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REVIEW ARTICLE

Ginsenoside Rg1 in neurological diseases: From bench to bedside

Shao-jie Yang[1], Jing-ji Wang[2], Ping Cheng[1], Li-xia Chen[1], Jia-min Hu[1] and Guo-qi Zhu[1]

Ginseng has been used in China as a superior medicinal material for thousands of years that can nourish the five internal organs, calm the mind and benefit wisdom. Due to its anti-inflammatory, antioxidant and neuroprotective activities, one of the active components of ginseng, ginsenoside Rg1, has been extensively investigated in the remedy of brain disorders, especially dementia and depression. In this review, we summarized the research progress on the action mechanisms of Rg1 ameliorating depression-like behaviors, including inhibition of hyperfunction of hypothalamic-pituitary-adrenal (HPA) axis, regulation of synaptic plasticity and gut flora. Rg1 may alleviate Alzheimer's disease in the early phase, as well as in the middle-late phases through repairing dendrite, axon and microglia- and astrocyte-related inflammations. We also proposed that Rg1 could regulate memory state (the imbalance of working and aversive memory) caused by distinct stimuli. These laboratory studies would further the clinical trials on Rg1. From the prospective of drug development, we discussed the limitations of the present investigations and proposed our ideas to increase permeability and bioavailability of Rg1. Taken together, Rg1 has the potential to treat neuropsychiatric disorders, but a future in-depth investigation of the mechanisms is still required. In addition, drug development will benefit from the clinical trials in one specific neuropsychiatric disorder.

Keywords: ginsenoside Rg1; neurological disease; depression; Alzheimer's disease; learning and memory

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INTRODUCTION

Neurological disorder is a general term for nervous system diseases and psychiatric diseases. It is a series of diseases that occur in the central nervous system (CNS) or peripheral nervous system and are mainly manifested by sensory, cognitive, emotional, behavioral and psychological disorders [1]. Neurological disorders, especially dementia and depression not only bring great pain to patients, but also increase the medical economic burden. Most worryingly, neurological disorders have become a major source of disability globally, with an increasing prevalence [2]. Alzheimer's disease (AD) and depression are two types of common and highly prevalent neurological disorders. Statistically, the number of AD patients is increasing year by year, and AD has become a fast-growing neurological disorder. From 1990–2015, the growth rate of AD patients was 111.7% and the mortality rate increased by 14.9%, and the number has reached 45,956,000, which may still continue to rise, as predicted from the analysis of population data [3]. Depression is not only a high incidence, but also a leading cause of disability and suicide worldwide. In the last 20 years, the rate of depression-induced suicide in the United States alone has increased by 35%. Treatment for depression will thus have significant medical and economic costs, which are expected to double by 2030 [4]. Of concern, human genetic and epidemiological studies have elucidated that depression may be a risk factor or early symptom of AD, and that 30%–40% of AD patients experience depression during disease progression [5, 6]. The risk of comorbidity of depression and AD is much greater than that of depression or AD. Therefore, it is more important to prevent the occurrence of comorbidity in the treatment of depression and AD. The medical community is still persistently developing chemical drugs that can treat AD, as well as depression, but the success rate is low [7]. Therefore, many researchers began to change their exploratory thinking and seek answers from natural components [8, 9].

Ginseng is derived from the root and rhizome of *Panax ginseng* C.A. Mey, a plant of *Araliaceae*. It has been used as a medicine in China for thousands of years. As recorded in *Sheng Nong's herbal classic* (the earliest pharmaceutical book in China), ginseng is proposed as a superior medicinal material. It is believed that ginseng can nourish the five internal organs, calm the mind and benefit wisdom, and taking ginseng for a long time has the effect of prolonging life. Because of its unique beneficial effect and the rarity of wild species resources, ginseng has become a valuable traditional Chinese medicine. Nowadays, ginseng is not only widely used in the prevention and treatment of diseases in traditional Chinese medicine, but also plays an important role in ethnic medicine in Republic of Korea, Democratic People's Republic of Korea, Japan and other countries [10]. Modern pharmacological studies have shown that the main active substances of ginseng are ginsenosides, such as ginsenoside Rb1 (Rb1), ginsenoside Rg1 (Rg1) and ginsenoside Rg3 (Rg3), etc. These steroidal saponins have a variety of pharmacological effects

[1]Key Laboratory of Xin'an Medicine, the Ministry of Education and Key Laboratory of Molecular Biology (Brain diseases), Anhui University of Chinese Medicine, Hefei 230012, China and [2]The Second Affiliation Hospital of Anhui University of Chinese Medicine, Hefei 230061, China
Correspondence: Jing-ji Wang (wjjglacial@163.com) or Guo-qi Zhu (guoqizhu@gmail.com)

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Table 1. Ginsenosides and therapeutic potential.

Ginsenosides	Molecular formula	Effects	References
Ra1	$C_{58}H_{98}O_{26}$	Immune regulation, treatment of coronary artery disease and cancer	[106, 107]
Ra2	$C_{58}H_{98}O_{26}$	Treatment of coronary artery disease and cancer	[107]
Ra3	$C_{59}H_{100}O_{27}$	Treatment of coronary artery disease and cancer	[107]
Rb1	$C_{54}H_{92}O_{23}$	Anti-angiogenic effect, anti-inflammatory effect, cardioprotective effect, anti-aging effect, anti-diabetic effect, antidepressant effect, neuroprotective effect, preventing alcoholic liver disease, ischemic stroke, AD, PD	[58, 108–117]
Rb2	$C_{53}H_{90}O_{22}$	Proangiogenic effect, neuroprotective effect, anti-inflammatory effect, attenuating platelet function, alleviating obesity, treatment of colorectal cancer	[118–123]
Rb3	$C_{53}H_{90}O_{22}$	Cardioprotective effect, alleviating lung and kidney injury	[124–126]
Rc	$C_{53}H_{90}O_{22}$	Cardioprotective effect and anti-inflammatory effect	[127, 128]
Rd	$C_{48}H_{82}O_{18}$	Alleviating lung injury, attenuating autoimmune neuritis, preventing cardiovascular diseases, ameliorating auditory cortex injury, alleviating anxiety/depression, ameliorating obesity	[129–134]
Re	$C_{48}H_{82}O_{18}$	Anti-diabetic, inhibiting neointimal thickening, alleviating cognitive deficits, attenuating myocardial injury	[135–138]
Rf	$C_{42}H_{72}O_{14}$	Anti-melanogenic effect, antidepressant effect, anti-inflammatory effect, antinociceptive effect	[139–142]
Rg1	$C_{42}H_{72}O_{14}$	Ameliorating traumatic brain injury, preventing cognitive impairment, cardioprotective effect, AD, PD, treatment of inflammatory bowel disease and diabetes, attenuating depression, preventing cell senescence, alleviating liver injury, ameliorating reproductive function injury, preventing post-traumatic stress disorder (PTSD), Huntington's disease (HD), ameliorating glomerular fibrosis, promoting sleep	[47, 56, 78, 80, 90, 104, 143–152]
Rg2	$C_{42}H_{72}O_{13}$	Ameliorating brain injury, affecting cell growth, improving memory impairment and neuronal death, antiarrhythmic effect, decreasing lipogenesis	[153–156]
Rg3	$C_{42}H_{72}O_{13}$	Ameliorating heart failure, anti-inflammatory effect and attenuating skin inflammatory diseases, alleviating bone impairment, attenuating cellular senescence, anti-angiogenic effect, alleviating endothelial dysfunction, preventing atherosclerosis, inhibiting hepatocellular carcinoma and gastric ulcer	[157–165]
Rh1	$C_{36}H_{62}O_{9}$	Immune regulation, improving diabetic nephropathy, alleviating cognitive deficits	[106, 166, 167]
Rh2	$C_{36}H_{62}O_{8}$	Anti-tumor effect, antibacterial and antiviral activity, anti-inflammatory effect, improving memory deficits, immune regulation, alleviating lung injury	[168–174]
Rh3	$C_{37}H_{62}O_{7}$	Anti-inflammatory effect and renoprotective effect	[175, 176]

(Table 1). As one of the main components of ginseng, Rg1 has attracted wide attention in the prevention of neurological disorders, especially in dementia and depression. In order to further the development of Rg1, this review focuses on the recent experimental studies of Rg1 in depression, AD, and learning and memory dysfunction, and summarizes the mechanism of Rg1 in the treatment of dementia and depression. At the same time, the clinical potential of Rg1 and challenges are extensively discussed.

THE REASONS FOR RG1 IN TREATMENT OF DEPRESSION AND ALZHEIMER'S DISEASE

Although depression and AD belong to two different types of neurological disorders, the presence of comorbidity suggests that the two diseases are related, and the occurrence of depression and AD has the same mechanisms and targets. To support that point of view, antidepressants, like paroxetine could also improve AD [11]. This provided an important basis for Rg1 to effectively treat both depression and AD. In fact, the common pathological features of depression and AD include synaptic damage, oxidative stress and inflammatory response, etc [12–14].

