English articles and studies lacking substantial data were excluded. Key data were extracted and categorized based on cancer type and research applications.

Findings: The review synthesizes key findings across various studies, illustrating the diverse applications of cancer cell lines in drug discovery, genetic research, and cancer biology. Notable cell lines, such as HeLa, MCF-7, and A549, are discussed in detail, including their characteristics and relevance to specific cancer types. Trends in research methodologies and gaps in current knowledge are also identified.

A375

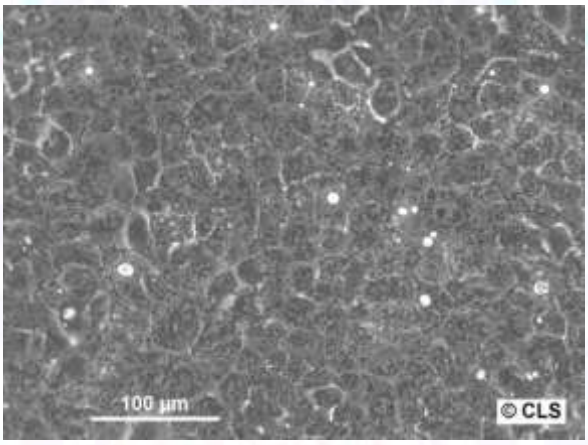
A375 is a human melanoma cell line initiated through explant culture of a solid tumor from a 54-year-old female. The cells are adherent with an epithelial morphology. The cells form tumors following implantation into immunocompromised mice.



A-431

A-431 cells are a human cell line derived from a solid epidermoid carcinoma tumor in an 85-year-old female patient. This cell line has an epithelial morphology and grows in clusters. Because of their high EGFR expression levels are frequently used as a positive control for EGFR expression in cancer, toxicity, and immuno-oncology studies. A-431 cells are grown in DMEM with 10% fetal bovine serum (FBS). A431 cells exhibit an atypical response due to their high EGFR expression. A-431 cells stimulated by EGF undergo rapid tyrosine phosphorylation of intracellular signaling proteins that control cellular processes such as growth, proliferation, and death. EGF promotes A-431 cell proliferation at low concentrations, but at higher concentrations, it inhibits cell growth by inducing terminal differentiation. Additional in vitro studies show that EGF significantly inhibits protein synthesis and DNA replication. Although several receptors are involved in the EGF-induced down-regulation of A431 cells, the loss of EGFR expression is less pronounced than in other cell types. Bradykinin inhibits both baseline and EGF-induced EGFR phosphorylation in A-431 cells. In response to phorbol esters and Sertoli cell-secreted growth factor (SCSGF), A-431 cells express the interleukin 1-related protein IL1H. Because of their high EGFR expression, A-431 cells are frequently used in cancer-related studies on the cell cycle and cell signaling pathways. They are highly susceptible to mitogenic stimulation because they lack a

functional copy of p53, a potent tumor suppressor gene. A-431 cells demonstrated antitumorigenic effects of additional EGF and radiation-sensitive characteristics in xenografts. The A-431 cell line is an appropriate cell model for evaluating cancer therapy because it has been engineered to express tumor antigens such as mesothelin and GPC3. A-341 cells are hypertriploid with a median chromosomal number of 74, which is found in 36% of them. They can proliferate in soft agar colonies and subcutaneous tumors in mice with compromised immunity. The cells express many isoenzymes, including AK-1, ES-D, G6PD, GLO-I, Me-2, PGM1 and PGM3.



A431 cells were established from an epidermoid carcinoma in the skin (epidermis) of an 85- year-old female patient. Epidermal growth factor (EGF) stimulation of A431 cells induces rapid tyrosine phosphorylation of intracellular signaling proteins which control cellular processes such as growth, proliferation and apoptosis. At low (picomolar) concentrations, EGF promotes cell growth of A431 cells whereas at higher (nanomolar) concentrations it inhibits growth by causing the cells to terminally differentiate. Treatment of A431 cells with bradykinin reduces basal and EGF-induced EGFR phosphorylation. Treatment with Sertoli cell secreted growth factor (SCSGF) strongly induces cell proliferation. Stimulation of A431 cells with phorbol esters induces expression of interleukin 1-related protein IL1H.

