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Review Article

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Asiatic Acid: A Promising Candidate for Anti-inflammation and Anti-cancer

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Abstract *Centella asiatica* is an important and commonly used herbal medicine that can be traced back a long way in the history of Chinese medicine. It contains a variety of active ingredients, mostly triterpenes. Asiatic acid (AA) is a pentacyclic triterpenoid that existed in *Centella asiatica*, which exhibits efficient anti-inflammatory and anti-cancer activities. Since there is a lack of review articles on the biological activities of AA for these two species, this paper reviews the relevant research progress in recent years to fill the gap.

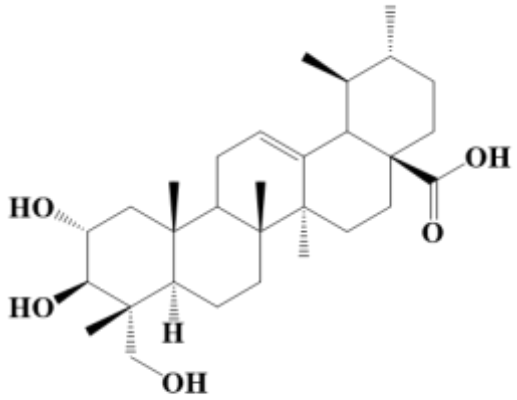
Keywords Asiatic acid, pentacyclic triterpenoid, anti-inflammation, anti-cancer

Introduction

Chinese herb *Centella asiatica*, the dried whole herb of *Centella asiatica* (L.) Urban (see Figure 1 for the morphology of it), family Umbelliferae, is a widely distributed and used traditional Chinese medicine, which is considered to have the effects of clearing heat and dampness, detoxifying, and reducing swelling in Chinese medicine [1].

Figure 1: The Morphology of Centella asiatica (L.) Urban

It has received much attention because of its numerous and significant therapeutic effects. Studies have shown that its main components include triterpenoids, volatile oils, polynyl olefins, flavonoids, etc. [1], and mainly triterpenoids, such as asiaticoside, madecassoside, asiatic acid (AA), madecassic acid, etc [1, 2]. AA (molecular formula $C_{30}H_{48}O_5$, molecular weight 488.7, see Figure 2 for the structure), a pentacyclic triterpenoid that existed in *Centella asiatica*, *Potentilla chinensis*, is ursane substituted by a carboxy group at position 28 and hydroxy groups at positions 2, 3 and 23 (the 2α, 3β stereoisomer). AA has been shown to have antioxidant [3] and anti-inflammatory [4-7] activities, while the anticancer activities of AA has been extensively studied [8-11]. However, no article summarizing the progress of research on the anti-inflammatory and anti-cancer activities of AA has appeared, so this paper will review the above issues.



Asiatic acid (AA)

Figure 2: The Structure of Asiatic acid (AA)

Anti-inflammatory activities of AA

Inflammation is an important cause of various human diseases. There are many triggers of inflammation, such as inflammation induced by some compounds (such as lipopolysaccharide (LPS), 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), N_ω-nitro-L-arginine methyl ester hydrochloride (L-NAME), doxorubicin (DXR), Cisplatin (CIS), bleomycin (BLM), dextran sulfate sodium (DSS), palmitate (PA), 1-methyl-4-phenyl- pyridine (MPP+), methamphetamine (METH), 2,4-dinitrocholrlbenzene (DNCB), cyclophosphamide (CYP), tetrachloromethane (CCl4)), inflammation due to trauma or organismal injury reactions, and inflammation triggered by other factors such as cigarette smoke. Therefore, drugs with excellent anti-inflammatory activity are needed. As research continues to expand and deepen, various aspects of the anti-inflammatory activity of AA are gradually unveiled.

Studies have shown that LPS is able to induce inflammatory responses in the body through multiple factors or pathways and is a non-negligible etiology of inflammatory responses. Therefore, many researchers have used LPS to induce inflammation in animal models and thus validate the anti-inflammatory properties of some compounds through a further series of experiments. This is a common and practical approach. Ma et al. found that AA can protect against D-galactosamine (D-GalN)/LPS-induced hepatotoxicity in part through the redox-regulated leukotriene C4 synthase (LTC4S) expression pathway [4]. Chen et al. conducted a study in LPS-intervened human corneal epithelial cells (HCECs). In this study, the biological effects of LPS at a concentration of 300 ng/mL for one hour were examined. The results showed that it can significantly promote the inflammatory factors interleukin-8 (IL-8), IL-6, IL-1β, tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) mRNA expression in HCECs. In addition, the effect of AA on altered discourse production was also evaluated, and the results showed that it effectively reversed the expression of those inflammatory factor mRNAs induced by LPS, and also had the ability to reduce reactive oxygen species (ROS) in cells, promote the production of Glutathione (GSH) and inhibit

