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Mapping the Anticancer Mechanism of Asiatic Acid : A systematic review of preclinical evidence

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Abstract
Studies have demonstrated that Asiatic acid (AA) from *Centella asiatica* has anticancer properties in cancer cell lines, but translating these findings into clinical research remains challenging. This review aims to provide a robust scientific foundation for enhancing the translational potential of AA-based anticancer therapy. The PubMed, Scopus, and ScienceDirect databases were searched electronically using specific keywords and screened in accordance with the PRISMA 2020 guidelines. Fourteen studies meet the criteria. All research was conducted *in vitro*; four studies were conducted both *in vitro* and *in vivo*, and three were conducted *in silico*. Asiatic acid (AA) demonstrates potent anticancer activity by modulating key signaling pathways, including PI3K/Akt and NF-κB, thereby inhibiting proliferation, promoting apoptosis, and reducing metastasis. Its cytotoxic effects are time- and dose-dependent (1–50 μM) and minimal in normal cells. While AA and its derivatives consistently outperform controls, limitations such as missing control dose data warrant further investigation. Future studies should focus on *in vivo* validation, clinical translation, and advanced strategies such as targeted delivery and AI-assisted drug development to fully realize AA's therapeutic potential.

Keywords: asiatic acid, anticancer, in vitro, mechanism

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Pemetaan Mekanisme Antikanker Asam Asiatat : Tinjauan Sistematis Studi Preklinis

Abstrak
Asam asiatat (AA) dari *Centella asiatica* telah terbukti memiliki aktivitas anti-kanker pada berbagai sel kanker, namun masih sulit untuk dilakukan penelitian translasi praklinis. Tinjauan ini bertujuan untuk memberikan landasan ilmiah yang kuat guna meningkatkan potensi translational research dari terapi anti-kanker berbasis AA. Basis data elektronik yang berasal dari PubMed, Scopus, dan ScienceDirect dicari dengan menggunakan kata kunci spesifik dan diskrining dengan metode PRISMA 2020. Terdapat 14 studi yang memenuhi kriteria. Semua artikel merupakan penelitian *in vitro* dan 4 diantaranya merupakan penelitian *in vitro* dan *in vivo*, serta 3 artikel disertai studi *in silico*. Asam asiatat (AA) menunjukkan aktivitas antikanker yang kuat melalui modulasi jalur pensinyalan utama seperti PI3K/Akt dan NF-κB, yang berperan dalam menghambat proliferasi, meningkatkan apoptosis, serta menekan invasi dan metastasis sel kanker. Efek sitotoksik AA bersifat bergantung waktu dan dosis (1–50 μM), dengan toksisitas minimal terhadap sel normal, sehingga mendukung potensinya sebagai agen antikanker selektif. Meskipun AA dan turunannya secara konsisten menunjukkan hasil terapeutik yang lebih baik dibandingkan kontrol, keterbatasan seperti tidak adanya data dosis kontrol dalam beberapa studi menekankan perlunya penelitian lebih lanjut. Studi mendatang sebaiknya difokuskan pada validasi *in vivo*, uji klinis, serta strategi lanjutan seperti sistem penghantaran bertarget dan pengembangan obat berbasis kecerdasan buatan untuk mengoptimalkan potensi terapeutik AA.

Kata Kunci: asam asiatat, antikanker, mekanisme, in vitro

1. Introduction

Cancer is a disease marked by cells that have undergone transformation growing and invading other body parts. Metastasis can continue to develop if left untreated and can cause death.[1,2] According to WHO, 7 million new cancer cases are diagnosed, with a percentage of 50% in developing countries, and 5 million people die of cancer. This number is expected to continue increasing due to environmental changes that expose people to carcinogens, pollutants, and unhealthy lifestyles.[3] Currently, surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapy are the most prevalent treatments for cancer.[4]

The most commonly utilized chemotherapy medications over the years have been high-dose chemotherapy agents, including methotrexate, cisplatin, doxorubicin, 5-fluorouracil, and ifosfamide, among others. While these treatments aim to increase patient survival rates and reduce symptoms, some patients may experience side effects that significantly impact their quality of life.[5]

Consequently, to enhance cancer therapy, novel medications with significant effects and low toxicity must be investigated. Hence, identifying effective anticancer agents with reduced toxicity is important.[6] Natural compounds, such as plant-derived compounds, have been researched by scientists to discover anti-cancer agents that can inhibit proliferation, induce apoptosis, and inhibit cancer development, but with lower toxic effects.[7] Asiatic acid/AA, a pentacyclic triterpenoid extracted from *Centella asiatica*, exhibits significant potential as a therapeutic agent.[8] This compound has been shown to have pharmacological benefits, such as anti-inflammatory,[9] antioxidative,[10] anti-tumor,[6] neuroprotective,[11] and accelerate in wound healing[12] properties, as documented in various studies.

AA and its derivatives display anti-tumor effects across numerous cancer cell lines. AA restricts the development of cancer in the lungs, brain, ovaries, and liver.[13,14] Although the anticancer effect of AA have been explored in numerous studies, the findings remain fragmented and challenging to translate into coherent preclinical strategies. Existing narrative reviews underscore the multi-target potential of AA but also reveal significant methodological heterogeneity, limited cross-model validation, and a lack of comprehensive pharmacokinetic and toxicological data.[15] In light of these gaps, a systematic review is warranted to synthesize current evidence, evaluate the consistency of research outcomes, identify key molecular pathways and associated biomarkers, and map out unresolved questions in the field. This review aims to provide a robust scientific foundation that enhances the translational potential of AA-based anticancer interventions by consolidating and critically analyzing available data.

2. Materials and Method

The research question was developed by PICO framework.16 Does asiatic acid (I) have an anticancer effect (O) on human cancer cell line (P compared with other drugs/compounds (C)? The review process adhered to the PRISMA 2020 guidelines17 as in Figure 1. This study has already been registered in the Open Science Framework (https://doi.org/10.17605/OSF.IO/VEPCS)

Full-text articles were considered eligible based on the following criteria: articles published in English in the last 10 years (2014-2024), research articles on the effects of AA and/or AA combination and/or AA derivatives to analyze the latest studies related to improving the effectiveness of AA-based therapy, and in vitro experiments in human cancer cells. All letters to the editor, reviews, and reports that lacked validation and did not mention the anticancer mechanism of AA were excluded.

PubMed, Scopus, and ScienceDirect databases were electronically searched in April 2024 using the following keywords (Table 1). Two reviewers (LRA and DFS) examined the studies that met the criteria. The third reviewer, YSW, was consulted if there is any disagreement.

