REVIEW

The Anticancer Potential of Maslinic Acid and Its Derivatives: A Review

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Abstract: Cancer is still an insurmountable problem for humans and critically attacking human health. In recent years, natural products have gained increasing attention in the field of anti-tumor due to their extensive sources and minimal side effects. Maslinic acid (MA), a pentacyclic triterpene acid mainly derived from the olive tree (*Olea europaea* L.) has been confirmed to possess great anti-cancer effects. This paper reviewed the inhibitory effect of MA and its derivatives on lung cancer, colon cancer, ovarian cancer, gastric cancer, lymphatic, leukemia, breast cancer, pancreatic cancer, melanoma, prostate cancer, renal cell carcinoma, gallbladder cancer, and bladder cancer, among others. MA inhibited the proliferation of various tumor cells and showed lower IC_{50} values in melanoma 518A2 cells and gastric cancer MKN28 cells compared with other cell lines. A series of semi-synthetic derivatives obtained by modifying MA chemical structure have been shown to have high cytotoxicity to human tumor cell lines, but low cytotoxicity to non-malignant cells, which is conducive to developing its potential as a chemotherapeutic agent. These studies suggest that MA derivatives have broad prospects in the development of antitumor therapeutics in the future and warrant further study.

Keywords: maslinic acid, tumor, mechanism, derivatives

Introduction

Cancer, generally characterized by uncontrolled growth and spread of abnormal cells, is the second leading cause of death worldwide, following cardiovascular diseases.[1] The occurrence of cancer is complex and multi-factorial, which involves excessive oxidative stress, chronic inflammation, cell cycle disorders, abnormal expression of proto-oncogenes, and angiogenesis disorders.[2–5] Chemotherapy is a primary treatment for cancer. However, due to low selectivity and drug resistance of chemotherapeutic drugs, chemotherapy does not achieve the best possible results. Therefore, finding more effective chemotherapy agent is needed.[6,7] Natural compounds derived from Traditional Chinese Medicine (TCM), a class of drugs that are widely distributed in nature with many pharmacological applications, have been recognized as a rich source for new drug discovery.[8–11] According to reports, approximately half of small molecule anti-tumor drugs approved from the 1940s to 2018 were derived from natural products or analogs.[12,13] Therefore, natural products as promising candidates for anti-cancer treatment have broad application prospects.

Pentacyclic triterpenes are an important class of plant secondary metabolites. Due to their extensive antitumor activity and lack of obvious toxicity, pentacyclic triterpenes are promising leading compounds for developing new multi-targeting

antitumor agents.[14–17] Maslinic acid [MA, (2α,3β)-2,3-dihydroxylolean-12-en-28-oic acid] (Figure 1) is a pentacyclic triterpene acid primarily derived from the olive tree (*Olea europaea* L.) and shanzha (*Crataegus pinnatifida Bunge*), with a $C_{30}H_{48}O_4$ molecular formula, molecular weight of 472.7, and melting point and boiling point of 267–269°C and 570.0 ± 50.0°C, respectively.[18–20] MA possesses a wide range of pharmacological benefits, including anti-cancer,[21] anti-inflammatory and analgesic effects,[22–24] antiplatelet aggregation,[25,26] cardioprotective and anti-inflammatory,[27,28] antimicrobial,[29,30] hepatoprotective,[31] anti-diabetic, and anti-hyperlipidemic,[32,33] to name a few. Among these effects, it has strong clinical potential. Recent studies have focused on anticancer activity of MA, emphasizing its promising properties as an anticancer agent and as a candidate for developing anticancer drugs. In this review, we searched all relevant research papers on MA as an effective anti-cancer treatment published by PubMed and Web of Sciences in the past ten years. The search strategy implemented was to use several keywords to track related research articles, including "pentacyclic triterpenes acid," "Maslinic acid," "cancer," "tumour," "anti-cancer," and "cell death." We then analyzed and summarized all retrieved data. This review provides a basis for MA application in cancer prevention and treatment.

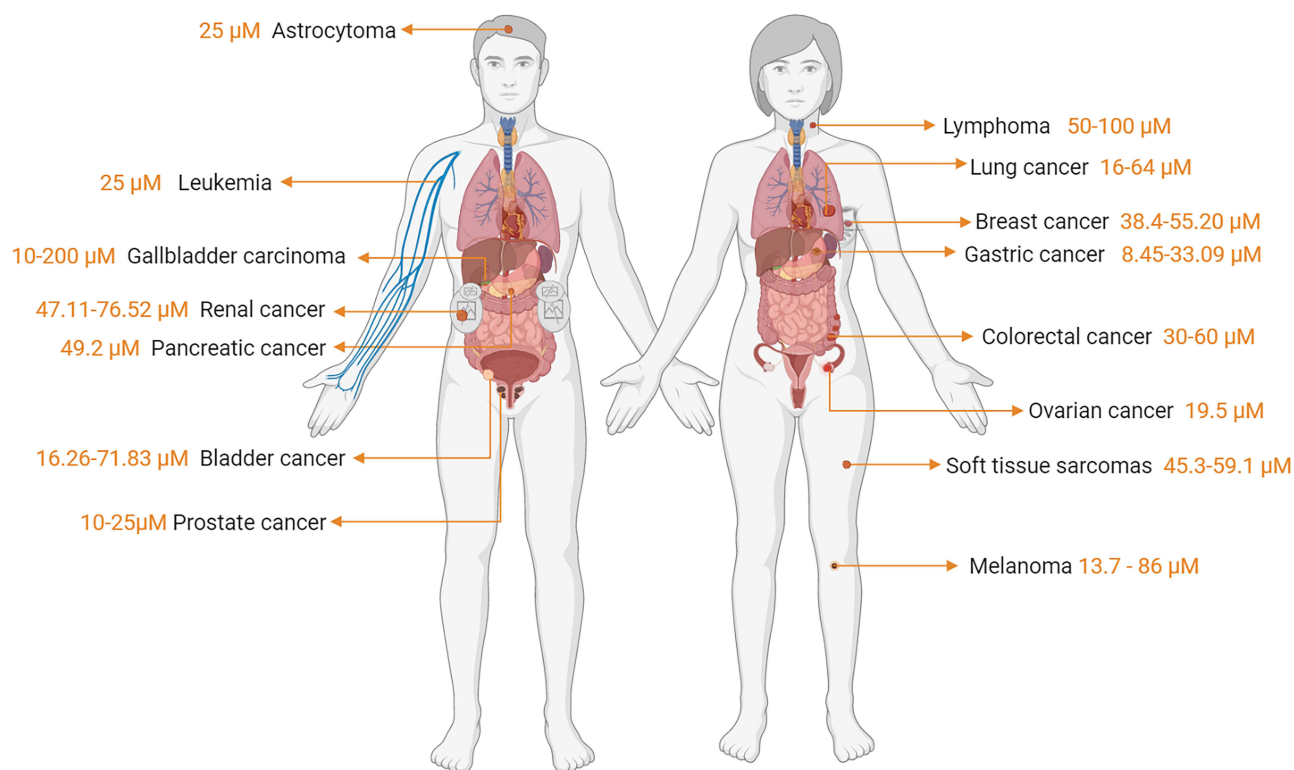## Anticancer Properties of Maslinic Acid

The therapeutic potential of MA for different cancers has been confirmed by a large number of preclinical experiments highlighting its role in regulating different cancer effects (ie, inhibiting proliferation, promoting apoptosis, regulating autophagy, and blocking angiogenesis). The cytotoxicity of MA to different cancer cells and corresponding IC50 values are briefly summarized below (Figure 2).