Synaptic deficit is an important factor leading to depression and AD. As an important neurotrophic factor, brain-derived neurotrophic factor (BDNF) could prevent neuronal apoptosis and synaptic deficit by activating downstream tropomyosin receptor kinase B (TrkB) and mitogen-activated protein kinase (MAPK)/extracellular regulated protein kinase (ERK) signaling pathways [15]. AD studies revealed that the decrease of BDNF in the brain was inversely proportional to the increase of amyloid β-protein (Aβ), and BDNF had an antagonistic effect on Aβ toxicity [16, 17]. In depression, the decrease of BDNF reduced the formation of hippocampal neurons and the activity of downstream signaling molecules, leading to depressive behavior [18]. Excitotoxicity caused by excessive activation of *N*-methyl-*D*-aspartate receptor (NMDAR) is considered to be the common pathophysiological basis of depression and AD. In AD, Aβ-induced synaptic inhibition was related to the activation of NMDAR caused by glutamate overrelease, and the activation of extra-synaptic NMDAR induced the overexpression of Tau [19, 20]. Our team also found that depression-like behavior and hippocampal synaptic dysfunctions could be antagonized by inhibiting the overactivation of NMDAR and calpain, which is consistent with the results of many antidepressant drugs [21].

In AD, mitochondrial dysfunction could lead to excessive ROS production, subsequently causing oxidative damage of protein, DNA and RNA, and promote the appearance of clinical symptoms and Aβ pathology of AD [22]. Clinical study also supported the involvement of DNA oxidative damage in the early phase of AD development [23]. In depression, the increase of ROS regulated the activation of hypothalamic-pituitary-adrenal (HPA) axis, thus increasing oxidative stress damage [24]. Therefore, the inhibition of HPA axis is also one of the mechanisms of antidepressants [25].

Table 2. Differences in brain regions, damage degree and reversibility between depression and Alzheimer's disease.

	Depression	Alzheimer's disease
Brain regions	Prefrontal cortex, hippocampus, amygdala, ventral tegmental area-nucleus accumbens, striatum, anterior cingulate cortex, insula [177–180]	Cingulate, cerebellum, parietal, thalamus, hippocampus, prefrontal cortex, frontal, temporal, amygdala [71, 181–183]
Damage degree	The pathological damage of depression is mainly manifested by neuronal damage (including neuronal atrophy/apoptosis and synaptic number reduction), and the volume reduction of PFC and hippocampus [184–186]	The pathological damage of AD is characterized by neurofibrillary tangles, senile plaques, neuronal degeneration/loss/apoptosis, and synaptic loss, and atrophy in various brain regions, with the hippocampus being the most severe [187–189]
Reversibility	Neuronal damage and reduction of brain region volume could be rescued or relieved [38, 190, 191]	Hippocampal atrophy is irreversible, but neuronal damage could be reduced by drugs [192, 193]

Clinical study revealed that oxidative stress, especially lipid peroxidation, in elderly patients with depression was significantly higher than that in non-depressed ones [26].

Neuroinflammation is the most common pathogenic factor in neurological diseases and plays a catalytic role in the occurrence of depression and AD. In the pathological state of depression, the activation of microglia resulted in the production and release of inflammatory factors, including interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), which further mediated the depressive symptoms and dysfunction of synaptic plasticity [27]. Therefore, anti-inflammation is an effective way to fight against depression. Similarly, in the early stage of AD, Aβ could activate microglia, promote neuroinflammation, damage synaptic function and cause neuronal death [28]. In our study, it has also been confirmed that improving neuroinflammation is beneficial for the prevention of AD-like phenotypes [29].

In addition to the common pathological mechanisms of synaptic damage, oxidative stress and inflammation, we also analyzed the differences in brain regions, damage degree and reversibility between depression and AD. These similarities of pathogenesis and molecular mechanisms for the two disorders would be beneficial for the understanding of the treatment of depression and AD with Rg1 (Table 2).

RG1 AND DEPRESSION

It is believed that the occurrence of depression is mainly related to the dysfunction of HPA axis [30], impairment of synaptic plasticity [31], disturbance of neuronal regeneration [32], increased release of inflammatory factors and increased level of oxidative stress [27]. According to the meta-analysis of the antidepressant effect of ginsenosides on animal model of depression, Rg1 is one of the most investigated ginsenosides [33]. Although the antidepressant mechanism of Rg1 has not been clearly elucidated, the improvement effect of Rg1 on depression has been verified in several well-recognized pathogenesis of depression. Rg1 may exert its antidepressant effect by inhibiting the hyperfunction of HPA axis, regulating synaptic plasticity, inhibiting neuroinflammation and oxidative stress at the same time (Table 3, Fig. 1).

Rg1 inhibits the hyperfunction of HPA axis

As an important neuroendocrine system in the body, HPA axis is involved in the regulation of stress and emotional coordination [34]. Research has shown that the HPA axis feedback loop is closely related to the occurrence of depression, and affects the occurrence and development of depression by acting on the neuroendocrine system and the neuroimmune system [35]. Therefore, the effective regulation of HPA axis has become an important antidepressant stratagem.

Mou et al. used chronic unpredictable mild stress (CUMS) rats to evaluate the antidepressant effect of Rg1. The results showed that the CUMS rats showed obvious depression-like behavior, and the level of serum corticosterone (CORT) increased and the expression of glucocorticoid receptor decreased in the hippocampus. After oral administration of Rg1, the depression-like behaviors were alleviated, the level of serum CORT decreased and the expression of glucocorticoid receptor increased in CUMS rats [36]. Zheng et al. established a rat model of depression induced by lipopolysaccharide (LPS). Sucrose consumption test showed that the modeled rats showed depression-like behaviors, and the levels of IL-1β, IL-6, TNF-α and plasma CORT were significantly higher than those of the control rats. After intraperitoneal injection of Rg1, the depression-like behaviors of the modeled rats were significantly improved, and the contents of pro-inflammatory factors and plasma CORT were down-regulated [37]. Jiang et al. also found that Rg1 could reduce the abnormal increase of serum CORT in chronic mild stress (CMS) depressed mice [9]. This study shows that the mechanism of Rg1 in improving depression-like behavior is not only due to its anti-inflammatory effect, but also related to the fact that Rg1 can block neuroendocrine disorders. Based on those results, we believe that down-regulating the level of CORT in depression model, increasing the expression of glucocorticoid receptor protein and inhibiting the hyperfunction of HPA axis are the important mechanisms underlying antidepressant effect of Rg1.

Rg1 regulates synaptic plasticity

Depression-like behaviors are closely linked to interruption of key signaling pathways in synaptogenesis, and at the cellular and molecular levels, are also characterized by neuronal atrophy and a decrease in the number of synapses in the prefrontal cortex (PFC) or hippocampus [38, 39]. Rg1 has excellent neuroprotective effect and can theoretically prevent synaptic deficit during depression, which is also confirmed by experimental results.

Fan et al. found that CUMS rats exhibited depression-like behaviors, with reduced dendritic spine density and synapse numbers in the ventral medial prefrontal cortex (vmPFC) region, and decreased expression of cAMP response element-binding protein (CREB), BDNF, postsynaptic density protein 95 (PSD95), and synapsin. Intraperitoneal injection of Rg1 could ameliorate the depression-like behaviors and the decreased expression of synaptic-related proteins in CUMS rats [40]. Liu et al. also explored the antidepressant effects and neuroprotective mechanism of Rg1 in CUMS rat model. The results showed that CUMS rats had decreased number and density of synapses in basolateral amygdala (BLA) neurons, as well as low levels of protein kinase A (PKA), CREB and BDNF in the BLA. Five-week intraperitoneal injection of Rg1 improved the number and density of synapses of BLA neurons, and the expression of PKA, CREB and BDNF [41]. Similarly, Rg1 can also reverse the decrease of CREB and BDNF in the PFC of CUMS rats [42].

Rg1 has antidepressant-like effect not only in depressed rats, but also in depressed mice. In the study of the antidepressant effect of Rg1 on CMS mice, Jiang et al. found that CMS mice showed decrease in neurogenesis and dendritic spine density, and a low expression level of BDNF in the hippocampus. Rg1 can

Table 3. Main mechanism and effect sites of Rg1 on depression.