The included studies' quality was evaluated with the QUIN tool. Each criterion is scored separately as follows: 2 indicates that the requirement is adequately specified; a score of 1 signifies that the requirement is inadequately specified; 0 is assigned if the requirement is not specified; and a score of 0 is also assigned if the requirement is not applicable, in which case it is excluded from the requirements. The scores were then summed and grouped into categories of high, medium, or low risk based on a predefined scale, specifically: scores above 70% were classified as low risk of bias, scores between 50% and 70% as medium risk of bias, and scores below 50% as high risk of bias, according to the following formula.:

$$\text{Final score} = \frac{(Total\ Score \times 100)}{(2 \times number\ of\ criteria\ applicable)}$$

The quality of each study is presented in Table 2.[18]

3. Result

There are 14 studies that meet the inclusion and exclusion criteria. All research was conducted *in vitro*; four studies were carried out both *in vitro* and *in vivo*, and three studies were carried out *in silico*.

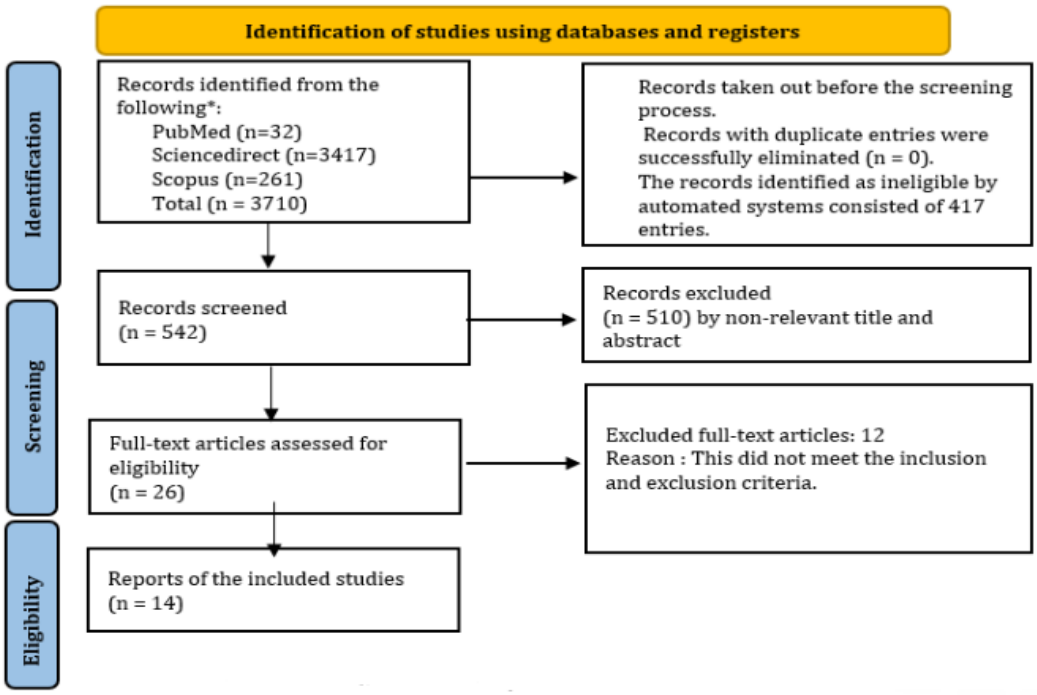

Figure 1. PRISMA Flowchart for Screening Protocols

Syntheses of AA derivatives have been developed and successfully enhanced the anticancer activity of AA. All included *in vitro* studies are described in Table 3, while *in vivo* studies are described in Table 4.Previous research on the target molecules of AA against cancer cells has been conducted using in silico studies, and the results have shown that the target aligns with the mechanisms by which AA hinders cancer progression.

4. Discussion

In recent years, numerous studies have detailed the potential of *C. asiatica* for ulcers, large wounds, neuroprotection, dermatology, and cosmetology medicine. One of the primary ingredient in *Centella asiatica*, which has also demonstrated a variety of biological activities, is Asiatic Acid.[20] Asiatic acid (AA) is the most important saponin compound in *C. asiatica* and naturally occurs in the form of pentacyclic triterpenoids. This compound displays a variety of biological benefits, which encompass anti-inflammatory, anticancer, antidiabetic, wound healing, hepatoprotective, antioxidant, antiviral, and neuroprotective characteristics. AA is the aglycone form of asiaticoside with a molecular weight of 488.70 kD, formed through the hydrolysis of the sugar moiety from the asiaticoside molecule in an acidic environment.[6,22,32]

Based on the results above, AA can inhibit cancer by inhibiting proliferation, inducing apoptosis, and inhibiting migration, invasion, and metastasis.

4.1. Asiatic acid to inhibit the proliferation

Tumor cells exhibit characteristics such as interference with growth signals, loss of cell proliferation control, evasion of apoptosis, and the ability to invade and metastasize.[21,33] The proliferative ability of cancer cells depends on and is regulated by the cell cycle. It is a strictly regulated process that is important for the growth and normal functioning of cells. When a disorder occurs, it becomes a hallmark of cancer development. Cell cycle dysregulation also leads to increased genome instability. This further intensifies the abnormal behavior of cancer cells and accelerates

Table 1. Enumerates the various terms used in the literature search.

Database	Keyword	Result
PubMed	(asiatic acid[Title/Abstract] AND (y_10[Filter]) AND (((cancer cell*[Title/Abstract]) OR (cancer in vitro[Title/Abstract]) OR (cancer cell line[Title/Abstract]) AND (y_10[Filter]))	32
Scopus	"asiatic acid" AND "cancer cell" OR "in vitro"	261
ScienceDirect	"asiatic acid"AND"cancer cell"OR"cancer in vitro"	3,417
	Total	3,710

Table 2. Quality assessment from QUIN tool

Reference	QUIN Tool (Quality Assessment Tool for In Vitro Studies)												Score	Risk
	1	2	3	4	5	6	7	8	9	10	11	12		
[20]	2	2	1	2	2	-	1	2	-	2	2	2	90%	Low
[21]	2	2	1	2	2	-	1	2	-	1	2	2	85%	Low
[5]	2	2	1	2	2	-	1	2	-	1	2	2	85%	Low
[22]	2	2	1	2	2	-	1	2	-	1	2	2	85%	Low
[23]	2	2	1	2	2	-	1	2	-	1	2	2	85%	Low
[24]	2	2	1	2	2	-	1	2	-	1	2	2	85%	Low
[25]	2	1	0	2	2	-	0	2	-	0	1	2	60%	Medium
[26]	2	2	1	2	2	-	1	2	-	1	2	2	85%	Low
[27]	2	1	1	2	2	-	1	2	-	0	1	2	70%	Medium
[28]	2	2	1	2	2	-	1	2	-	1	2	2	85%	Low
[29]	2	1	1	2	2	-	1	2	-	1	2	2	80%	Low
[11]	2	2	1	0	2	-	1	2	-	1	2	2	75%	Low
[30]	2	2	1	0	2	-	1	2	-	1	2	2	75%	Low
[31]	2	2	1	2	2	-	1	2	-	1	2	2	85%	Low

Note: 1. Clearly defined objectives; 2. Explanation of the detailed process for determining a sample size is explained 3. A detailed account of the sampling method is provided. 4. Details of comparison group; 5. Detailed overview of the methodological approach; 6. Details of the operator; 7. Randomization; 8. Method of outcome measurement; 9 Outcome assessor details; 10. Blinding; 11. Statistical analysis details; 12. Display of the findings.

the development of cancer.[34] All of these effects and changes are influenced by proteins that regulate the cell cycle, such as cyclins, CDKs, and CDK inhibitors. These proteins have a crucial function in regulating the transition phase of the cell cycle.[35]

AA can suppress cell growth and halt cell division in a specific phase. AA inhibits cell proliferation in the G2 phase in osteosarcoma based on flow cytometry assay.[36] This finding is in line with other studies such as in bone invasive-SCC, AA can induced arrest in the G2/M phase, while the decline occurs in the S phase.[37] Another research found that cell cycle progression was arrested in the G1-S phases following the treatment of AA in human cervical adenocarcinoma, human glioblastoma, and human breast adenocarcinoma cell lines.[38] These data showed that AA inhibited proliferation by arresting cells in the G1–S and S–G2/M phases.

