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Review

Amarogentin: A review of its pharmacology, pharmacokinetics and toxicity

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Abstract: This review provides a comprehensive analysis of Amarogentin (AMA), a secoiridoid glycoside from the Gentianaceae family, highlighting its significant pharmacological effects. AMA demonstrates liver protection, anticancer, anti-inflammatory, antioxidant and antibacterial properties. Pharmacokinetic studies show rapid elimination and wide distribution of AMA in the body. Toxicity research indicates low toxicity to most cell types, although long-term and high-dose animal toxicity data are lacking. The therapeutic potential of AMA for liver fibrosis, cancer and diabetes is promising but further research is needed to explore its mechanisms, targets, toxicity and enhance oral bioavailability.

Keywords: Amarogentin; Pharmacology; Pharmacokinetic; Toxicity

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INTRODUCTION

AMA is a notable natural organic compound derived from plants that exhibits significant biological activity. Recent studies have identified AMA as a key active component in herbal remedies, such as those from *Swertia davidii Franch*. As a result, considerable research has investigated the pharmacological properties of AMA, including its hepatoprotection, antitumour, antidiabetic, antiviral, antibacterial, antiosteoporotic, antioxidant and anti-inflammatory effects. This body of research indicates that AMA may offer therapeutic benefits for a range of conditions, including liver disorders, various cancers, diabetes and inflammatory diseases.

Over the past several decades, the pharmacological effects of AMA have been extensively studied, with recent research delving into its pharmacokinetics and toxicity profiles. Nonetheless, prior findings have often been disjointed, lacking a cohesive summary and synthesis. Consequently, this review seeks to offer a thorough examination and analysis of the pharmacological actions, toxicological properties and pharmacokinetic traits of AMA, aiding in the more efficient and secure advancement and application of this secoiridoid glycoside.

Chemical properties and plant sources of AMA

AMA is classified as an iridoid glycoside with the molecular formula $C_{27}H_{28}O_{14}$ and a molecular weight of 576.52. Its chemical name is (4aS,5R,6S)-5-ethenyl-4,4a,5,6-tetrahydro-6-[[2-O-[(3,3',5-trihydroxy[1,1'-biphenyl]-2-yl)carbonyl]-β-D-glucopyranosyl]oxy]-1H,3H-pyrano[3,4-c]pyran-1-one (fig. 1, table 1). AMA is known as the most bitter secoiridoid glycoside and functions as an agonist for the hTAS2R50 receptor. It is a major bitter constituent in the Swertia genus and is primarily AMA. AMA is isolated from natural sources through organic extraction. Common sources include *Swertia mussotii Franch* (Sakamoto S *et al*., 2018), *Swertia davidii Franch* (Tan G *et al*., 2000; Li ZY *et al*., 2016), *Swertia speciosa D. Don* (Singh PP *et al*., 2012; Ray S *et al*., 1996), *Gentiana lutea L* (Qin J *et al*., 2012; Akileshwari C *et al*., 2012) and *Lomatogonium rotatum* (Yu Qing-fen *et al*., 2007) (fig. 2, table 2). While several analytical techniques for detecting AMA have been described, complete chemical synthesis of AMA has not been reported in the literature.

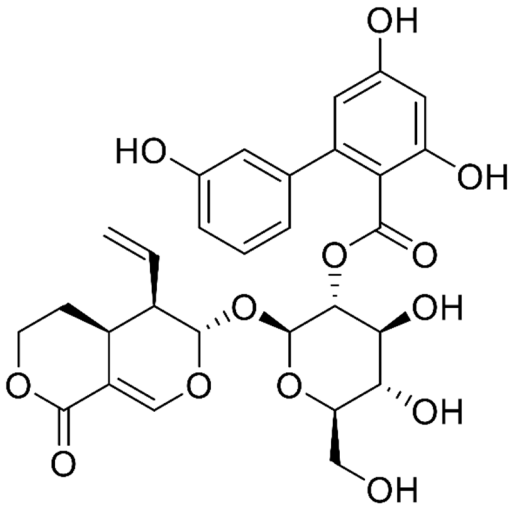

Fig. 1: Chemical structures of amarogentin.

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Table 1: The chemical properties of amarogentin.

Contents	Information
IUPAC Name	[(2S,3R,4S,5S,6R)-2-[[(3S,4R,4aS)-4-ethenyl-8-oxo-4,4a,5,6-tetrahydro-3H-pyrano[3,4-c]pyran-3-yl]oxy]-4,5-dihydroxy-6-(hydroxymethyl)oxan-3-yl] 2,4-dihydroxy-6-(3-hydroxyphenyl)benzoate
SMILES	C=C[C@@H]1[C@@H]2CCOC(=O)C2=CO[C@H]1O[C@H]3[C@@H]([C@H]([C@@H] [C@H](O3)CO)O)O)OC(=O)C4=C(C=C(C=C4O)O)C5=CC(=CC=C5)O
Molecular Formula	$C_{29}H_{30}O_{13}$
Molecular weight	586.5 g/mol
Rotatable Bond Count	8
Hydrogen Bond Donor Count	6
Hydrogen Bond Acceptor Count	13
PubChem CID	115149
CAS number	21018-84-8
Appearance	white crystalline powder
Taste	odorless and bitter
Solubility	soluble in methanol, ethanol, DMSO and other organic solvents
Melting point	229-230° (monohydrate)
Specific optical rotation	D20 -116.6° (methanol)

