Journal of Ethnopharmacology 349 (2025) 119868

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Ganoderic acid A: an in-depth review of pharmacological effects and molecular docking analysis

Qi Sui [a,c], Chengkai Zhu [a,c], Sha Shi [a,c], Jiaqi Xu [a,c], Jingnan Zhang [a,c], Ao Wang [a,b,c,d], Peng Chen [b,*], Guang Liang [a,c,d,**], Yi Zhang [a,c,***]

[a] School of Pharmaceutical Sciences, Hangzhou Medical College, Hangzhou, Zhejiang, 310012, China
[b] Department of Pharmacy, School of Medicine, Hangzhou City University, 50 Huzhou Rd, Hangzhou, Zhejiang, 310015, China
[c] Zhejiang TCM Key Laboratory of Pharmacology and Translational Research of Natural Products, Hangzhou Medical College, Hangzhou, Zhejiang, 310012, China
[d] Chemical Biology Research Center, School of Pharmaceutical Sciences, Wenzhou Medical University, Wenzhou, Zhejiang, 325035, China

ARTICLE INFO

Keywords:
Ganoderic acid A
Pharmacology
Pharmacokinetics
Network pharmacology
Molecular docking

ABSTRACT

Ethnopharmacological relevance: Ganoderic acid A (GAA, $C_{30}H_{44}O_7$) is one of the most abundant and active components of Ganoderic acids (GAs). GAs are highly oxidized tetracyclic triterpenoid compounds mainly derived from *Ganoderma lucidum* (Curtis) P. Karst (Chinese: 灵芝). GAA is primarily isolated from the fruiting body of *Ganoderma lucidum*. Modern pharmacological investigations have established the broad pharmacological effects of GAA, highlighting its notable influence on managing various conditions, including inflammatory diseases, neurodegenerative diseases, and cancer. This review provides a comprehensive summary of GAA's pharmacological activities.

Material and methods: The literature in this review were searched in PubMed and China National Knowledge Infrastructure (CNKI) using the keywords "Ganoderic acid A", "Pharmacology" and "Pharmacokinetics". The literature cited in this review dates from 2000 to 2024.

Results: According to the data, GAA exerts anti-inflammatory, antioxidant, antitumor, neuropsychopharmacological, hepatoprotective, cardiovascular, renoprotective, and lung protective effects by regulating a variety of signal transduction pathways, such as nuclear factor kappa-B (NF-κB), Janus kinase/signal transducer and activator of transcription (JAK/STAT), Toll-like receptor 4 (TLR4), nuclear factor erythroid 2-related factor-2 (Nrf2), phosphoinositide-3-kinase (PI3K)/AKT, mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), and Notch. Given its promising pharmacological activity, GAA holds excellent potential for treating human diseases. The pharmacokinetic properties of GAA have also been reviewed, revealing low bioavailability but high absorption and elimination rates. In addition, network pharmacology and molecular docking analyses verified that GAA plays a role in multiple diseases through MAPK3, tumor necrosis factor (TNF), caspase-3 (CASP3), peroxisome proliferator-activated receptor gamma (PPARG), and β-catenin (CTNNB1) signaling pathways.

Conclusion: GAA plays a pivotal role in various pathological and physiological processes, boasting broad application prospects. Furthermore, the network pharmacological results reveal the mechanisms of GAA in the treatment of multiple diseases. In the future, it is necessary to conduct further experiments to elucidate its specific mechanism of action, thus laying the foundation for the scientific utilization of GAA.

Abbreviations

AD	Alzheimer's disease	ERK	extracellular signal-regulated kinase

(*continued on next column*)

(*continued*)

Abbreviations

ALT	alanine aminotransferase	ESR1	estrogen receptor 1

(*continued on next page*)

*** Corresponding author.
** Corresponding author. School of Pharmaceutical Sciences, Hangzhou Medical College, Hangzhou, Zhejiang, 310012, China.
* Corresponding author. School of Pharmaceutical Sciences, Hangzhou Medical College, Hangzhou, Zhejiang, 310012, China.
E-mail addresses: chenp@zucc.edu.cn (P. Chen), wzmcliangguang@163.com (G. Liang), 1020437493@qq.com (Y. Zhang).

https://doi.org/10.1016/j.jep.2025.119868
Received 20 November 2024; Received in revised form 24 March 2025; Accepted 22 April 2025
Available online 30 April 2025

(*continued*)

Abbreviations			
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid	FD	functional dyspepsia
AMPK	AMP-activated protein kinase	FXR	farnesoid X receptor
AP-1	activator protein-1	GAA	ganoderic acid A
AS	atherosclerosis	GAs	ganoderic acids
AST	aspartate aminotransferase	GBM	glioblastoma
ATG5	autophagy-related proteins 5	GO	Gene Ontology
AUC	area under the curve	GPX	glutathione peroxidase
Axl	Axl receptor tyrosine kinase	GSH	glutathione
Aβ	amyloid-β	H_2O_2	hydrogen peroxide
Bax	Bcl-2-associated X	HCC	human hepatocellular carcinoma
Bcl-2	B-cell lymphoma 2	HDL-C	high-density lipoprotein cholesterol
BDNF	brain-derived neurotrophic factor	HFD	high-fat diet
BIM	Bcl-2-like protein 11	HLA	human leukocyte antigen
BP	biological process	ICAD	inhibitor of caspase-activated DNase
CASP3	caspase-3	IL	interleukin
CaSR	calcium-sensing receptor	iNOS	inducible nitric oxide synthase
CC	cellular component	IκBα	inhibitor of κB α
CCl_4	carbon tetrachloride	JAK	Janus kinase
CD36	cluster of differentiation 36	JNK	c-Jun N-terminal kinase
Cdks	cyclin-dependent kinases	KEGG	Kyoto Encyclopedia of Genes and Genomes
CIA	collagen-induced rheumatoid arthritis	LC3	microtubule-associated Protein 1 Light Chain 3
circFLNA	circRNA flamin A	LDH	lactate dehydrogenase
CK	creatine kinase isoenzyme	LPS	lipopolysaccharide
CKIs	cyclin-dependent kinase inhibitors	LRRK2	leucine-rich repeat protein kinase-2
Cmax	peak drug concentration	MAPK	mitogen-activated protein kinase
CNKI	China National Knowledge Infrastructure	Mcl-1	myeloid leukemia-1
COVID-19	coronavirus disease 2019	MDA	malondialdehyde
COX-2	cyclooxygenase 2	MF	molecular function
CREB	cAMP-response element-binding protein	MIR	myocardial ischemia-reperfusion
CTNNB1	β-catenin	MMP	matrix metalloproteinase
CYP1A1	cytochrome P450 family 1 subfamily A member 1	MPO	myeloperoxidase
CYP450s	cytochrome p450s	MS	multiple sclerosis
DDP	cisplatin	mTOR	mammalian target of rapamycin
DNA-PKcs	DNA-dependent protein kinase catalytic subunit	MyD88	Myeloid differentiation factor 88
EBV	Epstein-Barr virus	NAFLD	non-alcoholic fatty liver disease
ECM	extracellular matrix	NASH	non-alcoholic steatohepatitis
ER	endoplasmic reticulum	NDRG2	N-myc downstream-regulated gene 2
NF-κB	nuclear factor kappa-B	SH	src homology
NGF	nerve growth factor	Smad3	mothers against decapentaplegic homolog 3
NLRP3	nucleotide-binding domain leucine-rich repeat pyrin domain containing 3	SOCS1	suppressor of cytokine signaling 1
NO	nitric oxide	SOD	superoxide dismutase
NP	nucleus pulposus	SR	scavenger receptors
NR3C1	nuclear receptor subfamily 3 group C member 1	SR-A	SR class A
Nrf2	nuclear factor erythroid 2-related factor-2	SREBP	sterol regulatory element-binding protein
OPG	osteoprotegerin	STAT	signal transducer and activator of transcription

(*continued on next column*)

(*continued*)

Abbreviations			
ox-LDL	oxidized low-density lipoprotein	t1/2	half-life
PADI4	peptidyl arginine deiminase type IV	TBIL	total bilirubin
Pak1	CDC42-activated kinase 1	TC	cholesterol
PARP	poly(ADP ribose) polymerase	TCM	traditional Chinese medicine
PD	Parkinson's disease	TG	triglyceride
pG4DNA	parallel G-quadruplex DNA	TGF-β	transforming growth factor-β
PGC-1α	peroxisome proliferator-activated receptor γ coactivator 1-α	TGL	triterpenoids of Ganoderma lucidum
PGE2	prostaglandin E2	Th17	T helper 17
PI3K	phosphoinositide-3-kinase	TLR4	Toll-like receptor 4
PPARG	peroxisome proliferator-activated receptor gamma	Tmax	time to peak concentration
PPARγ	peroxisome proliferator-activated receptor gamma	TNF	tumor necrosis factor
PPI	protein-protein interaction	Treg	regulatory T
PPRE	PPAR-responsive element	Trx	thioredoxin
PSD	post-stroke depression	Txnip	Trx interaction protein
RA	rheumatoid arthritis	UFLC-MS/MS	ultra-fast liquid chromatography-tandem mass spectrometry
RANKL	receptor activator of nuclear factor kappa- B ligand	uPA	urokinase-type plasminogen activator
RB	retinoblastoma protein	UPLC-MS/MS	ultra-high performance liquid chromatography-tandem mass spectrometry
RhoA	ras homolog family member A	UVB	ultraviolet radiation B
ROCK	Rho-associated protein kinase	W/D	wet dry weight
ROS	reactive oxygen species	XRCC1	X-ray repair cross-complementing 1
RXR	retinoid X receptor		
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2		

1. Introduction

Ganoderma lucidum (Curtis) P. Karst, commonly known as Lingzhi, is an extensively used medicinal substance in China, highly valued for its therapeutic benefits. Its medicinal properties have been recorded in several ancient texts, including the Shen Nong Ben Cao Jing (Shennong Materia Medica) and Ben Cao Gang Mu (Compendium of Materia Medica) (Lin, 2019). *Ganoderma lucidum* comprises two parts: the mycelium and the fruiting body. It includes various active compounds, such as polysaccharides, triterpenoids, sterols, adenosine, and amino acids (Gong et al., 2019). Active ingredients play a significant role in the human body. With further research, it has been discovered that the active substances found in *Ganoderma lucidum* have various benefits such as immunoregulation, anti-inflammatory, anti-oxidative, anti-tumor, anti-atherosclerotic, hypolipidemic, anti-fibrotic, hepatoprotective, and other positive effects (Sanodiya et al., 2009). Ganoderic acids (GAs) are the main bioactive triterpenoid compound with high medicinal value in *Ganoderma lucidum*. There are about 171 known GAs (Baby et al., 2015), among which Ganoderic acids A, B, C2, D, DM, F, H, S, X, and Y are the compounds that exhibit the main biological activities in GAs (He et al., 2023; Liang et al., 2019).

Ganoderic acid A (GAA), one of the major triterpene constituents in *Ganoderma lucidum*, is the most abundant and biologically active form of GAs, which has garnered significant attention from researchers due to its superior pharmacological potential compared to other classes of GAs (Ma et al., 2021). In recent years, there has been extensive research on the pharmacological effects of GAA. Results from these studies have

revealed that GAA possesses multiple beneficial properties, including anti-inflammatory, antioxidant, antitumor, neuro-psychopharmacological, hepatoprotective, cardiovascular, renoprotective, and lung protective effects (Jiang et al., 2018; Meng et al., 2020; Wan et al., 2019; Xu et al., 2019; Y.G. Yang et al., 2018; Zhang et al., 2020, 2021; Zheng et al., 2022). As a result, GAA may hold promise as a potential drug candidate for the treatment of various diseases, including inflammatory diseases, neoplastic diseases, and neurological disorders such as Alzheimer's disease (AD), epilepsy, and depression.

However, despite the growing body of research on GAA, there is currently a lack of systematic review on its pharmacological properties and pharmacokinetic characteristics. To address this gap, this paper aims to conduct a comprehensive and systematic summary of the pharmacological activities, mechanisms of action, and pharmacokinetic properties of GAA, based on literature from the last 24 years, from 2000 to 2024, retrieved from the China National Knowledge Infrastructure (CNKI) and PubMed databases. In addition, proteins or genes and their associated signaling pathways that contribute to the disease-fighting capabilities of GAA were collected for protein-protein interaction (PPI) analysis. This was complemented by molecular docking studies involving proteins (or genes) with significant connectivity and GAA, along with bioinformatics assessments encompassing Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses. These approaches are expected to generate innovative concepts for future studies and potentially enhance the pharmaceutical development of GAA, offering fresh perspectives for its investigative exploration.

2. Physical and chemical properties of GAA

GAA ($C_{30}H_{44}O_7$, Fig. 1) is a triterpenoid mainly present in *Ganoderma lucidum* and is one of the most common GAs (Ahmad et al., 2022; Liang et al., 2019). Its basic skeleton is a highly oxidized lanostane-type tetracyclic triterpenoid structure. Lanostane-type triterpenoids are a class of natural compounds with specific skeletons. These compounds exhibit a range of biological effects within living organisms, such as anti-inflammatory, antioxidant, and antitumor properties. As a representative of this class of compounds, GAA contains multiple hydroxyl (-OH) and carbonyl (C=O) functional groups in its structure, which give GAA its diverse biological activities (Gill et al., 2017; Liang et al., 2019; Yao et al., 2019). The polycyclic structure and the presence of double bonds in the molecular structure of GAA lead to its high degree of unsaturation, which may be one of the reasons for its biological activity (Gill et al., 2016a, 2019). Specific chiral centers in the GAA molecule, such as the hydroxyl groups at positions C-7 and C-15, exist in an α configuration, while the carbonyl groups at C-11 and C-23 exhibit specific stereochemical features. GAA appears as a white or off-white powder with a molecular mass of 516.673 and a specific gravity of 1.22 g/cm^3. A summary of its physicochemical attributes can be found in Table 1.

Table 1
Physical and chemical properties of GAA.

Name	Ganoderic acid A
Alias	lanost-8-en-26-oic acid, 7, 15-dihydroxy-3, 11, 23-trioxo-, (7b,15a,25R)-
Source	Ganoderma
CAS No	81907-62-2
Molecular formula	$C_{30}H_{44}O_7$
Molecular weight	516.673
Form	Powder
Color	White to off-white
Density	1.22
Melting point	118~123 °C
Boiling point	690.1 ± 55.0 °C at 760 mmHg
Refractive index	1.565
Solubility	DMSO: soluble 62.5 mg/mL, Ethanol: soluble≥50 mg/mL
Flash point	385.1 °C
Vapor pressure	0.0 ± 4.9 mmHg at 25 °C
Polar surface area	129 Å^2
LogP	2.18
pKa	4.78 ± 0.23 (Predicted)
Polarizability	54.4 ± 0.5*10^{-24} cm^3
Enthalpy of vaporization	115.7 ± 6.0 kJ/mol
Surface tension	53.2 ± 5.0 dyne/cm
Molar refractivity	137.2 ± 0.4 cm^3
Molar volume	421.5 ± 5.0 cm^3
Storage conditions	4 °C, sealed storage, away from moisture and light (In solvent: −80 °C, 2 years; −20 °C, 1 year)

3. Pharmacological activities of GAA

Numerous investigations have shown that GAA manifests a spectrum of pharmacological effects by modulating multiple signaling pathways, including the nuclear factor kappa-B (NF-κB), Janus kinase/signal transducer and activator of transcription (JAK/STAT), TLR4, nuclear factor erythroid 2-related factor-2 (Nrf2), phosphoinositide-3-kinase (PI3K)/AKT, and mitogen-activated protein kinase (MAPK).

3.1. Anti-inflammatory activity of GAA

Inflammation is a natural process that helps the body fight off foreign pathogens and maintain equilibrium. It serves as a protective response to infection, injury, or irritation and plays a crucial role in restoring damaged tissue structure and function (Medzhitov, 2008; Tracey, 2002). The inflammatory response typically involves several components, including inducers, pattern recognition receptors, inflammatory mediators, and target tissues, each of which plays a distinct role in the inflammatory pathway. When our body experiences an inflammatory response that lasts for a long time, it can lead to tissue dysfunction, which may eventually develop into a chronic disease (Medzhitov, 2010).

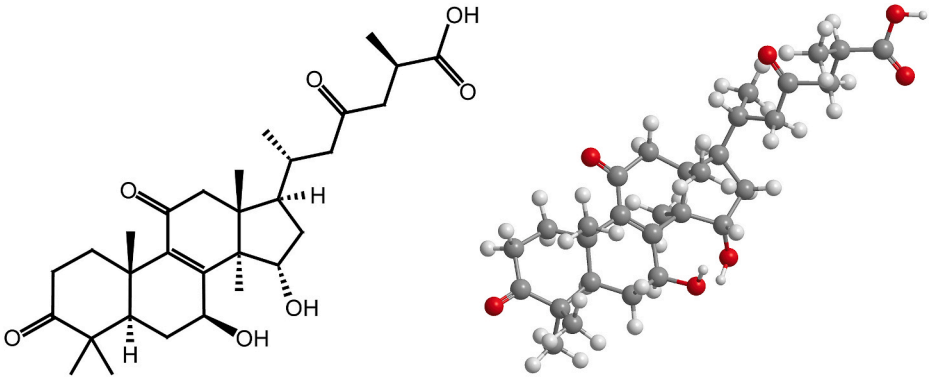

Fig. 1. 2D structure diagram and 3D optimized structure of GAA (PubChem CID: 471002).

Therefore, pursuing drugs that can diminish inflammation has gained much attention in research. Several experimental studies have demonstrated that GAA has therapeutic properties in different models of inflammation (Cao et al., 2020; Lu et al., 2021; Wu et al., 2022). To elaborate, the signaling pathways typically associated with GAA treatment for inflammation are briefly outlined below.

NF-κB is a group of nuclear protein factors that play a significant role in regulating gene expression. These factors are essential for the transcriptional regulation of genes involved in a wide range of biological processes, such as the inflammatory response, cellular proliferation, differentiation, apoptosis, immune response, and tumorigenesis (Hayden et al., 2006; Oh and Ghosh, 2013). The activity of NF-κB in cells is strictly regulated. If NF-κB activation goes out of control, it can disrupt the body's balance and lead to the development of various conditions, including cancers, neurodegenerative diseases, telangiectasia, chronic inflammation, and autoimmune diseases (Bonizzi and Karin, 2004; Karin and Greten, 2005). Therefore, studying the regulation mechanism of NF-κB activity is essential for understanding the basic theory of cell signal transduction and developing new treatments for related diseases (Hayden and Ghosh, 2008). In the collagen-induced rheumatoid arthritis (CIA) model, GAA (20 and 40 mg/kg) can inhibit the NF-κB signaling pathway and reduce the levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β in serum and synovium, thus playing a therapeutic role in rheumatoid arthritis (RA) (Cao et al., 2020). In human nucleus pulposus (NP) cells induced by IL-1β, GAA (6.25, 12.5, and 25 μM) reduces inflammation by inhibiting the NF-κB pathway. It also suppresses the levels of nitric oxide (NO), prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX-2), TNF-α, and IL-6 in cells (Zheng et al., 2022). At the same time, GAA inhibited the expression of matrix metalloproteinase (MMP)-3 and MMP-13 and promoted the expression levels of extracellular matrix (ECM) proteins, collagen II, and aggrecan, thereby reducing ECM degradation in NP cells (Zheng et al., 2022). Another experimental study showed that GAA (25 and 50 μM) plays an anti-inflammatory role in osteoarthritis by inhibiting the up-regulation of p65 phosphorylation and the down-regulation of inhibitor of κB α (IκBα), inhibiting the activation of the NF-κB pathway, reducing the expression of COX-2 and iNOS, and inhibiting endoplasmic reticulum (ER) stress (Liu et al., 2024). GAA can also protect chondrocytes from apoptosis by increasing the level of anti-apoptotic proteins B-cell lymphoma 2 (Bcl-2) and inhibiting the expression of pro-apoptotic proteins Bcl-2-associated X (Bax) and caspase-3 induced by IL-1β (Liu et al., 2024). In addition, in the destabilization of the medial meniscus model, GAA can inhibit the secretion of MMP-13 by regulating the receptor activator of nuclear factor kappa-B ligand (RANKL)/osteoprotegerin (OPG) ratio, thereby improving osteoarthritis (Wu et al., 2022).

The molecular complex formed by TLR4 and NF-κB is an important signaling pathway that regulates the expression of various cytokines and mediates the immune response to pathogens (Medvedev, 2013). Activation of TLR signaling pathways further promotes downstream NF-κB signaling (Kawai and Akira, 2007). Experimental studies have shown that in the mouse asthma model established in vitro by ovalbumin, GAA (20 and 40 mg/kg) down-regulates the levels of TLR4, Myeloid differentiation factor 88 (MyD88), and p-NF-κB in lung tissue by inhibiting the TLR/NF-κB signaling pathway, and reduces the expression of IL-4, IL-5, and IL-13, thus alleviating lung inflammation in asthmatic mice (Lu et al., 2021). In cells of the NP induced by hydrogen peroxide (H_2O_2), GAA (4 and 8 μM) prevents H_2O_2-induced apoptosis, oxidative stress, and inflammation by inhibiting the TLR4/nucleotide-binding domain leucine-rich repeat pyrin domain containing 3 (NLRP3) signaling pathway. This effect was demonstrated by a decrease in the levels of inflammatory cytokines IL-1β, IL-6, and TNF-α, as well as a decrease in the levels of matrix-degrading proteases (MMP-3, MMP-13, ADAMTS4, and ADAMTS5), and an increase in the expression levels of collagen II and aggrecan (Wang et al., 2022).

The JAK/STAT signaling pathway is a fundamental regulatory mechanism controlling gene transcription in various biological processes, including inflammation (Leonard and O'Shea, 1998). This pathway is initiated by JAKs in response to extracellular signal activation, which phosphorylates and activates STATs (Boyle et al., 2015). The JAK/STAT signaling pathway has become a promising therapeutic target for inflammatory treatment interventions. In the CIA mouse model, GAA (20 and 40 mg/kg) significantly reduced the levels of P-STAT3 and suppressor of cytokine signaling 1 (SOCS1), regulating the JAK/STAT signaling pathway by down-regulating the expression of P-JAK3 and P-STAT3 proteins, thereby improving RA (Cao et al., 2020).

Taken together, GAA exerts significant anti-inflammatory activity by regulating the involvement of NF-κB, TLR4, JAK/STAT signaling pathway, and inflammatory cytokines, making it a valuable therapeutic option for inflammation-related diseases. While preclinical evidence is promising, further studies are needed to validate its efficacy and safety in clinical settings, particularly for conditions like RA and osteoarthritis. Future research should also explore optimal dosing and potential synergies with existing therapies.

3.2. Antioxidant activity of GAA

Its antioxidant effect is another important biological property of GAA, helping to combat oxidative stress. Oxidative stress results from an imbalance between intracellular oxides and the body's ability to neutralize their hazardous effects. Various risk factors often trigger this imbalance and can damage the body's biological system (Valko et al., 2006). Specifically, oxides mainly refer to reactive oxygen species (ROS), which are generally produced by the body's regular metabolism. They can kill harmful microorganisms in the body, participate in the body's immune process, and also participate in signal transduction as intracellular second messengers to maintain the normal function of tissues and cells (Forrester et al., 2018). However, when the production rate is greater than the clearance rate, excessive or persistent ROS accumulation in the body can cause various adverse biological reactions, leading to the occurrence of diseases(Yang and Lian, 2020). Two main antioxidant systems rely on the presence of thiol groups: the glutathione (GSH) antioxidant system and the thioredoxin (Trx) antioxidant system. Both systems possess protective mechanisms to safeguard the body against oxidative stress, which induces cellular and tissue damage (Georgiou-Siafis and Tsiftsoglou, 2023; Lu and Holmgren, 2014).

Experimental studies have shown that GAA reduces oxidative stress levels in prostate cancer cells by inhibiting the activation of the STAT3 pathway through binding to the src homology (SH) 2 domain of STAT3. In addition, GAA exerts antioxidant effects by up-regulating the expression of antioxidant enzymes (SOD1, SOD2, and SOD3) and inhibiting ROS and DPPH (Gill et al., 2016a). The Nrf2 signaling pathway plays a crucial role in protecting our body against free radicals by activating various antioxidant genes (Lacher et al., 2015). Imbalances in free radical scavenging are known to cause several diseases (Liu et al., 2022). It has been reported that GAA effectively inhibits cellular proliferation, reduces ROS levels, and down-regulates mRNA expression of Nrf2. When cells were treated with H_2O_2, it increased free radicals, but GAA (20, 50, and 80 μM) could scavenge free radicals and improve antioxidant capacity in a dose-dependent manner (Gill et al., 2017). In human neuroblastoma cells (IMR-32), GAA (20, 50, and 80 μM) scavenges free radicals induced by H_2O_2 and enhances antioxidant capacity in a dose-dependent manner (Gill et al., 2019). Another experimental study found that GAA reduced oxidative stress in NP cells by inhibiting H_2O_2-induced depletion of GSH, superoxide dismutase (SOD), and glutathione peroxidase (GPX) (Wang et al., 2022). In addition, GAA can significantly increase the SOD activity of hippocampal neurons in the epilepsy model, stabilize mitochondrial membrane potential, reduce the damage caused by oxidative stress, and inhibit the apoptosis process, thereby playing an antioxidant role (Jiang et al., 2018).

In conclusion, GAA demonstrates significant antioxidant properties by mitigating oxidative stress through mechanisms such as STAT3

pathway inhibition, up-regulation of antioxidant enzymes, and activation of the Nrf2 signaling pathway. Its ability to scavenge free radicals and stabilize mitochondrial function underscores its potential therapeutic value in addressing oxidative stress-related diseases. However, further research is essential to fully elucidate its mechanisms and explore its clinical applications.

