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Review

Research Progress on the Biological Activity of Ganoderic Acids in *Ganoderma lucidum* over the Last Five Years

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Abstract: *Ganoderma lucidum* (*G. lucidum*) is a traditional edible and medicinal mushroom in China. The main bioactive components in *G. lucidum* include triterpenoids, polysaccharides, steroids, and sterols. Ganoderic acids (GAs) are one of the most abundant triterpenoids found in *G. lucidum*, garnering significant attention from researchers in the fields of medicine and health care. We summarize the extensive studies on the physiological function of GAs in anti-cancer, anti-inflammatory, radiation protection, anti-aging, liver protection, anti-microbial, and neuroprotection areas, among others. This review provides a comprehensive overview of the recent advances in the bioactivities and pharmacological mechanisms of GAs, aiming to delineate the current research directions and the state of the art in this field. This analysis helps to rapidly identify new bioactivities of GAs and understand their mechanisms, leading to more effective treatments for various diseases.

Keywords: ganoderic acids; bioactivity; pharmacological mechanism

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1. Introduction

Ganoderma lucidum (*G. lucidum*) is a white rot fungus belonging to the *Basidiomycota* phylum, the *Agaricomycetes* class, the *Polyporales* order, and the *Ganodermataceae* family [1]. *G. lucidum* has been used as medicine in China for thousands of years. The earliest record is found in the *Shennong's Classic of Materia Medica*, the first pharmacological work of the Eastern Han Dynasty in China [2]. *G. lucidum* has many beneficial effects on human health and is known in folklore as the elixir of life and immortal grass. The *Compendium of Materia Medica* records that *G. lucidum* tastes bitter, is non-toxic, and can nourish the body and enhance wisdom [3].

G. lucidum has considerable nutritional and health properties, and is revered as a valuable medicinal mushroom. The extraction of various bioactive constituents from the fruiting body, spores, and mycelium has extensive therapeutic functions, revealing the profound potential of *G. lucidum* in the fields of medicine and pharmacology. For example, the polysaccharides of *G. lucidum* modulate the immune system and ameliorate inflammatory responses, showing promise in the treatment of chronic inflammatory diseases [4,5]. The triterpenoids from various medicinal fungi such as *G. lucidum*, *Poria cocos* and *Antrodia camphorata* have been reported to have a wide range of biological properties, such as anti-cancer activity against breast, prostate, and lung cancer cells [6,7]. These triterpenoids, consisting of six isoprene units, are mainly categorized into two classes: pentacyclic and tetracyclic triterpenes. They can be further differentiated into C30, C27, and C24 groups based on the number of carbon atoms in their molecules, with a relative molecular mass ranging from 400 to 600 [8]. The identification of these constituents has significantly broadened the horizon for the application of medicinal fungi in anti-tumor therapies. In addition to polysaccharides and triterpenoids, *G. lucidum* also contains a spectrum of other bioactive

substances, including steroids, sterols, and so on [9–11]. This intricate chemical composition underpins the broad pharmacological activities of the mushroom and provides a substantial basis for its diverse therapeutic applications.

Ganoderic acids (GAs), as the main component of triterpenes in *G. lucidum*, are highly oxidized lanostane-type triterpenes, including ganoderic acid A (GA-A), ganoderic acid B (GA-B), ganoderic acid C (GA-C), ganoderic acid DM (GA-DM), ganoderic acid D (GA-D), ganoderic acid T (GA-T), and others [12,13]. Statistical evidence indicates that the main functions of GAs include anti-cancer, anti-inflammatory, immunomodulator, anti-radiation, anti-aging, liver protection, anti-microbiology, anti-parasitic, neuroprotection, bone protection, cardioprotective, anti-platelet, and anti-diabetes activities [4,13–22] (Figure 1).

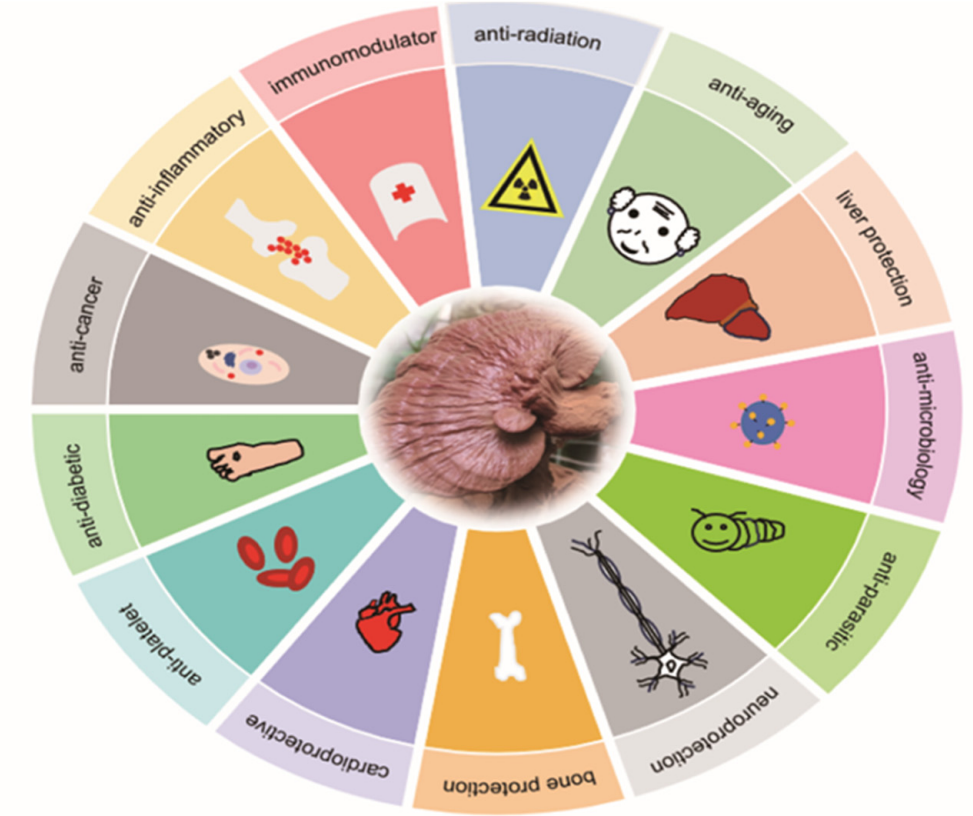


Figure 1. Diverse pharmacological actions exhibited by GAs.

This review provides an overview of the research progress on GAs by summarizing experimental papers published over the past 5 years (from 2020 to 2024) using the PubMed and Web of Science databases with the keywords "ganoderic acids", "biological activity", and "pharmacological activity". Additionally, it includes review articles published over the past decade (from 2014 to 2024) using the same databases with the keyword "ganoderic acids" (Figure 2). The primary objective is to provide a comprehensive synthesis of the existing literature on the biological activities and pharmacological mechanisms of these secondary metabolites, thereby providing a holistic and up-to-date perspective on the research directions in this specialized field. This work will accelerate the discovery of novel bioactive properties of GAs, revealing new horizons in the therapeutic potential of these compounds and laying the groundwork for the development of more effective and targeted therapeutic strategies against a wide range of diseases.

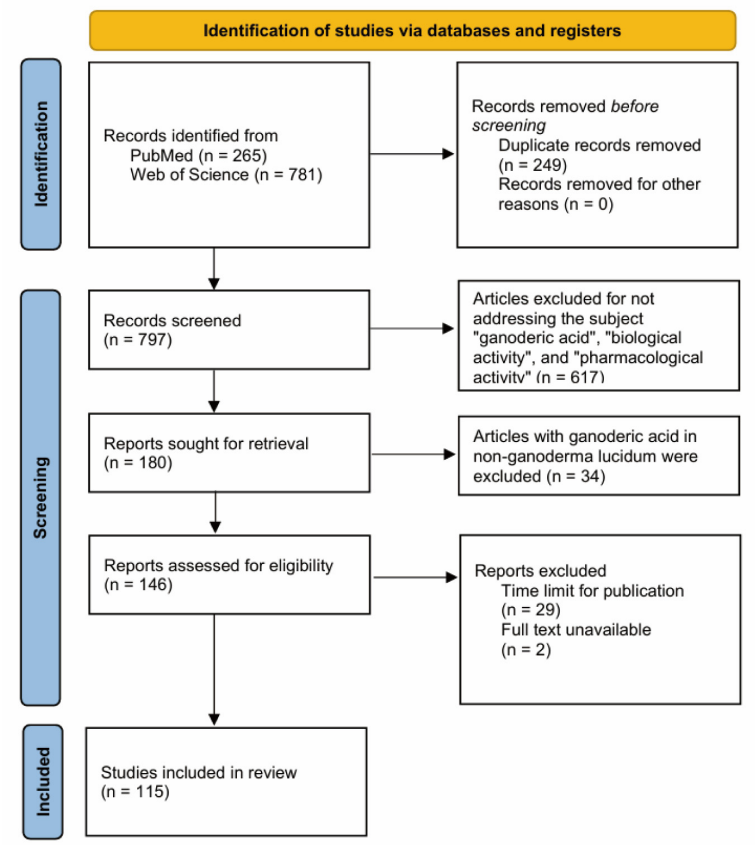


Figure 2. Flowchart of the article selection process for GA-related articles.

2. Anti-Cancer

Cancer represents a significant social, public health, and economic challenge of the 21st century, accounting for the majority of mortality cases attributed to non-communicable diseases (NCDs) globally [23–25]. A substantial body of experimental research has been conducted on the application of GAs across a range of cancer types, including lung cancer [26–28], breast cancer [29,30], prostate cancer [31–33], liver cancer [34–39], cervical cancer [40–42], neuroblastoma [43], and human glioblastoma [44]. In recent years, the evolution of scientific technology has facilitated novel discoveries regarding the anti-cancer properties of GAs, thereby enhancing our comprehension of the underlying mechanisms of action in oncology.