Colorectal Cancer

Colorectal cancer (CRC) has maintained high incidence rates in western countries. About 60,000 people in Germany are diagnosed with CRC every year and two-thirds of tumors are located in the colon.[34–36] With alterations in people's lifestyle and dietary structure, the incidence of CRC is increasing among the young population.[37] In the United States, morbidity and mortality rates among adults over the age of 50 have declined since the early 1990s, owing to advances in
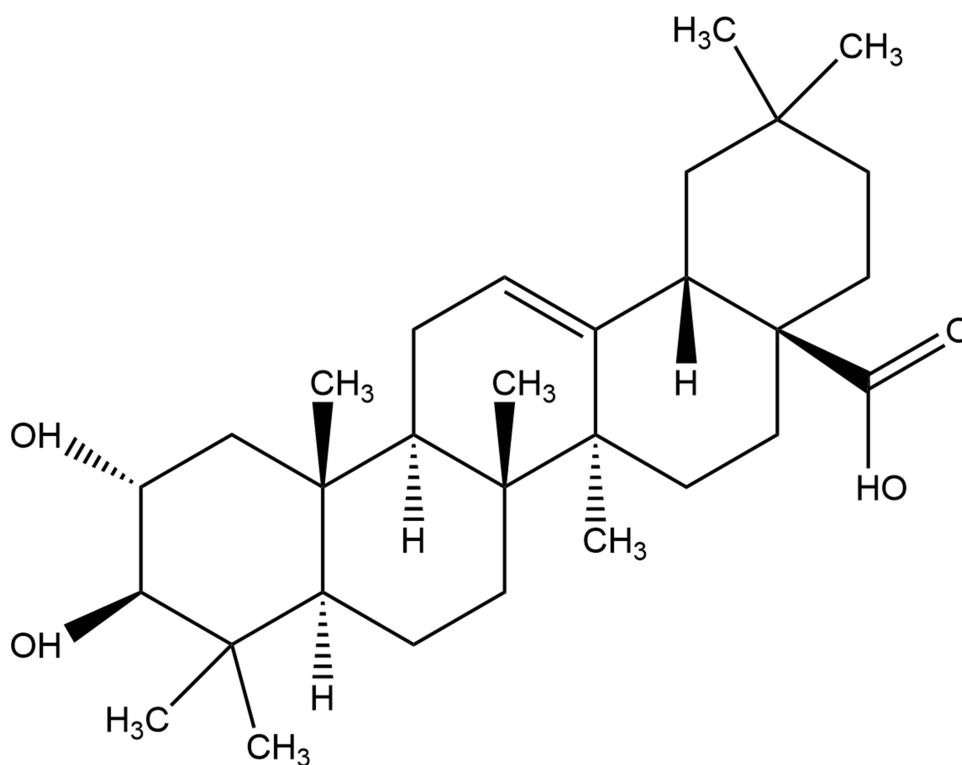
Figure 1 Chemical structure of MA.

Figure 2 Anticancer properties of MA and its corresponding IC_{50} values.
Note: Created with BioRender.com.

screening and treatment. However, CRC incidence in adults under the age of 50 continues to rise.[38,39] Currently, most CRC deaths are caused by metastasis. In recent years, MA has shown excellent efficacy in treating CRC. In vivo, MA could reduce the content of preneoplastic biomarkers in 1,2-dimethylhydrazine -induced colon cancer rat models and 5 mg/kg MA could decrease aberrant crypt foci and mucin-depleted foci amount by 15% and 27%, respectively; when MA was 25 mg/kg, the amount decreased by 33% and 51%, respectively (Table 1).[40] Further, the $Apc^{Min/+}$ mouse model is widely used in the study of human chemotherapeutic agents because it can simulate human spontaneous intestinal tumorigenesis. A recent study showed that $Apc^{Min/+}$ mice treated with 100 mg/kg MA for six weeks reduced the formation of total intestinal polyps by 45%.[41] In addition, the anti-colon cancer properties of MA have been demonstrated in vitro. Recent studies revealed that MA exerted anti-colon cancer effects by inhibiting cell proliferation and promoting cell apoptosis.[42] MA at IC_{50} of 39.7 ± 0.4 μg/mL and IC_{80} of 56.8 ± 0.1 μg/mL remarkably reduced Caco-2 human colon cancer cell proliferation and increased apoptosis (Table 2).[43] Another experiment exhibited similar results by illustrating IC_{50} and IC_{80} of MA in colon cancer cells were

40.7 ± 0.4 μg/mL and 56.8 ± 0.1 μg/mL, respectively.[44] For HT29 cells, IC_{50} (28.8 ± 0.9 μg/mL) and IC_{80} (37.5 ± 0.2 μg/mL) concentrations at 72 hours of MA could significantly induce cell apoptosis.[45] Another study demonstrated that MA negatively affected HT29 cell proliferation at concentrations of 3.7 μM ($IC_{50}/8$) and 30 μM (IC_{50}).[46]

Melanoma

Cutaneous melanoma is a serious malignant tumor, ranking third in skin malignant tumors and becoming the first fatal skin disease. The increased risk of skin melanoma is related to factors such as exposure to ultraviolet light and genetics.[47,48] Mokhtari et al proved that MA can influence B16F10 melanoma cells grown under stressful conditions, where MA showed different IC_{50} values for B16F10 melanoma cells under different conditions. When 10% FBS was added to the medium, its IC_{50} value was 36.88 μg/mL (86 μM) and when the medium was 0% FBS, its IC_{50} value became 1.48 μg/mL (3.5 μM). It is possible that the lack of FBS reduces cell activity, which in turn reduces the IC_{50} value of MA.[49] Moreover, Mokhtari et al demonstrated the inhibitory effect of MA on melanoma cells by adding 0.15 mM H_2O_2 to murine skin melanoma (B16F10)