3.3. Antitumor activity of GAA

Tumors are atypical cell clusters within the body that can either be non-cancerous or cancerous. Cancerous tumors rank as the second most common cause of mortality globally (Siegel et al., 2019). Due to the increasing prevalence of cancer worldwide, it is imperative to explore the development of prospective medications capable of efficiently addressing and inhibiting tumor formation and advancement. Recently, increasing attention has been given to the antitumor effects of GAA. GAA exhibits antitumor effects against a spectrum of tumor types, encompassing breast cancer, osteosarcoma, glioblastoma (GBM), meningioma, liver cancer, lung cancer, and nasopharyngeal cancer. A multitude of research has validated that GAA primarily exerts its antitumor effects through the inhibition of cell growth and proliferation (Yang et al., 2018), inducing cell cycle arrest (Wang et al., 2017), inducing cell apoptosis (Cheng and Xie, 2019), and inhibiting cell migration and invasion (Jiang et al., 2008). A synopsis of the principal cellular signaling pathways and associated proteins that contribute to the antitumor effects of GAA is depicted in Fig. 2.

3.3.1. Inhibition of cell growth and proliferation

Malignant tumors are characterized by their swift expansion and multiplication, which underpins the progression of cancer. Consequently, limiting the growth and proliferation of these tumor cells can significantly impede the advancement of cancer. GAA has an inhibitory effect on cell proliferation in a variety of cancer types. GAA can inhibit the proliferation, viability, and ROS levels in lung and liver cancer cells (Gill et al., 2016b, 2017). Studies have reported that GAA can inhibit tumor growth and proliferation by down-regulating the expression of STAT3 in prostate cancer cells (PC-3) (Gill et al., 2016a). GAA can also inhibit the proliferation and viability of neuroblastoma by down-regulating the expression of Notch-1 mRNA (Gill et al., 2019). Molecular docking showed that GAA targeted β-catenin in the Wnt signaling pathway and inhibited the proliferation, viability, and intracellular ROS in pancreatic cancer RIN-5F cells in a dose-dependent manner (Gill et al., 2018). In addition, studies have proven that inducing cell cycle arrest and inducing apoptosis can effectively inhibit the proliferation and growth of cancer cells (Das et al., 2020; Radwan et al., 2015; Yao et al., 2012).

3.3.1.1. Induction of cell cycle arrest. The irregular disruption of cell cycle regulation is a crucial factor in the evolution of tumors, and halting the cell cycle can directly impede cell growth. As a result, cell cycle arrest serves as a means to inhibit tumor growth (Schwartz and Shah, 2005).

Many molecules related to cell cycle regulation can be divided into three categories: cyclin-dependent kinases (Cdks), cyclins, and small cyclin-dependent kinase inhibitors (CKIs). Existing studies have found that GAA-induced cell cycle arrest involves the first two classes. The cell cycle's orchestration is governed by an array of genes, with Cdks at the heart of this regulatory framework. Cdks function as positive regulatory elements within the cell cycle control system. Activated Cdks exhibit protein kinase activity and initiate or regulate major cell cycle events by phosphorylating different substrate proteins. The abnormal expression of cyclins combines with Cdks to form a complex, leading to continuous activation of Cdks, abnormal cell cycle activity, dysregulation, and ultimately uncontrolled cell proliferation and tumor formation (Lim and Kaldis, 2013). Experimental studies indicate that GAA (0.10, 0.25, and 0.50 mM) may curtail the proliferation of breast cancer cells by disrupting the cell cycle progression. It does so by down-regulating the expression of Cdk4, which inhibits the formation of the cyclin D1/Cdk4

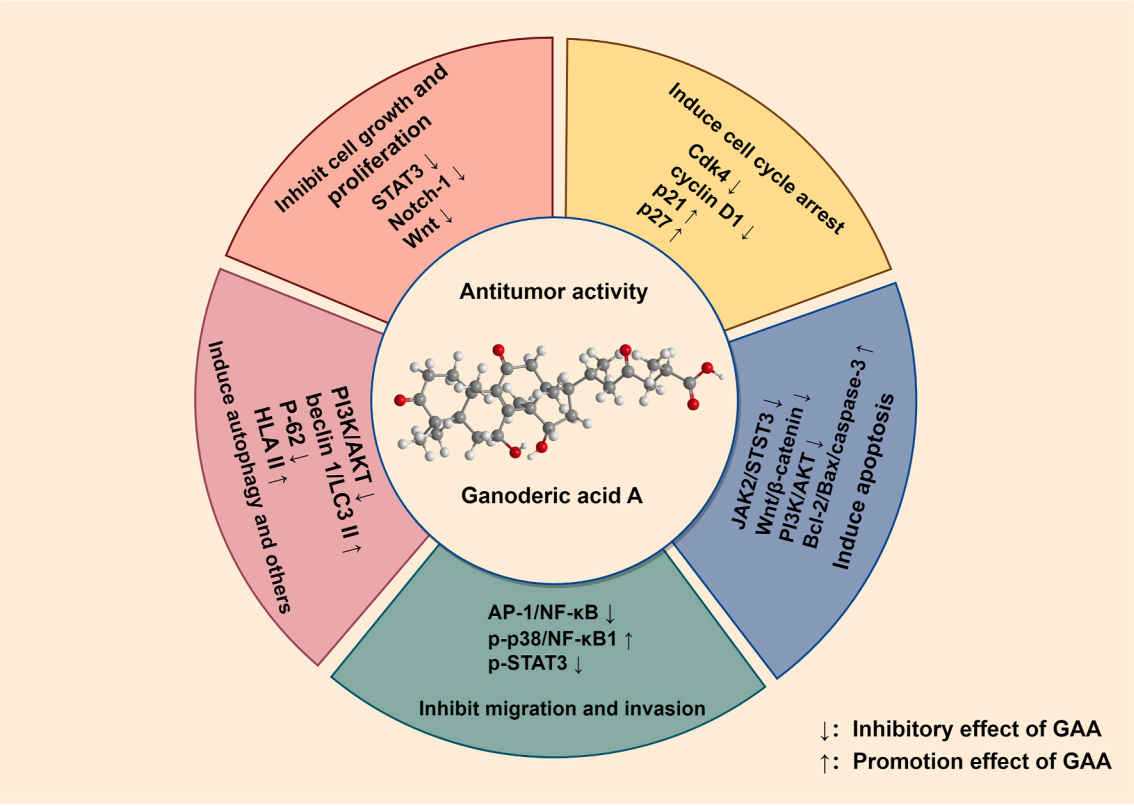

Fig. 2. A summary of the major cell signaling pathways and related proteins involved in the antitumor activity of GAA.

complex. This eventually leads to cell cycle inhibition, causing the cells to remain at the G0/G1 phase, thus preventing cell proliferation. Specifically, GAA blocks the cell cycle of MDA-MB-231 cells at G0/G1, thereby hindering their growth (Jiang et al., 2008). Another experimental study showed that GAA (0.1, 0.2, and 0.4 mmol/L) inhibited the growth of MDA-MB-231 cells by inducing cell cycle arrest at the G0/G1 phase through up-regulating the expression of p27 and p21 and down-regulating the expression of cyclin D1 (Yang et al., 2018). Furthermore, GAA (75 and 100 μmol/L) was found to similarly induce a G0/G1 phase cell cycle arrest in human hepatocellular carcinoma (HCC) cells, which was attributed to the elevation of p21 and the reduction of cyclin D1, thus suppressing their growth (Wang et al., 2017).

In summary, GAA may significantly contribute to the suppression of cancer progression by modulating the activity of Cdks and cyclins, leading to the halt of the cell cycle at the G0/G1 phase, which curtails the proliferation of cancerous cells.

3.3.1.2. Induction of apoptosis. Cell apoptosis, a form of programmed cell demise, is pivotal in sustaining cellular equilibrium. A hallmark of malignancy is reduced apoptosis, which usually involves two major pathways: the endogenous and exogenous pathways (Nagata, 2018). Therefore, inducing apoptosis of cancer cells has been shown to effectively inhibit tumor growth and proliferation (Cheng and Xie, 2019).

The JAK/STAT signaling cascade is crucial for various fundamental biological processes, including cell death, proliferation, differentiation, and the progression of inflammatory responses (Bowman et al., 2000; O'Shea et al., 2013). Excessive activation of STAT proteins can lead to the formation of cancer, thus targeting their abnormal activation is a strategic approach for cancer therapy (Lee et al., 2019; Wu et al., 2019). It has been reported that GAA (0.1, 0.2, and 0.4 mmol/L) significantly increases the levels of proteins associated with the mitochondrial apoptosis pathway by suppressing the JAK2/STAT3 signaling pathway, downregulates the expression of Bcl-xL and myeloid cell leukemia 1 (Mcl-1), and triggers cell apoptosis, thereby promoting apoptosis and curbing the growth of breast cancer (Yang et al., 2018). In addition, Bcl-2 and Mcl-1 can also block cell death induced by multiple chemotherapy agents while increasing chemotherapy resistance (Brotin et al., 2010; Chanvorachote et al., 2009; Varin et al., 2010; Yde and Issinger, 2006). Studies have confirmed that GAA (60 μM) can down-regulate the expression of Bcl-xL and Mcl-1 by inhibiting the JAK/STAT pathway, thereby enhancing the sensitivity of HepG2 cells to cisplatin (DDP) and promoting DDP-induced cell death (Yao et al., 2012). In human osteosarcoma cell lines HOS and MG-63, GAA (0.50 mmol/L) markedly suppresses STAT3 activation by decreasing its phosphorylation while also activating the p38-NF-κB signaling pathway, leading to the inhibition of cell proliferation and induction of apoptosis (Shao et al., 2015). GAA also induces HCC cell apoptosis by increasing the expression level of caspase-3 protein (Wang et al., 2017). Another study showed that GAA curbs lymphoma growth through the induction of apoptosis. This apoptotic effect is mediated by activating the caspase-dependent pathway, which involves the stimulation of caspase-3 and 9, the upregulation of Bax and Bcl-2-like protein 11 (BIM), and the facilitation of cytochrome *c* release (Radwan et al., 2015). In addition, GAA (25 μM) can inhibit the expression of AKT, Bcl-xL, and Mcl-1 as anti-apoptotic genes, and up-regulate the expression of Bax and caspase-3, which has antitumor activity on human meningioma cells by inhibiting the Wnt/β-catenin signaling pathway (Das et al., 2015). Recent studies have found that GAA (5 μM) can target IL-1R1 and disrupt the binding of IL-1β in human cancer cells, increasing the activity of caspase-3, reducing mitochondrial membrane potential, and inhibiting the cell viability of A549 and HeLa cells, thus exerting antitumor effects (Bashir et al., 2024). It has been reported that GAA (20 mg/mL) inhibits the growth and induces apoptosis of human GBM cells by inducing the inactivation of the PI3K/AKT signaling pathway, up-regulating the expression levels of Bax and caspase-3, and down-regulating the expression levels of p-AKT, P- mammalian target of rapamycin (mTOR), and cyclin D1 (Cheng and Xie, 2019). In addition, GAA promotes tumor inhibition and induces Bax expression through up-regulation of N-myc downstream-regulated gene 2 (NDRG2), while inhibiting the expression of MMP-9, p-PI3K, p-AKT, p-mTOR, and Wnt-2 proteins, thereby inducing cell death and inhibiting the growth of advanced meningioma (Das et al., 2020).

To summarize, GAA has the potential to modulate the expression of genes and proteins involved in apoptosis, including Bax, cytosolic cytochrome *c*, Bcl-xL, Mcl-1, Bcl-2, caspase-9, and caspase-3, by influencing various signaling pathways such as JAK2/STAT3, NF-κB, Wnt/β-catenin, PI3K/AKT, and AKT/mTOR. Therefore, GAA may trigger cell death in tumor cells via intrinsic mitochondrial mechanisms and extrinsic apoptotic pathways, thereby significantly contributing to the suppression of tumor progression.

3.3.2. Inhibition of cell migration and invasion

Cell migration and invasion play a critical role in the advancement of cancer and are primary contributors to the high mortality rates associated with many types of cancer (Novikov et al., 2021; Zhang et al., 2005). Therefore, impeding the migration and invasion of cells could be instrumental in preventing and controlling the progression of tumors.

The activation of activator protein-1 (AP-1) and NF-κB signaling pathways is associated with the invasive behavior of breast cancer cells (Eferl and Wagner, 2003; Sliva et al., 2002a, 2002b). In MDA-MB-231 cells, GAA (0.10, 0.25, and 0.50 mM) inhibited cell adhesion, migration, and invasion in a dose-dependent manner. The results showed that the mechanism was mainly mediated through the inhibition of AP-1/NF-κB-dependent secretion of urokinase-type plasminogen activator (uPA) (Jiang et al., 2008). Another study also reported the ability of GAA to inhibit the invasion of MDA-MB-231 cells (Yang et al., 2018). In addition, GAA has anti-invasion and anti-metastatic functions in HCC cells (Wang et al., 2017). It has been reported that GAA may suppress the invasive capabilities of human osteosarcoma HOS and MG-63 cells in vitro by increasing the levels of p-p38 and NF-κB1 and decreasing the levels of p-STAT3 (Shao et al., 2015).

Overall, GAA has demonstrated the ability to inhibit tumor cell migration and invasion and may have potential therapeutic applications in cancer therapy.

3.3.3. Regulating of autophagy

Autophagy is a vital cellular process that plays a crucial role in maintaining intracellular environmental homeostasis. Dysregulation of this intricate process has been closely associated with a multitude of pathological conditions (Lozy and Karantza, 2012). Therefore, a thorough understanding of autophagy and its regulation is of paramount importance for the elucidation of various disease mechanisms.

Within the U251 glioma model, GAA stimulates autophagy in U251 GBM cells by modulating the PI3K/AKT signaling pathway. This process involves the up-regulation of two autophagy-associated proteins, beclin 1 and microtubule-associated protein 1 light chain 3 (LC3) II, and the down-regulation of the autophagy substrate P62 (Cheng and Xie, 2019). Currently, enhancing autophagy has been shown to enhance the efficacy of chemotherapy drugs. DDP is a commonly used chemotherapeutic drug in the clinical treatment of lung cancer (Hu et al., 2020; Shi et al., 2016; Wu et al., 2018). Some studies have reported that A549/DDP cells treated with GAA exhibit marked autophagic signatures. GAA inhibits autophagy by regulating the circRNA flamin A (circFLNA)/-miR-486-3p/cytochrome P450 family 1 subfamily A member 1 (CYP1A1)/X-ray repair cross-complementing 1 (XRCC1) axis and enhances the sensitivity of lung cancer cells to DDP (Gong et al., 2024).

In sum, these findings demonstrate that GAA modulates autophagy through distinct molecular pathways in different cancer types. Its ability to regulate autophagy highlights its potential as a therapeutic agent in cancer treatment.

3.3.4. Other mechanisms

Beyond the effects mentioned above, GAA may also demonstrate anti-neoplastic capabilities through alternative mechanisms of action. For example, GAA enhances antitumor immunity by up-regulating the expression of human leukocyte antigen (HLA) class II proteins in cancer cells and restoring the function of antigen-presenting $CD4^+$ T cells (Radwan et al., 2015). It is well known that the development of drug resistance often reduces the efficacy of chemotherapy drugs in the treatment of tumors. In the mouse colon cancer xenograft model established by HT-29 cells, GAA was combined with the chemotherapy drug oxaliplatin to enhance the antitumor effect of oxaliplatin by inducing the cytotoxicity of T cells (Song et al., 2023). In a 7,12-dimethylbenz (a) anthracene (DMBA)-induced rat breast tumor model, tamoxifen and GAA drug-loaded nanoparticles significantly reduced cell viability, decreased relative tumor volume, and improved the therapeutic effect of breast cancer (Barkat et al., 2022). Telomerase inhibition is a possible therapeutic strategy for the treatment of cancer (Feldser and Greider, 2007). Molecular docking experiments have shown that GAA can moderately inhibit telomerase activity, thereby inhibiting Epstein-Barr virus (EBV) infection and preventing nasopharyngeal carcinoma (Zheng and Chen, 2017). In addition, GAA has a high binding affinity and can selectively bind to the side loops of parallel G-quadruplex DNA (pG4DNA), thereby inhibiting telomerase or down-regulating oncogenes, and can act as an anticancer agent (Sillapapongwarakorn et al., 2017). The experimental study found that the development of PMBN-A.Her2-GA targeting nanosystem successfully improved GAA's cytotoxic and necrotic activity against HER2-overexpressed breast cancer cells, providing a potential alternative treatment strategy for traditional chemotherapy (Motamed Fath et al., 2021).

In summary, GAA demonstrates significant antitumor potential through multiple mechanisms, including inhibition of cell proliferation, induction of cell cycle arrest, apoptosis, and suppression of cell migration and invasion. Its ability to modulate key signaling pathways such as JAK/STAT, PI3K/AKT, and Wnt/β-catenin highlights its versatility in targeting various cancer types. Additionally, GAA's role in enhancing autophagy and overcoming drug resistance further underscores its therapeutic promise. While these findings are promising, further research is essential to fully elucidate its mechanisms and optimize its clinical applications, paving the way for GAA as a potential anticancer agent.

3.4. Neuropsychopharmacological activity of GAA

Psychiatric and nervous system diseases are a group of diseases manifested in nervous system lesions, behavior, and psychological activity disorders, including neuropsychiatric diseases and neurodegenerative diseases (Gupta et al., 2023). Neurological and psychiatric diseases are one of the main causes that affect people's normal life (Baxter et al., 2016). Therefore, finding effective drugs to promote nerve growth, prevent and treat nerve injury and nerve degeneration is a topic of great concern in current medical research (Arias-Carrión and Drucker-Colín, 2007). Numerous experimental studies have shown that GAA exerts neuroprotective effects mainly by mediating autophagy and reducing neuroinflammation (Jia et al., 2021b; Shen et al., 2021). Autophagy is a dynamic process of degrading cellular contents that occurs steadily in cells. It is crucial for nerve cells because it helps to clear pathological proteins such as amyloid-β (Aβ) and tau, thereby maintaining nerve cell homeostasis (Reddy and Oliver, 2019). Neuroinflammation plays an essential role in the occurrence and development of neurodegenerative diseases. Neuroinflammation is a prevalent characteristic in neurodegenerative conditions, including AD, epilepsy, Parkinson's disease (PD), and multiple sclerosis (MS), and it correlates with the progressive deterioration of neural architecture and functionality (Jia et al., 2019; Neri et al., 2022; Piirainen et al., 2017). Neuroinflammation is also a significant factor in the development of major depressive disorder (Wang et al., 2018).

3.4.1. Anti-Alzheimer's disease

AD is a type of neurodegenerative condition marked by a gradual decline in cognitive abilities (Ballard et al., 2011). The accumulation of Aβ in the central nervous system due to inadequate clearance is the main cause of AD (Mawuenyega et al., 2010). The development of AD is associated with the buildup of Aβ peptides in brain tissue and the creation of neurofibrillary tangles due to the hyperphosphorylation of tau protein (Lane et al., 2018). The release of Aβ polymers outside nerve cells can cause neuroinflammation and exacerbate AD symptoms; however, autophagy can promote the clearance of Aβ precursor proteins (Gouras et al., 2010). It has been reported that in the mouse model of AD established with Aβ42, GAA activates autophagy in BV2 cells through the Axl receptor tyrosine kinase (Axl)/CDC42-activated kinase 1 (Pak1) signaling pathway and promotes the clearance of Aβ42 by microglia, thereby ameliorating cognitive deficits in AD (Qi et al., 2021). Peptidyl arginine deiminase type IV (PADI4) has a positive effect on inducing autophagy in AD cells (Fan et al., 2018). Experimental studies have shown that in the mouse model of AD established with Aβ25-35, GAA (40 and 60 μmol/L) inhibited the expression of pro-senescence-related proteins p16, p21, and Hmgal in a concentration-dependent manner by regulating the expression of PADI4. At the same time, it can reduce the expression of autophagy-related proteins 5 (ATG5) and Beclin 1 and increase the expression level of LC3B I/II to exert autophagy, and its mechanism is to delay the senescence of AD cells by regulating the AKT/mTOR signaling pathway (Shen et al., 2021). In addition, Okadaic acid can lead to neurotoxic effects in PC12 cells by promoting tau phosphorylation. Conversely, GAA (12.5, 25, and 50 μg/mL) may provide neuroprotection by suppressing the hyperphosphorylation of tau protein, suggesting its potential as a therapeutic agent for AD (Cui et al., 2023). An experimental study investigated the impact of chronic administration of triterpenoids from *Ganoderma lucidum* (TGL) on the decline in brain physiology, with its mechanism primarily involving the modulation of sphingolipid metabolism and the enhancement of autophagy. This study also found that GAA may be an effective component of TGL against brain aging in AD mice (Zeng et al., 2021). In addition, in neurodegenerative diseases, T helper 17 (Th17) cells and regulatory T (Treg) cells can penetrate brain tissue through the damaged blood-brain barrier and participate in the occurrence of AD (Zhang et al., 2013). GAA (20 mg/kg) reduces the expression of proinflammatory cytokines IL-17A, IL-17F, IL-21, and IL-22 by regulating the imbalance of Th17/Tregs axis, and inhibits the JAK/STAT signaling pathway to regulate brain mitochondrial dysfunction, thereby reducing neuroinflammation in AD (Y. Zhang et al., 2021). These findings indicate that GAA could play various functions in addressing AD, including promoting Aβ clearance, regulating autophagy, inhibiting tau phosphorylation, and anti-neuroinflammatory effects.

3.4.2. Antiepileptic effect

Epilepsy is a long-term neurological disease characterized by recurrent seizures. It is a common neurological disorder characterized by recurrent and refractory seizures (Devinsky, 2004). Microglia dysfunction can lead to seizures or promote the development of epilepsy by releasing proinflammatory cytokines such as IL-1β, IL-6, and TNF-α (Dambach et al., 2014). Experimental studies have found that GAA (10, 20, 50, and 100 μg/mL) reduces the release of these cytokines from mouse cortical microglia at least in part by inhibiting the lipopolysaccharide (LPS)-induced NF-κB signaling pathway and also inhibits the elevation of mitochondrial metabolic activity stimulated by LPS, thus playing a potential role in the treatment of epilepsy (Chi et al., 2018). Certain seizures can cause hippocampal neuronal damage (Henshall et al., 2016), which may lead to mitochondrial dysfunction accompanied by a large number of apoptotic cells (Waldbaum and Patel, 2010; Zsurka and Kunz, 2015). Experimental studies have shown that GAA has neuroprotective effects on epileptic hippocampal neurons by improving

mitochondrial function and antioxidant status, which may provide a new therapeutic strategy for the treatment of epilepsy (Jiang et al., 2018). In addition, GAA (10 mg/kg) may reduce the expression of apoptosis and calcium-sensing receptor (CaSR), reduce the expression of p-c-Jun N-terminal kinase (JNK), p-p38, Bax, and cleaved caspase-3, and increase the expression of the p-extracellular signal-regulated kinase (ERK) and Bcl-2 through the MAPK pathway, thus improving epileptic behavior and brain tissue damage caused by epilepsy and show anti-epileptic effects (Pang et al., 2022). These findings indicate GAA's potential to exert a range of therapeutic effects on epilepsy, encompassing anti-inflammatory properties, neuroprotection, and anti-epileptic capabilities.

3.4.3. Anti-depression

Depression is a prevalent and persistent disorder, and neuroinflammation is a crucial factor in the pathogenesis of this disorder (Duman et al., 2016; Troubat et al., 2021). In a rat model of post-stroke depression (PSD), GAA reduced levels of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in the hippocampus, activated the ERK/cAMP-response element-binding protein (CREB) pathway, and mitigated neuronal damage. GAA also inhibited the polarization of M1 (pro-inflammatory) microglia and promoted the polarization of M2 (anti-inflammatory) microglia, thereby alleviating the depression-like behavior induced by PSD in rats (L. Zhang et al., 2021). Numerous investigations have demonstrated a correlation between depression and the farnesoid X receptor (FXR), a significant element in the emergence of behaviors indicative of depression (Boehlig et al., 2022; Li et al., 2023; C.C. Yang et al., 2018). FXR is a bile acid receptor that engages with the inflammasome, facilitating anti-inflammatory and reparative processes crucial for maintaining brain equilibrium (W.G. Chen et al., 2018; Fiorucci et al., 2010). It has been reported that GAA (0.5, 1, and 2.5 mg/kg) can help alleviate major depressive disorder by regulating bile acid receptor FXR, blocking the activity of NLRP3 inflammasome, enhancing the expression of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor, and reducing brain inflammation (Bao et al., 2021). These findings indicate a positive correlation between FXR activation and anti-depressant effects. Together, the evidence suggests that GAA could play a multifaceted role in combating depression, encompassing anti-inflammatory effects, neuroprotection, and the regulation of neuroimmune reactions.

3.4.4. Other neuropsychopharmacological activity

Neuroinflammation, driven by microglial activity, is a pivotal contributor to the development of neurodegenerative conditions (Kwon and Koh, 2020). In LPS-stimulated BV2 microglial cells, GAA facilitates a shift from a pro-inflammatory to an anti-inflammatory phenotype by activating the FXR signaling pathway. This transition notably decreases the secretion of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, while enhancing the synthesis of the neurotrophic factor BDNF, consequently mitigating LPS-induced neuroinflammation (Jia et al., 2021b). Reports indicate that the FXR serves a protective function in the context of MS (Ho and Steinman, 2016). In two independent animal models of MS, GAA can promote anti-inflammatory response and myelin regeneration by activating FXR, increasing the expression of anti-inflammatory cytokine IL-4 and growth factor BDNF, and inhibiting the expression of pro-inflammatory cytokines IL-6 and IL-1β, thereby contributing to the improvement of central demyelinating diseases (Jia et al., 2021a). Alterations in the leucine-rich repeat kinase 2 (LRRK2) gene can disrupt dopaminergic signaling, which is associated with the development of PD (Sosero and Gan-Or, 2023). Experimental studies have shown that GAA is the best recognition molecule for LRRK2 and can become a potential drug for the treatment of PD (Ahmad, 2023). In addition, NO damage can lead to various neurological diseases (Yun et al., 1997). The adrenergic system mediates the inhibitory effects of some antipsychotics in neurological disorders (Dziedzicka-Wasylewska et al., 2004; Gallager and Aghajanian, 1976). GAA can protect isolated nerve cells from NO-induced stress injury by stimulating β-adrenergic receptors (Yu et al., 2020).