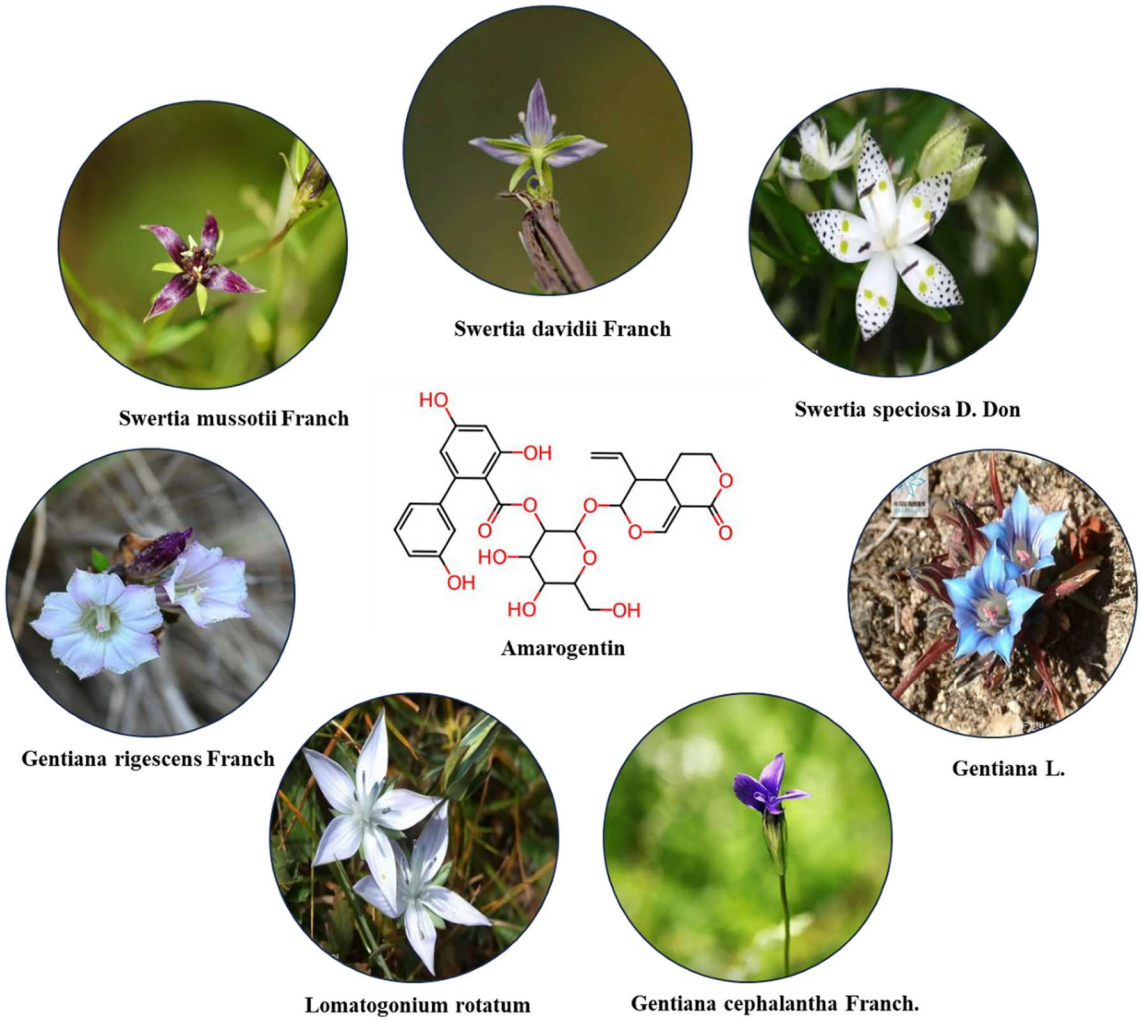

Fig. 2: The plant sources of amarogentin.

Table 2: The plant sources of amarogentin.

Plant species	Family	Used part	Amount isolated (mg/g)	Re
Swertia mussotii Franch	Swertia	Whole herb	0.004%	[1]
Swertia davidii Franch	Swertia	Whole herb	0.113%-0.3%	[2,3]
Swertia speciosa D. Don	Swertia	Above ground	0.013%	[4,5]
Gentiana cruciata L	Gentiana	root	0.01%-0.4%	[6,7]

Pharmacological activities of AMA

Hepatoprotective

Anti-hepatic fibrosis effects

Liver fibrosis is a consequence of ongoing tissue repair processes. If left untreated, liver damage can progress to liver failure or hepatocellular carcinoma (HCC). However, effective antifibrotic medications with minimal side effects have yet to be identified. Consequently, the quest for novel therapeutic agents is ongoing. Swertia mileensis T. N. Ho and W. L. Shih, traditional folk medicines in China, have been utilized for centuries to treat viral hepatitis. Additionally, Swertia chirayita (Roxb. ex Fleming) H. Karst. has demonstrated hepatoprotective effects against CCl_4- and paracetamol-induced liver damage in rats.

In a study examining the protective effects of AMA on carbon tetrachloride (CCl_4)-induced liver fibrosis in mice and the mechanisms involved, biochemical assessments revealed that AMA significantly decreased the levels of alanine aminotransferase, aspartate aminotransferase, malondialdehyde and hydroxyproline in a CCl_4-induced fibrosis model compared with those in controls. In contrast, the levels of albumin, cyclic guanosine monophosphate, glutathione peroxidase and superoxide dismutase were elevated. Immunohistochemical and Western blot analyses indicated that AMA reduced SMA and TGF-1 levels. Additionally, the phosphorylation of extracellular signal-regulated kinase, c-Jun N-terminal kinase and p38 was significantly diminished in a dose-dependent manner across all AMA-treated groups. These results suggest that AMA provides substantial hepatoprotection against CCl_4-induced fibrosis in mice, potentially through antioxidant effects and the inhibition of mitogen-activated protein kinase pathways (Zhang Y *et al*., 2017a).

In another study, Ya Zhang and colleagues utilized serum metabolomics to explore the hepatoprotective effects of AMA on CCl4-induced liver fibrosis in mice. This research demonstrated that AMA effectively mitigated CCl_4-induced liver damage and fibrosis and the validity of the model and the protective effects of AMA were evaluated using histopathological and biochemical indicators. AMA notably lowered the levels of ALT, AST and hydroxyproline, thus enhancing liver function. It also reduced inflammatory cell infiltration and collagen accumulation in liver tissue. By employing GC-TOF-MS coupled with pattern recognition techniques such as PCA and OPLS-DA, the model and control groups were successfully differentiated, with the AMA-treated group aligning more closely with the control group. Additionally, nine potential biomarkers related to the antifibrotic effects of AMA were identified (Zhang Y *et al*., 2018b).