In addition to changes to the cell cycle distribution, changes also occur in proteins that regulate the cell cycle, such as inhibiting the binding between cyclin E-Cdk2, cyclin D3-Cdk4/6,[23] cyclin D1, p15, and pRb. Treatment with AA affects cell cycle protein expression levels, such as C-MYC, which acts as an oncogene. C-myc and PCNA expression levels are reduced after treatment with AA.[21]

AA derivatives have a more effective antiproliferative effect than AA. Compound 14 significantly downregulated the levels of cyclin D3 and slightly decreased the levels of cyclin E. It also increased the amounts of proteins that bind to and inhibit the cyclin complexes. All these alterations result in cell cycle arrest.[23] The mechanism of AA in inhibiting proliferation is illustrated in Figure 3.

4.2. Asiatic acid induces apoptosis

One of the most common targets for cancer treatment is to induce apoptosis via extrinsic and intrinsic pathways. Ligand-gated death receptors in transmembrane, such as the TNF-α receptor, trigger the activation of caspase-8 and caspase-3, thus starting apoptosis through the extrinsic pathway.[19]In intrinsic pathway, activation of the Bcl-2 family on the mitochondrial membrane increases the permeability of the outer mitochondrial membrane and decreases the mitochondrial membrane potential, ultimately triggering apoptosis. It can trigger the production of a pro-apoptotic protein, activate caspase-3, and obstruct the anti-apoptotic proteins of the Bcl-2 family, ultimately leading to apoptosis.[39]

According to some studies, AA can cause apoptosis via the intrinsic pathway. The compound AA enhanced the expression of BAX, BAD, cleaved-PARP and cleaved caspase-3 while decreasing the expression of PARP and Bcl-2.[20] In addition, AA upregulates p53 and Bax expression but downregulates Bcl2, cyclin E, B, Cdc2, and Cdc25 expression in bone-invasive carcinoma.[36]

Table 3. Evaluation of the anticancer effects of AA in vitro

AA Dose and Control Group	Cancer cell	Results	Mechanism	Reference
AA(0-160μM) Tamoxifen Paclitaxel	MCF-7/DOXR(doxorubicin-resistant breast cancer)	●AA increased the sensitivity of doxorubicin-resistant MCF-7 cells	●ROS production induces apoptosis, accompanied by a decrease in ATP levels and a readjustment of the adaptive immune system ●The AMPK, PD-L1, and NF-κB transcriptional pathways ●Increase drug sensitivity by improving P-gp function.	[19]
AA (0-50 μM)	Human normal kidney cells (HK2) and human renal cancer cells (786-O, A-98, Caki-1, and ACHN)	●AA 50μM inhibit cell viability ●Decreased number of cell migration, transcriptional and translational MMP-15	Prevent metastasis by targeting MMP-15 and blocking ERK 1/2 and p38MAPK kinase activity	[20]
AA (0-55 μM)	Human osteosarcoma cell lines 143B, MG63, and human normal cell lines HEB (human brain astrocyte), HS5 (human bone marrow stromal cell), LO2 (human normal liver cell) , and HK2 (human renal cortical proximal tubule epithelial cell)	●Proliferation inhibition by time and concentration-dependent but with little inhibitory effect in normal human cells ●Reduce proliferation protein (PCNA and c-myc) ●Increase apoptosis rate in the early and late phases ●Increase expression levels of Bac, Bad, cleaved PARP, cleaved caspase 3, and reduced BCl2 ●decrease the expression level of EMT-related proteins and increase E-cadherin,reduce ECM-related protein	●Induction of apoptosis and inhibition of proliferation-related proteins. ●Regulate the PI3K/AKT and NF-κB signaling pathways to prevent cell migration, invasion, and cancer development.	[21]
AA (0-100 μM) DMSO	Human Tongue Cancer Cell Line (Tca8113)	●suppressed the viability and colony-forming activity, and increased cell apoptotic death with an IC50 40°μM ●The anti-apoptotic BCl-2 level was lowered and the pro-apoptotic Bax and Cleaved Caspase-3 levels were elevated. ●Activation of AA results in elevated intracellular calcium levels and increased calpain expression. ●Increased Grp78 & P-IRE1α and JNK levels	●Trigger apoptosis through the mitochondrial pathway by elevating calcium levels and activating Calpain, while also activating the Grp78 IRE1α/JNK pathway.	[22]
Compund 14 of AA derivatives in concentration 0.67μM, 1.34μM and 2,68 μM DMSO 0,5%	Human cervical cancer (HeLa) Human colon cancer (HT-29, MCF-7, Jurkat, PC-3, MIA PaCa-2, and A375) non-tumoral human fibroblasts (BJ).	●All fluorinated derivatives of AA were successfully synthesized and showed improved antiproliferative activity compared to cisplatin, except compound 1. ●Compounds 2 and 3 showed significant increases in their antiproliferative activities. ●Compound 9-16 showed higher activity than AA ●Esterification of the C23 hydroxy cluster with a lipophilic substituent increased the antiproliferative activity, whereas it was decreased by hydrophilic substituents. ●Compounds 11, 12, and 14 displayed higher activity levels than AA. Compound 14	●Disruption of membrane asymmetry leads to phosphatidylserine (PS) translocation from the inner to the outer cell membrane, ultimately resulting in apoptosis. ●The cell cycle is halted by the increased production of p21cip1/waf1 and p27kip1, which can bind and inhibit the cyclin E/Cdk2 and cyclin D3-Cdk 4/6 complexes. ●Induce apoptosis in the extrinsic and intrinsic pathways	[23]