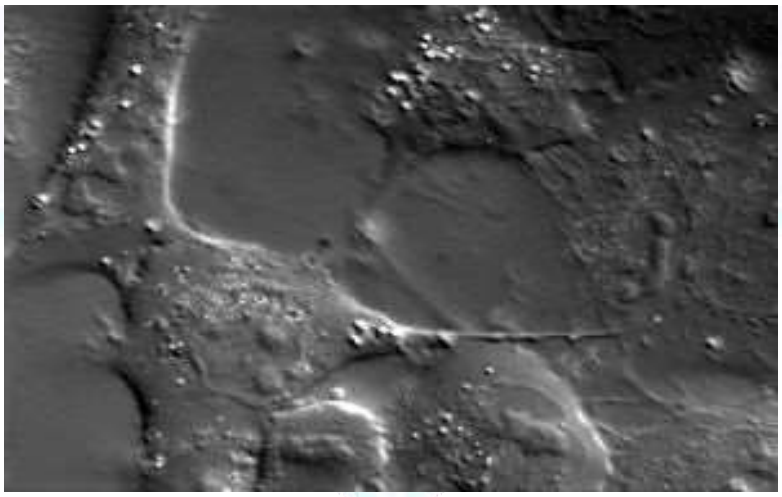
A431 cells are used in studies of the cell cycle and cancer-associated cell signalling pathways since they express abnormally high levels of the Epidermal growth factor receptor (EGFR). They are often used as a positive control for EGFR expression. They contain no functional p53, a potent tumor suppressor gene, and are highly sensitive to mitogenic stimuli. In xenografts, A431 cells have shown antitumorigenic properties of introduced EGF and related radiation sensitization characteristics. Other *in vitro* studies have found EGF to also cause substantial lowering of DNA replication and protein synthesis. The A431 lines engineered to express tumor antigens such as mesothelin and GPC3 have been made as cell models to test cancer therapeutics.

A498

The A498 cell line is a human kidney cancer cell line that was derived from the renal cell carcinoma of a patient in 1975. A498 cells are commonly used in cancer research to study the biology of kidney cancer and test new therapies. Renal cancer is responsible for nearly 63,000 new cases diagnosed annually with an average age at diagnosis of 64 years, as per the National Cancer Institute. The exact cause of renal cancer is unknown, and scientists often rely on preclinical research in the development of innovative kidney therapeutics. Despite the improvements in outcomes for patients with advanced RCC, the 5-year relative survival rate remains low, signaling that improved therapeutic regimens are still required. Xenograft studies have a significant impact on the development of cancer treatment. The A498 epithelial cell line was isolated from the kidney carcinoma of a 52-year-old male by D.J. Giard in 1973. The A498 cell line is tumorigenic in nude mice. A 2017 study in Cancer Science demonstrates with the A498 model line that simultaneous targeting of tumor cell growth and angiogenesis by a combination of lenvatinib and everolimus resulted in enhanced antitumor activity and led to tumor regression and that the inhibition of both VEGF and FGF signaling pathways by the combination proves its anti-angiogenic activity in the A498 RCC xenograft model. The 2008 study by Wu et al. used the A498 cell model to characterize the drug YC-1 ({3-(5′-hydroxy methyl-2′-furyl)-1-benzylindazole}) which was first discovered for its antiplatelet activity and was later shown to target HIF-1 pathways including VEGF and erythropoietin. Results from the study showed increased phosphorylation of JNK, cytotoxicity induced by YC-1 and an increase in apoptosis via mitochondria and caspase mediated pathways. In 2013 Fang et al. released a study using the A498 cells to test 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors to improve renal cell carcinoma prognosis. Data demonstrated the ability of simvastatin to reduce proliferation, motility and in vivo tumor growth; results also suggest this mechanism is via inhibition of IL-6 induced phosphorylation of STAT3 AND JAK2 (AKT/mTOR and ERK were also downregulated) that results in reduction metastasis and promotion of apoptosis. A 2011 study (Zhang et al.) used A498 cells to demonstrate that the cytokine interleukin-22 (IL-22) suppresses proliferation of renal cell carcinoma via a STAT1 pathway and cell cycle arrest. It was previously thought that the mechanism was through apoptosis induction and upregulation of inflammatory cytokines; understanding drug mechanisms is important for the development of appropriate therapies. The A498 cell line (human kidney) is used to create the CDX (Cell Line Derived Xenograft) A498 xenograft mouse model. The A498 xenograft model is currently utilized in preclinical studies involving apoptosis thru activation of JNK pathway (e.g. YC-1), inhibitors targeting hypoxia-inducible factor (HIF; e.g. ELR510444) and anti-tumor efficacy.