Extracts from plants containing iridoids, seco-iridoids and their derivatives have been shown to provide protection to various human tissues. A study investigated the hepatoprotective potential of these compounds derived from Gentianaceae plants. Notably, AMA exhibited the most significant induction in CYP3A4 mRNA expression in HepG2 cells. Following a 48-hour treatment with AMA, aconitine-induced decreases in mtDNA content, ATP levels, oxidative stress and the mitochondrial membrane potential in HepG2 hepatocytes were counteracted in a dose-dependent manner. These findings indicate that the hepatoprotective effects of AMA may be attributed to its ability to increase drug metabolism, improve mitochondrial function and mitigate oxidative stress (Dai K *et al*., 2018). The latest research suggests that AMA may protect HepG2 and THLE-2 cells by scavenging ROS produced by arachidonic acid and the mitochondrial electron transport chain, thereby exerting a protective effect on metabolic dysfunction-associated steatosis liver disease (Boateng AO *et al*., 2025)

Anti-liver cancer effects

Liver cancer ranks among the deadliest cancers worldwide and its prognosis following surgery is generally poor, compounded by the side effects of chemotherapy. Therefore, traditional Chinese herbal medicines, which have long been used for treating malignancies, may offer advantages in HCC therapy. One study examined the ability of AMA to induce apoptosis in mouse hepatocellular carcinoma cells, primarily through p53 upregulation and human telomerase reverse transcriptase (hTERT) downregulation. Compared with normal liver cells, AMA more effectively inhibited the proliferation of hepatocellular carcinoma cells, selectively inducing the apoptosis of cancer cells. At both the gene and protein levels, compared with those for the controls, Akt, RelA and hTERT expressions were significantly lower in the prevention and treatment groups, with hTERT downregulation coinciding with p53 upregulation. One study revealed that AMA enhances apoptosis in hepatocellular carcinoma cells via p53 upregulation and hTERT downregulation, preventing their malignant transformation (Huang C *et al*., 2017). The ability of AMA to inhibit hepatocellular carcinoma cell proliferation and induce apoptosis is a promising adjunctive approach for liver cancer treatment.

A different research team explored the role of AMA in a mouse model of hepatocarcinogenesis, focusing on its chemopreventive and therapeutic potential. The findings revealed that mice treated with AMA presented improved survival rates, increased body weights and no signs of toxicity. In the AMA-treated group, there was a decrease in cell proliferation and an increase in apoptosis. Moreover, AMA significantly promoted apoptosis by increasing the Bax-to-Bcl2 ratio and activating caspase-3 and PARP cleavage. This study revealed that AMA can effectively prevent HCC by modulating the G1/S cell cycle checkpoint and inducing apoptosis. This is the first report documenting the chemopreventive/therapeutic effects of AMA in hepatocarcinogenesis through the regulation of the cell cycle and apoptosis (Pal D *et al*., 2012). This research provides initial evidence of the potential of AMA in liver cancer prevention and may pave the way for a new treatment strategy, laying the groundwork for further investigations into the antihepatoma mechanisms and clinical applications of AMA.

Expanding on previous findings, researchers have investigated the inhibitory impact of AMA on liver cancer initiation and its underlying mechanisms. This study extensively examined the role of AMA in liver cancer progression via a mouse model and the human hepatocellular carcinoma cell line HepG2. Initially, a mouse liver cancer model was established using CCl_4 and NDEA to monitor the pathological changes associated with liver cancer onset. The results indicated that AMA significantly curtailed the development of liver cancer, with the most notable effects in the early stages. Subsequent analysis revealed that AMA markedly reduced the expression of CD44, a marker associated with cancer stem cells. This study also explored the influence of AMA, such as Wnt and Hh, on stem cell self-renewal pathways. AMA was found to inhibit these pathways, thereby suppressing liver cancer development. Additionally, AMA modulated the expressions of E-cadherin and EGFR, which are linked to these pathways and affect liver cancer progression. This comprehensive study elucidated the inhibitory effects of AMA on liver cancer and its underlying mechanisms, offering new insights and strategies for liver cancer prevention and treatment (Sur S *et al*., 2016).

In another investigation, researchers examined the effects of AMA on angiogenesis in liver cancer cells following inadequate radio-frequency ablation and the associated mechanisms. This study revealed that AMA could inhibit angiogenesis by influencing tumour stem cell characteristics and the p53-dependent VEGFA/Dll4/Notch1 signalling pathway, preventing liver cancer malignancy after RFA. Specifically, AMA decreased the proportions of CD133-positive cells and VEGFA expressions, inhibiting angiogenesis in both in vitro and in vivo models. The antiangiogenic effects of AMA were nullified in p53-silenced cells, highlighting the critical role of p53. These findings suggest a novel therapeutic approach for residual liver cancer after inadequate RFA treatment (Zhang Y *et al*., 2020c). In the digestive system, in addition to treating liver cancer, AMA can also decrease gastric carcinoma multiplication, clone formation and migration and induce apoptosis via modulating circKIF4A/miR-152-3p expression (Zhi Tan *et al*., 2022).

Other anticancer effects

AMA is employed as an adjuvant in cancer therapy because of its potent antitumour properties. β-glucosidase is an enzyme that cleaves the glycosidic linkages between aryl and sugar moieties, releasing glucose. When it interacts with AMA, β-glucosidase catalyses its conversion to produce substantial amounts of hydrocyanic acid. This acid inhibits cytochrome C oxidase, the final enzyme in the mitochondrial respiratory chain, halting adenosine triphosphate synthesis and leading to cell death. Hydrocyanic acid is a nonspecific cell cycle agent that targets cancer cells. Consequently, β-glucosidase can be conjugated with tumour-specific monoclonal antibodies. It binds to cancer cell surface antigens, converting AMA into an active form that targets cancer cells and surrounding antibodies, inducing cell death. β-glucosidase is administered intravenously and is guided by antibodies to recognize surface antigens on cancer cells. After β-glucosidase reaches the target site, the prodrug AMA is infused. The coupling of cell membrane peptides with β-glucosidase enables the enzyme to penetrate capillary endothelial cells, accessing deep solid tumours and eliminating cancer cells. Thus, prodrug systems combined with monoclonal antibodies can increase drug concentrations at tumour sites while minimizing damage to healthy tissues. The use of cell-penetrating peptides can increase drug permeability, improving therapeutic efficacy. However, future research should focus on the use of genetic engineering to develop humanized antibodies and modify mammalian enzymes. Additionally, efforts are needed to miniaturize antibody fragments and reduce the molecular weight of activating enzymes to further optimize this therapeutic strategy (Li YL *et al*., 2020).