		displayed the highest activity level with a low IC50 value, showing greater selectivity toward cancer cells than non-tumor fibroblasts. ●Compound 14 inhibits proliferation by arresting cell cycle at the G0/G1 phase and triggering apoptosis.		
AA (0-1000 nmol/L,10-100 µmol/L) DMSO 0.05, ETOH 2,5%, 250 µmol/L cholesterol	Differentiated SH-SY5Y neuroblastoma cells	●Exposure to AA may slightly improve the viability of cells previously treated with cholesterol, but this increase is not significant. ●The duration of exposure to AA and cholesterol affects the cell viability, with longer exposure to cholesterol(96h) reducing the positive effect of AA on cell viability.	● AA exerts a protective effect against cholesterol-induced cell toxicity.	24
Synthesis of 10 components of AA Gefitinib, Adriamycin	HepG2 and SGC-7901 cell lines.	●Compounds I6 and II4 showed more potency than the control drugs gefitinib and adriamycin	●Improve antitumor activity by binding the active site of survivin	25
AA (5-80 µmol/l), TGF-β1(10ng/ml)	The human lung cancer cell line (A549)	●AA decreased cell viability in a dose-dependent manner ●Inhibited TGF-β1-induced EMT, ●Decreases in β-catenin and p-GSK-3β protein expression levels, as well as N-cadherin, vimentin, and Snail, were observed. ●Increased Ecadherin expression levels	●Prevent metastasis by inhibiting EMT through increased E-cadherin and Snail, N-cadherin, and vimentin expression	26
Sythetisized new derivatives AA isolated from C. asiatica Ellipticine	Human Cancer KB, HepG2, SK-LU-1, NIH/3T3 cell line	●Twenty-four new compounds (4–22, 25, 26, and 28–30) and four new compounds (2, 23, 24, and 27) were successfully synthesized ●Compounds 9, 12, and 15-17 can induce apoptosis	●New compounds can induce apoptosis by modified amidation of the carboxyl group and acetylation of the hydroxy and amino groups	27
AA (0-80 µM), 5-FU	Human lung cancer cell lines (A549 and H1299)	●AA-induced ROS production was elevated and mitochondrial dysfunction was triggered ●Induce programed cell death morphologically, affect apoptosis-related proteins and inhibit proliferation in a dose- and time-dependent manner	●Induced apoptosis and inhibition of cell growth via mitochondrial dysfunction	28
AA (25-100 µM)	Human hepatocellular carcinoma (HepG2)	●AA caused HepG2 apoptosis in a concentration-dependent manner at 24 h and 100 µM AA induced rapid apoptosis at 6 h.	●Triggered cell death through the mitochondrial release of cytochrome c into the cytosol, decreased ATP production in the mitochondria, and dissipation of mitochondrial membrane potential.	29
AA (0-50 µg/ml)	Human colon cancer cells (SW480 and HCT116)	●Inhibits cell growth, colony formation, and apoptosis and influences cell cycle in a dose-dependent manner ●Increased Ecadherin and Pdcd4 expression levels and reduced vimentin and Ncadherin expression ●Decreased expression of pAkt (Ser473), pPI3K, pmTOR, pp70S6K, and rapamycin	●Prevent the spread of cancer by expressing proteins, such as N-cadherin, E-cadherin, and Vimentin that indicate epithelial-to-mesenchymal transition ●Pdcd4 regulation is achieved via the PI3K/Akt/mTOR/p70S6K signaling pathway.	8

AA and AA-PMe (0- 50 μM)	Metastatic lymph node carcinomaSGC7901)	●AA and its derivative AA-PMe suppressed STAT3 activation. ●AA-PMe had lower inhibition than AA (10-50 μM) ●Cell cycle arrest induced in the G0/G1 phase by AA-PMe ●AA-PMe reduced the number of invasive cells and inhibited invasion	●AA-PMe blocks the JAK2 enzyme, thereby preventing JAK2 and activation of STAT3. ●The expression levels of cyclin D1, Bax, Bcl-2,Cyclin D1, MMP-2, MMP-9 and c-myc are altered.	30
AA and AAPMe (1-100 μM) DMSO	Human gastric epithelial mucosa (GES-1), gastric cancer cell lines (SGC7901 and HGC27)	●IC50 of AA-PMe is much lower than that of AA ●No significant viability effect on normal gastric mucosa cells was observed except at high concentrations (100 μM) ●Both AA and its derivative arrested the cell cycle in the G0 / G1 phase and influenced cell cycle regulator proteins ●AA-PMe induced apoptosis at a lower concentration than AA ●Inhibition of migration and invasion	●Induced cell cycle arrest by influencing cell cycle proteins (p15, CDK4, CDK6, Cyclin D1, pRb) ●It upregulated the expression of the proapoptotic protein Bax and gene mRNA while downregulating the expression of Bcl-2, c-Myc and caspase-3 ●downregulated MMP-9 and MMP-2 expression to inhibit migration and invasion	31

ROS overproduction can also cause apoptosis via both internal and external mechanisms. Furthermore, ATP serves as an energy source, and tumor cells need large amounts of ATP to proliferate, survive, and spread.[40] AA increases ROS production, reduces ATP content, and decreases ER stress by changing cancer cell metabolism.[22]

Another pathway influencing cancer cell apoptosis is the NF-κB pathway. Both proapoptotic and antiapoptotic genes, including TNFα, c-myc, and the IL-1β converting enzyme protease, can be upregulated by NF-κB activation. Studies of DOX-resistant breast cancer cells have shown that AA can cause cell death by activating the NF-κB transcription factor indirectly.[19]

The anticancer action of AA involves the PI3K/Akt/mTOR/p70S6K pathway, that controls several crucial biological functions, including cancer cell migration, apoptosis, and proliferation. Some anticancer medications block cancer growth and metastasis by focusing on the PI3K/Akt/mTOR/p70S6K pathway. To determine the involvement of this pathway, p-PI3K, p-Akt (Ser473), p-mTOR, and p-p70S6K were among the key proteins examined.[40] Pdcd4 is a downstream factor of p70S6K that inhibits protein synthesis through translational suppression, so that p70S6K activity regulates Pdcd4 expression. Pdcd4 can also inhibit cancer cell invasion by activating protein-1 activator (AP-1). After AA treatment, Pdcd4 protein expression increased. This suggests that AA might suppress the PI3K/Akt/mTOR/p70S6K pathway, that controls several crucial biological functions, including cancer cell migration, apoptosis, and proliferation. Some anticancer medications block cancer growth and metastasis by focusing on the PI3K/Akt/mTOR/p70S6K pathway. To determine the involvement of this pathway, p-PI3K, p-Akt (Ser473), p-mTOR, and p-p70S6K were among the key proteins examined.[40]

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In addition to the induction of apoptosis through mitochondria, excessive stress on the ER can lead to cell apoptosis. Cells respond to endoplasmic reticulum stress through various sensors and pathways. If this stress is not resolved, cell apoptosis will occur. The mechanism begins with an accumulation of unfolded protein (UPR) in the ER, disrupting cell homeostasis.[42] The three main sensor proteins in the ER, namely IRE1α, PERK, and ATF6, can detect and respond to ER stress. These sensors transmit information about the status of protein folds in ER to the cytosol and the nucleus to restore protein homeostasis. The