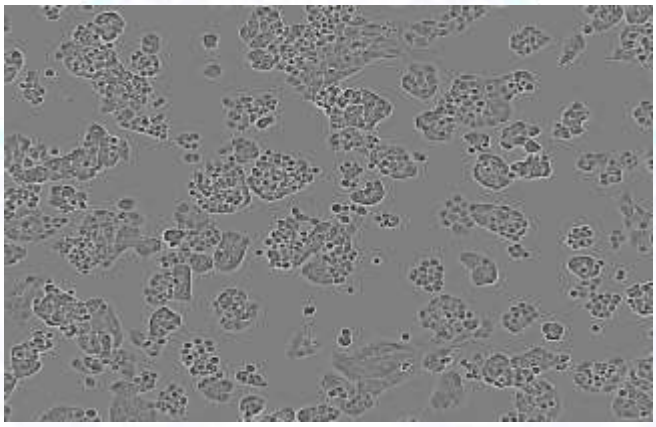
A549

A549 cells are adenocarcinomic human alveolar basal epithelial cells, and constitute a cell line that was first developed in 1972 by D. J. Giard, et al. through the removal and culturing of cancerous lung tissue in the explanted tumor of a 58-year-old caucasian male. The cells are used as models for the study of lung cancer and the development of drug therapies against it.
A549 cells, as found in the lung tissue of their origin, are squamous and responsible for the diffusion of some substances, such as water and electrolytes, across alveoli. If A549 cells are cultured *in vitro*, they grow as a monolayer; adherent or attaching to the culture flask. The cells are able to synthesize lecithin and contain high levels of unsaturated fatty acids, which are important to maintain membrane phospholipids. A549 cells are widely used as a type II pulmonary epithelial cell model for drug metabolism and as a transfection host. When grown for a sufficiently long time in cell culture, A549 cells may begin to differentiate, as signaled by the presence of multilamellar bodies. A549 cells have served as models of alveolar Type II pulmonary epithelium, finding utility in research examining the metabolic processing of lung tissue and possible mechanisms of drug delivery to the tissue. In context of lung cancer drug development, the cells have served as testing grounds for novel drugs - such as paclitaxel, docetaxel, and bevacizumab - both *in vitro* and *in vivo* through cell culture and xenografting, respectively. Single-cell tracking of A549 has enabled the elaboration of pedigree-tree profiles and demonstrate correlations in behavior among sister cells. Such observations of correlations can be used as proxy measurements to identify cellular stress and inheritance as a response to drug treatment. A549 has also been employed in viral research and associated protein expression changes as a consequence of viral infection. Although A549 is a cancer cell line, it has also been studied for its response to tuberculosis, specifically the production of chemokines as it is induced by the invading bacteria.