LPS-stimulated Akt phosphorylation (p-Akt) [5]. Lv et al. found that AA inhibited MAPK and NF-κB activation by inducing programmed cell death 4 (PDCD4) expression and upregulating AMP-activated protein kinase (AMPK) / glycogen synthase kinase-3β (GSK3β) pathway activation by Nrf2, thereby protecting the liver from inflammation and oxidative stress injury [6]. Yun et al. studied LPS-induced RAW 264.7 macrophages and found that the production of nitric oxide (NO) and prostaglandin E2 (PGE2) was increased. After AA intervention, these changes were abolished, and the protein and mRNA expression levels of inducible NOS (iNOS) and cyclooxygenase-2 (COX-2) enzymes were inhibited in a concentration-dependent manner. In addition, IL-6, IL-1β and TNF-α production decreased in LPS-stimulated RAW 264.7 macrophages in a dose-dependent manner. LPS-induced activation of nuclear factor kappa-B (NF-κB) was also inhibited. In addition, phosphorylation of IκB kinase (IKK), p38, extracellular regulated protein kinases (ERK1/2), and c-Jun N-terminal kinase (JNK) (i.e., mitogen-activated protein kinases (MAPK) signaling pathway) was also inhibited by AA in a dose-dependent manner [7]. Xiong et al. found that AA was able to reduce serum levels of alanine aminotransferase and blood urea nitrogen after LPS intervention, and also to improve survival in mice with experimental sepsis. More strikingly, AA was shown to be a novel small molecule inhibitor of the Notch signaling pathway. It can upregulate Notch receptor (Notch3) and delta-like ligand (DLL4), inhibits Notch3 binding to the IL-6 promoter, and regulates mitochondrial function. This adds an important piece to the map of anti-inflammatory activity of AA [12]. Cao et al. investigated the effect of AA on the inflammatory response generated in LPS-stimulated endometrial epithelial cells. This study found that AA was able to inhibit LPS-induced Toll-like receptor 4 (TLR4) expression and NF-κB activation in a concentration-dependent manner, and also increased peroxisome proliferator-activated receptor γ (PPARγ) expression [13]. Hao et al. investigated the effect of AA on the inflammatory response generated in LPS-induced human gingival fibroblasts (HGFs). It was shown that in HGFs, AA was able to activate PPARγ and subsequently inhibit LPS-induced activation of NF-κB and production of inflammatory mediators (e.g., IL-6, IL8, PGE2, NO) [14]. Therefore, AA has the potential to treat periodontitis. Li et al. investigated the therapeutic effect of AA on LPS-induced Acute Lung Injury (ALI) in mice. The results showed that AA significantly inhibited LPS-induced histopathological changes in the lung, myeloperoxidase (MPO) activity, and the number of inflammatory cells in bronchoalveolar lavage fluid (BALF). In addition, this study also successfully replicated the conclusion reached in the above study that AA can inhibit LPS-induced TLR4 expression and NF-kB activation and TNF-α, IL-6 and IL-1β production [15]. AA has better anti-inflammatory activity and therapeutic effects in ALI. Han et al. compared the anti-inflammatory ability between AA and Oleanolic acid as well as maslinic acid by LPS-induced inflammation assay in RAW264.7 cells, and the results showed that between the three, AA has excellent anti-inflammatory activity, excluding the replication of the above experimental results (MAPKs and NF-κB pathway), and also came to an unexpected It was concluded that AA promoted LPS-induced nuclear factor erythroid 2-related factor 2 (Nrf2) expression and reduced Kelch-like ECH-associated protein (Keap) expression in RAW264.7 cells. Meanwhile, AA could effectively inhibit LPS-induced intracellular ROS production and improve mitochondrial membrane potential depletion [16]. The above study showed that LPS is an excellent pro-inflammatory agent and can feed back the anti-inflammatory activities of AA from multiple pathways.

In addition to studying the therapeutic efficacy of AA on LPS-induced inflammation in the body, some other researchers have tried to investigate whether AA can treat inflammation induced by compounds depart from LPS (e.g., MPTP, L-NAME, DXR, CIS, BLM, DSS, PA, MPP+, METH, DNCB, CYP, CCl4, etc.). Chao et al. investigated the effect of AA on striatal damage induced by MPTP treatment in mice. It was found that AA deposited in the striatum of MPTP-treated mice and increased the glutathione (GSH) content and decreased the production of ROS in the striatum. AA treatments at 20–80 mg/kg/day can dose-dependently lower striatal levels of NO、3-nitrotyrosine、IL-1β、IL-6、TNF-α and PGE2. In addition, AA treatments at 40 and 80 mg/kg/day can down-regulate the expression of striatal $p47^{phox}$, $gp91^{phox}$, Bax, apoptosis-inducing factor and caspase-3 expression in the striatum, but enhance the expression of Bcl-2. Furthermore, AA at 20–80 mg/kg/day can increase striatal tyrosine hydroxylase expression, and inhibit the expression of Toll-like receptors 2 (TLR2) and NF-kB p65. Moreover, AA treatments at 40 and 80 mg/kg/day can decrease striatal levels of α-synuclein and TLR4, and also can increase striatal levels of dopamine, brain-derived nerve growth factor and glial cell line-derived neurotrophic factor