The research team has demonstrated that GA-DM can effectively trigger and enhance autophagic and apoptotic processes in A549 and NCI-H460 non-small cell lung cancer (NSCLC) cells. This is achieved by exerting inhibitory effects on the PI3K/Akt/mTOR signaling cascade, thereby exerting a suppressive effect on cancer progression [45]. GA-A and GA-DM have been demonstrated to suppress the growth of anaplastic meningioma by modulating N-myc downstream-regulated gene 2 (NDRG2) and altering intracellular signaling pathways, thereby reducing tumor volume, inhibiting in vitro cell proliferation, and enhancing in vivo survival rates. These findings suggest that they may have therapeutic potential for the treatment of meningiomas [46]. GA-D downregulates the expression of phosphorylated proteins in the mTOR signaling pathway, including PI3K, AKT, and mTOR, thereby synergistically promoting apoptosis and autophagic cell death in esophageal squamous cell carcinoma cells, achieving effective adjuvant anti-cancer activity [47].

Moreover, research has focused on enhancing the anti-cancer efficacy of GAs through combination with other materials. For instance, the conjugation of the anti-human epidermal receptor 2 (HER2) monoclonal antibody (A. Her2) with the nanocarrier PMBN (poly [MPC-co-(BMA)-co (MEONP)]), followed by the loading of GA-A, has been demonstrated

to enhance the inhibitory effect on the proliferation of HER2-overexpressing breast cancer cells [48]. Polymeric nanoparticles (PNP) loaded with tamoxifen (TF) and GA-A exhibit superior anti-cancer activity in the 7,12-dimethylbenz(a)anthracene (DMBA)-induced rat mammary tumor model [49]. The combination of GA-A with a protease-activated targeting chimera has been demonstrated to exhibit optimal anti-tumor activity against p53-mutant breast cancer in both in vitro and in vivo models. This is achieved by the degradation of the murine double minute 2 (MDM2) protein and the subsequent upregulation of p53 and p21 [50].

3. Anti-Inflammatory

Inflammation is one of the most potent weapons of the immune system, which is initiated to eliminate inflammatory agents when the body encounters invasion by harmful organisms. It is an essential regulatory factor for maintaining homeostasis within the body. However, excessive or persistent inflammatory responses can promote the development of various chronic diseases [51]. There is substantial literature reporting the anti-inflammatory effects of Ganoderma polysaccharides, while studies on the anti-inflammatory effects of GAs are relatively scarce, such as in chronic gastrointestinal inflammatory diseases [52], asthma [53], and lung injury protection [54,55] (Figure 3). In recent years, exploration of the therapeutic potential of GAs for chronic inflammatory diseases has gradually increased [56].

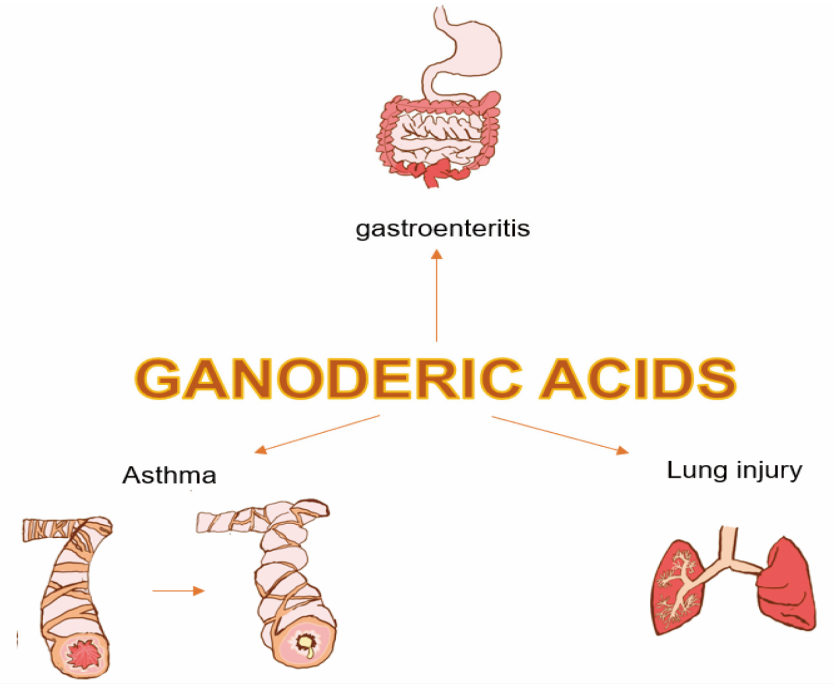


Figure 3. Diverse actions exhibited by GAs in anti-inflammation.

3.1. Anti-Atherosclerosis

Atherosclerosis (AS) is a chronic inflammatory disease characterized by the infiltration of lipids and the formation of plaques in the walls of blood vessels. Through the application of mouse models and in vitro experimentation with macrophages, it has been revealed that GAs can preserve the stability of atherosclerotic plaques and elicit anti-atherosclerotic effects. This is achieved through the modulation of the TLR4/MyD88/NF-κB signaling pathway, which results in the inhibition of M1 macrophage polarization [57,58]. Subsequent studies further reveal that GA-A can inhibit inflammation and lipid deposition inhuman monocyte (THP-1) cells induced by oxidized low-density lipoprotein (ox-LDL) through the Notch1/PPARγ/CD36 signaling pathway, providing theoretical guidance for the therapeutic application of GA-A in AS [59]. Furthermore, in Zheng et al.'s study, GA-A, B, C6, and G are found to promote cholesterol efflux mediated by ABCA1/G1, thereby

inhibiting inflammation in macrophages, and to suppress the osteogenic function mediated by RUNX2 in vascular smooth muscle cells (VSMCs), thus alleviating atherosclerosis [60] (Figure 4).

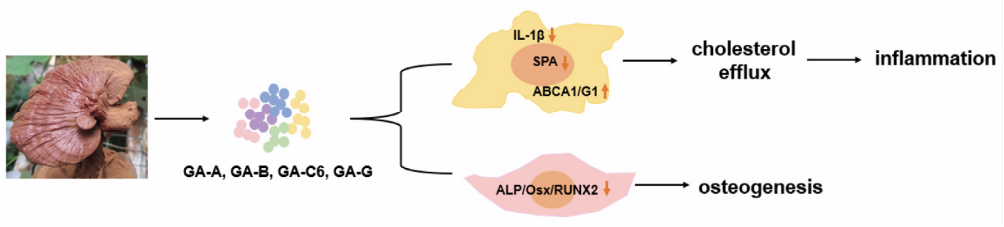


Figure 4. GA attenuates atherosclerosis by specific mechanisms. The upward arrow (↑) indicates that the addition of ganoderic acid leads to an increase in the expression of ABCA1/G1, while the downward arrow (↓) indicates that the addition of ganoderic acid results in a decrease in the expression of IL-1β, SPA, and ALP/Osx/RUNX2.

3.2. Anti-Arthritis

GA-A has demonstrated a significant therapeutic effect on the inflammation of the tarsal joints in collagen-induced arthritis (CIA) rat models, through the modulation of the JAK3/STAT3 and NF-κB signaling pathways [61]. Similarly, it has been demonstrated to improve osteoarthritis by inhibiting the secretion of matrix metallopeptidase 13 (MMP-13) through the relative expression of the nuclear factor kappa-B ligand (RANKL)/osteoprotegerin (OPG) ratio [62]. Subsequent studies have further revealed that it can slow the progression of osteoarthritis by alleviating endoplasmic reticulum stress and blocking the NF-κB pathway [63].

3.3. Anti-Asthma

Asthma is a heterogeneous airway inflammatory disease associated with inflammation driven by T helper 2 cell (Th2) cytokines and non-Th2, TNF-α-mediated inflammation. GA-A exerts an anti-asthmatic effect by inhibiting the TLR/NF-kB signaling pathway, reducing inflammatory cells, decreasing the expression of interleukin-4 (IL-4), IL-5, IL-13, and TLR/NF-kB signaling proteins, thereby alleviating the inflammatory response in bronchial asthmatic mice [64]. GA-B suppresses the production of IL-5 by inhibiting GATA3 while maintaining the expression of Foxp-3 and T-bet genes, enhancing the levels of IL-10 and Interferon gamma (IFN-γ), thus reducing the incidence of allergic asthma [65]. GA-C1 achieves the goal of treating asthma by reducing pulmonary inflammation and neutrophils, inhibiting the levels of TNF-α, IL-4, and IL-5, decreasing MUC5AC gene expression, and reducing the production of reactive oxygen species (ROS) [66].

3.4. Anti-Neuroinflammation

Neuroinflammation plays a pivotal role in the initiation and progression of neurodegenerative diseases. Microglial-mediated neuroinflammation has been identified as a primary cause of neurodegenerative disorders. GA-A has been demonstrated to exert a pronounced inhibitory effect on lipopolysaccharide (LPS)-induced neuroinflammation in BV2 microglia by activating the farnesoid X receptor (FXR), inhibiting the release of pro-inflammatory factors, and promoting the expression of the neurotrophic factor BDNF [67]. Similarly, deacetylated GA-F, a strategic structural modification, enhances its bioactivity by potentiating its anti-inflammatory capabilities. This alteration enables deacetylated GA-F to effectively target neuroinflammation in microglial cells through the NF-κB pathway, thereby providing a therapeutic approach to treating neuroinflammation [68].

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system, representing a major cause of non-traumatic neurological dysfunction in young individuals. GA-A modulates neuroimmunity by enhancing anti-inflammatory and regenerative markers such as IL-4 and BDNF, while suppressing inflammatory mark-

ers such as IL-1β and IL-6, and activating an FXR-dependent mechanism to ameliorate neuroimmunological imbalance and promote remyelination in MS [69].

3.5. Anti-Intervertebral Disc Degeneration

The primary cause of low back pain is intervertebral disc (IVD) degeneration, with nucleus pulposus (NP) cells being the most significantly affected. GA-A can alleviate the dysfunction of NP cells by modulating the NF-κB pathway to reduce inflammation and extracellular matrix (ECM) degradation induced by IL-1β, thereby treating intervertebral disc degeneration [70]. In the study conducted by Wang et al., GA-A mitigates IVD degeneration by inhibiting the TLR4/NLRP3 signaling axis to suppress apoptosis, oxidative stress, and inflammatory responses in NP cells induced by H_2O_2 [71].

