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Review

The pharmacokinetic property and pharmacological activity of acteoside: A review

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ABSTRACT

Acteoside (AC), a phenylpropanoid glycoside isolated from many dicotyledonous plants, has been demonstrated various pharmacological activities, including anti-oxidation, anti-inflammation, anti-cancer, neuroprotection, cardiovascular protection, anti-diabetes, bone and cartilage protection, hepatoprotection, and anti-microorganism. However, AC has a poor bioavailability, which can be potentially improved by different strategies. The health-promoting characteristics of AC can be attributed to its mediation in many signaling pathways, such as MAPK, NF-κB, PI3K/AKT, TGFβ/Smad, and AMPK/mTOR. Interestingly, docking simulation study indicates that AC can be an effective candidate to inhibit the activity of SARS-CoV2 main protease and protect against COVID-19. Many clinical trials for AC have been investigated, and it shows great potentials in drug development.

1. Introduction

Acteoside (AC, also named as verbascoside or kusagin), [β-(3,4-dihydroxyphenylethyl)-*O*-α-$_L$-rhamnopyr-anosyl-(1→3)-β-$_D$-(4-*O*-caffeoyl)-glucopyranoside], is abundant in many dicotyledonous plants, such as Oleaceae, Bignoniaceae, Verbenaceae, and Labiatae [1]. Chemically, AC (Fig. 1), a formula of $C_{29}H_{36}O_{15}$ and a molecular weight of 624 daltons, is a phenylpropanoid glycoside featured as a binding of caffeic acid and hydroxytyrosol to a glucose moiety by forming ester and glycosidic bonds, respectively [2]. As a bioactive natural ingredient, AC is an important secondary metabolite in medicinal plants [3]. The biosynthesis, including natural and transgenic technology-modified, of AC has been reviewed [4]. AC is susceptible to be hydrolyzed in gastrointestinal ducts and degraded into several products before being absorbed into the blood [5]. AC is chemically stable at pH3 after 24 h in two human intestinal cell lines (HT-29 and Caco-2). However, it may be transformed (up to 62.4 %) into isoverbascoside or other oxidative products at pH7. This chemical transformation can significantly decrease the activity in the anti-oxidant assays in HT-29 and Caco-2 cells [6].

It has been demonstrated the association between the biological effects of phenolic compounds and their affinity and distribution in the lipid membranes. AC has a great affinity for phospholipid membranes, particularly to those formed by phospholipids with negative charge. The caffeoyl moiety of AC locates deep inside the phospholipid palisade in phosphatidylcholine (PC) but not phosphatidylglycerol (PG) membranes. AC forms a stabilized phospholipid complex at a high concentration and perturbs PC membranes resulting in formation of different membrane domains. Interestingly, AC increases vesicle curvature and decreases the particle size of PG unilamellar vesicles through increasing the phospholipid head group area [7]. AC exhibits protective activity against free radical-induced oxidation of low-density lipoprotein (LDL), blocking the development of atherosclerosis [8]. The anti-oxidative activity against DPPH radicals and the inhibitory activity against Cu^{2+}-induced LDL lipid peroxidation by AC have been reported with IC_{50} values of 19.89 μg/mL and 63.31 μg/mL, respectively [9]. The neuroprotective activity of AC is also reported by inhibiting the activity of NF-κB signaling in Aβ-treated N2a cells [10]. Recently, the reviews on AC have been studied [1,2,11–13]. For example, Khan [11] focuses on the anticancer activity of AC. Srivastava [12] reports the comprehensive review of phytochemistry and pharmacology of *Duranta erecta* Linn, which can be a significant source of AC. In addition, Srivastava also discusses some pharmacological activities of AC [12]. From the sophisticate literature research, we find that AC has been reported various pharmacological activities, including anti-oxidation [14], anti-inflammation [15], anti-cancer [11], neuroprotection [16],

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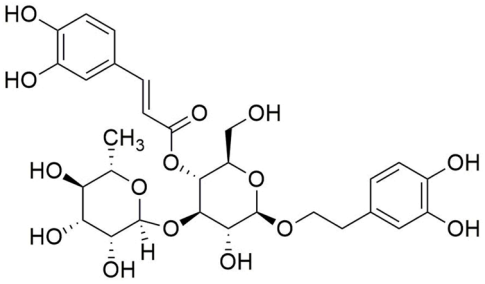

Fig. 1. The chemical structure of AC.

cardiovascular protection [17], anti-diabetes [18], bone and cartilage protection [19], hepatoprotection [20], and anti-microorganism [21]. In this review, we will mainly focus on these fields and summarize the research progress of AC, including the pharmacokinetic profiles. This article will fully elucidate the comprehensive pharmaceutics and pharmacology of AC, providing a novel platform for discussing and developing AC as a potential candidate in the therapeutic management of diseases.

2. Literature search strategy

The search terms "acteoside", "verbascoside", and "kusagin" were employed to obtain the necessary information from electronic database, including Pubmed, Web of Science, Sciencedirect, Wiley, Springerlink, Taylor & Francis, and Oxford Journals. Traditional uses, biological activities, pharmacokinetic characteristics, and clinical trials were summarized.

3. Pharmacokinetic profiles

The pharmacokinetic properties of AC after single intravenous administration can be suitably interpreted by a two-compartmental pharmacokinetic model. The distribution and elimination of half-lives of unbound AC are 5 min and 28 min, respectively, in the blood [22]. After intravenous administration of AC for 15 min in rats, the binding of AC to the protein in the rat plasma is 75.5 % and the bioavailability is only 0.12 %. Furthermore, the C_{max} values by oral (100 mg/kg) and intravenous (3 mg/kg) administration are 0.13 μg/mL and 48.6 μg/mL, respectively. The $T_{1/2}$ values are 92.1 min and 10.7 min, respectively [5] (Table 1). Another study reports that the plasma level of AC is 135.3 ng/mL in rats after oral administration of 10 g/kg Plantago asiatica decoction. The C_{max} value of AC is 135.4 ng/mL, the T_{max} value is 13.3 min, and the AUC is 187.1 μg h/L [23]. In beagle dogs, the absolute bioavailability of AC is about 4 %. After single oral administration of 10 mg/kg, 20 mg/kg, and 40 mg/kg AC, the values of AUC are 47.28 mg min/L, 87.86 mg min/L, and 183.14 mg min/L, respectively. The C_{max} values are 0.42 μg/mL, 0.72 μg/mL, and 1.44 μg/mL, respectively [24].

Elucidation of the pharmacokinetic properties is important for the prediction of drug disposition in vivo, and it is useful for drug therapeutic effects evaluation, dose adjustment, and drug's rational use. In chronic kidney disease (CKD) and normal rats, the $AUC_{0\text{-}t}$ values of AC after oral administration of *Rehmannia glutinosa* extract are 61.15 ± 10.56 μg min/mL and 32.69 ± 7.63 μg min/mL, respectively. The values of C_{max} are 0.31 ± 0.05 μg/mL and 0.19 ± 0.05 μg/mL, respectively. The T_{max} values are 24.00 ± 13.42 min and 15.00 ± 7.45 min, respectively [25] (Table 1). AC is the main effective compound from TLR (leaves of *Rehmannia*) and DTG (Dihuangye total glycoside capsule) extracts. After oral administration of TLR and DTG, the $AUC_{0\text{-}t}$ values of AC in diabetic nephropathy (DN) rats are 324.59 μg/L and 396.81 μg/L, respectively, lower than those in the control rats (1161.45 μg/L and 1465.13 μg/L, respectively). The C_{max} values in DN rats are 69.08 μg/L

Table 1
The metabolism and biological effects of AC in different models.