Table 1 The Anticancer Effects of MA in vivo

Cancer Types	Animals	Models	MA Concentrations	Route of Administration	Administration Times	Effects	References
Colorectal cancer	4-week-old male mice	ApcMin/+ intestinal polyp mouse model	100 mg MA/kg feed	Diet supplemented	6 weeks	Reduced total intestinal polyp formation by 45%	[41]
	6-week-old male C57BL/6J mice	Azoxymethane (AOM)/dextran sulfate sodium (DSS) mice model	10 mg/kg and 30 mg/kg day-1	Orally	40 days	Protects against DSS-induced acute colitis, attenuated the increase of tumors. ↓IL-6, ↓TNF-α, ↑IL-10,	[42]
	5-week-old male BALB/c nude mice	HCT116 xenograft model	10 mg/kg and 30 mg/kg day-1	Orally	17 days	Suppressed the tumorigenesis, ↓p-mTOR, ↓p-4EBP1, ↓p70S6K,↑p- AMPK.	[42]
Leukemia	5-week-old male BALB/c mice	WEHI-3 xenograft model	0, 8, 16, 32 mg/Kg	Intraperitoneal injection	2 weeks	Increase immune responses: enhanced macrophage phagocytosis and NK cell activities	[80]
Pancreatic cancer er	4–5 week-old athymic nu/nu male mice	Panc-28 xenograft model	10, 50 mg/kg MA every 2 day	Subcutaneous injected	36 days	Suppressed pancreatic tumor growth, induced tumor apoptosis, and inhibited NF-B-regulated anti-apoptotic gene expression, such as Survivin and Bcl-xl.	[112]
Gallbladder cancer	6-week-old athymic nu/nu male mice	EH-GB2 xenograft model	30 mg/kg MA every 2 days +GEM	Subcutaneously injected	30 days	Inhibitory tumor volume, and decreased NF-κB-regulated gene products expression.	[90]

cells and healthy cells (A10) to stress the cells and explore the role of MA in protecting cell lines from oxidative damage under stress conditions. The results showed that MA could reestablish superoxide dismutase, glutathione S-transferase, and glutathione peroxidase activity caused by H2O2 in B16F10 cells compared to A10. MA showed significant cytotoxicity in B16F10 cells with an IC$_{50}$ value of 42 μM, but no obvious toxicity for A10 cells at concentrations up to 210 μM.[50]

Lymphoma

Lymphoid malignancies differ from other malignant tumors and are widely regarded as neoplastic and inflammatory diseases. They are part of the immune system and consist of inflammation/immune cell microenvironments.[51] Hsum et al demonstrated that MA inhibits proliferation of Raji cells by inhibiting Cox-2 expression with an IC$_{50}$ value of 100 μM.[52] Similarly, Hsum et al revealed that MA suppressed cell proliferation of Raji cells in a dose- and

Table 2 The Anticancer Effects of MA in vitro

Cancer Types	Cell Lines	MA Concentration	IC$_{50}$	Exposure Time	Effects	References
Colorectal cancer	Caco-2 colon cancer cells	0 −100 μg/mL	39.7 ±0.4μg/mL	72h	↑caspase-8 /caspase-3, ↑ caspase-9, ↑JNK, ↓Bid, ↓Bcl-2	[43]
	HCT116, SW480 cells	5, 10, 20, 30μM	SW480: 19.04μM HCT116: 18.48 μM	12h	↑cleaved caspase-3, −9, ↓Bcl-2; ↑p-AMPK, ↑(AMP+ADP)/ATP; ↓p-mTOR, ↓p-4EBP1 and p70S6K	[42]
	Caco-2 colon cancer cells	IC$_{50}$: 40.7μg/mL IC$_{80}$: 56.8 μg/mL	40.7μg/mL	72h	↑cleavage of caspases −8 and −3, ↑ t-Bid, ↑ cytochrome C release	[44]
	HT29 cells	0 −100 μg/mL	39.7 ±0.4μg/mL;	72h:	↓Bcl-2,↑Bax, ↑ cytochrome C, ↑Caspase-9 and Caspase-3	[45]
	HT29 cells	3.75, 7.5, 15 and 30 μM	30 μM	3, 12, 24, 48, 72 h	–	[46]
Melanoma	B16F10 cells	10–100μg/mL	–	24 h	↑ROS	[49]
	B16F10 and A10 cells	IC$_{50}$/4, IC$_{50}$/2, IC$_{50,}$ 2·IC$_{50}$	42.3μM	–	↓ SOD, ↓GSTs, ↓GSH-Px.	[50]
Lymphoma	Raji cells	12.5, 25, 50, 100 μM	100 μM	8h	↓COX-2, ↓NF-κB, ↓AP-1	[52]
	Raji cells	IC$_{50}$: 0.1μm/mL	100 μM	72 h	–	[54]
	Raji cells	12.5, 25, 50, 100 and 200μM	–	4, 8, 16, 24 48, and 72 h	↓dUTPase, ↓stathmin, ↓cyclin D1, ↑p21 protein, ↓NF-κB	[53]
Lung cancer	A549 cells	0, 9, 12, 15, 18, 21μg/mL	–	24 h	↓caspase-3, −8 and −9, ↑cleaved caspase-3, −8 and −9. ↑Smac, ↓ c-IAP1, c-IAP2, X-linked inhibitor of apoptosis protein, ↓(XIAP) and Survivin	[58]
	A549 cells	0, 4, 8, 16, 32, 64 μM	–	–	↓ Bcl-2, ↓Na+-K+-ATPase activity, ↑caspase-3/8, ↑cytochrome c, ↓HIF-1α, ↓VEGF, ↓ survivin, ↓iNOS	[59]
Triple negative breast carcinoma	MDA-MB-231, MDA-MB-468, MCF7 cells	30–50 μM	–	24h	↓ CDK4, ↓ CDK2 (TNBCs) ↑ CDK2 (MCF7); ↑ Bax, ↓ BCL2, ↑ Bax/Bcl-2 ratio. ↓survivin	[64]
	MDA-MB-231 cells	0–20μM	–	24h	MA+DOC: ↓MELK, ↓FoxM1, ↓ FoxM1, ↓ ABCB1	[65]

(*Continued*)

Table 2 (Continued).