In summary, GAA plays a neuroprotective role in AD, epilepsy, depression, PD, MS, and other diseases by reducing neuroinflammation and mediating autophagy through regulating JAK/STAT, NF-κB, MAPK, and FXR signaling pathways. These findings highlight the potential of GAA as a multifaceted therapeutic agent, offering promising avenues for the treatment of complex neurodegenerative and psychiatric conditions.

3.5. Hepatoprotective activity of GAA

Liver disease is a widely prevalent and critically important health concern that arises from exposure to chemical toxins, leading to liver damage and subsequent metabolic and circulatory dysfunctions (Bhondave et al., 2014). The disease encompasses various presentations, such as hepatic impairment and hepatic inflammation, and is linked to a range of factors, including viral hepatitis, alcohol consumption, bile acids, and obesity (Devarbhavi et al., 2023). Due to the severity and complexity of liver disease, it is crucial to understand the various factors that contribute to its onset and progression. The liver plays a crucial role in maintaining lipid balance in the body by regulating several metabolic pathways to maintain physical health and prevent metabolic disorders such as obesity, hyperlipidemia, and other diseases (Badmus et al., 2022; Santos et al., 2024). Numerous studies have shown that GAA has protective effects on the liver.

In cyclophosphamide-induced liver injury in mice, GAA (20 and 40 mg/kg) inhibited the (Txnip)/Trx/NF-κB pathway activation, reducing the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and cytokines in the serum and liver of mice, thereby reducing liver injury and hepatocyte apoptosis (Xu et al., 2019). Another experimental study showed that GAA, as the main component of GL, could significantly improve the survival rate and liver function of α-amanita toxin-poisoned mice, and may reduce liver injury by inhibiting the JAK2/STAT3 pathway (Xiao, 2024). In rats with non-alcoholic fatty liver disease (NAFLD) induced by high-fat diet (HFD), pretreatment with GAA (20 and 40 mg/kg) alleviated liver injury, reduced serum AST, ALT, total bilirubin (TBIL) levels, total cholesterol (TC), and triglyceride (TG), and increased high-density lipoprotein cholesterol (HDL-C) levels (Liu et al., 2020). Its hepatoprotective mechanism is mainly attributed to the reduction of lipid oxidation and liver inflammation through AMP-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α) and AMPK/NF-κB signaling pathways (Liu et al., 2020). Another experimental study showed that treatment with GAA (25 and 50 mg/kg) reduced serum ALT and AST levels by reducing the mRNA expression of inflammatory factors such as IL-1β, TNF-α, and IL-6, alleviating non-alcoholic steatohepatitis (NASH) induced by high-fat and high-cholesterol diet. In addition, GAA treatment increased ERp57, p-AKT, and p-MAPK levels and improved liver inflammation and fibrosis by reducing hepatic oxidative stress and ER stress responses (Zhu et al., 2022). GAA has also been reported to have some protective effect against alcohol-induced liver injury. A high dose of GAA (40 mg/kg) alleviates alcohol-induced liver injury by regulating intestinal microbial composition, liver metabolomics characteristics, and mRNA levels of genes related to lipid metabolism and inflammatory response in the liver, while increasing antioxidant enzyme activity and inhibiting oxidative stress (Lv et al., 2022). Cytochrome p450s (CYP450s) are essential drug metabolism enzymes in the liver and intestine (X.B. Shi et al., 2016). In vitro studies have shown that GAA has the potential to interact with other drugs metabolized by CYP3A4, CYP2D6, and CYP2E1 (Xu et al., 2020). In an HFD-induced obesity mouse model, GAA (25 and 50 mg/kg) reduced intracellular cholesterol and fatty acid levels by inhibiting sterol regulatory element-binding protein (SREBP) expression, and improved weight gain, fat accumulation in the liver or adipose tissue, serum lipid levels, and insulin sensitivity in obese mice

(Zhu et al., 2018). In addition, in mice with hyperlipidemia induced by an HFD, GAA has the potential to alleviate lipid metabolism disorders and intestinal microbiome imbalances by regulating intestinal microbiota and liver metabolite characteristics, as well as by influencing the expression of genes involved in lipid metabolism and bile acid regulation within the liver, thus potentially improving hyperlipidemia (Guo et al., 2020).

In summary, GAA exhibits significant hepatoprotective effects by reducing oxidative stress, inflammation, and lipid accumulation, while enhancing metabolic regulation. Its potential in treating liver diseases, such as NAFLD and alcohol-induced injury, is promising. However, further clinical studies are needed to confirm its efficacy and safety. GAA represents a promising candidate for the development of liver-protective therapies.

3.6. Cardiovascular protective effects of GAA

Cardiovascular disease continues to be the leading cause of death and illness worldwide. The incidence of atherosclerosis (AS), acute myocardial infarction, and other cardiovascular diseases is progressively on the rise due to certain risk factors (Goldsborough et al., 2022; Paisible et al., 2015). Therefore, it is imperative to identify these risk factors and adopt the necessary measures to mitigate their effects. Recent research suggests that GAA could possess therapeutic potential for cardiovascular disease.

Numerous experiments have shown that inflammation and lipid deposition increase the risk of AS (Kraaijenhof et al., 2021). GAA (20, 50, and 70 μM) was found to significantly inhibit the release of oxidized low-density lipoprotein (ox-LDL)-induced inflammatory factors, including TNF-α, IL-1β, and IL-6, and to reduce levels of markers of oxidative stress such as ROS and malondialdehyde (MDA). In addition, GAA effectively reduced ox-LDL-induced lipid deposition and inhibited the expression of scavenger receptors (SR) associated with lipid metabolism and foam cell formation, such as SR class A (SR-A) and cluster of differentiation 36 (CD36). Its mechanism of action is mainly through the intervention of the Notch-1/peroxisome proliferator-activated receptor gamma (PPARγ)/CD36 signaling pathway to exert anti-inflammatory and anti-lipid deposition effects. Therefore, GAA has a potential therapeutic effect on AS (Wang and Lu, 2021). Cardiovascular disease, especially acute myocardial infarction, is the most important health problem worldwide (Pollard, 2000). Myocardial ischemia-reperfusion (MIR) is an important cause of acute myocardial infarction (Algoet et al., 2023). In the MIR rat model, GAA (20 and 40 mg/kg) down-regulated the levels of TNF-α, IL-6, and IL-1β in serum and heart, reduced the levels of creatine kinase isoenzyme (CK)-MB and lactate dehydrogenase (LDH), improved ST and pathological changes of myocardial infarction, and reduced myocardial infarction size by regulating the JAK/STAT3/NF-κB signaling pathway, thereby protecting the rats from ischemia-reperfusion injury (Zhang et al., 2020).

In conclusion, GAA exhibits cardiovascular protective effects by targeting inflammation, oxidative stress, and lipid metabolism, offering potential therapeutic benefits for conditions like atherosclerosis and myocardial injury. Its modulation of key signaling pathways underscores its promise, though further clinical validation is essential.

3.7. Renoprotective effects of GAA

Kidney diseases, which encompass several conditions such as kidney injury, kidney fibrosis, and polycystic kidney disease, significantly contribute to global health issues and death rates (Bergmann et al., 2018; Lan, 2011; Peek and Wilson, 2023). Therefore, the identification and development of effective drugs to treat kidney disease are of paramount importance. Some studies have reported that GAA has a protective effect on the kidneys.

In a carbon tetrachloride (CCl_4)-induced kidney injury mouse model, GAA (25 and 50 mg/kg) could effectively reduce renal inflammation and fibrosis, and improve renal function by reducing serum creatinine, urea, and uric acid levels. In addition, GAA reduced oxidative stress and inflammatory response by activating the Trx/TrxR antioxidant system and inhibiting JAK/STAT3 and ras homolog family member A (RhoA)/Rho-associated protein kinase (ROCK) signaling pathways, thereby providing renal protection (Ma et al., 2021). It has been reported that GAA dose-dependently reversed transforming growth factor-β (TGF-β) 1-upregulated levels of fibrosis markers in a TGF-β1-stimulated HK-2 cell model, showing a potent anti-renal fibrosis effect (Geng et al., 2020). In the Madin-Darby canine kidney cystogenesis model and kidney-specific Pkd1 knockout mice, GAA inhibited the expression of proliferating cell nuclear antigen by dose-dependently down-regulating the Ras/MAPK signaling pathway and significantly inhibited the growth of cysts, thereby reducing the development of renal cysts (Meng et al., 2020). In summary, GAA demonstrates therapeutic potential through diverse mechanisms such as anti-inflammatory, antioxidant actions, and cell proliferation inhibition, positioning it as a promising agent for the management of renal disorders.

3.8. Lung protective effects of GAA

Lung diseases are a serious threat to human health, such as lung injury and pulmonary fibrosis, which can cause extensive damage to the respiratory system, impair lung function, and reduce the overall quality of life (Cheng et al., 2021). Studies have reported that GAA has a protective effect on the lungs.

In a mouse model of LPS-induced acute lung injury, GAA (20 and 40 mg/kg) significantly decreased the lung wet/dry weight (W/D) ratio, myeloperoxidase (MPO) activity, MDA content, and pro-inflammatory cytokine levels, while increasing SOD activity. These effects were attributed to the suppression of the Rho/ROCK/NF-κB signaling pathway, which in turn mitigated the acute lung injury in the mouse (Wan et al., 2019). Another experimental study showed that in bleomycin-induced pulmonary fibrosis, GAA (25 and 50 mg/kg) down-regulates the levels of TNF-α, IL-1β, IL-6, and MDA and up-regulates the levels of SOD by regulating the TGF-β/mothers against decapentaplegic homolog 3 (Smad3)/NF-κB signaling pathway. Additionally, GAA improved MPO activity, W/D ratio, and pathological changes of lung tissue, thus playing a protective role in pulmonary fibrosis (Wen et al., 2020). In conclusion, GAA could emerge as a potential therapeutic agent for addressing lung injury and combating pulmonary fibrosis.

3.9. Other pharmacological activities

It has been found that GAA has other pharmacological benefits besides its known uses. In late 2019, an outbreak of pneumonia of unknown origin in China was identified as coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. The disease affects multiple body systems, with symptoms ranging from mild to severe or asymptomatic, and was declared a public health emergency by the World Health Organization (Gorbalenya et al., 2020; Zhu et al., 2020). Fortunately, the natural compound GAA has shown inhibition of COVID-19 protease in laboratory studies and is promising as a therapeutic agent for the disease (Le et al., 2023). In addition, GAA protects lens epithelial cells and the rat lens from the harmful effects of ultraviolet radiation B (UVB). GAA showed protective effects on human lens epithelial cell line (SRA01/04 cells) and rat lens by improving cell viability and antioxidant activity, inhibiting apoptosis, activating the PI3K/AKT signaling pathway, and delaying lens opacities, which may protect against UVB-induced damage (Kang et al., 2020). Experimental research has confirmed that GAA significantly ameliorates functional dyspepsia (FD) in rats by enhancing gastric emptying and intestinal motility, while reducing pathological damage to the stomach and duodenum. Moreover, GAA positively modulates the secretion of brain-gut axis proteins and bolsters the

duodenal mucosal barrier function in affected rats, thereby improving the barrier function of duodenal mucosa in FD rats (Yang et al., 2022). Experimental studies have found that GAA can improve endothelial function in estrogen-deficient mice. GAA can effectively alleviate the damage of aortic endothelial function in ovariectomized mice by reducing the level of ROS and inhibiting the ER stress pathway involving Grp78 and ATF6α (Zhu, 2023). The findings imply that GAA possesses extensive therapeutic advantages, potentially serving as a versatile treatment option.

The listed pharmacological activities of GAA can be found in Table 2, with the molecular pathways that contribute to its pharmacological effects illustrated in Figs. 3 and 4. Moreover, the operational mechanisms of GAA in neuropsychiatric and liver diseases are outlined in Figs. 5 and 6.

4. Pharmacokinetics of GAA

Pharmacokinetic studies are pivotal for comprehending how drugs are absorbed, distributed, metabolized, and excreted, which aids in optimizing clinical medication practices to ensure therapeutic efficacy and minimize adverse reactions. Currently, the pharmacokinetics of GAA in rat plasma are predominantly assessed using ultra-high performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) and ultra-fast liquid chromatography-tandem mass spectrometry (UFLC-MS/MS) techniques (Cao et al., 2017b; Rahman et al., 2021). The pharmacokinetic parameters of GAA from the four studies are compared, with the results summarized in Table 3.

It can be seen from the data in the table that GAA can be absorbed by both oral and intravenous injection in rats. In male Wistar rats, after oral administration of GAA (25 mg/kg), the rate of absorption is the slowest, which is reflected in the time to peak concentration (Tmax) of 4 h (Rahman et al., 2021). In addition, the area under the curve (AUC) after oral administration from time zero to the last sampling time $AUC_{0\text{-}t}$ was 332730 ± 0.21 ng h/mL, indicating a large amount of GAA exposure in vivo (Rahman et al., 2021). In contrast, when GAA (20 mg/kg) was orally administered to male Sprague–Dawley rats, the absorption degree was higher, and the peak time was the shortest (about 9 min, Tmax = 0.15 ± 0.03 h), while the peak drug concentration (Cmax) was relatively high, Cmax = 0.91 ± 0.57 μmol/L, equivalent to 469.023 ng/mL (Cao et al., 2017b). After intravenous injection, GAA can rapidly penetrate the blood-brain barrier, manifested in a Tmax of 0.25 h, and is eliminated from the brain relatively quickly, with a half-life ($t_{1/2}$) of 1.40 h and bioavailability-corrected total body clearance (CL/F) of 89.21 L/h/kg (Cao et al., 2017b). It is worth noting that the oral bioavailability and brain permeability of GAA are estimated at 8.68 % and 2.96 %, respectively, suggesting that GAA is less bioavailable in vivo but has some ability to cross the blood-brain barrier (Cao et al., 2017b). In addition, GAA has a distribution in the blood, brain, liver, and gastrointestinal tract, and is excreted in the urine in the kidney, suggesting that the distribution of GAA in the body is quite broad. It has been found that the apparent volume of distribution (Vd)/F and CL/F of GAA in the body differ among different administration modes and species, which may be related to the metabolic and excretory pathways of GAA (Cao et al., 2017b; Rahman et al., 2021). Another study found that when healthy male volunteers took MG2FB-WE (containing GAA 1417.80 ± 40.74 mg/kg) orally on an empty stomach, a Cmax of 10.99 ± 4.02 ng/mL was observed, indicating that GAA can also be effectively absorbed orally in humans. Both rapid absorption and short elimination half-life have been shown (Tawasri et al., 2016; Teekachunhatean et al., 2012). In the metabolic study of GAA, the researchers found that GAA can undergo a wide range of metabolism, including reduction, oxidation, and hydroxylated phase I metabolism, as well as glucuronidation and sulfated phase II metabolism. Its main metabolic soft spots are 3, 7, 11, 15, 23-carbonyl (or hydroxyl groups) and 12,20,28 (29)-carbon atoms (Cao et al., 2017a).

In general, GAA showed absorbability and elimination in rats and human volunteers, with low oral bioavailability, wide distribution, and large distribution volume. To improve the bioavailability of GAA, researchers have developed GAA formulations based on nano lipid carriers, which not only improve the solubility of GAA but also enhance its oral absorption (Rahman et al., 2021). Moreover, subsequent research may improve the oral bioavailability of GAA by investigating alternative pharmaceutical formulations and chemical alterations. Consequently, additional pharmacokinetic evaluations of GAA are anticipated to yield valuable insights, facilitating the development of innovative dosage forms and broadening its clinical utility.

5. Derivatives of GAA

Although GAA has shown great potential in pharmacology, it still has some limitations regarding solubility, bioavailability, and pharmacokinetic properties in practical applications. To overcome these challenges, the researchers have begun to explore derivatives (Fig. 7) of GAA with a view to enhancing their pharmacological activity and clinical application potential through chemical modification and structural optimization.

Chang et al. have been working on GAA derivatives in recent years, which are mainly produced by microbial transformation processes, in particular by using specific glycosyltransferases in Bacillus subtilis ATCC 6633 strain, such as BsUGT398, BsUGT489, and BsGT110. These derivatives, including GAA-15-O-β-glucoside (Chang et al., 2018a, 2018c, 2019b), 3-O-acetyl GAA (Chang et al., 2018b), and GAA-26-O-β-glucoside (Chang et al., 2019a), exhibit higher water solubility and possibly enhanced pharmacological activity than the original GAA. In particular, a new triterpene disaccharide saponin, GAA-15, 26-O-β-diglucoside (Chang et al., 2021), was successfully prepared by sequential transformation of BtGT_16345 and BsGT110, with significantly increased water solubility. These provide a promising strategy for the development of TGL saponins with novel biological activities (Chang et al., 2021). However, they did not conduct pharmacological activity studies on derivatives of GAA, and further studies are needed to determine whether these derivatives also have higher biological activity than GAA.

Jia et al. modified the carboxyl group of GAA by chemical synthesis to generate a series of amide compounds (A1-A15) and investigated their antitumor activity in vitro. The structural modifications included aliphatic amines, benzylamines, phenylethylamines, and piperazine derivatives, revealing key structure-activity relationships: aliphatic amines with longer carbon chains (A2, hexyl) showed higher activity than shorter chains (A1, butyl); benzylamines with electron-withdrawing groups (A6, A7, A8) were more active than those with electron-donating groups (A5); and piperazine derivatives with hydrophobic groups (A15) exhibited enhanced activity. Among the derivatives, A2 demonstrated significant antiproliferative activity in multiple tumor cell lines (MCF-7, HepG2, SJSA-1) with low toxicity to normal cells. Mechanistically, A2 induces apoptosis by binding to MDM2 and inhibiting the MDM2-p53 interaction, highlighting its potential as a novel antitumor agent (Jia et al., 2023).

Future studies will be devoted to in-depth exploration of the diverse pharmacological activities of GAA derivatives, including but not limited to their antitumor effects. Through innovative optimization of chemical structures, the therapeutic efficacy of these compounds is enhanced. This aims to develop new compounds with improved solubility, bioavailability, and pharmacokinetic properties, providing a wider range of therapeutic strategies and approaches for the treatment of cancer and other related diseases.

6. Network pharmacology and molecular docking analysis

6.1. Network pharmacology analysis

We first searched the target genes of GAA using Swiss Target

Table 2
The pharmacological activities of GAA.

Pharmacological effects	In vivo	In vitro	Dosage	Mechanisms	Reference
Anti-inflammatory effects	Adjuvant-induced arthritis in rats		20, 40 mg/kg	↓phosphorylation of Janus Kinase 3 (p-JAK3); ↓p-signal transducer and activator of transcription 3 (STAT3); ↓suppressor of cytokine signaling 1 (SOCS1); ↓p-nuclear factor kappa-B (NF-kB) p65; ↓p-inhibitor of κB α (IκBα)	Cao et al. (2020)
		Human NP cells	6.25, 12.5, 25 μM	↓nitric oxide (NO); ↓prostaglandin E2 (PGE2); ↓inducible nitric oxide synthase (iNOS); ↓cyclooxygenase-2 (COX-2); ↓tumor necrosis factor-α (TNF-α); ↓interleukin (IL)-6; ↑collagen II; ↑aggrecan; ↓matrix metalloproteinase (MMP)-3; ↓MMP-13; ↓p-p65; ↑IκBα	Zheng et al. (2022)
	OA mouse model		20 mg/kg	↓Bcl-2-associated X (Bax); ↑caspase-3; ↓COX-2; ↓iNOS; ↓glucose-regulated protein 78 (GRP78); ↓activating transcription factor 4 (ATF4); ↓CHOP; ↓p-p65; ↑IκBα; ↑aggrecan; ↑collagen II; ↑SOX9; ↓ADAMTS5; ↓MMP-3; ↓MMP-13	Liu et al. (2024)
		Human chondrocytes (CHONs), C28/I2 cells	25, 50 μM		
	Destabilization of the medial meniscus mice model		20 mg/kg	↓osteoprotegerin (OPG); ↑receptor activator of nuclear factor kappa-B ligand (RANKL); ↓MMP-13	Wu et al. (2022)
		HC-A cells	10, 50 mM		
	ovalbumin-induced asthma in mice		20, 40 mg/kg	↑IL-4, ↑IL-5, ↑IL-13, ↓Toll-like receptor 4 (TLR4), ↓p-NF-kB	Lu et al. (2021)
		NP cells	4, 8 μM	↓IL-6, ↓IL-1β, ↓TNF-α, ↓glutathione (GSH), ↓superoxide dismutase (SOD), ↓glutathione peroxidase (GPX), ↓malondialdehyde (MDA), ↓MMP-3, ↓MMP-13, ↓ADAMTS4, ↓ADAMTS5, ↑collagen II; ↑aggrecan	Wang et al. (2022)
Antioxidant effects		PC-3 cells	10, 20, 50, 80 μM	↓ROS, ↓2,2-diphenyl-1-picrylhydrazyl (DPPH), ↓SOD1, ↓SOD2, ↓SOD3	Gill et al. (2016a)
		Lung cancer cell line (H460)	10, 20, 50, 80 μM	↓nuclear factor erythroid 2-related factor-2 (Nrf2), ↓ROS	Gill et al. (2017)
		Human neuroblastoma cell line (IMR-32)	20, 50, 80 μM	↓Notch-1, ↓ROS,	Gill et al. (2019)
Antitumor effects		Human breast cancer cell line (MDA-MB-231)	0.10, 0.25, 0.50 mM	↓urokinase-type plasminogen activator (uPA), ↓cyclin-dependent kinase 4 (Cdk4)	Jiang et al. (2008)
		MDA-MB-231 breast cancer cells	0.1, 0.2, 0.4 mmol/l	↑ROS, ↓cyclin D1, ↑p21, ↑p27, ↓myeloid leukemia-1 (Mcl-1), ↓B-cell lymphoma (Bcl)-xL, ↑Bak, ↑Bax, ↑cytosolic cytochrome *c*	Yang et al. (2018)
		HepG2 and SMMC7721 human HCC cells	75, 100 μmol/l	↓cyclin D1, ↑p21, ↑caspase-3	Wang et al. (2017)
		HepG2 cells	60 μM	↓p-JAK1, ↓p-JAK2, ↓Mcl-1, ↓Bcl-2, ↓cyclin D1, ↓caspase-3, ↓poly ADP-ribose polymerase (PARP)	Yao et al. (2012)
		Human osteosarcoma HOS and MG-63 cells	0.50 mmol/L	↓p-STAT3, ↑p-p38, ↑p38, ↑NF-κB1	Shao et al. (2015)
	EL4 tumor-bearing mouse model		60, 50, 40 mg/kg	↑caspase-3, ↑caspase-8, ↑caspase-9, ↑caspase-3/7, ↓Bcl-2, ↓survivin, ↑Bax, ↑Bcl-2-like protein 11 (BIM), ↑apoptotic protease-activating factor 1 (APAF-1), ↑cytochrome *c*, ↑HLA class II, ↓p-STAT3	Radwan et al. (2015)
		Human pre-B acute lymphocytic leukemia (NALM-6), Burkitt lymphoma (Ramos, GA-10, CA-46, and Daudi), non-Hodgkin's lymphoma (Toledo and DB) cell lines, and Human Epstein-Barr virus (EBV)-transformed B-lymphoblastoid cell lines (B-LCL)	5, 10, 20, 40 mM		
		Human meningioma cell lines (IOMM-Lee, CH157MN)	25 μM	↓Wnt5α/β, ↓β-catenin, ↑p-GSK3β, ↓AKT, ↓Bcl-xL, ↓Mcl-1, ↑Bax, ↑caspase-3	Das et al. (2015)
		A549 and HeLa Cell lines	0.5, 2.5, 5, 10 μM	↑caspase-3, ↓MMP	Bashir et al. (2024)
		U251 GBM cells	20 mg/mL	↓Bcl-2, ↑Bax, ↑caspase-3, ↑beclin 1, ↑microtubule-associated proteins 1A/1B light-chain (LC) 3 II, ↓p-62, ↓p-AKT, ↓p-	Cheng and Xie (2019)

(*continued on next page*)

Table 2 (*continued*)