[17]. L-NAME treatment was able to trigger hypertensive symptoms in an animal model of cardiovascular remodeling. Decreased plasma nitrate and nitrite (NOx) and increased plasma TNF-α are observed in hypertensive rats. And the content of malondialdehyde (MDA) in plasma, aortic and heart tissues are significantly increased in hypertensive rats. Bunbupha et al. found that AA significantly reduced L-NAME-induced hypertension, alleviated cardiovascular remodeling, and restored plasma MDA, and restored plasma NOx and TNF-α and endothelial nitric oxide synthase (eNOS)/iNOS expression in cardiac and aortic tissue [18]. Kamble et al. investigated the effects of AA on DXR-induced organ toxicity and Nrf2 expression. Changes in AA administration were observed after 7 days of treatment following DXR-induced toxic injury in an animal model. AA was found to prevent DXR-induced histological changes, including structural necrosis and congestion in the heart; leukocytic inflammation, centrilobular necrosis, apoptosis and fatty changes in the liver; and necrosis and AA treatment (20 mg/kg) reversed DXR-induced toxic injury by promoting the expression of Nrf2 protein [19]. CIS is a well-known chemotherapeutic agent used to treat a variety of human cancers, but is limited by its side effect of triggering nephrotoxicity. Yang et al. investigated the interventional effects of AA on CIS-induced kidney injury. AA pretreatment significantly inhibited CIS-induced elevations in serum creatinine, blood urea nitrogen and histological changes, and also significantly reduced the expression of kidney injury molecule-1 (KIM-1) and the number of apoptotic cells, and upregulated the expression of the apoptosis inhibitor AA inhibited the abnormal increase in mRNA expression of pro-inflammatory cytokines IL-1β, TNF-α, monocyte chemotactic protein 1 (MCP-1), and caspase-1 in the kidney. In addition, AA pretreatment may have the potential to inhibit NF-κB activation and inflammatory response through upregulation of smad7. In conclusion, AA protects against cisplatin-induced renal impairment through anti-apoptosis and anti-inflammation [20]. Dong et al. explored the effect of AA on BLM-induced pulmonary fibrosis in mice. The results showed that AA reduced inflammatory cell infiltration in BLM-induced bronchoalveolar lavage fluid (BALF) and expression of pro-inflammatory cytokines in lung tissue specimens. AA prevented the expression of transforming growth factor-β1 (TGF-β1) in lung tissues, a phenomenon associated with This phenomenon coincided with the reduction of collagen I and III, α-smooth muscle actin (α-SMA) and matrix metalloproteinase (TIMP)-1, as well as the inactivation of smads and ERK1/2. In addition, AA was able to reduce the NOD-like receptor, pyrin domain containing-3 (NLRP3) inflammasome [21]. Yu et al. evaluated the protective effects of AA on PA-induced human chondrocytes and high-fat diet (HFD)-fed chondrocytes. It was shown that AA treatment could reverse inflammation and extracellular matrix degradation induced by PA by inhibiting activation of the NF-κB pathway. The MD-2/TLR4 complex was found to be one of the targets of AA. Furthermore, AA supplementation not only prevented HFD-induced Osteoarthritis changes, but also reduced the production of pro-inflammatory cytokines and adipokines in obese mice. Moreover, AA could protect cartilage by inhibiting TLR4/myeloid differentiation 2 (MD-2) pathway [22]. Chen et al. investigated the effects of AA on LPS-induced BV2 microglia and MPP+ -induced SH-SY5Y cells to explore its inflammatory potential in treating Parkinson's disease (PD). They found that AA reduced intracellular mitochondrial ROS production, altered mitochondrial membrane potential to regulate mitochondrial dysfunction, and inhibited NLRP3 inflammasome activation in microglia, thus functioning to protect dopaminergic neurons from inflammation. In addition, AA directly promoted the enhancement of SH-SY5Y cell viability and improved MPP+ -induced mitochondrial dysfunction. These findings may provide a strong basis for AA treatment of PD [23]. Guo et al. investigated the changes of DSS-induced colitis under AA treatment. The experimental results showed that the protein and mRNA expression levels of DSS-induced colonic inflammatory cytokines, including TNF-α, IL-1β, IL-6 and IFN-γ, were significantly inhibited by AA. In addition, AA inhibited the activation of mitochondrial-mediated NLRP3 inflammasome thereby causing a decrease in caspase-1 activation in peritoneal macrophages. The above studies suggest that AA has additional therapeutic potential for colitis [24]. Park et al. investigated the therapeutic effects of AA on METH-induced neurotoxicity and inflammation. They found that AA significantly inhibited METH-induced TNF receptor (TNFR) expression in a concentration-dependent behavior and suppressed the increase of TNF-α and IL-6 expression in METH-stimulated neuronal cells. In addition, AA protects METH-induced NF-κB/ STAT3 translocation and ERK phosphorylation, while inhibiting METH-induced protein hydrolysis fragments of caspase-3 and PARP. In addition, AA promotes the secretion of the anti-apoptotic protein Bcl-xL in METH-acting cells. Moreover, the results of flow cytometry and

immunofluorescence staining showed that AA could maintain mitochondrial membrane integrity to some extent [25]. Moon et al. investigated the effects of AA on DNCB-induced atopic dermatitis (AD). In an animal model of DNCB-induced AD, AA administration reduced the mRNA expression levels of AD-related cytokines, such as Th1 (TNF-α and IL-1β and -12) and Th2 (IL-4, -5, -6, -13, and -31)-related cytokines, as well as COX-2 and C-X-C Motif Chemokine Ligand 9 (CXCL9) expression. This suggests that AA may modulate the symptoms of AD by suppressing inflammation [26]. Wróbel et al. explored the ability of AA to affect the CYP-induced cystitis model in rats. After CYP treatment, AA treatment was found to have some anti-inflammatory efficacy. AA significantly improved the thickness of the urothelium and bladder edema in CYP-induced rats and restored the concentrations of biomarkers in the bladder urothelium (including BDNF, CGRP, OCT-3, IL-1β, IL-6, NGF, nitrotyrosine, MDA, TNF- α, SV2A, SNAP23, SNAP25, PAC-1, ORM1, ocludin, IGFBP-3, HB-EGF, T-H protein, Z01, and HPX) [27]. Wei et al. investigated the potential role of AA in treating CCl4-induced liver fibrosis in rats. AA administration attenuated CCl4-induced oxidative stress, inflammation and hepatocyte apoptosis, and modulated the Bcl-2/Bax signaling pathway in the liver. In addition, the results showed that AA also inhibited hepatic stellate cell activation and extra cellular matrix (ECM) synthesis by modulating PI3K/AKT/mTOR signaling pathway, which provides a valid basis for AA treatment of liver fibrosis [28]. There is a paucity of research on these compounds that can trigger inflammation, and there may be other pathways involved that could be explored.