Table 4. Evaluation of the anticancer effect of AA in an *in vivo* experiment

Animal Model	AA Dose and Delivery	Results	Ref.
Five-week-old male C. B17/SCID mice injected with 786-O RCC cells in tail vein 1 × 106 of ACHN cells	AA (0, 25, 50 mg/kg) by oral gavage (100 µl/mice) twice a week for 45 days	Decreased expression of cell proliferation marker : Ki-67, MMP15, p-ERK, and pp38MAPK compared with the control group	20
BALB/c nude mice (female, 18 ± 2 g) were injected with 60µl of 143B cells (2 × 107) in tibial plateau of the mice	AA at concentrations of 20, 35, and 50 mg/kg, intragastric, once every 2 days for 21 days	AA can reduce tumor size and reduce PCNA, p-AKT, p-P65, Bcl-2 and Vimentin expression. Reduced tumor cell density and change in cell morphology showed nuclear pyknosis and nuclear fragmentation. No change in the heart, liver, and kidney tissues	21
Male BALB/cANNCjr nu/nu mice (20-25 g, 8 weeks old) injected with 2×106 Tca8113 cells in the flank region subcutaneously until volume tumor ~100 mm3	intraperitoneally injected once per day with AA in 0.1% DMSO (15 mg/kg/d) and 0.1% DMSO only as a control for 4 weeks	AA treatment significantly reduced tumor volume and weight compared with the control group. TUNEL staining revealed more apoptotic tumor cells in AA-treated mice.	22
Female C57BL6/J mice (6–8 weeks old injected subcutaneously in the right flanks with LLC cells (1x107 cells/mL) for 3 days	AA (50 and 100 mg/kg) (i.g.) every day for 13 days	AA suppressed tumor growth and proliferation in a dose-dependent manner. AA maintains body weight better than 5-fluorouracil	28

mechanism of action of the sensor protein includes: IRE1α is activated by misfolded protein binding or BiP dissociation from the sensor when there is ER stress. IRE1α governs various cellular pathways, including JNK, p38, ERK, and NF-κB,[36,43] modulating distinct cellular responses independently of XBP1. When activated, PERK activates p-eIF2α, which induces the expression of CHOP and promotes apoptosis. When ER stress happen, ATF6 is relocated to the Golgi apparatus, where it is subsequently processed by S1P and S2P. It releases its transcription factor cytosolic domain to activate genes encoding chaperone proteins, XBP1, ERAD components and also there is an increase in intracellular calcium levels. The rise in calcium activates proteases and calpain, which break down pro-caspase-12 into caspase-12, thereby triggering apoptosis mediated by ER stress. Through this mechanism, AA increases intracellular calcium ion levels in tongue cancer. AA also increases calpain expression, a protease activated by calcium. Increased calcium and calpain levels contribute to apoptosis induced by AA.[22]

Furthermore, AA increases the expression of Grp78, a marker for ER stress, and IRE1α/JNK signaling, which is linked to the control of ER stress-induced apoptosis. Grp78 separates from IRE1α during ER stress, enabling IRE1α to interact with ASK1 and TRAF2. This IRE1α complex triggers JNK, then triggers pathways leading to mitochondrial death. The release of cytochrome C is triggered by lower expression levels of the anti-apoptotic protein Bcl-2 and higher expression levels of the pro-apoptotic protein Bax. Caspase-9 is activated in the cytoplasm due to an interaction with cytochrome

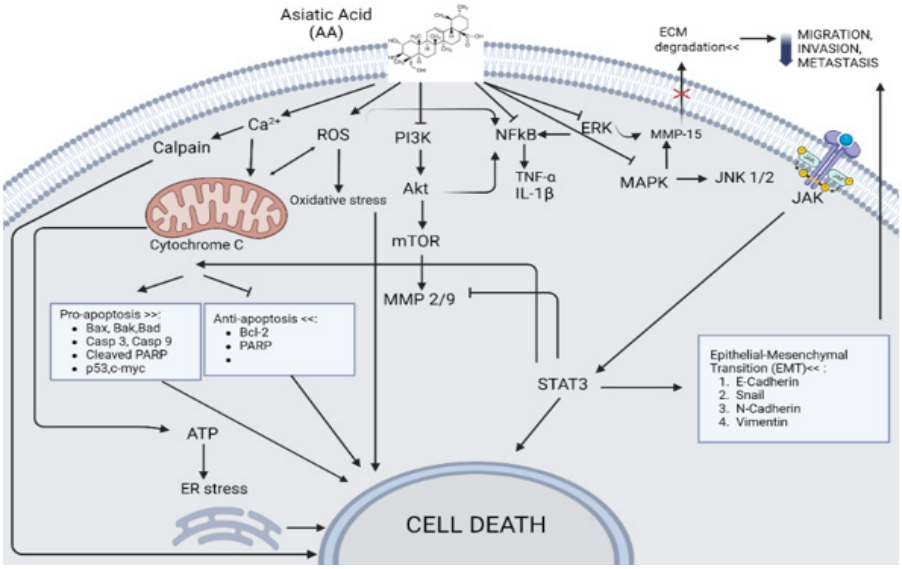

Figure 2. Asiatic acid induces apoptosis and inhibits invasion, migration, and metastasis

C, which then leads to the activation of caspase-3, ultimately starting the apoptotic process.[22]
AA and its derivatives act as anticancer agents in gastric cancer through the STAT3 pathway. Once activated, STAT3 undergoes several changes, including phosphorylation of tyrosine residues, dimerization (the merging of two molecules), binding to DNA, and activation of transcription (the process of making RNA copies of DNA). STAT3 activation is mediated by interaction with JAKs and TYK2 (a non-JAK tyrosine kinase). Under normal conditions, STAT3 phosphorylation is temporary. However, STAT3 is continuously activated in many tumor cells, indicating aberrant STAT3 signals and plays a role in tumor formation.[6,30]

Numerous gene products critical for angiogenesis, cell motility, and cell survival and proliferation are among the downstream targets of STAT3. Substances that suppress STAT3 activation could be effective in preventing and treating cancer as STAT3 plays an impostant role in the growth and metastasis of cancer cells.[30,44]
Morphological changes also characterize apoptosis. The administration of AA derivative compounds induced significant morphological changes in HeLa cells compared to normal cells, as observed with Hoechst 33258 staining. The cell underwent morphological changes, including cell shrinkage, chromatin condensation, a decrease in the number of adherent cells, cell membrane rupture, and nuclear fragmentation.[23] In colon carcinoma, the cells became smaller and pyknotic, the cytoplasm more condensed and swollen of organelles.[11] The mechanism of AA-induced apoptosis is illustrated in Figure 2.

