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REVIEW

Acteoside as a multifunctional natural glycoside: therapeutic potential across various diseases

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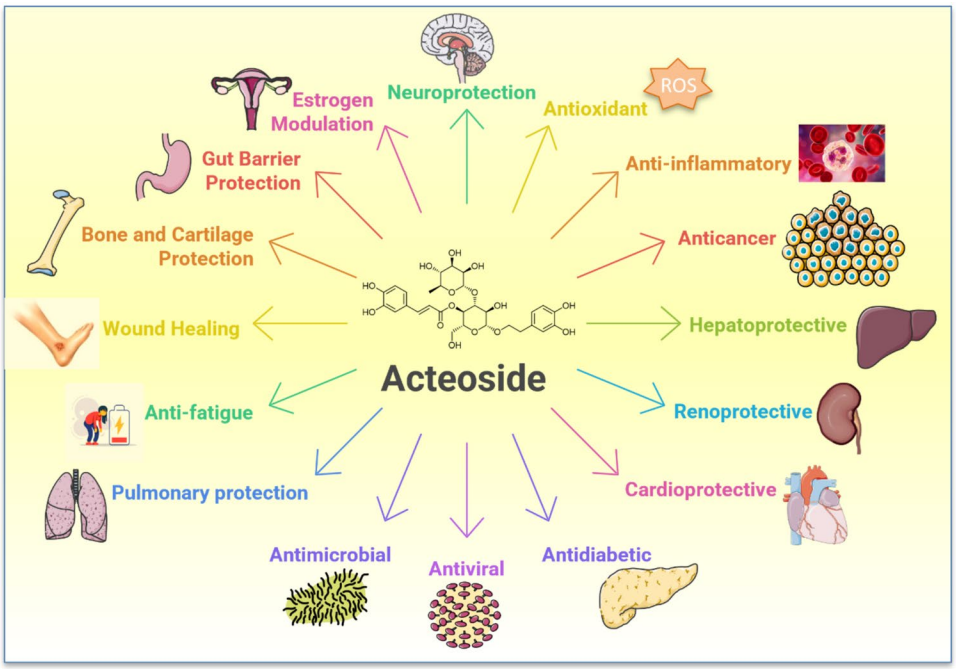
Abstract

Phenylethanoid glycosides are naturally occurring water-soluble molecules with remarkable biological characteristics that are abundant throughout the plant world. Acteoside (AC) is a phenylethanoid glycoside that was first discovered in mullein, but is also found in various other plant species. It has four moieties: caffeic acid, glucose, rhamnose, and phenylethyl alcohol. AC is an important bioactive natural compound isolated from many plant species. Extracts from different plant species, including *Barleria prionitis*, *B. lupulina*, *Rhinacanthus nasutus*, *Orthosiphon aristatus*, and *Nicoteba betonica*, have high quantities of AC. AC is hydrophilic in nature, and it has several bioactivities such as anti-inflammatory, antibacterial, antiviral, antioxidant, antidiabetic, neuroprotective, cardioprotective, anticancer, and wound-healing properties. In this review, we discuss its prominent pharmacological properties. The findings provide valuable insights for future research on AC which exhibit promising anti-inflammatory activities.

Graphical abstract



Keywords Verbascoside · Acteoside · Kusaginin · Acetoside · Anti-inflammatory · Phenylethanoid glycoside

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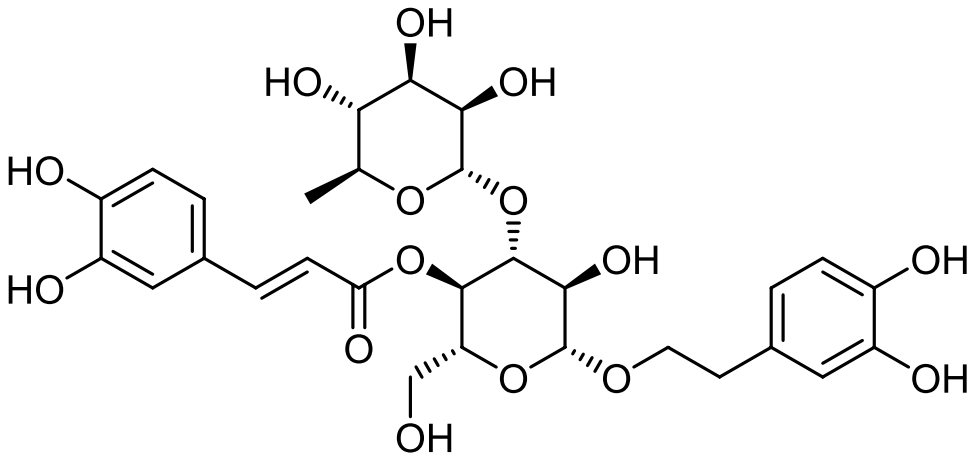

Fig. 1 Chemical structure of AC

Introduction

Phenylethanoid glycosides are naturally occurring, water-soluble chemicals found across the plant world, with the majority of them identified from medicinal plants. Cinnamic acid (C6–C3) and hydroxyphenylethyl (C6–C2) moieties form a glycosidic bond with a β-glucopyranose (e.g., apiose, galactose, rhamnose, xylose) (Dembitsky 2005). In recent years, there has been a surge of interest in aromatic compounds, particularly phenylethanoid glycosides, due to the rapidly rising body of research demonstrating their clear significance in the prevention and treatment of a variety of human diseases and conditions. Acteoside (AC), also known as verbascoside or kusagin [β-(3,4-dihydroxyphenylethyl)-*O*-α-L-rhamnopyranosyl-(1 → 3)-β-D-(4-*O*-caffeoyl)-glucopyranoside], is prevalent in many dicotyledonous plants, such as Oleaceae, Bignoniaceae, Verbenaceae, and Labiatae (Alipieva et al. 2014). In 1963, Italian scientists reported the extraction of a phenylethanoid glycoside from mullein (*Verbascum sinuatum* L.; Scrophulariaceae), which they named verbascoside (Scarpati and Delle Monache 1963). Chemically, AC (Fig. 1), with a formula of $C_{29}H_{36}O_{15}$ and a molecular weight of 624 Da, is a phenylpropanoid glycoside characterized by the binding of caffeic acid and hydroxytyrosol to a glucose moiety by establishing ester and glycosidic linkages, respectively (He et al. 2011; Zhou et al. 2020a, b), and is soluble in DMSO (≥ 100 mg/mL) and methanol (5 mg/mL). The shikimic acid pathway is a multi-step enzymatic metabolic method for producing aromatic chemicals using shikimic acid as a starting point (Xu et al. 2014; Torrens-Spence et al. 2018).

AC, a bioactive natural component, is a crucial secondary metabolite in therapeutic plants (Huang et al. 2022). According to literature research, AC has been linked to a variety of pharmacological activities, including antioxidation (Lee et al. 2020), anti-inflammation (Song et al. 2012), anticancer (Khan et al. 2022), neuroprotection (Sheng et al. 2002), cardiovascular protection (Lau et al. 2004), antidiabetic (Lu et al. 2017), bone and cartilage protection (Lim et al. 2021), hepatoprotection (Khullar et al. 2019), and antimicrobial action (Avila et al. 1999). Acute and sub-acute toxicity studies in animal models have demonstrated that AC is well tolerated, with no significant adverse effects observed upon both single and repeated administrations. These findings suggest a favorable safety profile in preclinical settings (Etemad et al. 2015). This article will provide a fresh platform for debating and developing AC as a possible option in disease treatment management by thoroughly elucidating its entire pharmacology.

Pharmacokinetic properties of AC

Elucidating the pharmacokinetic characteristics is critical for predicting drug distribution in vivo, as well as for evaluating drugs' therapeutic effects, adjusting doses, and using drugs rationally. The pharmacokinetic features of AC after a single intravenous dose can be understood using a two-compartmental pharmacokinetic model. Unbound AC has half-lives of 5 and 28 min, respectively, in the bloodstream (Wu et al. 2007). After 15 min of intravenous injection, AC binds to protein in rat plasma at 75.5% and has a bioavailability of 0.12%. Oral (100 mg/kg) and intravenous (3 mg/kg) dosing resulted in Cmax values of 0.13 and 48.6 µg/mL, respectively. The T1/2 values are 92.1 and 10.7 min, respectively (Wu et al. 2006). In rats, oral treatment of 10 g/kg *Plantago asiatica* decoction results in a plasma level of 135.3 ng/mL of AC. AC has a Cmax of 135.4 ng/mL, Tmax of 13.3 min, and AUC of 187.1 µg/L (Li et al. 2014). In beagle dogs, AC has an absolute bioavailability of approximately 4%. Single oral dose of 10 mg/kg, 20 mg/kg, and 40 mg/kg AC resulted in AUC values of 47.28 mg min/L, 87.86 mg min/L,

and 183.14 mg min/L. The Cmax values are 0.42, 0.72, and 1.44 μg/mL, respectively (Zhang et al. 2015). In chronic kidney disease and normal rats, after oral administration of *Rehmannia glutinosa* extract, the AUC0-t values of AC are 61.15 ± 10.56 and 32.69 ± 7.63 μg min/mL, respectively, where the values of Cmax are 0.31 ± 0.05 and 0.19 ± 0.05 μg/mL, respectively, and the Tmax values are 24.00 ± 13.42, and 15.00 ± 7.45 min, respectively (Zhao et al. 2015). After oral administration of *Rehmannia glutinosa* leaf extract and Dihuangye total glycoside capsule extract, the AUC0-t values of AC in diabetic nephropathy rats are 324.59 μg/L and 396.81 μg/L, respectively, vs. the control rats which are 1161.45 μg/L and 1465.13 μg/L, respectively. The Cmax values in diabetic nephropathy rats are 69.08 μg/L and 70.53 μg/L, respectively, vs. control rats which are 109.77 μg/L and 443.03 μg/L, respectively (Dai et al. 2017). A study found that AC is quickly absorbed in healthy colonic mucosal sections from various patients, reaching peak tissue concentration within 15–30 min. The entire accumulation efficiency is around 0.12%, which corresponds to the average intracellular level of 0.29 μg/cm^2 tissue. Furthermore, absorption is time dependent and connected with certain intestinal segments. AC is primarily absorbed in the proximal tract (5–15 min, 0.50 μg/cm^2), followed by the descending tract (30 min, 0.38 μg/cm^2) and the sigmoid colon (60 min, 0.34 μg/cm^2). This disparity can be linked to the unique functional distinction between the colon segments (Cardinali et al. 2013).

AC has been considered with high potential as a dietary supplement, where its chemical stability, potential bioavailability, and intestinal uptake were evaluated using in vitro, in vivo, and ex vivo experiments. The results documented that AC remained stable and bioaccessible (Cardinali et al. 2011, 2013; Cardinali et al. 2012). Additionally, AC is chemically stable at acidic pH (pH 3) for up to 24 h in human intestinal cell lines, though, at neutral pH (pH 7), AC undergoes significant transformation (up to 62.4%) into isoverbascoside or other oxidative products (Xiao et al. 2022). AC exhibits low oral bioavailability. This is attributed to its poor absorption, limited bioaccessibility, and active efflux transport (Xiao et al. 2022). In vitro digestion models indicate a bioaccessibility of approximately 50%, while Caco-2 cell models reveal an absorption rate of only 0.461–0.698% and a low permeability (Papp = 4.75×10^{-7} cm/s). P-glycoprotein (P-gp) plays a role in AC's efflux transport, though some studies report low permeability without significant efflux activity (Gao et al. 2015; Zhou et al. 2018a, b). AC exhibits poor oral bioavailability primarily due to its large molecular size and hydrophilic nature, which limit its absorption through the intestinal and topical barriers (Saha et al. 2024). This pharmacokinetic limitation poses a significant challenge for its therapeutic application, as only a small fraction of orally administered AC reaches systemic circulation, reducing its efficacy in vivo. To address this, recent research has focused on developing advanced drug delivery systems, particularly nanoformulations. The large molecular size limits AC ability to permeate biological membranes, necessitating the use of carrier systems for effective drug delivery. Among these, liposomal formulations have been most extensively studied and successfully enhanced both the stability and skin penetration of AC. Early work demonstrated that multilamellar liposomes containing cholesterol and surfactants could entrap AC with high efficiency (57–66%), promoting drug accumulation in the stratum corneum for localized delivery and maintaining stability for up to 90 days (Sinico et al. 2008). More advanced formulations, such as chitosan-coated liposomes and liposome–tripolyphosphate particles, have further improved AC's bioavailability—one such system increased AC bioavailability by over fivefold and achieved high entrapment efficiency (up to 92.74%), as well as enhanced tissue concentrations in animal models (Zhou et al. 2018a, b). Additionally, complexing AC with β-cyclodextrin and loading it into specialized liposomes improved its localization in the stratum corneum and epidermis, with minimal systemic absorption, supporting its use in topical applications (Mazzacuva et al. 2010). AC has also been incorporated into cosmeceutical formulations, where stability studies showed that certain bases could significantly reduce the loss of active compound during storage. Overall, these advances in liposomal and nanocarrier-based delivery systems have addressed AC's permeability and stability challenges, expanding its therapeutic potential for topical and localized treatments.

Additionally, co-administration with the P-gp inhibitor EGCG enhances oral bioavailability by 1.43-fold, though it does not affect AC's stability during digestion and storage (Zhou et al. 2020a, b). Also, AC undergoes extensive metabolism, including oxidation, glucuronidation, sulfation, and methyl conjugation, yielding a wide range of metabolites. Studies have identified up to 44 metabolites, with hydrolysis playing a key role in AC's metabolic transformation, producing degradation products such as caffeic acid and hydroxytyrosol (Su et al. 2016). When incubated with human or rat intestinal bacteria, AC generates 14 hydrolyzed metabolites, including degradation products, isomers, and parent drug metabolites, highlighting its complex metabolic fate (Cui et al. 2016). The compound had a high affinity for phospholipid membranes, particularly negatively charged phospholipids, forming stabilized complexes that influence membrane dynamics (Xiao et al. 2022). Liquid chromatography is widely used for quantifying AC in biological fluids and tissues due to its sensitivity and specificity. It is often coupled with UV detection or mass spectrometry (MS) or nuclear magnetic resonance (NMR) for enhanced accuracy (Wen et al. 2016; Zhao et al. 2016).