A2780

Ovarian Cancer cell line A2780 (ECACC catalogue no. 93112519) The ovarian cancer cell line A2780 is uniquely deposited with ECACC and is one of its most frequently requested cell lines. This cell line was established from an ovarian endometroid adenocarcinoma tumour in an untreated patient and is commonly used as a model for ovarian cancer to observe the effects and test the potency of various chemicals, methods of delivery and treatments.



A2780, 48 hours post seeding

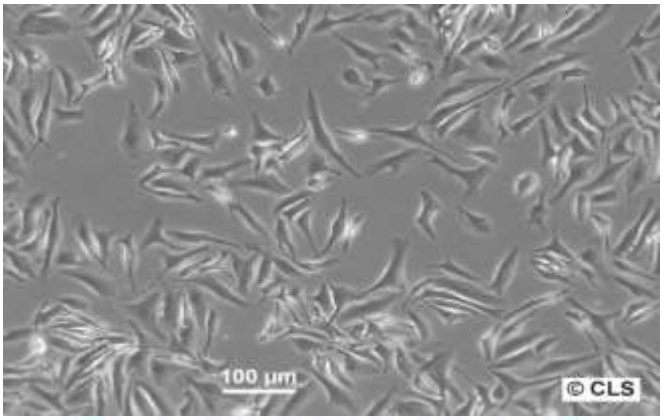
A2780 is an ovarian cancer cell line that was established from an Ovarian endometroid adenocarcinoma tumour in an untreated patient. It was deposited with ECACC by Dr T H Ward, from the Cell Culture Unit of the Patterson Laboratories, at the Christie Hospital in Manchester. The cell line has an epithelial morphology and cells grow as a monolayer in tissue culture flasks and in suspension in spinner cultures. The patient from whom the A2780 cell line was established, did not receive treatment for their tumour before tissue was taken, and so the cell line has not been exposed to any anticancer drugs or chemicals. It is commonly used as a model to observe the effects of, and test the potency of various chemicals, methods of delivery and treatments for ovarian cancer.

Two drug resistant A2780 cell line variants are also available from the ECACC general collection:

B16-F1

B16-F1 is a murine cell line of melanoma, which was derived from the pulmonary melanoma nodule from the first serial passage of B16-F0 parent cell line in C57BL/6 mice. The model is suited for the evaluation of anti-cancer immunotherapy efficacy and PD.

B16-F1 is an animal cell line exhibiting morphology that is a mixture of spindle-shaped and epithelial-like cells. It was isolated from the skin of a mouse with melanoma. This product has applications in toxicology.



BE(2)-C

BE(2)-C is a clone of the SK-N-BE(2) neuroblastoma cell line (see ATCC CRL-2271) that was established in November of 1972 from a bone marrow biopsy taken from a child with disseminated neuroblastoma after repeated courses of chemotherapy and radiotherapy. The cells grow as clusters of flattened neuroblastic cells with occasional fine cell processes (neurites). Unlike the parent line, they generally do not detach and float.

BT-20

BT-20 is a breast cancer cell line derived from a 74-year-old human female in 1958 by E.Y. Lasfargues and L. Ozzello. The cells technically came from a triple-negative breast cancer, which was caused by an invasive ductal carcinoma in the mammary gland.

BxPC-3 (BxPC3)

BxPC-3 (BxPC3) is a human pancreatic cancer cell line used in the study of pancreatic adenocarcinomas and treatments thereof. BxPC-3 cells were derived from a 61-year-old female in 1986, and were confirmed to be tumorigenic in athymic nude mice, with moderate differentiation.

The cells produce mucin, and exhibit an epithelial morphology. BxPC-3 cells lack a KRAS mutation, though it is commonly found in pancreatic cancers. BcPC-3 cells, along with JoPaca-1 cells, have high expression of cancer stem cell markers.