Animal or cell line	Model	Main mechanism	Effect sites (receptor, cell, axon or dendrite)	Reference
Male kunming mice and male Sprague-Dawley rats	CUMS	Regulating the HPA and the hypothalamic-pituitary-gonadal (HPG) axis	Glucocorticoid receptor (GR) and androgen receptor (AR)	[36]
Male Wistar rats	LPS treatment	Regulation of neuroinflammation by targeting the peripheral immune system	Microglia	[37]
Male C57BL/6 J mice	CMS	Activation of the BDNF signaling pathway and up-regulation of hippocampal neurogenesis	Progenitor cells in DG and pyramidal neurons dendrite in CA3	[9]
Male Wistar rats	CUMS	Anti-inflammatory effect, improve neuronal structural changes and anti-apoptosis	Microglia, astrocytes, and dendrite and synapse of vmPFC neurons	[40]
Male Wistar rats	CUMS	Regulating the CREB-BDNF pathway within the amygdala	Amygdala neurons	[41]
Male C57BL/6 J mice	CUMS	Regulation of hippocampal synaptic proteins and inhibition of inflammatory responses	Microglia and astrocytes	[43]
Male C57BL/6 mice, human leukemia cell line THP-1 cells and human astrocytoma cell line U251 MG	LPS treatment or CSDS	Disrupting downstream signaling of CCL2- C-C motif chemokine receptor 2 (CCR2) interaction and inhibiting the pro-inflammatory potential of $Ly6C^{hi}$ monocytes	$Ly6C^{hi}$ monocytes and astrocytes	[45]
Male Sprague-Dawley rats	Chronic unpredictable stress (CUS)	Protection of astrocyte gap junctions within the PFC	Astrocytes	[46]
Primary prefrontal cortical and hippocampal astrocytes	CORT treatment	Alleviating CORT-induced gap junction dysfunction	Astrocytes	[48]
Primary hippocampal astrocytes and Male Sprague-Dawley rats	CORT treatment or CUS	Improving hippocampal astrocyte gap junction dysfunction	Astrocytes	[49]
Primary prefrontal cortical astrocytes, CTX TNA2 cell line and male Sprague-Dawley rats	CORT or carbenoxolone (CBX) or Gap26 treatment	Astrocyte gap junctions formed by Cx43 mediate antidepressant effects	Astrocytes	[50]
Male Wistar rats and primary rat glial cells	CUS or LPS treatment	Inhibition of Cx43 ubiquitination to improve neuroinflammation	Glial cells	[47]
Male Wistar rats	CUMS	Prevent oxidative stress, thereby preventing neuronal degeneration caused by inflammation	Microglia, astrocytes and CA1 neurons	[53]

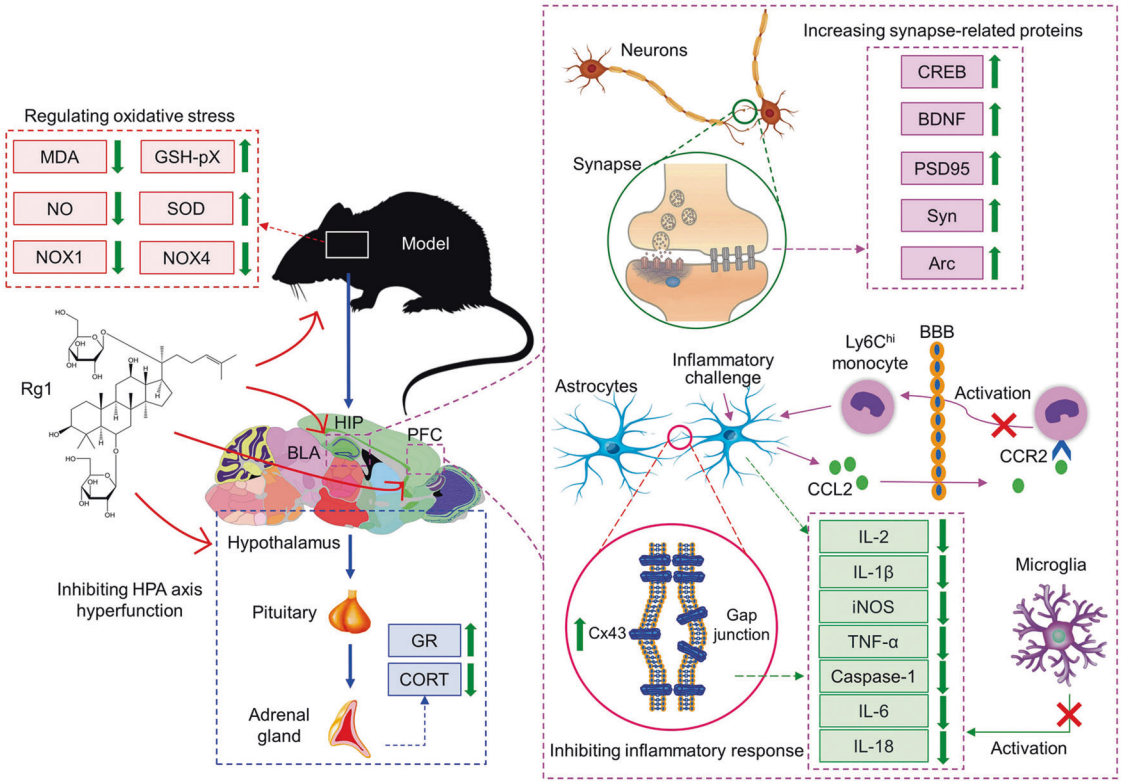

Fig. 1 The mechanism of antidepressant effect of Rg1. Rg1 inhibits the hyperfunction of HPA axis, increases the expression of GR and decreases the level of CORT. Rg1 increases the expression of synaptic-related proteins in the hippocampus, cortex and amygdala and regulates synaptic plasticity. Rg1 protects the gap junction function of astrocytes and inhibits inflammation by increasing the level of Cx43. Rg1 can also inhibit the activation of Ly6C^{hi} monocytes by CCL2-CCR2 interaction in inflammatory environment, destroy the inflammatory loop and reduce the level of pro-inflammatory factors. At the same time, Rg1 can also inhibit microglia activation and inflammation. Additionally, Rg1 can regulate the level of oxidative stress.

increase the density of dendritic spines and the expression of BDNF in the hippocampal neurons of CMS mice, which may be the mechanism of Rg1 improving depression-like behavior in CMS mice [9]. Our group also investigated the antidepressant effect of Rg1 in CUMS mice. The results showed that the expression of PSD95, activity-regulated cytoskeletal-associated protein (Arc) and BDNF in the hippocampus of CUMS mice was lower than that of control mice, while intraperitoneal injection of Rg1 could up-regulate the expression of synaptic-related proteins and improve the depression-like behavior of CUMS mice [43].

Rg1 prevents neuroinflammatory response

When neuroinflammation occurs, glial cells are activated and simultaneously release a series of inflammatory mediators such as cytokines and chemokines, which in turn lead to oxidative stress injury and damage to the CNS, ultimately resulting in depression [44]. Zheng et al. used LPS-induced neuroinflammation mouse model, chronic social defeat stress (CSDS)-induced depression mouse model and in vitro cellular experiment to evaluate the antidepressant effect of Rg1. It was found that peripheral Ly6C^{hi} monocytes (also known as pro-inflammatory monocytes) in LPS-induced depression were activated and migrated into the inflamed brain. In vitro experiments demonstrated that Ly6C^{hi} monocytes could promote astrocytes to secrete C-C motif chemokine ligand 2 (CCL2), a ligand driving the activation and migration of Ly6C^{hi} monocytes, and CCL2 activates P38/MAPK and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathways (the key to controlling monocyte activation and migration), thus forming an inflammatory circuit. Interestingly, the accumulation of Ly6C^{hi} monocytes was also found in the brain of CSDS mice. Intraperitoneal injection of Rg1 can inhibit the migration of peripheral Ly6C^{hi} into the brain, thereby blocking the pro-inflammatory potential of astrocytes and improving depression-like behavior in mice [45]. In recent years, Chen et al. investigated the effects of gap junction of astrocytes on depression-like behaviors, and explored the improving effect and mechanism of Rg1 on depression in a variety of depressive animal models and in vitro cellular experiments. Studies have shown that the dysfunction of gap junction function of astrocytes in the cortex and hippocampus contributes to depression-like behaviors, and connexin 43 (Cx43) is the main protein that constitutes the gap junction of astrocytes, which is closely related to the occurrence of depression [46]. Multiple studies have revealed that Cx43 is involved in the antidepressant effect of Rg1. Rg1 up-regulates the expression of Cx43 mRNA, inhibits the ubiquitin-proteasome and autophagy-lysosome degradation pathway of Cx43, reduces the degradation of Cx43, then increases the level of Cx43, protects the gap junction function of astrocytes in the cortex and hippocampus, reduces neuronal inflammation, and exerts antidepressant effect [47–51].