4. Anti-Radiation

The impact of GA-T on radiation sensitivity is investigated utilizing HeLa cells that have been exposed to gamma radiation. It has been demonstrated that GA-T not only induces apoptosis in ionizing radiation-exposed HeLa cells but also induces necrosis as the concentration of GA-T increases, which may be related to the inhibition of caspase 8, depletion of ATP, and increased production of ROS [72]. Using a model of lens epithelial cells (LECs) exposed to UVB radiation, it has been discovered that GA-A offers protective effects on SRA01/04 cells and rat lenses by enhancing cell viability and antioxidant activity, activating the PI3K/AKT pathway, inhibiting apoptosis, and delaying cataract formation [73].

5. Anti-Aging

In recent years, GAs have achieved significant success in the cosmeceutical field, with triterpenoids from *G. lucidum* frequently appearing in cosmetic formulations [51,74]. They are employed as photoprotective agents to regulate excessive pigmentation and suppress inflammatory skin diseases. However, the mechanisms of action and biological targets underlying their beneficial effects on dermatology are not yet fully understood. It has been demonstrated that GA-A induces the proliferation of keratinocytes, accompanied by an increase in the expression of cyclin-dependent kinase proteins, and a significant increase in migration rate and activation of tissue remodeling factors has been observed. Additionally, it exhibits antioxidant effects, providing evidence for the anti-aging properties of GAs and its potential development as a cosmeceutical skin product [75].

Aging is a significant risk factor for the development of many chronic diseases. The senescence and exhaustion of adult stem cells are considered hallmarks of organismal aging. Using a model of oxidatively stressed, senescent human amniotic mesenchymal stem cells (hAMSCs) induced by hydrogen peroxide in vitro reveals that GA-D delays hAMSC senescence by activating the endoplasmic reticulum kinase (PERK)/nuclear factor-erythroid 2-related factor (NRF2) signaling pathway [76]. In Yuan et al.'s study, it was further discovered that GA-D targets 14-3-3ε to activate the Ca2+ calmodulin (CaM)/CaM-dependent protein kinase II (CaMKII)/nuclear erythroid 2-related factor 2 (Nrf2) signaling pathway, thereby delaying the senescence of hAMSCs, with 14-3-3ε identified as a target of GA-D [77] (Figure 5).

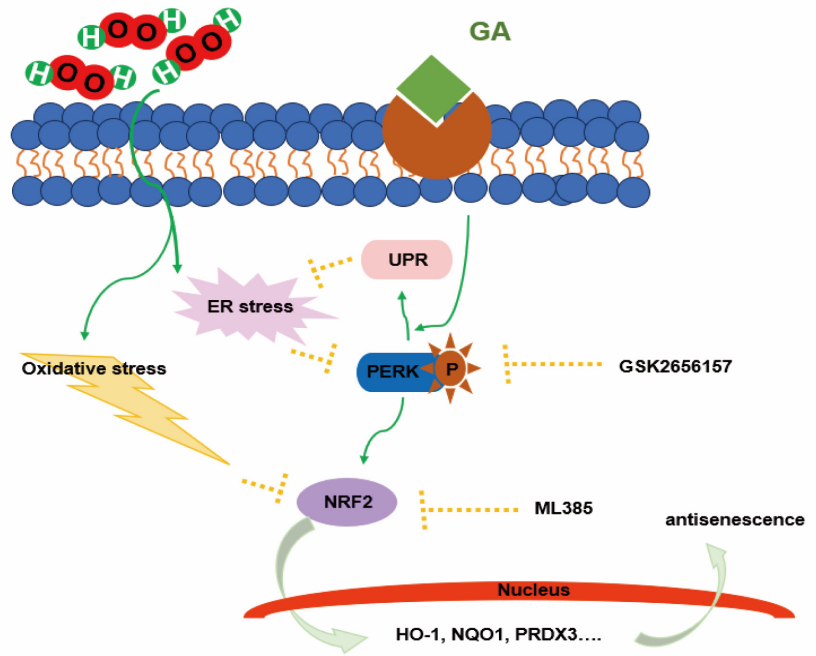


Figure 5. The proposed antisenescence mechanism of GA-D in hAMSCs.

6. Anti-Alzheimer's Disease

Alzheimer's disease (AD) is considered to be caused by the accumulation of amyloid-β (Aβ) in the central nervous system for insufficient clearance. Using an Aβ25-35-treated HT22 cell model to establish an AD model, it has been found that GA-A can change the effects of Aβ25-35 in inhibiting cell viability, promoting apoptosis, and senescence, and it has been hypothesized that GA-A delays the senescence of AD cells through the modulation of immune-inflammatory mechanisms via the JAK-PI3K-AKT-mTOR signaling pathway [78]. In a separate study utilizing microglia, it is discovered that GA-A enhances Axl phosphorylation, activates Pak1, boosts autophagy, promotes the clearance of Aβ42, and improves cognitive deficits in an AD mouse model [79]. An imbalance in the Th17/regulatory T (Treg) cell axis exists in the neuroinflammatory process of AD. Using a D-galactose mouse model, it is found that GA-A modulates Treg cells to suppress Th17-induced JAK/STAT signaling pathways, enhances mitochondrial oxidative phosphorylation, and thereby improves mitochondrial dysfunction and alleviates neuroinflammation in AD mice [80].

7. Liver Protection

Ganoderic acid XL (GA-XL), GA-AM, and GA-A have hepatoprotective effects [81,82]. In Zhang's study, it is also found that 12 derivative GAs exhibit significant hepatoprotective activity against H_2O_2-induced HepG2 cells [83].

The consumption of mushrooms containing α-amanitin, a representative toxin of the Amanita genus, can cause severe liver injury. GA-A has been demonstrated to prevent α-amanitin-induced liver injury by regulating retinol metabolism, tyrosine and tryptophan biosynthesis, fatty acid biosynthesis, sphingosine biosynthesis, as well as the biosynthesis of spermine and spermidine, and branched-chain amino acid metabolism, exerting a protective intervention [84]. Subsequent studies further discover that GA-A may enhance the survival rate and liver function of mice poisoned with α-amanitin by inhibiting the JAK2-STAT3 pathway, and achieve detoxification [85].

Furthermore, GA-A has been demonstrated to offer protection against both non-alcoholic and against alcoholic liver injury. It improves non-alcoholic fatty liver disease by modulating the levels of free fatty acid synthesis, lipid oxidation, and liver inflammation-related signaling pathways such as NF-κB and AMPK [86]. Furthermore, it ameliorates liver inflammation and fibrosis through oxidative stress and the endoplasmic reticulum

stress response [87]. Additionally, it has been demonstrated to improve alcoholic liver injury by enhancing lipid metabolism, modulating the levels of inflammation-associated mRNA, and regulating the gut microbiota composition [88].

8. Anti-Microbial

Previous studies have demonstrated that GAs can inhibit the Hepatitis B virus (HBV) [89], Human Immunodeficiency Virus-1 (HIV) [90,91], and Enterovirus 71 (EV71) [92]. In recent years, it has been discovered that GA-T exerts its pharmacological effects against Sendai virus by inhibiting the mTOR signaling pathway, regulating the innate immune system and the inflammatory response to the IL-17 signaling pathway [93].

GA-A has been demonstrated to possess anti-microbial properties. When encapsulated with novel nanoparticles, it exhibits a broad-spectrum anti-microbial effect, demonstrating potent antibacterial activity against drug-resistant Escherichia coli and Staphylococcus aureus [94]. Furthermore, through molecular docking simulations, GA-A, GA-AM1, GA-D, and others have been identified for their activity against Staphylococcus aureus [95]. In addition, GAs have also shown significant anti-microbial activity against Bacillus subtilis [96].

9. Neuroprotection

The administration of chemotherapy can result in considerable adverse effects for patients, leading to a notable decline in their overall quality of life. Additionally, chemotherapy can impair various physical and social functions, as well as cause cognitive deficits. GAs can prevent and treat cognitive dysfunction caused by 5-Fluorouracil (5-FU) by improving hippocampal neurons, preventing mitochondrial damage, enhancing the expression of proteins related to mitochondrial biogenesis and mitochondrial dynamics markers in the hippocampus, upregulating the expression of neuron survival and growth-related proteins, and strengthening neuronal function [97]. GAs can also alleviate peripheral muscle fatigue and central fatigue-like behaviors by improving muscle mass and mood damage, inhibiting IL-6 and TNF-α, alleviating the decrease in glycogen content, enhancement of glycolysis, reduction in ATP production, and chronic activation of AMPK, thereby reducing peripheral muscle fatigue. Furthermore, GAs can suppress the TLR4/Myd88/NF-κB pathway and downregulate the expression of IL-6, iNOS, and COX2 in hippocampal tissue [98].

GA-A has been demonstrated to mitigate the inflammatory response in the hippocampus induced by post-stroke depression (PSD) by activating the ERK/CREB pathway, preventing pro-inflammatory (M1) polarization, and promoting anti-inflammatory (M2) polarization. This has been shown to reduce neuronal damage and depressive-like behaviors in PSD rats, as well as cerebral inflammation [99]. Moreover, it can treat mood disorders and inhibit depressive-like behaviors by modulating the bile acid receptor farnesoid X receptor (FXR), directly inhibiting the activity of the NLRP3 inflammasome, activating the phosphorylation and expression of AMPA receptors, and regulating synaptic activity [100] (Figure 6). Additionally, in Xu et al.'s study, GA-A is found to exert antidepressant properties by affecting the expression of factors related to the regulation of mitochondrial activity and synaptic transmission signaling, providing a new perspective on the antidepressant effects of GA-A [101].