AC metabolism includes oxidation, glucuronidation, sulfation, and methyl conjugation. Nineteen metabolites of

the parent drug and 16 metabolites of the breakdown products have been validated. AC functions as a prodrug and is hydrolyzed into breakdown products, specifically caffeic acid and hydroxytyrosol. In another study, 44 metabolites were found and identified. 35 of these chemicals are parent drug metabolites. When cultured with human or rat intestinal bacteria, AC creates 14 metabolites via hydrolysis, the primary metabolic route. These metabolites include eight breakdown metabolites, two isomers in intestinal bacteria and enzyme samples, and four parent metabolites detected solely in intestinal enzyme samples (Qi et al. 2013; Cui et al. 2016; Su et al. 2016). The microbial metabolism of AC plays a key role in its pharmacological effects. Gut bacteria hydrolyze AC into bioactive metabolites, particularly caffeic acid and hydroxytyrosol, which possess well-documented antioxidant, anti-inflammatory (Jalal et al. 2018), and neuroprotective properties (Nardi et al. 2023; Pérez et al. 2023). These metabolites may significantly contribute to AC's in vivo efficacy, supporting the view that AC acts as a prodrug whose therapeutic effects are mediated, at least in part, through its microbial transformation products.

The toxicity prediction has been investigated. AC has a maximum tolerance dose of 0.443 mg/kg/day in humans and oral acute and chronic toxicity levels of 2.527 and 3.783 mg/kg, respectively, in rats (Kallingal et al. 2022). AC at over 50 µg/mL causes cytotoxicity in V79 cells, with IC_{50} values of 73.80 µg/mL for MTT and 41.42 µg/mL for neutral red uptake (NRU) tests. However, AC does not exhibit any genotoxic action or phototoxicity (Henn et al. 2019).

The pharmacokinetic profile of AC in both rats and beagle dogs is marked by rapid absorption and elimination, but low systemic availability. In rats, AC exhibits an oral bioavailability of only 0.12%, with Cmax values ranging from 0.13 to 135.4 ng/mL and short half-lives of 10.7 to 92.1 min. In beagle dogs, the absolute bioavailability reaches approximately 4%, with Cmax values of 0.42–1.44 µg/mL following oral doses of 10–40 mg/kg and corresponding AUC values of 47.28–183.14 mg.min/L. These pharmacokinetic characteristics reflect AC's poor gastrointestinal absorption, high first-pass metabolism, and possible efflux by transporters such as P-gp, which together significantly limit its oral bioavailability and therapeutic translation.

Pharmacological activities

Based on literature, AC possess various pharmacological properties that directly contribute to its therapeutic potential. Being an antioxidant, the compound has powerful free radical-scavenging effects with upregulation of antioxidant enzymes (Dell'Aquila et al. 2014) reflecting its potential in neuroprotection, hepatoprotection, and cardioprotection. In addition, AC has shown potent anti-inflammatory effects mainly through inhibiting NF-κB as well as MAPK pathways with a consequent suppression of pro-inflammatory cytokines (Ma et al. 2020a, b), adding to its credit in treating inflammatory diseases such as arthritis, colitis, and neuroinflammation. AC has also shown anticancer activity through inducing apoptosis, inhibiting proliferation and metastasis, and modulating cell cycle-related proteins (Jia et al. 2020). The antimicrobial and antiviral effects of AC are mainly through disrupting microbial membranes and inhibiting key viral replication enzymes (Chathuranga et al. 2019). The glycoside has also shown antidiabetic effects through enhancing insulin sensitivity, modulating glucose uptake, and regulating lipid metabolism (Uchida et al. 2005; Srinivasan and Ramarao 2007).

Role of AC in inflammatory diseases

Inflammation is a common pathway for multiple chronic illnesses including cardiovascular, central nervous system, bowel diseases, arthritis, diabetes, and cancer (Libby 2007). Inflammatory response mechanisms always include pattern recognition of cell surface receptors to detrimental stimuli, activation of inflammatory pathways, and recruitment of inflammatory cells to the damaged organ (Chen et al. 2018). Medicinal plants with high AC content have been widely used to treat inflammatory conditions among others. Key molecular mechanisms of AC's anti-inflammatory activity are generally through NF-κB inhibition, where AC inhibits the phosphorylation and degradation of IκB-α, thus preventing the nuclear translocation of NF-κB p65. This results in the downregulation of pro-inflammatory genes including TNF-α, IL-1β, IL-6, COX-2, and iNOS (Ling et al. 2022). AC also reduces the release and nuclear-to-cytoplasmic translocation of high-mobility group box 1 (HMGB1) with consequent downregulation of HMGB1-mediated activation of TLR4 and RAGE receptors (Ling et al. 2022). Further, AC blocks the phosphorylation of key MAPKs including ERK1/2, JNK, and p38 as the upstream regulators of transcription factors involved in inflammation (Ling et al. 2022). AC additionally inhibits the activation of the NLRP3 inflammasome complex, ROS, and oxidative stress-induced inflammation (Liao et al. 2024).

The anti-inflammatory properties of AC have been linked to the reduced production of superoxide radicals and inducible nitric oxide synthase (iNOS), events that were attributed to suppressing the activator protein-1 (AP-1) (Rossi et al. 2023). AC treatment could also inhibit p38, TNF-α, PI3K/AKT, and NF-κB signaling pathways in the LPS-induced RAW264.7 cells (Muhtar et al. 2025). Indeed, rats treated with AC have shown a lower production of tumor necrosis factor (TNF)-α and the pro-inflammatory interleukins, viz., IL-1β and IL-6 (Ma et al. 2020a, b). Further, lower levels of IL-12 and TNF-α, along with higher

levels of the anti-inflammatory cytokine IL-10 have been observed (Chang et al. 2022). Interestingly, the anti-inflammatory properties of AC have been also related to inhibiting the cytosolic Ca^{2+}-dependent phospholipase A2, thus reducing arachidonic acid formation (Song et al. 2012). Further, AC was shown to interfere with the catalytic cavity of cyclooxygenase-2 (COX-2) and hinder the production of prostaglandin E2 (PGE2), with reduced impact on COX-1 activity in free fatty acid-treated RAW 264.7 and THP-1 macrophage cells (Ma et al. 2017).

Inflammation is closely engaged in the pathogenesis of viral lung infections. AC has shown efficacy in alleviating respiratory syncytial virus (RSV) and COVID-19 viral lung infections through possessing antiviral, anti-inflammatory, and antioxidant effects (Chathuranga et al. 2019; Ling et al. 2022; Han et al. 2024a, b) where the compound could inhibit viral replication, although its direct antiviral activity is modest compared to traditional antivirals (Chathuranga et al. 2019). Further, AC was shown to suppress the activation of NF-κB, a key transcription factor involved in pro-inflammatory cytokine production, thus reducing the cytokine storm seen in severe COVID-19 and RSV-induced inflammation (Ling et al. 2022). It also modulates the ERK, JNK, and p38 MAPK signaling cascades, reducing the expression of inflammatory mediators and adhesion molecules (Ling et al. 2022). Finally, AC regulates macrophage polarization (favoring M2 over pro-inflammatory M1 phenotype), which can promote tissue repair and resolution of inflammation (Ren et al. 2022). Due to its phenolic structure, AC directly scavenges reactive oxygen species and activates nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which upregulates antioxidant enzymes like HO-1 and NQO1, providing cytoprotection against oxidative damage (Wang et al. 2024), an event that is known to contribute to lung injury in viral infections. In line with the previous findings, AC has effectively shown antiviral effects against RSV as the main cause of acute lower respiratory infections in childhood. The glycoside alleviated mitochondrial dysfunction and suppressed the pro-inflammatory cytokines that are vital for the onset and progression of the disease through inhibiting high-mobility group box 1/nuclear factor kappa beta (HMGB1/NF-κB) pathway (Ling et al. 2022). A recent study has shown that the hyper-inflammatory response revealed as a main cause of severity and mortality from coronavirus (COVID-19) is ameliorated in vitro and in vivo using a Chinese decoction (*Xuanfei baidu*) that contains AC among its constituents. The same study reported that AC possesses high binding affinity to IL17A that is positively correlated to the severity of the disease (Wang et al. 2022). Moreover, post-COVID complications are ameliorated by AC as a SARS-CoV-2 main protease inhibitor (Kallingal et al. 2022). Further, AC was proven to reduce the biosynthesis of 5-hydroxyeicosatetraenoic acid and leukotriene B4 in isolated human leukocyte cells, thus reducing inflammation during the course of the disease (Nawrot et al. 2022). AC has been also reported among the natural products involved in osteoporosis treatment due to its anti-inflammatory and antioxidant effects (Martiniakova et al. 2020). In the central nervous system (CNS), inflammation is considered as a common mechanism in neurodegenerative diseases, characterized by activation of astrocytes and microglia in response to brain injury. Generally, microglial activation is followed by elevated cytokine expression as a defense mechanism against pathogens to maintain brain homeostasis and protect the CNS. However, amplified or persistent microglial activation can lead to marked pathological changes and neurobehavioral consequences including cognitive deficits among others (DiSabato et al. 2016). In this context, and due to its inhibitory effects on microglial pro-inflammatory markers, AC has been shown to play a neuroprotective role in Alzheimer's disease (AD) through blocking the NF-κB–p65 pathway (Chen et al. 2022a; b). Studies have shown protective effects of AC on hepatocytes through NF-κB inhibition and consequent reduction of TNF-α, thus improving steatosis (Khullar et al. 2019; Salvoza et al. 2022). In addition, AC was evidenced to inhibit the expression of cell adhesion molecules (CAMs), including intercellular CAM (ICAM-1) and vascular CAM (VCAM-1), thus inducing anti-inflammatory effects to protect vascular endothelial cells (Chen et al. 2009). Further, AC facilitates nitric oxide (NO) production through regulation of inducible nitric oxide synthase (iNOS) to ameliorate the inflammatory response (Seo et al. 2013). AC also played a role in hepatic ischemia–reperfusion injury as a common reaction in liver surgery, leading to sustained liver dysfunction (Jia et al. 2023). A study by Jia et al. (2023) stated that liver sinusoidal endothelial cells, being most vulnerable to damage, secrete damage-associated molecular patterns (DAMPs) dominated by HMGB1 to impact the whole liver microenvironment. This study has reported that AC could efficiently restore sinusoidal networks through targeting high-mobility group box 1/toll like receptor 3/interferon regulatory factor 1 (HMGB1/TLR3/4-IRF1) signaling to reduce inflammatory events (Jia et al. 2023). Concentration-dependent effects of AC against ethanol-induced hepatotoxicity were also noted in LO2 and HepG2 cells, confirming its potential hepatoprotection (Liu et al. 2025a, b). The anti-inflammatory effects of AC have been extended to kidney injury diseases as well. In a rat model of unilateral ureteral obstruction, AC was shown to improve renal function through regulating the high-mobility group nucleosome-binding protein 1/toll-like receptor 4/triggering receptor expressed on myeloid cells-1(HMGN1/TLR4/TREM1) inflammatory pathway (Mao et al. 2023). Moreover, AC and its iso-derivative were shown to alleviate inflammation in a model of lipopolysaccharide-induced acute kidney injuries by regulating the NF-κB pathway (Lian

et al. 2024). AC also ameliorated diabetic kidney disease by regulating the phosphatidylinositol 3-kinase (PI3K)/AKT/NF-κB signaling pathway and alleviating pyroptosis (Zhang et al. 2024a, b). Atopic dermatitis as an inflammatory skin condition is better alleviated by the potent anti-inflammatory effect of AC in 2,4-dinitrochlorobenzene (DNCB)-treated mice (Li et al. 2018). In a previous study, AC ameliorated the severity of skin lesions and the scratching behavior possibly through inhibiting the pro-inflammatory cytokine release (Li et al. 2018). Management of methotrexate-induced intestinal mucositis included the anti-inflammatory glycoside AC that was shown to ameliorate the histological severity scores in the duodenum, jejunum, and ileum, decrease the crypt depth, and increase the villus height (Reinke et al. 2015). A study by Rossi et al. (2023) has implicated AC as a dietary intervention in animal nutrition for modulation of the inflammatory phenomena, based on the fact that the inflammatory process is accompanied by inadequate intake of nutrients due to increased energy and trace element requirements for basal energy expenditure, increased synthesis of immune system constituents, and increased muscle catabolism (Rossi et al. 2023). The anti-inflammatory effects of AC have been strongly related to its antioxidant role, where in an osteoarthritis rat model, the reduction in NF-κB was accompanied by diminished reactive oxygen species (ROS) production (Ma et al. 2020a, b).

Role of AC in oxidative stress

AC, as the main bioactive compound of various medicinal plants, has strong antioxidant properties. It attenuates reactive oxygen species (ROS)-induced damage by hindering reactions of ROS generation, scavenging free radicals, chelating metals that fasten the oxidative process, and enhancing glutathione transferase (GST) activity (Dell'Aquila et al. 2014). A study by Treml et al. (2021) showed that AC has direct free radical-scavenging activity, but has no effect on the expression of antioxidant enzymes (Treml et al. 2021). Recently, AC antioxidant activity has been verified using a cell-free system bioassay based on copper (Cu^{+})-induced low-density lipoproteins (LDL) peroxidation in vitro as well as the in vitro cultured cell system (HT-29 intestinal cell line) (Cardinali et al. 2012).

As a main constituent of *Abeliophyllum distichum*, AC reduced phosphorylated p53 and γ-H2AX levels in ROS-treated NIH 3T3 cells and protected against ROS-induced DNA double-strand damage (Jang et al. 2020). Another study using the same plant reported that AC in the leaves and stems of *A. distichum* (25 μg/mL) resulted in a radical-scavenging activity against DPPH by 82.84%, $^{\bullet}OH$ by 89.46%, and O_2^- by 30.31% (Lee et al. 2020). Interestingly, AC from the leaves of *Odontonema strictum* have demonstrated high levels of DPPH radical-scavenging activity as compared to ascorbic acid (Pierre Luhata and Usuki 2022).