Rg1 prevents oxidative stress

In addition, there were abnormal changes in cells and molecules in the brain during the occurrence of depression, the gene expression regulating oxidative stress changed, and the content of oxidative stress indicators increased significantly, which indicated that the level of oxidative stress was inseparable from the occurrence of depression [52]. Li et al. demonstrated that the content of oxidative stress products malondialdehyde (MDA) and nitric oxide (NO) in the hippocampal CA1 region of CUMS rats increased, the activities of antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GSH-pX) decreased,

and the expression of nicotinamide adenine dinucleotide phosphate oxidase 1 (NOX1)/NOX4 in oxidative stress pathway was abnormal. Intraperitoneal injection of Rg1 could significantly adjust the levels of oxidative stress products and antioxidant enzymes, and inhibit the increase of NOX1 and NOX4 levels induced by chronic stress. It is suggested that the mechanism of antidepressant effect of Rg1 may be related to the reduction of oxidative stress injury [53].

Potential targets involved in the protection of Rg1 against depression

In addition to the above mechanism of action of Rg1 for depression, we screened the targets of Rg1 for depression by network pharmacology. Firstly, all probable action targets of Rg1 were obtained by SwissTargetPrediction (http://www.swisstargetprediction.ch/), and then the GeneCards database (https://www.genecards.org/) was used to screen (score >1) the relevant genes for depression. The obtained targets were imported into Cytoscape 3.8 software to make drug-targets-disease network and combined with String database (https://cn.string-db.org/) to complete protein-protein interaction (PPI) network. Finally, we selected targets that were both present in the PPI network and explored in the experimental evidence described above, and used AutoDockTools 1.5 and PyMOL software in combination with the PDB database (https://www.rcsb.org/) for molecular docking to verify the reliability of the targets obtained by network pharmacology. The results revealed 105 probable action targets of Rg1 and 3170 depression disease-related targets, including 56 intersecting targets. IGF1R (PDB ID: 2OJ9) and EGFR (PDB ID: 3POZ) were selected from the intersecting targets for molecular docking, and both showed high docking effects (Fig. 2).

RG1 AND ALZHEIMER'S DISEASE

Many kinds of ginsenosides have definite neuroprotective effects and have been used in the research of anti-AD, among which Rg1 is one of the most investigated ginsenosides [54]. Rg1 can reduce the activity of inflammatory factors induced by inflammasome activation and inhibit oxidative stress and apoptosis through anti-inflammatory and antioxidant effects. Rg1 improved AD-like symptoms by down-regulating the expression of beta-site APP cleaving enzyme 1 (BACE1) and APP, reducing the production of Aβ and increasing the level of insulin-degrading enzyme (IDE), accelerating the clearance of excess Aβ in the brain, and inhibiting the abnormal phosphorylation and deposition of Tau. In addition, Rg1 can regulate synaptic plasticity, reduce neuronal damage and apoptosis, and protect neurons, which is also helpful for AD treatment (Table 4, Fig. 3).

Rg1 reduces Aβ accumulation in the brain

The Aβ protein deposited in the form of amyloid plaque in the hippocampus will recruit more Aβ protein to form insoluble aggregates, which will induce mitochondrial damage and lead to synaptic dysfunction [55]. In addition, Aβ aggregation can also activate microglia and astrocytes, induce neuroinflammation, and eventually lead to a series of pathological reactions such as neuronal dysfunction and apoptosis [55].

Zhang et al. explored the anti-AD effect and mechanism of Rg1 in amyloid precursor protein/presenilin 1 (APP/PS1) mice. The results suggest that long-term treatment with Rg1 can improve cognitive and behavioral impairment and neuronal damage in APP/PS1 AD mice, and reduce the expression of amyloid precursor protein (APP) and the production of Aβ. The main mechanism of this effect is that Rg1 inhibits the activity of NOX2 and reduces the damage of neurons, and finally reduces the production of Aβ in APP/PS1 mice [56]. Huang et al. treated primary rat hippocampal neurons with $A\beta_{25-35}$ to study the effect and mechanism of Rg1 on hippocampal neurons after $A\beta_{25-35}$ exposure. The results showed that Rg1 could promote the axonal growth of hippocampal neurons and reverse the apoptosis of hippocampal neurons induced by $A\beta_{25-35}$. Interestingly, this effect of Rg1 can be blocked by API-2 (AKT inhibitor) and PD98059 (MAPK/ERK inhibitor), which means that Rg1 can increase the phosphorylation level of AKT and ERK [57]. The results suggest that Rg1 attenuates $A\beta_{25-35}$-induced hippocampal neuronal injury and protects hippocampal neurons by activating AKT and ERK signaling pathways. Yang et al. evaluated the ameliorating effect of Rg1 on cognitive impairment in senescence accelerated mice P8 (SAMP8) mice. The results showed that Rg1 can enhance the spatial memory of model mice, and can regulate the nod-like-receptor-protein-3 (NLRP3) inflammasome, reduce the level of TNF-α and the expression of inducible nitric oxide synthase (iNOS), inhibit the activation of astrocytes and microglia, and reduce the accumulation of Aβ in the hippocampus, which may be an important mechanism for Rg1 to improve the cognitive impairment of AD [58]. Interestingly, cyclin-dependent kinase 5 (CDK5) mediated phosphorylation of peroxisome proliferator-activated receptor γ (PPARγ) at Ser273. Quan et al. found that Rg1 inhibited the expression of CDK5 and the level of p-PPARγ, thus decreasing the p-PPARγ/PPARγ ratio [59]. Moreover, the reduction of p-PPARγ could upregulate IDE and downregulate the level of BACE1 [59, 60]. Since BACE1 is an enzyme necessary for Aβ production by APP hydrolysis, and Aβ is considered to be the substrate of IDE [61]. Thus, these results demonstrated that Rg1 not only reduced BACE1 and prevented Aβ production, but also increased IDE to promote Aβ degradation, thus improving AD.

Rg1 reduces abnormal deposition and phosphorylation of Tau

Tau is a microtubule-associated protein involved in regulating the growth and transport of axons in the brain, helping to maintain the stability of axonal microtubules. Overexpression or abnormal phosphorylation of Tau can depolymerize microtubules and impair axonal transport, and phosphorylation and aggregation of Tau also make it the main component of neurofibrillary tangles. Pathological accumulation of Tau further leads to neuronal degeneration, resulting in neuronal apoptosis [62]. Clinical studies have found that the level of Tau in the brain of AD patients with cognitive impairment was higher than that of the normal population, and the level of Tau was correlated with the severity of cognitive impairment [63]. This indicates that Tau has been regarded as a pathological marker of AD.

In the experiment of Rg1 improving cognitive impairment and neuronal damage in APP/PS1 mice, Zhang et al. found that long-term oral administration of Rg1 not only improved the cognitive impairment of AD mice, but also decreased the level of p-Tau, blocked the production of ROS and the expression of NOX2 in the cortex and hippocampus, and increased the expression of PSD95 [56]. The mechanism of this effect is related to the inhibition of NOX2 activation by Rg1. In addition, overexpression of glycogen synthase kinase-3β could induce phosphorylation of Tau. In exploring the mechanism of Rg1 inhibiting the phosphorylation of Tau, Li et al. thought that Rg1 inhibited the phosphorylation of Tau and promoted the clearance of deposited Tau by up-regulating the expression of BDNF to inhibit glycogen synthase kinase-3β activity [64].

Rg1 adjusts the intestinal flora

The relationship between intestinal flora and AD is an interesting topic. Studies have revealed that intestinal flora could affect brain activity through the microbiota-gut-brain axis, and the imbalance of flora could cause brain dysfunction [65]. Wang et al. explored the mechanism of Rg1 improving AD cognitive impairment in AD tree shrews for the first time. The results showed that Rg1 could restore the cognitive function of AD tree shrews and reduce the expression of Tau in the hippocampus and cortex. Meanwhile,