Pharmacological effects	In vivo	In vitro	Dosage	Mechanisms	Reference
				mammalian target of rapamycin (mTOR), ↓p-70 kDa ribosomal protein S6 kinase (P70S6K), ↓cyclin D1	
	IOMM-LEE orthotopically xenografted SCID mice		10 mg/kg	↑N-myc downstream-regulated gene 2 (NDRG2), ↓NDRG2 promoter methylation, ↑Bax, ↓MMP-9, ↓p-phosphoinositide-3-kinase (PI3K), ↓p-AKT, ↓p-mTOR, ↓Wnt-2	Das et al. (2020)
		IOMM-Lee cell lines	25 μM		
	Xenograft tumor modeling in BALB/c nude mice		1 g/kg	↓circRNA flamin A (circFLNA), ↓cytochrome P450 family 1 subfamily A member 1 (CYP1A1), ↓X-ray repair cross-complementing 1 (XRCC1), ↑miR-486-3p	Gong et al. (2024)
		A549 cells	80 μM		
		Human nasopharyngeal carcinoma 5–8 F cells (NPC 5–8 F cells)	1 mM, 10 μM	↓Epstein-Barr virus (EBV) early antigen (EA), ↓EBV capsid antigen (CA), ↓telomerase	Zheng and Chen (2017)
Neuropsychopharmacological effects	AD mouse model		100 mg/kg	↓amyloid-β (Aβ) 42, ↑autophagy-related 5 (ATG5), ↑beclin 1, ↑microtubule-associated proteins 1A/1B LC3B (Map1lc3b), ↑p-Axl receptor tyrosine kinase (Axl), ↑p-CDC42-activated kinase 1 (Pak1)	Qi et al. (2021)
		BV2 microglial cells	20 μM		
		HT22 cells	40, 60 μmol/L	↓p16, ↓p21, ↓Hmgal, ↑ATG5, ↑Beclin 1, ↓LC3B I/II, ↓p-AKT, ↓p-mTOR, ↑Bcl-2, ↓Bax, ↓C-caspase-3	Shen et al. (2021)
		PC12 cells	12.5, 25, 50 μg/mL	↓Bax, ↓Bad, ↓caspase-3, ↓p-tau (S199), ↓p-tau (T231)	Cui et al. (2023)
	AD mice		20 mg/kg	↓IL-17A, ↓IL-6, ↓p-JAK2, ↓p-STAT3, ↓retinoid-associated orphan receptor-γt (ROR-γt), ↑IL-10, ↑IL-35, ↑transforming growth factor-β (TGF-β) 1, ↑forkhead box p3 (Foxp3)	Zhang et al. (2021)
		Mouse cortical microglia cells	10, 20, 50, 100 μg/ml	↓IL-1β, ↓IL-6, ↓TNF-α, ↓p-IκBα, ↓NF-κB (p65)	Chi et al. (2018)
		Hippocampal neuronal cells of Wistar rats	10, 20, 30, 40, 50 μg/ml	↑SOD, ↓MMP	Jiang et al. (2018)
	Epileptic rat model		10 mg/kg	↓calcium-sensing receptor (CaSR), ↓p-c-Jun N-terminal kinase (JNK), ↓p-p38, ↓Bax, ↓cleaved caspase-3, ↑p-extracellular signal-regulated kinase (ERK), ↑Bcl-2	Pang et al. (2022)
	Rat model of PSD		10, 20, 30 mg/kg	↑brain-derived neurotrophic factor (BDNF), ↑nerve growth factor (NGF), ↓TNF-α, ↓IL-1β, ↓IL-6, ↑IL-10, ↓iNOS, ↓CD86, ↑arginase-1 (Arg-1), ↑CD206, ↑p-ERK, ↑p-cAMP-response element-binding protein (CREB)	Zhang et al. (2021)
	Tail suspension, forced swim, and chronic social defeat stress (CSDS) depression models.		0.5, 1, 2.5 mg/kg	↓farnesoid X receptor (FXR), ↓nucleotide-binding domain leucine-rich repeat pyrin domain containing 3 (NLRP3), ↓pro-caspase-1, ↓caspase-1, ↓pro-IL-1β, ↓IL-1β, ↑α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), ↑p-GluA1, ↑GluA1, ↑GluA2	Bao et al. (2021)
		Murine BV2 microglial cell line	50 μg/ml	↓FXR, ↓IL-1β, ↓IL-6, ↓TNF-α, ↑BDNF, ↓iNOS, ↑Arg-1	Jia et al. (2021b)
	Cuprizone (CPZ) mouse model and EAE mouse demyelination model		1, 2.5, 5 mg/kg	↓FXR, ↑IL-4, ↑BDNF, ↓IL-6, ↓IL-1β	Jia et al. (2021a)
		SH-SY5Y and PC12 cell lines	10 μM	↓NO, ↑adrenaline (AD), ↑norepinephrine (NE)	Yu et al. (2020)
Hepatoprotective effects	CP-induced hepatotoxicity in mice		20, 40 mg/kg	↓IL-1β, ↓IL-6, ↓TNF-α, ↓alanine aminotransferase (ALT), ↓aspartate aminotransferase (AST), ↓Txnip, ↓p-NF-κB, ↓p-IκBα, ↓Bax, ↓caspase-3, ↓caspase-9, ↑thioredoxin (Trx), ↑Bcl-2	Xu et al. (2019)
	HFD-induced NAFLD in rats		20, 40 mg/kg	↓AST, ↓ALT, ↓TBIL, ↓cholesterol (TC), ↓triglyceride (TG), ↑high-density lipoprotein cholesterol (HDL-C), ↓TNF-α, ↓IL-1β, ↓IL-6, ↓liver x receptor (LXRs), ↓acetyl-CoA carboxylase (ACC) 1, ↓fatty acid synthase (FAS), ↑sterol regulatory element-binding protein (SREBP)-1c, ↑AMP-activated protein kinase (AMPK), ↑peroxisome proliferator-activated receptor (PPAR) α, ↑peroxisome	Liu et al. (2020)

(*continued on next page*)

Table 2 (*continued*)

Pharmacological effects	In vivo	In vitro	Dosage	Mechanisms	Reference
				proliferator-activated receptor γ coactivator 1-α (PGC-1α), ↓PPARγ, ↓p-NF-κB, ↓p-IκBα	
	HFHC diet-induced NASH model		25, 50 mg/kg	↓TG, ↓TC, ↓low-density lipoprotein cholesterol (LDL-C), ↓ALT, ↓AST, ↓IL-1β, ↓TNF-α, ↓IL-6, ↓α-smooth muscle actin (α-SMA), ↓TGF-β, ↓MMP-13, ↓MDA, ↑SOD, ↓GRP78, ↓p-eIF-2α, ↓p-JNK, ↑ERp57, ↑p-AKT, ↑p-mitogen-activated protein kinase (MAPK)	Zhu et al. (2022)
	Alcohol-induced liver injury in mice		10, 20, 40 mg/kg	↓TG, ↓TC, ↓LDL-C, ↓ALT, ↓AST, ↓lactate dehydrogenase (LDH), ↓MDA, ↑catalase (CAT), ↑SOD, ↑alcohol dehydrogenase (ADH), ↑aldehyde dehydrogenase (ALDH), ↑GSH, ↓acetyl-CoA acetyltransferase 2 (ACAT2), ↓ACC1, ↓cluster of differentiation 36 (CD36), ↓CCAAT/enhancer binding protein alpha (C/EBP-α), ↓hydroxymethylglutaryl-CoA reductase (HMGCR), ↓SREBP-1c, ↓cytochrome P4502E1 (CYP2E1), ↑acyl-CoA oxidase 1 (ACOX1), ↑acyl-CoA synthetase long-chain family member 1 (ACSL1), ↑bile salt export pump (BSEP), ↑cholesterol 7α hydroxylase (CYP7A1), ↑LDL receptor (LDLR), ↑Na+/taurocholate cotransporting polypeptide (NTCP), ↑PPARα	Lv et al. (2022)
	HFD-induced obese mouse model		25, 50 mg/kg	↓SREBP, ↓TG, ↓TC, ↓LDL-C, ↑HDL-C, ↓ALT, ↓AST, ↑uncoupling protein 1 (UCP-1), ↑lipoprotein lipase (LPL), ↑adiponectin, ↓FAS, ↓SCD-1, ↓HMGCR, ↓ fatty acid synthase (FASN), ↓acetyl-CoA synthetase (ACS), ↓ACC, ↓ACL, ↓FASD-2, ↓HMGCS, ↓LDLR, ↓farnesyl diphosphate synthase (FDPS), ↑ sterol regulatory element-binding proteins (SRBI), ↑LPL, ↑ApoE, ↓glucose-6-phosphate dehydrogenase (G-6-PD), ↓phosphoenolpyruvate carboxkinase (PEPCK)	Zhu et al. (2018)
		HL-7702 cells	10, 20 μM		
	HFD-fed hyperlipidemic mice		15, 75 mg/kg	↓TG, ↓TC, ↓LDL-C, ↓nonesterified free fatty acids (NEFA), ↓bile acids (BAs), ↓PPARα, ↓SREBP-1c, ↓C/EBPα, ↓FAS, ↓ACC1, ↓fatty acid transporter protein (FATP), ↓CD36, ↓HMGCR, ↓ACAT2, ↑CYP7A1, ↑NTCP, ↑FXR, ↑LDLR, ↑ACOX1	Guo et al. (2020)
Cardiovascular protective effects		Human monocytes (THP-1)	20, 50, 70 μM	↓TNF-α, ↓IL-1β, ↓IL-6, ↓NF-κB p65, ↓ROS, ↓MDA, ↓TC, ↓scavenger receptors class A (SR-A), ↓lectin-like oxidized LDL 1 receptor (LOX-1), ↓Notch1, ↓PPARγ, ↓CD36	Wang and Lu (2021)
	MIR rat model		20, 40 mg/kg	↓LDH, ↓creatine Kinase (CK), ↓TNF-α, ↓IL-1β, ↓IL-6, ↓p-JAK2, ↓p-STAT3, ↓p-NF-κB	Zhang et al. (2020)
Renoprotective effects	CCl4-induced kidney injury in mice		25, 50 mg/kg	↓MDA, ↑GSH, ↑SOD, ↑GPx, ↑TrxR, ↑Trx, ↓NF-κB (p-p65), ↓TNF-α, ↓IL-6, ↓p-JAK2, ↓p-STAT3, ↓ras homolog family member A (RhoA), ↓Rho-associated protein kinase (ROCK) 2, ↓TGF-β1, ↓p-mothers against decapentaplegic homolog 3 (Smad) 3	Ma et al. (2021)
		HK-2 cells (human proximal tubular epithelial cells)	100 μg/mL	↓fibronectin, ↓α-SMA	Geng et al. (2020)
	kidney-specific Pkd1 knockout (kPKD) mice		50 mg/kg	↓B-raf, ↓p-ERK, ↓early growth response protein 1(Egr-1), ↓c-fos, ↑Raf-1, ↓proliferating cell nuclear antigen (PCNA)	Meng et al. (2020)
		Madin-Darby canine kidney (MDCK) cells	6.25, 25, 100 μM		
Lung protective effects	LPS-induced acute lung injury in mice		20, 40 mg/kg	↓myeloperoxidase (MPO), ↓MDA, ↑SOD, ↓TNF-α, ↓IL-1β, ↓IL-6, ↓ROCK-I, ↓ROCK-II, ↓p-p65, ↓p-IκBα, ↑RhoA	Wan et al. (2019)
	Bleomycin-induced lung fibrosis in mice		25, 50 mg/kg	↓MPO, ↓MDA, ↑SOD, ↓TNF-α, ↓IL-1β, ↓IL-6, ↓TGF-β, ↓p-Smad3, ↓p-IκBα, ↓p-NF-κB	Wen et al. (2020)
Other pharmacological effects		Human lens epithelial cell line (SRA01/04 cells)	100 μmol/L	↓cleaved caspase-3, ↓Bax, ↑Bcl-2, ↓MDA, ↑SOD, ↑p-PI3K, ↑p-AKT	Kang et al. (2020)
	FD rat model		40 mg/kg	↑motilin (MTL), ↑gastrin (GAS), ↑somatostatin (SS), ↓vasoactive intestinal peptide (VIP), ↓leptin, ↓calcitonin gene-related peptide (CGRP), ↑occludin, ↑zonula	Yang et al. (2022)

(*continued on next page*)

Table 2 (*continued*)

Pharmacological effects	In vivo	In vitro	Dosage	Mechanisms	Reference
				occluden-1 (ZO-1), ↑junctional adhesion molecule-1 (JAM-1)	
	Ovariectomized (OVX) mouse model		50 mg/kg	↓ROS, ↓GRP78, ↓ATF6α, ↑CAT, ↑glutathione peroxidase 1 (GPx1), ↑UCP-1, ↑SOD1, ↑SOD2, ↑SOD3, ↓caspase-3, ↓caspase-7, ↓intercellular adhesion molecule 1 (ICAM-1), ↓methyl-accepting chemotaxis protein I (MCP-1), ↓NLRP3	Zhu (2023)

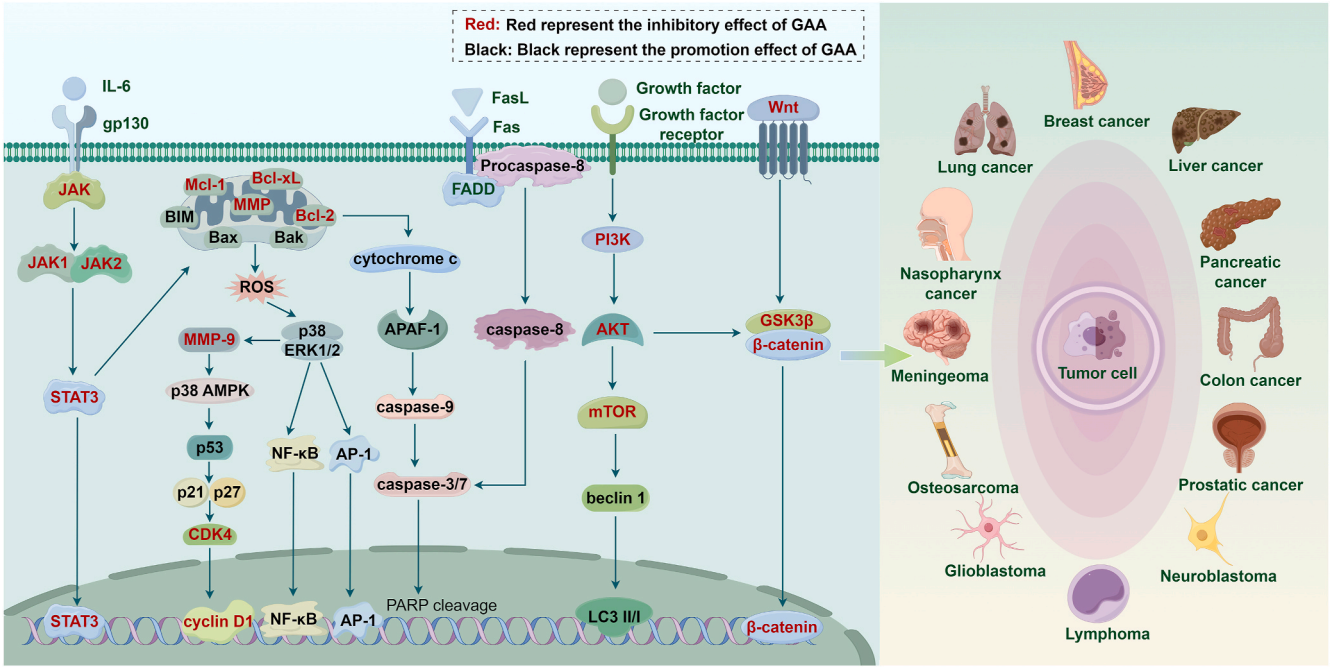

Fig. 3. Molecular pathways involved in the antitumor pharmacological effects of GAA. GAA exerts potent antitumor effects through the regulation of JAK/STAT3, NF-κB, Wnt/β-catenin, PI3K/AKT, and AKT/mTOR signaling pathways.

Prediction (http://www.swisstargetprediction.ch/) and obtained 100 target genes (Supplementary Table S1). Subsequently, a PPI network was produced for all target genes using STRING (https://cn.string-db.org/) (Fig. 8A), and the PPI network cores were screened by Cytoscape (Shannon et al., 2003) software (Fig. 8B).

The PPI network contains 97 nodes and 592 edges. The darker a protein node appears, the more connections it has, indicating it is more likely to play a role. In the network, MAPK3, TNF, caspase-3 (CASP3), peroxisome proliferator-activated receptor gamma (PPARG), β-catenin (CTNNB1), estrogen receptor 1 (ESR1), and nuclear receptor subfamily 3 group C member 1 (NR3C1) were the core targets. The identification of these core targets provides a comprehensive understanding of the multifaceted pharmacological activities of GAA, as discussed in previous sections. MAPK3 and TNF are pivotal in mediating inflammatory responses, with GAA exerting its anti-inflammatory effects by down-regulating the MAPK3 signaling pathway and suppressing TNF-α expression (Cao et al., 2020; Jia et al., 2021b; Meng et al., 2020; Pang et al., 2022; Wang et al., 2022; Wang and Lu, 2021; Wen et al., 2020; Zhang et al., 2020; Zheng et al., 2022; Zhu et al., 2022). In metabolic regulation, GAA suppresses inflammation, reduces oxidative stress, and improves lipid homeostasis through PPARG, exerting anti-atherosclerotic effects and offering therapeutic potential for metabolic diseases (Wang and Lu, 2021). Additionally, CASP3 and CTNNB1 contribute to GAA's anti-tumor properties, with studies showing that GAA induces apoptosis through caspase-3 activation and inhibits tumor proliferation by modulating the Wnt/β-catenin signaling pathway (Bashir et al., 2024; Cheng and Xie, 2019; Das et al., 2015; Gill et al., 2018; Liu et al., 2024; Pang et al., 2022; Radwan et al., 2015; Wang et al., 2017). Furthermore, TNF and CASP3 also play significant roles in the treatment of neurological disorders by GAA (Jia et al., 2021b; Pang et al., 2022).

In summary, as predicted by network pharmacology, GAA shows potential therapeutic effects in inflammation, tumors, neurological diseases, and metabolic diseases. These conditions remain major public health challenges with limited effective treatments. While chemical interventions are widely used, they often cause side effects like organ damage and drug resistance. Naturally derived compounds like GAA offer a promising alternative. Although ESR1 and NR3C1 have not been thoroughly studied in relation to GAA, their presence in the core network suggests potential roles in mediating GAA's effects on hormone-related diseases and stress responses. These findings highlight GAA's potential as a multi-target therapeutic agent, though further research is needed to fully understand its mechanisms and applications. Overall, GAA demonstrates significant pharmacological potential in addressing these complex diseases.

6.2. *Molecular docking analysis*

The GeneCards database (https://www.genecards.org/) was employed to summarize genes associated with diseases potentially treatable by GAA. Initially, we summarized the genes related to major inflammatory diseases treated with GAA, including rheumatoid arthritis

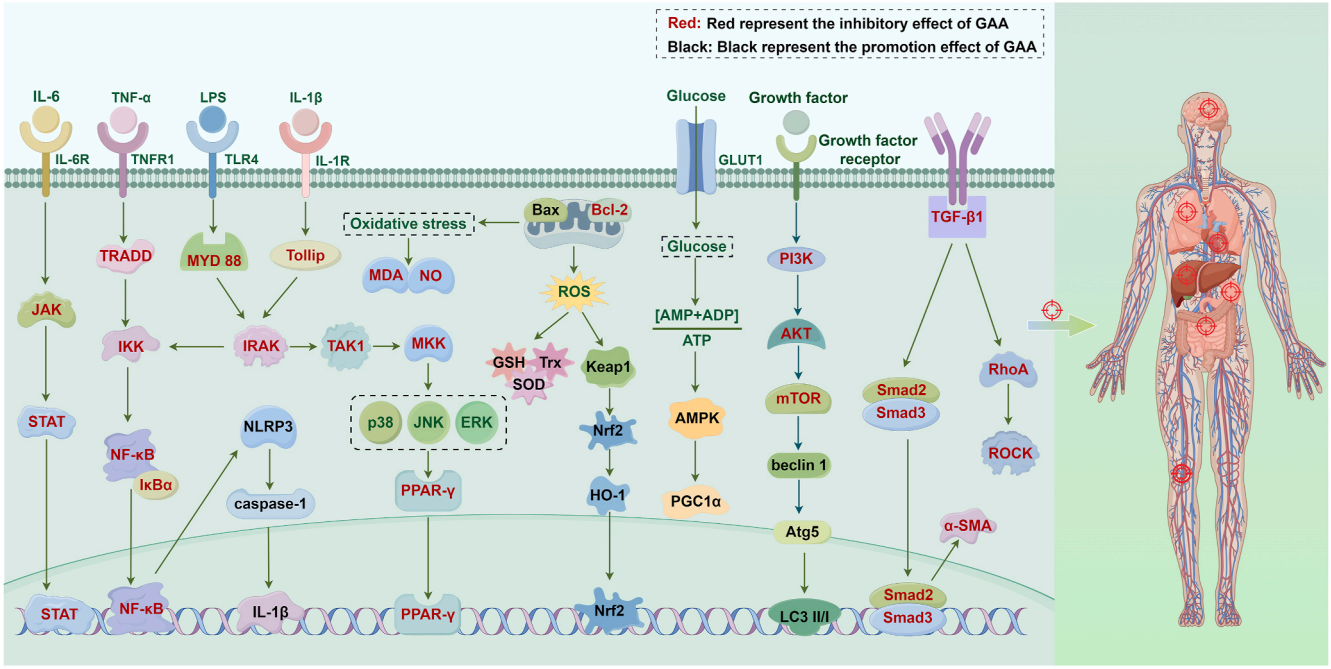

Fig. 4. Molecular pathways involved in the non-antitumor pharmacological effects of GAA. GAA exerts significant anti-inflammation, antioxidant, neuropsychopharmacological activities, hepatoprotective, cardiovascular protective, renoprotective, and lung protective effects by regulating these signal transduction pathways.

and osteoarthritis. After removing duplicate genes, a total of 9722 genes were retained. Subsequently, using the same search criteria and methods, we summarized genes associated with major cancers, such as breast cancer, prostate cancer, HCC, lung cancer, GBM, osteosarcoma, and lymphoma, resulting in 28,549 genes. Furthermore, genes linked to major neurological diseases, including AD, epilepsy, depression, neuroinflammation, and PD, were retrieved, yielding 26,383 genes. Additionally, genes associated with major metabolic diseases, such as NAFLD, MS, and AS, were collected, totaling 22,635 genes. As illustrated in Fig. 8C–F, the overlap between GAA target genes and disease-related genes was analyzed using Venny 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/).

We utilized the bioinformatics online server (https://www.bioinformatics.com.cn/) to perform GO and KEGG enrichment analysis on all 100 target genes of GAA (Fig. 9). GO enrichment analysis was mainly based on three categories: biological process (BP), cellular component (CC), and molecular function (MF). Histograms and bubble plots of GO analysis are shown in Fig. 9A and C. The top 10 items with BP, CC, and MF scores were listed based on the P score. To gain insight into the molecular mechanism of disease treatment by GAA, 114 signaling pathways were obtained by KEGG enrichment analysis (Supplementary Table S2), and the top 30 key signaling pathways were listed in histograms and bubble plots (Fig. 9B and D).

GO analysis revealed the multifaceted roles of GAA target genes in cell biology. These genes not only participate in the positive regulation of neuronal apoptosis and fine regulation of gene expression, but also respond to external stimuli. Through their localization in the nucleus and cytoplasm, they exert key functions such as transcriptional regulation and enzyme activity, thus playing a significant role in cell signaling and disease development. These genes play an important role in cell signaling and disease pathogenesis by regulating the modification of key proteins in cells. KEGG analysis indicates that GAA target genes may have a role in crucial biological processes, including cancer-related pathways, lipid metabolism and atherosclerosis, apoptosis, and the TNF signaling pathway. These findings highlight the complexity of GAA target genes in the regulation of cellular and organismal functions and their potential applications in disease therapy.

The TNF signaling pathway is a critical pathway regulating inflammatory responses, cell apoptosis, and immune modulation. The TNF signaling pathway, which has been frequently mentioned in published studies and scored highly in KEGG analysis, has already been validated as an important pathway for GAA in treating diseases. Research has shown that GAA significantly alleviates inflammatory responses and cellular damage by inhibiting the expression of TNF-α and its downstream signaling, providing a molecular basis for GAA's therapeutic effects in inflammation-related diseases. Pathways in cancer and lipid and atherosclerosis also achieved high scores in the KEGG analysis. Combined with the core targets identified in the PPI network, TNF and MAPK are implicated in the anti-inflammatory effects of GAA, further supporting its therapeutic potential in inflammation-related diseases, while CASP3 and CTNNB1 are implicated in cancer-related mechanisms, and PPARG shows potential in regulating metabolic diseases. Although there is no fixed standard, it has been reported that the binding energy of docking molecules can be spontaneously combined below 0 kJ/mol. According to previous studies, docking results with binding energies lower than −5.0 kJ/mol are often associated with good binding capacity, while those lower than −7.0 kJ/mol are suggested to represent excellent binding capacity (Gao et al., 2022).

Subsequently, the crystal structures of these target proteins were downloaded from the UniProt protein database (https://www.uniprot.org/). We used AutoDock Vina 1.1.2 software (Trott and Olson, 2010) for molecular docking of GAA (PubChem CID: 471002) with the proteins. The proteins were pre-treated with PyMOL 2.4 (https://www.pymol.org/) (removing water molecules and unwanted ligands, and adding hydrogen atoms). AutoDock Tools 1.5.6 was used to generate PDBQT files for docking simulations. The docking results were set to output the top 9 optimal docking positions. The docking conformation with the lowest binding energy and the highest clustering frequency was considered to be the most potential binding mode between the ligands and proteins. Finally, we used PLIP (Adasme et al., 2021) and PyMOL 2.4 software to visualize the docking results (Fig. 10). In this way, we could visually observe the binding of the ligand to the receptor and further analyze the stability and interactions of the complex.