Category	Models	Biological effects	Ref.
Metabolism	Rats	The bioavailability is 0.12 %. C_{max} can be 0.13 μg/mL (oral, 100 mg/kg) or 48.6 μg/mL (intravenous, 3 mg/kg).	[5]
	Beagle dogs	The absolute bioavailability is about 4 %. C_{max} is 0.42 μg/mL (oral, 10 mg/kg).	[24]
	CKD rats	C_{max} is 0.31 μg/mL.	[25]
	DN rats	C_{max} can be 69.08 μg/L or 70.53 μg/L.	[26]
	Caco-2, HT-29	The total accumulation efficiency is about 0.10 %.	[27,28]
Anti-inflammation	RBL-2H3	Inhibits the activity of cPLA2 with a K_i value of 5.9 μM.	[15]
	Raw264.7	Inhibits iNOS/NO expression by attenuating AP-1activation.	[39]
	RAW 264.7, THP-1	Inhibits free fatty acid-induced COX-2/PGE2 expression.	[40]
	A549	Decreases NF-κB, IL-1β, IL-6, IL-8, and caspase-3/-8/-9, increases NRF2, HO-1, NQO-1, and GCLC.	[42]
	U937	Induces SHP-1 phosphorylation, attenuates the activation of TAK1/JNK/AP-1, and decreases COX and NOS expression.	[44]
	Dendritic cells	Increases IL-10 expression by activating AhR expression.	[46]
	KU812	Suppresses MAPK/JNK signaling and inhibits CCL1–4, FCER1A, and NFATC1 expression.	[48]
	HMC-1	Decreases STAT5/6, IL-6, IL-13, TNFα, and IL-1β expression, down regulates MDM2, and up regulates p53.	[50]
	TRPV3-HEK293	Selectively inhibits 2-APB-activated human TRPV3 channel with an IC_{50} value of 14.1 μM.	[53]
Anti-oxidative stress	SY5Y	Protects against Aβ-induced ROS generation and mitochondrial dysfunctions and apoptosis.	[57]
	Rats	Alleviates I/R-induced increased production of SOD, GSH-Px, TAS, and TT and decreased levels of TOS, OSI, and MDA.	[59]
	Sheep oocytes	Reduces ROS production and lipid peroxidation and protects mitochondrial functions.	[64]
Anti-cancers	B16F10	Attenuates tyrosinase activity and inhibit melanin biosynthesis by activating ERK signaling and down regulating the expression of MITF, tyrosinase, and TRP-1.	[69]
	4T1	Inhibits the proliferative activity (IC_{50} = 117 μM).	[71]
	GBM cells	Inhibits metastasis and promotes cell apoptosis and autophagy by let-7 g-5p/HMGA2/Wnt/β-catenin signaling.	[73]
	Caco-2, HCT-116	Induces G1 cell cycle arrest and increases cell apoptosis by PI3K/AKT signaling.	[78]
	Du-145, PC-3	Decreases HMGB1/RAGE/TGFβI/II/Smad2/3, inhibits EMT.	[79]
	Mouse	Inhibits metastasis by decreasing NF-κB/MMP-2 signaling and promotes cell apoptosis by Bcl-2/Bcl-XL.	[82]
	JHH-7	Increases p53 expression and decreases KLK-1, -2, -4, -9, and -10 expression.	[84]
Neuro-protection	Mice	Protects against I/R-induced expression of HIF-1α, NF-κB, and VEGF.	[94]
	Rats	Decreases Aβ 1–40 production, inhibits Aβ 1–42 oligomerization	[96]

(*continued on next page*)

Table 1 (*continued*)

Category	Models	Biological effects	Ref.
	PC12	Activates NRF2/HO-1 signaling, protects neuron against Aβ-induced injury.	[98]
	BV-2	Acts as an inhibitor of NF-κB and an agonist of AMPK.	[99]
	Rats	Increases Glut1, Glut3, and Glut4 expression, reduces ROS production, and protects against ICV-STZ-induced learning and cognitive impairment.	[102]
	Zebrafish	Protects against 6-OHDA-induced movement disorders and dopaminergic neuron death.	[105]
	RGC-5	Protects against H_2O_2-induced injury by mediating CASC2/miR-155/mTOR signaling.	[110]
Cardio-vascular protection	Rat serum	Inhibits ACE activity with an IC_{50} value of 365 μM.	[113]
	H9c2	Increases mitochondrial biogenesis, inhibits apoptosis.	[115]
	Rats	Improves the lipid profiles and the organ coefficients by AMPK/mTOR signaling.	[118]
Anti-diabetes	Caco-2	Inhibits SGLT1-mediated glucose absorption.	[120]
	βtc3 cells	Increases insulin biosynthesis and secretion by inhibiting oxidative stress and ERS.	[121]
Bone and cartilage protection	Rats	Inhibits MMP-13, MMP-3, and MMP-1 expression by decreasing MAPK/NF-κB signaling.	[19]
	Mice	Reduces osteoclastogenesis by attenuation of NF-κB pathway and stimulation of PI3K/AKT pathway.	[125]
	MC3T3-E1	Enhances proliferation and differentiation by increasing IGF-1/BMP/PI3K/mTOR signaling	[127]

and 70.53 μg/L, respectively, lower than those in the control rats (109.77 μg/L and 443.03 μg/L, respectively) [26].

In Caco-2 cell models, the rapid absorbance of AC with peak accumulation occurs within 30 min, and the total accumulation efficiency is about 0.10 %. The digestive recovery (bioaccessibility) of AC is 35.5 ± 0.55 % in vitro, indicating potential sensitivity to the gastrointestinal conditions [27]. Consistently, the total accumulation efficiency of AC reaches about 0.12 % in HT-29 cell models [28]. A study reports that AC can be absorbed rapidly in the normal healthy colonic mucosal sections from different individual patients, reaching the highest tissue concentration within 15–30 min. The total accumulation efficiency is also about 0.12 %, which is equal to the mean intracellular level of 0.29 μg/cm^2 tissue. Furthermore, the absorption is time-dependently associated with the different colonic segments. Specifically, AC is absorbed in the proximal tract within 5–15 min (0.50 μg/cm^2) mainly, in the descending tract within 30 min (0.38 μg/cm^2), and in the sigmoid colon within 60 min (0.34 μg/cm^2). This discrepancy can be attributed to the specific functional difference the colon segments [29].

The low bioavailability of AC might be related to its low absorption, poor bioaccessibility, and efflux transport. A study shows that the bioaccessibility of AC is 50.1 ± 3.04 % in the digestion model in vitro. The absorption of AC is 0.461–0.698 % in Caco-2 cell models. The value of P_{app} is 4.75 × 10^{-7} cm/s, indicating low permeability. Moreover, the active efflux by P-glycoprotein (P-gp) is also involved in the permeation mechanism [30]. Consistently, the low permeability of AC in Caco-2 cell models with the P_{app} value of 1.15 × 10^{-7} cm/s is reported. However, the efflux and active transport are not observed [31]. Promisingly, the bioavailability of AC can be improved by encapsulation with liposomes and chitosan, as shown by the improved pharmacokinetic parameters of chitosan-coated AC liposome (CS-AC-Lip). The C_{max} value for CS-AC-Lip is 0.76 μg/mL at 1.83 h (T_{max}). In contrast, the value for AC is 0.44 μg/mL at 0.54 h (T_{max}) [32]. Another study shows that the oral bioavailability of AC can be enhanced to 1.43-fold by the P-gp inhibitor EGCG. However, EGCG has no effects on the storage and digestion stability of AC [33].

The oxidization, glucuronidation, sulfation, and methyl conjugation are involved in the metabolic processes of AC (Fig. 2). 19 metabolites of the parent compound and 16 metabolites of the degradation products are verified. AC acts as a prodrug and is hydrolyzed into degradation products, particularly caffeic acid and hydroxytyrosol [34]. Another study shows that 44 metabolites are detected and identified. Among them, 35 compounds are the parent drug metabolites [35]. When incubated with human or rat intestinal bacteria, AC produces 14 metabolites by hydrolyzation, which is the main metabolic pathway. Of these metabolites, they include 8 degradation metabolites, 2 isomers in intestinal bacteria and intestinal enzyme samples, and 4 parent metabolites only found in intestinal enzyme samples [36].

The toxicity prediction has been explored. The maximum tolerance dose of AC is 0.443 mg/kg/day in human, and the oral acute toxicity and oral chronic toxicity are 2.527 mol/kg and 3.783 mg/kg, respectively, in rats [37]. In V79 cells, AC at the dose of more than 50 μg/mL exhibits cytotoxic effects with IC_{50} values of 73.80 μg/mL for MTT assays and of 41.42 μg/mL for NRU assays. However, AC does not show any genotoxic activity and phototoxicity [38].