Studies of the effects of AA on other non-compound-induced inflammation could follow. GÜRCAN et al. found that AA reduced lipid peroxidation products (MDA) and pro-inflammatory cytokines (TNF-α, IL-1β) after traumatic spinal cord injury (SCI), and also partially restored Tarlov function in rats [29]. Qian et al. found that AA promoted Sirt1 expression, reduced NF-κB p65 acetylation, and inhibited NF-κB activation after LPS stimulation. However, EX-527, an inhibitor of Sirt1, counteracted the inhibitory effect of AA on LPS-stimulated microglia activation. These findings suggest that AA can ameliorate LPS-induced neuroinflammation by modulating the Sirt1/NF-κB signaling pathway [30]. Kong et al. found that AA treatment significantly reduced abnormal cytokine and chemokine production and inhibited MPO activity and activation of NLRP3 inflammasome, NF-κB and caspase-3, as well as oxidative stress. Due to the above-mentioned mechanisms, AA exhibited potent anti-inflammatory and antioxidant effects in pathogen-induced pelvic inflammatory disease (PID) rats [31]. Maneesai et al. showed that AA attenuated hemodynamic alterations, RAS activation, oxidative stress and inflammation in 2K-1C hypertensive rats, which suggests that AA may have therapeutic potential for hypertension. The mechanism may include one or both of the following two mechanisms: one is the direct effect of AA on RAS activation, oxidative stress, and inflammation, and the other is the ability of AA, as an ACE inhibitor, to inhibit the Ang II-AT1R-NADPH oxidase-NF-κB pathway [32]. The results gained by Yang et al. indicated that AA significantly inhibited IL-1β-induced expression levels of iNOS and COX-2 proteins in chondrocytes. In addition, AA increased the formation of extracellular matrix components of cartilage (including glycosaminoglycans (GAGs) and collagen type II (Col II)) and significantly increased the mRNA expression of chondrogenic markers (including Aggrecan, Sox9, Col II and Fibronectin). In addition, AA inhibited chondrocyte inflammation by directly inhibiting IL-1β-induced IκBα phosphorylation and NF-κB/p65 translocation [33]. Lee et al. showed that AA inhibited ROS production and NE activity, and suppressed the release of pro-inflammatory cytokines in BALF. In addition, AA reduced the increasement of inflammatory cells and the expression of MCP-1 in the lung tissue of cigarette smoke-exposed mice. Notably, AA also promoted the expression of HO-1 and improved the abnormal expression of Superoxide Dismutase 3 (SOD3) in lung tissue [34]. Fong et al. found that AA significantly inhibited the hyperpermeability of endothelial cells and increased the expression of vascular cell adhesion molecule -1 and TNF-α-triggered soluble cell adhesion molecules (sE-selectin, sICAM-1, sVCAM-1 and sPECAM-1) levels were increased. In addition, AA was found to inhibit the increase in IκB phosphorylation induced by the stimulation of TNF-α [35]. Uddandrao et al. found that AA inhibits the secretion of the transcription factor PPARγ and its TNF-α, fatty-acid synthase (FAS), adipocyte protein-2 (aP2) and uncoupling protein-2 (UCP-2) by reversing adipogenesis, thereby reducing the production of fatty acids and pro-inflammatory factors in adipose tissue [36]. These studies suggest that AA has good anti-inflammatory activity in multiple signaling pathways, but because there are relatively few studies on inflammation models induced by factors other than LPS-induced inflammation, the aspects of experimental results

generated at the same time are also limited, and further in-depth studies in various aspects are needed. The authors suggest that the effects of AA on other inflammation-related indicators and signaling pathways could be investigated.

Anti-cancer activities of AA

Studies on the anticancer activity of AA have been developed in parallel with the studies on anti-inflammatory activity and have been found to have therapeutic activity against various types of cancers such as liver, colon and breast cancers.

Studies have found AA to be more effective in the treatment of liver cancer. Chen et al. found that AA inhibited the expression of nuclear Dbf2-related (NDR)1/2 kinase and promoted p21WAF1/ CIP1-dependent phosphorylation to promote the stability of p21WAF1/CIP1 protein [8]. In addition, Chen et al. found that AA concentration-dependently and significantly inhibited cell viability, migration, invasion and epithelial mesenchymal transition (EMT) in Hepatocellular carcinoma (HCC) cells. Meanwhile, the expression of proteins involved in EMT and TGF-β/Smad pathway, such as TGF-β1, Smad4 and Vimentin, was decreased, while E-cadherin was up-regulated [9].

For colon cancer, AA has good therapeutic effect. Tang et al. showed that AA inhibited cell proliferation of SW480 human colon cancer cells. In addition, AA induced caspase-9 activity by increasing mitochondrial membrane permeability and cytochrome c release from mitochondria into the cytosol, which further activated the cleavage of caspase-3 and poly (ADP-ribose) polymerase, leading to irreversible apoptosis of tumor cells [10]. Siddique et al. found that AA treatment produced the following phenomena in DHC-induced colon cancer cells: a significant decrease in the levels of aberrant crypt foci (ACF) and phase I xenobiotic enzymes, and an increase in phase II xenobiotic enzymes and mucin. In addition, AA treatment reversed the expression of mast cells, argyrophilic nucleolar organizer regions (AgNORs), proliferating cell nuclear antigen (PCNA) and cyclin D1 in DMH-alone-exposed rats was increased. Similarly, AA induced apoptosis in DMH-alone-exposed rats by down-regulating Bcl-2 expression and up-regulating Bax, cytochrome c, caspase-3 and -9 [11]. Hao et al. found that the proliferation and migration of colon cancer cells were inhibited by AA in a dose-dependent and time-dependent manner, and the G2/M and S phases of AA-treated colon cancer cells progression was delayed. In addition, AA upregulated Pdcd4 expression through PI3K/Akt/mTOR/ribosomal protein S6 kinase (p70S6K) signaling pathway, which inhibited proliferation, migration and induced apoptosis of colon cancer cells [37].

Research on AA treatment for breast cancer continues to evolve. Hsu et al. found that AA exhibited effective cell growth inhibition by inducing S-G2/M phase arrest and apoptosis in cancer cells. In addition, AA can also weaken the function of Cdc2 by increasing the binding of p21/WAF1/Cdc2 complex and the levels of inactivated phospho-Cdc2 and phospho-Cdc25C. AA treatment can also trigger the mitochondrial apoptotic pathway by altering the Bax/Bcl-2 ratio, cytochrome c release and caspase-9 activation. Of interest, experiments also identified MAPKs, ERK1/2 and p38 as important signals in AA-induced growth inhibition of breast cancer cells [38]. Gou et al. found that AA significantly inhibited the expression of WAVE3, P53, SOD, p-PI3K, p-AKT and other proteins in a concentration-dependent manner. In addition, AA significantly inhibited MDA-MB-231(F10) xenografted tumor in nude mice. These suggest that AA interferes with the invasive and proliferative ability of breast cancer cells by inhibiting the expression and activation of WAVE3 [39]. Tian et al. showed that AA inhibits vascular endothelial growth factor (VEGF) in human umbilical vein endothelial cells (HUVECs). (VEGF) expression and subsequently downregulated phosphorylation of vascular endothelial growth factor receptor 2 (VEGFR2) and its downstream target proteins (including ERK1/2, Src and FAK), thereby inhibiting angiogenesis and vascular permeability, which in turn inhibited the growth and metastasis of breast cancer [40]. Zhu et al. found that AA induced cell death in multiple ways, including promoting ROS production, reducing adenosine triphosphate (ATP) levels, and through intrinsic apoptosis, AMP-activated protein kinase (AMPK), programmed death-ligand 1 (PD-L1) and NF-κB transcriptional pathways for adaptive immune homeostasis. In addition, AA enhanced the sensitivity of DXR-resistant MCF-7 cells to DXR by improving P-glycoprotein (P-gp) function. This suggests that AA can function as an adjuvant therapy by eliminating the drug resistance of breast cancer cells [41].