Cancer Types	Cell Lines	MA Concentration	IC₅₀	Exposure Time	Effects	References
Ovarian cancer	A2780 cells	1, 24, 60 μM	–	6, 12, 24h	–	[104]
Gastric Cancer	SGC-790 cells	0–50μM	33.09 ±3.15	6, 24h	↑p38 MAPK, ↑ caspase	[69]
	MKN28 cells	0, 0.1, 1, 10 μM	8.45 μM	24h	↓Bcl2, Bax and Bad; ↓IL-6/JAK/STAT3 signaling cascade: (↓ p-STAT3 and JAK2, ↓ IL-6	[70]
Pancreatic cancer er	Panc-28 cells	6.25, 12.5, 25, 50, 100, and 200 μM	49.2±0.5 μM	48 h	↑LC3-II/LC3-I, ↑ Atg7, Atg16L, Atg5, Atg12 and Atg3, ↓p-mTOR, ↑p-ULK1 (via ↑HSPA8)	[73]
	Panc-28 cells	10μM	–	6, 12, 24, 48 h	MA+TNFα ↑p65; ↓cell proliferation gene (Cyclin D1, CO-2 and c-Myc), ↓ apoptosis (Survivin), Bcl-2, Bcl-xl, XIAP, IAP-1), ↓ invasion (MMP-9 and ICAM-1), ↓ angiogenesis (VEGF)	[112]
Bladder cancer	T24, 253J, MRC-5 cells	0–100μM	T24:32.98 ± 4.06μM 253J:71.83 ± 5.42μM MRC-5:328.75 ± 40.64μM	48h	↑ P38 MAPK	[77]]
Prostate canc	DU145 cells	0–25μM	–	24h	↓uPAR, E-cadherin, VEGF and MMP; ↓ HIF-1a, ↓ Akt and ERK	[84]
Renal cancer	RCC, SN12K1, HUVEC, PTEC cells	0–100μM	–	24h	↓VEGF	[87]
Gallbladder carcinoma	–EH-GB1, EH-GB2 and GBC-SD cells	10–200μM	–	0, 12, 24, 48h	MA+ GEM ↓NF-κB, ↓ cyclin D1, Bcl-2, Bax, MMP-2 and MMP-9. .	[90]
Astrocytoma	1321N1 cells	1–50μM	25μM	24h	↑ caspase-3, ↑ ROS	[93]
Adenoid cystic carcinoma	ACC-2 and ACC-M cells	0–100μM	ACC-2: 43.68 μM, ACC-M: 45.76 μM,	24h, 48h, 72h	↑[Ca2+]ⁱ, ↑p38 MAPK phosphorylation, ↑caspase-3	[117]
Pheochromocytoma	PC12 cells	1, 3, 5, 10 μM,	–	24h	↑ LC3-I/II conversion, ↓Beclin1	[96]

(*Continued*)

Table 2 (Continued).

Cancer Types	Cell Lines	MA Concentration	IC$_{50}$	Exposure Time	Effects	References
Neuroblastoma	SHSY-5Y cells	0, 5, 10, 20, 40, 80μM	–	12h, 48h	↑ ROS, ↓MAPK/ERK	[97]
Soft tissue sarcomas	SW982 and SK-UT-1 cells	10–100 μM	–	24 h	MA+DXR: ↓ MRP-1	[98]

time-dependent manner, where the proliferation inhibition rates of MA (50 μM) at 24 h, 48 h, and 72 h were 46%, 76%, and 97%, respectively.[53] Furthermore, another study also showed that MA inhibited Epstein–Barr virus (EBV) early-antigen expression in Raji cells with an IC$_{50}$ value of 0.1 ± 0.04 μg/mL. Phorbol 12-myristate 13-acetate (PMA) can also induce early-antigen EBV expression; the anti-tumor activity of MA may be attributed to its hydrophilic moieties interacting with protein kinase C, which prevents PMA from binding and activating protein kinase C.[54]

Lung Cancer

Lung cancer is a crucial public disease with the highest mortality rate. According to reports, the 5-year survival rate of lung cancer patients has increased in the past 10 years.[55–57] Consequently, lung cancer caused a heavy burden on public health. Bai et al found that MA in the concentration range of 9–21 μg/mL significantly suppressed cell proliferation and accelerated apoptosis of A549 lung cancer cells in a dose-dependent manner after 24 h treatment.[58] Likewise, Hsia et al reported MA exhibited a significant pro-apoptotic effect when targeting A549 cells under normoxic and hypoxic conditions at concentration ranges of 4–64 μM and 16–64 μM, respectively. Notably, the stronger pro-apoptotic effect of MA on A549 cells was observed under normoxic than hypoxic conditions at the same dose.[59]

Breast Cancer

To date, breast cancer remains the second leading cause of cancer-related deaths among women worldwide. Finding molecular markers and targeted therapies for specific subgroups of breast cancer patients is currently an urgent task.[60,61] Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer that accounts for approximately 15–20% of all breast carcinomas. Compared with hormone receptor- or HER2-positive breast carcinoma, TNBC has an earlier onset age, a more invasive clinical course, and a bleak prognosis, which mainly relies on cytotoxic chemotherapy. However, due to the lack of expression of three effective breast cancer molecular markers, such as estrogen and progesterone receptors, as well as HER-2/Neu amplification, TNBC chemotherapy is not sufficiently effective.[62,63] A recent study confirmed the anti-tumor effect of MA on TNBC by suppressing cell proliferation for both estrogen positive MCF7 and TNBC cells (namely, MDA-MB-231 and MDA-MB-468). In MDA-MB-231 cells, the IC$_{50}$ value of MA at 24 h was 38.34 μM; in MDA-MB-468, the IC$_{50}$ value of MA was 49.57 μM; in MCF7 cell lines, the IC$_{50}$ value of MA was 55.20 μM. MA also initiated apoptosis and cell death, which was positively associated with the adhesive and migratory capabilities of cancer cells.[64] Docetaxel is a commonly used chemotherapy agent for treating TNBC. However, drug resistance caused by long-term use reduces its therapeutic effects. Wang K et al proved that docetaxel combined with different doses of MA (2.5, 5, and 10 μM) could significantly improve the sensitivity of MDA-MB-231 cells to docetaxel and reduce drug resistance in a dose-dependent manner, which supports MA as a promising contributor of docetaxel resistance in human TNBC therapy.[65]

Gastric Cancer

Gastric cancer (GC) is a leading global cause of cancer mortality. Due to the inapparent clinical symptoms during early stages, many GC patients miss the optimal treatment period. In addition to radical gastrectomy, fluorouracil-based adjuvant chemotherapy is the first-line adjuvant therapy for patients with advanced GC. Cardia cancer is the most common subtype of GC, with increasing incidence rate and poor prognosis, whose 5-year survival rate is reportedly only 16.7%.[66–68] Chang T et al established a tumor model by subcutaneously injecting SGC-7901 into

nude mice to investigate the preventative properties of MA against GC. They found that MA significantly inhibited tumor growth in a dose-dependent manner and 20 mg/kg MA could suppress growth of xenograft tumors by approximately 50%. Further, the latter study revealed IC_{50} values of MA on SGC-7901 and BGC-823 cells were 33.09 μM and 23.85 μM, respectively.[69] Furthermore, another study manifested that MA supplements significantly inhibited proliferation of MKN28 GC cells and induced apoptosis in a dose-dependent manner, with an IC_{50} value of 8.45 μM.[70]

Pancreatic Cancer

Pancreatic cancer ranks as the fourth leading cause of cancer death in the USA, with surgical resection being the only cure method as pancreatic cancer responds poorly to most chemotherapeutic agents. However, this cancer typically acts as a hidden disease evading early diagnosis and most patients lose the chance of surgical excision. Hence, finding new strategies for comprehensive treatment of pancreatic cancer is urgent.[71,72] MA can inhibit human pancreatic cancer Panc-28 cells with an IC_{50} value of 49.2 ± 0.5 μM. MA also significantly induced autophagy at a concentration of 50 μM.[73]