BxPC-3 has been used in tumorigenicity studies, pancreatic cancer therapy research, and other biomedical applications. The cells have been additionally studied for their phenotypic and genotypic properties as they can be applied to pancreatic cancer drug development; in particular, BxPC-3 cells have high expression of the angiogenic factors IL-8, VEGF, and PGE2, which can serve as potential drug targets.

Caco-2 [Caco2]

Caco-2 [Caco2] are epithelial cells isolated from colon tissue derived from a 72-year-old, White, male with colorectal adenocarcinoma. This cell line is a suitable transfection host and has applications in cancer and toxicology research.

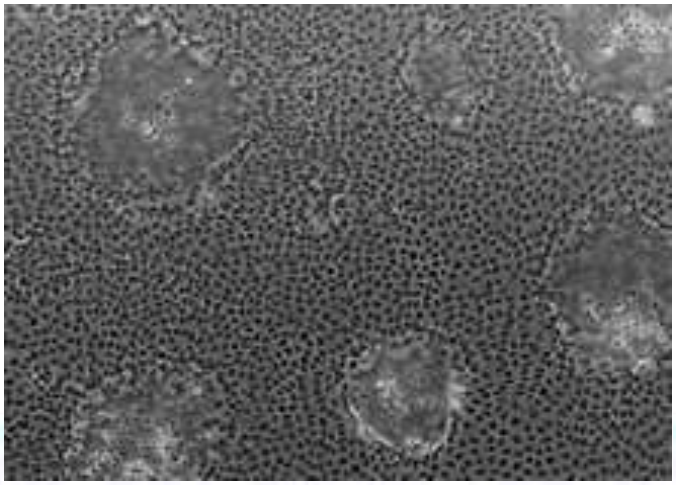
The Caco-2 cell line is originally derived from a colon carcinoma. However, one of its most advantageous properties is its ability to spontaneously differentiate into a monolayer of cells with many properties typical of absorptive enterocytes with brush border layer as found in the small intestine.

Caco-2 (from Cancer coli, "colon cancer") is an immortalized cell line of human colorectal adenocarcinoma cells. It is primarily used as a model of the intestinal epithelial barrier. In culture, Caco-2 cells spontaneously differentiate into a heterogeneous mixture of intestinal epithelial cells. It was developed in 1977 by Jorgen Fogh at the Sloan-Kettering Institute for Cancer Research. The line was developed in 1977 by Jorgen Fogh at the Sloan-Kettering Institute for Cancer Research. The research application of Caco-2 cells was developed during the 1980s by Ismael Hidalgo, at the Borchardt laboratory, University of Kansas and Tom Rauband at the Upjohn Company.

Characteristics. Although derived from a colon (large intestine) carcinoma, when cultured under specific conditions the cells become differentiated and polarized such that their phenotype, morphologically and functionally, resembles the enterocytes lining the small intestine. Polarized caco-2 cells express tight junctions, microvilli, and a number of enzymes and transporters that are characteristic of such enterocytes: peptidases, esterases, P-glycoprotein, uptake transporters for amino acids, bile acids, carboxylic acids, etc.

Research applications. Microscopically, Caco-2 cell cultures show obvious heterogeneity likely reflecting the complex mixture of cells found in the epithelial lining of the large and small intestine i.e. enterocytes, enteroendocrine cells, goblet cells, transit amplifying cells, paneth cells and intestinal stem cells. Over time, the characteristics of the cells used in different laboratories have diverged, introducing inter-laboratory variation. Despite such heterogeneity, Caco-2 cells are used in cell invasion studies, viral transfection research, and lipid transport.

Caco-2 cells may be used as a confluent monolayer on a cell culture insert filter (e.g., Transwell). In this format, Caco-2 cells form a polarized epithelial cell monolayer that provides a physical and biochemical barrier to the passage of ions and small molecules.[4][8] The Caco-2 monolayer can be used as an in vitro model of the human small intestinal mucosa to predict the absorption of orally administered drugs. Kits, such as the CacoReady, have been developed to simplify this procedure.[9] A correlation between the in vitro apparent permeability across Caco-2 monolayers and the in vivo fraction absorbed has been reported.