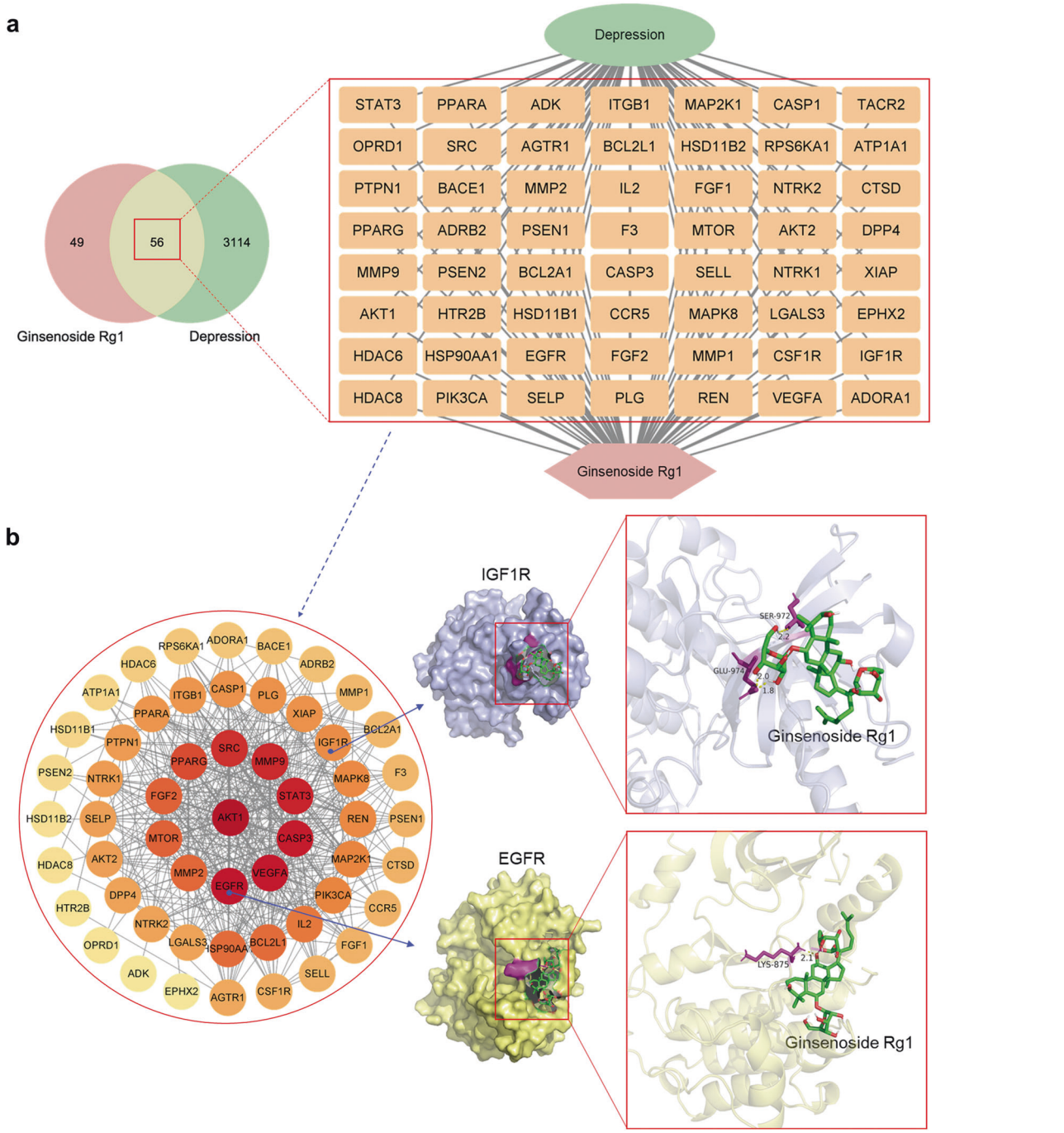

Fig. 2 Potential targets and molecular docking of Rg1 against depression. a Venn diagram and drug-targets-disease network of Rg1 action targets and depression-related genes. There are 105 Rg1 action targets and 3170 depression-related genes, 56 of which are common targets. **b** PPI network and molecular docking of IGF1R and EGFR. The PPI network contains 55 key targets. The binding energy of IGF1R and EGFR were −2.09 kcal/mol and −1.57 kcal/mol, respectively, indicating a good docking effect.

Rg1 significantly improved the intestinal flora abundance of AD tree shrews, and *Proteobacteria* and *Verrucomicrobia* were identified as two of them key flora. This study suggested that improving intestinal flora abundance may be an effective mechanism for Rg1 to treat AD [66]. Coincidentally, while exploring the improving effect and mechanism of Rg1 on AD tree shrews, Guo et al. found that Rg1 could reduce the levels of Aβ, pS404-Tau and Bcl2-associated X protein (Bax) in the hippocampus and cortex, up-regulate the expression of Bcl-2, inhibit β-secretase1 and increase the expression of microtubule-associated protein 2 (MAP2) and Fox-3. Meanwhile, Rg1 significantly reduced the abundance of *Bacteroidetes* in AD tree shrews. The findings revealed that Rg1 may inhibit apoptosis and protect neurons by decreasing the abundance of intestinal flora, ultimately improving AD [67].

Rg1 reduces neuroinflammation and oxidative stress

Clinical research has shown that in the early stage of AD, the increase of chitinase-3-likeprotein 1 (YKL-40) was related to the accumulation of Aβ and increased the risk of AD dementia, while the high expression of IL-15 aggravated the cognitive deterioration of AD [68]. IL-17 was involved in the short-term memory and

Table 4. Main mechanism and effect sites of Rg1 on AD.

Animal or cell line	Model	Main mechanism	Effect sites (receptor, cell, axon or dendrite)	Reference
Male APP/PS1 mice and wild type (WT) mice	APP/PS1 AD model	Inhibition of NOX2 expression and accumulation of ROS to alleviate cognitive impairment and Aβ production	Hippocampal and cortical neurons	[56]
Primary hippocampal neurons	$A\beta_{25-35}$ treatment	Activation of AKT and ERK1/2 signaling pathways	Neurite in hippocampal neurons	[57]
Male SAMP8 mice and male SAMR1 mice	SAMP8 AD model	Repair of hippocampal neuronal cell loss and inhibition of astrocyte and microglia activation	Hippocampal neurons, microglia and astrocytes	[58]
Male tree shrews	$A\beta_{25-35}$ treatment	Changing the abundance of gut microbiota	Proteobacteria and Verrucomicrobia	[66]
Male tree shrews	$A\beta_{25-35}$ treatment	Inhibiting the expression of pro-apoptotic proteins, protecting hippocampal and cortical neurons, and reducing the abundance of Bacteroidetes	Hippocampal and cortical neurons and Bacteroidetes	[67]
HT22 cells	LPS treatment	Inhibition of NOX2-NLRP1 inflammasome protects against LPS-induced neuronal damage	HT22 cells	[72]
Primary hippocampal neurons	H_2O_2 treatment	Reducing NOX2-mediated ROS production, inhibiting NLRP1 inflammasome activation, and inhibiting neuronal aging and damage	Hippocampal neurons	[73]
Male ICR mice	Dexamethasone treatment	Protecting against neuroinflammation and neuronal damage from chronic glucocorticoid exposure and inhibiting the NLRP-1 inflammasome	Hippocampal and frontal cortex neurons	[74]
Neuroglial cell line NG108-15	$A\beta_{25-35}$ treatment	Inhibiting TLR3 and TLR4 signaling transduction pathways and reducing $A\beta_{25-35}$-induced cellular inflammatory factors	Neuroglial cell	[75]

dysfunction of synaptic plasticity in the early stage of the disease in 3xTg-AD mice [69]. Glutathione (GSH) is an important antioxidant in the body. Clinical evidence revealed that the decrease of GSH constituted a potential biomarker for mild cognitive impairment (MIC) and AD diagnosis [70]. It was suggested that neuroinflammation and oxidative stress might play a key role in the early stage of AD, and the brain damage in the development of AD was earlier than Aβ-induced neuronal loss [71]. Therefore, it is considered that AD can be improved by reducing neuroinflammation and oxidative stress, especially in the early stage of AD.

Zhang et al. exposed HT22 cells to LPS to mimic neuronal inflammatory damage in AD and observed the protective effect of Rg1. LPS could induce the activation of NOX2-NLRP1 inflammasome in HT22 cells, resulting in an inflammatory response, and at the same time, excessive ROS were generated and neurons were damaged. Rg1 has neuroprotective effects on LPS-exposed HT22 cells by inhibiting NOX2-NLRP1 inflammasome activation and reducing ROS generation, which may also be an important pathway for Rg1 to alleviate neuronal damage in AD [72]. Xu et al. established an AD model different from the above study by inducing primary rat hippocampal neurons with H_2O_2, and observed the protective effect on the injury of hippocampal neurons after treatment with Rg1. The results showed that after H_2O_2 induction, ROS increased in hippocampal neurons, the expressions of NOX2 and NLRP1 increased, and hippocampal neurons appeared senescent and were damaged. Rg1 blocked the up-regulation of H_2O_2 on the above indicators, and reduced the pathological changes of hippocampal neurons [73]. This study points out that Rg1 exerts a protective effect on hippocampal neurons by reducing NOX2-mediated ROS production and inhibiting NLRP1 inflammasome activation. Zhang et al. also demonstrated that Rg1 could protect neurons by inhibiting NLRP1 inflammasome and reducing the expression of apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC), caspase-1, caspase-5, IL-1β and IL-18 in the hippocampus of AD mice through the AD mouse model of neuronal inflammatory injury induced by dexamethasone [74]. Zhao et al. treated the $A\beta_{25-35}$-induced glial cell line NG108–15 with Rg1. The results showed that Rg1 could down-regulate the increase of TNF-α in NG108–15 induced by $A\beta_{25-35}$ and inhibit the expression of toll-like receptor 3 (TLR3) and TLR4 protein. It is suggested that the mechanism of Rg1 in the treatment of AD may be related to the inhibition of TLR3 and TLR4 signaling pathways and the decrease of the activity of inflammatory factors induced by $A\beta_{25-35}$ [75]. In addition, Kwan et al. compared the antioxidant activities of Rb1, Rd, Re and Rg1, and concluded that Rg1 has the strongest antioxidant capacity, which also suggests that among many ginsenosides, Rg1 may be the most potential therapy for AD [76].