Tumor necrosis factor-alpha (TNF-α) is a key proinflammatory factor. Generally, endogenous TNF-α physiologically secreted in the epithelial-to-mesenchymal transition of cancer patients promotes tumor growth and spread. Recently, TNF-α showed anti-tumor activity in several preclinical models and in non-comparative clinical trials.[74] However, TNF-α is not established as an effective anti-cancer agent due to its systemic cytotoxicity and resistance to tumor cells. A recent study showed that MA inhibited TNF-α in pancreatic cancer cell proliferation in a dose-dependent manner at significant concentrations of 1.5 μM. Notably, the lethality of pancreatic cancer is due to its high invasiveness and tendency to metastasize rapidly in the lymphatic system. Pretreatment with 25 μM MA for 12 h can inhibit pancreatic cancer cell invasion. Further, MA promoted TNF-α-induced cell apoptosis. Moreover, treatment with two different doses (10 mg/kg or 50 mg/kg) of MA can suppress tumor growth induced by Panc-28 pancreatic cancer cells in mice. Compared with the control group, MA treatment reduced tumor volume and weight of mice in a dose-dependent manner.[75]

Bladder Cancer

Bladder cancer is one of the ten most common malignant tumors and has the highest incidence among malignant tumors of the urinary system, which seriously threatens people's lives and health. Therefore, finding new molecular targeted drugs for treating bladder cancer is clinically pertinent.[76] A recent study demonstrated that MA selectively inhibited growth of bladder cancer cells. In different bladder cancer cells, the IC_{50} values were as follows: T24 (32.98 ± 4.06 μM), TCCSUP (27.95 ± 3.72 μM), 253J (71.83 ± 5.42 μM), PBC-1 (44.05 ± 3.83 μM), and PBC-2 (16.26 ± 1.79 μM). Meanwhile, MA shows no obvious cytotoxicity to human lung fibroblasts (MRC-5) and normal liver cells (L-O2), with IC_{50} values of 328.75 ± 40.64 μM and 196.95 ± 25.60 μM, respectively. In addition, different doses (5 and 20 mg/kg) of MA significantly inhibited tumor growth in a BALB/C nude bladder cancer model induced by T24 and 253J cells, suggesting MA has significant therapeutic effects on bladder cancer.[77]

Leukemia

Leukemia is a malignant tumor of the hematopoietic system characterized by uncontrolled proliferation of immature blood cells, which has become a huge challenge due to high mortality and morbidity.[78] Recently, MA of 25 μM concentration inhibited proliferation of HL-60 cells without obvious inhibitory effects on proliferation of normal skin fibroblasts (NHSF46 and NB1RGB).[79] Further, Lai et al confirmed the anti-leukemia effect of MA in mice leukemia models established by injecting WEHI-3 cells into the abdominal cavity of normal BALB/c mice. Following intraperitoneal injection with MA at different concentrations (0, 8, 16, and 32 mg/kg) for two weeks, body weight of leukemia mice became slightly upregulated with no observed toxic reactions during treatment. In addition, the survival rate of leukemia mice improved with high MA doses (32 mg/kg).[80]

Prostate Cancer

Prostate cancer is a common urogenital malignancy in aging men, accounting for approximately 15% of male cancer patients worldwide. Prostate cancer is almost always an adenocarcinoma that originates in glandular epithelial tissue, without obvious symptoms in its early stage. In its middle stage, it often manifests lower urinary obstruction symptoms, such as urinary frequency, urgency, and urinary incontinence.[81,82] Epidermal growth factor

(EGF) has previously been shown to stimulate migration, invasion, and adhesion of DU145 cells.[83] A recent study suggested that MA could inhibit metastatic capacity of prostate cancer. First, cell proliferation experiments showed cell viability did not change after treatment with 10–25 μM of MA for 18 h. Differing doses (10 and 25 μmol/l) of MA were then applied to prostate cancer cells, showing MA can inhibit basal and EGF-induced migration (27–64%), invasion (23–60%), and adhesion (8–40%) of DU145 cells.[84]

Renal Cancer

Renal cell carcinoma (RCC) is diagnosed in approximately 300,000 people worldwide annually and causes more than 100,000 deaths. RCC is not a single disease, as it possesses many histological characteristics and clinical manifestations caused by different genes. Currently, the complexity and increasing incidence of kidney cancer, as well as the poor efficacy and high drug resistance of existing treatments, have increased the need for targeted therapies and precision medicine for kidney cancer.[85,86] A recent study showed that dietary MA supplementation could reduce kidney cancer risk, as well as present an auxiliary method to improve efficacy of existing anti-angiogenesis treatment. Treatment with MA for three RCC cell lines (Caki-1, SN12K1, and ACHN) showed SN12K1 was the most sensitive cell, with an IC_{50} value of 47.11 μM, while ACHN was the most tolerant cell, with an IC_{50} value of 76.52 μM. Further, under similar experimental conditions, MA was more toxic to RCC cell lines than kidney proximal tubular epithelial cells (PTEC), highlighting the selective toxicity of MA to RCC cells. Further studies showed that MA can inhibit proliferation, reduce proliferating cell nuclear antigen and suppress colony formation on RCC cells.[87]

Gallbladder Carcinoma

Gallbladder cancer is a malignant tumor originating from mucosal epithelial cells of the gallbladder. It is the most common malignant tumor in the biliary system, accounting for more than 70% of biliary malignancies.[88,89] Gemcitabine (GEM) is a chemotherapeutic agent for treating advanced metastatic cholangiocarcinoma and gallbladder cancer. However, GEM resistance is seen in many types of cancer. Recently, an experiment treated GBC cell lines with five MA doses (10, 25, 50, 100, and 200 μM) and GEM (25 nM) for 48 h, revealing MA applied alone may significantly inhibit proliferation of GBC cells in a dose-dependent manner, but also combining MA and GEM may synergistically inhibit cell proliferation in GBC cells by strengthening apoptosis and inhibiting cell invasion.[90]

Other Cancers

Astrocytoma is a glioma with good prognosis, is an invasive growth tumor, and can occur at any age.[91,92] Recently, MA showed an anti-astrocytoma effect by inhibiting cell proliferation and inducing apoptosis. Specifically, Martín et al treated 1321N1 cells with 1–50 μM/L MA, demonstrating an IC_{50} value of MA after 24 h was approximately 25 μM/L.[93]

Phaeochromocytomas are rare neuroendocrine tumors with a highly variable clinical presentation and common manifestations of headaches, sweating, palpitations, and hypertension. Closely related tumors, called extra-adrenal paragangliomas, can arise in extra-adrenal sites. If pheochromocytoma is detected in time and removed surgically, the prognosis is promising.[94,95] LC3-I/II is an autophagy marker, whose content reflects autophagy levels. MA treatment showed a stimulatory effect on LC3-I/II conversion of rat pheochromocytoma PC12 cells, suggesting MA inhibited pheochromocytoma by promoting autophagy.[96]

Neuroblastoma is a malignant tumor originating from the sympathetic nerve, which is common in children and has a poor prognosis. MA (0, 10, 40, and 80 μM) significantly suppressed proliferation of SHSY-5Y neuroblastoma cells, which was dose and time dependent. In addition, MA can inhibit cell migration and invasion.[97]