Anti-skin carcinogenesis effects

The induction of Cox-II in response to mitogenic stimuli, oncogenes and tumour promoters is associated with cell proliferation, making it crucial to assess how compounds that inhibit carcinogenesis and cell proliferation affect Cox-II expressions, as this contributes to the overall carcinogenic process. A research team reported that AMA can curb excessive cell proliferation by downregulating cyclooxygenase-2 (Cox-II) and promoting apoptosis. Immunohistochemical analysis revealed that AMA treatment led to a reduction in the number of proliferating cells and an increase in the number of apoptotic cells in skin lesions, which was also evident in the altered protein

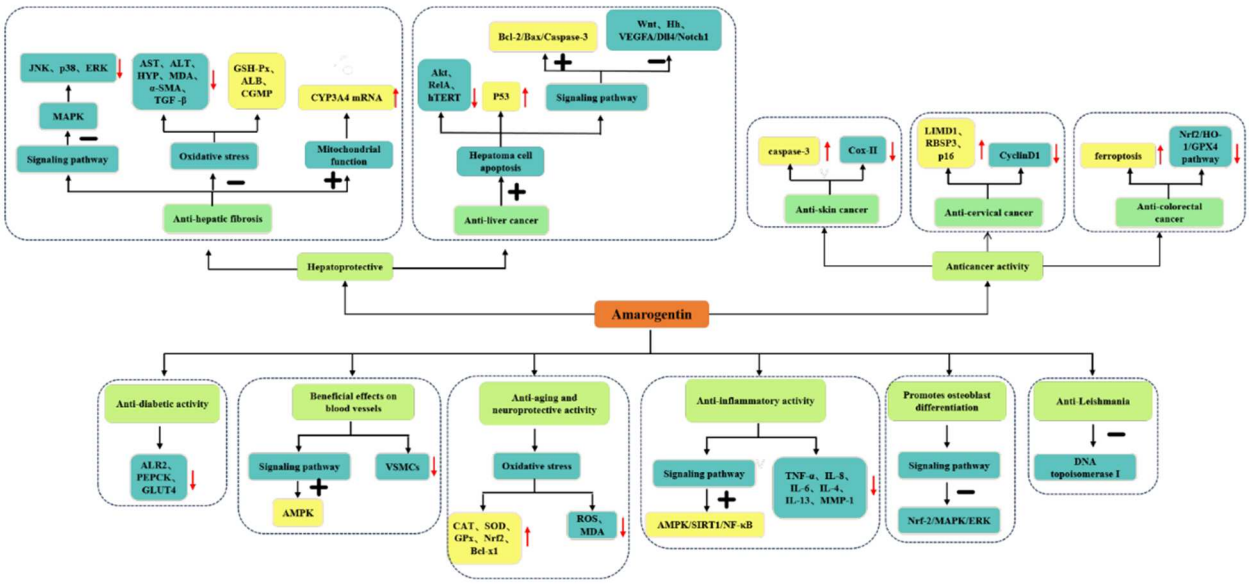

Fig. 3: The main biological activities and possible molecular mechanisms of amarogentin. ↑ indicates increase, ↓ indicates decrease. ＋ indicates activation, − indicates inhibition.

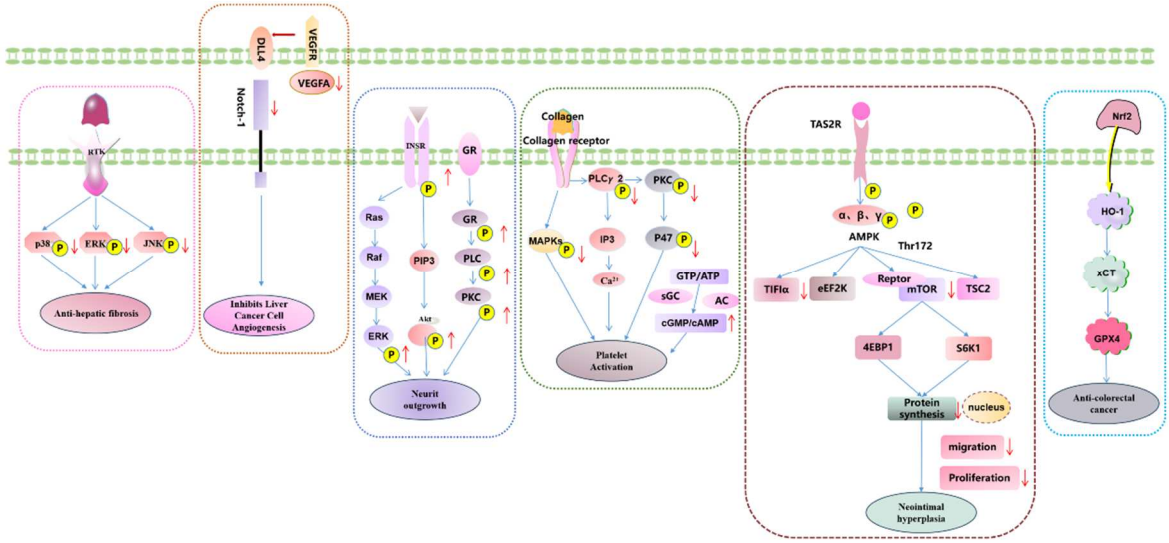

Fig. 4: Schematic summary of the major targets and signaling pathways modulated by amarogentin. ↑ indicates increase, ↓ indicates decrease.

expressions of the Cox-II and caspase-3 molecular markers. This study further investigated the potential of calculating the relative risk, relative protection and attributable risk by examining the effects on cell proliferation and apoptosis (Saha P *et al*., 2006). This research represents the first exploration of the chemopreventive effects of AMA in a mouse model of skin carcinogenesis, revealing its anticancer mechanisms and effectively demonstrating its potential for cancer prevention and treatment.