Potential targets involved in the protection of Rg1 against AD

In order to obtain more information on the targets of Rg1 for AD, we performed a network pharmacology screen and molecular docking of targets from experimental evidence to show the reliability of the targets obtained by network pharmacology. The results revealed 105 probable action targets of Rg1 and 9128 AD disease-related targets, including 56 intersecting targets. BACE1 (PDB ID: 4B78) and PPARG (PDB ID: 2YFE) were selected from the intersecting targets for molecular docking, and both showed good docking effects (Fig. 4).

RG1 AND LEARNING AND MEMORY DYSFUNCTION

Besides AD, other types of dementia, especially vascular cognitive disorders were also featured by impairment of learning and memory [77]. Interestingly, our group has previously shown that Rg1 prevented the memory impairment caused by bilateral ligation of common carotid artery [78]. In addition, memory could be divided into declarative and non-declarative memory, and cue-based fear

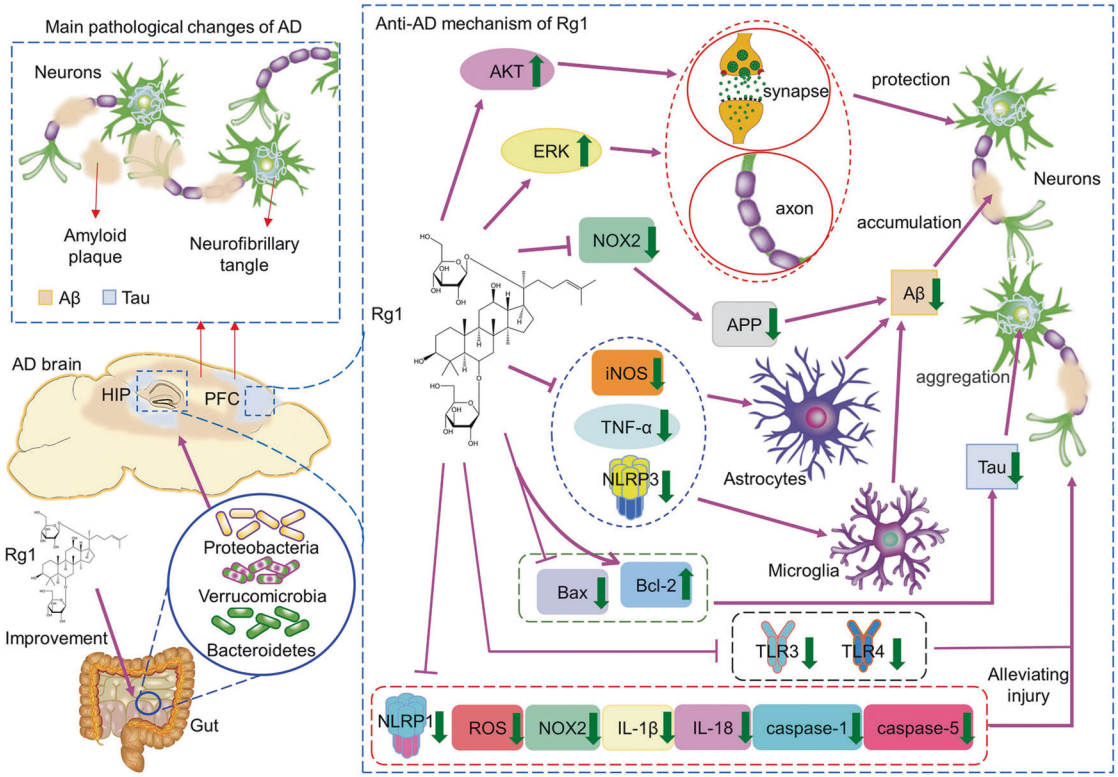

Fig. 3 The mechanisms involved in the effects of Rg1 against Alzheimer's disease. The main pathological changes of AD are amyloid plaques formed by Aβ aggregation and neurofibrillary tangles formed by abnormal aggregation of phosphorylated Tau. Rg1 alleviates amyloid plaques and neurofibrillary tangles by improving gut microbiota. Rg1 can improve AD by increasing synaptic protein expression, promoting axonal growth, inhibiting Aβ generation and abnormal increase in the phosphorylation of Tau, as well as improving oxidative stress and inflammatory response and protecting neurons.

memory is one important type of non-declarative memory. Especially, over-activation of fear memory was related to development of psychiatric disorders, like depression and anxiety [79]. Therefore, we specifically discuss the role and mechanism of Rg1 on learning and memory dysfunction as an independent part of this review.

Our group established a mouse model of vascular dementia (VD) to explore the preventive effect of Rg1 on cognitive impairment. The results of Morris water maze showed that Rg1 could improve the spatial memory of model mice, and the effect was consistent with G1, a G protein-coupled estrogen receptor 1 (GPR30) agonist. In the study of drug mechanism, we confirmed that promoting the expression of GPR30 to prevent cognitive impairment in VD mice is a key way for Rg1 to play a role [78]. At the same time, we also found that the generalization of fear memory in PTSD model mice is severe and difficult to extinct, and administration of Rg1 can promote the extinction of fear memory [80]. In the Barnes maze test, Miao et al. pointed out that Isoflurane/surgery (I/S) could induce hippocampus-dependent learning and memory impairment in mice, increased the escape latency and error times of model mice in Barnes maze, while Rg1 improved the learning and memory impairment induced by I/S. Through the correlation analysis between behaviors and biochemical indexes, it was considered that the improving effect of Rg1 on learning and memory was related to the decrease of ROS level and up-regulation of oxygen consumption rate (OCR) [81]. Wang et al. used reward devaluation test and conditional visual discrimination task to evaluate the effect of Rg1 on cognitive impairment in chronic restraint stress (CRS) rats. The results showed that Rg1 had an improvement effect on the learning and memory of CRS rats. The mechanism of this improvement was related to the activation of BDNF/TrkB/ERK signaling pathway in the PFC by Rg1 [82]. In addition, study has also pointed out that the effect of Rg1 on learning and memory impairment is related to the cholinergic system [83].

In the above studies, no matter which model is used to simulate the learning and memory impairment, Rg1 has a good behavioral improvement effect, although the mechanism involved is different. However, it is not difficult to find that the improvement effect of Rg1 in these studies is still inseparable from its excellent neuroprotective effect, as well as anti-inflammatory and antioxidant functions. Based on the experimental evidences, it is sufficient to support its extensive and in-depth preclinical research in the field of neuropsychiatric disorders. Interestingly, memory is divided into various types (such as working memory and fear memory), and different diseases can induce the impairment of different types of memory. In PTSD, aversive memory is abnormally active and easily reactivate, which leads to the generalization of fear memory and fear extinction disorder [84–86]. In AD, the loss of working memory is the main factor leading to memory impairment and decreased decision-making ability [87, 88]. Therefore, Rg1 has a good effect on memory impairment in different pathological states. In addition, the previous research of our group showed that long-term administration of Rg1 can enhance the long-term memory ability of middle-aged mice under normal conditions [89]. This well explains part of the mechanism of ginseng's nootropic effect (Table 5, Fig. 5).