4. Anti-inflammation and immune-mediation

Inflammatory responses include activation of phospholipase A2 (PLA2). Cytosolic Ca^{2+}-dependent PLA2 (cPLA2) and secretory PLA2 (sPLA2) are the members of the PLA2 superfamily. It has been demonstrated that AC can dose-dependently block melittin-induced release of [^{3}H]arachidonic acid by inhibiting the activity of cPLA2, rather than sPLA2, with a K_i value of 5.9 μM in RBL-2H3 cells [15]. Nitric oxide (NO) produced by NO synthase (NOS) exhibits double effects. Constitutive NOS (cNOS)-produced NO is essential for the maintenance of cellular functions, and inducible NOS (iNOS)-produced NO is a mediator of acute or chronic inflammation. AC has been demonstrated to inhibit LPS-induced NO release and suppress iNOS mRNA and protein expression by selectively attenuating the activation of AP-1 in Raw264.7 macrophage cells [39]. It is interesting to find that AC can selectively interact with the catalytic cavity of COX-2 and inhibit the production of PGE2, without affecting COX-1 activity in free fatty acid-treated RAW 264.7 and THP-1 macrophage cells [40] (Fig. 3, Table 1).

Anti-inflammation therapy has been considered as an effective strategy for clinical management of mucositis. In methotrexate (MTX)-induced mice mucositis, AC may ameliorate the histological severity scores by 75 %, 78 %, and 88 % in the duodenum, jejunum, and ileum, respectively on day 5, compared with those in the MTX group. In addition, AC decreases the crypt depth by 49 %, 51 %, and 33 %, respectively, and increase the villus height by 19 %, 38 %, and 10 %, respectively. The possible mechanism might be associated with the inhibitory activity of AC against metallothionein by 50 % and against myeloperoxidase by 60 % and 30 % in the duodenum and jejunum, respectively [41]. AC has been shown to dose-dependently ameliorate TNFα-induced IL-1β, IL-6, IL-8, and caspase-3/-8/-9 expression, ROS generation, and cell apoptosis. In addition, AC increases the expression of NRF2, HO-1, NADPH quinone oxidoreductase (NQO-1), and glutamate cysteine ligase catalytic subunit (GCLC) and decreases the activity of NF-κB signaling pathway in TNFα-treated A549 cells [42]. In lipopolysaccharide (LPS)-induced acute lung injury, AC exhibits protective activity against the histopathological changes, the increase of proinflammatory cytokines, and the enhancement of NF-κB signaling pathway [43]. LPS can dephosphorylate and activate Src homology region 2 domain-containing phosphatase-1 (SHP-1), which is a negative regulator of many signaling pathways, such as MAPK and NF-κB/AP-1. AC may induce phosphorylation of SHP-1, attenuate the activation of TGFβ-activated kinase-1 (TAK1)/JNK/AP-1, and decrease the

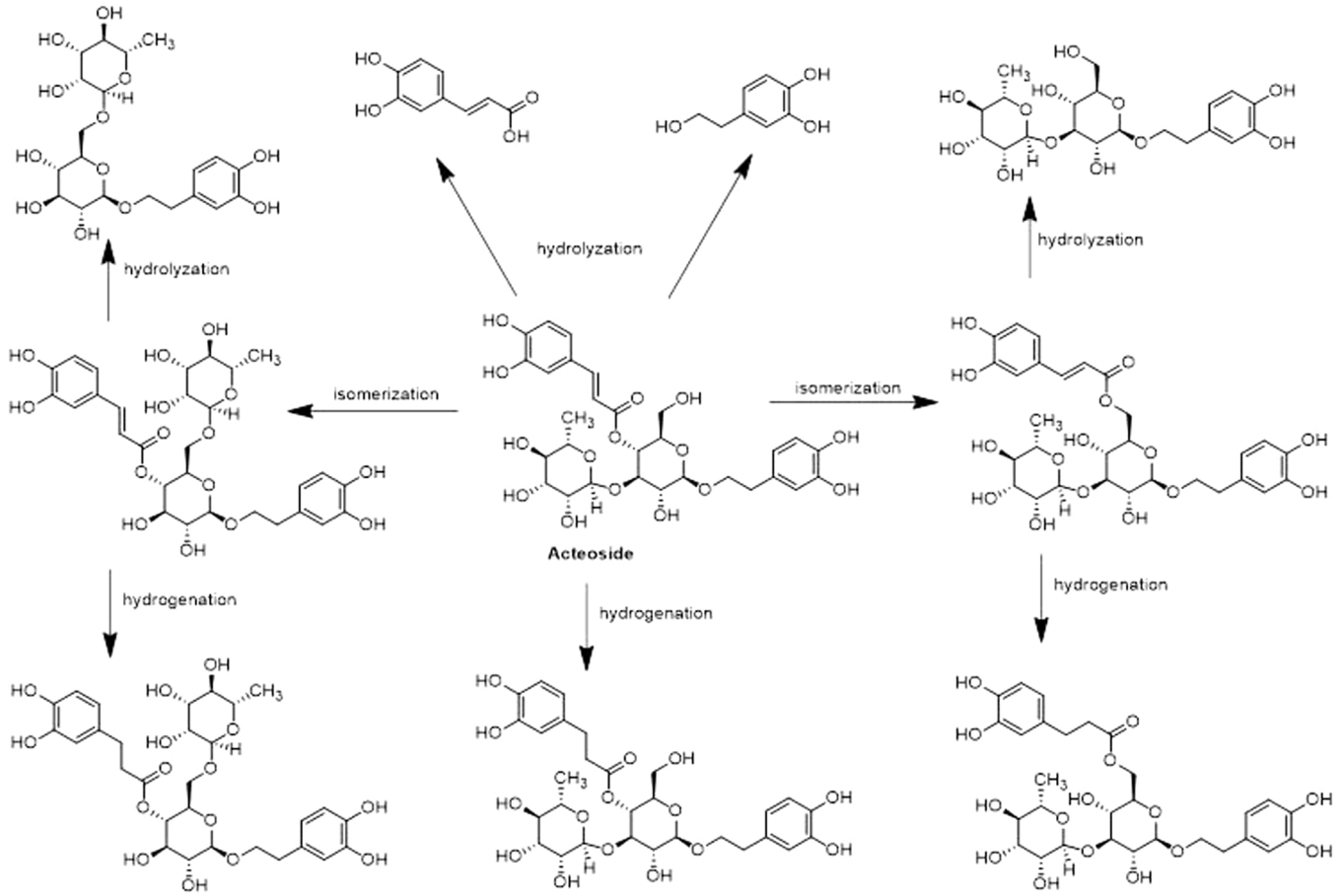

Fig. 2. The metabolic pathways of AC. AC can be transformed by the reactions of isomerization, hydrolyzation, and hydrogenation.

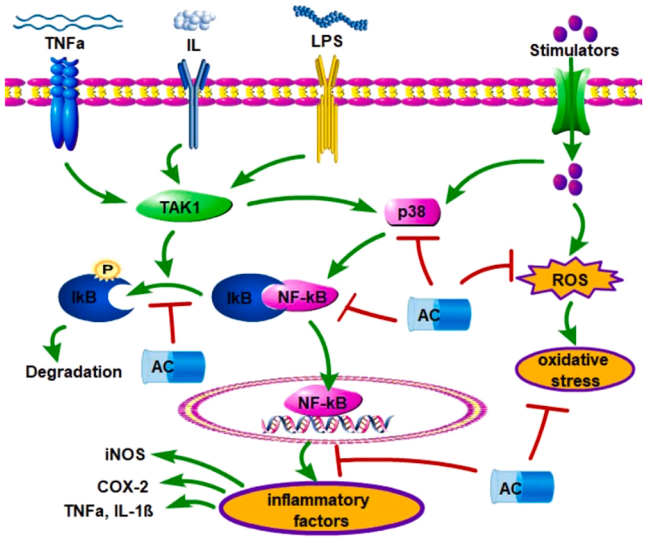

Fig. 3. AC exhibits the inhibitory activity against inflammatory responses and oxidative stress. NF-κB signaling can be activated by the upstream factors, such as ILs, TNFα, LPS, and p38 MAPK. Active NF-κB enters the nucleus to promote the transcriptional expression of inflammatory factors. Extracellular stimulators can also induce ROS production, leading to oxidative stress. These can be effectively abolished by AC treatment.

production of COX and NOS in LPS-treated U937 cells [44] (Fig. 3, Table 1).

