Review Article

# Review on anti-tumor effect of triterpene acid compounds


## ABSTRACT

Recent studies have found that triterpene acid type compounds has many effects including antiinflammatory, regulating blood sugar level, antiviral and antitumor activity. More importantly, triterpene acid type compounds has become one of the most popular topics recently because its selective toxic effects on cancer cells and harmless to normal cells at the same time. This review summarized the antitumor activity and the mechanism of triterpene acid type compounds, providing guideline for further research and development of new antitumor natural products.


**KEY WORDS:** Antitumor activity, apoptosis, mechanism, proliferation, triterpene acid

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## INTRODUCTION

Studies on triterpene acid type compounds have caught broad attention recently. Triterpene acid type compounds are widely distributed in Chinese traditional medicine (TCM), which is the most common one in terpene. Triterpene acid is one of the triterpene acid type exists in unbound state, which can be divided into tetracyclic triterpene and pentacyclic triterpene, of which pentacyclic triterpenes are most common in TCM. Common triterpenoids can be divided into lupane, oleanane type, Ursane type, cork type and lanostane type triterpene acid. Among them, lanostane belong to the tetracyclic triterpenes.

Triterpene acid type compounds have many excellent physiological and pharmacological activities, including antiinflammatory,[1,2] antiviral,[3,4] antibacterial[5] and the role of calming the nerves.[6] Literatures also reviewed its immune regulation, regulation of blood sugar, blood pressure lowering and antitumor activity.[7-10] It is popular especially for the feature of prevention and treatment of tumor with natural components, low toxicity and high efficiency. *In vivo* and *in vitro* studies have found many antitumor effects of triterpene acid type components, such as inhibition of cell proliferation, effects of signal transduction, apoptosis, inhibition of the secretion of matrix metalloproteinases and tumor invasion etc.[11] This review introduces antitumor activity of many subtypes of triterpene acid type components including the lupane, oleanane, Ursane, cork and lanostane, and the progress of antitumor mechanism is also reviewed.

## ANTITUMOR ACTIVITY OF TRITERPENE ACID COMPOUNDS

Recent reports indicate that, triterpene acid type compounds can directly inhibit tumor growth both *in vivo* and *in vitro*, which can induce tumor cell apoptosis, and cause cell cycle arrest.[12]

### Antitumor activity of the lupane type pentacyclic triterpenoid

Lupeol, a kind of triterpene acid, can be extracted from a variety of vegetables such as cabbage, pepper and cucumber. *In vivo* and *in vitro* studies have identified that lupane type pentacyclic triterpenoid have many pharmacological activities, including strong antitumor and antiinflammatory effects.[13] *In vitro* and *in vivo* experiments show the strong antimutation effect of the lupane type pentacyclic triterpenoid, moreover, it can also reduce the DNA damage caused by chemical reagent.[14]

Wisconsin university has launched a study of antitumor effect of the lupane type pentacyclic triterpenoid on many kinds of tumor such as: Prostate cancer, skin cancer and breast cancer. Experimental results show that, in the mouse skin carcinogenesis model, local application of lupeol for 28 weeks can inhibit the growth of tumor and prolong the latency of tumor cells. The mechanism might be related to the nuclear factor kappa B (NF-κB)/phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway.[15] In addition, studies also evidenced that the lupane type pentacyclic triterpenoid anti-tumor by regulating Bax/Bcl-2 ratio in nude mice that was transplanted with high metastatic human melanoma.[16]


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Aratanechemuge *et al*., found that hypodiploid apoptotic peak can be detected after the lupane type pentacyclic triterpenoid treatment on HL-60 leukemia cells, with time- and dose-dependency.[17]

Betulinic acid, botulin and 23-hydroxyl betulinic acid are all belong to lupane type pentacyclic triterpenoids, among which betulinic acid and its derivatives, can suppress the proliferation of human melanoma cells, and can also prevent proliferations of various nerve tumor cells, sarcoma sarcoid tumor cells and children malignant brain tumor cells.[18] *In vitro* study showed that 23-hydroxyl betulinic acid has inhibitory effect on the proliferation of multiple types of tumor cells such as HeLa cell line, human leukemia cell line HL-60, especially on human melanoma B16 cell line, inducing the differentiation of B16 melanoma cells with low doses treatment and inhibiting its proliferation with high doses.[19,20]