GA-A mitigates the neurotoxin-induced apoptosis of dopaminergic neurons by inhibiting nuclear receptor co-activator 4 (NCOA4)-mediated ferritin autophagy, reducing the neurotoxicity, motor dysfunction, and loss of dopaminergic neurons induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 1-methyl-4-phenylpyridinium (MPP+), thereby alleviating the nervous system and providing a protective effect against Parkinson's disease (PD) [102]. GA-A can protect neuronal cells (PC) from nitric oxide (NO) stress damage by stimulating β-adrenergic receptors [103]. GA-A significantly inhibits the apoptosis of PC12 cells by downregulating Bax and markedly suppressing the phosphorylation of tau protein at sites S199 and T231, while GA-B also downregulates Bax and Bad, inhibits the activity of glycogen synthase kinase-3β (GSK-3β) to reduce the

hyperphosphorylation of tau, and exhibits a better neuroprotective effect on PC12 cells damaged by okadaic acid than GA-A [104].

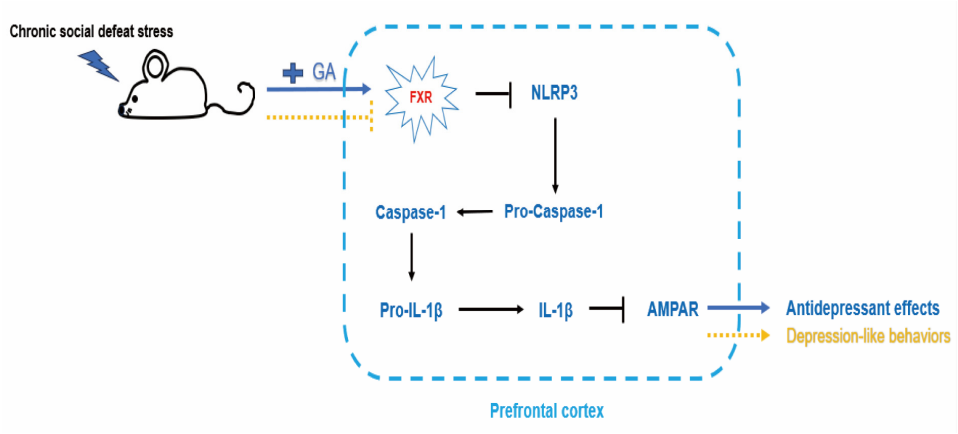


Figure 6. GA-A regulates neuroimmune and antidepressant behaviors.

10. Other Functions

GA-A downregulates the Ras/MAPK signaling pathway in a dose-dependent manner, inhibits the expression of proliferating cell nuclear antigen (PCNA), alleviates the growth and progression of renal cysts, and delays the progression of autosomal dominant polycystic kidney disease (ADPKD) [105]. It can also inhibit renal tubular epithelial–mesenchymal transition and hinder renal fibrosis by suppressing the TGF-β/Smad and MAPK signaling pathways, providing a means to block the advancement of kidney diseases [106]. Furthermore, it can improve inflammation, renal fibrosis, and oxidative stress by modulating the Trx/TrxR, JAK2/STAT3, and RhoA/ROCK pathways, thereby protecting the kidneys [107].

In addition to the aforementioned cisplatin, GA-B can reverse ABCB1-mediated multidrug resistance [108]. GA-D can reverse the resistance to gemcitabine (GEM) in triple-negative breast cancer (TNBC), activating the p53/MDM2 pathway, promoting the ubiquitination and proteasomal degradation of HIF-1α, downregulating HIF-1α-dependent glycolytic genes such as GLUT1, HK2, and PKM2, and significantly reducing the growth of GEM-resistant TNBC cells [109].

In addition, GA-A can also improve hyperlipidemia by regulating liver lipid metabolism, the expression of genes related to bile acid homeostasis, and intestinal flora imbalance [110].

11. Limitations

In assessing the review on the bioactivity of GAs, it is important to be aware of some limitations in this area of research. First, although the review may provide some insights into their mechanisms, the specific molecular pathways and signaling networks of many bioactivities are still not fully understood, suggesting that our understanding of how GAs exert their effects needs to be further explored. Second, the review may focus more on research conducted under laboratory conditions, lacking clinical and application data, which limits our understanding of the potential of GAs in practical applications. Finally, the review may not adequately consider the dose–response effects, side effects, and drug interactions of GAs, or fully account for the diversity of population responses, such as the effects of age, gender, and disease status. Therefore, although this review provides valuable resources for understanding the bioactivity of GAs, caution should be exercised in interpreting its conclusions, and the impact of these limitations on research interpretation and future research directions should be recognized.

12. Conclusions and Perspectives

Ganoderic acids (GAs) are significant medicinal components reported in the medicinal fungus *Ganoderma lucidum* (*G. lucidum*) [1]. To date, researchers have investigated and

reported many biological activities and regulatory mechanisms of *G. lucidum* [4,10–19]. However, studies on the biological effects and molecular mechanisms of GAs are at a preliminary stage and need further in-depth exploration and investigation.

GAs are a complex mixture from which over 100 different compounds have been isolated to date [4,8]. Among them, GA-A is the most extensively studied and explored. As shown in Table 1, GA-A has potential applications in the treatment of several types of cancer, including liver, prostate, breast, and gastric cancers, as well as protective effects on multiple organs such as the liver, myocardium, and bones. Additionally, GA-A possesses properties like radiation protection, antiviral, and anti-aging capabilities. GAs have a variety of functional groups and side chain structures. The structural diversity of GAs is responsible for their variable pharmacological profiles. For example, in terms of anti-tumor activity, GA-A and GA-B, which are among the earliest triterpenoid compounds isolated from *G. lucidum*, induce apoptosis in tumor cells by compromising the integrity of cellular membrane structures. In contrast, GA-D downregulates the mTOR signaling pathway in esophageal squamous cell carcinoma cells, thereby inducing apoptosis and autophagy. Preliminary studies on the physiological functions of other GAs are also available (Table 1).

Table 1. The summary table of GAs bioactivities covered in this review.

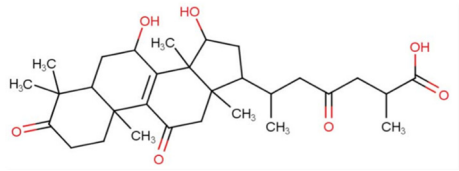
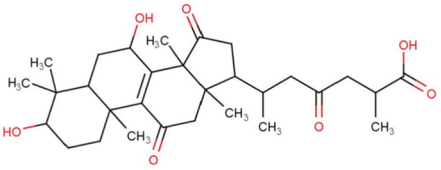
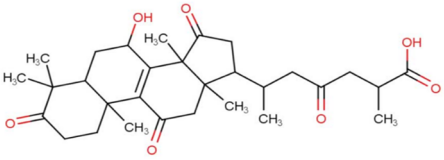
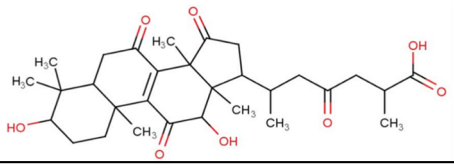
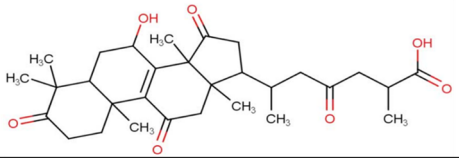
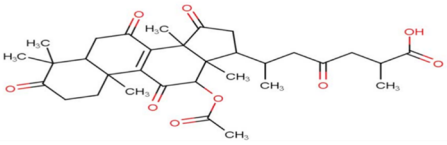
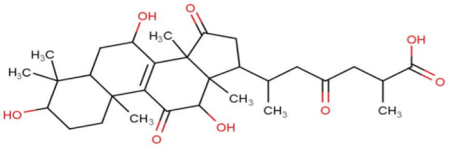
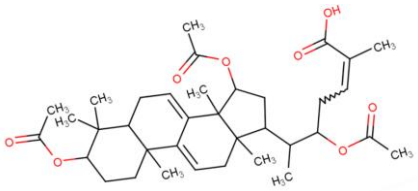
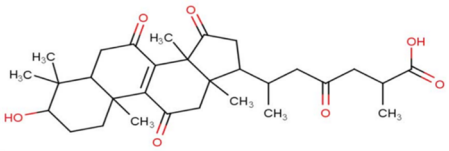
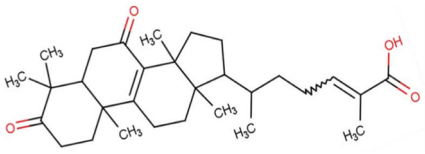
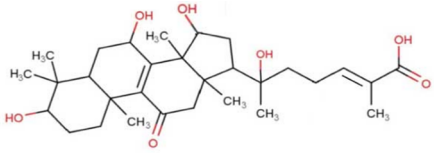
Compound Name		Biological Activity	Citation Numbers
Ganoderic acid A		anti-anaplastic meningioma	[46]
		anti-breast cancer	[48–50]
		anti-atherosclerosis	[59,60]
		anti-arthritis	[61–63]
		anti-asthma	[64]
		anti-neuroinflammation	[67]
		anti-multiple sclerosis	[69]
		anti-intervertebral disc degeneration	[70,71]
		anti-radiation	[73]
		anti-aging	[75]
		anti-Alzheimer's disease	[78–80]
		liver protection	[81,82,84–88]
		anti-microbial properties	[94,95]
		inhibits depression	[100,101]
		anti-Parkinson's disease	[102–104]
		protects the kidneys	[105–107]
		improves hyperlipidemia	[110]
Ganoderic acid B		anti-atherosclerosis	[60]
		anti-asthma	[65]
		neuroprotection	[104]
		resistance to drug resistance	[108]
Ganoderic acid C1		anti-asthma	[66]
Ganoderic acid C6		anti-atherosclerosis	[60]

Table 1. *Cont.*

Compound Name		Biological Activity	Citation Numbers
Ganoderic acid D		anti-esophageal squamous cell carcinoma anti-aging anti-microbial properties resistance to drug resistance	[47] [76,77] [95] [109]
Ganoderic acid F		anti-neuroinflammation	[68]
Ganoderic acid G		anti-atherosclerosis	[60]
Ganoderic acid T		anti-radiation against Sendai virus	[72] [93]
Ganoderic acid AM		liver protection anti-microbial properties	[81,82] [95]
Ganoderic acid DM		anti-lung cancer anti-anaplastic meningioma	[45] [46]
Ganoderic acid XL		liver protection	[81,82]

The mechanisms by which GAs exert their various biological activities have been confirmed by a large body of research. At the cellular level, GAs exert their effects through precise mechanisms, such as directly targeting cancer cells, interfering with the cell cycle, promoting cellular differentiation and apoptosis, and enhancing oxidative stress responses, thereby combating diseases [13–22]. The presence of hydroxyl and carboxyl groups in the structure of GAs can modulate their interaction with cell membranes. At the signaling molecular level, GAs modulate the release of inflammatory mediators by interfering with key signaling pathways, including PI3K/AKT/mTOR, NF-κB, Notch1, JAK3/STAT3, and others, thus regulating disease progression. Future research should use advanced methods such as high-throughput screening and molecular biology techniques to further elucidate the therapeutic mechanisms of GAs against various diseases, to investigate their regulatory roles on signaling pathways, and to explore the specificity of these pathways in different diseases.