Regulatory B cells, a source of IL-10 production, has been well known for maintaining immune tolerance. AC has been shown to ameliorate experimental Sjogren's syndrome by increasing Breg cells biological functions and decreasing the activity of T effector cells [45]r. In LPS-treated dendritic cells, AC significantly decreases the production of IL-12 and TNFα and increases the levels of IL-10 by activating the expression of AhR, which promotes the generation of Foxp3^{+} regulatory T cells, leading to protection against pulmonary inflammation in asthmatic mice [46]. Type I allergy can be induced by antigens, which stimulate the generation of antibodies that bind to mast cells or basophils. In immunoglobulin E (IgE)-regulated RBL-2H3 and KU812 cells, act as type I allergy cell models, the release of β-hexosaminidase and histamine is induced, the level of intracellular calcium is increased, and the production of TNFα and IL-4 is enhanced [47]. These can be significantly attenuated by AC treatment. The microarray analysis reveals that AC-mediated allergy inhibition might be related to suppression of MAPK/JNK signaling and down regulation of CCL1–4, FCER1A, and NFATC1 expression in KU812 cells [48]. IL-32 is a cytokine that promotes the productions of IL-1β, IL-6, IL-8, and TNFα and plays a critical role in the development of allergic rhinitis. In IL-32-treated THP-1 cells, AC attenuates inflammatory cytokines expression and alleviates NF-κB signaling and caspase-1 expression. Additionally, AC also suppresses IL-32-activated macrophage-like cells differentiation [49] (Fig. 3).

AC shows significant anti-inflammation and anti-proliferation in thymic stromal lymphopoietin (TSLP)-induced human mast cells, as indicated by decreased expression of STAT5/6, IL-6, IL-13, TNFα, and IL-1β. The possible mechanism might be associated with down regulation of murine double minute 2 (MDM2) and up regulation of p53 by AC in TSLP-induced HMC-1 cells [50] (Table 1). Neutrophils is a factor in the host defense system against infection. Inhibition of neutrophil

recruitment and functions becomes a useful therapeutic strategy. In LPS-stimulated neutrophils, AC has been shown to selectively inhibit the expression of CD11b and CXCR2 and attenuate p38 MAPK phosphorylation, decreasing TLR2- and TLR4-mediated apoptosis [51]. Atopic dermatitis is a skin disease characterized by chronic inflammation. AC may be effective against atopic dermatitis, as shown that AC can relieve the scratching behaviors and skin lesion in 2,4-dinitrochlorobenzene (DNCB)-treated mice. The possible mechanism might be associated with the inhibitory activity of AC against DNCB-induced inflammatory cytokines production and NF-κB signaling. In human monocyte THP-1 models, AC suppresses the expression of CD54 and CD86 induced by DNCB at the cell surface [52]. Another study shows that AC can selectively inhibits 2-APB-activated human TRPV3 channel with an IC_{50} value of 14.1 ± 3.3 μM and mouse TRPV3 channel, which stimulates thymic stromal lymphopoietin (TSLP) and pro-inflammatory cytokines [53].

5. Anti-oxidative stress

AC has been identified as one of the main constituents responsible for the anti-oxidative activity of *Abeliophyllum distichum*. At the dose of 25 μg/mL, AC has been shown the scavenging activity against DPPH, •OH, and O_2^- radicals by 82.84 %, 89.46 %, and 30.31 %, respectively [14]. Consistently, AC is also demonstrated the anti-oxidant activity in ABTS radical cation decoloration assay, DPPH radical scavenging assay, and ferric reducing anti-oxidant power assay [54]. Another study shows that AC exhibits a high activity in DPPH radical scavenging with an IC_{50} value of 0.09 μg/mL. In addition, AC shows more potent in scavenging H_2O_2 with an IC_{50} value of 2.6 μg/mL than ascorbic acid (IC_{50} = 4.0 μg/mL) [55]. The anti-oxidative activity can be divided two groups, including the direct and the indirect anti-oxidative activity. The former can be evaluated by the free radical scavenging assays, and the later can be determined by the expression of anti-oxidant enzymes. Interestingly, one study reports that AC shows no effects on the expression of anti-oxidant enzymes but the direct scavenging activity [56].

Oxidative damage has become one of the main pathological mechanisms of amyloid β-peptide (Aβ)-induced AD. AC exhibits anti-oxidative stress and protects against Aβ-induced ROS generation and mitochondrial dysfunctions, inhibiting mitochondrial apoptosis in SY5Y cells [57] (Table 1). Cerebral ischemia-reperfusion (I/R) injury often induces oxidative stress. It has been shown that AC can protect against I/R-induced oxidative stress, as indicated by decreased levels of reactive oxygen species (ROS) and malondialdehyde (MDA) and increased productions of superoxide dismutase (SOD) and catalase (CAT). AC significantly ameliorates I/R-induced pathological changes by regulating PKR/eIF2α signaling [58]. Similarly, AC also alleviates I/R-induced pathological damages and exhibits anti-oxidative activity by increasing the production of SOD, GSH-Px, TAS, and TT and decreasing the levels of TOS, OSI, and MDA in colon mucosa of rats [59]. Exposure to glutamate can induce oxidative stress and stimulate apoptosis in PC12 cells. Treatment with AC may alleviate glutamate-induced the loss of cell viability, the apoptosis rate, the decreased productions of SOD and GSH-Px, and the increased levels of lipid peroxide formation, ROS generation, and intracellular calcium influx, resulting in neuroprotection against excitotoxicity [60].

Oocytes and embryos are vulnerable to oxidative stress in the culture environment in vitro. Supplementation with AC has been shown beneficial effects on the development of matured equine oocytes by intracytoplasmic sperm injection and embryos in vitro [61]. AC also protects oocytes during in vitro maturation of embryo development and quality against di-(2-ethylhexy) phthalate (DEHP)-induced oxidative stress [62]. Consistently, AC acts as an anti-oxidant to improve the quality of porcine oocytes and the subsequent mature of pre-implantation embryos in vitro [63]. In sheep oocytes, AC at the nanomolar concentration may increase the formation and quality of blastocyst and promote the development of embryo in vitro by reducing ROS production and lipid peroxidation and protecting mitochondrial functions and gene expression from oxidative stress [64] (Table 1).

Protein glycation is non-enzymatic modification and can be one of the important sources of ROS production. Glycation may produce intermediates, such as glyoxal or methylglyoxal (MGO), to induce the formation of advanced glycation end products (AGE) irreversibly. AC has been shown to exhibit anti-glycation activity in high glucose-treated models [65]. Aging is characterized by a decline in physiological functions, and oxidative stress contributes to aging. Natural compounds have screened for developing potential candidates against aging [66]. AC has been exhibited the protective activity against D-galactose-induced mice aging, as shown by improved spatial learning and memory impairment, decreased escape latency, increased zone time, and improved platform crossing times. The possible mechanisms might be associated with the anti-oxidative activity of AC in alleviating the production of AGE and 8-hydroxy-2'-deoxyguanosine [67].

6. Anti-cancers

The anti-cancer effects of AC have been reviewed that it exhibits anti-angiogenesis, anti-proliferation, anti-invasion, anti-metastasis, and apoptosis-promotion in various cancers [11]. AC has been shown cellular toxicity to cancer cells independently of the status of p53, Rb1, and H-Ras by mediating many signaling pathways, including anti-oxidant, immune, and proteostatic system. The anti-cancer effects of AC are associated with the achieved concentration in the tumor [68]. Abnormal stimulation of melanin synthesis may lead to esthetic issues and development of malignant melanoma. The melanin biosynthesis is under the control of tyrosinase, tyrosinase-related protein-1 (TRP-1), and TRP-2, which are mediated by microphthalmia-associated transcription factor (MITF) and ERK signaling. AC can attenuate the activity of tyrosinase and inhibit the biosynthesis of melanin in B16F10 cells by activating ERK signaling and down regulating the expression of MITF, tyrosinase, and TRP-1 [69] (Table 1). Estrogen and its receptor ER are involved in the suppression of many tumors, including melanoma. AC has been reported to exhibit estrogenic effects, and it inhibits melanoma growth and inflammation by mediating ERβ/Ras/Raf-1/STAT3 signaling [70].