MA can also inhibit soft tissue sarcomas (STS). As a single agent, MA inhibited cell proliferation in a dose-dependent manner, with IC_{50} values of 45.3 μM (SW982 cells) and 59.1 μM (SK-UT-1 cells) in both STS cells. Inhibition rates of MA 80 μM against the two cell lines were 70.3 ± 1.1% and 68.8 ± 1.5%, respectively. Moreover, when MA was combined with doxorubicin, MA significantly improved the anti-tumor effects of doxorubicin by inhibiting cell viability and inducing cell death. For both STS cell lines, MA combined with doxorubicin facilitated the antiproliferative effect of doxorubicin by 1.3–2.3 times.[98]

Derivatives

Identifying new cytotoxic agents to enhance or restore apoptosis of malignant cancer cells is essential for more effective anti-cancer drugs.[99] The IC_{50} values of MA in many cancer cell lines mentioned above are larger than 10

micromolar. By structural modification, a series of MA derivatives can ameliorate IC$_{50}$ values on cancer cells. Further, other drug-related properties, such as bioavailability and solubility, are improved in derivatives. Many MA derivatives have anti-cancer effects and part of their structures is shown in Figure 3.
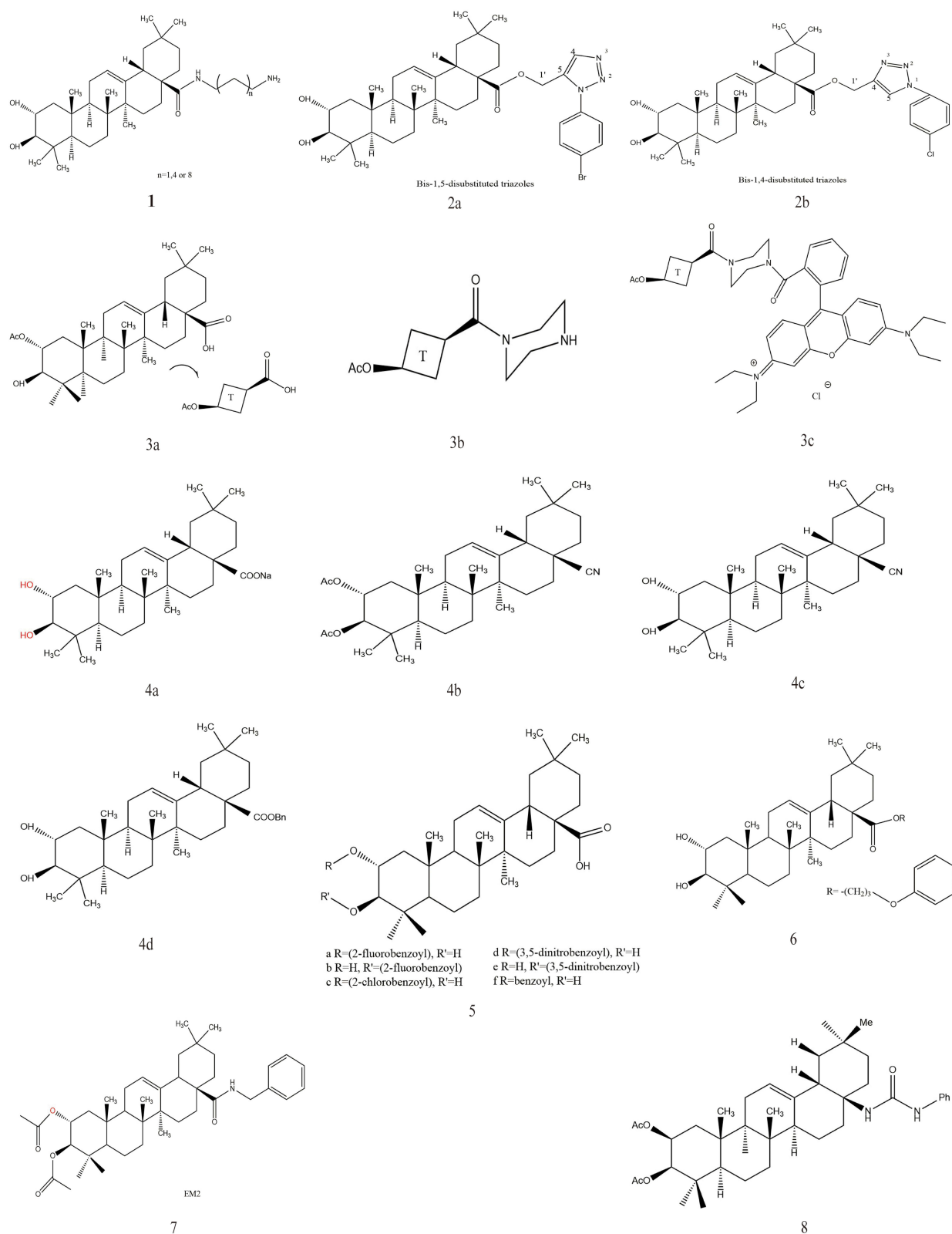
Figure 3 Chemical structure of MA derivatives.

PEG polymer is considered a strong candidate for pro-drug conjugation due to its high aqueous solubility.[100] Experiments by Medina-O'Donnell et al showed that diamine and PEGylated-diamine derivatives of MA **1** have considerable anti-cancer potential. In non-tumor HPF cell lines, the cell viability range of all diamine conjugates of MA was 81% and 94%. In tumor cell lines, the MA diamine conjugate with the shortest and longest diamine chain shows the best cytotoxic effects (IC_{50} values from 0.76 μM to 1.76 μM). In B16-F10 cell lines, they were 140- and 20-fold more effective than their corresponding precursors.[101] Chouaib et al tested the anti-proliferative effects of MA and its 24 synthetic triazole derivatives on mouse EMT-6 (Breast) and human SW480 (Colon) cancer cell lines, showing that MA has significant anti-proliferation effects on EMT-6 and SW480 cancer cells, with cell survival rates of 5% and 9% (100 μM), respectively. The proliferation experiment of its derivatives demonstrated in most cases 1.4-regioisomers type presented better anti-proliferative activity compared with 1.5-regioisomers type, Compound **2a** displayed the most activity in this series against EMT- 6 and SW480, with a cell viability of 13% and 34% (100 μM). For the 1.4-regioisomers, compound **2b** was the most active against both EMT-6 and SW480, with a cell viability of 6% and 10% (30μM). This activity may be explained by the aryl group attaching to the triazole in relation to the triterpene moiety in cellular space.[102]

MA acetylation produced acetates **3a**. Reaction of **3a** with oxalyl chloride, followed by a reaction with piperazine, furnished amides **3b**, after which a reaction of rhodamine B with **3b** produced violet-colored compounds **3c**. As a result, compound **3c** is approximately 1000-fold more cytotoxic than parent MA, and the selectivity F_{Si} (defined as EC_{50} A2780 tumor cell line compared with EC_{50} non-malignant mouse fibroblasts NIH 3T3) increased by 50. Here, rhodamine B is not cytotoxic (up to a concentration of 30 μM). Therefore, to the best of our knowledge, compound **3c** is the most toxic triterpenoic acid derivative to date of cytotoxic compounds in nano-molar concentrations, where its cytotoxicity is comparable to commercial and well-established cytotoxic therapeutics, such as doxorubicin or paclitaxel.[103]