Molecular docking results showed that the binding energies of

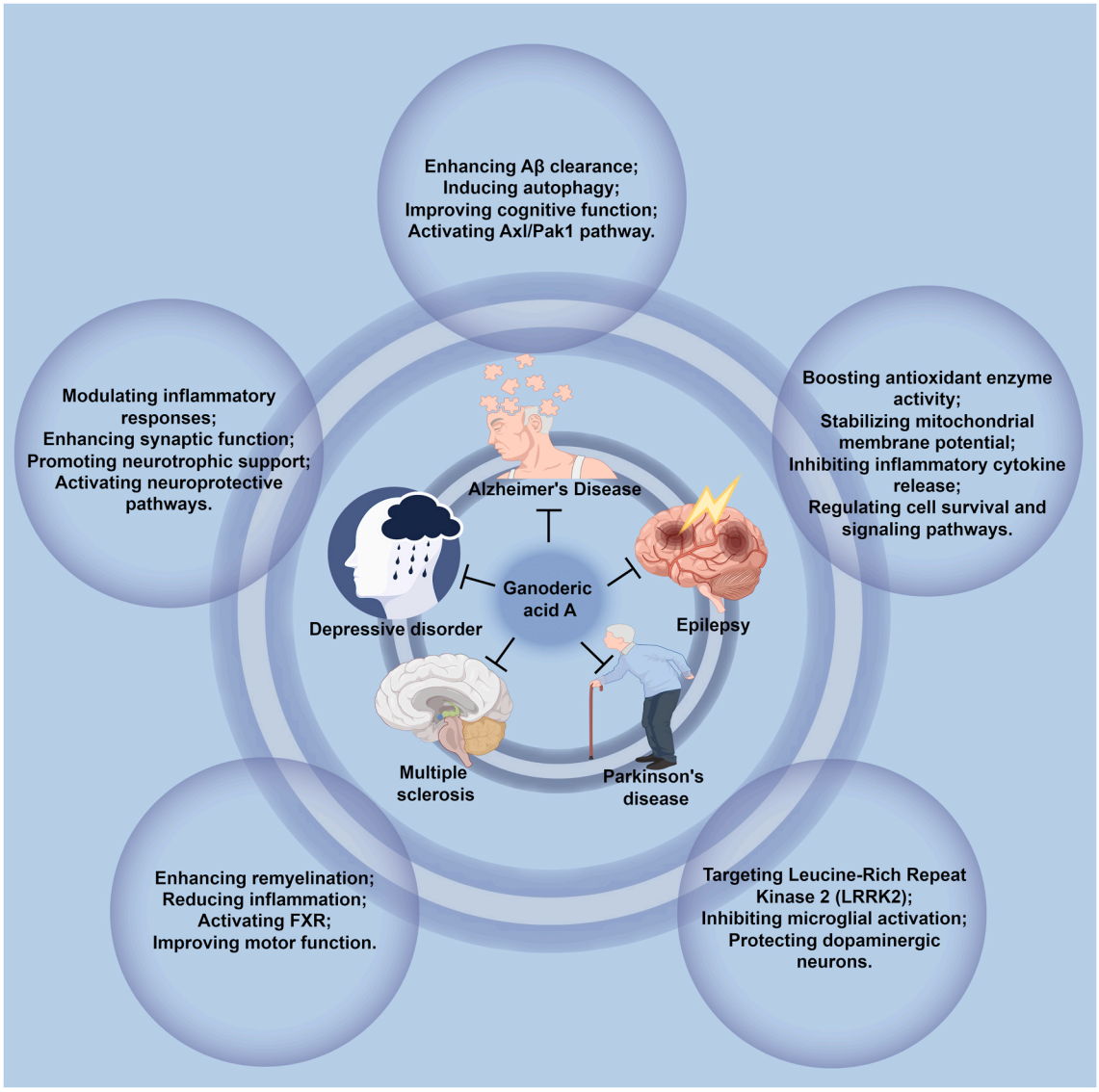

Fig. 5. Mechanisms of protective action of GAA against neurological and psychiatric disorders.

CTNNB1 was −6.7 kJ/mol, respectively, showing good binding ability; the binding energies of TNF, CASP3, PPARG, and MAPK3 were −7.3 kJ/mol, −7.9 kJ/mol, −7.9 kJ/mol, and −8.7 kJ/mol,showing excellent binding ability.

CASP3 is an effector cysteine protease that plays a central role in the execution phase of apoptosis. When cells receive apoptotic signals, CASP3 is activated to cleave a variety of intracellular substrates, leading to morphological changes and programmed cell death (Vaughan et al., 2002). Activation of CASP3 triggers a series of downstream events, including the cleavage of a variety of cytoskeletal proteins and nuclear proteins such as inhibitors of caspase-activated DNase (ICAD), poly (ADP ribose) polymerase (PARP), DNA-dependent protein kinase catalytic subunit (DNA-PKcs), and retinoblastoma protein (RB) (Dou, 1998; Nagata, 2000; Pajonk et al., 2005; Tarquini et al., 2014). These lysis events directly promote cellular morphological changes and programmed cell death. According to research reports, GAA has antitumor properties, and through molecular docking studies, we found that GAA forms hydrogen bonds, hydrophobic interactions, or other types of non-covalent interactions with specific amino acid residues LYS-278, PHE-280, ILE-242, ILE-282, ARG-286, GLY-241, and LEU-258 at the active site of CASP3. The interaction between GAA and LYS-278 may form key hydrogen bonds, which play a crucial role in regulating CASP3 activity. GAA may promote the activation of CASP3 by stabilizing or altering its conformation, thereby cleaving downstream proteins such as ICAD, PARP, DNA-PKcs, and RB, leading to the destruction of cell structure and loss of cell function, triggering cell apoptosis, and ultimately exerting antitumor effects. In the future, by gaining a deeper understanding of the molecular mechanisms between GAA and CASP3, new strategies may be developed to enhance CASP3's ability to induce apoptosis, providing more precise and effective means for tumor treatment. This is not only expected to improve treatment efficacy but may also bring new hope for the treatment of cancer patients who have developed resistance to existing therapeutic drugs, opening a new chapter in cancer treatment.

PPARG, a member of the nuclear receptor superfamily, plays a crucial role in inflammatory response (Yang et al., 2020). In cells, PPARG forms heterodimers by binding to its ligands and binds to the retinoid X receptor (RXR) to the PPAR-responsive element (PPRE) on DNA, thereby promoting gene transcription and regulating the expression of many genes. The activation of PPARG can inhibit the activity of downstream signaling pathways such as NF-κB and MAPK, reduce the production of inflammatory mediators TNF-α and IL-6, and thus reduce the inflammatory response. According to research reports, GAA has anti-inflammatory effects. Through molecular docking, we found that

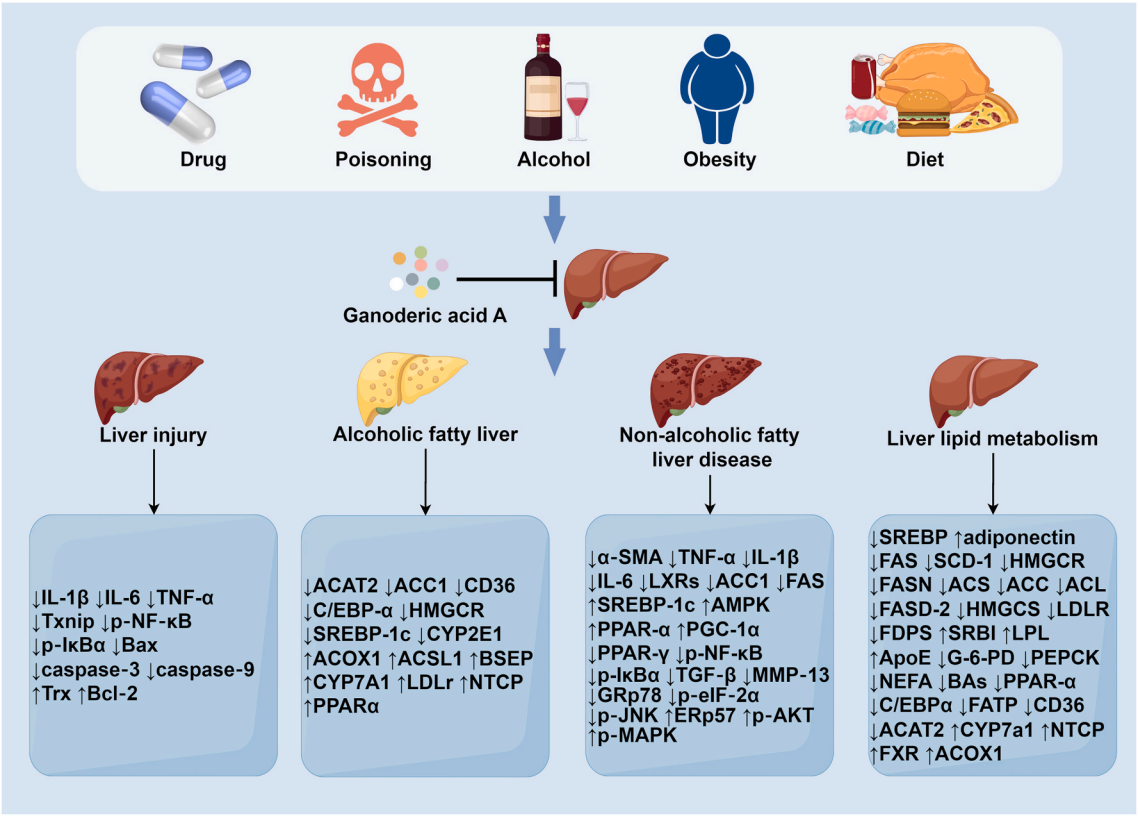

Fig. 6. The hepatoprotective mechanism of GAA.

Table 3
Pharmacokinetic parameters of GAA.

Method of administration	Species	Plasma/ Brain	Dose (mg/ kg, equivalent to GAA)	Pharmacokinetic parameters								References
				Tmax (h)	AUC0-t (a: μmol*h/ L; b: ng*h/ mL)	AUC0-∞ (a: μmol*h/ L; b: ng* h/mL)	t1/2 (h)	Vd/F (L/kg)	CL/F (L/ kg/h)	Cmax (a: ng/ mL; b: μmol/ L)	MRT (a: MRT0-t (h); b: MRT0-∞ (h); c: MRT (h))	
Oral	Rats (male, Wistar)	Plasma	25	4	332730 ± 0.21 (b)	N/A	1.65 ± 0.00	N/A	N/A	440 ± 0.03 (a)	2.43 ± 0.02 (a)	Rahman et al. (2021)
Oral	Rats (male, SD)	Plasma	20	0.15 ± 0.03	1.24 ± 0.36 (a)	1.35 ± 0.46 (a)	2.46 ± 0.75	106.24 ± 26.42	32.38 ± 13.45	0.91 ± 0.57 (b)	3.31 ± 1.11 (a); 4.11 ± 1.65 (b)	Cao et al. (2017b)
i.v.	Rats (male, SD)	Plasma	20	N/A	14.31 ± 4.54 (a)	14.34 ± 4.54 (a)	2.40 ± 0.35	10.21 ± 3.47	2.91 ± 0.81	N/A	0.16 ± 0.04 (a); 0.19 ± 0.06 (b)	Cao et al. (2017b)
i.v.	Rats (male, SD)	Brain	20	0.25 ± 0.00	0.42 ± 0.11 (a)	0.45 ± 0.09 (a)	1.40 ± 0.93	190.61 ± 146.36	89.21 ± 16.21	0.61 ± 0.18 (b)	0.80 ± 0.30 (a); 1.17 ± 0.51 (b)	Cao et al. (2017b)
Oral	Healthy male volunteers	Plasma	1417.80 ± 40.74	0.54 ± 0.18	9.58 ± 4.08 (b)	10.53 ± 4.32 (b)	0.62 ± 0.17	N/A	N/A	10.99 ± 4.02 (a)	N/A	Teekachunhatean et al. (2012)
Oral	Healthy male volunteers	Plasma	1417.80 ± 40.74	0.54 ± 0.10	1.93 ± 0.96 (b)	2.71 ± 1.09 (b)	0.66 ± 0.33	N/A	N/A	2.24 ± 1.31 (a)	N/A	Tawasri et al. (2016)

Oral: oral administration; i.v.: intravenous administration; N/A: not applicable.

GAA can form hydrogen bonds, hydrophobic interactions, or other types of non-covalent interactions with specific amino acid residues LYS-240, THR-241, THR-242, ASP-337, PHE-347, THR-349, and LEU-237 of PPARG. The interaction between GAA and PPARG may affect the substrate recognition and binding ability of PPARG, thereby regulating its control of inflammatory response genes. GAA may exert

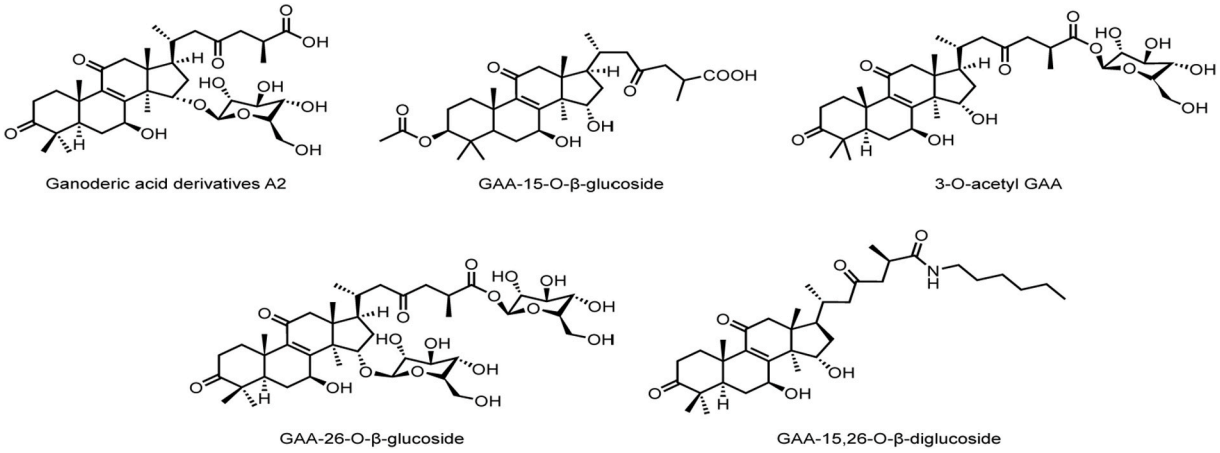

Fig. 7. Structure diagrams of GAA derivatives.

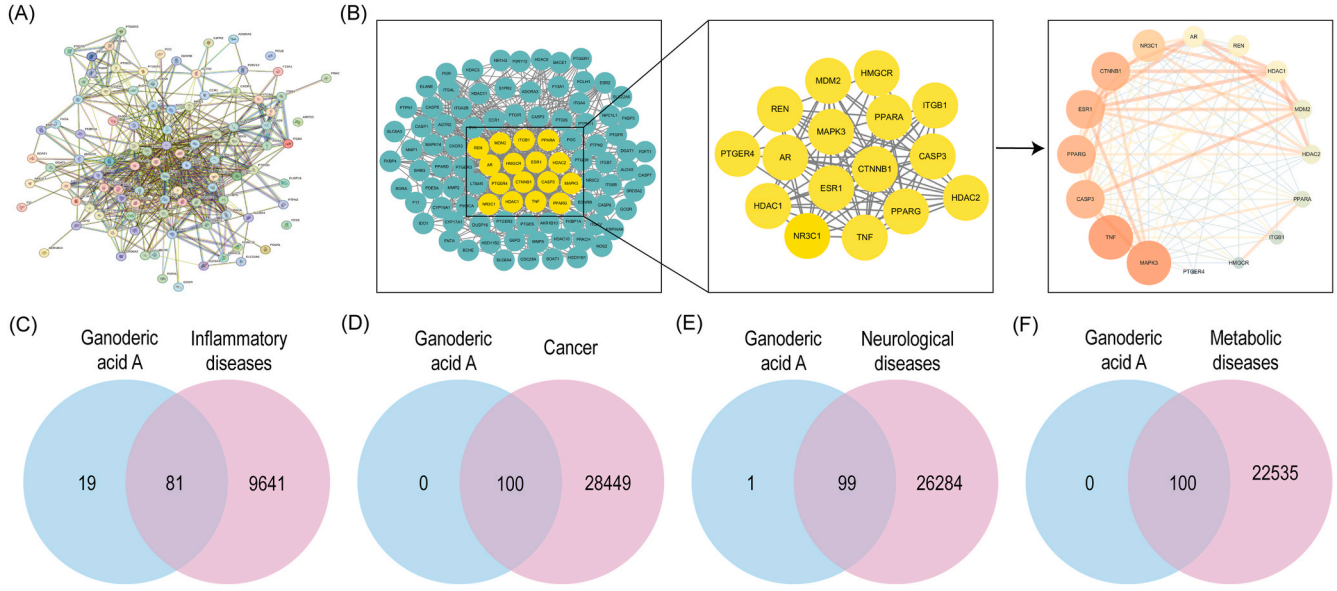

Fig. 8. Network pharmacology revealed the targets characteristics of GAA. (A) The PPI network based on targets of GAA, (B) PPI protein network cores, (C) Venn diagram of common targets of GAA for inflammatory diseases, (D) Venn diagram of common targets of GAA for cancer, (E) Venn diagram of common targets of GAA for neurological diseases, and (F) Venn diagram of common targets of GAA for metabolic diseases.

anti-inflammatory effects by activating PPARG, inhibiting the activity of downstream NF-κB and MAPK, and reducing the production of TNF-α and IL-6. This mechanism may involve precise regulation of inflammatory response, providing a molecular level explanation for the potential application of GAA in the treatment of inflammatory diseases. With further research on the interaction between GAA and PPARG, we look forward to revealing more potential and applications of this natural product in the treatment of inflammatory diseases.

MAPK3, also known as ERK1, is a key component of the MAPK/ERK signaling pathway, which regulates cellular processes such as proliferation, differentiation, and survival (Zhang and Liu, 2002). MAPK3 is activated through a cascade of phosphorylation events initiated by upstream signals, such as growth factors or cytokines, and subsequently phosphorylates a variety of downstream substrates, including transcription factors and other kinases, to modulate gene expression and cellular responses (Pearson et al., 2001). The activation of MAPK3 is crucial for transmitting extracellular signals to the nucleus, where it influences the expression of genes involved in cell cycle progression, apoptosis, and inflammation (Chang and Karin, 2001). Dysregulation of MAPK3 signaling has been implicated in various diseases, including cancer, inflammatory disorders, and metabolic syndromes (Dhillon et al., 2007). According to research reports, GAA exhibits anti-inflammatory and anti-tumor properties. Through molecular docking studies, we found that GAA can form hydrogen bonds, hydrophobic interactions, or other types of non-covalent interactions with specific amino acid residues such as LYS-54, THR-105, LEU-103, ILE-84, and ILE-31 at the active site of MAPK3. The interaction between GAA and LYS-54 may form key hydrogen bonds, which play a crucial role in regulating MAPK3 activity. GAA may inhibit the activation of MAPK3 by stabilizing or altering its conformation, thereby suppressing downstream signaling pathways such as NF-κB and reducing the production of inflammatory mediators like TNF-α and IL-6 (Zhu et al., 2022). This mechanism may provide a molecular-level explanation for the potential application of GAA in the treatment of inflammatory diseases and cancer. In the future, by gaining a deeper understanding of the molecular mechanisms between GAA and MAPK3, new strategies may be developed to modulate MAPK3 signaling, offering more precise and effective means for treating diseases associated with MAPK3 dysregulation.

Finally, it is crucial to determine the precise objectives and working principles of GAA. This includes a comprehensive screening of potential

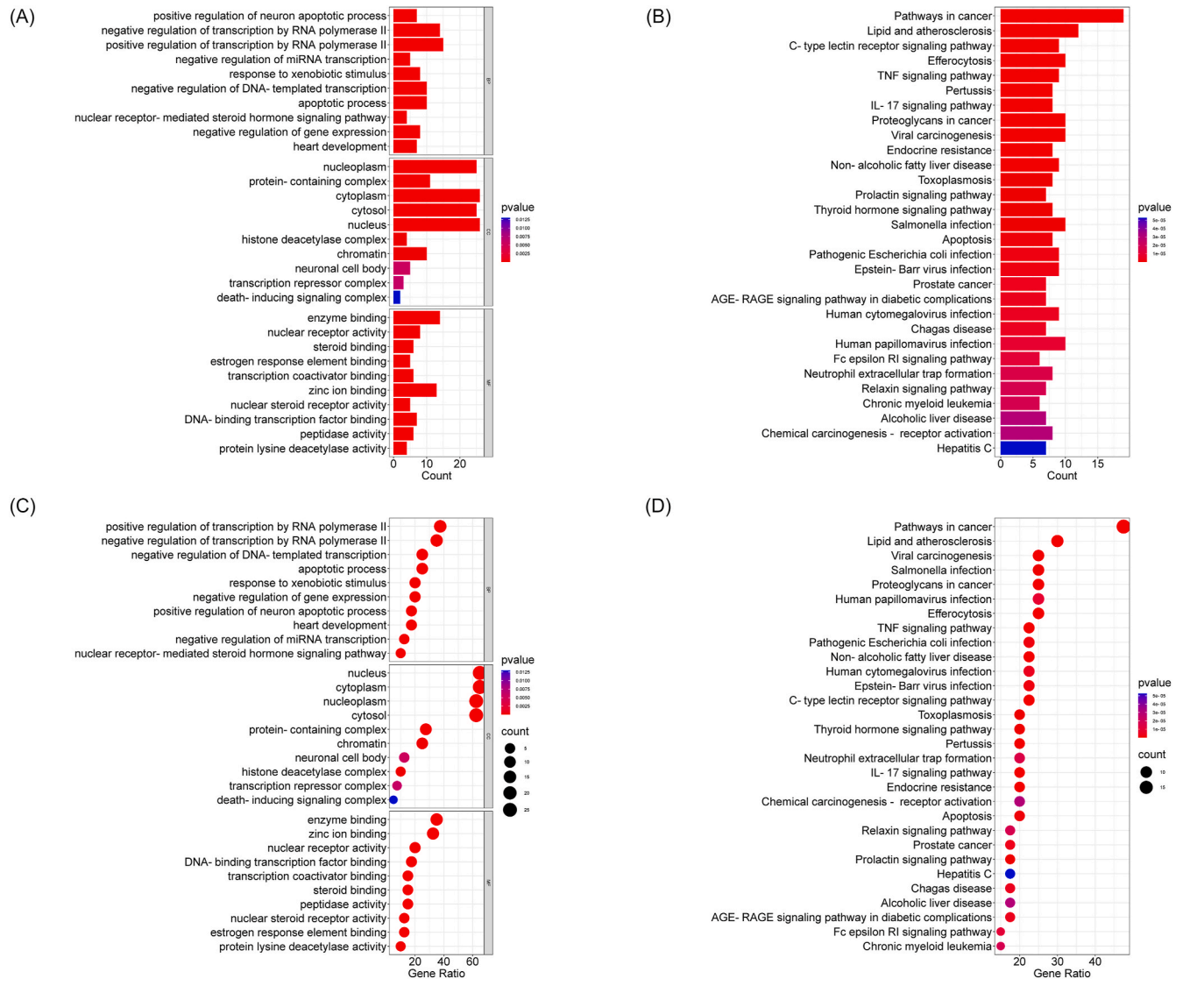

Fig. 9. Bioinformatics analysis based on target genes of GAA. (A) The histogram diagram of GO analysis, (B) the histogram diagram of KEGG analysis, (C) the bubble diagram of GO analysis, and (D) the bubble diagram of KEGG analysis.

GAA targets using techniques such as target capture and molecular docking. These preliminary findings need to be confirmed through methods such as co-crystallization of small molecules and proteins, gene editing techniques, and various biochemical assays. These methods will help reveal the actual molecular targets and specific pathways of GAA treatment for multiple diseases.

7. Conclusion and future perspectives

Traditional Chinese medicine (TCM) constitutes an invaluable asset of Chinese civilization, having contributed significantly to the prosperity of the Chinese nation throughout history (Cheung, 2011; Hesketh and Zhu, 1997). In recent years, there has been significant progress in material-based research on human diseases and clinical efficacy evaluation of TCM (J.G. Wang et al., 2018). This development has opened up new avenues for the scientific validation of TCM's therapeutic potential and has facilitated its integration into contemporary health practices. For example, TCM such as Fuzhenghuayu capsules, are designed to promote liver health by harmonizing the body's internal balance. Meanwhile, other Chinese patent medicines, represented by the Lianhuaqingwen capsule, are gradually showing the unique advantages of TCM in the treatment of COVID-19 (Hu et al., 2021; Li et al., 2020). In addition, monomer components such as oxymatrine, tanshinone, and artemisinin have also received attention for their antiviral, anti-inflammatory, and immunomodulatory potential (Huan et al., 2023; Li et al., 2020; Talman et al., 2019). The research of these monomer components not only enriches the scientific connotation of Chinese medicine, but also provides a new opportunity for the discovery of drugs with good efficacy and low side effects, which will bring hope to human health.