AC inhibits the proliferative activity of breast cancer 4T1 cells with an IC_{50} value of 117 μM. Additionally, AC up regulates the expression of Bax and caspase-3 and down regulates the expression of Bcl-2, leading to cell apoptosis. Furthermore, at the dose of 130 μM, AC increases TLR4 expression [71]. RNA metabolism regulation by microRNA or long noncoding RNA has been implicated in regulation of gene expression in cancer development [72]. In glioblastoma, AC inhibits cell viability, invasion, migration, and tumor growth and promotes cell apoptosis and autophagy by mediating the expression let-7 g-5p/HMGA2/Wnt/β-catenin signaling pathway [73] (Fig. 4). Exosomes are the small vesicles characterized by single membrane with 30–200 nm in diameter. Tumor-derived exosomes play an important role in carcinogenesis, proliferation, and metastasis. Many studies reports that PI3K/AKT signaling pathway has been involved in the regulation of cancer development, and it has become the potential target for screening natural candidates [74–76]. In GBM cells AC has been reported to increase the expression of miR-7–5p, which then inhibits the expression of epidermal growth factor receptor (EGFR) and subsequently inactivates PI3K/AKT signaling pathway, resulting in inhibition of cell proliferation, migration, invasion, and microtubule formation [77]. Treatment failure of colorectal cancer (CRC) with 5-Fluorouracil (5-FU) can be attributed to the intrinsic and acquired resistance. AC may re-sensitize CRC cells to 5-FU and inhibit cellular proliferation in vitro. Specifically, 5-FU, by cooperating with AC, induces G1 cell cycle arrest and increases cell apoptosis by targeting the activity of PI3K/AKT signaling pathway in Caco-2 and HCT-116 cells [78] (Table 1).

In prostate cancer Du-145 and PC-3 cells, AC inhibits cell

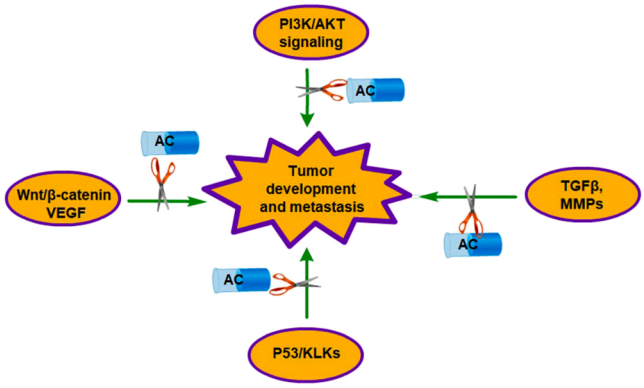

Fig. 4. The inhibitory effects of AC against tumor development and metastasis. The activation of PI3K/AKT, Wnt/β-catenin, VEGF, and p53/KLKs signaling might promote the development of tumor development. Up regulation of TGFβ/SMAD and MMPs expression induces tumor metastasis.

proliferation, migration, and invasion by down regulating the expression of HMGB1/RAGE axis and their downstream TGFβI/II/Smad2/3 signaling pathway. Epithelial-mesenchymal transition (EMT) is involved in the carcinogenesis and metastasis of various cancers. AC inhibits the expression of EMT transcription factors, such as Slug and Snail, and enhances the expression of E-cadherin [79]. In GBM cells, AC significantly suppresses c-Met-induced EMT in vivo and in vitro. Mechanistically, AC may interact with c-Met protein directly and then promote its degradation by the ubiquitination-proteasome pathway [80]. In human fibrosarcoma HT-1080 cells, AC has been reported to inhibit PMA-induced MMP-9 expression, invasion, and migration by decreasing the Ca^{2+}-dependent CaMK/ERK and JNK/NF-κB signaling pathways [81]. In a xenograft human oral squamous cell carcinoma (OSCC) mouse model, AC significantly inhibits the metastasis by down regulation of NF-κB/MMP-2 signaling and promotes cell apoptosis by mediation of Bcl-2/Bcl-XL expression in vivo [82]. HIPK2 expression is negatively correlated with CRC invasion and Dukes stage. AC dose-dependently enhances the protein expression of pro-apoptosis factors p-p53 and Bax and decreases the expression of Bcl-2 [83]. AC can inhibit the tube formation and cell migration of HUVECs and produce stronger inhibition by combination with sorafenib in HCC cell lines. In JHH-7 cells, AC increases the expression of p53 and decreases the expression of kallikrein-related peptides (KLK1, 2, 4, 9, and 10) [84] (Fig. 4, Table 1).

Two mutagenic tests (chromosome aberrations test and sister chromatid exchanges test) have been used to identified that AC shows no mutagenic activity in rabbit lymphocytes [85]. Oxidative DNA damage has been involved in the pathogenesis of many diseases, including cancers. γ-H2AX and p53 are the two important factors that play distinct roles in DNA damage responses. It has been demonstrated that AC reduces the phosphorylation of γ-H2AX and p53 in 150 μM $FeSO_4$- and 600 μM H_2O_2-treated NIH 3T3 cells [86]. AC is considered as an anti-genotoxic compound against H_2O_2-induced damage and shows no genotoxic activity in the somatic mutation and recombination test of *Drosophila melanogaster* [87]. Consistently, in the Drosophila wing spot test, AC exhibits no genotoxic activity at any tested concentrations [88]. Although one study reports an increase in CAs and SCEs and a decrease in the mitotic index in AC-treated in human normal lymphocytes in vitro, accompanied by up regulation of PARP-1 and p53 expression [89].

7. Neuroprotective activity

The neuroprotective activity of AC has been demonstrated that AC may significantly reduce MPP^+-induced collapse of mitochondrial membrane potential, activation of caspase-3, and cell apoptosis in PC12 cells [16]. AC can be found as one of the main ingredients from *Achyranthes aspera* Linn., which has been shown anti-oxidative and anti-inflammatory activities to alleviate I/R-induced cerebral pathological changes [90]. The neuroprotective activity of AC is consistently associated with its anti-oxidative activity, which are demonstrated by DPPH scavenging assay (IC_{50} = 58.1 μM), xanthine oxidase assay (IC_{50} = 24.4 μM), and hydroxyl radical scavenging assay (IC_{50} = 357 μM) in HepG2 and SH-SY5Y cells. Furthermore, AC significantly inhibits the activity of tyrosinase, MAO-A (IC_{50} = 3.44 μM), and acetylcholinesterase [91]. It has been demonstrated that AC, derived from Chinese traditional medicine *Radix Rehmanniae*, can reduce neurological deficit score and delay the onset of multiple sclerosis. The possible mechanisms might be associated with the inhibitory effects of AC on $ONOO^-$-induced excessive mitophagy, which contributes to inflammation, peripheral activation, and central nervous system (CNS) infiltration of encephalitogenic $CD4^+$ T cells and $CD11b^+$ activated microglia/macrophages [92].

Hypoxic-ischemic brain damage often results in neurological dysfunction and acute death in neonates. It has been demonstrated that AC may exhibit neuroprotective activity, as shown by decreased neurofunctional latency, reduced brain infarct volume, and ameliorated neuronal degeneration. The possible underlying mechanism might be associated with the inhibitory activity of AC against the formation of autophagosome [93]. Cerebral I/R injury often causes neurological, motor, and cognitive deteriorating dysfunctions, along with alteration of brain morphology and biochemical factors expression. AC can effectively protect against I/R-induced pathological changes by regulating the expression of HIF-1α, NF-κB, and VEGF [94] (Fig. 5) (Table 1). The differentially expressed genes (DEGs) were analyzed to predict the possible targets of AC in rats with middle cerebral artery occlusion. CCL2, CXCL10, and ICAM1 have been identified as the potential targets, and their expression are increased in MACO rats and OGD/R-induced cells. AC exhibits protective activity in cell proliferation promotion and apoptosis inhibition by mediating IL-10/STAT3 signaling [95].