RG1 HAS THE POTENTIAL FOR DRUG DEVELOPMENT, BUT THE PROCESS FACES CHALLENGES

Moreover, we also obtained the "drug-disease" targets of Rg1 and depression and AD through network pharmacology, and did Gene Ontology (GO) (Top 10) and Kyoto Encyclopedia of Genes

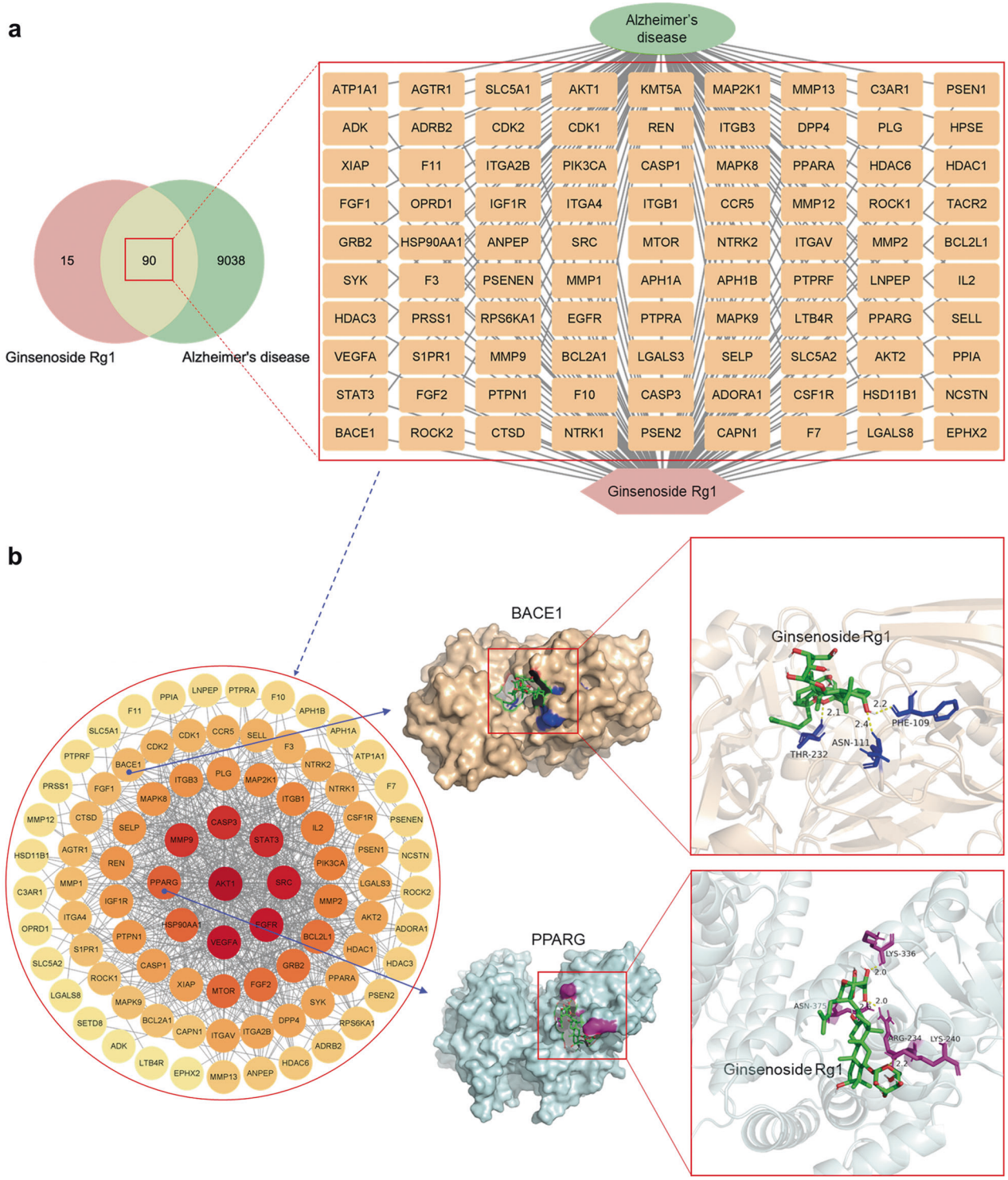

Fig. 4 Potential targets and molecular docking of Rg1 against AD. a Venn diagram and drug-targets-disease network of Rg1 action targets and AD-related genes. There are 105 Rg1 action targets and 9128 AD-related genes, 90 of which are common targets. **b** PPI network and molecular docking of BACE1 and PPARG. The PPI network contains 88 key targets. The binding energy of BACE1 and PPARG were −1.93 kcal/mol and −1.91 kcal/mol, respectively, indicating a good docking effect.

and Genomes (KEGG) (Top 30) analysis (http://metascape.org/), including neuronal cell body, dendrite, axon, and MAPK signaling pathway. This also confirmed the possible biological pathways of Rg1 in the treatment of depression and AD (Fig. 6). It also suggests that Rg1 has the potential to be developed as a promising drug.

In addition to the above-mentioned effects of Rg1 on depression, AD, and learning and memory impairment, it has also been extensively investigated in other neuropsychiatric disorders, such as HD [90]. In addition, our group investigated the preventive and therapeutic effect of Rg1 on PTSD. The results showed that Rg1 could exert a protective effect on PTSD-like behaviors by

Table 5. Modulating effects, main mechanism and effect sites of Rg1 on learning and memory dysfunction.

Animal or cell line	Model	Modulating effects on learning and memory	Main mechanism	Effect sites (receptor, cell, axon or dendrite)	Reference
Male C57BL/6 J mice	Bilateral common carotid artery stenosis (BCAS) model	Spatial memory (↑)	Promoting GPR30 expression to prevent cognitive impairment and hippocampal neuronal apoptosis in VD mice	GPR30 and hippocampal neurons	[78]
Male C57BL/6 J mice	Isoflurane plus abdominal surgery treatment	Spatial learning and memory (↑)	Improving learning and memory function, reducing ROS levels and ameliorating the OCR, mitochondrial membrane potential, expression and deacetylation activity of Sirtuin3	Mitochondria	[81]
Male Wistar rats	CRS	Episodic memory (↑)	Activation of the BDNF/TrkB/ERK signaling pathway in the PFC	PFC	[82]
Male Wistar rats	LPS treatment	Working and spatial memory (↑)	Regulating acetylcholine levels, acetylcholinesterase activity, and expression of the alpha7 nicotinic acetylcholine receptor (α7 nAChR)	α7 nAChR in PFC and hippocampus	[83]
Male Kunming mice	D-galactose and $AlCl_3$ induced aging	Spatial learning and memory (↑)	Up-regulating fibroblast growth factor 2 and BDNF levels, activating TrkB/AKT signaling pathway in hippocampus and prefrontal cortex to inhibit apoptosis	Hippocampus and PFC neurons	[194]
Female 3xTg-AD mice	AD model	Spatial learning and memory (↑)	Up-regulating the expression of complexin-2 (CPLX2), synapsin-2 (SYN2) and synaptosoma-associated protein 25 (SNP25)	Hippocampus	[195]
Male tree shrews	$A\beta_{25-35}$ induced AD model	Spatial memory (↑)	Regulating Wnt/GSK-3β/β-catenin signaling pathway, reducing oxidative stress injury, improving neuroinflammation, and protecting neurons	Hippocampus	[196]
Male C57BL/6 J mice	Single-prolonged stress model	Fear memory (↓)	Promoting synaptic protein expression and reducing Kir4.1 and TNF-α in hippocampus	Astrocytes and microglia	[80]

inhibiting the expression of inflammatory factors and promoting synaptic proteins [80]. Findings such as those suggest that Rg1 has the potential to be developed into a neuropsychiatric drug. However, when we searched the Rg1 drug information on the official websites of the drug regulatory agencies of China (National Medical Products Administration), the United States (Food and Drug Administration), Republic of Korea (Ministry of Food and Drug Safety) and Japan (Pharmaceuticals and Medical Devices Agency), we found that only one Rg1 drug, *Qishengli* tablet (Z20027165) on the National Medical Products Administration official website of China. Therefore, we think, since Rg1 has a potential for prevention and treatment of various neuropsychiatric disorders, what are the factors that hinder the further development of Rg1 drugs? Based on the experimental research of Rg1, we propose that there are three reasons.

The mechanism of Rg1 still needs to be further explored

It is currently believed that the role of Rg1 in neuropsychiatric disorders is mainly related to anti-inflammatory, antioxidant and neuronal protection [91, 92]. However, the treatment of diseases by drugs is often based on the pathogenesis of existing diseases. With the in-depth study of the mechanism of disease, the mechanism of drug action should be updated rapidly. Taking AD research as an example, neurofibrillary tangles formed by the aggregation of Aβ and phosphorylated Tau are considered to be the main factor in AD pathogenesis. Studies have shown that transactive response DNA-binding protein of 43 kDa (TDP-43) (a DNA-binding protein predominantly found in the nucleus) and Aβ or Tau protein co-occur in neurons of neurofibrillary tangles through protein co-localization, and there is a direct interaction with Aβ or Tau protein, which is involved in Aβ fibrosis or the aggregation of Tau protein, and then aggravates AD-like pathology [93–95]. Clinical studies have found that TDP-43 deposition is common in patients with typical and limbic AD, accounting for 59% and 67%, respectively [96]. TDP-43 pathological changes were found in 49.4% of brain samples from autopsy of deceased aging and AD patients [97]. Therefore, TDP-43 is a factor that cannot be ignored in the pathogenic mechanism of AD. As mentioned earlier, Rg1 can reduce the production of Aβ, inhibit the aggregation of Tau protein and improve AD, which has been elucidated in many experimental studies, but there is no direct experimental evidence to support whether this mechanism is related to the regulation of TDP-43 expression. Therefore, we speculate that TDP-43 may also be an important target of Rg1, and may participate in the inhibition of Aβ and Tau protein phosphorylation through this target. In addition, regarding the effects of Rg1 on Aβ, most of the studies focused on the influence of Rg1 against Aβ production. Whether Rg1 could help or assist the clearance of Aβ was rarely investigated. This is also important point that needs to be improved in Rg1 studies. It also suggests that with the continuous study of the mechanism of AD, the prevention and treatment mechanism of Rg1 should be discussed more deeply. The limitation of exploring the mechanism of Rg1 is also applicable to other neuropsychiatric disorders.