GAs are composed of ganoderic acids A-Z, among which ganoderic acids A, B, C2, D, DM, F, H, S, X, and Y (Fig. 11) exert the main pharmacological activity. Ganoderic acids D, DM, F, H, S, and X mainly play antitumor activity (Bryant et al., 2017; Jiang et al., 2008; Li et al., 2005; Liu and Zhong, 2011; Luo et al., 2024). Ganoderic acids D, DM, F, and H can inhibit the growth and invasion of breast cancer cells (Jiang et al., 2008; Luo et al., 2024; Wu et al., 2012). In addition to the above effects, ganoderic acid D has a potential antitumor effect on colon cancer and ovarian cancer (Cen et al., 2022; Liu et al., 2018), and ganoderic acid DM has a certain inhibitory effect on meningioma, lung cancer, and prostate cancer (Das et al., 2020; Johnson et al., 2010; Xia et al., 2020). Ganoderic acid B can play a role in lung preservation (Shi et al., 2020). In addition, ganoderic acid B and Y also have antiviral effects, such as HIV, EBV, and EV71 (Akbar and Yam, 2011; Zhang et al., 2014; Zheng

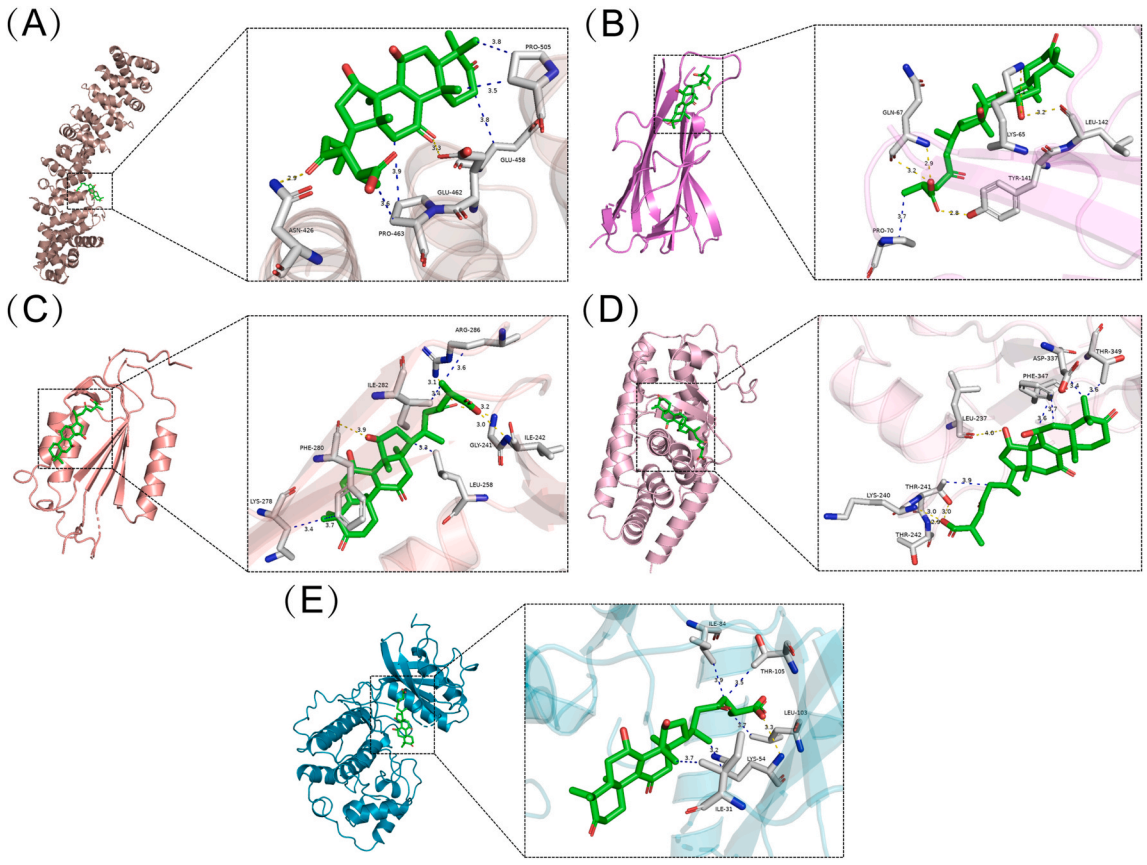

Fig. 10. Molecular docking of core proteins. (A) GAA-CTNNB1, (B) GAA-TNF, (C) GAA-CASP3, (D) GAA-PPARG, and (E) GAA-MAPK3.

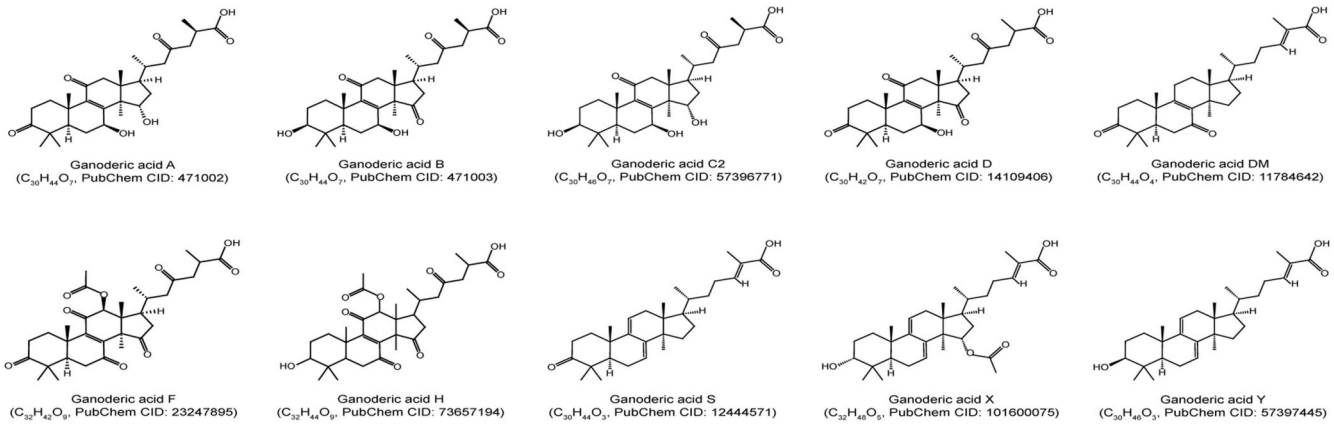

Fig. 11. Structure diagrams of main ganoderic acids. The chemical structures of compounds were derived from PubChem (https://pubchem.ncbi. nlm.nih.gov/).

and Chen, 2017). Ganoderic acid C2 has potential immunomodulatory and neuroprotective effects (Chen et al., 2012; Liu et al., 2023). Ganoderic acid Y is also an α-glucosidase inhibitor (X.Q. Chen et al., 2018). In comparison with other ganoderic acids, GAA has more extensive pharmacological activities. Therefore, GAA and its derivatives have been widely studied.

GAA is an important bioactive triterpenoid derived from *Ganoderma lucidum*. In recent decades, GAA has demonstrated a range of therapeutic effects, including anti-inflammatory, antioxidant, and antitumor properties, as well as benefits for neurological and psychological health, liver health, cardiovascular function, kidney function, and lung health. For inflammatory diseases, GAA has shown significant anti-inflammatory effects in a variety of inflammatory models by regulating NF-κB, JAK/STAT, and TLR signaling pathways. Its effective anti-inflammatory and antioxidant properties make it a valuable neuroprotective agent. In addition, GAA has significant advantages in antitumor activity. GAA exhibits a significant capacity to curb cancer cell proliferation, prevent invasion, and trigger apoptosis via multiple mechanisms, offering promising prospects in the fight against cancer. In terms of neuroprotective effects, GAA exerts its protective role in a variety of neurodegenerative diseases by regulating the FXR receptor, AKT/mTOR signaling pathways, Notch signaling pathway, Wnt signaling pathways, immune cells, and the production of inflammatory cytokines. The therapeutic potential of GAA for AD, depression, and epilepsy has been demonstrated in several animal studies. GAA alleviates the harmful effects of oxidative stress and inflammation on brain function by exerting

anti-inflammatory and antioxidant activities. The main biological activities and some possible molecular mechanisms are summarized in Fig. 12. This study provides a reference for future GAA research and development.

Network pharmacology and molecular docking analyses have further elucidated the molecular mechanisms underlying GAA's pharmacological effects. Through network pharmacology, we identified 100 target genes of GAA and constructed a PPI network, revealing core targets such as MAPK3, TNF, CASP3, PPARG, and CTNNB1. These targets are implicated in GAA's anti-inflammatory, antitumor, neuroprotective, and metabolic regulatory effects. Molecular docking studies demonstrated strong binding affinities between GAA and key proteins, including TNF (−7.3 kJ/mol), CASP3 (−7.9 kJ/mol), PPARG (−7.9 kJ/mol), and MAPK3 (−8.7 kJ/mol), suggesting excellent binding capacity. These findings provide a molecular basis for GAA's therapeutic effects and highlight its potential as a multi-target therapeutic agent.

The pharmacokinetic results of GAA vary depending on the route of administration, animal species, dose administered, and assay method. Overall, pharmacokinetic studies of GAA indicate that its oral bioavailability is low, making it difficult to use for disease prevention and treatment. This is an important question to address in future research. Increasing the oral bioavailability of GAA is essential to improve its efficacy in the treatment of diseases. Therefore, the oral bioavailability of GAA can be improved by chemical modification and combination therapy. These strategies are potentially beneficial in optimizing the therapeutic efficacy of GAA.

This study provides a comprehensive review and summary of the pharmacological activity and pharmacokinetic properties of GAA and will serve as a valuable resource for researchers and scientists in the field of drug discovery and development. The information provided in this study is expected to significantly contribute to the development of novel drugs and therapies from TCM monomers, thereby expanding the scope of natural product-based drug discovery. However, despite significant progress in research on GAA's pharmacological activities, several limitations remain. While numerous in vitro and animal studies have demonstrated GAA's antitumor, anti-inflammatory, and antioxidant effects, clinical research is still lacking to validate its efficacy and safety in humans. Additionally, the precise molecular targets and mechanisms of action of GAA are not fully elucidated, and the causal relationship between its pharmacological activities and therapeutic effects remains unclear. Future research should focus on addressing these gaps, particularly through clinical trials, direct target validation, and mechanistic studies to establish a clearer understanding of GAA's therapeutic potential.

GAA, a natural compound found in GL, has been shown to have a variety of biological activities with potential therapeutic applications. To give full play to the clinical potential of GAA, future research should focus on the following key areas: (1) Although GAA has shown a wide range of pharmacological activities, the exact mechanisms underlying some of its effects remain unclear. Future research needs to explore the mechanism of action of the GAA and its derivatives further, especially how they adjust different signaling pathways to exert their biological effect. (2) As single-drug therapy may face challenges such as insufficient efficacy, large side effects, or drug resistance in many cases, it is of great clinical significance and application value to further study the combination of GAA with other drugs to explore the synergistic effect, improve the therapeutic effect, and reduce side effects and drug resistance associated with single-drug use. (3) Given the paucity of literature on GAA pharmacokinetics, future research needs to focus more on this area to provide useful information for the clinical application of GAA. (4) The oral bioavailability of GAA is low, which may be related to its structure and properties. Therefore, it can be improved by nanotechnology or chemical modification to improve the solubility and stability of GAA, make it easier to be absorbed in the gastrointestinal tract, and reduce its decomposition and metabolism in vivo, thereby increasing the oral bioavailability and drug therapeutic potential of GAA.

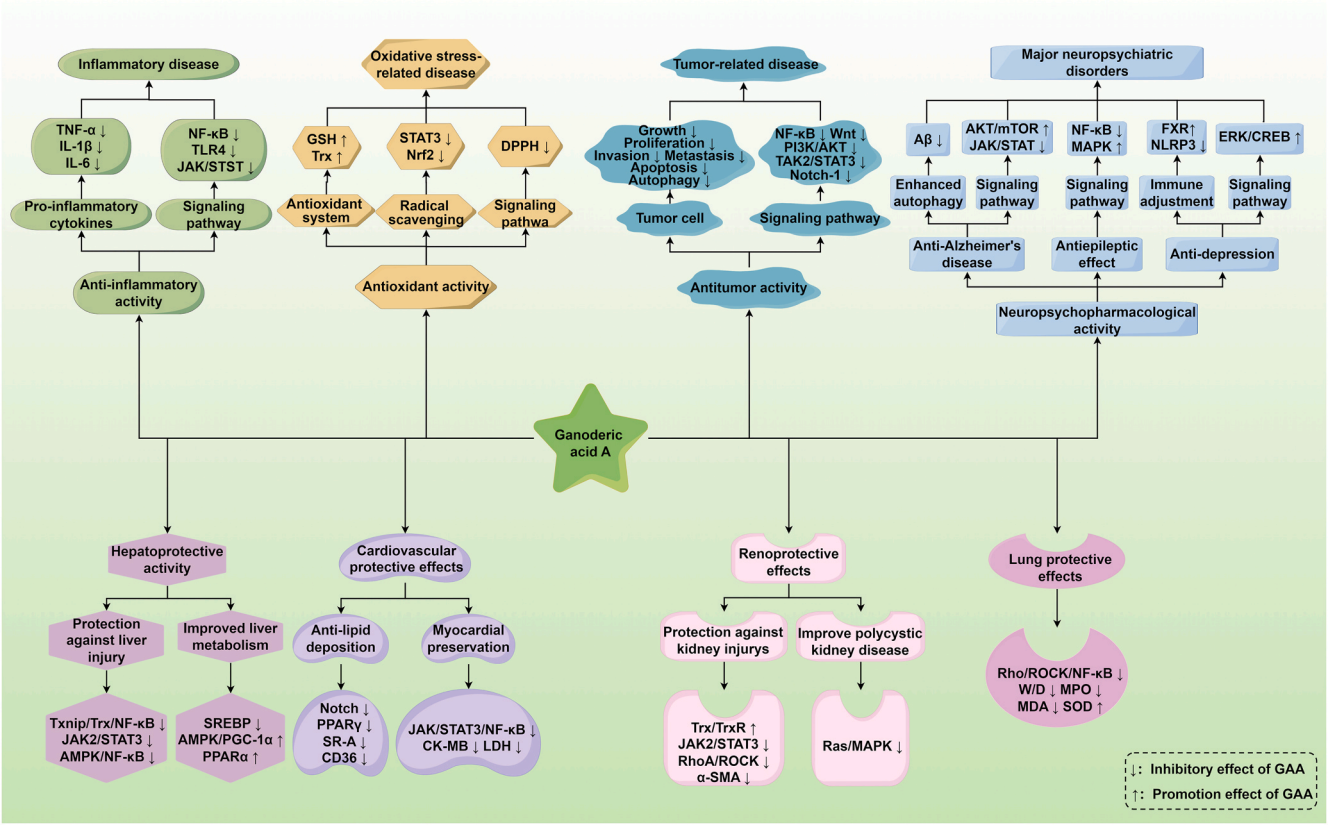

Fig. 12. The main biological activities and possible molecular mechanisms of GAA.

In summary, GAA research is progressing rapidly, and it can be predicted that in the coming years, GAA will receive more attention in the treatment of tumors, neurological diseases, inflammatory diseases, and other related diseases.

CRediT authorship contribution statement

Qi Sui: Writing – original draft. **Chengkai Zhu:** Data curation. **Sha Shi:** Methodology. **Jiaqi Xu:** Methodology. **Jingnan Zhang:** Software. **Ao Wang:** Methodology. **Peng Chen:** Software. **Guang Liang:** Resources, Methodology. **Yi Zhang:** Writing – review & editing.

Funding

This study was supported by National Natural Science Foundation of China (82304840 to Y.Z.), Zhejiang Provincial Natural Science Foundation of China under Grant No. LQ23H280021 to Y.Z., Traditional Chinese Medicine Science and Technology Project of Zhejiang Province (2024ZF006 to Y.Z.), Basic Scientific Research Project of Hangzhou Medical College (KYYB202106 to Y.Z.), National Innovation and Entrepreneurship Training Program for College Students (202113023001).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The main figures were assembled by Figdraw (www.figdraw.com).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2025.119868.

Data availability

Data will be made available on request.

References

Adasme, M.F., Linnemann, K.L., Bolz, S.N., Kaiser, F., Salentin, S., Haupt, V.J., Schroeder, M., 2021. Plip 2021: expanding the scope of the protein-ligand interaction profiler to DNA and RNA. Nucleic Acids Res. 49, W530–W534. https://doi.org/10.1093/nar/gkab294.

Ahmad, F., 2023. Ganoderic acid A targeting leucine-rich repeat kinase 2 involved in Parkinson's disease–A computational study. Aging Medicine 6, 272–280. https://doi.org/10.1002/agm2.12235.

Ahmad, M.F., Wahab, S., Ahmad, F.A., Ashraf, S.A., Abullais, S.S., Saad, H.H., 2022. Ganoderma lucidum: a potential pleiotropic approach of ganoderic acids in health reinforcement and factors influencing their production. Fungal Biol Rev 39, 100–125. https://doi.org/10.1016/j.fbr.2021.12.003.

Akbar, R., Yam, W.K., 2011. Interaction of ganoderic acid on HIV related target: molecular docking studies. Bioinformation 7, 413–417. https://doi.org/10.6026/97320630007413.

Algoet, M., Janssens, S., Himmelreich, U., Gsell, W., Pusovnik, M., Van den Eynde, J., Oosterlinck, W., 2023. Myocardial ischemia-reperfusion injury and the influence of inflammation. Trends Cardiovasc. Med. 33, 357–366. https://doi.org/10.1016/j.tcm.2022.02.005.

Arias-Carrión, O., Drucker-Colín, R., 2007. Neurogenesis as a therapeutic strategy to regenerate central nervous system. Rev Neurol 45, 739–745.

Baby, S., Johnson, A.J., Govindan, B., 2015. Secondary metabolites from ganoderma. Phytochemistry 114, 66–101. https://doi.org/10.1016/j.phytochem.2015.03.010.

Badmus, O.O., Hillhouse, S.A., Anderson, C.D., Hinds, T.D., Stec, D.E., 2022. Molecular mechanisms of metabolic associated fatty liver disease (MAFLD): functional analysis of lipid metabolism pathways. Clin. Sci. (Lond.) 136, 1347–1366. https://doi.org/10.1042/CS20220572.

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., Jones, E., 2011. Alzheimer's disease. Lancet 377, 1019–1031. https://doi.org/10.1016/S0140-6736(10)61349-9.

Bao, H., Li, H., Jia, Y., Xiao, Y., Luo, S., Zhang, D., Han, L., Dai, L., Xiao, C., Feng, L., Feng, Y., Yang, Y., Wang, H., Wang, G., Du, J., 2021. Ganoderic acid A exerted antidepressant-like action through FXR modulated NLRP3 inflammasome and synaptic activity. Biochem. Pharmacol. 188. https://doi.org/10.1016/j.bcp.2021.114561.

Barkat, A., Rahman, M., Alharbi, K.S., Altowayan, W.M., Alrobaian, M., Afzal, O., Altamimi, A.S.A., Alhodieb, F.S., Almalki, W.H., Choudhry, H., Singh, T., Beg, S., 2022. Biocompatible polymeric nanoparticles for effective codelivery of tamoxifen with ganoderic acid A: systematic approach for improved breast cancer therapeutics. J. Clust. Sci. 34, 1483–1497. https://doi.org/10.1007/s10876-022-02332-4.

Bashir, M.A., Shao, C.-S., Abdalla, M., Lin, X., Li, L., Wu, Y., Huang, Q., 2024. Ganoderic acid A targets IL-1R1 and disrupts IL-1β binding in human cancer cells. J. Mol. Struct. 1301, 137431. https://doi.org/10.1016/j.molstruc.2023.137431.

Baxter, A.J., Charlson, F.J., Cheng, H.G., Shidhaye, R., Ferrari, A.J., Whiteford, H.A., 2016. Prevalence of mental, neurological, and substance use disorders in China and India: a systematic analysis. Lancet Psychiatry 3, 832–841. https://doi.org/10.1016/S2215-0366(16)30139-0.

Bergmann, C., Guay-Woodford, L.M., Harris, P.C., Horie, S., Peters, D.J.M., Torres, V.E., 2018. Polycystic kidney disease. Nat. Rev. Dis. Primers 4, 50. https://doi.org/10.1038/s41572-018-0047-y.

Bhondave, P.D., Devarshi, P.P., Mahadik, K.R., Harsulkar, A.M., 2014. "ashvagandharishta" prepared using yeast consortium from Woodfordia fruticosa flowers exhibit hepatoprotective effect on CCl4 induced liver damage in wistar rats. J. Ethnopharmacol. 151, 183–190. https://doi.org/10.1016/j.jep.2013.10.025.

Boehlig, A., Gerhardt, F., Petroff, D., van Boemmel, F., Berg, T., Blank, V., Karlas, T., Wiegand, J., 2022. Prevalence of pruritus and association with anxiety and depression in patients with nonalcoholic fatty liver disease. Biomedicines 10, 451. https://doi.org/10.3390/biomedicines10020451.

Bonizzi, G., Karin, M., 2004. The two NF-κB activation pathways and their role in innate and adaptive immunity. Trends Immunol. 25, 280–288. https://doi.org/10.1016/j.it.2004.03.008.

Bowman, T., Garcia, R., Turkson, J., Jove, R., 2000. STATs in oncogenesis. Oncogene 19, 2474–2488.

Boyle, D.L., Soma, K., Hodge, J., Kavanaugh, A., Mandel, D., Mease, P., Shurmur, R., Singhal, A.K., Wei, N., Rosengren, S., Kaplan, I., Krishnaswami, S., Luo, Z., Bradley, J., Firestein, G.S., Kvien, T.K., 2015. The JAK inhibitor tofacitinib suppresses synovial JAK1-STAT signalling in rheumatoid arthritis. Ann. Rheum. Dis. 74, 1311–1316. https://doi.org/10.1136/annrheumdis-2014-206028.

Brotin, E., Meryet-Figuière, M., Simonin, K., Duval, R.E., Villedieu, M., Leroy-Dudal, J., Saison-Behmoaras, E., Gauduchon, P., Denoyelle, C., Poulain, L., 2010. Bcl-xL and MCL-1 constitute pertinent targets in ovarian carcinoma and their concomitant inhibition is sufficient to induce apoptosis. Int. J. Cancer 126, 885–895. https://doi.org/10.1002/ijc.24787.

Bryant, J.M., Bouchard, M., Haque, A., 2017. Anticancer activity of ganoderic acid DM: current status and future perspective. J. Clin. Cell. Immunol. 8. https://doi.org/10.4172/2155-9899.1000535.

Cao, F.-R., Feng, L., Ye, L.-H., Wang, L.-S., Xiao, B.-X., Tao, X., Chang, Q., 2017a. Ganoderic acid A metabolites and their metabolic kinetics. Front. Pharmacol. 8. https://doi.org/10.3389/fphar.2017.00101.

Cao, F.R., Xiao, B.X., Wang, L.S., Tao, X., Yan, M.Z., Pan, R. Le, Liao, Y.H., Liu, X.M., Chang, Q., 2017b. Plasma and brain pharmacokinetics of ganoderic acid A in rats determined by a developed UFLC–MS/MS method. J Chromatogr B Analyt Technol Biomed Life Sci 1052, 19–26. https://doi.org/10.1016/j.jchromb.2017.03.009.

Cao, T., Tang, C., Xue, L., Cui, M., Wang, D., 2020. Protective effect of ganoderic acid A on adjuvant-induced arthritis. Immunol. Lett. 226, 1–6. https://doi.org/10.1016/j.imlet.2020.06.010.

Cen, K., Chen, M., He, M., Li, Z., Song, Y., Liu, P., Jiang, Q., Xu, S., Jia, Y., Shen, P., 2022. Sporoderm-broken spores of Ganoderma lucidum sensitizes ovarian cancer to cisplatin by ROS/ERK signaling and attenuates chemotherapy-related toxicity. Front. Pharmacol. 13. https://doi.org/10.3389/fphar.2022.826716.

Chang, L., Karin, M., 2001. Mammalian MAP kinase signalling cascades. Nature 410, 37–40. https://doi.org/10.1038/35065000.

Chang, T.-S., Chiang, C.-M., Wang, T.-Y., Lee, C.-H., Lee, Y.-W., Wu, J.-Y., 2018a. New triterpenoid from novel triterpenoid 15-O-Glycosylation on ganoderic acid A by intestinal bacteria of zebrafish. Molecules 23, 2345. https://doi.org/10.3390/molecules23092345.

Chang, T.-S., Ko, H.-H., Wang, T.-Y., Lee, C.-H., Wu, J.-Y., 2018b. Biotransformation of ganoderic acid A to 3-O-Acetyl ganoderic acid A by soil-isolated streptomyces sp. Fermentation 4, 101. https://doi.org/10.3390/fermentation4040101.

Chang, T.-S., Wu, J.-Y., Wang, T.-Y., Wu, K.-Y., Chiang, C.-M., 2018c. Uridine diphosphate-dependent glycosyltransferases from Bacillus subtilis ATCC 6633 catalyze the 15-O-Glycosylation of ganoderic acid A. Int. J. Mol. Sci. 19, 3469. https://doi.org/10.3390/ijms19113469.

Chang, T.-S., Chiang, C.-M., Kao, Y.-H., Wu, J.-Y., Wu, Y.-W., Wang, T.-Y., 2019a. A new triterpenoid glucoside from a novel acidic glycosylation of ganoderic acid A via recombinant glycosyltransferase of Bacillus subtilis. Molecules 24, 3457. https://doi.org/10.3390/molecules24193457.

Chang, T.-S., Wang, T.-Y., Hsueh, T.-Y., Lee, Y.-W., Chuang, H.-M., Cai, W.-X., Wu, J.-Y., Chiang, C.-M., Wu, Y.-W., 2019b. A genome-centric approach reveals a novel glycosyltransferase from the GA A07 strain of Bacillus thuringiensis responsible for catalyzing 15-O-Glycosylation of ganoderic acid A. Int. J. Mol. Sci. 20, 5192. https://doi.org/10.3390/ijms20205192.

Chang, T.-S., Chiang, C.-M., Wu, J.-Y., Tsai, Y.-L., Ting, H.-J., 2021. Production of a new triterpenoid disaccharide saponin from sequential glycosylation of ganoderic acid A by 2 *bacillus* glycosyltransferases. Biosci. Biotechnol. Biochem. 85, 687–690. https://doi.org/10.1093/bbb/zbaa055.

Chanvorachote, P., Pongrakhananon, V., Wannachaiyasit, S., Luanpitpong, S., Rojanasakul, Y., Nimmannit, U., 2009. Curcumin sensitizes lung cancer cells to cisplatin-induced apoptosis through superoxide anion-mediated Bcl-2 degradation. Cancer Invest. 27, 624–635. https://doi.org/10.1080/07357900802653472.

Chen, L.W., Horng, L.Y., Wu, C.L., Sung, H.C., Wu, R.T., 2012. Activating mitochondrial regulator PGC-1α expression by astrocytic NGF is a therapeutic strategy for Huntington's disease. Neuropharmacology 63, 719–732. https://doi.org/10.1016/j.neuropharm.2012.05.019.

Chen, W.-G., Zheng, J.-X., Xu, X., Hu, Y.-M., Ma, Y.-M., 2018. Hippocampal FXR plays a role in the pathogenesis of depression: a preliminary study based on lentiviral gene modulation. Psychiatry Res. 264, 374–379. https://doi.org/10.1016/j.psychres.2018.04.025.

Chen, X.Q., Zhao, J., Chen, L.X., Wang, S.F., Wang, Y., Li, S.P., 2018. Lanostane triterpenes from the mushroom Ganoderma resinaceum and their inhibitory activities against α-glucosidase. Phytochemistry 149, 103–115. https://doi.org/10.1016/j.phytochem.2018.01.007.