Amyloid β peptide (Aβ) plays a critical role in Alzheimer's disease (AD). Aβ 1-42 production is associated with memory impairment and neuronal degeneration in AD patients. AC has been shown to increase Aβ 1-40 degradation, decrease Aβ 1–40 production, and inhibit Aβ 1-42 oligomerization, leading to amelioration of Aβ 1-42-induced cognitive dysfunction in rats [96] (Fig. 5) (Table 1). The inhibitory effects of AC on Aβ42 aggregation have been investigated with an IC_{50} value of 8.9 μM, and the two catechol moieties of AC might be responsible for such inhibitory activity [97]. Aβ-induced neuronal injury is associated with oxidative stress, which has become a potential therapeutic strategy for AD management. Recently, AC has been shown to activate NRF2/HO-1 signaling pathway and protect neuron against Aβ-induced injury in PC12 cells. NRF2 siRNA or HO-1 inhibitors may significantly abolish the

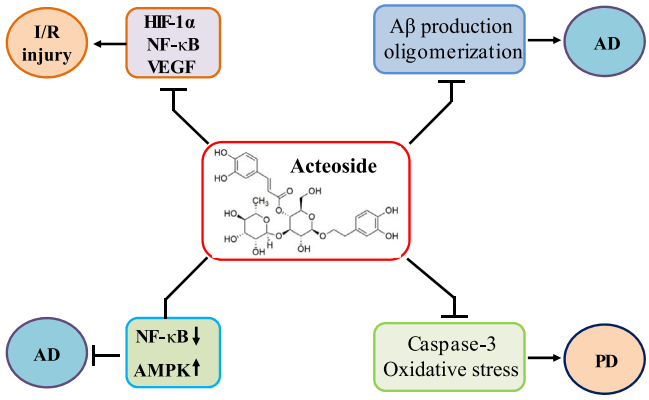

Fig. 5. AC shows neuroprotective activity. AC ameliorates I/R injury by attenuating the expression of HIF-1α, NF-κB, and VEGF. AC protects against AD development by activating AMPK, attenuating NF-κB, and decreasing Aβ production and oligomerization. In addition, AC inhibits caspase-3 expression and oxidative stress, leading to amelioration of PD development.

protective activity of AC. Furthermore, ERK inhibitor PD98059 and PI3K inhibitor LY294002 also block the neuroprotection of AC [98] (Table 1).

Microglia-driven inflammation contributes to neuron damage and neurodegeneration, promoting the progression of AD. A computational network model has been analyzed and verified that AC acts as an inhibitor of NF-κB and an agonist of AMPK in $AlCl_3$-induced AD and LPS-treated BV-2 cells. AC inhibits M1 polarization, stimulates M2 polarization, and ameliorates mitochondrial dysfunction by mediating NF-κB and AMPK/PGC-1α/UCP2 signaling pathways [99] (Fig. 5). In PC12 cells, melittin can enhance the intracellular Ca^{2+} mobilization but not cause the intracellular Ca^{2+} release. In addition, melittin also induces arachidonic acid (AA) activation by stimulating the secretion of Ca^{2+}-dependent phospholipase A2 (PLA2) and catecholamine. However, these melittin-induced pathological changes can be significantly ameliorated by AC [100]. In mice treated with a combination of D-galactose and $AlCl_3$, AC may effectively improve learning and memory impairment. This might be associated with the inhibitory activity of AC against the expression of nitric oxide, nitric oxide synthase, and caspase-3 in the hippocampus [101]. Intracerebroventricular administration of streptozotocin (ICV-STZ) may induce cognitive impairment, glucose metabolism dysregulation, and oxidative stress. AC up regulates the protein expression of Glut1, Glut3, and Glut4 and reduces the production of ROS, protecting against ICV-STZ-induced learning and cognitive impairment [102].

The progressive degeneration of the dopaminergic neurons is the main pathological mechanism of Parkinson's disease (PD). Caspase-3 inhibition has been demonstrated to protect against dopaminergic neurons degeneration (Fig. 5). AC is reported to interact with and inhibit caspase-3 activity by forming hydrogen bonds with Thr177, Ser178, Gly238, Ser339, Arg341, and Trp348 in the active site [103]. In the network pharmacology and experimental study of PD, the protective activity of AC against PD is associated with the induction of mitophagy and inhibition of neuronal apoptosis [104]. In 6-hydroxydopamine (6-OHDA)-induced PD zebrafish models, AC has been demonstrated to penetrate the blood-brain-barrier (BBB). AC can protect against 6-OHDA-induced movement disorders and dopaminergic neuron death by up regulating the activity of NRF2/ARE signaling pathway in zebrafish [105]. Due to the short half-life and low bioavailability, AC can be constructed into a nanomicelle composite AC-PLA-mPEG-CTA-pDNA-NGF (APPDN) with a size of about 160 nm and being capable of penetrating the BBB easily. It has been shown that APPDN may effectively inhibit Lewy body formation in MPTP-induced PD mice and block α-syn aggregation in MPP^+-lesioned PD cell models [106].

L-Glutamate is one of the main excitatory neurotransmitters. AC, isolated from the leaves of *Callicarpa dichotoma*, exhibits neuroprotective effects against glutamate-induced intracellular Ca^{2+} influx, oxidative stress, and mitochondrial dysfunction [107]. γ-aminobutyric acid (GABA) dysregulation has been involved in the pathogenesis of epilepsy. AC is reported to exhibit anti-convulsant activity in pentylenetetrazole (PTZ)-induced mice by up regulating GABA and $GABA_A$ receptor expression. In addition, AC does not produce central side effects, such as motor incoordination and locomotor deficits [108]. Chronic spinal cord injury often induces skeletal muscle atrophy, accompanied by decreased secretion of axonal growth factors. AC can stimulate the secretion of pyruvate kinase isoform M2 (PKM2) and the proliferation of skeletal muscle cells, resulting in recovery of skeletal muscle weight reduction and motor function impairment [109]. Loss of retinal ganglion cells (RGCs) may lead to optic nerve atrophy and vision loss. AC has been demonstrated to protect RGC-5 cells from H_2O_2-induced injury by mediating CASC2/miR-155/mTOR signaling [110] (Table 1). Furthermore, AC can inhibit autophagy-mediated apoptosis of RGCs through regulating the activity of PI3K/AKT pathway and the expression of caveolin 1 [111]. Glaucoma progressively impairs the eyesight and causes blindness, and protection of RGCs from apoptosis can be a useful strategy. AC has been demonstrated to inhibit autophagy-induced RGCs apoptosis by regulating the expression of optineurin and PI3K/AKT/mTOR signaling pathway [112].

8. Cardiovascular protection

NO may induce vasodilation by stimulating the expression of cGMP. NO pathway inhibitors have been shown to abolish the induction of AC (at the dose of 30 μM) in enhancing phenylephrine-induced contractions in endothelium-intact rat arteries. The underlying mechanism of AC on attenuation of endothelial NO-regulated aortic relaxation might be associated with the inhibition of Ca^{2+}-dependent NO generation in the endothelia [17]. Angiotensin (Ang)-converting enzyme (ACE) has been considered as the critical protease to synthesize Ang II in the renin-angiotensin-aldosterone system. AC has been demonstrated to inhibit the activity of ACE with an IC_{50} value of 365 μM dose-dependently [113]. Consistently, AC is one of the major bioactive constituents from the extract of *Plantago asiatica* L. seeds and alleviates hypertension in spontaneously hypertensive rats by inhibiting the expression of ACE [114]. Septic cardiomyopathy is a common dysfunction in the sepsis of organ with a ventricular dilation and decreased contractility. In LPS-induced sepsis, AC greatly enhances cardiac functions by amelioration of inflammation and oxidative stress. Specifically, AC increases mitochondrial biogenesis and restores sepsis-induced mitochondrial changes, inhibiting apoptosis in cardiomyocytes [115] (Fig. 6, Table 1).

Intracerebral hemorrhage (ICH), a devastating cerebrovascular disease, is associated with high morbidity and mortality. A secondary neuronal injury can be stimulated by inflammation, hematoma toxicity, and microglial activation. Treatment with AC shows protective effects against ICH-induced pathological changes by inhibiting NLRP3 expression and increasing neuronal viability [116]. Another study reports that AC may improve the behavioral score, decrease the hematoma volume, alleviate the brain edema, and inhibit neuronal apoptosis in mice ICH models. Consistently, the possible mechanism might be associated with the inhibition of TLR-4-regulated inflammation [117]. High fat diets (HFD)-induced dyslipidemia contributes to atherosclerosis development. AC has been shown the protective activity against HFD-induced atherosclerosis, as indicated by amelioration of the serum productions of inflammatory cytokines and improvement of the lipid profiles and the organ coefficients in rats. The molecular mechanisms might include the attenuation of AMPK/mTOR signaling pathway by AC [118] (Table 1).