The therapeutic effects of AA on other cancers (e.g., melanoma, ovarian cancer, lung cancer, glioblastoma, kidney cancer, osteosarcoma, etc.) are gradually being investigated and reported. Park et al. found that AA reduced the viability and induced apoptosis in human melanoma SK-MEL-2 cells in a time- and dose-dependent manner due to its ability to induce the production of ROS, alter the Bax/Bcl-2 ratio and activation of caspase-3 [42]. Ren et al. found that AA halved the viability of ovarian cancer cells, but did not affect the viability of normal human ovarian epithelial cells. AA also caused cell cycle arrest in the G0/G1 phase and a 7-10-fold increase in apoptosis in cancer cells. In addition, AA treatment was able to significantly reduce the phosphorylation levels of PI3K, Akt and mTOR in cancer cells, thus exerting a therapeutic effect on ovarian cancer [43]. Wu et al. showed that AA can target the mitochondria of lung cancer cells and cause the collapse of mitochondrial membrane potential and ROS production, thereby promoting apoptosis in cancer cells. In addition, it caused a significant decrease in the expression of proliferating cell nuclear antigen (PCNA) [44]. Thakor et al. found that AA had more advantages than CIS in reducing the viability of U87-MG cells in a time- and concentration-dependent manner [45]. Sakonsinsiri et al. found that AA effectively inhibited the activity of Cholangiocarcinoma cells by inducing apoptosis, as evidenced by apoptotic vesicles, downregulation of anti-apoptotic genes (Bcl-2 and Survivin/BIRC5), and an increase in early and late apoptotic cells [46]. The results gained by Yan et al. showed that AA inhibits the proliferation of human Osteosarcoma (OS) cells in a concentration- and time-dependent manner and induces apoptosis of OS cells through the mitochondrial pathway. Due to the fact, AA can induce apoptosis of OS cells induced by mitochondrial damage by inhibiting the expression of JAK2/STAT3 pathway and MCL-1 [47]. Li et al. found that AA can increase calcium and calcium-dependent protease calpain levels during the treatment of tongue cancer, which further induces endoplasmic This further induced endoplasmic stress and Grp78-related phosphorylation of IRE1α and JNK, ultimately causing caspase-3 activation and apoptosis [48]. Huang et al. found that AA inhibits Renal cell carcinoma (RCC) by suppressing the phospho-extracellular regulated protein kinases (p-ERK)/p38 MAPK axis and the subsequent downregulation of MMP-15 in vitro and in vivo metastatic properties of the cells [49]. Cheng et al. found that AA reversed P-gp-mediated multidrug resistance (MDR) by inhibiting P-gp expression mediated by NF-kB and MAPK-ERK pathways. The above mechanism could ensure that AA plays a role in sensitizing Lung Adenocarcinoma A549/DDP Cells with MDR to CIS [50]. Cheng et al. further found through their study that AA could promote miR-1297 expression by inhibiting the expression of Metastasis-related lung adenocarcinoma transcript 1 (MALAT1), p300, β-catenin and MDR1 in A549/DDP cells, and inhibited nuclear translocation of β-catenin to increase the apoptosis rate of lung adenocarcinoma cells and restored the sensitivity of A549/DDP cells to CIS [51]. In addition, Lian et al. demonstrated that the combination with AA and naringenin greatly inhibited the translation and phosphorylation of Smad3, while restoring Smad7 expression. Thus, they can promote NK cell differentiation, maturation and anticancer cytotoxicity through Id2/IRF2-related mechanisms [52]. Fang et al. found that AA can enhance the intratumoral delivery and antitumor effect of polyethylene glycol liposomal DXR by reducing intertumor collagen, and thus can be used as an adjuvant to indirectly exert some anticancer activity [53]. It can be seen from the above studies that AA has good anti-cancer activity and involves a wide range of cancers, and has great potential to be developed into a clinically accessible anti-cancer drug. For the present, the research on AA for cancer treatment is relatively limited. Although more types of cancers have been explored, there are only a few relevant experimental studies, and more research data and theories are lacking.

Conclusion

AA has been shown to exert better anti-inflammatory and anti-cancer activities in a variety of ways. The use of LPS stimulation to create models of inflammation is particularly common in studies of anti-inflammatory capacity, and other types of compounds (MPTP, L-NAME, DXR, CIS, BLM, DSS, PA, MPP+, METH, DNCB, CYP, CCl4) can also elicit inflammatory responses. Studies have shown that AA can effectively reduce the expression and secretion of inflammation-related factors such as IL-8, IL-6, IL-1β, TNF-α, TGF-β, NO, and PGE2, and also inhibit the activation of NF-κB pathway, phosphorylation of IKK, ERK1/2, and JNK, and the opening of other inflammatory signaling pathways. In terms of anticancer activity, AA can inhibit the proliferation of various types of cancer cells and promote apoptosis through multiple pathways, as well as interfere with cancer progression in other ways. AA

can also act as an adjuvant by inhibiting P-gp expression-mediated MDR in cancer cells. However, most studies have been limited to the cellular level and have not yet explored its effects in live animals by conducting more experiments in animal models. Studies have shown that AA has good anti-inflammatory and anti-cancer activities and has great potential to be developed into a clinical drug. However, more researchers are needed to conduct multifaceted and broad field studies to obtain more novel experimental data and theories. In conclusion, this paper reviews the research progress of AA in anti-inflammatory and anti-cancer activities, which will provide an existing and more comprehensive experimental and theoretical reference for the subsequent studies on the above two activities of AA.