To date, scientists have developed many precise and effective methods for the clinical application of GAs. For example, the combination of GAs with novel drug delivery vehicles, such as proteolytic targeted chimeras and nanomaterials, has demonstrated the potential to improve resistance to disease treatment. In addition, some studies have optimized the structure of GAs through chemical synthesis, genetic engineering, or biosynthetic strategies to improve the biological activity and targeting selectivity of GAs [48,49,90]. Furthermore, the pharmacokinetic profile of GAs can be optimized through pharmaceutical design and formulation techniques.

There are still some challenges in the clinical application of GAs. Studies have indicated that GA-A inhibits the activities of CYP3A4, CYP2D6, and CYP2E1 in human liver, which may affect the contribution of the hepatic clearance during the metabolism of the drug [111]. Additionally, GAs may cause hypersensitivity reactions in certain populations, exacerbate conditions for patients with asthma and allergic rhinitis, and potentially cause adverse reactions such as rash, paresthesia, abdominal bloating, and dysuria [112–114]. In animal models, extracts of *G. lucidum* have shown potential toxic effects on the development of zebrafish embryos [115]. The high lipophilicity of GAs may lead to incomplete dissolution and absorption in the gastrointestinal tract, challenge the distribution to hydrophilic tissues due to biological barriers, and result in a short half-life within the body. These factors contribute to the low bioavailability of GAs [13]. To address these challenges, strategies such as improving their solubility, enhancing permeability, and developing controlled-release formulations can be employed to enhance their therapeutic efficacy. Additionally, it is essential that future studies investigate the synergistic effects of GAs with other drugs or treatment strategies, using multi-drug combination therapies to increase treatment efficacy and reduce side effects. Concurrently, considering the impact of individual differences on drug response, the exploration of personalized medicine strategies will tailor GA treatment based on the genetic background and pathological conditions of patients.

In summary, the prospects for research and application of GAs are promising yet challenging. Through interdisciplinary collaboration and innovative research, GAs have the potential to become an integral component of future medical fields, offering new strategies and methods for the treatment of a variety of diseases.

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References

1. Richter, C.; Wittstein, K.; Kirk, P.M.; Stadler, M. An assessment of the taxonomy and chemotaxonomy of *Ganoderma*. *Fungal Divers.* **2015**, *71*, 1–15. [CrossRef]
2. Cui, B.K.; Wu, S.H. The scientific name of the widely cultivated *Ganoderma* species. *Mycosystema* **2020**, *39*, 7–12. [CrossRef]
3. Ma, X.; Xu, B.; Song, H.; Hu, Y.; Sun, X.; Li, W. Research progress on chemical constituents of *Ganoderma lucidum* and its prevention and treatment of tumor diseases. *Chin. Pharm. J.* **2023**, *58*, 1437–1446.
4. Yuan, D.; Li, C.; Huang, Q.; Fu, X.; Dong, H. Current advances in the anti-inflammatory effects and mechanisms of natural polysaccharides. *Crit. Rev. Food Sci. Nutr.* **2023**, *63*, 5890–5910. [CrossRef] [PubMed]

5. Wen, L.; Sheng, Z.; Wang, J.; Jiang, Y.; Yang, B. Structure of water-soluble polysaccharides in spore of *Ganoderma lucidum* and their anti-inflammatory activity. *Food Chem.* **2022**, *373*, 131374. [CrossRef]
6. Miranda, R.S.; de Jesus, B.D.S.M.; da Silva Luiz, S.R.; Viana, C.B.; Adão Malafaia, C.R.; Figueiredo, F.S.; Carvalho, T.D.S.C.; Silva, M.L.; Londero, V.S.; da Costa-Silva, T.A.; et al. Antiinflammatory activity of natural triterpenes—An overview from 2006 to 2021. *Phytother. Res. PTR* **2022**, *36*, 1459–1506. [CrossRef]
7. Galappaththi, M.C.A.; Patabendige, N.M.; Premarathne, B.M.; Hapuarachchi, K.K.; Tibpromma, S.; Dai, D.Q.; Suwannarach, N.; Rapior, S.; Karunarathna, S.C. A Review of *Ganoderma* Triterpenoids and Their Bioactivities. *Biomolecules* **2022**, *13*, 24. [CrossRef]
8. Chen, H.Y.; Lei, J.Y.; Li, S.L.; Guo, L.Q.; Lin, J.F.; Wu, G.H.; Lu, J.; Ye, Z.W. Progress in biological activities and biosynthesis of edible fungi terpenoids. *Crit. Rev. Food Sci. Nutr.* **2023**, *63*, 7288–7310. [CrossRef]
9. Liu, C.; Song, X.; Li, Y.; Ding, C.; Li, X.; Dan, L.; Xu, H.; Zhang, D. A Comprehensive Review on the Chemical Composition, Pharmacology and Clinical Applications of *Ganoderma*. *Am. J. Chin. Med.* **2023**, *51*, 1983–2040. [CrossRef]
10. He, X.; Chen, Y.; Li, Z.; Fang, L.; Chen, H.; Liang, Z.; Abozeid, A.; Yang, Z.; Yang, D. Germplasm resources and secondary metabolism regulation in Reishi mushroom (*Ganoderma lucidum*). *Chin. Herb. Med.* **2023**, *15*, 376–382. [CrossRef]
11. Ahmad, R.; Riaz, M.; Khan, A.; Aljamea, A.; Algheryafi, M.; Sewaket, D.; Alqathama, A. *Ganoderma lucidum* (Reishi) an edible mushroom; a comprehensive and critical review of its nutritional, cosmeceutical, mycochemical, pharmacological, clinical, and toxicological properties. *Phytother. Res. PTR* **2021**, *35*, 6030–6062. [CrossRef] [PubMed]
12. Wang, L.; Li, J.Q.; Zhang, J.; Li, Z.M.; Liu, H.G.; Wang, Y.Z. Traditional uses, chemical components and pharmacological activities of the genus Ganoderma P. Karst.: A review. *RSC Adv.* **2020**, *10*, 42084–42097. [CrossRef] [PubMed]
13. Ahmad, M.F.; Wahab, S.; Ahmad, F.A.; Ashraf, S.A.; Abullais, S.S.; Saad, H.H. *Ganoderma lucidum*: A potential pleiotropic approach of ganoderic acids in health reinforcement and factors influencing their production. *Fungal Biol. Rev.* **2022**, *39*, 100–125. [CrossRef]
14. Renda, G.; Gökkaya, İ.; Şöhretoğlu, D. Immunomodulatory properties of triterpenes. *Phytochem Rev.* **2022**, *21*, 537–563. [CrossRef]
15. Liang, C.; Tian, D.; Liu, Y.; Li, H.; Zhu, J.; Li, M.; Xin, M.; Xia, J. Review of the molecular mechanisms of *Ganoderma lucidum* triterpenoids: Ganoderic acids A, C2, D, F, DM, X and Y. *Eur. J. Med. Chem.* **2019**, *174*, 130–141. [CrossRef]
16. Ye, T.; Ge, Y.; Jiang, X.; Song, H.; Peng, C.; Liu, B. A review of anti-tumour effects of *Ganoderma lucidum* in gastrointestinal cancer. *Chin. Med.* **2023**, *18*, 107. [CrossRef]
17. Blundell, R.; Camilleri, E.; Baral, B.; Karpiński, T.M.; Neza, E.; Atrooz, O.M. The Phytochemistry of *Ganoderma* Species and their Medicinal Potentials. *Am. J. Chin. Med.* **2023**, *51*, 859–882. [CrossRef]
18. Swallah, M.S.; Bondzie-Quaye, P.; Wu, Y.; Acheampong, A.; Sossah, F.L.; Elsherbiny, S.M.; Huang, Q. Therapeutic potential and nutritional significance of *Ganoderma lucidum*—A comprehensive review from 2010 to 2022. *Food Funct.* **2023**, *14*, 1812–1838. [CrossRef]
19. Ahmad, M.F.; Ahmad, F.A.; Zeyaullah, M.; Alsayegh, A.A.; Mahmood, S.E.; AlShahrani, A.M.; Khan, M.S.; Shama, E.; Hamouda, A.; Elbendary, E.Y.; et al. *Ganoderma lucidum*: Novel Insight into Hepatoprotective Potential with Mechanisms of Action. *Nutrients* **2023**, *15*, 1874. [CrossRef]
20. Luz, D.A.; Pinheiro, A.M.; Fontes-Júnior, E.A.; Maia, C.S.F. Neuroprotective, neurogenic, and anticholinergic evidence of *Ganoderma lucidum* cognitive effects: Crucial knowledge is still lacking. *Med. Res. Rev.* **2023**, *43*, 1504–1536. [CrossRef]
21. Ahmad, M.F. *Ganoderma lucidum*: A rational pharmacological approach to surmount cancer. *J. Ethnopharmacol.* **2020**, *260*, 113047. [CrossRef] [PubMed]
22. Wang, J.; Cao, B.; Zhao, H.; Feng, J. Emerging Roles of *Ganoderma lucidum* in Anti-Aging. *Aging Dis.* **2017**, *8*, 691–707. [CrossRef] [PubMed]
23. He, S.; Xia, C.; Li, H.; Cao, M.; Yang, F.; Yan, X.; Zhang, S.; Teng, Y.; Li, Q.; Chen, W. Cancer profiles in China and comparisons with the USA: A comprehensive analysis in the incidence, mortality, survival, staging, and attribution to risk factors. *Sci. China Life Sci.* **2024**, *67*, 122–131. [CrossRef] [PubMed]
24. Bray, F.; Laversanne, M.; Sung, H.; Ferlay, J.; Siegel, R.L.; Soerjomataram, I.; Jemal, A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **2024**, *74*, 229–263. [CrossRef]
25. Siegel, R.L.; Miller, K.D.; Wagle, N.S.; Jemal, A. Cancer statistics, 2023. *CA Cancer J. Clin.* **2023**, *73*, 17–48. [CrossRef]
26. Wang, G.; Zhao, J.; Liu, J.; Huang, Y.; Zhong, J.J.; Tang, W. Enhancement of IL-2 and IFN-gamma expression and NK cells activity involved in the anti-tumor effect of ganoderic acid Me in vivo. *Int. Immunopharmacol.* **2007**, *7*, 864–870. [CrossRef]
27. Chen, N.H.; Liu, J.W.; Zhong, J.J. Ganoderic acid Me inhibits tumor invasion through down-regulating matrix metalloproteinases 2/9 gene expression. *J. Pharmacol. Sci.* **2008**, *108*, 212–216. [CrossRef]
28. Que, Z.; Zou, F.; Zhang, A.; Zheng, Y.; Bi, L.; Zhong, J.; Tian, J.; Liu, J. Ganoderic acid Me induces the apoptosis of competent T cells and increases the proportion of Treg cells through enhancing the expression and activation of indoleamine 2,3-dioxygenase in mouse lewis lung cancer cells. *Int. Immunopharmacol.* **2014**, *23*, 192–204. [CrossRef]
29. Jiang, J.; Grieb, B.; Thyagarajan, A.; Sliva, D. Ganoderic acids suppress growth and invasive behavior of breast cancer cells by modulating AP-1 and NF-kappaB signaling. *Int. J. Mol. Med.* **2008**, *21*, 577–584.
30. Yang, Y.; Zhou, H.; Liu, W.; Wu, J.; Yue, X.; Wang, J.; Quan, L.; Liu, H.; Guo, L.; Wang, Z.; et al. 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.* **2018**, *16*, 6515–6521. [CrossRef]