Cheng, Y., Xie, P., 2019. Ganoderic acid A holds promising cytotoxicity on human glioblastoma mediated by incurring apoptosis and autophagy and inactivating PI3K/AKT signaling pathway. J. Biochem. Mol. Toxicol. 33. https://doi.org/10.1002/jbt.22392.

Cheng, P., Li, S., Chen, H., 2021. Macrophages in lung injury, repair, and fibrosis. Cells 10. https://doi.org/10.3390/CELLS10020436.

Cheung, F., 2011. Traditional medicine. Nature Outlook 480, S82–S83.

Chi, B., Wang, S., Bi, S., Qin, W., Wu, D., Luo, Z., Gui, S., Wang, D., Yin, X., Wang, F., 2018. Effects of ganoderic acid A on lipopolysaccharide-induced proinflammatory cytokine release from primary mouse microglia cultures. Exp. Ther. Med. 15, 847–853. https://doi.org/10.3892/etm.2017.5472.

Cui, J., Meng, Y.H., Wang, Z.W., Wang, J., Shi, D.F., Liu, D., 2023. Ganoderic acids A and B reduce Okadaic acid-induced neurotoxicity in PC12 cells by inhibiting tau hyperphosphorylation. Biomed. Environ. Sci. 36, 103–108. https://doi.org/10.3967/bes2023.011.

Dambach, H., Hinkerohe, D., Prochnow, N., Stienen, M.N., Moinfar, Z., Haase, C.G., Hufnagel, A., Faustmann, P.M., 2014. Glia and epilepsy: experimental investigation of antiepileptic drugs in an astroglia/microglia co-culture model of inflammation. Epilepsia 55, 184–192. https://doi.org/10.1111/epi.12473.

Das, A., Miller, R., Lee, P., Holden, C.A., Lindhorst, S.M., Jaboin, J., Vandergrift, W.A., Banik, N.L., Giglio, P., Varma, A.K., Raizer, J.J., Patel, S.J., 2015. A novel component from citrus, ginger, and mushroom family exhibits antitumor activity on human meningioma cells through suppressing the Wnt/β-catenin signaling pathway. Tumor Biol. 36, 7027–7034. https://doi.org/10.1007/s13277-015-3388-0.

Das, A., Alshareef, M., Henderson, F., Martinez Santos, J.L., Vandergrift, W.A., Lindhorst, S.M., Varma, A.K., Infinger, L., Patel, S.J., Cachia, D., 2020. Ganoderic acid A/DM-induced NDRG2 over-expression suppresses high-grade meningioma growth. Clin. Transl. Oncol. 22, 1138–1145. https://doi.org/10.1007/s12094-019-02240-6.

Devarbhavi, H., Asrani, S.K., Arab, J.P., Nartey, Y.A., Pose, E., Kamath, P.S., 2023. Global burden of liver disease: 2023 update. J. Hepatol. 79, 516–537. https://doi.org/10.1016/j.jhep.2023.03.017.

Devinsky, O., 2004. Effects of seizures on autonomic and cardiovascular function. Epilepsy Curr. 4, 43–46. https://doi.org/10.1111/j.1535-7597.2004.42001.x.

Dhillon, A.S., Hagan, S., Rath, O., Kolch, W., 2007. MAP kinase signalling pathways in cancer. Oncogene 26, 3279–3290. https://doi.org/10.1038/sj.onc.1210421.

Dou, Q. Ping, 1998. RB and apoptotic cell death. Front. Biosci. 3, A288. https://doi.org/10.2741/A288.

Duman, R.S., Aghajanian, G.K., Sanacora, G., Krystal, J.H., 2016. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nat Med 22, 238–249. https://doi.org/10.1038/nm.4050.

Dziedzicka-Wasylewska, M., Faron-Górecka, A., Rogóz, Z., Solich, J., 2004. The effect of combined treatment with imipramine and amantadine on the behavioral reactivity of central alpha1-adrenergic system in rats. Behavioural pharmacology 15, 159–165. https://doi.org/10.1097/00008877-200403000-00008.

Eferl, R., Wagner, E.F., 2003. AP-1: a double-edged sword in tumorigenesis. Nat. Rev. Cancer 3, 859–868. https://doi.org/10.1038/nrc1209.

Fan, Tingting, Zhang, Changsong, Zong, Ming, Fan, Lieying, 2018. Hypoxia-induced autophagy is inhibited by PADI4 knockdown, which promotes apoptosis of fibroblast-like synoviocytes in rheumatoid arthritis. Mol. Med. Rep. 17. https://doi.org/10.3892/mmr.2018.8501.

Feldser, D.M., Greider, C.W., 2007. Short telomeres limit tumor progression in vivo by inducing senescence. Cancer Cell 11, 461–469. https://doi.org/10.1016/j.ccr.2007.02.026.

Fiorucci, S., Cipriani, S., Mencarelli, A., Renga, B., Distrutti, E., Baldelli, F., 2010. Counter-regulatory role of bile acid activated receptors in immunity and inflammation. Curr. Mol. Med. 10, 579–595. https://doi.org/10.2174/1566524011009060579.

Forrester, S.J., Kikuchi, D.S., Hernandes, M.S., Xu, Q., Griendling, K.K., 2018. Reactive oxygen species in metabolic and inflammatory signaling. Circ. Res. 122, 877–902. https://doi.org/10.1161/CIRCRESAHA.117.311401.

Gallager, D.W., Aghajanian, G.K., 1976. Effect of antipsychotic drugs on the firing of dorsal raphe cells. I. Role of adrenergic system. Eur. J. Pharmacol. 39, 341–355. https://doi.org/10.1016/0014-2999(76)90144-8.

Gao, X.-F., Zhang, J.-J., Gong, X.-J., Li, K.-K., Zhang, L.-X., Li, W., 2022. Ginsenoside Rg5: a review of anticancer and neuroprotection with network pharmacology approach. Am. J. Chin. Med. 50, 2033–2056. https://doi.org/10.1142/S0192415X22500872.

Geng, X. qiang, Ma, A., He, J. zhao, Wang, L., Jia, Y. li, Shao, G. ying, Li, M., Zhou, H., Lin, S. qian, Ran, J. hua, Yang, B. xue, 2020. Ganoderic acid hinders renal fibrosis via suppressing the TGF-β/Smad and MAPK signaling pathways. Acta Pharmacol. Sin. 41, 670–677. https://doi.org/10.1038/s41401-019-0324-7.

Georgiou-Siafis, S.K., Tsiftsoglou, A.S., 2023. The key role of GSH in keeping the redox balance in mammalian cells: mechanisms and significance of GSH in detoxification via formation of conjugates. Antioxidants 12, 1953. https://doi.org/10.3390/antiox12111953.

Gill, B.S., Kumar, S., Navgeet, 2016a. Evaluating anti-oxidant potential of ganoderic acid A in STAT 3 pathway in prostate cancer. Mol. Biol. Rep. 43, 1411–1422. https://doi.org/10.1007/s11033-016-4074-z.

Gill, B.S., Navgeet, Kumar, S., 2016b. Ganoderic acid targeting multiple receptors in cancer: in silico and in vitro study. Tumor Biol. 37, 14271–14290. https://doi.org/10.1007/s13277-016-5291-8.

Gill, B.S., Kumar, S., Navgeet, 2017. Ganoderic acid targeting nuclear factor erythroid 2–related factor 2 in lung cancer. Tumor Biol. 39, 101042831769553. https://doi.org/10.1177/1010428317695530.

Gill, B.S., Kumar, S., Navgeet, 2018. Ganoderic acid A targeting β-Catenin in wnt signaling pathway: in silico and in vitro study. Interdiscip Sci 10, 233–243. https://doi.org/10.1007/s12539-016-0182-7.

Gill, B.S., Navgeet, Kumar, S., 2019. Antioxidant potential of ganoderic acid in Notch-1 protein in neuroblastoma. Mol. Cell. Biochem. 456, 1–14. https://doi.org/10.1007/s11010-018-3485-7.

Goldsborough, E., Osuji, N., Blaha, M.J., 2022. Assessment of cardiovascular disease risk. Endocrinol Metab Clin North Am 51, 483–509. https://doi.org/10.1016/j.ecl.2022.02.005.

Gong, T., Yan, R., Kang, J., Chen, R., 2019. Chemical components of ganoderma. Adv. Exp. Med. Biol. 1181, 59–106. https://doi.org/10.1007/978-981-13-9867-4_3.

Gong, E., Pan, J., Ye, Z., Cai, X., Zheng, H., Yin, Z., Jiang, Y., Wang, X., Cao, Z., 2024. Ganoderic acid A suppresses autophagy by regulating the circFLNA/miR-486-3p/CYP1A1/XRCC1 axis to strengthen the sensitivity of lung cancer cells to cisplatin. J. Pharm. Pharmacol. 76, 354–367. https://doi.org/10.1093/jpp/rgad116.

Gorbalenya, A.E., Baker, S.C., Baric, R.S., de Groot, R.J., Drosten, C., Gulyaeva, A.A., Haagmans, B.L., Lauber, C., Leontovich, A.M., Neuman, B.W., Penzar, D., Perlman, S., Poon, L.L.M., Samborskiy, D.V., Sidorov, I.A., Sola, I., Ziebuhr, J., 2020. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat. Microbiol. 5, 536–544. https://doi.org/10.1038/s41564-020-0695-z.

Gouras, G.K., Tampellini, D., Takahashi, R.H., Capetillo-Zarate, E., 2010. Intraneuronal β-amyloid accumulation and synapse pathology in Alzheimer's disease. Acta Neuropathol. 119, 523–541. https://doi.org/10.1007/s00401-010-0679-9.

Guo, W.L., Guo, J. Bin, Liu, B.Y., Lu, J.Q., Chen, M., Liu, B., Bai, W.D., Rao, P.F., Ni, L., Lv, X.C., 2020. Ganoderic acid A from: ganoderma lucidum ameliorates lipid metabolism and alters gut microbiota composition in hyperlipidemic mice fed a high-fat diet. Food Funct. 11, 6818–6833. https://doi.org/10.1039/d0fo00436g.

Gupta, R., Advani, D., Yadav, D., Ambasta, R.K., Kumar, P., 2023. Dissecting the relationship between neuropsychiatric and neurodegenerative disorders. Mol. Neurobiol. 60, 6476–6529. https://doi.org/10.1007/s12035-023-03502-9.

Hayden, M.S., Ghosh, S., 2008. Shared principles in NF-κB signaling. Cell 132, 344–362. https://doi.org/10.1016/j.cell.2008.01.020.

Hayden, M.S., West, A.P., Ghosh, S., 2006. NF-κB and the immune response. Oncogene 25, 6758–6780. https://doi.org/10.1038/sj.onc.1209943.

He, X., Chen, Y., Li, Z., Fang, L., Chen, H., Liang, Z., Abozeid, A., Yang, Z., Yang, D., 2023. Germplasm resources and secondary metabolism regulation in reishi mushroom (Ganoderma lucidum). Chin Herb Med 15, 376–382. https://doi.org/10.1016/j.chmed.2023.01.005.

Henshall, D.C., Hamer, H.M., Pasterkamp, R.J., Goldstein, D.B., Kjems, J., Prehn, J.H.M., Schorge, S., Lamottke, K., Rosenow, F., 2016. MicroRNAs in epilepsy: pathophysiology and clinical utility. Lancet Neurol. 15, 1368–1376. https://doi.org/10.1016/S1474-4422(16)30246-0.

Hesketh, T., Zhu, W.X., 1997. Health in China. Traditional Chinese medicine: one country, two systems. BMJ 315, 115–117. https://doi.org/10.1136/bmj.315.7100.115.

Ho, P.P., Steinman, L., 2016. Obeticholic acid, a synthetic bile acid agonist of the farnesoid X receptor, attenuates experimental autoimmune encephalomyelitis. Proc. Natl. Acad. Sci. U. S. A. 113, 1600–1605. https://doi.org/10.1073/pnas.1524890113.

Hu, Z., Cai, M., Zhang, Y., Tao, L., Guo, R., 2020. miR-29c-3p inhibits autophagy and cisplatin resistance in ovarian cancer by regulating FOXP1/ATG14 pathway. Cell Cycle 19, 193–206. https://doi.org/10.1080/15384101.2019.1704537.

Hu, K., Guan, Wei-jie, Bi, Y., Zhang, W., Li, L., Zhang, B., Liu, Q., Song, Y., Li, X., Duan, Z., Zheng, Q., Yang, Z., Liang, J., Han, M., Ruan, L., Wu, C., Zhang, Y., Jia, Zhen-hua, Zhong, Nan-shan, 2021. Efficacy and safety of lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: a multicenter, prospective, randomized controlled trial. Phytomedicine 85, 153242. https://doi.org/10.1016/j.phymed.2020.153242.

Huan, D.Q., Hop, N.Q., Son, N.T., 2023. Oxymatrine: a current overview of its health benefits. Fitoterapia 168, 105565. https://doi.org/10.1016/j.fitote.2023.105565.

Jia, Y., Li, H., Bao, H., Zhang, D., Feng, L., Xiao, Y., Zhu, K., Hou, Y., Luo, S., Zhang, Y., Xiao, L., Chen, X., Zhou, J., Wang, C., Wang, G., Yu, H., Xiao, C., Du, J., 2019. Cordycepin (3′-deoxyadenosine) promotes remyelination via suppression of neuroinflammation in a cuprizone-induced mouse model of demyelination. Int. Immunopharmacol. 75, 105777. https://doi.org/10.1016/j.intimp.2019.105777.

Jia, Y., Zhang, D., Li, H., Luo, S., Xiao, Y., Han, L., Zhou, F., Wang, C., Feng, L., Wang, G., Wu, P., Xiao, C., Yu, H., Du, J., Bao, H., 2021a. Activation of FXR by ganoderic acid A promotes remyelination in multiple sclerosis via anti-inflammation and regeneration mechanism. Biochem. Pharmacol. 185, 114422. https://doi.org/10.1016/j.bcp.2021.114422.

Jia, Y., Zhang, D., Yin, H., Li, H., Du, J., Bao, H., 2021b. Ganoderic acid A attenuates LPS-induced neuroinflammation in BV2 microglia by activating farnesoid X receptor. Neurochem. Res. 46, 1725–1736. https://doi.org/10.1007/s11064-021-03303-3.

Jia, Y., Li, Y., Shang, H., Luo, Y., Tian, Y., 2023. Ganoderic acid A and its amide derivatives as potential anti-cancer agents by regulating the p53-MDM2 pathway: synthesis and biological evaluation. Molecules 28, 2374. https://doi.org/10.3390/molecules28052374.

Jiang, J., Grieb, B., Thyagarajan, A., Sliva, D., 2008. Ganoderic acids suppress growth and invasive behavior of breast cancer cells by modulating AP-1 and NF-kappaB signaling. Int. J. Mol. Med. 21, 577–584.

Jiang, Z.M., Qiu, H.B., Wang, S.Q., Guo, J., Yang, Z.W., Zhou, S.B., 2018. Ganoderic acid A potentiates the antioxidant effect and protection of mitochondrial membranes and reduces the apoptosis rate in primary hippocampal neurons in magnesium free medium. Pharmazie 73, 87–91. https://doi.org/10.1691/ph.2018.7108.

Johnson, M., B, 2010. Ganoderic acid DM: an alternative agent for the treatment of advanced prostate cancer. Open Prost Cancer J 3, 78–85. https://doi.org/10.2174/1876822901003010078.

Kang, L.H., Zhang, G.W., Zhang, J.F., Qin, B., Guan, H.J., 2020. Ganoderic acid A protects lens epithelial cells from UVB irradiation and delays lens opacity. Chin. J. Nat. Med. 18, 54–60. https://doi.org/10.1016/S1875-5364(20)60037-1.

Karin, M., Greten, F.R., 2005. NF-κB: linking inflammation and immunity to cancer development and progression. Nat. Rev. Immunol. 5, 749–759. https://doi.org/10.1038/nri1703.

Kawai, T., Akira, S., 2007. Signaling to NF-κB by toll-like receptors. Trends Mol. Med. 13, 460–469. https://doi.org/10.1016/j.molmed.2007.09.002.

Kraaijenhof, J.M., Hovingh, G.K., Stroes, E.S.G., Kroon, J., 2021. The iterative lipid impact on inflammation in atherosclerosis. Curr. Opin. Lipidol. 32, 286–292. https://doi.org/10.1097/MOL.0000000000000779.

Kwon, H.S., Koh, S.-H., 2020. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. Transl. Neurodegener. 9, 42. https://doi.org/10.1186/s40035-020-00221-2.

Lacher, S.E., Lee, J.S., Wang, X., Campbell, M.R., Bell, D.A., Slattery, M., 2015. Beyond antioxidant genes in the ancient Nrf2 regulatory network. Free Radic. Biol. Med. 88, 452–465. https://doi.org/10.1016/j.freeradbiomed.2015.06.044.

Lan, H.Y., 2011. Diverse roles of TGF-β/Smads in renal fibrosis and inflammation. Int. J. Biol. Sci. 7, 1056–1067. https://doi.org/10.7150/ijbs.7.1056.

Lane, D.J.R., Ayton, S., Bush, A.I., 2018. Iron and alzheimer's disease: an update on emerging mechanisms. J. Alzheim. Dis. 64, S379–S395. https://doi.org/10.3233/JAD-179944.

Le, Q.H., Far, B.F., Sajadi, S.M., Jahromi, B.S., Kaspour, S., Cakir, B., Abdelmalek, Z., Inc, M., 2023. RETRACTED: analysis of conocurvone, ganoderic acid A and oleuropein molecules against the main protease molecule of COVID-19 by in silico approaches: molecular dynamics docking studies. Eng. Anal. Bound. Elem. 150, 583–598. https://doi.org/10.1016/j.enganabound.2023.02.043.

Lee, H., Jeong, A.J., Ye, S.-K., 2019. Highlighted STAT3 as a potential drug target for cancer therapy. BMB Rep. 52, 415–423. https://doi.org/10.5483/BMBRep.2019.52.7.152.

Leonard, W.J., O'Shea, J.J., 1998. Jaks and stats: biological implications. Annu. Rev. Immunol. 16, 293–322. https://doi.org/10.1146/annurev.immunol.16.1.293.

Li, C.H., Chen, P.Y., Chang, U.M., Kan, L.S., Fang, W.H., Tsai, K.S., Lin, S. Bin, 2005. Ganoderic acid X, a lanostanoid triterpene, inhibits topoisomerases and induces apoptosis of cancer cells. Life Sci. 77, 252–265. https://doi.org/10.1016/j.lfs.2004.09.045.

Li, R., Hou, Y., Huang, J., Pan, W., Ma, Q., Shi, Y., Li, C., Zhao, J., Jia, Z., Jiang, H., Zheng, K., Huang, S., Dai, J., Li, X., Hou, X., Wang, L., Zhong, N., Yang, Z., 2020. Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2). Pharmacol. Res. 156, 104761. https://doi.org/10.1016/j.phrs.2020.104761.

Li, Z., Zou, J., Cao, D., Ma, X., 2020. Pharmacological basis of tanshinone and new insights into tanshinone as a multitarget natural product for multifaceted diseases. Biomed. Pharmacother. 130, 110599. https://doi.org/10.1016/j.biopha.2020.110599.

Li, H., Zhu, X., Xu, Jinjie, Li, L., Kan, W., Bao, H., Xu, Jiyi, Wang, W., Yang, Y., Chen, P., Zou, Y., Feng, Y., Yang, J., Du, J., Wang, G., 2023. The FXR mediated anti-depression effect of CDCA underpinned its therapeutic potentiation for MDD. Int. Immunopharmacol. 115, 109626. https://doi.org/10.1016/j.intimp.2022.109626.

Liang, C., Tian, D., Liu, Y., Li, H., Zhu, J., Li, M., Xin, M., Xia, J., 2019a. Review of the molecular mechanisms of Ganoderma lucidum triterpenoids: ganoderic acids A, C2, D, F, DM, X and Y. Eur. J. Med. Chem. https://doi.org/10.1016/j.ejmech.2019.04.039.

Liang, C., Tian, D., Liu, Y., Li, H., Zhu, J., Li, M., Xin, M., Xia, J., 2019b. Review of the molecular mechanisms of Ganoderma lucidum triterpenoids: ganoderic acids A, C2, D, F, DM, X and Y. Eur. J. Med. Chem. https://doi.org/10.1016/j.ejmech.2019.04.039.

Liang, C., Tian, D., Liu, Y., Li, H., Zhu, J., Li, M., Xin, M., Xia, J., 2019c. Review of the molecular mechanisms of Ganoderma lucidum triterpenoids: ganoderic acids A, C2, D, F, DM, X and Y. Eur. J. Med. Chem. 174, 130–141. https://doi.org/10.1016/j.ejmech.2019.04.039.

Lim, S., Kaldis, P., 2013. Cdks, cyclins and CKIs: roles beyond cell cycle regulation. Development 140, 3079–3093. https://doi.org/10.1242/dev.091744.

Lin, Z., 2019. Ganoderma (lingzhi) in traditional Chinese medicine and Chinese culture. In: Advances in Experimental Medicine and Biology. Springer New York LLC, pp. 1–13. https://doi.org/10.1007/978-981-13-9867-4_1.

Liu, R.M., Zhong, J.J., 2011. Ganoderic acid Mf and S induce mitochondria mediated apoptosis in human cervical carcinoma HeLa cells. Phytomedicine 18, 349–355. https://doi.org/10.1016/j.phymed.2010.08.019.

Liu, Z., Li, L., Xue, B., 2018. Effect of ganoderic acid D on Colon cancer warburg effect: role of SIRT3/cyclophilin D. Eur. J. Pharmacol. 824, 72–77. https://doi.org/10.1016/j.ejphar.2018.01.026.

Liu, F., Shi, K., Dong, J., Jin, Z., Wu, Y., Cai, Y., Lin, T., Cai, Q., Liu, L., Zhang, Y., 2020. Ganoderic acid A attenuates high-fat-diet-induced liver injury in rats by regulating the lipid oxidation and liver inflammation. Arch Pharm. Res. (Seoul) 43, 744–754. https://doi.org/10.1007/s12272-020-01256-9.

Liu, T., Sun, L., Zhang, Y., Wang, Y., Zheng, J., 2022. Imbalanced GSH/ROS and sequential cell death. J. Biochem. Mol. Toxicol. 36. https://doi.org/10.1002/jbt.22942.

Liu, Y., Tan, D., Cui, H., Wang, J., 2023. Ganoderic acid C2 exerts the pharmacological effects against cyclophosphamide-induced immunosuppression: a study involving molecular docking and experimental validation. Sci. Rep. 13, 17745. https://doi.org/10.1038/s41598-023-44394-y.

Liu, Y., Zhou, C., Tan, J., Wu, T., Pan, C., Liu, J., Cheng, X., 2024. Ganoderic acid A slows osteoarthritis progression by attenuating endoplasmic reticulum stress and blocking NF-Kb pathway. Chem. Biol. Drug Des. 103. https://doi.org/10.1111/cbdd.14382.

Lozy, F., Karantza, V., 2012. Autophagy and cancer cell metabolism. Semin. Cell Dev. Biol. 23, 395–401. https://doi.org/10.1016/j.semcdb.2012.01.005.

Lu, J., Holmgren, A., 2014. The thioredoxin antioxidant system. Free Radic. Biol. Med. 66, 75–87. https://doi.org/10.1016/j.freeradbiomed.2013.07.036.

Lu, X., Xu, C., Yang, R., Zhang, G., 2021. Ganoderic acid A alleviates OVA-induced asthma in mice. Inflammation 44, 1908–1915. https://doi.org/10.1007/s10753-021-01468-1.

Luo, B., Song, L., Chen, L., Cai, Y., Zhang, M., Wang, S., 2024. Ganoderic acid D attenuates gemcitabine resistance of triple-negative breast cancer cells by inhibiting glycolysis via HIF-1α destabilization. Phytomedicine 129, 155675. https://doi.org/10.1016/j.phymed.2024.155675.

Lv, X.C., Wu, Q., Cao, Y.J., Lin, Y.C., Guo, W.L., Rao, P.F., Zhang, Y.Y., Chen, Y.T., Ai, L. Z., Ni, L., 2022. Ganoderic acid A from Ganoderma lucidum protects against alcoholic liver injury through ameliorating the lipid metabolism and modulating the intestinal microbial composition. Food Funct. 13, 5820–5837. https://doi.org/10.1039/d1fo03219d.

Ma, J.-Q., Zhang, Y.-J., Tian, Z.-K., 2021. Anti-oxidant, anti-inflammatory and anti-fibrosis effects of ganoderic acid A on carbon tetrachloride induced nephrotoxicity by regulating the Trx/TrxR and JAK/ROCK pathway. Chem. Biol. Interact. 344, 109529. https://doi.org/10.1016/j.cbi.2021.109529.

Mawuenyega, K.G., Sigurdson, W., Ovod, V., Munsell, L., Kasten, T., Morris, J.C., Yarasheski, K.E., Bateman, R.J., 2010. Decreased clearance of CNS beta-amyloid in Alzheimer's disease. Science 330, 1774. https://doi.org/10.1126/science.1197623.

Medvedev, A.E., 2013. Toll-like receptor polymorphisms, inflammatory and infectious diseases, allergies, and cancer. J. Interferon Cytokine Res. 33, 467–484. https://doi.org/10.1089/jir.2012.0140.

Medzhitov, R., 2008. Origin and physiological roles of inflammation. Nature 454, 428–435. https://doi.org/10.1038/nature07201.

Medzhitov, R., 2010. Inflammation 2010: new adventures of an old flame. Cell 140, 771–776. https://doi.org/10.1016/j.cell.2010.03.006.