References

[1]. Gohil, K. J., Patel, J. A. and Gajjar, A. K. (2010). Pharmacological Review on Centella asiatica: A Potential Herbal Cure-all. *Indian Journal of Pharmaceutical Sciences*, 72(5): 546-556.

[2]. Sun, B., Wu, L., Wu, Y., Zhang, C., Qin, L., Hayashi, M., Kudo, M., Gao, M. and Liu, T. (2020). Therapeutic Potential of Centella asiatica and Its Triterpenes: A Review. *Frontiers in Pharmacology*, 11: 568032.

[3]. Meng, Z., Li, H., Si, C., Liu, Y. and Teng, S. (2019). Asiatic acid inhibits cardiac fibrosis throughNrf2/HO-1 and TGF-β1/Smads signaling pathways in spontaneous hypertension rats. *International Immunopharmacology*, 74: 105712.

[4]. Ma, K., Zhang, Y., Zhu, D. and Lou, Y. (2009). Protective effects of asiatic acid against D-galactosamine/lipopolysaccharide-induced hepatotoxicity in hepatocytes and kupffer cells co-cultured system via redox-regulated leukotriene C4 synthase expression pathway. *European Journal of Pharmacology*, 603(1-3): 98-107.

[5]. Chen, H., Hua, X., Ze, B., Wang, B. and Wei, L. (2017). The anti-inflammatory effects of asiatic acid in lipopolysaccharide-stimulated human corneal epithelial cells. *International journal of ophthalmology*, 10(2): 179-185.

[6]. Lv, H., Qi, Z., Wang, S., Feng, H., Deng, X. and Ci, X. (2017). Asiatic Acid Exhibits Anti-inflammatory and Antioxidant Activities against Lipopolysaccharide and d-Galactosamine-Induced Fulminant Hepatic Failure. *Frontiers in Immunology*, 8: 785.

[7]. Yun, K. J., Kim, J. Y., Kim, J. B., Lee, K. W., Jeong, S. Y., Park, H. J., Jung, H. J., Cho, Y. W., Yun, K. and Lee, K. T. (2008). Inhibition of LPS-induced NO and PGE2 production by asiatic acid via NF-kappa B inactivation in RAW 264.7 macrophages: possible involvement of the IKK and MAPK pathways. *International Immunopharmacology*, 8(3): 431-441.

[8]. Chen, J., Chen, J., Xu, Q., Xu, H. and Huang, Z. (2014). Asiatic acid promotes p21(WAF1/CIP1) protein stability through attenuation of NDR1/2 dependent phosphorylation of p21(WAF1/ CIP1) in HepG2 human hepatoma cells. *Asian Pacific Journal of Cancer Prevention*, 15(2): 963-967.

[9]. Chen, T., Zhu, C., Wang, X., Pan, Y. and Huang, B. (2021). Asiatic Acid Encapsulated Exosomes of Hepatocellular Carcinoma Inhibit Epithelial-Mesenchymal Transition Through Transforming Growth Factor Beta/Smad Signaling Pathway. *Journal of Biomedical Nanotechnology*, 17(12): 2338-2350.

[10]. Tang, X., Yang, X., Jung, H., Kim, S., Jung, S., Choi, D., Park, W. and Park, H. (2009). Asiatic acid induces colon cancer cell growth inhibition and apoptosis through mitochondrial death cascade. *Biological and Pharmaceutical Bulletin*, 32(8): 1399-1405.

[11]. Siddique, A. I., Mani, V., Renganathan, S., Ayyanar, R., Nagappan, A. and Namasivayam, N. (2017). Asiatic acid abridges pre-neoplastic lesions, inflammation, cell proliferation and induces apoptosis in a rat model of colon carcinogenesis. *Chemico-Biological Interactions*, 278: 197-211.

[12]. Xiong, Y., Cheng, X., Yin, Q., Xia, L., Ke, R. and Sun B., (2018). Asiatic acid attenuates lipopolysaccharide-induced injury by suppressing activation of the Notch signaling pathway. *Oncotarget*, 9(19): 15036-15046.

[13]. Cao, S., Wang, W., Nan, F., Liu, Y., Wei, S., Li, F. and Chen, L. (2018). Asiatic acid inhibits LPS-induced inflammatory response in endometrial epithelial cells. *Microbial Pathogenesis*, 116: 195-199.