In another study, computer-aided drug discovery techniques were utilized to further investigate the inhibitory mechanism of AMA on Cox-II and to evaluate its selectivity towards induced isomers. Theoretical models of both isoforms were subjected to molecular docking analyses with AMA and twenty-one other FDA-approved lead molecules. The binding energy profile of AMA after docking was comparable to those of the FDA-approved selective Cox-II inhibitors. Subsequent molecular dynamics simulation analysis revealed differences in the stability of the complexes, with the AMA-Cox-II complex being more stable after 40 ns of simulation. The total binding free energy calculated by MMGBSA for the AMA-Cox-II complex was -52.35 kcal/mol, whereas it was -28.57 kcal/mol for the AMA-

COX-1 complex, suggesting potential selective inhibition of the Cox-II protein by the natural inhibitor. AMA achieves this selectivity through small but significant structural differences in the binding cavities of the two isoforms. It may block the entry of natural substrates into the hydrophobic binding channel of Cox-II, inhibiting the cyclooxygenation step. In summary, this work highlights the mechanism of possible selective Cox-II inhibition by AMA, supporting the potential for developing efficient, targeted therapeutic agents for inflammation and malignancy from this phytochemical source (Shukla S *et al*., 2014). This study underscores the potential of AMA as an anti-inflammatory and anticancer therapeutic agent.

Anticervical cancer effects

While various studies have documented the downregulation of DNMT1 (DNA methyltransferase 1) by EGCG (epigallocatechin gallate), similar findings have not been reported for eugenol or AMA. This research employed diverse experimental methods to evaluate the antitumour effects of EGCG (a primary component of green tea polyphenols), eugenol (an active constituent of cloves) and AMA (an active compound from the Chirata plant), individually or in combination on the cervical cancer cell line HeLa. The findings revealed that combining EGCG with eugenol or AMA significantly suppressed cell proliferation and colony formation and induced apoptosis more effectively than any single compound. The anti-proliferative effects were linked to the upregulation of the G1/S phase cell cycle inhibitors, LIMD1, RBSP3 and p16 and the downregulation of the cell cycle promoter CyclinD1. Additionally, these compounds induced hypomethylation of the LIMD1 and p16 genes, which was associated with reduced DNMT1 expression. This study suggested that the combination of EGCG with eugenol or AMA has superior chemotherapeutic effects on the HeLa cell line, potentially because epigenetic modifications, particularly DNA hypomethylation, are achieved by downregulating DNMT1 (Pal D *et al*., 2018). However, further experiments are necessary to validate the anticervical cancer activity of AMA.

Anticolorectal cancer effects

This study investigated the role of AG in colorectal cancer (CRC) and revealed that AG can suppress the proliferation and epithelial–mesenchymal transition (EMT) of CRC cells by inducing ferroptosis. It was also demonstrated that AG achieves this by inhibiting the activation of the Nrf2/HO-1/GPX4 signalling pathway. In vitro experiments revealed that AG significantly reduced CRC cell viability and accelerated apoptosis by triggering ferroptosis. Moreover, AG was found to inhibit tumour growth in in vivo models. These findings indicate that AG has the potential to be an effective therapeutic agent for CRC (Wang C *et al*., 2025). However, further experiments are necessary.

Beneficial effects on blood vessels

Platelet activation is widely recognized as a factor contributing to intravascular thrombosis and cardiovascular diseases. Research has investigated the ability of AMA to inhibit platelet activation. These findings indicate that AMA can modulate platelet activation via the PLCγ2-PKC and MAPK pathways and that it also has an inhibitory effect on thrombogenesis in vivo. However, the antiplatelet effects of AMA do not seem to be mediated by changes in cAMP and cGMP levels. These findings suggest that AMA may have therapeutic potential for preventing or treating thromboembolic diseases (Yen TL *et al*., 2025).

AMP-activated protein kinase (AMPK) is a target for managing metabolic and cardiovascular disorders. Studies have shown that AMA can activate AMPK, resulting in positive vascular metabolic effects. AMA binds to the β2 subunit of AMPK, activating the trimeric kinase in vitro. In cellular experiments, AMA triggers the phosphorylation of AMPK and its downstream targets ACC and eNOS, promoting glucose uptake in myotubes and inhibiting TNF-α-induced endothelial inflammation. In streptozotocin-induced diabetic mice, AMA significantly reduced diabetes-related aortic neointima thickening, collagen and lipid deposition. Additionally, AMA improved lipid profiles and liver function in diabetic mice. Thus, by activating AMPK, AMA exerts beneficial vascular metabolic effects and represents a promising candidate for treating dyslipidaemia and cardiovascular diseases (Potunuru UR *et al*., 2025).

A recent study provided initial evidence that AMA can inhibit the proliferation and migration of vascular smooth muscle cells (VSMCs) and reduce neointimal hyperplasia in both cultured saphenous veins and ligated carotid arteries of mice through AMPK activation. These findings suggest that AMA could serve as a potential drug for restenosis. AMA blocks the cell cycle transition of VSMCs from the G0/G1 phase to the S phase, thereby inhibiting proliferation. Additionally, it suppresses the migration and nascent protein synthesis of VSMCs. These findings indicate that AMA may play a beneficial role in preventing neointimal hyperplasia. Importantly, at concentrations effective for inhibiting VSMC proliferation and migration, AMA does not affect endothelial cell activity, suggesting that it may not interfere with the reendothelialization process, making it a promising candidate against neointimal hyperplasia (Jia FL *et al*., 2023).

Other studies have shown that the root extract of Gentiana lutea can significantly inhibit the proliferation of rat aortic smooth muscle cells induced by platelet-derived growth factor-BB (PDGF-BB), with AMA potentially contributing to this effect. The extract appears to block the activation of ERK1/2 and the subsequent increase in intracellular nitric oxide (NO) levels triggered by PDGF-

BB, indicating that AMA may be involved in this signalling pathway. Molecular docking analysis via AutoDock4 software suggested that AMA may have a binding affinity for the inhibitory site of MEK1 (mitogen-activated protein kinase kinase). Given its presence in the root extract of Gentiana lutea, AMA may influence the formation of atherosclerotic lesions, particularly by inhibiting the ERK1/2-iNOS signalling pathway (Kesavan R *et al*., 2013). However, further experimental validation is needed.

Anti-diabetic activity

The inhibition of aldose reductase by AMA is recognized as an antidiabetic mechanism. A study explored the effects of AMA on diabetes in animal models and revealed that it could reduce hyperglycaemia in type 1 diabetic rats in a dose-dependent manner, even without insulin. Additionally, AMA improved insulin resistance in type 2 diabetes models induced by high-fructose diets. The study also revealed that AMA could restore GLUT4 levels in the skeletal muscles of type 1 diabetic rats and decrease PEPCK expressions in their livers. These findings suggest that AMA may enhance glucose homeostasis in diabetic rats, indicating its potential as an anti-diabetic agent (Niu HS *et al*., 2016).