4.3. Asiatic acid inhibited migration, invasion, and metastasis

Metastases are often found in advanced stages of cancer and are associated with a poor prognosis for patients.[30] AA prevents renal carcinoma migration and invasion by decreasing the activity of the p-ERK/p-p38 MAPK pathway, which subsequently reduces MMP-15 regulation. MMPs, such as MMP-9 and MMP-2, are associated with metastasis because of their ability to degrade collagen and other ECM proteins. In renal cell carcinoma, the inhibition of MMP-9 can decrease cell invasion and lead to the breakdown of collagen IV in the basement membrane. This breakdown makes it possible for cancer cells to pass through the basement membrane, which encourages tumor invasion and metastasis. MMP-2 is important for patient prognosis. In addition, MMP-1,-3,-7, and MMP-15 are considered viable targets for slowing the growth of cancer.[45]

Mitogen-activated protein kinases, such as p38 MAPK,JNK1/2 and ERK1/2 have the potential to target the progression and spread of cancerous tumors and are being investigated as possible cancer treatments. AA downregulates the expression of ERK1/2, JNK1/2, and p38MAPK in renal and nasopharyngeal cancer cells.[20,32]

AA inhibits EMT in lung cancer and osteosarcoma cells by increasing E-cadherin expression and reducing Snail, N-cadherin, and vimentin expression. E-cadherin is a protein that binds to calcium and is essential for maintaining the integrity of the network structure. Decreased E-cadherin expression indicates EMT. N-cadherin is a protein that can cause morphological changes that increase cell motility and aggressiveness when expressed in epithelial cells. This protein is often upregulated in cancer cells to promote tumor invasion. The transcription factor Snail can initiate EMT by downregulating E-cadherin expression, which in turn can induce EMT and enhance the invasive characteristics of cancer cells. Vimentin functions as a protein which modulates cell adhesion and migration through its interaction with other adhesion proteins. Reduced vimentin levels can impair the migratory capacity of cells.[8,26,46,47] In addition, AA also influences these proteins in lung cancer cells induced by TGF-β1, which is a factor that can induce EMT.[26] The mechanism by which AA inhibits migration, invasion, and metastasis is shown in Figure 2.

4.4. Concentration, dose, combination, and derivatives of asiatic acid for effective anticancer

The effective and cytotoxic dose of AA varies between 40 μM and greater than 50 μM. The higher the dose of AA, the lower the cell viability. Exposure to AA for more than 24 hours decreased cell cancer viability. The longer the exposure to AA, the less the dose required. This is supported by several studies that show the IC_{50} ranges from 50 μM.[20,21,26,48] Smaller doses of AA (15-25 μM) are effective enough to reduce cell viability and inhibit proliferation in colon cancer cells.[20] As an ideal cancer therapy goal, AA exhibits low toxicity to normal cells.[21]

Various chemical modifications are performed on specific functional groups in the AA molecule to affect its anticancer activity. The synthesis methods used include esterification.

To ascertain the structure of the synthesized derivative, various spectroscopic techniques, such as Infrared (IR) spectroscopy and Mass Spectrometry (MS), are used to determine the molecular mass and fragment structure. Nuclear Magnetic Resonance Spectroscopy (NMR) is used to detect characteristic signals from hydrogen and carbon atoms, indicating the presence of

specific functional groups, such as fluorine, imidazole, or nitrile.[23]

Other studies that developed AA derivatives found that synthesized derivatives have better anticancer effects than the original AA. Two derivative compounds showed excellent antitumor activity against liver and gastric cancers with low IC_{50} values. This suggests the potential of the new compound as an anticancer agent. Even compound I6, in particular, showed activity comparable to Adriamycin, a chemotherapy drug frequently used.[49]

The synthesis of AA derivatives yields compounds that are 3.5 times more potent than AA and cisplatin in terms of their effect on HeLa cells.[23] In addition to having cytotoxic effects, AA also has a protective effect against irritant-induced neuroblastoma cells, such as H_2O_2, rotenone, glutamate, and cholesterol.[24] AA derivatives demonstrated significant cytotoxic activity with IC_{50} from 0.67 to 37.39 μM. The five compounds exhibited the strongest cytotoxic activity against all cancer cell lines, but only moderate cytotoxicity against noncancerous NIH/3T3 cells. This suggests that the new compound has a selective target effect on cancer cells.

The acetylation of amino and hydroxyl groups, along with other chemical changes, significantly increases the cytotoxicity of the examined cell types. The transformation of carboxyl groups at position 28 (28-COOH) at AA to amides also increases cytotoxicity, whereas compounds 25 and 26, whose carboxyl groups are missing, show only moderate cytotoxicity. Therefore, certain modifications to the chemical structure of ursan triterpenoids can enhance their effectiveness in cancer treatment.[27]

N-(2α,3β,23-acetoxyurs-12-en-28-oyl)-l-proline methyl ester (AA-PMe) has also been developed by structural modification. The increase in anticancer activity better than AA may be due to increased solubility in water and optimization of the hydrophilic-lipophilic balance. The proline methyl ester and acetic group in AA-PMe may exert a synergistic effect that enhances its anticancer activity.

The IC_{50} level of AA-PMe for gastric cancer cells is 5 μM, which is significantly lower than that of AA at a concentration of 50 μM. However, neither AA-PMe nor AA substantially affects the viability of normal gastric epithelial cells. Additionally, normal human embryonic kidney cells exhibit relatively little toxicity to AA-PMe, suggesting that the compound has remarkable selectivity against tumor cells relative to normal cells. This is critical for the development of effective and safe anticancer drugs.[29]

4.5. Asiatic acid as a molecular target for an anticancer agent

Several studies have verified the main target of AA treatment as anticancer, using molecular docking with AutoDock. The PI3K/AKT and NF-κB core targets were examined in relation to AA molecules. The findings indicated the minimal binding energy of the bonds between AA and PIK3CA, PIK3CG, AKT1, AKT2, P65, and IκKβ. More stable bonds and higher contact chances are found when ligands and receptors have lower binding energies. Overall, the binding energy was less than -5.0 kJ-mol-1, suggesting that both receptors and ligands had potent binding properties. AA inhibits osteosarcoma cells by targeting the NF-κB and PI3K/AKT pathways.[22]

In the osteosarcoma cells, AA decreased gene expression in the NF-κB and PI3K/AKT signaling pathways. To confirm the pathway's efficacy, we investigated the activators of the PI3K/AKT pathway, such as SC79 and activators of the NF-κB pathway, like PMA. These findings imply that both activators can partially counteract the inhibitory effects of AA on osteosarcoma. In conclusion, AA can stop osteosarcoma progression by blocking the PI3K/AKT and NF-κB signaling pathways. [22]

5. Conclusion

Asiatic acid (AA) exhibits promising anticancer properties across diverse cancer cell types by modulating key molecular pathways such as PI3K/Akt and NF-κB. These mechanisms contribute to the inhibition of cell proliferation, induction of apoptosis, and suppression of invasion and metastasis. AA demonstrates time- and dose-dependent cytotoxicity (1–50 μM) with minimal toxicity to normal cells, supporting its potential as a selective anticancer agent. Although AA and its derivatives consistently show superior therapeutic outcomes, limitations such as missing control dose data in several studies highlight the need for more rigorous experimental designs.