## Antitumor activity of oleanane type pentacyclic triterpenoids

Oleanolic acid (OA) and its derivatives, e.g. 2-cyan-3, 12-dioxo oleanane -1, 9, diene-28 acid (CDDO) and variety of derivatives of C17 bits (CDDO-Me) etc., are oleanane type pentacyclic triterpenoids, which are widely distributed in many plants such as ginseng, licorice, clove, panax pseudoginseng, with considerable antitumor activity. In nude mice transplanted with pancreatic cancer L3.6PL cells, the tumor inhibition rate can reach 74.2% by intragastric administration with CDDO-Me.[21]

Soybean saponins are oleanane type pentacyclic triterpene compounds extracted from soybean and all kinds of beans.[22] Recent research showed that, the total extract of soybean saponins can inhibit growth of HeLa,[23] Hep-G2[24] and colon adenocarcinoma HCT-15[25] cells by inducing programmed cell death, early apoptosis and autophagy. Among them, LC50 of HEPG2 cells is 0.6 mg/mL, and 0.4 mg/mL of HeLa cells.[23,24]

3-O-β-d-glucopyranosyl-hederagenin 23-O-α-d-ribofuranoside is a kind of oleanane type pentacyclic triterpene compounds extracted from the root of Chinese Pulsatilla, with growth prevention effect on tumor cells.[26]

Oleanane type pentacyclic triterpene compounds extracted from the root of red back anemone, can significantly block the growth of Ehrlich ascites hepatoma, HeLa, hepatocellular carcinoma cell lines SMMC-7721 and rat fibroblast cell line L929, with half inhibitory concentration (IC50) far less than 30 μg/mL. Among them, the strongest effect was on Ehrlich ascites hepatoma, with the highest tumor inhibitory rate reaching to 81%.[27]

## Anti-tumor activity of Ursane type pentacyclic triterpenoids

Ursolic acid (UA) belongs to Ursane type pentacyclic triterpenoids, which is widely distributed in natural environment. UA are found in many plants, such as leaves of Scrophulariaceae Paulownia, leaves and fruits of Ericaceae plant male fruit, Rubiaceae gardenia fruit and other plants. UA can obviously prohibit mouse S180 tumor growth, and also can inhibit proliferations of human tongue cancer cell line TSCC-α and HL-60 cell, as well as inducing apoptosis of breast cancer MCF-7 cell line, blocking tumor angiogenesis and enhancing the immune function.[28-30]

3α, 6α, 30-trihydroxy-ursan-28-oic acid, 3α,30-dihydroxy-6-oxo -ursan-28-oic acid and 3α, 6α, α,30-tetrahydroxy-ursan-28-oic, which are extracted from Torreya of Taxus family, are Ursane type pentacyclic triterpene compounds. They can prevent the growth of A549, HEPG2 and B16F10 cells, with an IC50 of 24.66 μM on A549 cells by compound 1, IC50 of 72.72 μM on B16F10 cells by compound 2.[31-33]

3β, 23-dihydroxy-20α(H)-urs-12-en-28-oic acid, 3β, 19A, 23-trihy droxy-20α(H)-urs-12-en-28-oic acid 3β-O-α-l-arabinopyranoside are two novel Ursane type triterpenoids extracted and isolated from traditional Chinese medicine *Ilex cornuta* root, with antitumor proliferation activity.[34]

## Antitumor activity of cork type pentacyclic triterpenoids

Although many studies identified that cork type pentacyclic triterpene compounds have antitumor activity, the mechanism is still limited to its cytotoxic activity. *In vitro* study reported that Celastrol, which belongs to the cork type pentacyclic triterpenoids, has strong cytotoxic activity on a variety of human tumor cell lines, including A549, HCT-8, MCF-7, KB, with IC50 values of 0.21, 0.25, 0.23 and 0.20 ng/mL respectively, which were all lower than 1 μg/mL.[35]

## Antitumor activity of lanostane type tetracyclic triterpene compounds

Ganoderic acid D, belonging to lanostane type tetracyclic triterpene compounds, is the extracted from *Ganoderma lucidum*. Research revealed that it can repress the proliferation of HeLa cells, with an IC50 of 17.3 μmol/L, by inducing cell apoptosis and cell cycle arrest in G2/M phase.[36] Ganoderiol F, another lanostane type pentacyclic triterpene compounds, is also extracted from *Ganoderma lucidum*, and reportedly prevent the proliferation of HepG2, Huh 7, and K562 cell lines with IC50 of 17, 8.5 and 4 μmol/L respectively.[37]