Oxidative stress has now become a major pathological machinery in various diseases. AC exhibited antioxidant effects against osteoporosis and helped in attenuation of bone resorption and suppression of osteoclastogenesis (Martiniakova et al. 2020). Osteoporosis is characterized by an imbalance between bone formation (osteoblast activity) and bone resorption (osteoclast activity). Notably, oxidative stress is a significant contributor to such imbalance, promoting osteoclastogenesis and inhibiting osteoblast function (Iantomasi et al. 2023). Obviously, AC, being a ROS scavenger, reduces oxidative damage to osteoblasts, preserving their function and survival (Akyer et al. 2023). AC-induced activation of the Nrf2/HO-1 pathway further augments the expression of antioxidant enzymes (e.g., HO-1, NQO1), enhancing cellular resilience to oxidative stress (Han et al. 2024a, b). In addition, owing to its antioxidant effects, AC suppresses receptor activator of nuclear factor kappa-B ligand (RANKL)-induced differentiation of osteoclasts (Lee et al. 2013). Hyperglycemia-induced oxidative stress leads to damage of retinal microvasculature, promoting inflammation, vascular leakage, and cell apoptosis (Wu et al. 2018). In an in vitro model of diabetes retinopathy, AC, reduced retinal pigment epithelial cell damage through inhibiting Keap1 expression, endorsing nuclear translocation of Nrf2, elevating NQO1 and HO-1 expression, reducing ROS, and increasing superoxide dismutase (SOD), total antioxidant capacity (T-AOC), and glutathione peroxidase (GSH-Px) (Yang et al. 2023). Colon ischemia–reperfusion (IR) injury also involves oxidative stress. It was reported that AC protects against IR-induced oxidative stress as evidenced by increased SOD, GSH-Px, total antioxidant status (TAS), and total thiol (TT) levels (Deger et al. 2021). Similarly, in a brain ischemia–reperfusion rat model, AC attenuated oxidative stress and neuronal apoptosis (Xia et al. 2018a, b). The cardioprotective role of AC has been partly revealed through inhibiting oxidative stress in lipopolysaccharide (LPS)-induced septic cardiomyopathy (Zhu et al. 2022). Notably, AC has been proven as a good candidate for treatment of leukemia, where it decreased total antioxidant status (TAS) and increased total oxidant status (TOS) levels in K562 and R-K562 cells when used together with dasatinib, lipopolysaccharide, and TNF (Akgun-Cagliyan et al. 2022). Accumulation of oxidative stress is also connected to the delay of wound healing, especially in diabetic patients. In this context, AC increased SOD, reduced the oxidative stress indicator 8-OHdG, and repressed PKC/HMGB1/RAGE/NFκB activation (Hsieh et al. 2021). A study has reported the antioxidant effect of AC upon incubation with mouse and human pancreatic β-cells (0.8–16 μM) for up to 5 days, where the glycoside showed a dose-dependent protective effect against oxidative stress through decreasing ROS

content, acrolein, and 4-hydroxynonenal (HNE) expression (Galli et al. 2020). Interestingly, AC has also shown efficacy against altitude-induced fatigue due to its antioxidant properties. In a hypobaric chamber, rats treated with AC (150 mg/kg, intragastrical) for seven consecutive days demonstrated antioxidant and anti-fatigue activity through improving glucose utilization, regulating energy metabolism, and maintaining normal physiological structure (Ziliang et al. 2023). AC effect was also examined in weaned piglets fed high doses of sunflower oil, where dietary administration of the glycoside effectively preserved gut morphology from oxidative stress induced by sunflower oil (Rossi et al. 2019). Another study has reported that AC exerted protective effect against ulcerative colitis in mice via regulation of the HO-1/HMGB1 signaling pathway where the alterations in MDA, CAT, GSH, and SOD were clearly improved after treatment with 60 mg/kg intraperitoneal injection of AC for seven consecutive days (Guo et al. 2022a; b). In a report by Xi et al. (2022), AC was evidenced to protect the retinal ganglion cells from oxidative and inflammatory damage in an experimental rat model of glaucoma through reducing ROS and MDA and elevating SOD levels. The study also highlighted the strong interaction between ROS and autophagy, which was reflected in the ability of autophagy to reduce ROS and vice versa. Accordingly, AC could efficiently reduce the expression of LC3-II, suggesting its efficacy to diminish cell autophagy and inhibit oxidative stress-linked retinal loss by regulating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway (Xi et al. 2022). Advanced glycation end products (AGEs) are heterogeneous molecules that are obviously elevated in diabetes, renal failure, and aging due to non-enzymatic protein glycation. AGEs are known to exert their effects by generation of ROS (Wautier and Schmidt 2004). Interestingly, AC has been shown to possess anti-glycation activity that might contribute to relief aging, where in a D-galactose-induced aging mouse model, AC showed protective effects as evidenced by improved memory dysfunction, shortened escape latency, increased zone time, and improved platform crossing times (Xiong et al. 2016).

Oxidative stress has been considered as a major challenge in assisted reproductive technology (ART) due to the lack of physiological defense mechanisms in the culture environment. In this perspective, a study by Dell'Aquila et al. (2014) has reported a paradoxical prooxidant effect of AC due to an excessively high tested concentration and prolonged incubation time in culture media (24 h) showing elevated oocyte intracellular ROS levels and CAT activity (Dell'Aquila et al. 2014).

In clinical trials, AC, being a phytoestrogen, has been tested for its effect on the levels of sex hormone, antioxidant-adaptive reactions, and oxidative stress induced by exercise. As a diet intervention for 26 days in female swimmers, AC (20 mg/100 mL) was supplemented in the form of *Lippia citriodora* extract-containing beverage, where it boosted the glutathione-dependent enzyme activities in erythrocytes and the SOD activity in lymphocytes in response to exercise. It also showed direct antioxidant effects, by elevating glutathione reductase activity in vitro. The beverage also reduced plasma steroid hormone levels, indicating its agonistic effect on regulation of estradiol synthesis in the hypothalamus (Mestre-Alfaro et al. 2011a, b). In agreement with the previous study, a trial conducted on university students, performing a 21-day aerobic training program, reported that the antioxidant effect induced by *Lippia citriodora* extracts is mainly due to AC, which represents 10% (w/w) of the extract content (Carrera-Quintanar et al. 2012). Interestingly, AC was featured as a potential strategy to improve donkey's milk for human use where its supplementation over 30 days improved lipid profiles, hepatic functions, as well as the oxidative status of jennies and their suckling foals (D'Alessandro et al. 2014).

Role of AC in cancer

AC has demonstrated anticancer activities that involve the modulation of several key signaling pathways across a range of cancers (Fig. 2) including the following.

Brain cancer

Glioblastoma (GBM) is among the most aggressive and the most common malignant tumors within gliomas, accounting for approximately half (46.1%) of primary malignant brain cancers (Wirsching and Weller 2017). Src homology region 2 domain-containing phosphatase-1 (SHP-1), a tyrosine phosphate protein, functions as a significant tumor-suppressor gene involved in various cancer types including GBM. SHP-1 restricts cancer progression primarily by suppressing signaling pathways that regulate cellular proliferation, migration, survival, and invasion (Varone et al. 2020). One of its downstream effectors is signal transducer and activator of transcription 3 (STAT3), which is activated upon phosphorylation to induce carcinogenesis in several human cancers including GBM, and is negatively regulated by SHP-1 (Bi et al. 2015). Small interfering RNA (siRNA) has been shown to inhibit SHP-1 activity (Yin et al. 2014). In 2018, a group of Chinese investigators reported that AC could constrain GBM via SHP-1 stimulation and STAT3 phosphorylation inhibition. Western blot analysis revealed elevated SHP-1 expression and reduced phosphorylated STAT3 (p-STAT3) expression in glioblastoma cells treated with AC compared to controls. Additionally, the critical role of SHP-1 in mediating AC's effects was confirmed when siRNA-SHP-1 inhibited the anticancer effects of AC on

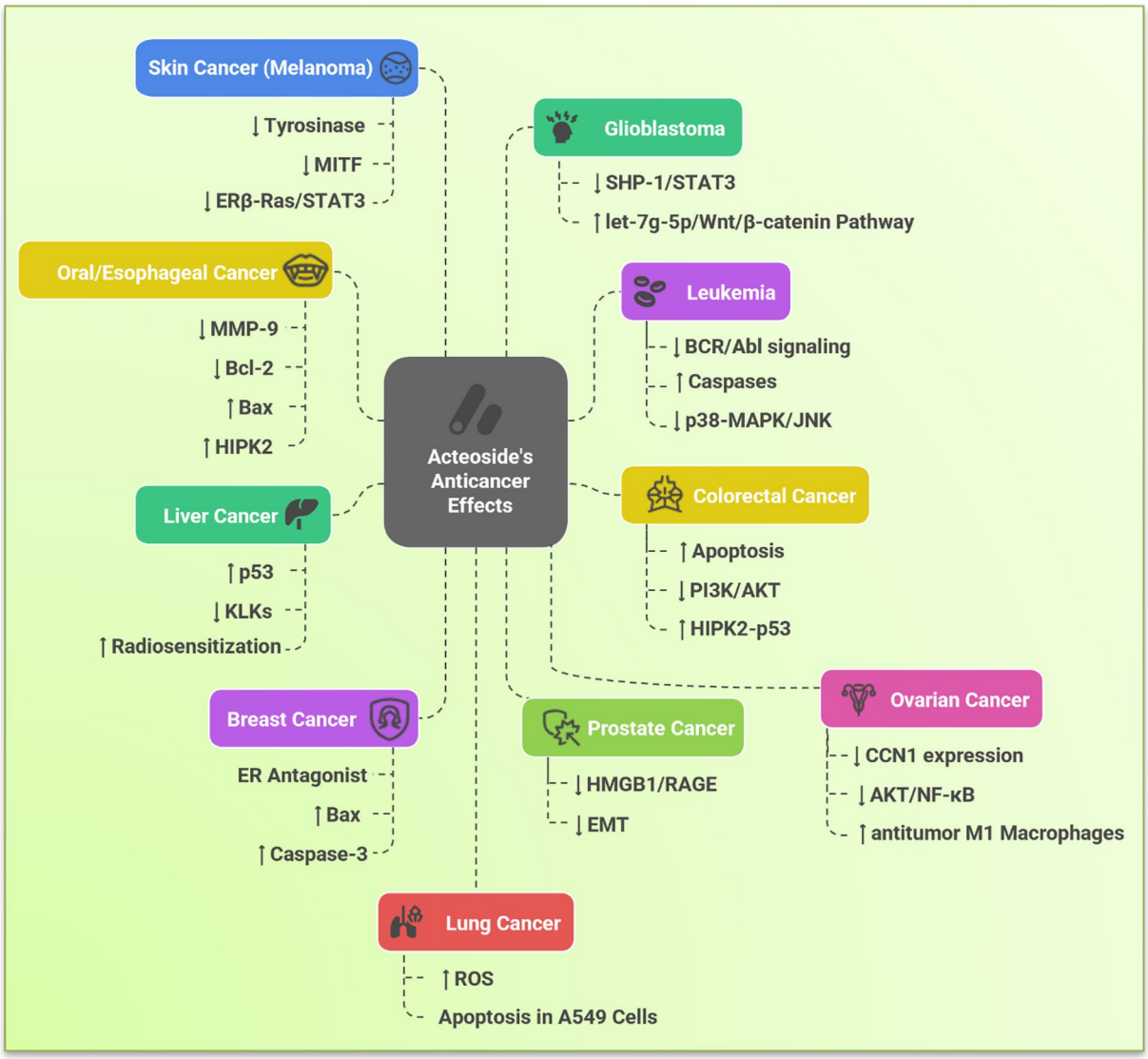

Fig. 2 Anticancer effects of AC. A549, human lung carcinoma cell line; Abl, Abelson oncoprotein; AKT, protein kinase B; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; Caspase-3, cysteine-aspartic protease 3; Caspases, cysteine-aspartic proteases; CCN1, cellular communication network factor 1; EMT, epithelial–mesenchymal transition; ERB, epidermal growth factor receptor family; HIPK2, homeodomain-interacting protein kinase 2; JNK, c-Jun N-terminal kinase; KLKs, kallikreins; MAPK, mitogen-activated protein kinase; MITF, microphthalmia-associated transcription factor; MMP-9, matrix metallopeptidase 9; Nf-kB, nuclear factor kappa b; p38, p38 MAP kinase; p53, tumor protein p53; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; SHP-1, Src homology region 2 domain-containing phosphatase-1; STAT3, signal transducer and activator of transcription 3; THIPK2, possibly homeodomain-interacting protein kinase 2; Wnt, wingless-related integration site; let-7g-5p, a microRNA involved in gene regulation

glioblastoma (Jia et al. 2018). In 2020, this research group has reported that AC could reduce GBM cell viability, invasion, and metastasis, while promoting cell autophagy and apoptosis through the induction of let-7g-5p expression with a resultant downregulation of high mobility group A2 (HMGA2) via Wnt/β-catenin cascade blockade (Jia et al. 2020). This direct evidence establishes the SHP-1/STAT3 pathway as a central mechanism in AC's anti-glioblastoma activity.

Moreover, AC exhibits significant anti-glioblastoma activity by targeting the c-Met-mediated epithelial-to-mesenchymal transition (EMT), a key process in tumor progression and metastasis. AC directly binds to the c-Met protein and promotes its degradation through the ubiquitin–proteasome pathway, rather than affecting its mRNA levels. Importantly, overexpression of c-Met in glioblastoma cells diminished the inhibitory effects of AC on cell growth and EMT marker expression, confirming that c-Met is a critical target of AC's action. These findings identify a novel mechanism

for AC's anticancer effects in glioblastoma, highlighting its potential as a therapeutic agent by suppressing EMT and tumor aggressiveness through ubiquitin-mediated degradation of c-Met (Hei et al. 2019).

Numerous studies indicate that phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway plays a critical role in cancer progression, making it a promising target for screening natural therapeutic candidates (Ong et al. 2016; Iksen et al. 2021; Narayanankutty 2021). In the context of GBM cells, AC has been shown to augment microRNA-7-5p expression, which subsequently suppresses the epidermal growth factor receptor (EGFR) expression, leading to PI3K/AKT axis inactivation and a resultant reduction in cellular proliferation and microtubules formation (Wang et al. 2021a, b).

Hematologic cancer

Hematopoietic stem cell dynamics play a role in the early stages of various blood cancers, such as myeloproliferative neoplasms, acute myeloid leukemia, and chronic lymphocytic leukemia (CML) (Genovese et al. 2014). Lee et al. (2007) examined the in vitro effects of AC on proliferation, cell cycle regulation, as well as differentiation in HL-60 promyelocytic human leukemia cells. They reported that AC could suppress HL-60 cell proliferation in a time- and concentration-dependent fashion, with a half-maximal inhibitory concentration (IC_{50}) of approximately 30 µg/mL. Furthermore, DNA flow cytometry analysis in this study proved that AC arrested the leukemia cell cycle progression at the G1 phase through the inhibition of cyclin-dependent protein kinases CDK2, CDK4, and CDK6 activities and the upregulation of the CDK inhibitors, including p21 $^{CIP1/WAF1}$ and p27 ^{KIP1} (Lee et al. 2007). Ma et al. developed a new drug delivery system for enhancing chemotherapy efficacy in cancer treatment. Poly(*N*-isopropyl acrylamide) (PNIPAM) microspheres were used as core structures coated with gold nanoshells (GNS) to deliver AC to drug-resistant leukemia cells (K562/A02; KA). Testing on KA xenografted mice showed that the PNIPAM/GNS structures with AC effectively induced apoptosis both in vivo and in vitro, increasing apoptosis rates and activating caspases more than AC or PNIPAM/GNS alone (Ma et al. 2016). Recently, AC has shown to inhibit cell growth and trigger apoptosis in both K562 and resistant K562 (R-K562) leukemia cells. Mechanistically, AC acts by inhibiting the Abelson (Abl) oncoprotein and modulating the downstream p38 mitogen-activated protein kinase (p38-MAPK)/c-Jun N-terminal kinase (JNK) pathway. AC disrupts the interaction between MAPK and Bcr/Abl signaling, enhancing CML cell sensitivity to tyrosine kinase inhibitors such as dasatinib or imatinib, suggesting its potential as an adjunct in CML treatment (Akgun-Cagliyan et al. 2022).