To fully realize AA's therapeutic potential, future research should focus on in vivo validation, pharmacokinetic profiling, and clinical translation. The development of targeted delivery systems and exploration of synergistic effects with existing therapies may enhance efficacy. Additionally, integrating omics technologies and AI-driven drug discovery could accelerate the identification of optimized AA derivatives with improved potency and selectivity.

Conflict of Interest

The authors declare no conflicts of interest.

Reference

1. Brown JS, Amend SR, Austin RH, Gatenby RA, Hammarlund EU, Pienta KJ. Updating the De fi nition of Cancer. Published online 2023:1142-1147. doi:10.1158/1541-7786.MCR-23-0411
2. Gerstberger S, Jiang Q, Ganesh K, et al. HHS Public Access. 2023;186(8):1564-1579. doi:10.1016/j.cell.2023.03.003.Metastasis
3. Antony JVM, Ramani P, Ramasubramanian A, Sukumaran G. Particle size penetration rate and effects of smoke and smokeless tobacco products – An invitro analysis. Heliyon. 2021;7(3):e06455-e06455. doi:10.1016/j.heliyon.2021.e06455
4. Ardhiansyah AO. Edisi 2 Dasar-Dasar Onkologi Dan Hallmark Of Cancer Dari Teori Preklinik Hingga Aplikasi Klinik. 2nd ed. Penerbit Airlangga University Press; 2021.
5. Ricco N, Kron SJ. Statins in Cancer Prevention and Therapy. Cancers (Basel). 2023;15(3948). doi:https://doi.org/10.3390/cancers15153948
6. Wiciński M, Fajkiel-Madajczyk A, Kurant Z, et al. Can Asiatic Acid from Centella asiatica Be a Potential Remedy in Cancer Therapy?—A Review. Cancers (Basel). 2024;16(7):1-17. doi:10.3390/cancers16071317
7. Chen YH, Wu JX, Yang SF, Hsiao YH. Synergistic Combination of Luteolin and Asiatic Acid on Cervical Cancer In Vitro and In Vivo. Cancers (Basel). 2023;15(2). doi:10.3390/cancers15020548
8. Hao Y, Huang J, Ma Y, et al. Asiatic acid inhibits proliferation, migration and induces apoptosis by regulating Pdcd4 via the PI3K/Akt/mTOR/p70S6K signaling pathway in human colon carcinoma cells. Oncol Lett. 2018;15(6):8223-8230. doi:10.3892/ol.2018.8417
9. Sun B, Wu L, Wu Y, et al. Therapeutic Potential of Centella asiatica and Its Triterpenes: A Review. Front Pharmacol. 2020;11(September):1-24. doi:10.3389/fphar.2020.568032
10. Kasema SM, Mahfouza ME, Miraa NM, Helalb IB. Evaluation of phytochemical profile, antioxidant activity, storage stability, in vitro release kinetics and cytotoxic effects of ultrasonicated Rosmarinus officinalis. Jokul J. 2023;6(73):29-68.
11. Nataraj J, Manivasagam T, Justin Thenmozhi A, Essa MMM. Neurotrophic Effect of Asiatic acid, a Triterpene of Centella asiatica Against Chronic 1-Methyl 4-Phenyl 1, 2, 3, 6-Tetrahydropyridine Hydrochloride/Probenecid Mouse Model of Parkinson's disease: The Role of MAPK, PI3K-Akt-GSK3β and mTOR Signalling Pathwa. Neurochem Res. 2017;42(5):1354-1365. doi:10.1007/s11064-017-2183-2
12. Prakash V, Jaiswal N, Srivastava M. A review on medicinal properties of Centella asiatica. Asian J Pharm Clin Res. 2017;10(10):69-74. doi:10.22159/ajpcr.2017.v10i10.20760
13. Gou XJ, Bai HH, Liu LW, et al. Asiatic Acid Interferes with Invasion and Proliferation of Breast Cancer Cells by Inhibiting WAVE3 Activation through PI3K/AKT Signaling Pathway. Biomed Res Int. 2020;2020. doi:10.1155/2020/1874387
14. Islam MT, Ali ES, Uddin SJ, et al. Anti-Cancer Effects of Asiatic Acid, a Triterpene from Centilla asiatica L: A Review. Anticancer Agents Med Chem. 2019;20(5):536-547. doi:10.2174/1871520619666191211103006
15. Chen R, Zhang W, Zhang M, Liu W, Feng W, Zhang Y. Asiatic acid in anticancer effects : emerging roles and mechanisms. 2025;(February):1-11. doi:10.3389/fphar.2025.1545654
16. Hosseini M salar. Journal of Medicine , Surgery , and Public Health Formulating research questions for evidence-based studies. J Med Surgery, Public Heal. 2024;2(December 2023):100046. doi:10.1016/j.glmedi.2023.100046
17. Page MJ, Mckenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement : an updated guideline for reporting systematic reviews Systematic reviews and Meta-Analyses. Res Methods Report. 2021;372(n71):1-9. doi:http://dx.doi.org/10.1136/bmj.n71
18. Sheth VH, Shah NP, Jain R, Bhanushali N. Development and validation of a risk-of-bias tool for assessing in vitro studies conducted in dentistry : The QUIN. Published online 2021:1038-1042.
19. Zhu Z, Cui L, et. al. Anticancer effects of asiatic acid against doxorubicin-resistant breast cancer cells via an AMPK-dependent pathway in vitro. Phytomedicine. 2021;92:153737. doi:10.1016/j.phymed.2021.153737
20. Huang CFF, Hung TWW, Yang SFF, et al. Asiatic acid from centella asiatica exert anti-invasive ability in human renal cancer cells by modulation of ERK/p38MAPK-mediated MMP15 expression. Phytomedicine. 2022;100. doi:10.1016/j.phymed.2022.154036
21. Huang Y, Xie Z, Jiwa H, et al. Asiatic acid affects the growth of human osteosarcoma cells by regulating PI3K/AKT and NF-κB dual signal pathways. J Funct Foods. 2023;111:105885.
22. Li J, Chen K, Huang J, et al. Asiatic Acid Induces Endoplasmic Reticulum Stress and Activates the Grp78/IRE1α/JNK and Calpain Pathways to Inhibit Tongue Cancer Growth. Front Pharmacol. 2021;12(May):1-8. doi:10.3389/fphar.2021.690612
23. Gonçalves BMF, Salvador JAR, Marín S, Cascante M. Synthesis and anticancer activity of novel fluorinated asiatic acid derivatives. Eur J Med Chem. 2016;114:101-117. doi:10.1016/j.ejmech.2016.02.057
24. Ternchoocheep K, Surangkul D, Ysothonsreekul S. The recovery and protective effects of asiatic acid on differentiated human neuroblastoma SH-SY5Y cells cytotoxic-induced by cholesterol. Asian Pac J Trop Biomed. 2017;7(5):416-420. doi:https://doi.org/10.1016/j.apjtb.2017.01.012
25. Meng YQ, Tong H, Li XX, Kuai ZY, Li QW, Xu CD. Synthesis and anti-tumor activity of derivatives of ring A of asiatic acid. J Asian Nat Prod Res. 2020;22(7):689-700. doi:10.1080/10286020.2019.1616693
26. Cui Q, Ren J, Zhou Q, Yang Q, Li B. Effect of asiatic acid on epithelial-mesenchymal transition of human alveolar epithelium A549 cells induced by TGF-β1. Oncol Lett. 2019;17(5):4285-4292. doi:10.3892/ol.2019.10140
27. Tran Van L, Vo Thi QNN, Tran Van C, et al. Synthesis of Asiatic Acid Derivatives and Their Cytotoxic Activity. Med Chem Res. 2018;27(6):1609-1623. doi:10.1007/s00044-018-2176-y
28. Wu T, Geng J, Guo W, Gao J, Zhu X. Asiatic acid inhibits lung cancer cell growth in vitro and in vivo by destroying mitochondria. Acta Pharm Sin B. 2017;7(1):65-72.