31. Johnson, B.M.; Doonan, B.P.; Radwan, F.F.; Haque, A. Ganoderic Acid DM: An Alternative Agent for the Treatment of Advanced Prostate Cancer. *Open Prostate Cancer J.* **2010**, *3*, 78–85. [CrossRef] [PubMed]
32. Gill, B.S.; Kumar, S.; Navgeet. Evaluating anti-oxidant potential of ganoderic acid A in STAT 3 pathway in prostate cancer. *Mol. Biol. Rep.* **2016**, *43*, 1411–1422. [CrossRef] [PubMed]
33. Johnson, B.M.; Radwan, F.F.Y.; Hossain, A.; Doonan, B.P.; Hathaway-Schrader, J.D.; God, J.M.; Voelkel-Johnson, C.V.; Banik, N.L.; Reddy, S.V.; Haque, A. Endoplasmic reticulum stress, autophagic and apoptotic cell death, and immune activation by a natural triterpenoid in human prostate cancer cells. *J. Cell. Biochem.* **2019**, *120*, 6264–6276. [CrossRef]
34. Yang, H.L. Ganoderic acid produced from submerged culture of *Ganoderma lucidum* induces cell cycle arrest and cytotoxicity in human hepatoma cell line BEL7402. *Biotechnol. Lett.* **2005**, *27*, 835–838. [CrossRef]
35. Li, C.H.; Chen, P.Y.; Chang, U.M.; Kan, L.S.; Fang, W.H.; Tsai, K.S.; Lin, S.B. Ganoderic acid X, a lanostanoid triterpene, inhibits topoisomerases and induces apoptosis of cancer cells. *Life Sci.* **2005**, *77*, 252–265. [CrossRef]
36. Yao, X.; Li, G.; Xu, H.; Lü, C. Inhibition of the JAK-STAT3 signaling pathway by ganoderic acid A enhances chemosensitivity of HepG2 cells to cisplatin. *Planta Medica* **2012**, *78*, 1740–1748. [CrossRef]
37. Wang, X.; Sun, D.; Tai, J.; Wang, L. Ganoderic acid A inhibits proliferation and invasion, and promotes apoptosis in human hepatocellular carcinoma cells. *Mol. Med. Rep.* **2017**, *16*, 3894–3900. [CrossRef]
38. Zhao, R.L.; He, Y.M. Network pharmacology analysis of the anti-cancer pharmacological mechanisms of *Ganoderma lucidum* extract with experimental support using Hepa1-6-bearing C57 BL/6 mice. *J. Ethnopharmacol.* **2018**, *210*, 287–295. [CrossRef] [PubMed]
39. Sun, Z.W.; Sun, L.B.; Li, W.W. Effect of ganoderic acid on diethylnitrosamine-induced liver cancer in mice. *Trop. J. Pharm. Res.* **2020**, *19*, 2639–2644. [CrossRef]
40. Liu, R.M.; Zhong, J.J. Ganoderic acid Mf and S induce mitochondria mediated apoptosis in human cervical carcinoma HeLa cells. *Phytomedicine* **2011**, *18*, 349–355. [CrossRef]
41. Liu, R.M.; Li, Y.B.; Zhong, J.J. Cytotoxic and pro-apoptotic effects of novel ganoderic acid derivatives on human cervical cancer cells in vitro. *Eur. J. Pharmacol.* **2012**, *681*, 23–33. [CrossRef]
42. Liu, R.M.; Li, Y.B.; Liang, X.F.; Liu, H.Z.; Xiao, J.H.; Zhong, J.J. Structurally related ganoderic acids induce apoptosis in human cervical cancer HeLa cells: Involvement of oxidative stress and antioxidant protective system. *Chem.-Biol. Interact.* **2015**, *240*, 134–144. [CrossRef]
43. Gill, B.S.; Navgeet; Kumar, S. Antioxidant potential of ganoderic acid in Notch-1 protein in neuroblastoma. *Mol. Cell. Biochem.* **2019**, *456*, 1–14. [CrossRef]
44. Cheng, Y.; Xie, P. 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.* **2019**, *33*, e22392. [CrossRef]
45. Xia, J.; Dai, L.; Wang, L.; Zhu, J. Ganoderic acid DM induces autophagic apoptosis in non-small cell lung cancer cells by inhibiting the PI3K/Akt/mTOR activity. *Chem.-Biol. Interact.* **2020**, *316*, 108932. [CrossRef]
46. Das, A.; Alshareef, M.; Henderson, F., Jr.; Martinez Santos, J.L., Jr.; Vandergrift, W.A.; Lindhorst, S.M., III; Varma, A.K.; Infinger, L.; Patel, S.J.; Cachia, D. Ganoderic acid A/DM-induced NDRG2 over-expression suppresses high-grade meningioma growth. *Clin. Transl. Oncol.* **2020**, *22*, 1138–1145. [CrossRef]
47. Shao, C.S.; Zhou, X.H.; Zheng, X.X.; Huang, Q. Ganoderic acid D induces synergistic autophagic cell death except for apoptosis in ESCC cells. *J. Ethnopharmacol.* **2020**, *262*, 113213. [CrossRef]
48. Motamed Fath, P.; Rahimnejad, M.; Moradi-Kalbolandi, S.; Ebrahimi Hosseinzadeh, B.; Jamshidnejad-Tosaramandani, T. 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.* **2022**, *12*, 1228–1237. [CrossRef]
49. 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.; et al. Biocompatible Polymeric Nanoparticles for Effective Codelivery of Tamoxifen with Ganoderic Acid A: Systematic Approach for Improved Breast Cancer Therapeutics. *J. Clust. Sci.* **2023**, *34*, 1483–1497. [CrossRef]
50. Li, Y.; Li, G.; Zuo, C.; Wang, X.; Han, F.; Jia, Y.; Shang, H.; Tian, Y. Discovery of ganoderic acid A (GAA) PROTACs as MDM2 protein degraders for the treatment of breast cancer. *Eur. J. Med. Chem.* **2024**, *270*, 116367. [CrossRef]
51. Xie, H.; Shi, H. Current status and advances in inflammation research. *Electron. J. Metab. Nutr. Cancer* **2024**, *11*, 9–19. [CrossRef]
52. Liu, C.; Dunkin, D.; Lai, J.; Song, Y.; Ceballos, C.; Benkov, K.; Li, X.M. Anti-inflammatory Effects of *Ganoderma lucidum* Triterpenoid in Human Crohn's Disease Associated with Downregulation of NF-κB Signaling. *Inflamm. Bowel Dis.* **2015**, *21*, 1918–1925. [CrossRef] [PubMed]
53. Liu, C.; Yang, N.; Song, Y.; Wang, L.; Zi, J.; Zhang, S.; Dunkin, D.; Busse, P.; Weir, D.; Tversky, J.; et al. Ganoderic acid C1 isolated from the anti-asthma formula, ASHMI™ suppresses TNF-α production by mouse macrophages and peripheral blood mononuclear cells from asthma patients. *Int. Immunopharmacol.* **2015**, *27*, 224–231. [CrossRef]
54. Wan, B.; Li, Y.; Sun, S.; Yang, Y.; Lv, Y.; Wang, L.; Song, M.; Chen, M.; Wu, C.; Pan, H.; et al. Ganoderic acid A attenuates lipopolysaccharide-induced lung injury in mice. *Biosci. Rep.* **2019**, *39*, BSR20190301. [CrossRef]
55. Wen, G.; Li, T.; He, H.; Zhou, X.; Zhu, J. Ganoderic Acid A Inhibits Bleomycin-Induced Lung Fibrosis in Mice. *Pharmacology* **2020**, *105*, 568–575. [CrossRef] [PubMed]