9. Anti-diabetes

Reduction of glucose absorption rate can be an effective strategy to control blood glucose concentrations in diabetes. α-Amylase acts as an

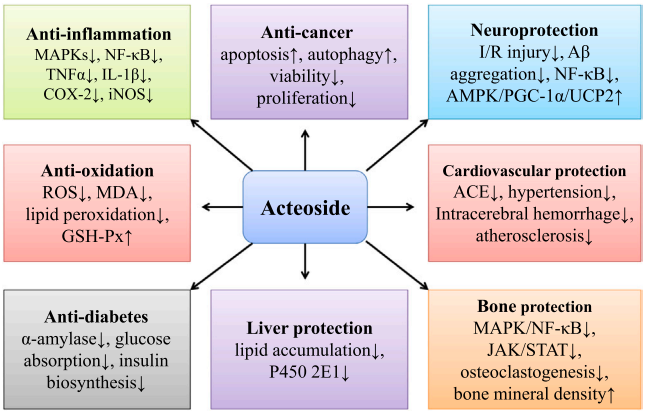

Fig. 6. The various biological activities of AC are discussed. These activities involve anti-inflammation, anti-oxidation, anti-cancer, neuroprotection, cardiovascular protection, anti-diabetes, liver protection, and bone protection.

important factor to regulate the digestion of carbohydrates and glucose absorption. AC has been found to interact with α-amylase and inhibit its activity with an IC_{50} value of 125.21 ± 7.87 mg/mL [18]. Hyperglycemia might be associated with chronic hyperalgesia and allodynia. AC has been found as one of the active compounds in the extract from the leaves of *Ligustrum vulgare* to treat diabetic neuropathy, decreasing hyperalgesia and allodynia. Controversially, the extract shows no effects on the blood glucose concentrations [119]. Sodium-dependent glucose cotransporter 1 (SGLT1), mainly expressed in the brush border membrane of the small intestine, can transport both glucose and galactose into enterocytes. SGLT1/GLUT2 coupling becomes one of the critical mechanisms in maintaining the blood glucose concentration. AC has been exhibited the inhibitory activity in SGLT1-mediated glucose absorption in Caco-2 cells [120]. Endoplasmic reticulum stress (ERS) caused by metabolic insults often results in a decrease of insulin biosynthesis and secretion. AC has been demonstrated to protect β cells against oxidative stress and ERS in clonal and human β cells, as shown by attenuated expression of PERK/eIF2α signaling [121] (Fig. 6, Table 1).

10. Bone and cartilage protection

Osteoarthritis is characterized by low chronic inflammatory joint diseases. AC has been shown to ameliorate IL-1β-induced MMP-13, MMP-3, and MMP-1 expression by decreasing the activity of MAPK/NF-κB signaling pathway in the primary rat chondrocytes [19] (Fig. 6, Table 1). Consistently, AC inhibits IL-1β-induced IL-6, IL-12, TNFα, and IFNγ expression, enhances chondrocyte proliferation, and attenuates cell apoptosis by down regulating the activity of JAK/STAT pathway. In addition, AC also ameliorates synovial inflammation in osteoarthritic rats [122]. The expression of P2X7R, MMP-13, substance P, and PGE2 are higher in rat OA chondrocytes, and these alterations can be reversed by treatment with AC through inactivation of NF-κB signaling pathway [123]. In collagen-induced arthritis mice, the cartilage destruction, synovial hyperplasia, and the expression of MMP-9, MMP-13, and ADAMTS-4/-5 can be significantly alleviated by Fufang Shatai Heji, which includes AC as one of the major active compounds. Molecular docking study indicates that AC can interact with Glu111 and Phe110 in the active pocket of MMP-9 [124].

In an ovariectomized (OVX) mice model, AC significantly enhances bone mineral density and bone biomechanical properties, improving the bone microarchitecture. AC effectively reduces osteoclastogenesis, and the possible mechanisms might be associated with attenuation of NF-κB pathway and stimulation of PI3K/AKT pathway [125]. Inflammatory cytokines are involved in the mediation of osteoclastogenesis, inducing the development of bone resorption and osteoporosis. AC may function as an anti-resorptive agent and inhibit osteoclast differentiation by inactivating the expression of RANKL, p38 MAPK, NF-κB, c-Fos, and NFATc1, resulting in reduction of bone loss [126]. Diabetes mellitus (DM) may cause the dysregulation of bone metabolism, resulting in bone loss and osteoporosis (OP). AC can enhance the proliferative activity and differentiation of high glucose-treated MC3T3-E1 cells. The underlying mechanism might be associated with the promotion of IGF-1/BMP/PI3K/mTOR signaling pathway by AC. Furthermore, the molecular docking study shows that AC can fit well with the active site of IGF-1R by forming 3 hydrogen bonds with Thr1080, Phe1044, and Lys1030 [127] (Table 1). In a rat model of OP combined with AD, AC can increase the mean bone mineral density, improve the trabecular bone mass and microarchitecture, and increase the ability of learning and memory by inhibition of oxidative stress, mediation of acetylcholine metabolism, and protection of neurons in hippocampus [128].

11. Anti-microorganism

The anti-bacterial activity of AC against *Staphylococcus aureus* has been investigated, and AC can inhibit leucine incorporation and affect protein synthesis [21] (Fig. 6). The eukaryotic-like serine/threonine phosphatase (Stp1), a protein phosphatase, has been associated with the mediation of various virulence factors of *Staphylococcus aureus*. Deficiency of Stp1 gene exhibits reduction of pathogenicity of *S. aureus*, indicating its potential roles in anti-virulence drug development. AC has been screened and identified as an effective inhibitor of Stp1 by competitive and allosteric mechanisms. M39, G41, H42, R161, and N162 have been associated with the affinity of AC for competitive binding, while R122, S136, D137, N142, and V145 have been involved in the allosteric binding [129]. Sortase A (SrtA) in Gram-positive pathogenic bacteria is responsible for anchoring to the cell wall and considered as the potential drug target. The bioactivity of SrtA from *S. aureus* is Ca^{2+}-dependent due to the interaction between Ca^{2+} and residues E105, E108, D112, and E171. In contrast, SrtA from *Streptococcus suis* is Ca^{2+}-independent, and Ca^{2+} position is replaced by a lysine residue. Specifically, K111 forms a salt bridge with D180. AC has been identified as a novel SrtA inhibitor with an IC_{50} value of 36.3 μM, and the endogenous SrtA activity indicates 86 % inhibition against *S. aureus* and 98 % against *Streptococcus suis* [130]. However, whether the discrepancy is associated with Ca^{2+} or the salt bridge is still needed to be further elucidated.

Respiratory syncytial virus (RSV) has become one of the main causes of lower respiratory tract infections. AC is the potential effective component of the herbs *Plantago asiatica* and *Clerodendrum trichotomum*. Both AC and the two herbs extract are active against RSV infection in vivo and in vitro [131]. When fighting against viral infections, T lymphocytes are essential for acquired immunity in the human body. AC exhibits inhibitory activity against vesicular stomatitis virus by increasing ERK activity and up regulating the expression of T-bet/IFN-γ in the CD^{4+} and CD^{8+} subsets of T cells particularly [132]. Pneumolysin is an important virulence factor for *Streptococcus pneumoniae* to infect the host and produce inflammatory responses. AC has been known not to exhibit bacteriostatic activity but to ameliorate pneumolysin-induced cytotoxicity. Molecular dynamic simulation and mutational analysis suggests that AC can interact with the cleft between domain 3 and domain 4 in pneumolysin, leading to inhibition of pneumolysin oligomerization and hemolytic activity [133].

Docking simulation shows that AC exhibits the best binding affinity among the tested compounds by forming the hydrogen bonds with Gly496 of the SARS-CoV2-CTD. However, AC does not inhibit ACE2, which plays a protective activity against acute respiratory distress syndrome and acute lung injury in vivo and is a value for the promising anti-SARS-CoV2 potentials [134]. A study reports that AC mainly binds to the residues F140, G138, Q189, and G170 by forming hydrogen bonds in the highly conserved and catalytic region of SARS-CoV2 main protease (3CLpro/Mpro) with a significant binding energy of − 42.686 kcal/mol [37]. Another docking study indicates that AC exhibits the highest activity of the tested compounds against SARS-CoV2 main protease by forming hydrogen bonds with Cys44, Met49, Asn142, Hie164, Glu166, and Thr190. In vitro on SARS-CoV2 Egyptian strain, AC shows similar biological activity to the positive drug GC376 and has an IC_{50} value of 43 nM [135].

AC, isolated from *Stachytarpheta cayennensis*, has been demonstrated to be effective against *Leishmania* infection (an EC_{50} value of 19 μM) by inhibiting the activity of arginase (K_i = 0.7 μM), which acts as an enzyme in the biosynthesis pathway of polyamines that contribute to the synthesis of the anti-oxidant compound trypanothione and the infectivity of parasite [136]. Deficiency of arginase substrate, L-arginine, may lead to oxidative stress, which can induce apoptosis and kill *Leishmania*. AC has been shown the inhibitory activity against extracellular promastigotes of *Leishmania amazonensis* [136]. In addition, AC selectively inhibits the parasite arginase and acts on the intracellular amastigotes of *L. amazonensis* (an EC_{50} value of 32 μM), which resists to the NO production induced by LPS and IFN-γ. However, AC does not affect the expression of enzyme and cytokines by murine macrophages [137].