Colorectal cancer

Colorectal cancer (CRC) globally ranks as the third leading cause of cancer-related mortality (Xi and Xu 2021). Despite 5-fluorouracil (5-FU) being a primary treatment for CRC, resistance to 5-FU often leads to treatment failure and relapses. This resistance of CRC cells to 5-FU can be linked to the activation of the PI3K/AKT signaling axis (Azwar et al. 2021). In vitro analysis by Attia et al. demonstrated that AC synergistically enhanced the cytotoxic abilities of 5-FU, caused G1 cell cycle arrest, and promoted apoptosis by modulating the anti-apoptotic B-cell lymphoma 2 (Bcl2) and the pro-apoptotic Bcl-2-associated X protein (Bax), and to a lesser degree, Bcl-xL and p53. Furthermore, the combination significantly suppressed PI3K/AKT, suggesting that AC can serve as an effective adjunct to overcome 5-FU resistance in CRC (Attia et al. 2018). When AC was administered alongside a p53-specific inhibitor in human CRC HCT-116 cells, the apoptosis rate was significantly declined. Thus, AC-induced apoptosis is largely mediated through the homeodomain-interacting protein kinase 2 (HIPK2)-p53 pathway augmentation (Zhou et al. 2014). Additionally, the metastatic phenotype remains a major obstacle in CRC treatment. It has been reported that AC inhibited the proliferation of HT29 human colon cancer cells in a dose-dependent manner with an IC_{50} of approximately 50 µg/mL, where it exhibited strong anti-metastatic and anti-invasive effects by inhibiting the Rac family small GTPase 1 (Rac-1), hypoxia-inducible factor-1 alpha (HIF-1α), and zinc finger E-box-binding homeobox 1 (Zeb-1) pathways (Seyfi et al. 2018). Administration of AC not only reduced tumor burden, but also ameliorated chemotherapy-induced muscle fatigue-like behavior. Several key enzymes, including CYP3A4, CYP19A1, CYP2E1, TNF, BCL-2, RYR2, and ATP2A1, were identified as potential targets underlying the anti-chemotherapy-related fatigue effect of AC (Zhang et al. 2025).

Liver cancer

Liver cancer globally ranks as the fourth leading cause of cancer-related mortality, with hepatocellular carcinoma (HCC) accounting for 90% of liver cancer cases, posing a significant threat to human life and health (Bray et al. 2018). A study by Peerzada et al. (2016) evaluated the chemopreventive, rather than the curative, effects of

AC against diethylnitrosamine (DEN)-induced HCC in rats. Pretreatment with AC significantly abated pre-hepatocarcinogenic indices proven by diminished HCC nodules, inflammatory interleukin-6, interferon-gamma, and tumor necrosis factor-alpha, as well as apoptotic caspase 3. Also, AC protected Hep3B liver cells in vitro from DEN-induced cytotoxicity, DNA damage, and reactive oxygen species (ROS) accumulation, while preventing mitochondrial membrane potential loss. Mechanistically, AC countered DEN-induced oxidative stress and apoptosis through modulating STAT3, nuclear factor-kappa B (NF-κB), Bax, cytochrome C, and Bcl-2 signaling (Peerzada et al. 2016). AC has shown the ability to inhibit cell proliferation, colony formation, and migration in human HCC cell lines BEL7404, HLF and JHH-7, as well as in vivo xenograft model using nude mice. These effects are achieved through an increase in tumor-suppressor protein p53 levels and a reduction in kallikrein-related peptidase (KLK1, 2, 4, 9, and 10) gene expression. Furthermore, AC's antitumor efficacy was enhanced when used alongside sorafenib, suggesting its potential as an adjunct therapy for HCC (Ma et al. 2020a, b). A recent study has demonstrated that AC enhances the radiosensitivity of HCC cells by boosting miR-101-3p and reducing WEE1 G2 checkpoint kinase (WEE1) expressions (Sun et al. 2022). The synergistic and toxicity-lowering effects of AC as an adjuvant to oxaliplatin in HCC therapy was also recently highlighted. Using in vitro and in vivo xenograft mouse model, AC synergized with oxaliplatin and lessened its neurotoxicity, potentially via the regulation of INPP4B to inhibit the PI3K/AKT signaling pathway (Wen et al. 2025).

Lung cancer

Lung cancer is an aggressive and widely prevalent disease, with approximately new 2.2 million cases and 1.8 million mortalities reported globally in 2020. It is the leading cause of cancer-related deaths among men worldwide and ranks second for women, after breast cancer (Sung et al. 2021). AC has been reported to have antitumor properties in pulmonary A549 cancer cells. At a concentration of 100 µg/mL over a 48-h incubation, AC demonstrated significant cytotoxicity by increasing the population of subG1 cells and enhancing apoptotic rates. Additionally, AC induced a time-dependent increase in intracellular ROS generation in tumor cells, with effects observed from 1 to 24 h. The potent antitumor effects of AC could be linked to its structural elements, particularly its phenolic hydroxyl groups (Vasincu et al. 2020). Another recent study has evaluated the anticancer effects of *Clerodendrum chinense* leaf ethanolic extract, specifically enriched with AC, on A549 lung cancer cells. The extract displayed dose- and time-dependent antiproliferative effects on A549 cells, with IC_{50} decreasing from 340.63 µg/mL at 24 h to 107.08 µg/mL at 72 h, indicating enhanced cytotoxicity over time. Additionally, at 250 µg/mL, the extract significantly increased late apoptotic cell populations and ROS levels, while also inhibiting colony formation and cell migration in A549 cells in a dose-dependent manner. Such findings suggested that the *C. chinense* leaf extract, chiefly its AC content, has a potent anticancer potential against lung cancer (Chittasupho et al. 2023).

Breast cancer

AC may function as either an estrogen agonist or antagonist by interacting with estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) (Papoutsi et al. 2006). These receptors vary in distribution in tissues and biochemical responses, and ligands binding to ERα and ERβ can display different levels of agonism or antagonism depending on both the estrogen-responsive tissue type and the concentration of the ligand (Nilsson et al. 2001). In MCF-7 breast cancer cells, AC acted as ER antagonist, mainly affecting ERα, leading to reduced cell viability and enhanced levels of insulin-like growth factor-binding protein 3 (IGFBP3). AC also demonstrated selective antiestrogenic activity in osteoblasts, but did not affect endometrial cells, highlighting its potential as a selective estrogen receptor modulator (SERM) with specific anticancer properties in breast cancer (Papoutsi et al. 2006; Budzianowska et al. 2023). Similarly, AC has been identified as a bioactive component in the traditional Chinese herbal formula Si-Wu-Tang (SWT), demonstrating significant antiproliferative effects against breast cancer cells (Zhang et al. 2020). In 2021, a group of Turkish researchers isolated AC from *Phlomis nissolii* and evaluated its potential to induce apoptosis in breast cancer cell lines. The IC_{50} of AC was determined for MCF-7 and MDA-MB-231 cell lines following exposure to various concentrations (100, 48, 25, 10, 1, 0.5, and 0.1 µg/mL). Results indicated that only the 100 µg/mL concentration demonstrated remarkable cytotoxic effects, with maximum activity in MCF-7 cells after 72 h and in MDA-MB-231 cells at 24, 48, and 72 h (Şenol and Tulay 2021). In line, AC has shown antiproliferative effects on 4T1 breast cancer cells, with an IC_{50} of 117 µg/mL, and has induced apoptosis by upregulating the pro-apoptotic proteins Bax and caspase-3, while downregulating the anti-apoptotic Bcl-2 protein. Mechanistically, AC increases toll-like receptor 4 (TLR4) expression, activates the myeloid differentiation primary response 88 (MyD88) axis, and reduces NF-κB mRNA levels, but shows no toxic

effects on normal cells (Daneshforouz et al. 2021). A recent preprint attributed AC's ability to arrest cell cycle and induce apoptosis of breast cancer cells to the suppression of the PI3K/AKT signaling cascade (Ou et al. 2022).

Ovarian cancer

Ovarian cancer (OC) is among the most deadly tumors affecting females' reproductive system. It ranks as the eighth most common cancer among women globally (Siegel and Miller 2021). AC demonstrates significant antitumor activity against OC by targeting the cellular communication network factor 1 (CCN1) signaling pathway. In OC, CCN1, a pro-inflammatory factor, promotes cell proliferation and tumor progression. AC binds directly to CCN1 at specific amino acid sites, effectively reducing its expression. It further suppresses the AKT/NF-κB trajectory which is crucial in OC cell proliferation and metastasis. Also, AC influences the immune response by promoting macrophage polarization toward the M1 phenotype, which is associated with antitumor effects. In vivo studies using xenograft models confirmed such findings (Ren et al. 2022). In support, it has been recently reported that AC, at a 200 µg/mL concentration, exhibited significant cytotoxicity against the ovarian OVAR-3 cancer cell line after 24 h of treatment (Budzianowska et al. 2023).

Prostate cancer

Prostate cancer ranks as the second most common malignancy in men globally, following lung cancer. Its incidence and mortality rates are closely linked to advancing age, with the average age at diagnosis being 66 years (Rawla 2019). AC in high dose has been reported to induce cell apoptosis in benign prostatic hyperplasia (BPH) model in rats (Sun WeiDong et al. 2008). Also, AC has shown strong inhibitory effects on the proliferation of the PC-3 prostate cancer cell line, reducing cancer cell proliferation by approximately 23–30% (Mulani et al. 2014). Similarly, treatment with AC markedly halted DU-145 and PC-3 prostate cancer cell proliferation and migration by downregulating the HMGB1/receptor for advanced glycation end products (RAGE) signaling cascade and its downstream transforming growth factor-beta I/II (TGF-βI/II)/SMAD family member 2/3 (Smad2/3) pathway. Epithelial–mesenchymal transition (EMT), a key process in cancer progression and metastasis, is also suppressed by AC where it downregulates EMT transcription factors including Slug and Snail, while upregulating E-cadherin expression (Wu et al. 2021a, b, c).

Oral and esophageal cancer

Oral cancer is a significant global health concern, ranking as the sixth most common malignancy. The most prevalent form of oral cancer is oral squamous cell carcinoma (OSCC), which arises from the accumulation of various genetic mutations that lead to damage in oral epithelial cells. OSCC represents a major cause of morbidity and mortality associated with head and neck cancers (Gharat et al. 2016). In 2018, a group of Chinese researchers have proven that AC suppressed the metastasis and induced apoptosis in OSCC HN4 and HN6 cells and in vivo. Mechanistically, this antitumor action of AC was achieved through inhibition of NF-κB/matrix metalloproteinase-9 (MMP-9) signaling, Bcl-2, and Bcl-xL, in addition to augmentation of Bax (Zhang and Yuan 2018). Recently, similar results were obtained by Huang et al. who attributed AC's effect against OSCC to methyltransferase-like 3 (METTL3) downregulation, which in turn disrupts N6-methyladenosine (m6A)-dependent processing of miR-31-5p, leading to enhanced homeodomain-interacting protein kinase 2 (HIPK2) activity and reinforcing AC's inhibitory effects on OSCC cell behavior (Huang et al. 2024a, b).

Esophageal cancer (EC) is a highly aggressive malignancy of the digestive tract with a rising incidence. The most prevalent subtype of EC is esophageal squamous cell carcinoma (ESCC), representing almost 80% of all EC cases worldwide (Arnold et al. 2015). AC has been shown to mitigate ESCC progression by downregulating HMGB1/RAGE expression and inhibiting cell division cycle 42 (CDC42) activation (Ji et al. 2022).

Skin cancer

Melanogenesis is a physiological process that helps protect the skin from harmful ultraviolet (UV) radiation and various environmental stressors. However, excessive activation of melanin production can lead to aesthetic concerns and increase the risk of malignant melanoma (Slominski et al. 2022). It has been reported that AC dose dependently inhibits tyrosinase activity, the main enzyme controlling melanin synthesis, and melanin production in B16 melanoma cells through the inhibition of adenyl cyclase and α-melanocyte stimulating hormone (α-MSH) (Song and Sim 2009). Similar results were obtained in cultured B16F10 melanoma cells where AC reduced levels of tyrosinase, tyrosinase-related protein-1 (TRP-1), and microphthalmia-associated transcription factor (MITF) proteins by activating extracellular signal-regulated kinase

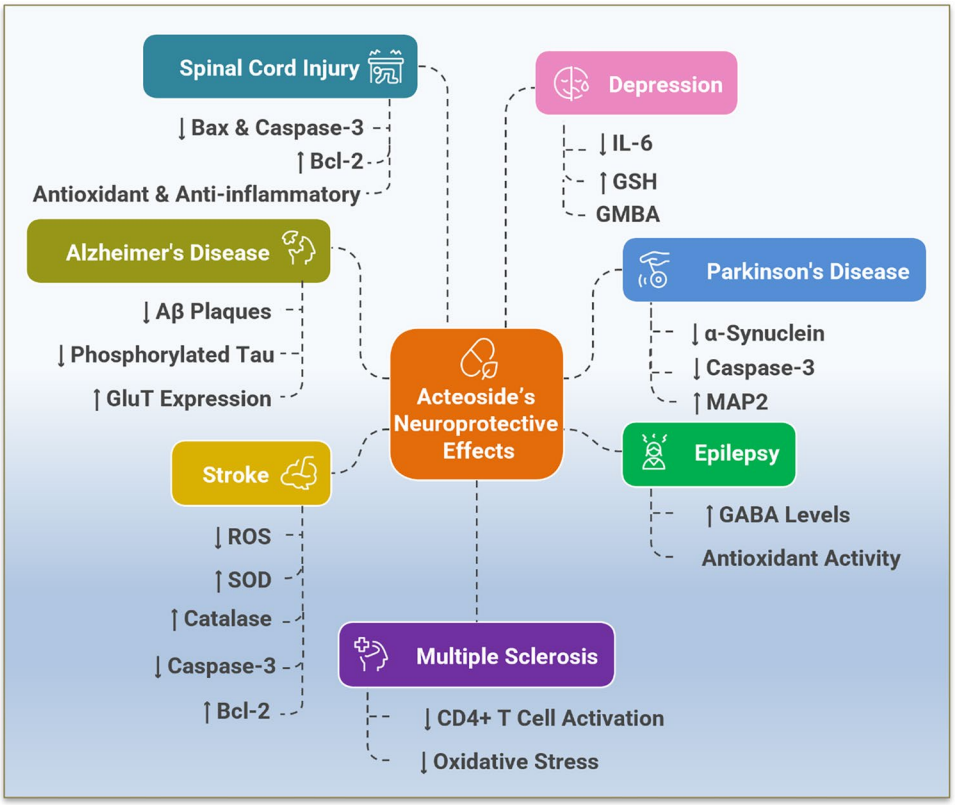

Fig. 3 Neuroprotective effects of AC. Aβ, amyloid beta; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; CD4+, cluster of differentiation 4 positive; GABA, gamma-aminobutyric acid; GluT, glucose transporter; GMBA, gut-microbiota-brain axis; GSH, glutathione; IL-6, interleukin 6; MAP2, microtubule-associated protein 2; ROS, reactive oxygen species; SOD, superoxide dismutase; α-synuclein, alpha-synuclein

(ERK) signaling (Son et al. 2011). Interestingly, estrogen and ER play a role in suppressing various tumors, including melanoma. AC has demonstrated estrogenic activity, promoted apoptosis, and inhibited melanoma progression and inflammation through modulating the (ERβ)-rat sarcoma protein (Ras)/rapidly accelerated fibrosarcoma 1 protein (Raf1)/STAT3 signaling axis (Wu et al. 2021a, b, c).