The accumulation of sorbitol within cells, due to increased aldose reductase (ALR2) activity, is associated with the progression of various diabetic complications. Inhibiting ALR2 could thus be an effective strategy for preventing or delaying these complications. The extract significantly and dose-dependently reduced sorbitol accumulations in human erythrocytes under hyperglycaemic conditions. Molecular docking studies with common constituents of Gentiana lutea suggest that gentiopicrin may serve as a potential ALR2 inhibitor (Akileshwari C *et al*., 2012). Further research could confirm whether gentiopicrin inhibits ALR2 activity, potentially aiding in the prevention or treatment of diabetic complications.

Antioxidant and neuroprotective activity

Identifying molecules with potent antioxidant capabilities is crucial for managing ageing and neurodegenerative disorders. A research team reported that AMA can significantly prolong the replicative lifespan of yeast and increase survival under oxidative stress by increasing the activity and gene expression of antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx). Moreover, AMA markedly improved the survival of PC12 cells under H2O2-induced oxidative stress, reducing reactive oxygen species (ROS) and malondialdehyde (MDA) levels while increasing the expressions of the SOD2, CAT, GPx, Nrf2 and Bcl-x1 genes. AMA also has neurotrophic effects on PC12 cells. As a natural antioxidant, AMA plays a vital role in combating oxidative stress in antiaging and neuroprotection, making it a promising candidate for developing drugs to treat neurodegenerative diseases (Disasa D *et al*., 2020).

On the basis of these findings, the team further examined the neurogenic induction effects of AMA in PC12 cells and its potential molecular targets. The NGF-mimicking and NGF-enhancing activities of AMAs were identified and the mechanism underlying AMA-induced neurite outgrowth was explored via the use of specific inhibitors and Western blotting. Cellular thermal shift assay (CETSA) and siRNA analyses predicted that AMA targets the insulin receptor, activating the PI3K/AKT and Ras/Raf/MEK/ERK signalling pathways. Additionally, the GR/PLC/PKC pathway is involved in the neuritogenic activity in PC12 cells (Cheng L *et al*., 2021). Thus, AMA is a potential candidate for treating neurodegenerative diseases and as an antiaging therapeutic agent.

Recently, researchers have studied secoiridoid bioactive compounds in Swertia chirayita and their potential to counteract skin photoaging via the AP-1/MMP pathway. Using molecular docking, binding mode modelling and molecular dynamics simulations, they investigated the inhibitory effects of these compounds on MMP-1, MMP-3, MMP-9 and the transcription factor AP-1. AMA showed high binding affinity for MMPs and AP-1, indicating its potential as an anti-aging agent (Singh PP *et al*., 2012). However, further experimental validation is needed.

Promotion of osteoblast differentiation

In an effort to overcome the limitations of traditional osteoporosis treatments, alternative therapeutic approaches have been explored in recent years. One study investigated the role of AMA in treating osteoporosis resulting from oestrogen deficiency. Both in vivo and in vitro experiments revealed that AMA can enhance osteoblast differentiation in osteoporotic rats by modulating the Nrf-2/MAPK/ERK signalling pathway. The in vivo results indicated that, compared with control rats, AMA-treated rats presented significantly greater bone densities, lower levels of inflammatory factors and greater levels of bone formation and resorption markers. In vitro, AMA increased the alkaline phosphatase activity and proliferation of MG63 human osteoblasts. Western blotting revealed significant changes in the expression of p-ERK protein in the presence of an ERK inhibitor. These findings suggest a novel potential strategy for managing osteoporosis caused by oestrogen deficiency (Li S *et al*., 2019).

Anti-inflammatory activity

Patients suffering from sepsis-induced brain injury, septic shock and multiorgan dysfunction have mortality rates between 80% and 90%. Therefore, identifying mechanisms that can reduce oxidative stress, neuroinflammation, autophagy and blood-brain barrier damage to alleviate sepsis-induced brain injury is crucial.

This study aimed to explore the protective effects of AMA against sepsis-induced brain injury and its underlying mechanisms. NSC-34 and HT22 cells were exposed to lipopolysaccharide (LPS) to establish an in vitro sepsis model, followed by treatment with various concentrations (1, 5, or 10 μM) of AMA. Cell proliferation and apoptosis were assessed, whereas inflammation and oxidative stress were evaluated via different methods. The expression of the AMPK/SIRT1/NF-κB pathway was determined through Western blotting. An in vivo sepsis model was established in adult C57BL/6J mice via caecal ligation and puncture and the mice were treated with different concentrations (25, 50, or 100 mg/kg) of AMA.

Neurological function was assessed via modified neurological severity scores and brain tissue damage was evaluated using hematoxylin-eosin and Nissl staining. Tissue apoptosis was detected via terminal deoxynucleotidyl transferase dUTP nick end labelling. The AMPK inhibitor Compound C was administered to confirm the mechanism mediated by AMA. The results revealed that AMA reduced LPS-induced neuronal damage, inflammation and oxidative stress; activated the AMPK/SIRT1 pathway; and inhibited NF-κB phosphorylation. Moreover, AMA improved neurological function in septic mice by alleviating neuroinflammation and oxidative stress. Inhibition of AMPK diminished the protective effects of AMA on neurons and brain tissues. In summary, AMA protects against sepsis-induced brain injury by modulating the AMPK/SIRT1/NF-κB pathway (Song B *et al*., 2022).

Immunomodulatory activity

This study aimed to evaluate the immunomodulatory effects of bitter compounds on immunocompetent skin cells, potentially targeting chronic inflammatory conditions such as atopic dermatitis and psoriasis. Research has investigated the immunomodulatory impact of AMA on human mast cells and keratinocytes. AMA, which acts as a TAS2R1 agonist, was found to promote keratinocyte differentiation. It also inhibited TNF-α production in substance P-stimulated LAD-2 cells (a human mast cell line) without affecting degranulation or prestored histamine release. In HaCaT keratinocytes, AMA reduced IL-8 and MMP-1 expressions that were induced by histamine and TNF-α, mirroring the effects of the antihistamine azelastine. This study revealed that the immunomodulatory effects of AMA on the skin, which are mediated through interactions with mast cells and keratinocytes, which could be promising targets for treating chronic inflammatory diseases such as atopic dermatitis and psoriasis (Zhang Q *et al*., 2023).