Parra et al showed that MA and its derivatives can suppress B16F10 melanoma cell growth by inducing apoptosis. MA was transformed into the corresponding sodium salt derivative **4a** via several steps. In addition, the diacetyl derivative of MA was converted into the corresponding

amide derivative first with thionyl chloride/DCM, then with MeOH/NH3, then converted into nitrile derivative **4b** via treatment with thionyl chloride in DCM, which was further deacetylated to form compound **4c**. Moreover, 28-benzyl maslinic acid **4d**, a derivative of MA treated with benzyl chloride and DMF, also showed significant anticancer effects. The details are as follows. At a concentration of 1 μM, the pro-apoptotic activities of some compounds were sodium maslinate **4a** at 56.67%, 2.3-diacetoxy-28-cyanide **4b** at 68.62%, 28-cyanide **4c** at 78.75%, and 28-benzoyl **4d** at 87.50%.[99] Serbian et al reacted MA and benzoyl chlorides to form two corresponding acylated compounds, 2-O-acylated and 3-O-acylated MA derivatives. Biological screening of these compounds by SRB assays showed cancer cell cytotoxicity increased compared with MA. The EC_{50} value of A2780 cells treated with MA for 96 h was 19.5 μM. However, the EC_{50} values of compounds (**5a-f**) were all lower than 10 μM.[104] Another experiment demonstrated that MA and MA analogue **6** showed cell membrane damaging activity in tumor cells. In A2780 cells, the IC_{50} values of MA and compounds were 19.5 μM and 10.6 μM, respectively. The latter study showed that, during cell culture, compound **6** and cholesterol formed crystals around or near the cells. Compound **6** then entered the cell membrane and the lipid raft compacted cholesterol, altering the cell membrane, decreasing cell volume, and inducing apoptosis.[105]

Another study also demonstrated that MA and its acetylated derivative (**7, EM2**) showed significant anti-melanoma effects. In 518A2 cells, MA showed an IC_{50} value of 13.7 μM, whereas **7** showed stronger toxicity with an IC_{50} value of 1.5 μM. In nonmalignant mouse fibroblasts (NiH 3T3 cell line), the IC_{50} value of **7** was 33.8 μM.[106]

Derivatization at position C-28 of MA could improve anti-proliferative activity, where the EC_{50} of 2, 3-di-o-acetyl-benzylamine **7** was 0.5 μM in A2780 ovarian cancer cells.[107] Structural modifications performed on **7** revealed the presence of these acetyl groups in **7** and the presence of (2b,3b)-configurated centers are required for high cytotoxicity combined with optimal selectivity between malignant cells and non-malignant mouse fibroblasts. Therefore, maslinic acid derived N-[2b,3b-di -O-acetyl-17bamino-28-norolean-12-en-17-yl]-phenylurea **8** was synthesized by replacing the benzylamide function for a phenylurea moiety, which improved results with EC_{50} values of 0.9 μM (for A2780 ovarian cancer cells)

with $EC_{50} > 120$ μM for fibroblasts (NIH 3T3) and triggered apoptosis.[108]

Discussion

Bioactive compounds isolated from TCM, as well as derivatives, are becoming increasingly more promising as complementary and alternative medicines for cancer treatment.[109–111] MA is widely distributed in many traditional Chinese medicines, such as olive tree (*Olea europaea* L.), shanzha (*Crataegus pinnatifida Bunge*), hongzao (*Ziziphus jujuba Mill.*), and pipaye (*Eriobotrya japonica Thunb.*). The literature shows MA can inhibit proliferation, migration, and invasion of cancer cells, promote apoptosis and autophagy of cancer cells, and suppress tumor growth to alleviate secondary diseases caused by tumor in mice xenograft tumor models. Specifically, we found IC_{50} values of MA against various cancer cells were all lower than 60 μM. In lung cancer A549 cells, MA showed significant inhibitory effects at 21 μM. In colon cancer HT29 cells, MA showed an IC_{50} value for 24h at 61 μM. In addition, for melanoma 518A2 cells, the IC_{50} value of MA was 13.7 μM, and when acting on GC MKN28 cells, the IC_{50} value was less than 10 μM. Further, different doses of MA (2.5, 5, and 10 μM) combined with docetaxel in MDA-MB-231 cells significantly increased sensitivity of MDA-MB-231 cells to docetaxel in a dose-dependent manner.[65] Similarly, MA can increase the proliferation inhibitory effect of TNF-α on pancreatic cancer cells, which was significant at concentrations of 1.5 μM.[112] In addition, MA can inhibit tumor growth in mouse xenograft tumor models and reduce secondary diseases caused by tumors. In summary, MA inhibited proliferation of various tumor cells and showed lower IC_{50} values in melanoma 518A2 cells and gastric cancer MKN28 cells compared with other cell lines. When applied with marketed chemotherapeutic drugs, MA could significantly increase sensitivity and promote anti-cancer effects.

MA and its derivatives have gained attention as dietary supplements and its efficacy as a functional food or medicine cannot be established without bioavailability studies.[113] Male Sprague-Dawley rats were orally administered MA at 1, 2, and 5 mg/kg. MA was then detected two days later in the jejunum, ileum, cecum, and colon segments, with the highest concentrations in the distal part of the intestine. In addition, eleven gut-derived metabolites formed by mono-, dihydroxylation, and dehydrogenation reactions were identified, suggesting MA undergoes Phase I reactions resulting in most monohydroxylated metabolites without the presence of Phase II derivatives.[114] Another study also proved that MA has relative rapid oral absorption, with a peak concentration after 50 mg/kg oral administration at 0.51 h and a bioavailability of 5.13%. After entering the bloodstream, it is widely distributed in the tissues, since the central and peripheral distribution volumes were 8.41 L/70 kg and 63.6 L/70 kg, respectively. The clearance (8 L/h/70 kg) was related to unaltered renal excretion.[115] Although based on Cmax (32.8 ± 10.4) and AUC0-10 (185.1 ± 66.5), the bioavailability of MA was 7-fold higher than similar structure oleanolic acids,[116] clinical application of MA is still limited by solubility and source.