Role of AC in neurological disorders

Studies have shown that AC possesses diverse pharmacological effects, including antiallergic, anti-inflammatory, and antiproliferative properties. More recently, research has highlighted its potential neuroprotective activities, suggesting its therapeutic value in conditions involving neurological damage and inflammation as Alzheimer's disease, Parkinson's disease, epilepsy, stroke, spinal cord injury, depression, and multiple sclerosis (Fig. 3).

Alzheimer's disease (AD)

Alzheimer's disease (AD) is characterized by the abnormal accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles of tau protein (Lanctôt et al. 2024). These pathological structures disrupt neural communication and trigger neuroinflammatory responses, leading to progressive neuronal damage and cognitive decline (Gao et al. 2024a, b; Hindam et al. 2024; Huang et al. 2024a, b). AC exhibits multifaceted neuroprotective effects (Chen et al. 2021) in AD through its potent antioxidant activity, reduction of amyloid-β toxicity (Shiao et al. 2017), anti-inflammatory properties (Xia et al. 2018a, b), and enhancement of mitochondrial function. It also supports cognitive function by modulating signaling pathways such as PI3K/Akt (Xiao et al. 2022), Nrf2/HO-1 (Han et al. 2024a, b), and NF-κB-p65 (Li et al. 2021), which are involved in neuronal survival and oxidative stress responses.

In 2023, a study by Li et al. reported that AC treatment reduced Aβ deposition in the serum, cortex and hippocampus of APP/PS1 mice, along with diminishing the levels of hyperphosphorylated tau. Also, AC showed beneficial effects of AD-associated anxious behaviors and cognitive impairment assessed by open field, Y maze, and novel object recognition tests in the same study. The insulin signaling pathway and glucose metabolism process are contemplated to contribute significantly to the pathological presentation of AD (Hindam et al. 2020). A study by Chen et al. (2021) showed that AC diminished the learning and cognitive impairment induced by intracerebroventricular (ICV) injection of streptozotozin (STZ) in rodents to induce AD like symptoms. AC increased the levels of glucose, insulin, and the protein expression of glucose transporters (Glu T1, Glu T3, and Glu T4) in the hippocampus, all of which

are necessary for preserving healthy learning and memory function. Furthermore, long-term oral treatment of AC augmented the ATP/ADP ratio, which in turn diminished the quantity of reactive oxygen species (ROS) and enhanced the cellular oxidative stress response. In 2020, a group of Chinese investigators conducted a study exploring the combined effects of echinacoside and AC in a rat model of osteoporosis concurrent with AD (Chen et al. 2020). The study confirmed that AC significantly improved learning and memory abilities and provided neuroprotective effects in the rat model. These findings suggest that AC may help preserve cognitive function and protect neurons in conditions where AD and osteoporosis co-occur. In 2021, this research group conducted another study utilizing the AlCl3-induced AD model in zebrafish larvae to determine the therapeutic potential of AC in AD (Li et al. 2021). This study demonstrated that AC could alleviate $AlCl_3$-induced dyskinesia and restore cholinergic system balance in zebrafish models. Additionally, AC exhibited strong anti-inflammatory effects in LPS-induced BV-2 microglial cells, highlighting its potential to reduce neuroinflammation alongside its neuroprotective properties.

Parkinson's disease (PD)

Parkinson's disease (PD) stands as the second most prevalent neurological disorder after AD among the elderly (Marras and Tanner 2004). PD is marked by the progressive degeneration of dopaminergic neurons in the substantia nigra (SN) (Morris et al. 2024). This loss of dopaminergic neurons is a primary pathological feature of PD and is strongly associated with abnormal α-synuclein expression, which contributes to dopaminergic neuronal cell loss (Höglinger et al. 2024). When α-synuclein clumps together in the neurons, it triggers harmful processes, including the increase of caspase-3 that promotes cell death (Bloem et al. 2021). A study by Yuan et al. (2016) highlighted the potential neuroprotective effect of AC in PD. Oral administration of AC in rotenone-induced PD rat models resulted in a significant decrease in the expressions of both α-synuclein and caspase-3, while also elevating the expression of MAP2, a protein essential for neuronal structure and survival, in the SN. These molecular changes suggest that AC may counteract the neurodegenerative processes characteristic of PD, potentially through downregulating apoptotic pathways and promoting cell survival signaling in the SN. Consequently, AC's modulation of α-synuclein, caspase-3, and MAP2 could underlie its neuroprotective effects, positioning it as a promising therapeutic candidate for alleviating PD symptoms. In 2021, another study by Aimaiti et al. (2021) also highlighted that AC has both therapeutic and preventative benefits on PD via inhibiting apoptosis in the rotenone-induced model of PD and reducing the levels of Pro-Caspase-3 and Cleaved-Caspase-3 protein expression. The study also showed that AC partially controls the expression levels of MAPK1, MAPK8, and MAPK14 to provide neuroprotective effects in PD models. A study by Han et al. (2024a; b) highlighted the pivotal role of ferroptosis in PD. Ferroptosis differs from apoptosis, necroptosis, and necrosis, ferroptosis is a special form of programmed cell death that is characterized by iron dependence, elevated polyunsaturated fatty acid peroxidation, and disruption of the glutathione system. AC was found to provide protective effects through the regulation of the Nrf2-mitophagy pathway, preservation of mitochondrial homeostasis, inhibition of ROS, and mitigation of lipid peroxide accumulation. A recent work of Zhang et al. has proposed similar effects, where activation of the Nrf2/HO-1/GPX4 pathway by AC was responsible for the inhibition of the erastin-induced ferroptosis in MN9D cells (Zhang and Yang 2025).

Epilepsy

Epilepsy is a multifaceted disorder with a wide range of clinical manifestations, making it unlikely to be driven by a single underlying mechanism (Anwar et al. 2020; Balestrini et al. 2021). The fundamental process of epileptogenesis arises from an imbalance between excitatory neurotransmitters, such as glutamate, and inhibitory neurotransmitters, such as gamma-aminobutyric acid (GABA), within the brain. Currently, various synthetic classes of antiepileptic drugs are available for treating epilepsy; however, long-term use of these medications often leads to significant side effects. This limitation highlights an urgent need for developing safer, more effective drugs for epilepsy management. In 2019, Viswanatha et al. (2020) conducted a study in which the methanolic root extracts of *Colebrookea oppositifolia* Smith was subjected to an anticonvulsant activity-guided isolation process, leading to the identification of AC as a potent anticonvulsant compound (Viswanatha et al. 2019). In 2020, the same group of researchers conducted another study that aimed to evaluate the anticonvulsant effects of AC and investigate its underlying mechanisms. AC was tested in maximal electroshock (MES), pentylenetetrazole (PTZ)-induced convulsions, and NMDA-induced mortality models in mice. AC demonstrated significant anticonvulsant activity in the PTZ model, with no effect in the MES and NMDA models. In PTZ-treated animals, AC restored altered levels of GABA, glutamate, and antioxidant markers in the cortex and hippocampus, suggesting a GABAergic mechanism for its anticonvulsant action. Additionally, AC did not cause motor incoordination or locomotor deficits, indicating a lack of central side effects.

Stroke

Stroke is considered the second leading cause of mortality worldwide (Prust et al. 2024). It is a prevalent neurological disorder classified either as ischemic or hemorrhagic (Maida et al. 2024). Ischemic stroke accounts for 80% of all stroke cases (Xu et al. 2024a). Following the promising results of AC as an antiepileptic agent in the 2020 study previously performed (Viswanatha et al. 2020). Viswanatha et al. (2021) conducted further research to evaluate the anti-stroke potential of AC. In this study, ischemia–reperfusion (I/R) brain injury was induced in Wistar rats to evaluate the anti-stroke effects of AC. I/R injury led to significant impairments in neurological, motor, and cognitive functions, increased brain volume and infarct size, elevated levels of MDA, TNF-α, IL-6, ICAM-1, HIF-1α, VEGF, and NF-κB, and reduced levels of SOD, catalase, GSH, and IL-10. Histological analysis revealed marked vascular changes, neutrophil infiltration, cerebral edema, and neuronal necrosis. Notably, AC prevented the functional deficits and reversed the morphological, biochemical, histological, and gene expression changes induced by I/R injury. Another study by Liao et al. (2024) investigated the protective mechanisms of AC against blood–brain barrier (BBB) damage utilizing a rat middle cerebral artery occlusion (MCAO) model. The results showed that AC reduced cerebral infarct size, improved neurological scores, and modulated the release of inflammatory factors. RNA sequencing and molecular docking studies suggested that AC's protective effects operate via the HMGB1/TLR4/NLRP3 pathway. Additionally, Western blotting and immunofluorescence confirmed that ACT preserved BBB integrity by stabilizing tight junction proteins. Similarly, a study by Xia et al. (2018a; b) utilized the same model to assess the effect of AC on I/R injury. Administration of AC reduced oxidative stress shown by lower ROS and MDA levels, alongside increased SOD and catalase levels. Additionally, AC modulated apoptosis-related proteins by downregulating cleaved caspase-3 proteins and upregulating Bcl-2 protein. A study by Wu et al. (2021a, b, c) utilized the MCAO model to explore how AC protected cells from oxygen–glucose deprivation/reoxygenation-induced injury and its underlying mechanisms. The study identified key target genes (CCL2, CXCL10, and ICAM1) that are elevated in ischemic rats and injured cells and found that AC reduced their expression. AC also promoted cell growth and reduced apoptosis. The effects of AC were further enhanced when combined with IL-10. Treatment with AC, IL-10, or both increased p-Stat3 levels, suggesting that AC exerts its protective effects through the IL-10/Stat3 signaling pathway. A recent study showed that 2-acetylacteoside improved nerve function by promoting neurogenesis in both living organisms and laboratory-grown cells (Wang et al. 2024). It showed effect through the PI3K/Akt signaling pathway activation, as shown by RNA sequencing. 2-Acetylacteoside boosted the growth and development of neural stem cells (NSCs) after oxygen–glucose deprivation/reoxygenation.

Spinal cord injury (SCI)

Spinal cord injury (SCI) is a serious condition affecting numerous patients annually, often resulting in paraplegia or quadriplegia (Patek and Stewart 2023). One of the major challenges in spinal cord injury is the failure of axons to regrow and reconnect with their target sites (Tohda 2025). A study showed that induction of SCI in mice by applying vascular clips to the dura following a four-level laminectomy at the T5–T8 vertebrae caused severe damage, including edema, tissue injury, increased apoptosis, and inflammation (Genovese et al. 2010). Treatment with AC significantly reduced these effects. AC lowered the expression of inflammatory markers such as nitrotyrosine, iNOS, poly (ADP-ribose), TNF-α, and IL-1β. It also reduced neutrophil infiltration (myeloperoxidase activity), NF-κB activation, and apoptosis-related proteins (Bax and Bcl-2), demonstrating its anti-inflammatory and protective effects in SCI. Another study showed that AC stimulated skeletal muscle cells to secrete axonal growth factors and promoted their proliferation (Kodani et al. 2019). Injecting AC into mice with chronic SCI improved muscle mass and motor function. The study also identified pyruvate kinase isoform M2 (PKM2) as a key factor secreted by muscle cells in response to AC. PKM2 boosted muscle cell growth and axonal development in neurons and also crossed the blood–brain barrier. Another recent study showed that after 28 days of AC treatment in rats with SCI, rats showed improved locomotor activity (Ning et al. 2024). AC boosted proteins promoting neuronal repair (MAP1LC3A, MAP-2) and reduced GFAP levels, indicating less glial scarring. It also balanced apoptosis by lowering harmful proteins (Bax, Caspase-3) and increasing protective ones (Bcl-2). Inflammatory markers (iNOS, TNF-α, IL-1β) and oxidative stress indicators (ROS, MDA) decreased, while antioxidant proteins (Nrf2, Keap-1) increased.

Depression

Depression is a prevalent mental health disorder that significantly impairs psychosocial functioning and diminishes overall quality of life (Oikonomou et al. 2024). It is a multifaceted mental health condition influenced by a combination of genetic, psychological, biochemical, and environmental

factors (Aljabali et al. 2024). A study by López-Rodríguez et al. (2019) demonstrated significant antidepressant activity of AC in a study evaluating its effects in stressed mice. The research utilized a cold restraint stress (CRS)-induced gastric ulcer model alongside behavioral assessments like the tail suspension test and forced swim test to investigate both gastroprotective and antidepressant properties. AC effectively mitigated stress-induced gastric damage while also exhibiting notable antidepressant effects, highlighting its potential as a dual-function therapeutic agent. In 2022, AC exhibited notable antidepressant-like effects in a study by Gomes et al. (2022) evaluating its impact on LPS-induced depressive-like behavior in mice. In the pretreatment protocol, mice received AC before LPS administration, while the posttreatment protocol assessed its therapeutic potential by administering AC after LPS exposure. Behavioral assessments using the open-field test and tail suspension test revealed a reduction in immobility time, indicating an antidepressant-like effect. AC also reduced hippocampal IL-6 levels and increased cortical GSH levels, showcasing its anti-inflammatory and antioxidant properties, which may contribute to its antidepressant activity. A recent study investigated the antidepressant effects of AC through gut-brain communication and explored its involvement in the gut-microbiota-brain axis (GMBA) (Mao et al. 2024). Using a chronic stress-induced depression model, AC improved depression-like behaviors, synaptic damage, and neuronal health. Gut microbiota composition analysis and fecal microbiota transplantation (FMT) confirmed that AC alleviated gut dysbiosis, reduced gut and brain inflammation, and restored neurotransmitter and brain–gut peptide levels in the prefrontal cortex. Additionally, AC demonstrated neuroprotective effects in corticosterone-induced nerve injury models by reversing cytotoxicity. Key gut microbiota, including *Lactobacillus*, *Parabacteroides*, *Bifidobacterium*, and *Ruminococcus*, were identified as contributors to AC's antidepressant effects via the GMBA, highlighting its potential for treating depression by targeting gut–brain communication.