56. Ahmad, M.F.; Ahmad, F.A.; Khan, M.I.; Alsayegh, A.A.; Wahab, S.; Alam, M.I.; Ahmed, F. *Ganoderma lucidum*: A potential source to surmount viral infections through β-glucans immunomodulatory and triterpenoids antiviral properties. *Int. J. Biol. Macromol.* **2021**, *187*, 769–779. [CrossRef]
57. Cheng, J.; Huang, H.; Chen, Y.; Wu, R. Nanomedicine for Diagnosis and Treatment of Atherosclerosis. *Adv. Sci.* **2023**, *10*, e2304294. [CrossRef]
58. Quan, Y.Z.; Ma, A.; Ren, C.Q.; An, Y.P.; Qiao, P.S.; Gao, C.; Zhang, Y.K.; Li, X.W.; Lin, S.M.; Li, N.N.; et al. Ganoderic acids alleviate atherosclerosis by inhibiting macrophage M1 polarization via TLR4/MyD88/NF-κB signaling pathway. *Atherosclerosis* **2024**, *391*, 117478. [CrossRef]
59. Wang, T.; Lu, H. Ganoderic acid A inhibits ox-LDL-induced THP-1-derived macrophage inflammation and lipid deposition via Notch1/PPARγ/CD36 signaling. *Adv. Clin. Exp. Med.* **2021**, *30*, 1031–1041. [CrossRef]
60. Zheng, G.; Zhao, Y.; Li, Z.; Hua, Y.; Zhang, J.; Miao, Y.; Guo, Y.; Li, L.; Shi, J.; Dong, Z.; et al. GLSP and GLSP-derived triterpenes attenuate atherosclerosis and aortic calcification by stimulating ABCA1/G1-mediated macrophage cholesterol efflux and inactivating RUNX2-mediated VSMC osteogenesis. *Theranostics* **2023**, *13*, 1325–1341. [CrossRef]
61. Cao, T.; Tang, C.; Xue, L.; Cui, M.; Wang, D. Protective effect of Ganoderic acid A on adjuvant-induced arthritis. *Immunol. Lett.* **2020**, *226*, 1–6. [CrossRef] [PubMed]
62. Wu, W.; Song, K.; Chen, G.; Liu, N.; Cao, T. Ganoderic acid A improves osteoarthritis by regulating RANKL/OPG ratio. *Chem. Biol. Drug Des.* **2022**, *100*, 313–319. [CrossRef]
63. Liu, Y.; Zhou, C.; Tan, J.; Wu, T.; Pan, C.; Liu, J.; Cheng, X. Ganoderic acid A slows osteoarthritis progression by attenuating endoplasmic reticulum stress and blocking NF-Kb pathway. *Chem. Biol. Drug Des.* **2024**, *103*, e14382. [CrossRef]
64. Lu, X.; Xu, C.; Yang, R.; Zhang, G. Ganoderic Acid A Alleviates OVA-Induced Asthma in Mice. *Inflammation* **2021**, *44*, 1908–1915. [CrossRef]
65. Liu, C.; Cao, M.; Yang, N.; Reid-Adam, J.; Tversky, J.; Zhan, J.; Li, X.M. Time-dependent dual beneficial modulation of interferon-γ, interleukin 5, and Treg cytokines in asthma patient peripheral blood mononuclear cells by ganoderic acid B. *Phytother. Res. PTR* **2022**, *36*, 1231–1240. [CrossRef]
66. Wang, Z.Z.; Li, H.; Maskey, A.R.; Srivastava, K.; Liu, C.; Yang, N.; Xie, T.; Fu, Z.; Li, J.; Liu, X.; et al. The Efficacy & Molecular Mechanisms of a Terpenoid Compound Ganoderic Acid C1 on Corticosteroid-Resistant Neutrophilic Airway Inflammation: In vivo and in vitro Validation. *J. Inflamm. Res.* **2024**, *17*, 2547–2561. [CrossRef]
67. Sheng, F.; Zhang, L.; Wang, S.; Yang, L.; Li, P. Deacetyl Ganoderic Acid F Inhibits LPS-Induced Neural Inflammation via NF-κB Pathway Both In Vitro and In Vivo. *Nutrients* **2019**, *12*, 85. [CrossRef]
68. Jia, Y.; Zhang, D.; Yin, H.; Li, H.; Du, J.; Bao, H. Ganoderic Acid A Attenuates LPS-Induced Neuroinflammation in BV2 Microglia by Activating Farnesoid X Receptor. *Neurochem. Res.* **2021**, *46*, 1725–1736. [CrossRef]
69. Jia, Y.; Zhang, D.; Li, H.; Luo, S.; Xiao, Y.; Han, L.; Zhou, F.; Wang, C.; Feng, L.; Wang, G.; et al. Activation of FXR by ganoderic acid A promotes remyelination in multiple sclerosis via anti-inflammation and regeneration mechanism. *Biochem. Pharmacol.* **2021**, *185*, 114422. [CrossRef]
70. Zheng, S.; Ma, J.; Zhao, X.; Yu, X.; Ma, Y. Ganoderic Acid A Attenuates IL-1β-Induced Inflammation in Human Nucleus Pulposus Cells Through Inhibiting the NF-κB Pathway. *Inflammation* **2022**, *45*, 851–862. [CrossRef]
71. Wang, D.; Cai, X.; Xu, F.; Kang, H.; Li, Y.; Feng, R. Ganoderic Acid A alleviates the degeneration of intervertebral disc via suppressing the activation of TLR4/NLRP3 signaling pathway. *Bioengineered* **2022**, *13*, 11684–11693. [CrossRef]
72. Shao, C.S.; Feng, N.; Zhou, S.; Zheng, X.X.; Wang, P.; Zhang, J.S.; Huang, Q. Ganoderic acid T improves the radiosensitivity of HeLa cells via converting apoptosis to necroptosis. *Toxicol. Res.* **2021**, *10*, 531–541. [CrossRef]
73. Kang, L.H.; Zhang, G.W.; Zhang, J.F.; Qin, B.; Guan, H.J. Ganoderic acid A protects lens epithelial cells from UVB irradiation and delays lens opacity. *Chin. J. Nat. Med.* **2020**, *18*, 934–940. [CrossRef]
74. Li, L.D.; Mao, P.W.; Shao, K.D.; Bai, X.H.; Zhou, X.W. *Ganoderma proteins* and their potential applications in cosmetics. *Appl. Microbiol. Biotechnol.* **2019**, *103*, 9239–9250. [CrossRef]
75. Abate, M.; Pepe, G.; Randino, R.; Pisanti, S.; Basilicata, M.G.; Covelli, V.; Bifulco, M.; Cabri, W.; D'Ursi, A.M.; Campiglia, P.; et al. *Ganoderma lucidum* Ethanol Extracts Enhance Re-Epithelialization and Prevent Keratinocytes from Free-Radical Injury. *Pharmaceuticals* **2020**, *13*, 224. [CrossRef]
76. Xu, Y.; Yuan, H.; Luo, Y.; Zhao, Y.J.; Xiao, J.H. Ganoderic Acid D Protects Human Amniotic Mesenchymal Stem Cells against Oxidative Stress-Induced Senescence through the PERK/NRF2 Signaling Pathway. *Oxid. Med. Cell. Longev.* **2020**, *13*, 8291413. [CrossRef]
77. Yuan, H.; Xu, Y.; Luo, Y.; Zhang, J.R.; Zhu, X.X.; Xiao, J.H. Ganoderic acid D prevents oxidative stress-induced senescence by targeting 14-3-3ε to activate CaM/CaMKII/NRF2 signaling pathway in mesenchymal stem cells. *Aging Cell* **2022**, *21*, e13686. [CrossRef]
78. Shen, S.; Wang, X.; Lv, H.; Shi, Y.; Xiao, L. 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.* **2021**, *85*, 1818–1829. [CrossRef]
79. Qi, L.F.; Liu, S.; Liu, Y.C.; Li, P.; Xu, X. 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.* **2021**, *22*, 5559. [CrossRef]