[14]. Hao, C., Wu, B., Hou, Z., Xie, Q., Liao, T., Wang, T. and Ma, D. (2017). Asiatic acid inhibits LPS-induced inflammatory response in human gingival fibroblasts. *International Immunopharmacology*, 50: 313-318.
[15]. Li, Z., Xiao, X. and Yang, M. (2016). Asiatic Acid Inhibits Lipopolysaccharide-Induced Acute Lung Injury in Mice. *Inflammation*, 39(5): 1642-1648.
[16]. Han, Y., Yuan, C., Zhou, X., Han, Y., He, Y., Ouyang, J., Zhou, W., Wang, Z., Wang, H. and Li, G. (2021). Anti-Inflammatory Activity of Three Triterpene from Hippophae rhamnoides L. in Lipopolysaccharide-Stimulated RAW264.7 Cells. *International Journal of Molecular Sciences*, 22(21): 12009.
[17]. Chao, P., Lee, H. and Yin, M. (2016). Asiatic acid attenuated apoptotic and inflammatory stress in the striatum of MPTP-treated mice. *Food & Function*, 7(4): 1999-2005.
[18]. Bunbupha, S., Prachaney, P., Kukongviriyapan, U., Kukongviriyapan, V., Welbat, J. U. and Pakdeechote, P. (2015). Asiatic acid alleviates cardiovascular remodelling in rats with L-NAME-induced hypertension. *Clinical and Experimental Pharmacology and Physiology*, 42(11): 1189-1197.
[19]. Kamble, S. M. and Patil, C. R. (2018). Asiatic Acid Ameliorates Doxorubicin-Induced Cardiac and Hepato-Renal Toxicities with Nrf2 Transcriptional Factor Activation in Rats. *Cardiovascular Toxicology*, 18(2): 131-141.
[20]. Yang, C., Guo, Y., Huang, T., Zhao, J., Huang, X., Tang, H., An, N., Pan, Q., Xu, Y. and Liu, H. (2018). Asiatic acid protects against cisplatin-induced acute kidney injury via anti-apoptosis and anti-inflammation. *Biomedicine & Pharmacotherapy*, 107: 1354-1362.
[21]. Dong, S., Liu, Y., Wei, F., Tan, H. and Han, Z. (2017). Asiatic acid ameliorates pulmonary fibrosis induced by bleomycin (BLM) via suppressing pro-fibrotic and inflammatory signaling pathways. *Biomedicine & Pharmacotherapy*, 89: 1297-1309.
[22]. Yu, X., Zheng, G., Hu, Z., Tang, S., Xu, J., Shang, P., Tang, Q. and Liu, H. (2020). Asiatic acid ameliorates obesity-related osteoarthritis by inhibiting myeloid differentiation protein-2. *Food & Function*, 11(6): 5513-5524.
[23]. Chen, D., Zhang, X., Sun, J., Cong, Q., Chen, W., Ahsan, H. M., Gao, J. and Qian, J. (2019). Asiatic Acid Protects Dopaminergic Neurons from Neuroinflammation by Suppressing Mitochondrial Ros Production. *Biomolecules & Therapeutics*, 27(5): 442-449.
[24]. Guo, W., Liu, W., Jin, B., Geng, J., Li, J., Ding, H., Wu, X., Xu, Q., Sun, Y. and Gao, J. (2015). Asiatic acid ameliorates dextran sulfate sodium-induced murine experimental colitis via suppressing mitochondria-mediated NLRP3 inflammasome activation. *International Immunopharmacology*, 24(2): 232-238.
[25]. Park, J. H., Seo, Y. H., Jang, J. H., Jeong, C. H., Lee, S. and Park, B. (2017). Asiatic acid attenuates methamphetamine-induced neuroinflammation and neurotoxicity through blocking of NF-kB/STAT3/ERK and mitochondria-mediated apoptosis pathway. *Journal of Neuroinflammation*, 14(1): 240.
[26]. Moon, G. H., Lee, Y., Kim, E. K., Chung, K. H., Lee, K. J. and An, J. H. (2021). Immunomodulatory and Anti-inflammatory Effects of Asiatic Acid in a DNCB-Induced Atopic Dermatitis Animal Model. *Nutrients*, 13(7): 2448.
[27]. Wróbel, A., Zapała, Ł., Kluz, T., Rogowski, A., Misiek, M., Juszczak, K., Sieńko, J., Gold, D., Stangel-Wójcikiewicz, K., Poleszak, E. and Radziszewski, P. (2021). The Potential of Asiatic Acid in the Reversion of Cyclophosphamide-Induced Hemorrhagic Cystitis in Rats. *International Journal of Molecular Sciences*, 22(11): 5853.
[28]. Wei, L., Chen, Q., Guo, A., Fan, J., Wang, R. and Zhang, H. (2018). Asiatic acid attenuates CCl(4)-induced liver fibrosis in rats by regulating the PI3K/AKT/mTOR and Bcl-2/Bax signaling pathways. *International Immunopharmacology*, 60: 1-8.
[29]. Gurcan, O., Gurcay, A. G., Kazanci, A., Senturk, S., Bodur, E., Karaca, E. U., Turkoglu, O. F. and Bavbek, M. (2017). Effect of Asiatic Acid on the Treatment of Spinal Cord Injury: An Experimental Study in Rats. *Turkish Neurosurgery*, 27(2): 259-264.
[30]. Qian, Y., Xin, Z., Lv, Y., Wang, Z., Zuo, L., Huang, X., Li, Y. and Xin, H. (2018). Asiatic acid suppresses neuroinflammation in BV2 microglia via modulation of the Sirt1/NF-κB signaling pathway. *Food & Function*, 9(2): 1048-1057.
[31]. Kong, D., Fu, P., Zhang, Q., Ma, X. and Jiang, P. (2019). Protective effects of Asiatic acid against pelvic inflammatory disease in rats. *Experimental and Therapeutic Medicine*, 17(6): 4687-4692.