12. Hepatoprotection activity

The pathological development of alcoholic hepatitis may involve oxidative stress, inflammatory responses, metabolic dysregulation, and apoptosis. These can be effectively inhibited by AC treatment, which significantly attenuates the activation of NF-κB signaling in HepG2 cells [20]. The effects of AC on lipid accumulation in HepG2 cells have been investigated, and the results from RNA-seq assays indicate that AC ameliorates the lipid accumulation by mediating the glycolysis, AMPK signaling, and fatty acid degradation [138]. These might be associated with the anti-oxidative activity of AC. In carbon tetrachloride (CCl_4)-induced mice, AC consistently decreases MDA production and increases GSH generation. AC also protects against $FeCl_2$-ascorbate-induced lipid peroxidation. Specifically, AC down regulates the bioactivity of cytochrome P450 2E1, including p-nitrophenol and aniline hydroxylation [139] (Fig. 6).

13. Renal protection

Leukocyte accumulation in the glomeruli is associated with the progression of crescentic anti-GBM nephritis. AC has been reported to suppress the accumulation of the total leukocytes, ED-1-positive cells, CD4-positive cells, CD8-positive cells, IL-2 receptor-positive cells, and Ia-positive cells in the rat glomeruli [140]. In addition, AC decreases the expression of ICAM-1, which can be activated by inflammatory cytokines in HUVECs and rat mesangial cells [141]. T helper type 22 (Th22) lymphocyte is involved in the progression of IgA nephropathy (IgAN) by activating the expression of CCL20, CCL22, and CCL27. It has been demonstrated that AC inhibits the proliferation of Th22 cells, suppresses the expression of CCL20, CCL22, and CCL27, and relieves the productions of inflammatory cytokines, such as IL-1, IL-6, and TNFα in mesangial cells. The expression of TGF-β1 is associated with mesangial cell fibrosis. AC can also significantly decrease the expression of TGF-β1 in mesangial cells, ameliorating the progression of IgAN [142].

14. Skin protection

Ultraviolet (UV) radiation-stimulated ROS is involved in photodamage, and long-term oxidative stress can induce skin photo-aging by increasing MMPs synthesis and collagen degradation. AC has been shown the protective activity against UV-stimulated ROS and thymus and activation-regulated chemokine (TARC) synthesis by up regulation of NRF2 signaling and down regulating NF-κB pathway. In addition, AC may effectively decrease the expression of MMP-1 by activating TGFβ/Smad signaling and inhibiting MAPK/AP-1 pathway [143]. In X-ray radiation-treated human skin fibroblasts, AC significantly inhibits the production of ROS, the up regulation of pro-caspase-3 expression, and the down regulation of Bcl-2 expression by ameliorating the activity of ERK and JNK pathways [144].

ECM remodeling plays a critical role in wound healing, MMP-2 is an ECM degrading enzyme involved in cell migration and proliferation during wound healing. AC has been shown to activate the expression of the precursor of MMP-2 (proMMP-2) but not MMP-2 in normal human dermal fibroblasts. The possible mechanism might be associated with activation of membrane-type 1 MMP expression and PI3K signaling pathway by AC [145]. Treatment with AC can increase the migration of keratinocytes and decrease the expression of TNFα, IL-6, IL-12p70, MCP-1 and IFNγ in LPS-treated N9 cells [146].

15. Miscellaneous section

Many traditional herbs have been used for treating the collapse and exhaustion. AC has been isolated as an active compound from *Pedicularis densispica* and found that it can prolong the time to exhaustion of rats in a treadmill exercise, attenuate the expression of 5-HT and TPH2, and enhance the expression of 5-HT1B [147]. Pancreatic lipase accounts for 50–70 % hydrolysis of the total dietary fats, controlling the fat absorption or obesity. AC, isolated from the Chinese tea Ligustrum purpurascens kudingcha, can act as a non-competitive lipase inhibitor with a binding constant K_a value of 1.88×10^4 M and by forming hydrogen bonds with Lys271, Leu272, and Thr68 residues of lipase [148]. In lacaune ewes, particularly in the first 20 days after parturition, foods supplemented AC can improve the production of milk. Additionally, AC also improve the blood lipid profile and liver functions. This might be associated with anti-oxidative activity of AC [149].

Varicocele within the scrotum is considered as a factor contributing to male-factor infertility. Specifically, varicocele may induce testicular dysfunction, including inflammation, oxidative stress, hormonal imbalance, and apoptosis. AC can significantly enhance sperm viability, increase Johnson's score, and decrease apoptotic index. These might be associated with up regulation of the hypothalamus-pituitary-gonadal axis by AC [150]. AC exhibits anti-estrogenic effects in ERα- and Erβ--transfected HeLa cells. In addition, AC can reverse the effects of E2 by ERα [151]. H^+ K^+-ATPase plays a critical role in gastric acid secretion. AC has been identified as the active component of Tectoma grandis for protecting against cold restraint- and pyloric ligation-induced gastric ulcer. AC inhibits H^+ K^+-ATPase activity with an IC_{50} value of 60.98 μg/mL [152]. In RBL-2H3 cells, AC inhibits the increase of intracellular Ca^{2+} mobilization, which is associated not with intracellular Ca^{2+} release of PLC activity but with the influx of extracellular Ca^{2+}, and inhibit melittin (1 μM)-induced histamine release by blocking the Ca^{2+}-independent PLA2 pathway [153].

Higher level of uric acid in the blood is associated with hyperuricemia and gout. Xanthine oxidase (XOD) is the key enzyme in the purine metabolic pathway. AC at the dose of 54 mg/kg can effectively reduce the serum level of uric acid in the hyperuricemic rats, and the IC_{50} value of inhibiting XOD activity is 81.15 μg/mL. Mechanically, the phenyl rings of AC can combine to the molybdopterin domain (a hydrophobic pocket) with a low binding energy of − 6.0 kcal/mol by forming hydrogen bonds with several residues, altering the hydrogen-bond network in the active center of XOD and changing its conformation [154]. Carbonic anhydrase (CA) is associated with carbon dioxide and ion transport, respiration, fluid balance, and acid-base balance and has been involved in many diseases, such as glaucoma, diabetes, and cancers. Targeting CA can be the potential therapeutic strategy. AC has been shown the inhibitory activity against human CA I and II isoenzymes with IC_{50} values of 1.73 μM and 1.90 μM, respectively. The docking study indicates the binding of AC to CA I and II with the K_i values of 2.00 μM and 1.49 μM, respectively [155].

16. Future perspective

Herbal medicines are good for the clinical management of chronic diseases, such as anxiety or depression. AC is one the main effective compound of the powdered leaves of *Aloysia polystachya*, which was involved in a phase-2 clinical trial for treating anxiety symptoms [156]. A single-center, double-blind, and randomized phase II study of AC on the efficacy and tolerability for modulating the platelet aggregation (PA) has been investigated. 100 subjects are included and 50 mg or 100 mg AC is administered. Two weeks of treatment with 50 mg AC does not modify PA values. However, two-week treatment with 100 mg AC significantly decreases the values of PA. No serious adverse effects are reported in this study. These indicates that AC at the dose of 100 mg might reduce PA values in patients with cardiovascular risk factors [157]. AC ameliorates PA values not by arachidonic acid but by ADP stimulation in the blood from aspirin-treated patients. In vitro study, AC may mildly attenuate PA triggered by arachidonic acid and ADP [158]. The anti-oxidative activity of polyphenols may be altered at different temperature and pH conditions due to alterations in chemical structure. Alternatively, mixture of parent form and its structure transformation make them to interact with each other in the biological activity for synergy or antagonism or additive effects, and these may be dependent

on the assays used and/or the mixture composition.

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CRediT authorship contribution statement

Longhuo Wu provided the idea of this paper. Yaosheng Xiao and Qun Ren conducted the experiments and revised and finalized the paper. All authors approved the final paper.

Conflict of Interests

The authors declare no conflict of interests.

Data Availability

The data used to support the findings of this study are included within the article.

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