80. Zhang, Y.; Wang, X.; Yang, X.; Yang, X.; Xue, J.; Yang, Y. 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.* **2021**, *69*, 14204–14214. [CrossRef]
81. Liu, L.Y.; Chen, H.; Liu, C.; Wang, H.Q.; Kang, J.; Li, Y.; Chen, R.Y. Triterpenoids of *Ganoderma theaecolum* and their hepatoprotective activities. *Fitoterapia* **2014**, *98*, 254–259. [CrossRef] [PubMed]
82. Lixin, X.; Lijun, Y.; Songping, H. Ganoderic acid A against cyclophosphamide-induced hepatic toxicity in mice. *J. Biochem. Mol. Toxicol.* **2019**, *33*, e22271. [CrossRef] [PubMed]
83. Zhang, X.; Gao, X.; Long, G.; Yang, Y.; Chen, G.; Hou, G.; Huo, X.; Jia, J.; Wang, A.; Hu, G. Lanostane-type triterpenoids from the mycelial mat of *Ganoderma lucidum* and their hepatoprotective activities. *Phytochemistry* **2022**, *198*, 113131. [CrossRef] [PubMed]
84. Zheng, C.; Lv, S.; Ye, J.; Zou, L.; Zhu, K.; Li, H.; Dong, Y.; Li, L. Metabolomic Insights into the Mechanisms of Ganoderic Acid: Protection against α-Amanitin-Induced Liver Injury. *Metabolites* **2023**, *13*, 1164. [CrossRef]
85. Xiao, C.; Huang, G.; Cao, X.; Li, X. Ganoderic acid A attenuated hepatic impairment by down-regulating the intracellular JAK2-STAT3 signaling pathway in induced mushroom poisoning. *Am. J. Transl. Res.* **2024**, *16*, 295–303. [CrossRef]
86. Liu, F.; Shi, K.; Dong, J.; Jin, Z.; Wu, Y.; Cai, Y.; Lin, T.; Cai, Q.; Liu, L.; Zhang, Y. Ganoderic acid A attenuates high-fat-diet-induced liver injury in rats by regulating the lipid oxidation and liver inflammation. *Arch. Pharmacal Res.* **2020**, *43*, 744–754. [CrossRef]
87. Zhu, J.; Ding, J.; Li, S.; Jin, J. Ganoderic acid A ameliorates non-alcoholic streatohepatitis (NASH) induced by high-fat high-cholesterol diet in mice. *Exp. Ther. Med.* **2022**, *23*, 308. [CrossRef]
88. 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. Ganoderic acid A from *Ganoderma lucidum* protects against alcoholic liver injury through ameliorating the lipid metabolism and modulating the intestinal microbial composition. *Food Funct.* **2022**, *13*, 5820–5837. [CrossRef]
89. Li, Y.Q.; Wang, S.F. Anti-hepatitis B activities of ganoderic acid from *Ganoderma lucidum*. *Biotechnol. Lett.* **2006**, *28*, 837–841. [CrossRef]
90. el-Mekkawy, S.; Meselhy, M.R.; Nakamura, N.; Tezuka, Y.; Hattori, M.; Kakiuchi, N.; Shimotohno, K.; Kawahata, T.; Otake, T. Anti-HIV-1 and anti-HIV-1-protease substances from *Ganoderma lucidum*. *Phytochemistry* **1998**, *49*, 1651–1657. [CrossRef]
91. Sato, N.; Zhang, Q.; Ma, C.M.; Hattori, M. Anti-human immunodeficiency virus-1 protease activity of new lanostane-type triterpenoids from *Ganoderma sinense*. *Chem. Pharm. Bull.* **2009**, *57*, 1076–1080. [CrossRef] [PubMed]
92. Zhang, W.; Tao, J.; Yang, X.; Yang, Z.; Zhang, L.; Liu, H.; Wu, K.; Wu, J. Antiviral effects of two *Ganoderma lucidum* triterpenoids against enterovirus 71 infection. *Biochem. Biophys. Res. Commun.* **2014**, *449*, 307–312. [CrossRef] [PubMed]
93. Jiang, L.; Zhang, W.; Zhai, D.D.; Wan, G.; Xia, S.; Meng, J.; Shi, P.; Chen, N. Transcriptome profiling and bioinformatic analysis of the effect of ganoderic acid T prevents Sendai virus infection. *Gene* **2023**, *862*, 147252. [CrossRef] [PubMed]
94. Zhang, W.; Yu, W.; Ding, X.; Yin, C.; Yan, J.; Yang, E.; Guo, F.; Sun, D.; Wang, W. Self-assembled thermal gold nanorod-loaded thermosensitive liposome-encapsulated ganoderic acid for antibacterial and cancer photochemotherapy. *Artif. Cells Nanomed. Biotechnol.* **2019**, *47*, 406–419. [CrossRef]
95. Nguyen, T.T.T.; Nguyen, T.T.T.; Nguyen, H.D.; Nguyen, T.K.; Pham, P.T.V.; Tran, L.T.T.; Pham, H.K.T.; Truong, P.C.H.; Tran, L.T.; Tran, M.H. Anti-Staphylococcus aureus potential of compounds from *Ganoderma* sp.: A comprehensive molecular docking and simulation approaches. *Heliyon* **2024**, *10*, e28118. [CrossRef]
96. Tajik, A.; Samadlouie, H.R.; Salek Farrokhi, A.; Ghasemi, A. Optimization of chemical conditions for metabolites production by *Ganoderma lucidum* using response surface methodology and investigation of antimicrobial as well as anticancer activities. *Front. Microbiol.* **2024**, *14*, 1280405. [CrossRef]
97. Abulizi, A.; Ran, J.; Ye, Y.; An, Y.; Zhang, Y.; Huang, Z.; Lin, S.; Zhou, H.; Lin, D.; Wang, L.; et al. Ganoderic acid improves 5-fluorouracil-induced cognitive dysfunction in mice. *Food Funct.* **2021**, *12*, 12325–12337. [CrossRef]
98. Abulizi, A.; Hu, L.; Ma, A.; Shao, F.Y.; Zhu, H.Z.; Lin, S.M.; Shao, G.Y.; Xu, Y.; Ran, J.H.; Li, J.; et al. Ganoderic acid alleviates chemotherapy-induced fatigue in mice bearing colon tumor. *Acta Pharmacol. Sin.* **2021**, *42*, 1703–1713. [CrossRef]
99. Zhang, L.; Zhang, L.; Sui, R. 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.* **2021**, *17*, 2671–2681. [CrossRef]
100. Bao, H.; Li, H.; Jia, Y.; Xiao, Y.; Luo, S.; Zhang, D.; Han, L.; Dai, L.; Xiao, C.; Feng, L.; et al. Ganoderic acid A exerted antidepressant-like action through FXR modulated NLRP3 inflammasome and synaptic activity. *Biochem. Pharmacol.* **2021**, *188*, 114561. [CrossRef]
101. Xu, J.J.; Kan, W.J.; Wang, T.Y.; Li, L.; Zhang, Y.; Ge, Z.Y.; Xu, J.Y.; Yin, Z.J.; Feng, Y.; Wang, G.; et al. Ganoderic acid A ameliorates depressive-like behaviors in CSDS mice: Insights from proteomic profiling and molecular mechanisms. *J. Affect. Disord.* **2024**, *358*, 270–282. [CrossRef] [PubMed]
102. Li, Q.M.; Wu, S.Z.; Zha, X.Q.; Zang, D.D.; Zhang, F.Y.; Luo, J.P. Ganoderic acid A mitigates dopaminergic neuron ferroptosis via inhibiting NCOA4-mediated ferritinophagy in Parkinson's disease mice. *J. Ethnopharmacol.* **2024**, *332*, 118363. [CrossRef] [PubMed]
103. Yu, Z.R.; Jia, W.H.; Liu, C.; Wang, H.Q.; Yang, H.G.; He, G.R.; Chen, R.Y.; Du, G.H. Ganoderic acid A protects neural cells against NO stress injury in vitro via stimulating β adrenergic receptors. *Acta Pharmacol. Sin.* **2020**, *41*, 516–522. [CrossRef] [PubMed]
104. Cui, J.; Meng, Y.H.; Wang, Z.W.; Wang, J.; Shi, D.F.; Liu, D. Ganoderic Acids A and B Reduce Okadaic Acid-Induced Neurotoxicity in PC12 Cells by Inhibiting Tau Hyperphosphorylation. *Biomed. Environ. Sci. BES* **2023**, *36*, 103–108. [CrossRef]

105. Meng, J.; Wang, S.-Z.; He, J.Z.; Zhu, S.; Huang, B.Y.; Wang, S.Y.; Li, M.; Zhou, H.; Lin, S.Q.; Yang, B.X. Ganoderic acid A is the effective ingredient of *Ganoderma triterpenes* in retarding renal cyst development in polycystic kidney disease. *Acta Pharmacol. Sin.* **2020**, *41*, 782–790. [CrossRef]
106. Geng, X.Q.; Ma, A.; He, J.Z.; Wang, L.; Jia, Y.L.; Shao, G.Y.; Li, M.; Zhou, H.; Lin, S.Q.; Ran, J.H.; et al. Ganoderic acid hinders renal fibrosis via suppressing the TGF-β/Smad and MAPK signaling pathways. *Acta Pharmacol. Sin.* **2020**, *41*, 670–677. [CrossRef]
107. Ma, J.Q.; Zhang, Y.J.; Tian, Z.K. 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.* **2021**, *344*, 109529. [CrossRef]
108. Liu, D.L.; Li, Y.J.; Yang, D.H.; Wang, C.R.; Xu, J.; Yao, N.; Zhang, X.Q.; Chen, Z.S.; Ye, W.C.; Zhang, D.M. *Ganoderma lucidum* derived ganoderenic acid B reverses ABCB1-mediated multidrug resistance in HepG2/ADM cells. *Int. J. Oncol.* **2015**, *46*, 2029–2038. [CrossRef]
109. Luo, B.; Song, L.; Chen, L.; Cai, Y.; Zhang, M.; Wang, S. Ganoderic acid D attenuates gemcitabine resistance of triple-negative breast cancer cells by inhibiting glycolysis via HIF-1α destabilization. *Phytomedicine* **2024**, *129*, 155675. [CrossRef]
110. Guo, W.L.; Guo, J.B.; Liu, B.Y.; Lu, J.Q.; Chen, M.; Liu, B.; Bai, W.D.; Rao, P.F.; Ni, L.; Lv, X.C. Ganoderic acid A from *Ganoderma lucidum* ameliorates lipid metabolism and alters gut microbiota composition in hyperlipidemic mice fed a high-fat diet. *Food Funct.* **2020**, *11*, 6818–6833. [CrossRef]
111. Xu, S.; Zhang, F.; Chen, D.; Su, K.; Zhang, L.; Jiang, R. In vitro inhibitory effects of ganoderic acid A on human liver cytochrome P450 enzymes. *Pharm. Biol.* **2020**, *58*, 308–313. [CrossRef] [PubMed]
112. Singh, A.B.; Gupta, S.K.; Pereira, B.M.; Prakash, D. Sensitization to *Ganoderma lucidum* in patients with respiratory allergy in India. *Clin. Exp. Allergy* **1995**, *25*, 440–447. [CrossRef] [PubMed]
113. Rivera-Mariani, F.E.; Nazario-Jiménez, S.; López-Malpica, F.; Bolaños-Rosero, B. Sensitization to airborne ascospores, basidiospores, and fungal fragments in allergic rhinitis and asthmatic subjects in San Juan, Puerto Rico. *Int. Arch. Allergy Immunol.* **2011**, *155*, 322–334. [CrossRef] [PubMed]
114. Gill, B.S.; Sharma, P.; Kumar, R.; Kumar, S. Misconstrued versatility of *Ganoderma lucidum*: A key player in multi-targeted cellular signaling. *Tumour Biol.* **2016**, *37*, 2789–2804. [CrossRef]
115. Dulay, R.M.; Kalaw, S.P.; Reyes, R.G.; Alfonso, N.F.; Eguchi, F. Teratogenic and toxic effects of Lingzhi or Reishi medicinal mushroom, *Ganoderma lucidum* (W.Curt.:Fr.) P. Karst. (higher Basidiomycetes), on zebrafish embryo as model. *Int. J. Med. Mushrooms* **2012**, *14*, 507–512. [CrossRef]

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