Multiple sclerosis (MS)

Multiple sclerosis (MS) is a chronic autoimmune disease of the CNS, marked by inflammation, demyelination, axonal injury, and neuronal damage. Affecting over 2.5 million people globally, MS leads to progressive neurological deficits. Experimental autoimmune encephalomyelitis (EAE) is a widely used animal model that replicates many features of MS. A recent study demonstrated the therapeutic effects of AC in EAE mice (Li et al. 2020). AC treatment significantly reduced neurological deficit scores and delayed disease onset. It mitigated inflammation and demyelination by inhibiting the activation and CNS infiltration of CD4+ T cells and CD11b+ microglia/macrophages. Additionally, AC reduced oxidative stress by scavenging ONOO−, decreasing iNOS and NADPH oxidase expression, and protecting against mitochondrial damage and neuronal apoptosis.

Role of AC in cardiovascular diseases

AC has attracted attention in cardiovascular research due to its potent antioxidant, anti-inflammatory, and vasorelaxant properties. These effects contribute to its potential in mitigating key mechanisms underlying cardiovascular diseases (CVDs), such as oxidative stress, endothelial dysfunction, and inflammation. Furthermore, Ac may improve vascular tone by modulating calcium signaling pathways, offering therapeutic promise for conditions like hypertension, atherosclerosis, and heart failure (Morikawa et al. 2019).

Hypertension

Hypertension is a chronic medical condition where the pressure of the blood against the walls of the arteries is consistently elevated. It is characterized by a sustained systolic blood pressure (SBP) of 130 mmHg or higher, or a diastolic blood pressure (DBP) of 80 mmHg or higher. It significantly raises the risk of cardiovascular events, including coronary heart disease, heart failure, stroke, and mortality (Carey et al. 2022). AC has shown potential in reducing blood pressure through several mechanisms. Firstly, it exhibits strong antioxidant activity by scavenging free radicals and reducing oxidative stress. Oxidative stress plays a key role in endothelial dysfunction, a major contributor to hypertension. By protecting endothelial cells and improving vascular function, AC can enhance vasodilation and reduce blood pressure (Luhata and Usuki 2022). Secondly, AC has demonstrated anti-inflammatory properties by modulating pro-inflammatory cytokines such as IL-6 and TNF-α. This reduces vascular inflammation, which can improve arterial stiffness and lower blood pressure (Saha et al. 2024). Moreover, AC has been shown to inhibit ACE activity in a dose-dependent manner, with an IC50 of 365 μM (Oh et al. 2003). IT also helps to reduce hypertension in spontaneously hypertensive rats by suppressing ACE expression (Tong et al. 2019). In a previous study, AC demonstrated antihypertensive effects by reducing both SBP and DBP in spontaneously hypertensive rats (Chao-Hsiang et al. 2012). In addition**,** pharmacological testing revealed that AC caused a dose-dependent reduction in systolic, diastolic, and mean arterial blood pressure in pentothal-anesthetized normotensive rats (Ahmad et al. 1995). While promising results is established, AC is not yet a mainstream treatment for hypertension. It is primarily investigated in preclinical settings. Its use could be considered

as part of nutraceutical or complementary therapies, particularly in patients with oxidative stress and inflammation-driven hypertension.

Coronary artery disease (CAD)

Coronary artery disease (CAD), also known as ischemic heart disease, is a condition where the coronary arteries, which supply oxygen-rich blood to the heart muscle, become narrowed or blocked. This is primarily caused by atherosclerosis, a process involving the buildup of fatty plaques on the arterial walls. CAD is one of the leading causes of death worldwide (Malakar et al. 2019).

Oxidative stress and inflammation are key contributors to the pathophysiology of CAD, including atherosclerosis and ischemic damage (Pashkow 2011). AC's potent antioxidant properties help neutralize reactive oxygen species, thereby reducing oxidative damage to vascular endothelial cells (Chiou et al. 2004). Additionally, its anti-inflammatory effects modulate cytokine activity and inhibit inflammatory pathways, which are critical in preventing plaque formation and progression. AC's anti-inflammatory properties were expanded on by a study, which demonstrates that AC decreased the levels of the pro-inflammatory cytokines, TNF-α, IL-1β, and IL-6 (Jing et al. 2015). Furthermore, AC exhibits a mild inhibitory effect on platelet aggregation in vitro, regardless of whether aggregation is induced by adenosine diphosphate or arachidonic acid (Campo et al. 2012).

Pretreatment with AC improved pain and myocardial pathological changes induced by ischemia–reperfusion injury. Via antioxidant mechanisms, AC could inhibit apoptosis and increase the expressions of PI3K and p-Akt in rat myocardial tissue (Li et al. 2025a, b).

High-fat diet (HFD)-induced dyslipidemia is a major contributor to the development of atherosclerosis. AC has demonstrated protective effects against HFD-induced atherosclerosis, as evidenced by the reduction in serum levels of inflammatory cytokines, improvement in lipid profiles, and normalization of organ coefficients in rats. These protective effects may be mediated through the modulation of the AMPK/mTOR signaling pathway (Fan and Zhang 2021). Other mechanisms include upregulation of ABCG1, LDL-R, LXRα, PPARγ and downregulation of SREBP-1 expression, all inhibiting cholesterol synthesis and accumulation (Khound et al. 2025). In addition, AC's potential to mitigate ischemia–reperfusion injury has been demonstrated in experimental studies, highlighting its utility in acute settings such as myocardial infarction (Yu et al. 2016). Furthermore, AC has been shown to exert vasorelaxant effects against noradrenaline (NA)-induced contractions in a time- and concentration-dependent manner, without affecting high K+-induced contractions. This suggests that hydroxyphenethyl glycosides, like AC, mediate vasorelaxation by inhibiting receptor-operated calcium channels rather than voltage-dependent calcium channels (Morikawa et al. 2019).

Congestive heart failure (CHF)

Congestive heart failure (CHF) is a chronic condition where the heart's ability to pump blood effectively is impaired. This results in insufficient oxygen and nutrient delivery to the body's tissues. CHF often arises from underlying conditions like coronary artery disease, hypertension, or myocardial infarction, which weaken or stiffen the heart muscle (Francis and Tang 2003).

AC has demonstrated potential benefits relevant to heart failure treatment, primarily due to its potent antioxidant and anti-inflammatory properties. It reduces oxidative stress by promoting pathways like Nrf2/HO-1 (Sciandra et al. 2023). It also enhances mitochondrial spare respiratory capacity, crucial for energy production. Therefore, improved mitochondrial function can lead to better cardiac efficiency and reduced symptoms of heart failure (Sciandra et al. 2023). These mechanisms may mitigate cardiac damage and improve overall cardiovascular health, which is beneficial in heart failure contexts. Natural products like AC are noted for their mild efficacy and low toxicity, making them suitable for long-term use in heart failure management. They may restore cardiac function and improve quality of life by addressing multiple pathophysiological mechanisms involved in heart failure (Chen et al. 2024).

Cardiomyopathy

Septic cardiomyopathy is a frequent complication of sepsis, characterized by ventricular dilation and reduced contractility. In LPS-induced sepsis, AC significantly improves cardiac function by reducing inflammation and oxidative stress. AC specifically enhances mitochondrial biogenesis, restores sepsis-induced mitochondrial alterations, and prevents apoptosis in cardiomyocytes (Zhu et al. 2022).

Role of AC in diabetes

Diabetes mellitus (DM) is a complex, chronic, fast growing metabolic disorder and, according to the International Diabetes Federation (IDF), it is estimated that 642 million people by 2040 will have diabetes (Ogurtsova et al. 2017). Several studies have pointed to the effective role of AC in controlling DM pathogenesis as well as preventing diabetic complications.

Hyperglycemia and insulin resistance.

The potential antihyperglycemic effect of AC was previously reported in several studies using plant extracts containing AC in experimental diabetic models. Xiong et al. (2013) have examined the effects of *Cistanche tubulosa*, a traditional Chinese medicine containing AC as a principal constituent, on hyperglycemia in db/db mice model of type 2 DM, which exhibits various characteristics of DM including hyperglycemia, insulin resistance, and obesity (Uchida et al. 2005; Srinivasan and Ramarao 2007). The results of this experiment have demonstrated that *Cistanche tubulosa* could effectively decrease both the elevated fasting and postprandial blood glucose levels in a dose-dependent manner. In addition, it could increase insulin sensitivity of db/db mice by restoring deficient insulin secretion when used in high dose, an effect which contributed to its antihyperglycemic activity.

Moreover, the potential hypoglycemic property of AC has been demonstrated in a study conducted by Morikawa et al. (2014), where AC could inhibit the elevated postprandial blood glucose levels in starch-loaded mice with significant improvement of glucose tolerance without significant food intake or body weight changes.

Furthermore, the antidiabetic effect of AC isolated from *Jacaranda mimosifolia* leaves in streptozotocin–nicotinamide (STZ–NA) diabetic rat model have been studied by El-Marasy et al. (2020). This model is considered a well-accepted experimental diabetic model for the screening of potential antidiabetic agents (Szkudelski 2012). In this study, AC effects were compared to that of pioglitazone, an insulin sensitizer acting by activation of peroxisome proliferator-activated receptor gamma (PPARγ). AC has shown significant antidiabetic and antioxidant properties comparable to pioglitazone, where it could significantly decrease serum glucose, as well as HbA1c of the diabetic rats. HbA1c is considered a reliable monitoring factor of glycemic control in diabetes (Monnier and Colette 2009). These favorable effects of AC on glycemic control were explained by its ability to scavenge STZ-produced free radicals with enhancement of both beta cell function and insulin levels as well as sensitivity. Besides, AC improved body weight of diabetic rats, an effect that could be explained by it antihyperglycemic activity, as well as pancreatic lipase inhibitory effect (Han et al. 2001).

The effects of total glycosides of *Cistanche tubulosa* (TGCT) in diet/STZ-induced diabetic rats were investigated by Zhu et al. (2021). This study attributed the antidiabetic effect of TGCT to their antioxidant and anti-inflammatory properties. TGCT could reduce the level of inflammatory cytokines, TNF-α, IL-6 and IL-1β, which are known to interfere with the insulin receptor signaling pathway, and thus lead to IR. Since inflammatory pathways are well recognized to be involved in the pathogenesis of DM (Tsalamandris et al. 2019), the anti-inflammatory effects of TGCT may be another antidiabetic mechanism (Zhu et al. 2021).

Another effective approach by which AC can control blood glucose concentrations in DM is its inhibitory effect on α-amylase activity reported by Lu et al. (2017). α-Amylase is known to be a key factor regulating carbohydrates digestion and glucose absorption. Therefore, decreasing glucose absorption rate mediated by AC contributes to its antidiabetic effect.

Moreover, in a study conducted by Shimada et al. (2017), AC has displayed a potent inhibitory effect on sodium-dependent glucose cotransporter 1 (SGLT1)-mediated glucose uptake by human enterocytes. Since SGLT1 is responsible for transportation of both glucose and galactose into enterocytes, its inhibition by AC represents additional mechanism by which AC can reduce dietary glucose absorption.

Advanced glycation end products (AGEs)

Persistent hyperglycemic state in DM could result in non-enzymatic glycation reaction of proteins and lipids and nucleic acid leading to the generation of advanced glycated end products (AGEs), which induce insulin resistance (Ottum and Mistry 2015) and have a vital role in the pathophysiology of diabetic complications (Khalid et al. 2022). Liu et al. (2013) have demonstrated that AC inhibited protein glycation in vitro, an effect that is usually associated with antidiabetic drugs, and this anti-protein glycation activity could be, in part, attributed to the antioxidant properties of its constituents; caffeic acid and 3,4-dihydroxyphenylethanol.

Hyperlipidemia and hepatocellular change

The liver is considered to be one of the most affected organs by changes in insulin levels or action occurring in DM. Since DM can result in increased hepatic glucose production, as well as lipid metabolism changes, it could result in an inflammatory environment, leading to the development of fatty liver (El-Marasy et al. 2020).

El-Marasy et al. (2020) have demonstrated that treatment of STZ–NA diabetic rats with AC showed significant reduction of total cholesterol and triglyceride (TG) levels. In addition, AC could ameliorate hepatic lipid peroxidation and successfully inibit hepatic histopathological damage induced by STZ–NA in those diabetic rats.

The lipid-lowering effects of AC in this study were explained by its antidiabetic potential. In addition, AC was

reported to target PPAR-α receptors which contributes to its antihyperlipidemic potential (Rigano et al. 2017) and/or Nrf2/HO-1 pathway (Hao et al. 2025), as well as anti-inflammatory effect (Esposito et al. 2010)**.** The hepatoprotective effect of AC was previously reported in diethyl nitrosamine-induced carcinogenesis experimental rat model (Peerzada et al. 2016).

B-Cell function

Oxidative stress and inflammation are considered the primary causes of β-cell dysfunction that occurs in T2D (Leibowitz et al. 2011; Gothai et al. 2016). β-Cells are considered very vulnerable to the effects of oxidative stress due to shortage of scavenger enzymes (Gerber and Rutter 2017), which results in the decline in the production of insulin and cytokines by β-cells, leading to inflammation and apoptosis (Galli et al. 2020).

Galli et al. (2020) conducted an experiment using clonal and human β-cells to examine the effect of AC on β-cells under basal and stress conditions. The results of the experiment have revealed that AC could protect β-cells against oxidative stress and inflammation, resulting in β-cell viability elevation, as well as increased insulin content in a dose-dependent manner. In this study, AC antioxidant effects were found to follow indirect pathways through the upregulation of gene transcription of some antioxidant enzymes. As they could detect SOD1 expression elevation along with significant ROS decline in AC- treated cells. In addition, AC could downregulate NF-κB inflammatory pathway in β-cells which represents the key inflammatory pathway that leads to in β-cell death by its sustained activation.

Diabetic neuropathy

Diabetic patients, suffering from diabetic neuropathy, usually feel painful sensations such as paresthesia, hyperalgesia, and allodynia (Jensen and Finnerup 2014). Czerwińska et al. (2018) have investigated the beneficial effects of aqueous extract of *Ligustrum vulgare* leaves, which contain AC as one of its active ingredients, against hyperalgesia and allodynia in (STZ)-induced diabetic rat model. The results of this study verified that administration of this extract was more effective than tramadol in controlling diabetic neuropathic pain. This attenuation of neuropathic pain occurs in a dose-dependent manner.