doi:10.1016/j.apsb.2016.04.003
29. Lu Y, Liu S, Wang Y, Wang D, Gao J, Zhu L. Asiatic acid uncouples respiration in isolated mouse liver mitochondria and induces HepG2 cells death. Eur J Pharmacol. 2016;786:212-223. doi:10.1016/j.ejphar.2016.06.010
30. Wang G, Jing Y, Cao L, et al. A novel synthetic asiatic acid derivative induces apoptosis and inhibits proliferation and mobility of gastric cancer cells by suppressing STAT3 signaling pathway. Onco Targets Ther. 2017;10:55-66. doi:10.2147/OTT.S121619
31. Jing Y, Wang G, Ge Y, Xu M, Tang S, Gong Z. AA-PMe, a novel asiatic acid derivative, induces apoptosis and suppresses proliferation, migration, and invasion of gastric cancer cells. Onco Targets Ther. 2016;9:1605-1621. doi:10.2147/OTT.S98849
32. Liu YT, Chuang YC, Lo YS, et al. Asiatic Acid, Extracted from
33. and Induces Apoptosis Pathway through the Phosphorylation p38 Mitogen-Activated Protein Kinase in Cisplatin. Biomolecules. Published online 2020.
34. Li Y, Huang X, Tang J. Inhibiting the growth of ovarian cancer cells in vitro and in vivo by a small molecular inhibitor targeting La-RNA interactions. Eur J Pharmacol. 2023;940:175471. doi:https://doi.org/10.1016/j.ejphar.2022.175471
35. Lee CC, Hsiao CY, Lee SC, et al. Suppression of oral cancer by induction of cell cycle arrest and apoptosis using Juniperus communis extract. Biosci Rep. 2020;40(9):1-11. doi:10.1042/BSR20202083
36. Engeland K. Cell cycle regulation: p53-p21-RB signaling. Cell Death Differ. 2022;29(5):946-960. doi:10.1038/s41418-022-00988-z
37. Pang H, Wu H, Zhan Z, et al. Exploration of anti-osteosarcoma activity of asiatic acid based on network pharmacology and in vitro experiments. Oncol Rep. 2024;51(2). doi:10.3892/or.2023.8692
38. Adtani PN, Narasimhan M, Girija DM. In vitro anticancer activity of a pentacyclic triterpenoid via the mitochondrial pathway in bone-invasive oral squamous cell carcinoma. J Oral …. 2021;25(2):313-321. doi:10.4103/0973-029X.325234
39. Ribeiro ABB, Ozelin SDD, da Silva LHDHD, et al. Influence of Asiatic acid on cell proliferation and DNA damage in vitro and in vivo systems. J Biochem Mol Toxicol. 2021;35(4). doi:10.1002/jbt.22712
40. Mokbel K, Mokbel K. The Intrinsic Pathway of Apoptosis and Carcinogenesis: An Update. J Tumor. 2018;6(1):520-525. doi:10.17554/j.issn.1819-6187.2018.06.106
41. Wang XX, Sun J, Liu F, Bian Y, Miao L, Wang XX. Asiatic acid attenuates malignancy of human metastatic ovarian cancer cells via inhibition of epithelial-to-mesenchymal transition. Trop J Pharm Res. 2017;16(6):1223-1229. doi:10.4314/tjpr.v16i6.3
42. Ren L, Cao QX, Zhai FR, Yang SQ, Zhang HX. Asiatic acid exerts anticancer potential in human ovarian cancer cells via suppression of PI3K/Akt/mTOR signalling. Pharm Biol. 2016;54(11):2377-2382. doi:10.3109/13880209.2016.1156709
43. Ha DP, Tsai YL, Lee AS. Suppression of ER-stress induction of GRP78 as an anti-neoplastic mechanism of the cardiac glycoside Lanatoside C in pancreatic cancer: Lanatoside C suppresses GRP78 stress induction. Neoplasia. 2021;23(12):1213-1226. doi:https://doi.org/10.1016/j.neo.2021.10.004
44. Cheng Q, Liao M, Hu H, Li H, Wu L. Asiatic Acid (AA) Sensitizes Multidrug-Resistant Human Lung Adenocarcinoma A549/DDP Cells to Cisplatin (DDP) via Downregulation of P-Glycoprotein (MDR1) and Its Targets. Cell Physiol Biochem. 2018;47(1):279-292. doi:10.1159/000489806
45. Nakhjavani M, Smith E, Yeo K, et al. Differential antiangiogenic and anticancer activities of the active metabolites of ginsenoside Rg3. J Ginseng Res. 2024;48(2):171-180. doi:https://doi.org/10.1016/j.jgr.2021.05.008
46. Huang RZZ, Wang CYY, Li JFF, et al. Synthesis, antiproliferative and apoptosis-inducing effects of novel asiatic acid derivatives containing α-aminophosphonates. RSC Adv. 2016;6(67):62890-62906. doi:10.1039/c6ra11397d
47. Fan L, Zheng M, Zhou X, et al. Molecular mechanism of vimentin nuclear localization associated with the migration and invasion of daughter cells derived from polyploid giant cancer cells. J Transl Med. 2023;21(1):1-18. doi:10.1186/s12967-023-04585-7
48. Pantia S, Kangsamaksin T, Janvilisri T, Komyod W. Asiatic Acid Inhibits Nasopharyngeal Carcinoma Cell Viability and Migration via Suppressing STAT3 and Claudin-1. Pharmaceuticals. 2023;16(6). doi:10.3390/ph16060902
49. Hu X, Li B, Li L, Li B, Luo J, Shen B. Asiatic acid protects against doxorubicin-induced cardiotoxicity in mice. Oxidative Med Cell. 2020;2020. doi:10.1155/2020/5347204
50. Meng YQ, Zhang WC, Ning ZT, Lu XY, Yang LN. Synthesis and anti-tumor activity of novel asiatic acid A ring-cleavage derivatives in vitro. Chinese J New Drugs. 2017;26(10):1157-1162. https://www.scopus.com/inward/record.uri?eid=2-s2.0-85024102451&partnerID=40&md5=928530b48537b647890d55a115e6ac1c