Dehydrotrametenolic acid, one of the lanostane type tetracyclic triterpenes extracted from *Poria cocos*, can induce apoptosis of J82 cell through activation of the caspase-3 pathway, and arresting cell cycle in G2/M phase. In addition, Dehydrotrametenolic acid can also regulate the expression of H-Ras, Akt and ERK.[38] 25-hydroxyporicoic acid H, 16α, 25-Dihydroxydehydroeburicoic acid, 5α, 8α-peroxydehydrotumulosic acid and 15α-hydroxy dehydrotumulosic acid, isolated from *Poria cocos*, all belong to lanostane type tetracyclic triterpenes, with inhibitory effect on EBV-EA.[10,39]

Impatienside A and bivittoside D are two lanostane type tetracyclic triterpenoids isolated from *Holothuria impatien*. It is found that in the impatienside A and bivittoside D treated tumor cell lines, including HCT-116, A549, HepG2, DU145, MCF-7 and KB cells, the cytotoxicity effects were better than the clinical applied anticancer drug etoposide, with an IC50 value of 0.25–1.9 μmol/L.[40]

Ananosic acids B and Ananosic acids C, extracted from *Kadsura longepedunculata*, belong to lanostane type tetracyclic triterpenoids, presenting antitumor proliferation activity on HeLa and HL-60 cells.[41] Lanostane type tetracyclic triterpenoids, seco-coccinic acids A-E, extracted from roots of *Kadsura coccinea*, also showed antiproliferative effects on HL-60 cell, all with IC50 values in range of 6.8–42.1 μmol/L.[42]

Daedaleasides B-E, isolated from fruit bodies of *Daedalea dickinsii*, have been identified as lanostane type tetracyclic triterpenoids. Evidence suggested that they can induce apoptosis in the HL-60 cell, through inducing the target cell internucleosomal DNA fragmentation.[43] Lanostane type tetracyclic triterpenoids, inonotsuoxides A, were isolated from sclerotia of Inonotus obliquus, has strong antitumor promoting effect on Raji cells from patients with lymphoma. In a two-stage carcinogenesis test on mouse skin, this compound exhibited significant antitumor effect. Observing the change of Epstein-Barr Virus (EBV) lymphoid stem cell viability by trypan blue staining, results showed that lanostane type tetracyclic triterpenoids, lanosta-8, 23E-diene-3b, 22R, 25-triollanosta-7, 9, 23E-triene-3b, 22R, 25-triol, isolated from *Inonotus obliquus*, all have antitumor activity, with the effect stronger than oleanolic acid positive control group.[44]

Isolated from green macroalga *Tydemania expeditionis*, lanosta-8-en-3,29-diol-23-oxo-3, 29-disodium sulfate is proven to have inhibitory effect on breast cancer, ovarian cancer, lung cancer, colon cancer and prostate cancer cells.[45] 24(E)-3-oxo-9βH-lanosta-7, 24-dien-26-ol, separated from the root bark of *Abies koreana* exhibited antitumor activity in human tumor cell lines.[46]

## THE ANTITUMOR MECHANISM OF TRITERPENE COMPOUNDS

### Inhibition of tumor cell proliferation

The cytological basis of tumor growth is the uncontrolled proliferation of tumor cells. The reason of uncontrolled proliferation of tumor cells is mainly due to their relative autonomously growth potential. Therefore, killing tumor cells with such potential uncontrolled growth capability is necessary during the therapy. Meanwhile, the basic requirements of antitumor drugs are their ability of effectively inhibits the proliferation of tumor cells.

Betulinic acid, one of the triterpenes, is very common in many plants. It exhibited antiproliferative activity on multiple tumor cells, for example, the GI50 of MCF-7 cells was 0.27 μmol/L,[47] and IC50 in the range of 2.4–4.5 μmol/L on SKNAS, TE671, T47D and 549 cells as well.[48]

A triterpenoid saponin compound TSP02, extracted from *Ardisia japonica*, inhibited HepG2 cells proliferation in a significant time- and dose-dependent manner by Thiazolyl Blue Tetrazolium Bromide (MTT) experiment analysis.[49] Methyl-2-cyano-3,12-dioxooleana-l, 9 (11)-dien-28-oate (CDDO-Me) is a kind of oleanane type pentacyclic triterpenoids. CDDO-Me treatment on pancreatic cancer MiaPaCa-2 and Pane-1 cells, prevented proliferation of tumor cells and induced cell apoptosis. The proliferation inhibition rate was 7% and 16% when the drug concentration was 0.63 μmol/L, and elevated to 84% and 80% with the concentration of 5 μmol/L.[50]