Neurotoxicity in diabetes may rise from the imbalance between hyperglycemia-induced ROS and endogenous antioxidants. Therefore, enhancement of antioxidant enzyme activity could explain the favorable effect of *Ligustrum vulgare* leaf extract in diabetic neuropathy (Czerwińska et al. 2018)**.**

Diabetic kidney disease (DKD)

Diabetic kidney disease (DKD) is one of the most overwhelming consequences of DM. Chronic hyperglycemia in DM can result in numerous cellular dysfunctions in the kidney (Zhang et al. 2024a, b), resulting in diabetic nephropathy (DN) which is regarded as the most common complication of DM (Gao et al. 2024a, b; Zhou et al. 2024) and a leading cause of end-stage renal disease (ESRD) (Xuan et al. 2021; Sawaf et al. 2022; Chen et al. 2023; Gao et al. 2024a, b). Notably, the pathogenesis of DKD is complicated and it may include several interacting factors (Zhang et al. 2024a, b). AC has been reported to have nephroprotective effects by acting against many aspects of DKD pathogenesis and progression. Zhang et al. have demonstrated, using network pharmacology analysis and experimental nephrectomy/STZ rat model that application of AC could delay the progression of DKD due to its antioxidant, anti-inflammatory, and antifibrotic properties. Furthermore, this study has also demonstrated that AC had a significant protective effect on DKD- induced podocyte damage by decreasing the levels of 24-urinary total proteins in rats, along with downregulating desmin protein expression, an indicator of the degree of podocyte injury, and upregulating nephrin protein expression, a marker of podocyte integrity. Podocyte injury is known to be one of the key factors in the progression of DKD and proteinuria (Chen et al. 2019) and it is characterized by the restructuring of the cytoskeleton with significant elevation in the expression of desmin protein (Zhang et al. 2024a, b). AC was also reported to delay DKD by decreasing urinary albumin and inhibiting podocytes apoptosis in db/db mice in a study by Li et al. (2023), where AC could block AKT/GSK-3β signaling pathway, which has a key role in podocyte apoptosis and has shown to be significantly elevated in the kidney tissue of db/db mice.

Moreover, in a study conducted by Bai et al. (2021), AC could successfully protect kidney function by alleviating podocyte injury both in vitro and in vivo in AGE-induced podocyte injury and STZ-induced diabetes rat model, respectively. In this study, AC exerted its protective effect by affecting peroxisome PPAR/β-catenin signaling pathway, which is reported to be involved in podocyte injury in DKD patients (Zhou et al. 2017; Pattarayan et al. 2018). AC could restore PPAR levels, inhibit the activation of β-catenin signaling, and reduce the apoptosis of AGEs-treated cells.

Furthermore, in a study designed by Wang et al. (2021a, b) in diabetic db/db mice and high glucose-induced HK-2 cells, AC could improve early renal damage induced by DM through regulating TGF-β/Smad signaling pathway,

which is implicated in regulating renal fibrosis in chronic kidney disease (Wang et al. 2016; Trionfini and Benigni 2017). Recently, molecular docking studies have highlighted SGLT2 inhibition as responsible for the renoprotective effects of AC. Via activating AMPK and suppressing pro-inflammatory cytokines (IL-6 and TNF-α), AC can ameliorate renal inflammation and fibrosis induced by high glucose in HK-2 cells (Ahmed et al. 2025). Chen et al. (2023) have pointed to the role of AC in DKD by downregulating NR4A1 and affecting the LKB1/AMPK pathway in diabetic db/db mice. NR4A1 is a member of the nuclear orphan receptor superfamily (NR4A), which can control numerous cellular activities, and affect metabolism, inflammation, as well as apoptosis (Pearen and Muscat 2010). In addition, Gao et al. (2024a, b) reported that AC could restore the disrupted amino acid metabolism in the kidney of *db/db* mice, where these metabolites might be suitable for the detection of the renal damage in DN.

The ultimate pathological renal alteration in kidney disease is renal fibrosis (Zeng et al. 2019), which is considered as a critical factor indicating the progression of DN to kidney failure (Calle and Hotter 2020). As mentioned before, AC could delay renal interstitial fibrosis in DN rats through its antioxidant properties (Wang et al. 2021a; b; Zhou et al. 2024). In addition, in AGE-treated podocytes, AC could downregulate miR-27a, an endogenous single-stranded RNA which reflects the degree of renal interstitial fibrosis in DKD (Bai et al. 2021).

Role of AC in pulmonary disorders

AC, a phenylethanoid glycoside, exhibits antioxidant, anti-inflammatory, and anti-apoptotic properties, making it a promising therapeutic agent for pulmonary disorders. Recent studies highlight its potential role in acute lung injury (ALI), asthma, pulmonary fibrosis (PF), antimicrobial resistance, and viral infections. The following summarizes the key findings on AC's protective mechanisms and therapeutic potential against lung diseases.

AC in acute lung injury (ALI)

ALI is a severe inflammatory lung condition characterized by increased vascular permeability, neutrophil infiltration, and excessive cytokine release, leading to pulmonary edema and respiratory distress. Studies demonstrate AC's protective effects through its ability to attenuate inflammation, oxidative stress, and apoptosis. AC demonstrated significant protective effects across various ALI models, confirming its efficacy against multiple etiological triggers of ALI. AC showed efficacy against lipopolysaccharide (LPS)-induced ALI. in in vivo model of BalB/c mice, AC reduced lung wet-to-dry weight ratio, myeloperoxidase (MPO) activity, and inflammatory cytokines (TNF-α, IL-1β, IL-6) in bronchoalveolar lavage fluid (BALF). Also, AC reverted LPS-induced inflammation in A549 cells by lowering the phosphorylation of IκBα, nuclear factor-κB (NF-κB) p65, inhibitor of nuclear factor kappa-B kinase-α (IKK-α) and inhibitor of nuclear factor kappa-B kinase-β (IKKβ).

Additionally, AC enhanced superoxide dismutase (SOD) activity and inhibited NF-κB pathway activation, preventing lung histopathological damage (Jing et al. 2015). On the other hand, AC showed comparable efficacy against TNF-α-induced ALI. In in vitro model of TNF-induced ALI in A549 cells, AC dose-dependently mitigated oxidative stress by upregulating Nrf2 signaling and inhibiting NF-κB phosphorylation. Moreover, AC attenuated apoptosis-related genes (caspase 3, caspase 8, and caspase 9) which underscores the genetic influence of AC. This influence was also noted in antioxidative character by enhancing mRNA levels of antioxidative enzymes NADPH quinone oxidoreductase (NQO1), glutamate cysteine ligase catalytic subunit (GCLC), heme oxygenase (HO-1). This led to reduced IL-1β, IL-6, and IL-8 production and ROS generation, highlighting its role in modulating oxidative–inflammatory cross talk (Zheng et al. 2021).

One of the ALI inducers is cobra venom factor (CVF) through complement activation. Injection of CVF triggers a systemic complement activation that induces acute inflammation response, followed by changes in lung function and morphology. This is characterized by enhanced permeability between pulmonary capillary endothelial cells and alveolar epithelial cells. This hallmark was characterized by the accumulation of a large edematous fluid in the alveolar space, dominated by neutrophils and inflammatory cells (Long et al. 2022). In in vitro and in vivo studies, AC suppressed the vascular endothelial injury induced by complement noted by lowered adhesion molecules (ICAM-1, VCAM-1), and NF-κB transcriptional activity, significantly reducing leukocyte infiltration, as well BALF protein content, and pulmonary MPO activity (Guo et al. 2022a; b). Mechanistically, AC exerts its anti-inflammatory effects by inhibiting crucial regulators of cytokine production and immune cell activation, viz., NF-κB and JAK/STAT pathways (Qiao et al. 2019; Guo et al. 2022a, b). Additionally, AC enhances Nrf2 signaling, promoting the expression of antioxidative enzymes (HO-1, NQO1, GCLC) and mitigating oxidative damage (Zheng et al. 2021). This study was the first to demonstrate AC's efficacy against complement-mediated ALI, suggesting its therapeutic relevance in immune-mediated lung injury.

AC in asthma and airway hyperresponsiveness

Asthma is a chronic inflammatory disorder characterized by airway hyperresponsiveness, remodeling, and immune dysregulation. In animal models, AC showed promising efficacy as bronchodilator through alleviating airway resistance, besides minimizing the immune and allergic components in asthma. Studies highlight AC's potential in lowering the inflammatory milieu, oxidative stress, and airway remodeling.

Anti-asthmatic effects in ovalbumin (OVA)-induced asthma models

The anti-asthmatic and bronchodilatory effects of AC were demonstrated in an ovalbumin (OVA)-sensitized murine asthma model. First in aerosolized ovalbumin (OA) challenge in the OA-sensitized guinea pigs, AC significantly reduced specific airway resistance (sRaw) during both the immediate-phase response (IAR) and late-phase response (LAR), similar to conventional anti-asthmatic drugs (Lee et al. 2011). The reduction in airway resistance has been attributed to the modulation of cellular and chemical mediators at the molecular level. At different dose levels, AC abrogated the recruitment of neurtophils, eosinophils, as well histamine content and phospholipase A2 activity in BALF during LAR comparable to dexamethasone and disodium cromoglycate. Jie Cui et al (2023) referred the anti-asthmatic property of AC to its anti-inflammatory and anti-oxidative characters. This was noted in ovalbumin (OVA)-sensitized mice where similar findings to Lee et al. (2011) were recorded. However, Jie Cui et al. (2023) explored the molecular signaling mechanisms of the ROS/NF-κB/MAPK pathway, highlighting its role in suppressing inflammatory cytokines (TNF-α, IL-4, IL-13, IL-33, VEGF, and active TGF-β1), oxidative markers (ROS, NOX4, iNOS), serum IgE levels, and TGF-β1 protein expression in an asthmatic mouse model. Furthermore, AC histologically significantly suppressed goblet cell and airway smooth muscle hyperplasia and collagen deposition. It is concluded that AC may have superior therapeutic efficacy over dexamethasone regarding airway remodeling (Chang et al. 2022; Cui et al. 2023).

Immunomodulatory effects in allergic asthma

In in vitro model using bone marrow-derived dendritic cell (DC) and in allergic asthma animal model, AC showed anti-allergic action through aryl hydrocarbon receptor (AhR) activation. This activation was abolished by the AhR antagonist. The anti-allergic activity of AC was figured out by suppressed pro-inflammatory cytokines; IL-12, TNF-α while increased IL-10, promoting regulatory T cell (Treg) differentiation. This shift toward immune tolerance significantly alleviated Th2-driven allergic asthma (Chang et al. 2022).

Antifibrotic potential of AC in pulmonary fibrosis (PF)

PF is characterized by irreversible scarring of lung tissue, leading to respiratory failure. AC demonstrates antifibrotic activity by modulating oxidative stress and TGF-β1/Smad signaling. AC inhibited collagen I deposition, Smad2/3 phosphorylation, and MAPK activation (ERK/p38) in both murine and human lung fibroblasts, preventing excessive extracellular matrix deposition (Chen et al. 2022a, b). This action suppressed TGF-β1-induced fibrosis. Also, AC enhanced antioxidant enzyme activity of SOD, HO-1, and catalase, while reducing ROS levels and alleviating oxidative damage-driven fibrosis (Kondeva-Burdina et al. 2023). These findings highlight AC's potential as an antifibrotic agent, possibly offering an alternative to nintedanib and pirfenidone, which exhibit limited efficacy in late-stage PF.

Protective effects of AC against paraquat-induced pulmonary toxicity

Paraquat (PQ) is one of the common herbicides where its prolonged exposure leads to severe oxidative stress, inflammation, and apoptosis that ends up with fatal lung injury. The rationale undergoes the imbalance between oxidative stress and the antioxidant defense system. AC showed preferential restoration of the antioxidant system by enhanced SOD, catalase, and GPx levels, counteracting PQ-induced oxidative stress. Besides oxidative stress correction, AC showed anti-inflammatory influence through reduced IL-6, TNF-α, NF-κB activation, and caspase-3 expression, mitigating PQ-induced pulmonary apoptosis (Khorashadizadeh et al. 2022). These results suggest AC as a potential therapeutic candidate for toxic inhalation-induced lung damage.

In conclusion, AC exhibits multifaceted protective effects against ALI, asthma, pulmonary infections, fibrosis, and viral-induced lung injuries. Its mechanisms involve modulating oxidative stress, inflammatory signaling, apoptosis, and immune regulation. These findings position AC as a promising therapeutic agent for treating a range of pulmonary disorders, warranting further clinical investigation.

Role of AC in skin disorders

As a bioactive natural compound, AC represents an important secondary metabolite found in medicinal plants (Huang et al. 2022). Literature highlights the wound-healing properties of AC and its natural herbal sources (Kanlayavattanakul et al. 2024; Liu et al. 2025a, b). Using in vitro assays, AC was found to enhance activation of the precursor pro-matrix metalloproteinase-2 (proMMP-2) and increase the expression of membrane-type 1 MMP (MT1-MMP) in dermal fibroblasts (Si et al. 2018). MMPs are enzymes that break down extracellular matrix (ECM) components in the skin under both normal and diseased conditions. Initial coordinated ECM proteolysis plays a crucial role in wound healing, keratinocyte and fibroblast migration, and angiogenesis. On the other hand, reductions in MMP-1, -3 (Si et al. 2018) and -9 (Kanlayavattanakul et al. 2024) expression were proposed as contributing to the wound-healing proficiency of AC. Even though MMP-1, -2, and -9 may facilitate the initial migration of keratinocytes into the wound area, sustained elevations of these MMPs appear to hinder wound healing, as the augmented fragility of the basement membrane compromises the reattachment of the new epidermis (Reiss et al. 2010). These findings indicate that AC's regulation of MMP expression varies among different MMP species (Si et al. 2018).

AC can modulate melanogenesis and melanocyte pigmentation (Matos et al. 2022). The microphthalmia-associated transcription factor (MITF) is a potent inducer of melanocyte-specific enzymes (Tachibana 1997). Alpha-melanocyte stimulating hormone (α-MSH), which elevates intracellular cAMP levels, facilitates melanin production by inducing MITF expression (Price et al. 1998). AC has been shown to suppress α-MSH-induced melanin synthesis in murine B16 melanoma cells by reducing adenylyl cyclase activity (Song and Sim 2009). MITF is a transcription factor that directly activates tyrosinase and tyrosine-related proteins (TRPs). Activation of the extracellular signal-regulated kinase (ERK) pathway blocks melanin synthesis through MITF degradation and subsequent downregulation of tyrosinase and TRPs (Kim et al. 2003). In the absence of α-MSH, downregulation of MITF triggered by ERK phosphorylation represents a pivotal event in the AC-mediated anti-melanogenesis (Son et al. 2011).

AC has also shown potent immune-modulating effects in 2,4-dinitrochlorobenzene (DNCB)-induced atopic dermatitis. It could alleviate skin lesions and lessen atopic dermatitis symptoms (Biasibetti et al. 2018; Li et al. 2018). Studies indicated that atopic dermatitis is the cutaneous manifestation of systemic immune dysregulation, a type 2 immune response which is characterized by the predominance of Th2 cells over Th1 cells (Roesner et al. 2016). At the systemic level, AC markedly lowered DNCB-induced IgE and Th2 cytokines in the blood. At the lymphocyte level, it inhibited the upregulation of the costimulatory molecules CD86 and CD54 on the cell surface. Finally, at the lesion level, it reduced pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-4 (Li et al. 2018).