Atopic dermatitis (AD) is a chronic inflammatory skin disorder resulting from the dysregulation of various inflammatory cytokines and specific treatments for AD are lacking. One study examined the anti-inflammatory effects of AMA on a DNCB-induced AD-like mouse model and HaCaT cells. AMA was found to inhibit IL-6 secretion in TNF-α-stimulated HaCaT cells and reduce IL-4 and IL-13 secretion in PHA-induced mouse splenocytes. In the AD-like mouse model, AMA treatment facilitated dermatitis recovery, decreased severity scores and scratching frequency, alleviated skin lesions, decreased epidermal thickness, reduced mast cell infiltration and decreased KLK7 and FLG protein and mRNA expression in skin tissue. This study revealed that AMA mitigates inflammation in specific dermatitis-model mice through cellular anti-inflammatory actions, alleviates itching and repairs the damaged skin barrier, suggesting that AMA is a potentially safe and effective drug candidate for AD treatment (Wölfle U *et al*., 2015).

Antiviral activity

A computational analysis investigated the potential of the plant-derived compounds, anisotine and AMA, which are sourced from the Indian plants, Justicia adhatoda, Ocimum sanctum and Swertia chirata, as inhibitors of SARS-CoV-2 proteins. This study utilized molecular docking techniques to evaluate the binding affinity of these compounds with key SARS-CoV-2 proteins, such as the spike protein, main protease Mpro and RNA-dependent RNA polymerase RdRp. The results showed that anisotine has inhibitory potential against the spike protein and Mpro, whereas AMA shows promise against RdRp. Molecular dynamics simulations and MM-PBSA energy scoring function analysis revealed high binding affinities of these compounds to SARS-CoV-2 proteins, indicating their potential as candidate drugs for COVID-19 treatment (Kar P *et al*., 2022). Similarly, molecular docking and dynamic simulation methods revealed a strong binding affinity of AMA for the RdRP of SARS-CoV-2. AMA is likely to inhibit viral replication by forming hydrogen bonds, salt bridges and water-mediated interactions with polar and charged amino acid residues in seven conserved motifs of RdRP (Koulgi S *et al*., 2021).

HIV enters human cells by interacting with the CD4 receptor and one of two chemokine receptors (CCR5 and CXCR4). These coreceptors are essential for viral entry and replication, making them key targets for antiviral drugs. AMA exhibits superior binding affinity and stability with the CXCR4 coreceptor, suggesting its potential as an inhibitor of HIV entry and offering new insights for the development of effective anti-HIV drugs（Kumar Bhardwaj V *et al*., 2021).

Anti-leishmania

Previous studies have explored the *in vivo* efficacy and safety of AMA as an anti-Leishmania agent, particularly when it is encapsulated in liposomes and niosomes (vesicles composed of nonionic surfactants). AMA combats Leishmania by binding to enzymes, preventing the formation of binary complexes and thus inhibiting DNA topoisomerase I.

Table 3: Pharmacology of amarogentin.

Pharmacological effect		Cell lines/model	Activity/mechanism(s) of action	Application	Year
3.1. Hepatoprotective	3.1.1. Anti-hepatic fibrosis	Male C57BL/6 mice	Regulates oxidative stress processes and MAPK pathways.	*In-vivo*	2017
		Male C57BL/6 mice	Modulates amino acid and fatty acid metabolism.	*In-vivo*	2018
		HepG2 cells	Ameliorates mitochondrial dysfunction and reduces oxidative stress.	*In-vitro*	2018
	3.1.2. Anti-liver cancer	Liver cancer cells (LO2, HepG2, and SMMC-7721 cells lines)	Upregulats p53 and downregulats human telomerase reverse transcriptase.	*In-vitro*	2016
		Female Swiss albino mice	Modulates G1/S cell cycle check point and inducts apoptosis.	*In-vitro*	2012
		HepG2 cells	Regulates Self Renewal Pathways.	*In-vivo* and *In-vitro*	2016
		HepG2 and Huh7 cells	Affects Stemness and the p53-dependent VEGFA/Dll4/Notch1 pathway.	*In-vitro*	2020
3.2. Other Anticancer activity	3.2.1. Anti-skin carcinogenesis	Swiss albino male mice	Downregulates Cox-2 activity and upregulates apoptosis.	*In-vivo*	2005
		Mouse models	Inhibits Cox-2 activity.	*In-vivo*	2014
	3.2.2. Anti-cervical cancer	Human cervical cancer cell line, Hela cells	Downregulatems DNMT1.	*In-vitro*	2018
	3.2.3. Anti-colorectal cancer	CRC cell lines and mouse.	Inhibits Nrf2/HO-1/GPX4 pathway. Modulated PTC cell viability and stim-ulated ferroptosis.	*In-vivo* and *In-vitro*	2025
3.3. Beneficial effects on blood vessels		Human platelet suspensions and mouse.	Inhibits PLCγ2-PKC cascade and MAPK pathway.	*In-vivo* and *In-vitro*	2014
		L6 myotube, HUH7 and endothelial cell.	Activats AMPK pathway.	*In-vivo*	2019
3.4. Anti-diabetic activity		Male C57BL6/J mice			
		Male Wistar rats	Ameliorates glucose homeostasis.	*In-vivo*	2016
		Red cells	Inhibites ALR2	*In-vitro*	2021
3.5. Antioxidant and neuroprotective activity		Yeast and PC12 cells	Increases activities of SOD and SOD2, and gene expression of SOD2, CAT, GPx, Nrf2, and Bcl-x1. Reduces reactive oxygen species (ROS) and malondialdehyde (MDA) .	*In-vitro*	2012
		PC12 cells	Activats PI3K/AKT and Ras/Raf/MEK/ERK signaling pathways.	*In-vitro*	2021

Table 3 is continue…….