COLO205

The COLO 205 cell line is made up of epithelial cells isolated in 1975 from ascitic fluid derived from a 70-year-old, White, male with colon cancer. The cells can be used for cancer and toxicology research. Discounts may be available for our fellow nonprofit organizations.

Cell Line Description: COLO 205, COLO 201 (ECACC Catalogue 87091201) and COLO 206 (ECACC Catalogue 93052620) were all established from the ascites fluid obtained from a 70-year-old male patient with adenocarcinoma of the colon (Dukes Classification Grade D). At time of isolation, COLO 205 displayed cuboidal morphology but with increasing passage the depositor reported that COLO 205 tends to display predominantly rounded cells in clumps in suspension with cuboidal cells in the monolayer.

Discussion: This section interprets the findings, discussing the implications of using cancer cell lines in research. While these models provide a controlled environment for studying cancer, limitations such as genetic variability and the absence of the tumor microenvironment are critical considerations. Future research directions and the potential for developing more representative models are also explored.

Conclusion: Cancer cell lines are invaluable in the study of cancer, providing insights into the disease's mechanisms and aiding in the development of new treatments. However, researchers must be aware of their limitations and complement cell line studies with in vivo models and patient-derived samples for more comprehensive insights. Cancer cell lines remain fundamental to understanding cancer biology and developing new treatments. Despite their limitations, they continue to be invaluable tools in research. Addressing the challenges associated with these models is essential for advancing cancer research and improving therapeutic outcomes.

References:

1. Puzyn T., Rasulev B., Gajewicz A., Hu X., Dasari T.P., Michalkova A., Hwang H.M., Toropov A., Leszczynska D., Leszczynski J. Using Nano-QSAR to predict

the cytotoxicity of metal oxide nanoparticles, Nature Nanotechnology, 2011, 6, 175-178

2. Turabekova, M.A., Rasulev, B., Dzhakhangirov, F.N., Leszczynska, D., Leszczynski, J., Aconitum and Delphinium alkaloids of curare-like activity. QSAR analysis and molecular docking of alkaloids into AChBP, European Journal of Medicinal Chemistry, 2010, 45 (9), 3885-3894
3. Gajewicz A., Rasulev B., Dinadayalane T., Urbaszek P., Puzyn T., Leszczynska D., Leszczynski J. Advancing risk assessment of engineered nanomaterials: Application of computational approaches, Advanced Drug Delivery Reviews, 2012, 64 (15), 1663-1693
4. Patnode K., Demchuk Z., Johnson S., Voronov A., Rasulev B. Combined Computational Protein-ligand Docking and Experimental Study of Bioplastic Films from Soybean Protein, Zein and Natural Modifiers, ACS Sustainable Chemistry and Engineering, 2021, 9, 10740-10748,
5. Abdulrahman, H.L., Uzairu, A. & Uba, S. QSAR, Ligand Based Design and Pharmacokinetic Studies of Parviflorons Derivatives as Anti-Breast Cancer Drug Compounds Against MCF-7 Cell Line. Chemistry Africa, 2021, 4, 175–187. doi.org/10.1007/s42250-020-00207-7
6. Bohari, M. H., Srivastava, H. K., & Sastry, G. N. Analogue-based approaches in anti-cancer compound modelling: the relevance of QSAR models. Organic and Medicinal Chemistry Letters, 2011, 1(1), 3. doi.org/10.1186/2191-2858-1-3
7. Xu-Yan Wang, Chuang-Jun Li, Jie Ma, Chuan Li, Fang-You Chen, Nan Wang, Cang-Jie Shen, Dong-Ming Zhang. Cytotoxic 9,19-cycloartane type triterpenoid glycosides from the roots of Actaea Dahurica. Phytochemistry, 2019, 160, 48-55, doi.org/10.1016/j.phytochem.2019.01.004.