Meng, J., Wang, Sai-zhen, He, J. zhao, Zhu, S., Huang, B. yue, Wang, yuan, S., Li, M., Zhou, H., Lin, S. qian, Yang, B. xue, 2020. Ganoderic acid A is the effective ingredient of ganoderma triterpenes in retarding renal cyst development in polycystic kidney disease. Acta Pharmacol. Sin. 41, 782–790. https://doi.org/10.1038/s41401-019-0329-2.

Motamed Fath, P., Rahimnejad, M., Moradi-Kalbolandi, S., Ebrahimi Hosseinzadeh, B., Jamshidnejad-Tosaramandani, T., 2021. Improvement of cytotoxicity and necrosis activity of ganoderic acid a through the development of PMBN-A.Her2-GA as a targeted nano system. RSC Adv. 12, 1228–1237. https://doi.org/10.1039/d1ra06488f.

Nagata, Shigekazu, 2000. Apoptotic DNA fragmentation. Exp. Cell Res. 256, 12–18. https://doi.org/10.1006/excr.2000.4834.

Nagata, S., 2018. Apoptosis and clearance of apoptotic cells. Annu. Rev. Immunol. 36, 489–517. https://doi.org/10.1146/annurev-immunol-042617-053010.

Neri, S., Mastroianni, G., Gardella, E., Aguglia, U., Rubboli, G., 2022. Epilepsy in neurodegenerative diseases. Epileptic Disord. 24, 249–273. https://doi.org/10.1684/epd.2021.1406.

Novikov, N.M., Zolotaryova, S.Y., Gautreau, A.M., Denisov, E.V., 2021. Mutational drivers of cancer cell migration and invasion. Br. J. Cancer 124, 102–114. https://doi.org/10.1038/s41416-020-01149-0.

Oh, H., Ghosh, S., 2013. NF-κB: roles and regulation in different CD4(+) T-cell subsets. Immunol. Rev. 252, 41–51. https://doi.org/10.1111/imr.12033.

O'Shea, J.J., Holland, S.M., Staudt, L.M., 2013. JAKs and STATs in immunity, immunodeficiency, and cancer. N. Engl. J. Med. 368, 161–170. https://doi.org/10.1056/nejmra1202117.

Paisible, A.-L., Chang, C.-C.H., So-Armah, K.A., Butt, A.A., Leaf, D.A., Budoff, M., Rimland, D., Bedimo, R., Goetz, M.B., Rodriguez-Barradas, M.C., Crane, H.M., Gibert, C.L., Brown, S.T., Tindle, H.A., Warner, A.L., Alcorn, C., Skanderson, M., Justice, A.C., Freiberg, M.S., 2015. HIV infection, cardiovascular disease risk factor profile, and risk for acute myocardial infarction. JAIDS Journal of Acquired Immune Deficiency Syndromes 68, 209–216. https://doi.org/10.1097/QAI.0000000000000419.

Pajonk, F., van Ophoven, A., Weissenberger, C., McBride, W.H., 2005. The proteasome inhibitor MG-132 sensitizes PC-3 prostate cancer cells to ionizing radiation by a DNA-PK-independent mechanism. BMC Cancer 5, 76. https://doi.org/10.1186/1471-2407-5-76.

Pang, W., Lu, S., Zheng, R., Li, X., Yang, S., Feng, Y., Wang, S., Guo, J., Zhou, S., 2022. Investigation into antiepileptic effect of ganoderic acid A and its mechanism in seizure rats induced by pentylenetetrazole. BioMed Res. Int. https://doi.org/10.1155/2022/5940372, 2022.

Pearson, G., Robinson, F., Beers Gibson, T., Xu, B., Karandikar, M., Berman, K., Cobb, M. H., 2001. Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. Endocr. Rev. 22, 153–183. https://doi.org/10.1210/edrv.22.2.0428.

Peek, J.L., Wilson, M.H., 2023. Cell and gene therapy for kidney disease. Nat. Rev. Nephrol. 19, 451–462. https://doi.org/10.1038/s41581-023-00702-3.

Piirainen, S., Youssef, A., Song, C., Kalueff, A.V., Landreth, G.E., Malm, T., Tian, L., 2017. Psychosocial stress on neuroinflammation and cognitive dysfunctions in Alzheimer's disease: the emerging role for microglia? Neurosci. Biobehav. Rev. 77, 148–164. https://doi.org/10.1016/j.neubiorev.2017.01.046.

Qi, L.-F.-R., Liu, S., Liu, Y.-C., Li, P., Xu, X., 2021. Ganoderic acid A promotes Amyloid-β clearance (in vitro) and ameliorates cognitive deficiency in alzheimer's disease (mouse model) through autophagy induced by activating axl. Int. J. Mol. Sci. 22, 5559. https://doi.org/10.3390/ijms22115559.

Radwan, F.F.Y., Hossain, A., God, J.M., Leaphart, N., Elvington, M., Nagarkatti, M., Tomlinson, S., Haque, A., 2015. Reduction of myeloid-derived suppressor cells and lymphoma growth by a natural triterpenoid. J. Cell. Biochem. 116, 102–114. https://doi.org/10.1002/jcb.24946.

Rahman, M., Almalki, W.H., Kazmi, I., Afzal, O., Katouah, H.A., Alrobaian, M., Altamimi, A.S.A., Al-Abbasi, F.A., Alshammari, M.S., Rub, R.A., Beg, S., Kumar, V., 2021. Development and validation of a new UPLC-MS/MS method for quantification of ganoderic acid-A loaded nanolipidic carrier in rat plasma and application to pharmacokinetic studies. J. Chromatogr. B 1163, 122501. https://doi.org/10.1016/j.jchromb.2020.122501.

Reddy, P.H., Oliver, D.M., 2019. Amyloid beta and phosphorylated tau-induced defective autophagy and mitophagy in alzheimer's disease. Cells 8, 488. https://doi.org/10.3390/cells8050488.

Sanodiya, B., Thakur, G., Baghel, R., Prasad, G., Bisen, P., 2009. Ganoderma lucidum: a potent pharmacological macrofungus. Curr. Pharm. Biotechnol. 10, 717–742. https://doi.org/10.2174/138920109789978757.

Santos, A.A., Delgado, T.C., Marques, V., Ramirez-Moncayo, C., Alonso, C., Vidal-Puig, A., Hall, Z., Martínez-Chantar, M.L., Rodrigues, C.M.P., 2024. Spatial metabolomics and its application in the liver. Hepatology 79, 1158–1179. https://doi.org/10.1097/HEP.0000000000000341.

Schwartz, G.K., Shah, M.A., 2005. Targeting the cell cycle: a new approach to cancer therapy. J. Clin. Oncol. 23, 9408–9421. https://doi.org/10.1200/JCO.2005.01.5594.

Shannon, P., Markiel, A., Ozier, O., Baliga, N.S., Wang, J.T., Ramage, D., Amin, N., Schwikowski, B., Ideker, T., 2003. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res. 13, 2498–2504. https://doi.org/10.1101/gr.1239303.

Shao, J., Li, Z., Jiao, G., Sun, G., Zhou, Z., 2015. [ganoderic acid A suppresses proliferation and invasion and induces apoptosis in human osteosarcoma cells]. Nan Fang Yi Ke Da Xue Xue Bao 35, 619–624.

Shen, S., Wang, X., Lv, H., Shi, Y., Xiao, L., 2021. PADI4 mediates autophagy and participates in the role of ganoderic acid A monomers in delaying the senescence of Alzheimer's cells through the Akt/mTOR pathway. Biosci. Biotechnol. Biochem. 85, 1818–1829. https://doi.org/10.1093/bbb/zbab054.

Shi, S., Tan, P., Yan, B., Gao, R., Zhao, J., Wang, J., Guo, J., Li, N., Ma, Z., 2016. ER stress and autophagy are involved in the apoptosis induced by cisplatin in human lung cancer cells. Oncol. Rep. 35, 2606–2614. https://doi.org/10.3892/or.2016.4680.

Shi, X., Zhang, G., Mackie, B., Yang, S., Wang, J., Shan, L., 2016. Comparison of the in vitro metabolism of psoralidin among different species and characterization of its inhibitory effect against UDP- glucuronosyltransferase (UGT) or cytochrome p450 (CYP450) enzymes. J Chromatogr B Analyt Technol Biomed Life Sci 1029–1030, 145–156. https://doi.org/10.1016/j.jchromb.2016.06.031.

Shi, J., Wang, H., Liu, J., Zhang, Y., Luo, J., Li, Y., Yang, C., Jiang, J., 2020. Ganoderic acid B attenuates LPS-Induced lung injury. Int. Immunopharmacol. 88, 106990. https://doi.org/10.1016/j.intimp.2020.106990.

Siegel, R.L., Miller, K.D., Jemal, A., 2019. Cancer statistics, 2019. CA Cancer J. Clin. 69, 7–34. https://doi.org/10.3322/caac.21551.

Sillapapongwarakorn, S., Yanarojana, S., Pinthong, D., Thithapandha, A., Ungwitayatorn, J., Supavilai, P., 2017. Molecular docking based screening of triterpenoids as potential G-quadruplex stabilizing ligands with anti-cancer activity. Bioinformation 13, 284–292. https://doi.org/10.6026/97320630013284.

Sliva, D., English, D., Lyons, D., Lloyd, F.P., 2002a. Protein kinase C induces motility of breast cancers by upregulating secretion of urokinase-type plasminogen activator through activation of AP-1 and NF-κB. Biochem. Biophys. Res. Commun. 290, 552–557. https://doi.org/10.1006/bbrc.2001.6225.

Sliva, D., Labarrere, C., Slivova, V., Sedlak, M., Lloyd, F.P., Ho, N.W.Y., 2002b. Ganoderma lucidum suppresses motility of highly invasive breast and prostate cancer cells. Biochem. Biophys. Res. Commun. 298, 603–612. https://doi.org/10.1016/S0006-291X(02)02496-8.

Song, Z., Wang, C., Ding, F., Zou, H., Liu, C., 2023. Ganoderic acid A enhances tumor suppression function of oxaliplatin via inducing the cytotoxicity of T cells. Anti Cancer Agents Med. Chem. 23, 832–838. https://doi.org/10.2174/1871520623666221103110934.

Sosero, Y.L., Gan-Or, Z., 2023. <scp>LRRK2</scp> and Parkinson's disease: from genetics to targeted therapy. Ann Clin Transl Neurol 10, 850–864. https://doi.org/10.1002/acn3.51776.

Talman, A.M., Clain, J., Duval, R., Ménard, R., Ariey, F., 2019. Artemisinin bioactivity and resistance in malaria parasites. Trends Parasitol. 35, 953–963. https://doi.org/10.1016/j.pt.2019.09.005.

Tarquini, F., Tiribuzi, R., Crispoltoni, L., Porcellati, S., Del Pino, A.M., Orlacchio, A., Coata, G., Arnone, S., Torlone, E., Cappuccini, B., Di Renzo, G.C., Orlacchio, A., 2014. Caspase 3 activation and PARP cleavage in lymphocytes from newborn babies of diabetic mothers with unbalanced glycaemic control. Cell Biochem. Funct. 32, 87–95. https://doi.org/10.1002/cbf.2975.

Tawasri, P., Ampasavate, C., Tharatha, S., Chiranthanut, N., Teekachunhatean, S., 2016. Effect of oral coadministration of ascorbic acid with ling zhi preparation on pharmacokinetics of ganoderic acid A in healthy Male subjects: a randomized crossover study. BioMed Res. Int. 2016, 1–7. https://doi.org/10.1155/2016/2819862.

Teekachunhatean, S., Sadja, S., Ampasavate, C., Chiranthanut, N., Rojanasthien, N., Sangdee, C., 2012. Pharmacokinetics of ganoderic acids A and F after oral administration of ling zhi preparation in healthy Male volunteers. Evid.-Based Complement. Altern. Med. 1–7. https://doi.org/10.1155/2012/780892, 2012.

Timothy, J., Pollard, M., 2000. The acute myocardial infarction. Prim Care 27, 631–649.

Tracey, K.J., 2002. The inflammatory reflex. Nature 420, 853–859. https://doi.org/10.1038/nature01321.

Trott, O., Olson, A.J., 2010. AutoDock vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J. Comput. Chem. 31, 455–461. https://doi.org/10.1002/jcc.21334.

Troubat, R., Barone, P., Leman, S., Desmidt, T., Cressant, A., Atanasova, B., Brizard, B., El Hage, W., Surget, A., Belzung, C., Camus, V., 2021. Neuroinflammation and depression: a review. Eur. J. Neurosci. 53, 151–171. https://doi.org/10.1111/ejn.14720.

Valko, M., Rhodes, C.J., Moncol, J., Izakovic, M., Mazur, M., 2006. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem. Biol. Interact. 160, 1–40. https://doi.org/10.1016/j.cbi.2005.12.009.

Varin, E., Denoyelle, C., Brotin, E., Meryet-Figuière, M., Giffard, F., Abeilard, E., Goux, D., Gauduchon, P., Icard, P., Poulain, L., 2010. Downregulation of Bcl-xL and Mcl-1 is sufficient to induce cell death in mesothelioma cells highly refractory to conventional chemotherapy. Carcinogenesis 31, 984–993. https://doi.org/10.1093/carcin/bgq026.

Vaughan, A.T.M., Betti, C.J., Villalobos, M.J., 2002. Surviving apoptosis. Apoptosis 7, 173–177. https://doi.org/10.1023/a:1014374717773.

Waldbaum, S., Patel, M., 2010. Mitochondrial dysfunction and oxidative stress: a contributing link to acquired epilepsy? J. Bioenerg. Biomembr. 42, 449–455. https://doi.org/10.1007/s10863-010-9320-9.

Wan, B., Li, Y., Sun, S., Yang, Y., Lv, Y., Wang, L., Song, M., Chen, M., Wu, C., Pan, H., Zhang, X., 2019. Ganoderic acid A attenuates lipopolysaccharide-induced lung injury in mice. Biosci. Rep. 39. https://doi.org/10.1042/BSR20190301.

Wang, T., Lu, H., 2021. Ganoderic acid A inhibits ox-LDL-induced THP-1-derived macrophage inflammation and lipid deposition via Notch1/PPARγ/CD36 signaling. Adv. Clin. Exp. Med. 30, 1031–1041. https://doi.org/10.17219/acem/137914.

Wang, X., Sun, D., Tai, J., Wang, L., 2017. Ganoderic acid a inhibits proliferation and invasion, and promotes apoptosis in human hepatocellular carcinoma cells. Mol. Med. Rep. 16, 3894–3900. https://doi.org/10.3892/mmr.2017.7048.

Wang, Jun, Hodes, G.E., Zhang, H., Zhang, S., Zhao, W., Golden, S.A., Bi, W., Menard, C., Kana, V., Leboeuf, M., Xie, M., Bregman, D., Pfau, M.L., Flanigan, M.E., Esteban-Fernández, A., Yemul, S., Sharma, A., Ho, L., Dixon, R., Merad, M., Han, M.-H., Russo, S.J., Pasinetti, G.M., 2018. Epigenetic modulation of inflammation and synaptic plasticity promotes resilience against stress in mice. Nat. Commun. 9, 477. https://doi.org/10.1038/s41467-017-02794-5.

Wang, Jigang, Wong, Y.-K., Liao, F., 2018. What has traditional Chinese medicine delivered for modern medicine? Expert Rev Mol Med 20, e4. https://doi.org/10.1017/erm.2018.3.

Wang, D., Cai, X., Xu, F., Kang, H., Li, Y., Feng, R., 2022. Ganoderic acid A alleviates the degeneration of intervertebral disc via suppressing the activation of TLR4/NLRP3 signaling pathway. Bioengineered 13, 11684–11693. https://doi.org/10.1080/21655979.2022.2070996.

Wen, G., Li, T., He, H., Zhou, X., Zhu, J., 2020. Ganoderic acid A inhibits bleomycin-induced lung fibrosis in mice. Pharmacology 105, 568–575. https://doi.org/10.1159/000505297.

Wu, G.S., Lu, J.J., Guo, J.J., Li, Y.B., Tan, W., Dang, Y.Y., Zhong, Z.F., Xu, Z.T., Chen, X. P., Wang, Y.T., 2012. Ganoderic acid DM, a natural triterpenoid, induces DNA damage, G1 cell cycle arrest and apoptosis in human breast cancer cells. Fitoterapia 83, 408–414. https://doi.org/10.1016/j.fitote.2011.12.004.

Wu, X., Xue, X., Wang, L., Wang, W., Han, J., Sun, X., Zhang, H., Liu, Y., Che, X., Yang, J., Wu, C., 2018. Suppressing autophagy enhances disulfiram/copper-induced apoptosis in non-small cell lung cancer. Eur. J. Pharmacol. 827, 1–12. https://doi.org/10.1016/j.ejphar.2018.02.039.

Wu, M., Song, D., Li, H., Yang, Y., Ma, X., Deng, S., Ren, C., Shu, X., 2019. Negative regulators of STAT3 signaling pathway in cancers. Cancer Manag. Res. 11, 4957–4969. https://doi.org/10.2147/CMAR.S206175.

Wu, W., Song, K., Chen, G., Liu, N., Cao, T., 2022. Ganoderic acid A improves osteoarthritis by regulating RANKL/OPG ratio. Chem. Biol. Drug Des. 100, 313–319. https://doi.org/10.1111/cbdd.14101.

Xia, J., Dai, L., Wang, L., Zhu, J., 2020. Ganoderic acid DM induces autophagic apoptosis in non-small cell lung cancer cells by inhibiting the PI3K/Akt/mTOR activity. Chem. Biol. Interact. 316, 108932. https://doi.org/10.1016/j.cbi.2019.108932.

Xiao, C., 2024. Ganoderic acid A attenuated hepatic impairment by down-regulating the intracellular JAK2-STAT3 signaling pathway in induced mushroom poisoning. Am J Transl Res 16, 295–303. https://doi.org/10.62347/ERWA6712.

Xu, L., Yan, L., Huang, S., 2019. Ganoderic acid A against cyclophosphamide-induced hepatic toxicity in mice. J. Biochem. Mol. Toxicol. 33. https://doi.org/10.1002/jbt.22271.

Xu, S., Zhang, F., Chen, D., Su, K., Zhang, L., Jiang, R., 2020. In vitro inhibitory effects of ganoderic acid A on human liver cytochrome P450 enzymes. Pharm. Biol. 58, 308–313. https://doi.org/10.1080/13880209.2020.1747500.

Yang, S., Lian, G., 2020. ROS and diseases: role in metabolism and energy supply. Mol. Cell. Biochem. 467, 1–12. https://doi.org/10.1007/s11010-019-03667-9.

Yang, C., Zhou, C., Li, J., Chen, Z., Shi, H., Yang, W., Qin, Y., Lü, L., Zhao, L., Fang, L., Wang, H., Hu, Z., Xie, P., 2018. Quantitative proteomic study of the plasma reveals acute phase response and LXR/RXR and FXR/RXR activation in the chronic unpredictable mild stress mouse model of depression. Mol. Med. Rep. 17, 93–102. https://doi.org/10.3892/mmr.2017.7855.

Yang, Y., Zhou, H., Liu, W., Wu, J., Yue, X., Wang, J., Quan, L., Liu, H., Guo, L., Wang, Z., Lian, X., Zhang, Q., 2018. Ganoderic acid a exerts antitumor activity against MDA-MB-231 human breast cancer cells by inhibiting the janus kinase 2/signal transducer and activator of transcription 3 signaling pathway. Oncol. Lett. 16, 6515–6521. https://doi.org/10.3892/ol.2018.9475.

Yang, J., Ma, W., Mei, Q., Song, J., Shu, L., Zhang, S., Li, C., An, L., Du, N., Shi, Z., 2020. Protective effect of fuzi lizhong decoction against non-alcoholic fatty liver disease via anti-inflammatory response through regulating p53 and PPARG signaling. Biol. Pharm. Bull. 43, 1626–1633. https://doi.org/10.1248/bpb.b20-00053.

Yang, W., Liu, R., Zhou, LinHua, Chen, X., Hu, YanYan, 2022. Effects of ganoderic acid A on gastrointestinal motility and brain-gut peptide in rats with functional dyspepsia. Evid.-Based Complement. Altern. Med. 1–7. https://doi.org/10.1155/2022/2298665, 2022.

Yao, X., Li, G., Xu, H., Lü, C., 2012. Inhibition of the JAK-STAT3 signaling pathway by ganoderic acid A enhances chemosensitivity of HepG2 cells to cisplatin. Planta Med. 78, 1740–1748. https://doi.org/10.1055/s-0032-1315303.

Yao, G., Ma, Y., Muhammad, M., Huang, Q., 2019. Understanding the infrared and raman spectra of ganoderic acid A: an experimental and DFT study. Spectrochim. Acta Mol. Biomol. Spectrosc. 210, 372–380. https://doi.org/10.1016/j.saa.2018.11.019.

Yde, C.W., Issinger, O.-G., 2006. Enhancing cisplatin sensitivity in MCF-7 human breast cancer cells by down-regulation of Bcl-2 and cyclin D1. Int. J. Oncol. 29, 1397–1404.

Yu, Z. ru, Jia, W. hua, Liu, C., Wang, H. qing, Yang, H. guang, He, G. rong, Chen, R. yun, Du, G. hua, 2020. Ganoderic acid A protects neural cells against NO stress injury in vitro via stimulating β adrenergic receptors. Acta Pharmacol. Sin. 41, 516–522. https://doi.org/10.1038/s41401-020-0356-z.

Yun, H.Y., Dawson, V.L., Dawson, T.M., 1997. Nitric oxide in health and disease of the nervous system. Mol Psychiatry 2, 300–310. https://doi.org/10.1038/sj.mp.4000272.

Zeng, M., Qi, L., Guo, Y., Zhu, X., Tang, X., Yong, T., Xie, Y., Wu, Q., Zhang, M., Chen, D., 2021. Long-term administration of triterpenoids from Ganoderma lucidum mitigates age-associated brain physiological decline via regulating sphingolipid metabolism and enhancing autophagy in mice. Front. Aging Neurosci. 13. https://doi.org/10.3389/fnagi.2021.628860.

Zhang, W., Liu, H.T., 2002. MAPK signal pathways in the regulation of cell proliferation in Mammalian cells. Cell Res. 12, 9–18. https://doi.org/10.1038/sj.cr.7290105.

Zhang, J., Shen, Y., Liu, J., Wei, D., 2005. Antimetastatic effect of prodigiosin through inhibition of tumor invasion. Biochem. Pharmacol. 69, 407–414. https://doi.org/10.1016/j.bcp.2004.08.037.

Zhang, J., Ke, K.-F., Liu, Z., Qiu, Y.-H., Peng, Y.-P., 2013. Th17 cell-mediated neuroinflammation is involved in neurodegeneration of Aβ1-42-Induced alzheimer's disease model rats. PLoS One 8, e75786. https://doi.org/10.1371/journal.pone.0075786.

Zhang, W., Tao, J., Yang, X., Yang, Z., Zhang, L., Liu, H., Wu, K., Wu, J., 2014. Antiviral effects of two Ganoderma lucidum triterpenoids against enterovirus 71 infection. Biochem. Biophys. Res. Commun. 449, 307–312. https://doi.org/10.1016/j.bbrc.2014.05.019.

Zhang, Y., Shi, K., Lin, T., Xia, F., Cai, Y., Ye, Y., Liu, L., Liu, F., 2020. Ganoderic acid A alleviates myocardial ischemia-reperfusion injury in rats by regulating JAK2/STAT3/NF-κB pathway. Int. Immunopharmacol. 84, 106543. https://doi.org/10.1016/j.intimp.2020.106543.

Zhang, L., Zhang, Lei, Sui, R., 2021. Ganoderic acid a-mediated modulation of microglial polarization is involved in depressive-like behaviors and neuroinflammation in a rat model of post-stroke depression. Neuropsychiatr Dis Treat 17, 2671–2681. https://doi.org/10.2147/NDT.S317207.

Zhang, Y., Wang, X., Yang, Xiaomei, Yang, Xiudong, Xue, J., Yang, Y., 2021. Ganoderic acid A to alleviate neuroinflammation of alzheimer's disease in mice by regulating the imbalance of the Th17/Tregs axis. J. Agric. Food Chem. 69, 14204–14214. https://doi.org/10.1021/acs.jafc.1c06304.

Zheng, D.S., Chen, L.S., 2017. Triterpenoids from Ganoderma lucidum inhibit the activationof EBV antigens as telomerase inhibitors. Exp. Ther. Med. 14, 3273–3278. https://doi.org/10.3892/etm.2017.4883.

Zheng, S., Ma, J., Zhao, X., Yu, X., Ma, Y., 2022. Ganoderic acid A attenuates IL-1β-Induced inflammation in human nucleus pulposus cells through inhibiting the NF-κB pathway. Inflammation 45, 851–862. https://doi.org/10.1007/s10753-021-01590-0.

Zhu, R., 2023. P23-083-23 ganoderic acid A ameliorates endothelial dysfunction in estrogen-deficient mice. Curr. Dev. Nutr. 7, 100191. https://doi.org/10.1016/j.cdnut.2023.100191.

Zhu, J., Jin, J., Ding, J., Li, S., Cen, P., Wang, K., Wang, H., Xia, J., 2018. Ganoderic acid A improves high fat diet-induced obesity, lipid accumulation and insulin sensitivity through regulating SREBP pathway. Chem. Biol. Interact. 290, 77–87. https://doi.org/10.1016/j.cbi.2018.05.014.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G.F., Tan, W., 2020. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 382, 727–733. https://doi.org/10.1056/nejmoa2001017.

Zhu, J., Ding, J., Li, S., Jin, J., 2022. Ganoderic acid A ameliorates non-alcoholic streatohepatitis (NASH) induced by high-fat high-cholesterol diet in mice. Exp. Ther. Med. 23, 308. https://doi.org/10.3892/etm.2022.11237.

Zsurka, G., Kunz, W.S., 2015. Mitochondrial dysfunction and seizures: the neuronal energy crisis. Lancet Neurol. 14, 956–966. https://doi.org/10.1016/S1474-4422(15)00148-9.