Pharmacological effect	Cell lines/model	Activity/mechanism(s) of action	Application	Year
3.6. Promotes osteoblast differentiation	Rats and MG63 human osteoblasts	Modulates the Nrf-/MAPK/ERK signalling pathway.	*in-vivo* and *In-vitro*	2019
3.7. Anti-inflammatory activity	NSC-34 and HT22 cells, adult C57/BL6J mice.	Activates the AMPK/SIRT1 pathway and choked NF-κB phosphorylation.	*In-vitro*	2022
	HaCat and splenocyte model	Inhibites IL-6 secreted by tumor necrosis factor (TNF)-α-induced HaCaT cells and reduced IL-4 and IL-13 secreted by phytohemagglutinin (PHA)-induced primary cells in the mice spleen.	*In-vivo* and *In-vitro*	2022
3.8. Immunomodulatory activity	LAD-2 human mast cells	Inhibites in LAD-2 cells substance P-induced production of newly synthesized TNF-α. TNF-α induced IL-8 and MMP-1 expression was reduced	*In-vitro*	2015
	-	Inhibits SARS-CoV-2 proteins	-	2020
	-	Bind RdRP of SARS-CoV-2	-	2021
	-	Bind to CCR5 and CXCR4 co-receptors	-	2021
3.10. Inhibits Leishmania donouani	Hamster model of experimental leishmania-sis	Inhibits type I DNA topoisomerase	*in-vivo*	2023

Note: - is presentive for the relevant literature has not been introduced in detail.

These findings suggest that AMA encapsulated in liposomes and niosomes is more effective against Leishmania than free AMA, with the niosomal form exhibiting greater potency. Moreover, toxicity assessments have shown that no significant adverse effects are associated with any form of AMA treatment (Alanazi AD, Ben Said M, 2023).

Toxicity

To date, there have been no reports on the toxic effects of AMA in experimental animal models. Swapna Medda *et al*. assessed the hepatotoxicity of gentiopicrin by measuring alanine aminotransferase concentrations in hamster plasma. The nephrotoxicity of AMA was ruled out by evaluating urea nitrogen and creatinine levels in the urine. Furthermore, pathological analysis of hamsters, including spleen staining, revealed no pathological alterations (Egger M *et al*., 1997). Prosenjit *et al*. administered a crude ethanol extract of Swertia chirata and 90-95% AMA to normal mice intraperitoneally at IC50 concentrations of 10 mg and 0.5 mg, respectively. These doses were deemed nontoxic on the basis of body weight changes and survival rates (Saha P *et al*., 2004). In acute toxicity studies, AMA was administered orally at a dose of 1000 mg/kg, with no toxic effects observed, with all animals surviving after 14 days (Potunuru UR *et al*., 2019). Compared with control mice, mice given 0.2 μg/kg·d AMA for 30 days presented no significant differences in liver, kidney, myocardium, or lung tissues upon sacrifice(Dai K *et al*., 2018). Patel K *et al*. reported no signs of toxicity in AMA-treated subjects, as assessed by haematopathology, histological staining and detection of liver function-related specific enzymes (Patel K *et al*., 2019).

Pharmacokinetics

The pharmacokinetic profile of AMA is characterized by a stable half-life and rapid plasma clearance. A study on rabbits intravenously administered AMA revealed that it has a quick plasma clearance rate, extensive tissue distribution and an elimination half-life of approximately 30 minutes (Potunuru UR *et al*., 2019; Lin S *et al*., 2013). Gentiopicrin has low oral bioavailability; even at a dose of 50 mg/kg, it is undetectable in plasma. When given at doses ranging from 6.25 to 25 mg/kg, the drug's maximum plasma concentration does not increase proportionally with the dose (Mateescu B *et al*., 2011). In vitro, gentiopicrin has good linearity and excellent stability under conditions such as freezing, cooling, drying and long-term storage. It also has a recovery rate above 90%, intraday accuracy below 15%, precision below 10% and an LC-MS lower limit of detection of 0.156 ng/ml (Torres A *et al*., 2011; Guo Q *et al*., 2015).

Future perspectives and conclusion

The preceding discussion details the origin of gentiopicrin and its initial physicochemical characteristics, biological activities, pharmacokinetics and safety assessment. AMA has been shown to potentially inhibit the progression of liver fibrosis, liver cancer, skin cancer and various human cervical cancer cell lines, as well as the formation of atherosclerotic plaques in arteries. It also addresses skin conditions stemming from barrier dysfunction, enhances metabolic function in diabetic mouse models and treats leishmaniasis by hindering the intracellular proliferation of the parasite. The main biological activities and some potential molecular mechanisms are summarized in fig. 3 and 4 and table 3. The therapeutic effects of AMA have been confirmed in multiple experimental animal models, indicating their promising potential as future clinical drugs. However, the specific mechanisms associated with AMA are not yet fully understood. Therefore, investigating its toxic effects and related mechanisms in experimental animals is essential for assessing its safety for human use. Toxicological studies have shown no adverse reactions at doses up to 200 mg/kg AMA. Nevertheless, to comprehensively evaluate its safety, a thorough toxicological assessment, including long-term exposure studies, reproductive and developmental toxicity studies and genetic toxicity studies, is recommended. Additionally, there is a lack of effective biological tools for research, such as the need for appropriate monoclonal antibodies to target AMA and β-glucosidase for cancer treatment. Significant advancements have been made in AMA research, but the experimental results are primarily based on cellular and animal experiments, with limited research on AMA dosage and formulation, thus hindering its application.

Future research should focus on establishing the dose-response relationship of AMA and further exploring its efficacy and safety within this dosage range. Moreover, research should investigate different formulations, such as liposomes or nanosuspensions, to increase AMA solubility and bioavailability. Clinical trials have shown that drug delivery via liposomes as carriers is an optimal choice for treating tumours, fungi and other parasitic infections and experiments conducted in hamsters have demonstrated greater drug activity and safety with liposomal delivery than with free forms. Additionally, the current data are insufficient to guide clinical practice. Preliminary experiments by some researchers have shown that AMA can inhibit the development of gliomas, but whether it can cross the blood-brain barrier due to the inherent properties of the drug remains to be experimentally confirmed.

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Authors' contributions

Conceptualization: Wenxiang Wang, Wei Xiong. Data curation: Dongmei Zhang. Writing - original draft: Ying Tan, Wenxiang Wang. Writing - review and editing: Ying Tan, Wenxiang Wang. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

There is no conflict of interest.

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