AC, isolated from *Orobanche cernua* Loefling, has also possessed remarkable anti-photo-aging activities (Gao et al. 2021). Espinosa-González et al. (Espinosa-González et al. 2016) reported that AC can inhibit UVB-induced erythema and delay carcinogenesis in SKH-1 mice. Chronic exposure to UV light is consistently linked to oxidative stress and premature skin aging. Prior research indicated that the upregulation of MMPs significantly contributes to UVB-induced ECM breakdown (Van Doren 2015). It appears that AC can suppress MMP-1 expression in cultured human epidermal keratinocytes, an effect that is probably mediated by modulation of MAPK/AP-1 and Iκ-βα/NF-κβ signaling pathways (Gao et al. 2021). On the other hand, AC can significantly enhance the biosynthesis of type I procollagen, an effect that is attributed to the activation of Nrf2 and TGF-β/Smad signaling pathways (Gao et al. 2021).

The protective effects of AC were also noted in the X-ray-radiated human skin fibroblasts. AC could dramatically reduce ROS production, downregulate caspase-3 and Bax expression, and upregulate Bcl-2 expression. Such anti-apoptotic effects were largely due to the suppression of the radiation-boosted ERK and JNK signaling pathways (Yang et al. 2015).

Antimicrobial and antiviral activities of AC

Antibacterial activity

Among the numerous bioactive properties of AC, its antimicrobial and antiviral effects have garnered significant interest. As infectious diseases continue to be a global health concern, natural compounds with antimicrobial potential are being extensively studied for their efficacy and safety (Chang et al. 2022; Xiao et al. 2022). This section explores AC's efficacy against bacterial and viral infections, emphasizing potential mechanisms of action and its relevance as a therapeutic compound.

AC exhibits antibacterial properties against both Gram-positive and Gram-negative bacterial strains. It has demonstrated significant efficacy against *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), as well as *Escherichia coli* and *Pseudomonas aeruginosa*. The compound's minimum inhibitory concentrations (MICs) in various studies indicate strong bacteriostatic and bactericidal activities. Additionally, research suggests that AC is active against multidrug-resistant bacteria, further highlighting its potential as an alternative antimicrobial agent (Bazzaz et al. 2018; Chang et al. 2022).

One of the factors that is essential in determining the pathogeniciy of *Staphayloccous aureus* is sortase A (SrtA) enzyme. SrtA is important for bacterial adherence and evasion of the immune system. In A549 lung cells, AC effectively inhibited sortase A (SrtA), which contributed to reducing MRSA colonization. In vivo efficacy of AC in MRSA-induced pneumonia was tested on C57BL/6J mice. AC protected against MRSA-induced pneumonia, reducing bacterial load and lung inflammation (Li et al. 2024). These findings suggest that AC's antivirulence properties could be complementary to the existing antibiotic therapies, addressing the rising challenge of antibiotic-resistant lung infections.

The antibacterial effects of AC are attributed to several mechanisms:

- **Cell membrane disruption**: AC disrupts bacterial cell membranes by altering their permeability, leading to the leakage of essential intracellular components such as ions, proteins, and nucleotides. This disruption compromises the structural integrity of bacterial cells, ultimately causing cell lysis and death. The loss of these vital components inhibits bacterial growth and replication, significantly reducing the risk of infection persistence (Shi et al. 2022).
- **Biofilm inhibition**: Biofilms are complex bacterial communities that adhere to the surfaces and provide bacteria with protection from antimicrobial agents. AC has been found to prevent biofilm formation by interfering with bacterial adhesion and extracellular matrix production. By disrupting the biofilm integrity, AC increases bacterial susceptibility to antibiotics and host immune responses, making it particularly effective in treating chronic and persistent infections where biofilms play a significant role (Zhang et al. 2022).

Antiviral activity

AC has demonstrated promising antiviral properties against a range of viruses, including herpes simplex virus (HSV), influenza virus, and coronaviruses. Computational and in vitro studies suggest that it may inhibit viral replication by targeting key viral enzymes. Additionally, preliminary studies indicate that AC may exert antiviral activity against emerging viral threats, making it a compound of interest in virology research (Oladosu et al. 2021; Umeoguaju et al. 2021; Wu et al. 2023).

Besides its antimicrobial activity, AC showed potential antiviral activity in respiratory disorders. AC exhibited strong docking affinity for SARS-CoV-2 protease and kinase, inhibiting SARS-CoV-2 replication (Bernardi et al. 2021). Remarkable molecular interactions with Mpro, TMPRSS2, Cath L, RdRp, Sgp, and hACE2 proteins also suggest AC as a potent multi-target anti-SARS-CoV-2 agent (Shode et al. 2025). Another respiratory virus, respiratory syncytial virus (RSV), causes lung tissue damage via enhancing necroptosis and inflammation. In BALB/c mice and A549 cells, AC significantly reduced RSV-induced necroptosis and inflammation by suppressing the HMGB1/NF-κB and RIP1/RIP3/MLKL pathways, preventing lung tissue damage and viral replication (Ling et al. 2022).

The antiviral mechanisms of AC are believed to involve:

- **Enzyme inhibition**: AC targets viral proteases and polymerases, key enzymes required for viral replication and assembly. By inhibiting these enzymes, AC disrupts viral protein processing and genome replication, preventing the virus from completing its life cycle. This effect has been observed in multiple viral families, making AC a promising antiviral agent (Abdallah et al. 2021).
- **Immune modulation**: AC exhibits strong anti-inflammatory and immunomodulatory properties, which can enhance the host's ability to clear viral infections. It has been shown to regulate cytokine production, reducing excessive inflammation while still supporting an effective immune response. This balanced modulation of immune activity helps in controlling viral replication without triggering harmful inflammatory responses that can lead to tissue damage (Song et al. 2016; Muhtar et al. 2024).
- **Reduction of viral load**: AC has been demonstrated to lower viral load in infected tissues by promoting the degradation of viral components within host cells. This effect further limits viral replication and helps in faster recovery from infections (Chathuranga et al. 2019; Shode et al. 2025).

Toxicological data

Previous toxicological research could not reveal any harmful effects of AC in living animals. On the other hand, acteoside might exert varying effects on different cell lines. IC_{50} values ranging between 100 µM and more than 600 µM suggest wide variability in cell line sensitivity and/or in vitro experimental conditions among different studies (Table 1).

Clinical studies

At present, clinical research on AC remains relatively limited. However, several interventional studies have begun to explore its therapeutic potential. As previously noted, AC, a phytoestrogen, has been investigated for its impact on sex hormone levels, antioxidant defenses, and exercise-induced oxidative stress. In a dietary intervention lasting 26 days, female swimmers were given a beverage containing *Lippia citriodora* extract (providing 20 mg/100 mL of AC). The

Table 1 Toxicity data of acteoside tracing acute/chronic effects across models with the therapeutic windows

Study	Type	Acute	Subacute
Etemad et al. (2015)	In vivo study	Male BALB/c Mice (25–30 g) Single i.p. AC injection (1, 2 and 5 g kg^{-1} b.wt) LD_{50}value > 5 g kg^{-1} b.wt. (practically nontoxic)	Male Wistar rats (200–250 g) i.p. AC (10, 30 and 60 mg kg^{-1} b.wt) for 21 days No significant differences in mean body weight food and water intake, hemoglobin, hematocrit, platelet count, white blood cell count, and red blood cell count No significant changes in color or texture of vital organs
Khullar et al. (2019)	In vivo study	Female Wistar rats (150–200 g) Single oral dose of AC (5–2000 mg/kg) The oral LD_{50} > 2000 mg/kg (nontoxic)	
Etemad et al. (2015)	In vitro study	HepG2 cells AC (100, 200, and 400 µM) for 24 and 72 h MTT test No cytotoxic effects at the concentrations up to 400 µM on HepG2 cell	
Reid et al. (2019)	In vitro study	Peripheral blood mononuclear cells (PBMC) and HepG2 cell lines AC (1.53–400 µg/mL) for 48 h IC_{50} value (PBMC) 169.55 ± 3.73 µM IC_{50} value (HepG2) > 640.42 µM	
Sipahi et al. (2016)	In vitro study	PBMCs AC (6.25–200 µM concentrations) for 48 h IC_{50}: 384 µM	
Santoro et al. (2008)	In vitro study	Mitogen-activated human lymphocytes AC (0.01–1.0 mM concentrations) for 72 h A concentration-related reduction of cell viability LD50 ~ 0.1 mM	
Budzianowska et al. (2023)	In vitro study	HepG2 and epithelial cell line MCF-12A AC (0–500 µM concentrations) for 48 h IC_{50} 346.8 ± 3.67 µM (MCF-12A) IC_{50} 219.6 ± 2.65 µM (HepG2)	

supplementation enhanced glutathione-dependent enzyme activity in erythrocytes and increased SOD activity in lymphocytes in response to physical exertion (Mestre-Alfaro et al. 2011a, b). Carrera et al. conducted a trial on university students performing a 21-day aerobic training program and reported that the antioxidant effect induced by *Lippia citriodora* extracts is mainly due to AC, which represents 10% (w/w) of the extract content (Carrera-Quintanar et al. 2012). In one randomized trial involving patients with SARS-CoV-2, olive leaf capsules, rich in phenolic compounds such as AC, luteolin-7-glucoside, apigenin-7-glucoside, hydroxytyrosol, and oleuropein were shown to reduce viral load and improve several clinical biomarkers, including complete blood count (CBC), C-reactive protein (CRP), ferritin, erythrocyte sedimentation rate (ESR), and lactate dehydrogenase (LDH) after 10 days of treatment (ClinicalTrials.gov Identifier: NCT04873349). Another randomized, controlled study investigated the effects of AC isolated from *Rehmannia* species in patients with immunoglobulin A (IgA) nephropathy. This trial aimed to assess AC's potential to prevent proteinuria relapse or achieve remission, slow the decline of renal function, and reduce hematuria (ClinicalTrials.gov Identifier: NCT02662283).

Campo et al. conducted a double-blind, randomized trial involved 100 participants to evaluate the impact of oral AC tablets (50 mg/kg) on platelet aggregation. The study reported a reduction from 51 to 39% after administration of the supplement twice daily for a couple of weeks (Campo et al. 2015). In a larger clinical study involving 479 patients with chronic primary glomerulonephritis, the combination of AC, isolated from *Rehmannia glutinosa*, and irbesartan led to a 36.42% reduction in proteinuria significantly greater than the 27.97% reduction observed in the control group receiving irbesartan alone (Qiu et al. 2014).

Although AC has demonstrated promising pharmacological activities in a wide range of in vitro and in vivo models, its clinical evaluation remains relatively limited. A few human studies have begun to explore its therapeutic potential, primarily through dietary interventions and herbal formulations containing AC-rich extracts. Despite these

encouraging findings, clinical research on AC is still in its early stages, and robust data in major disease areas such as cancer, Alzheimer's disease, Parkinson's disease, and diabetes remain largely absent. The current body of evidence is predominantly preclinical, limiting the extrapolation of therapeutic claims to clinical practice.

Therefore, well-designed, large-scale randomized controlled trials are critically needed to assess AC's efficacy, safety, optimal dosage, and pharmacokinetics in human populations. Future clinical research should focus on disease-specific end points, biomarker validation, long-term safety, and comparative effectiveness against existing standard treatments. Moreover, the development of optimized formulations to improve AC's bioavailability will be essential to enable meaningful translation from bench to bedside. In summary, AC holds substantial therapeutic promise, but further clinical validation is necessary to fully realize its potential as a treatment option in human disease.

Challenges and future prospects

While AC demonstrates significant therapeutic potential across a range of diseases due to its antioxidant, anti-inflammatory, neuroprotective, and anticancer properties, several challenges impede its clinical translation, most notably its poor bioavailability and the limited availability of robust clinical data (Alipieva et al. 2014; Wen et al. 2016). Current research is predominantly preclinical, with a lack of well-designed human trials to confirm efficacy and safety, and there is insufficient understanding of AC's precise molecular mechanisms and long-term toxicity profiles (Xiao et al. 2022). Addressing these gaps will require interdisciplinary approaches, including the development of advanced drug delivery systems to enhance bioavailability, comprehensive clinical studies to validate the therapeutic effects, and the use of omics technologies to elucidate multi-target actions and off-target effects. Looking forward, the field is poised for significant advancements through the integration of nanotechnology-based delivery methods, precision medicine strategies, and combination therapies with conventional drugs, which may not only improve AC's efficacy, but also its safety profile. Moreover, establishing standardized protocols for quality control and regulatory guidelines will be crucial for the safe clinical application of AC. These future directions and ongoing developments are expected to accelerate the translation of AC from bench to bedside, ultimately expanding its therapeutic utility across diverse disease contexts. Overall, the unique bioactivity of AC positions, it as a promising candidate for future drug development, but comprehensive studies on its biosynthesis, clinical utility, and formulation are still urgently required.

Conclusion

According to the evidence presented here, AC has neuroprotective properties via cholinergic, antioxidant, and anti-inflammatory processes and could be a suitable option for neuroprotective applications. Its highly favorable activities in gut inflammation models provide insight into its potential use in chronic inflammatory bowel illness. This compound holds considerable potential for the prevention and treatment of a wide range of skin problems. AC's health benefits stem from its role in various signaling pathways, including MAPK, NF-κB, PI3K/AKT, TGFβ/Smad, and AMPK/mTOR. Yet, trustworthy clinical data documenting the health consequences of AC are scarce and contentious; thus, these findings should be approached with caution, and more clinical trials on its efficacy and safety should be conducted. AC has not yet received approval as a therapeutic agent for human use by major regulatory agencies such as the US Food and Drug Administration or European Medicines Agency. It remains primarily a subject of research, particularly for its potential applications in neurodegenerative diseases and oncology. Ongoing clinical trials, including NCT02662283, assess the efficacy and safety of AC in various therapeutic contexts. The administration routes are an additional critical consideration for clinical application. Oral treatment is recommended because of the ease of intestine absorption compared to cutaneous absorption and the decreased risk of phenol moiety autooxidation. More rigorous investigations are needed to confirm AC's clinical potential, allowing it to be accepted as a therapeutic drug. It is also appealing for additional chemical alterations, since its structure provides an intriguing framework (with multiple reactive sites) for drug discovery. While this review focused on summarizing the pharmacological properties of AC, a direct comparative analysis with structurally related compounds or standard treatments was beyond its scope. Future reviews are warranted to critically evaluate AC's relative efficacy and therapeutic potential within a broader pharmacological context.

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Declarations

Conflict of interest The authors declare no competing interests.

Animal ethics declaration Not applicable.

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