Inotodiol is a lanostane tetracyclic triterpenoids from Inonotus obliquus, when treated on murine leukemia P388 cells, the tumor proliferation was repressed, the mechanism is the activation of Caspase-3, inducing cell apoptosis.[51]

β-escin is a triterpenoids extracted from horse chestnut seeds, which can inhibit the proliferation of HL-60 cells in drug concentration between 30–50 mg/ml. Apoptosis can be detected by AnnexinV-FITC analysis, typical DNA apoptosis ladders can also be observed in DNA ladder electrophoresis, indicating that β-escin can suppress the proliferation of HL-60 cells and induce apoptosis.[52]

Cimicifoetisides A and Cimicifoetisides B are two triterpenes isolated from the rhizome of Ranunculaceae *Cimicifuga foetida*, exhibiting anti-proliferative and cytotoxic effects against tumor cells of rat ascites carcinoma cell line EAC and the human breast cancer MDA-MB-A231 cell line, with IC50 values of 0.52 and 6.74 μmol/L by Cimicifoetisides A, IC50 with IC50 values of 0.19 and 10.21 μmol/L by Cimicifoetisides B.[53]

The main chemical constituent contained in *Ligustrum lucidum* Ait is terpenoid compound, UA and OA as the representative components.[54] Researchers found[55] *Ligustrum lucidum* containing rabbit serum inhibited the proliferation of HeLa cells, It resulted in growth inhibition of HeLa cells was 5.1 % after 3 days treatment and was 20.6% after 6 days treatment.[41]

Nimbolide, presenting in the edible parts of the neem tree (*Azadirachta indica*), is a triterpenoids, which can significantly inhibit the proliferation of HT-29 cells with concentration of 2.5 mmol/L. Nimbolide also induce cell cycle arrest of HT-29 cells.[56]

Oleanane and Ursane type pentacyclic triterpene compounds presented in Rosaceae *Potentilla chinensis* and cycloartane-type triterpene glycosides in *Cimicifugae foetidae*[53] both have strong inhibitory effect on proliferation of HeLa cell lines.[42,43]

### Induction apoptosis of tumor cells

Apoptosis, which caused initiative cell death process through the activation of a series of death signals, is quite different from cell necrosis. Defective apoptosis of tumor cells induces tumor constantly proliferation beyond the normal life span, meanwhile helps tumor cells avoid cell death due to ischemia or oxygen stress. Therefore, one of the important strategies for inhibiting tumor growth is to induce apoptosis of tumor cells.

3-O-acetyl-11-keto-β-boswellic acid is one of the triterpenoid compounds obtained from a plant named Boswellia. It can induce apoptosis of tumor cells, when treated on PC-3 and LNCaP cell lines, through the activation of death receptor DR-5 signaling pathway.[57,58] Many researches have demonstrated that betulinic acid might induce tumor cell apoptosis by upregulating

the expression of proapoptotic protein Bax and downregulating the antiapoptotic protein Bcl-2 expression.[47,48,59,60,61]

OA can induce apoptosis of NB4 cells, the molecular mechanism is the increasing expression of Bax mRNA and decreasing the expression of Bcl-2 mRNA, thus activated cysteine proteinases with specificity for aspartic acid residues-3 (caspase-3) and caspase-9.[62] A recent report revealed that OA upregulated Bax/Bcl-2 ratio in HepG2 cells transplanted BALB/c mice, possibly by increasing the levels of reactive oxygen species in HepG2 cells, thus increasing cytochrome C induced cell apoptosis; in addition, OA can inhibit tumor cell proliferation through inhibition of the Akt/mTOR signaling pathway.[63,64]

The asiatic acid belongs to the Ursane type pentacyclic triterpene compounds. Its content is very high in dry grass of Umbelliferae grass centella, which can induce apoptosis of human melanoma cells SK-MEL-2, of which the mechanism may be through increased levels of oxidative stress within the tumor cells, and activation of intracellular mitochondrial apoptosis pathway, and further induce apoptosis of SK-MEL-2 cells. In addition, asiatic acid can also induce the apoptosis of HepG2 cells, which might through increasing intracellular $Ca^{2+}$ levels, thus activating P53 expression.[33]

### Blockage of tumor cell cycle

Occurrence of tumor is associated with abnormal regulation of cell cycle. Mutation of tumor suppressor genes and oncogenes leads to cell proliferation cycle out of control and cell infinite proliferation, eventually leading to tumor formation. Regulation of cell growth and differentiation is closely related to cell cycle. Therefore, with the constantly in-depth understanding of the cell cycle, a view that "cancer may be a class of cell cycle disease" is raised. And the regulation of the cell cycle has become a hot spot in tumor research.