[32]. Maneesai, P., Bunbupha, S., Kukongviriyapan, U., Senggunprai, L., Kukongviriyapan, V., Prachaney, P. and Pakdeechote, P. (2017). Effect of asiatic acid on the Ang II-AT(1)R-NADPH oxidase-NF-κB pathway in renovascular hypertensive rats. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 390(10): 1073-1083.
[33]. Yang, Z., Feng, L., Huang, J., Zhang, X., Lin, W., Wang, B., Cui, L., Lin, S. and Li, G. (2021). Asiatic acid protects articular cartilage through promoting chondrogenesis and inhibiting inflammation and hypertrophy in osteoarthritis. *European Journal of Pharmacology*, 907: 174265.
[34]. Lee, J. W., Park, H. A., Kwon, O. K., Jang, Y. G., Kim, J. Y., Choi, B. K., Lee, H. J., Lee, S., Paik, J. H., Oh, S. R., Ahn, K. S. and Lee, H. J. (2016). Asiatic acid inhibits pulmonary inflammation induced by cigarette smoke. *International Immunopharmacology*, 39: 208-217.
[35]. Fong, L. Y., Ng, C. T., Cheok, Z. L., Mohd Moklas, M. A., Hakim, M. N. and Ahmad, Z. (2016). Barrier protective effect of asiatic acid in TNF-α-induced activation of human aortic endothelial cells. *Phytomedicine*, 23(2): 191-199.
[36]. Uddandrao, V. V. S., Rameshreddy, P., Brahmanaidu, P., Ponnusamy, P., Balakrishnan, S., Ramavat, R. N., Swapna, K., Pothani, S., Nemani, H., Meriga, B., Vadivukkarasi, S., P, R. N. and Ganapathy, S. (2020). Antiobesity efficacy of asiatic acid: down-regulation of adipogenic and inflammatory processes in high fat diet induced obese rats. *Archives of Physiology and Biochemistry*, 126(5): 453-462.
[37]. Hao, Y., Huang, J., Ma, Y., Chen, W., Fan, Q., Sun, X., Shao, M. and Cai, H. (2018). Asiatic acid inhibits proliferation, migration and induces apoptosis by regulating Pdcd4 via the PI3K/Akt/mTOR/p70S6K signaling pathway in human colon carcinoma cells. *Oncology Letters*, 15(6): 8223-8230.
[38]. Hsu, Y. L., Kuo, P. L., Lin, L. T. and Lin, C. C. (2005). Asiatic acid, a triterpene, induces apoptosis and cell cycle arrest through activation of extracellular signal-regulated kinase and p38 mitogen-activated protein kinase pathways in human breast cancer cells. *Journal of Pharmacology and Experimental Therapeutics*, 313(1): 333-344.
[39]. Gou, X., Bai, H., Liu, L., Chen, H., Shi, Q., Chang, L., Ding, M., Shi, Q., Zhou, M., Chen, W. and Zhang, L. (2020). Asiatic Acid Interferes with Invasion and Proliferation of Breast Cancer Cells by Inhibiting WAVE3 Activation through PI3K/AKT Signaling Pathway. *BioMed Research International*, 2020: 1874387.
[40]. Tian, M., Chen, K., Huang, J., Chu, D., Li, J., Huang, K. and Ma, C. (2021). Asiatic acid inhibits angiogenesis and vascular permeability through the VEGF/VEGFR2 signaling pathway to inhibit the growth and metastasis of breast cancer in mice. *Phytotherapy Research*, 35(11): 6389-6400.
[41]. Zhu, Z., Cui, L., Yang, J., Vong, C. T., Hu, Y., Xiao, J., Chan, G., He, Z. and Zhong, Z. (2021). Anticancer effects of asiatic acid against doxorubicin-resistant breast cancer cells via an AMPK-dependent pathway in vitro. *Phytomedicine*, 92: 153737.
[42]. Park, B. C., Bosire, K. O., Lee, E.-S., Lee, Y. S. and Kim, J.-A. (2005). Asiatic acid induces apoptosis in SK-MEL-2 human melanoma cells. *Cancer Letters*, 218(1): 81-90.
[43]. Ren, L., Cao, Q., Zhai, F., Yang, S. and Zhang, H. (2016). Asiatic acid exerts anticancer potential in human ovarian cancer cells via suppression of PI3K/Akt/mTOR signalling. *Pharmaceutical Biology*, 54(11): 2377-2382.
[44]. Wu, T., Geng, J., Guo, W., Gao, J. and Zhu, X. (2017). Asiatic acid inhibits lung cancer cell growth in vitro and in vivo by destroying mitochondria. *Acta Pharmaceutica Sinica B*, 7(1): 65-72.
[45]. Thakor, F. K., Wan, K. W., Welsby, P. J. and Welsby, G. (2017). Pharmacological effects of asiatic acid in glioblastoma cells under hypoxia. *Molecular and Cellular Biochemistry*, 430(1-2): 179-190.
[46]. Sakonsinsiri, C., Kaewlert, W., Armartmuntree, N., Thanan, R. and Pakdeechote, P. (2018). Anti-cancer activity of asiatic acid against human cholangiocarcinoma cells through inhibition of proliferation and induction of apoptosis. *Cellular and Molecular Biology*, 64(10): 28-33.
[47]. Yan, B., Chen, X., Liu, J., Liu, S., Zhang, J., Zeng, Q. and Duan, J. (2021). Asiatic Acid Induces Mitochondrial Apoptosis via Inhibition of JAK2/STAT3 Signalling Pathway in Human Osteosarcoma. *Folia Biologica*, 67(3): 108-117.
[48]. Li, J., Chen, K., Huang, J., Chu, D., Tian, M., Huang, K. and Ma, C. (2021). Asiatic Acid Induces Endoplasmic Reticulum Stress and Activates the Grp78/IRE1α/JNK and Calpain Pathways to Inhibit Tongue Cancer Growth. *Frontiers in Pharmacology*, 12: 690612.

[49]. Huang, C., Hung, T., Yang, S., Tsai, Y., Yang, J., Lin, C. and Hsieh, Y. (2022). Asiatic acid from centella asiatica exert anti-invasive ability in human renal cancer cells by modulation of ERK/p38MAPK-mediated MMP15 expression. *Phytomedicine*, 100: 154036.

[50]. Cheng, Q., Liao, M., Hu, H., Li, H. and Wu, L. (2018). Asiatic Acid (AA) Sensitizes Multidrug-Resistant Human Lung Adenocarcinoma A549/DDP Cells to Cisplatin (DDP) via Downregulation of P-Glycoprotein (MDR1) and Its Targets. *Cellular Physiology and Biochemistry*, 47(1): 279-292.

[51]. Cheng, Q., Zhang, S., Zhong, B., Chen, Z. and Peng, F. (2022). Asiatic acid re-sensitizes multidrug-resistant A549/DDP cells to cisplatin by down regulating long non-coding RNA metastasis associated lung adenocarcinoma transcript 1/β-catenin signaling. *Bioengineered*, 13(5): 12972-12984.

[52]. Lian, G., Wang, Q., Tang, P., Zhou, S., Huang, X. and Lan, H. (2018). Combination of Asiatic Acid and Naringenin Modulates NK Cell Anti-cancer Immunity by Rebalancing Smad3/Smad7 Signaling. *Molecular Therapy*, 26(9): 2255-2266.

[53]. Fang, L., Kong, S., Zhong, L., Wang, C., Liu, Y., Ding, H., Sun, J., Zhang, Y., Li, F. and Huang, P. (2019). Asiatic acid enhances intratumor delivery and the antitumor effect of pegylated liposomal doxorubicin by reducing tumor-stroma collagen. *Acta Pharmacologica Sinica*, 40(4): 539-545.