Current studies show anti-tumor activity of MA is related to its inhibition of proliferation, promotion of apoptosis, regulation of autophagy, and inhibition of angiogenesis (Figure 4). MA induces apoptosis via both extrinsic and intrinsic apoptotic pathways. First, MA can promote activation of caspase-8 and caspase-3, which further decreases Bcl-2 expression and increases Bid cleavage levels. Conversely, MA promoted expression of Smac, inhibited expression of c-IAP1, c-IAP2, XIAP, and survivin, activated caspase −9, and promoted the release of mitochondrial cytochrome C to eventually trigger cell apoptosis. The MAPK pathway is constituted by the ERK1/2 MAPK family, P38 MAPK family, and JNK/SAPK MAPK family. The ERK1/2 signaling pathway is the first RasRaf-MAPK classic signal transduction pathway, which is most closely related to cell proliferation. MA treatment can inhibit expression of major proteins in the ERK pathway, leading to apoptosis of cancer cells. In addition, MA activates the p38 MAPK signaling pathway by promoting [Ca2+]i activity, then activates Caspase-3 to stimulate apoptosis.[117] Furthermore, JNK may act directly upon the Bcl-2 protein family, thus inducing the mitochondrial pathway, as well as stimulate Bid. Bid-active targets the mitochondria to modulate other Bcl-2-like factors, such as Bax,[118,119] and MA treatment induces expression of JNK in cells, thereby activating p53 to promote cytochrome C release and increase caspase-9, −3, and −7 expression, leading to apoptosis. ERK1/2 activation can trigger STAT3, leading to gene expression that controls critical cellular functions, including cell proliferation, survival, differentiation, and development. IL-6 is a pleiotropic cytokine that plays an important role in tumor development by regulating immune and inflammatory responses and can participate in cell proliferation, differentiation,
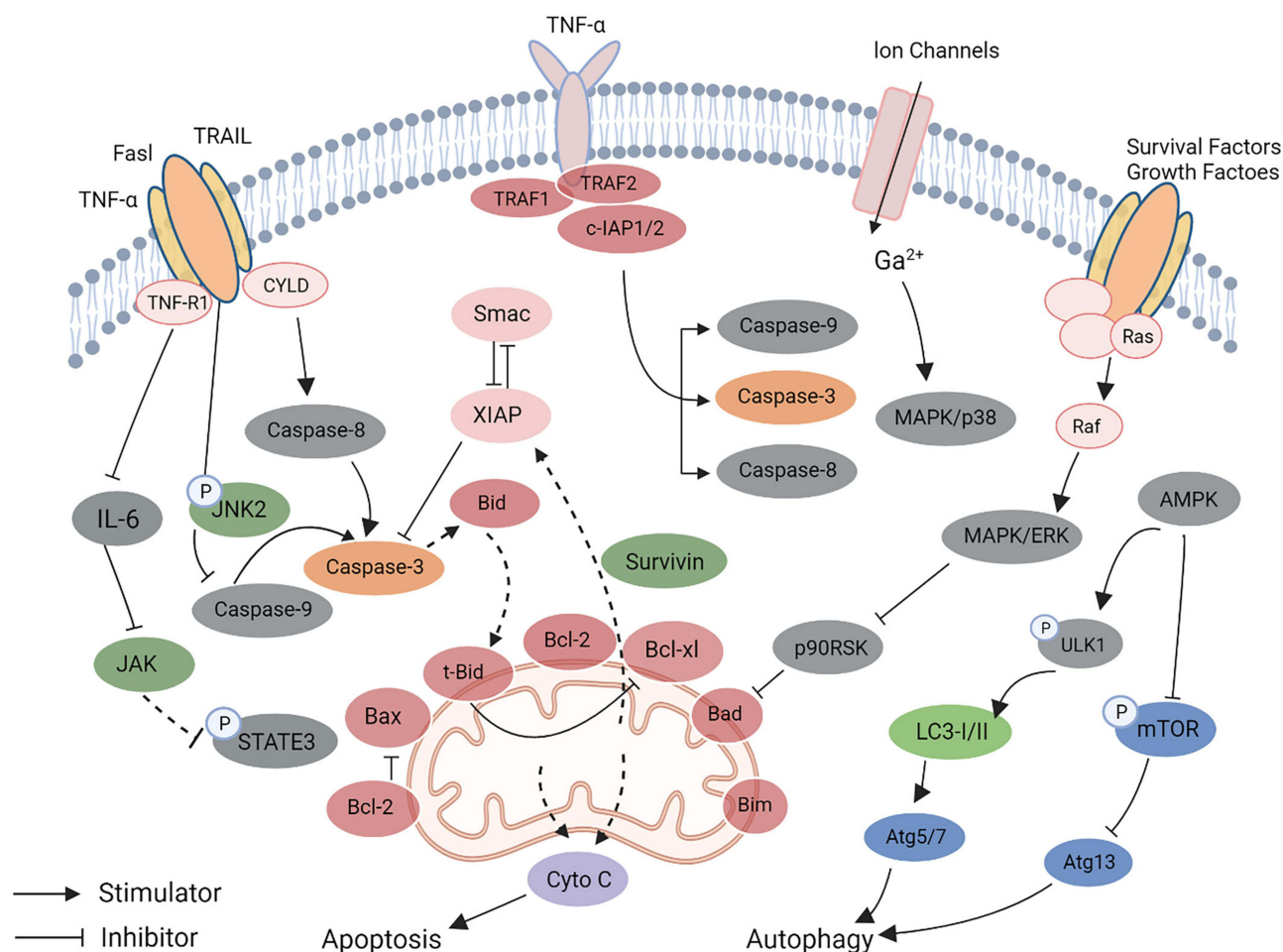
Figure 4 Partial molecular pathways involved in the anti-cancer mechanism of MA.
Note: Created with BioRender.com.

apoptosis, and metastasis.[120] IL-6 may activate the Janus kinase (JAK)/signal transducer and activator of STAT3 signaling pathway, as well as the MAPK signaling pathway.[121–123] Further, MA treatment can inhibit phosphorylated-STAT3 and JAK2 expression to decrease IL-6 protein levels. These results indicate MA inhibits growth of cancer cells when inducing apoptosis by suppressing the IL-6/JAK/STAT3 signaling cascade.

Conclusion and Perspective
Herein, we summarized the anti-cancer effects and mechanisms of MA and its derivatives. MA can inhibit lung cancer, colorectal cancer, breast cancer, bladder cancer, leukemia, lymphoma, melanoma, and prostate cancer, among others. The anti-cancer effect of MA is mainly related to inducing cell apoptosis, but also to inducing cell cycle arrest, regulation of autophagy, and

hindering angiogenesis. However, it is clear the anti-cancer mechanisms of MA are not sufficiently explained. Most studies are in vitro experiments, while in vivo experiments are inadequate, which requires further research. In vitro, MA showed anti-proliferative effects in HCT116, SW480, Caco-2, and Raji cells, among others. Nevertheless, MA showed high IC_{50} values within various cells. A series of derivatives obtained by modifying the MA structure show high cytotoxicity to human tumor cell lines, but low cytotoxicity to non-malignant cells. However, we find that the dose-effect relationship, toxicity and safety of MA and its derivatives is still obviously inadequate, which requires more in-depth and comprehensive study.

In summary, MA and its derivatives show inhibitory effects on a variety of tumors and are expected to become candidate anti-tumor agents in the future.

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Disclosure

The authors declare no conflicts of interest for this work.

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