*In vivo* and *in vitro* experiments identified that, OA can not only trigger apoptosis of HepG2 cells, but also arrest cell cycle in G2/M phase through decreasing Cyclin Bi/cdc2 activity.[60]

UA induces HaCat cell cycle arrest in G1 phase by up-regulating the expression of P21.[65] UA can block the MCF-7 and PC-3 cell cycles at G1 period without entering S phase in a concentration- and time-dependent manner.[66,67]

The molecular mechanism of Ganoderiol F inhibition of HepG2 cells is activating MAPK/EKR signaling pathway and upregulating CDK inhibitor P16, thus retards cell cycle at G1 phase.[37]

Terpenoids extract from almond hulls (*Prunus dulcis*), could induce apoptosis of A549 cells, and prevent A549 cells entering S phase, possibly by inhibiting the expression of cyclin A in a dose- and time-dependent manner.[47]

### Prevention of tumor cell invasion and metastasis

Invasion and metastasis of tumor cells are symbols of malignancy, which are also the most dangerous stage in the process of tumor occurrence, development and evolution. The golden aim of preventing tumor invasion and metastasis is to specifically block one or more steps of tumor process.

Glycyrrhizin, 18β-glycyrrhetinic acid, UA and OA are common terpenoids compounds in Chinese medicine. Recent studies evidenced that all of the four drugs have multiple effects on highly potentially metastatic lung cancer cell line (PGCL3), for example, the number of PGCL3 cell colony-formation in semi soft agar was significantly decreased, cells' adhesion to laminin, ability of migration and the secretion of cathepsin B were all significant reduced.[68]

Terpenoid soyasaponin I (SsaI) is potent sialyltransferase inhibitor. It can inhibit α2, 3-sialyltransferase activity and expression in MCF-7 and MDA-MB-23 cells, hence reducing the metastasis of tumor cells. SsaI can also enhance the adhesion of MCF-7 to extracellular matrix.[69,70]

UA has the similar efficiency on decreasing invasion and migration ability of ovarian carcinoma cells HO-8910PM, the mechanism by which is probably through reducing the expression of MMP-2 and MMP-9 protein and mRNA and repressing the activity of gelatinase.[71] UA may also limit DU145 prostate tumor cells invasion and metastasis via MMP blockade.[72,73]

Ginsenoside Rh2 is a kind of terpenoids extract from ginseng. In S180 ascites carcinoma mice orally administered Ginsenoside Rh2 monomer, tumor growth was repressed, further angiogenesis and lymphangiogenesis were inhibited by Ginsenoside Rh2 induced downregulation of intercellular junctional adhesion molecule (JAM) in tumor.[74,75] Tumor invasion and metastasis were also inhibited.[76,77]

### Inhibition of tumor angiogenesis

Unrestricted invasive growth and metastasis of malignant tumor are all depending on vascular angiogenesis. New formed blood vessels provide nutrition and oxygen for tumor, paracrine of capillary endothelial cells also affect tumor growth, meanwhile, tumor cells produce angiogenic factors stimulating the proliferation of endothelial cells. Based on these facts, inhibition of tumor angiogenesis and blocking the angiogenesis pathway can effectively prevent the growth of tumor and cut off the way of tumor metastasis, inducing tumor regression or dormant.

UA can reduce the intratumoral microvessel density in colorectal cancer mice, UA treatment suppressed human umbilical vein endothelial cells (HUVECs) growth, and inhibited the expression of key angiogenic factors VEGF-A and bFGF, as well as downregulating sonic hedgehog (SHH), STAT3, Akt and p70S6K pathways.[78,79] Hence, triterpene compounds can inhibit angiogenesis of tumor by inhibiting expression of vascular endothelial growth factor, achieving the goal of antitumor.

## SUMMARY

To date, tumor has become the most common disease threating human health. Development of high efficient and low toxic

anti-cancer drugs is one of the most urgent problems in medical field. Triterpene acid compounds have the characteristics of natural, low toxicity, high efficiency, which allows it a promising antitumor drug. This review summarized the current advancements of antitumor activity and mechanism of triterpene acid compounds, providing new insight for further research and investigations on the antitumor drug development.

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