Low blood-brain barrier (BBB) permeability and bioavailability of Rg1

The saponins in ginseng extract can be divided into three types: panaxadiol, panaxatriol and oleanolic acid. Rg1 belongs to the type of panaxatriol. Pharmacokinetic experiments showed that Rg1 could not effectively penetrate the BBB and distribute in the brain [98]. In addition, after oral administration, Rg1 and its metabolites in bile, urine and feces of rats were detected by LC-MS/MS. The results showed that the recovery rate of Rg1 and its metabolites was more than 70%, indicating that the bioavailability of Rg1 through oral administration was poor [99]. In pharmaceutical research, for drugs with strong pharmacological activity but low oral bioavailability, chemical structure modification and drug

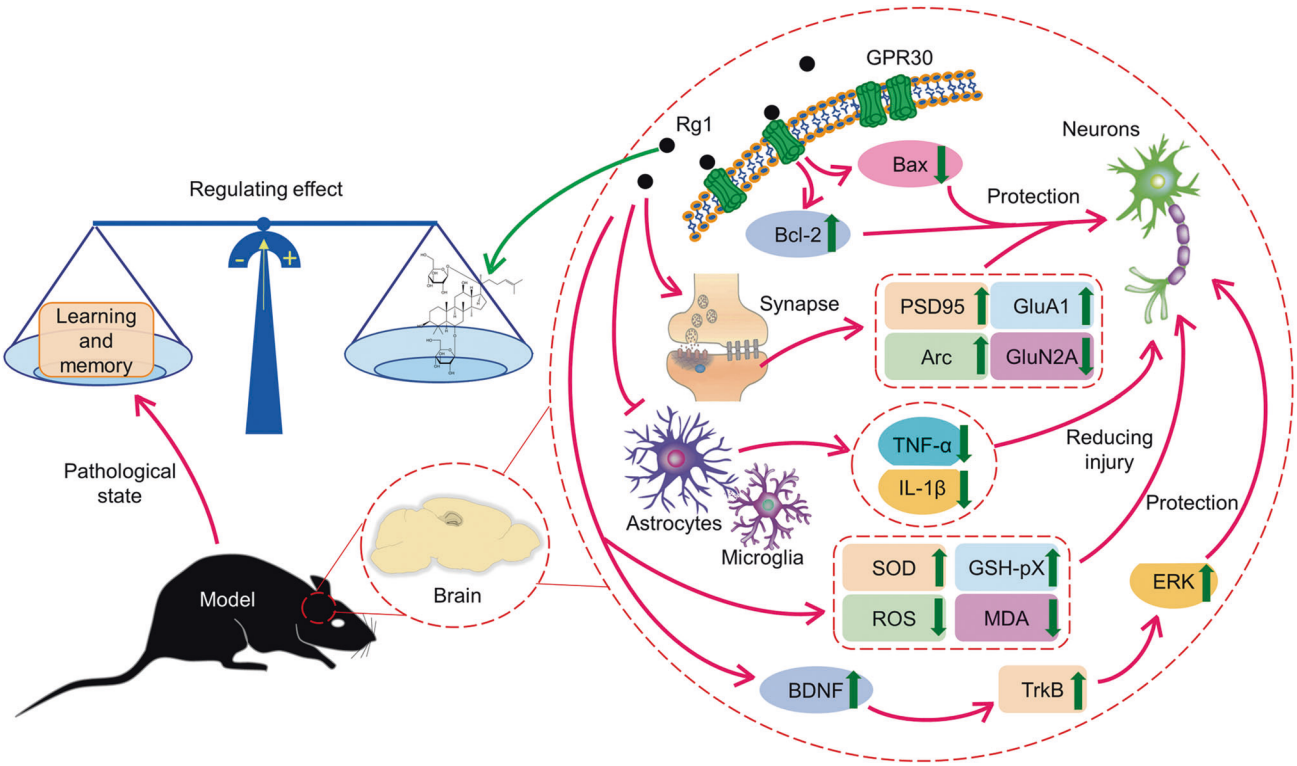

Fig. 5 Effects of Rg1 on learning and memory functions. Rg1 could regulate the learning and memory function in pathological state. Rg1 protects neurons by activating GPR30, inhibiting apoptosis, increasing the expression of synapse-related proteins and regulating synaptic plasticity. Rg1 can inhibit the activation of astrocytes and microglia, reduce inflammatory factors, and reduce neuronal damage. Rg1 can also protect neurons by regulating oxidative stress and activating the BDNF/TrkB/ERK signaling pathway.

dosage form modification are usually selected to improve bioavailability [8]. For Rg1 in the prevention and treatment of neuropsychiatric disorders, it is equally important to increase BBB permeability and bioavailability.

In terms of increasing the permeability of the BBB, it has been reported that depending on the high expression of transferrin receptor (TfR) in the capillary endothelium of BBB, Rg1 nanoparticles targeting TfR are designed to increase brain exposure of Rg1 through endocytosis penetrating BBB, which has been effectively verified in vivo and in vitro [100]. It has to be mentioned that the design of such brain-targeted drugs is interesting, but the mode of administration used in the study is intravenous injection. We believe that such drug design is more beneficial for the treatment of acute neuropsychiatric disorders. By contrast, diseases like AD, have slow progress, long course and need continuous drug treatment. The design of oral drug preparation is in line with the characteristics of long-term drug treatment. In addition, the experimental results of Liang et al. suggest that extract of ginkgo biloba (EGb) can activate the A1 adenosine receptor signaling pathway and reversibly increase the permeability of BBB, and the use of EGb combined with Rg1 can increase the intracerebral uptake of Rg1 [101]. The design of such a combination drug may be a good research method for increasing brain distribution of Rg1. In terms of improving bioavailability, Baek et al. developed an oral formulation of ginsenoside (containing Rg1 or Rb1) microspheres composed of an enteric-coated polymer and an adhesive polymer. The results of in vitro experiments showed that the oral preparation of microspheres was resistant to acidity, and the release of ginsenosides in the microspheres decreased under the acidic condition of pH=1.2. This means that the degradation of ginsenosides is reduced in the acidic environment of the stomach [102]. Although there are individual novel basic researches on improving the BBB permeability and bioavailability of Rg1, the transformation of Rg1 into a drug is still a long way off.

Insufficient clinical research on Rg1

We searched the information on clinical trials carried out by Rg1 in China, Republic of Korea, Japan, the National Institutes of Health (NIH) of the United States and the WHO international clinical trial registration platform, but did not retrieve the clinical trial information of Rg1 as a single component drug. Rg3, Rd and Re, which are also ginsenosides, all have clinical trial information about the use of single-component drugs to treat diseases including hepatocellular carcinoma, ischemic stroke and diabetes. Additionally, we found that clinical trials of Rg1 in combination with other ginsenosides such as Rb1 and Re have been conducted in vascular dementia and ischemic stroke. It is worth noting that among all ginsenosides, Rg3 is one of the most widely used agents in clinical research and proprietary medicine. At present, the China National Medical Products Administration has approved Rg3 single-component *Shenyi* capsule (Z20030044) and Rg3 active pharmaceutical ingredient (Z20030043).

In pharmacological study, the effectiveness of Rg1 has been confirmed, and toxicological experiments also indicate that Rg1 has no adverse reactions and potential toxicity [103]. This shows that Rg1 has the characteristics of safety and efficacy of drugs, and meets the basic conditions for entering into clinical trials as therapeutic drugs. Rg1 can fully refer to proprietary drug model of Rg3, that is, focused drug research in the scope of treatment. Although Rg3 has many pharmacological effects, in the research of proprietary medicine, it only focuses on the adjuvant therapy of tumors. Therefore, we believe that Rg1, as a single-component drug to quickly enter clinical research and promote proprietary medicine, should also focus on the therapeutic effect of a single disease. From the results of searching “ginsenoside Rg1” and “ginsenoside Rg3” in PubMed database, the number of experimental studies related to Rg1 is much higher than that of Rg3, so we have more reason to believe that Rg1 has the potential to become a clinical drug.

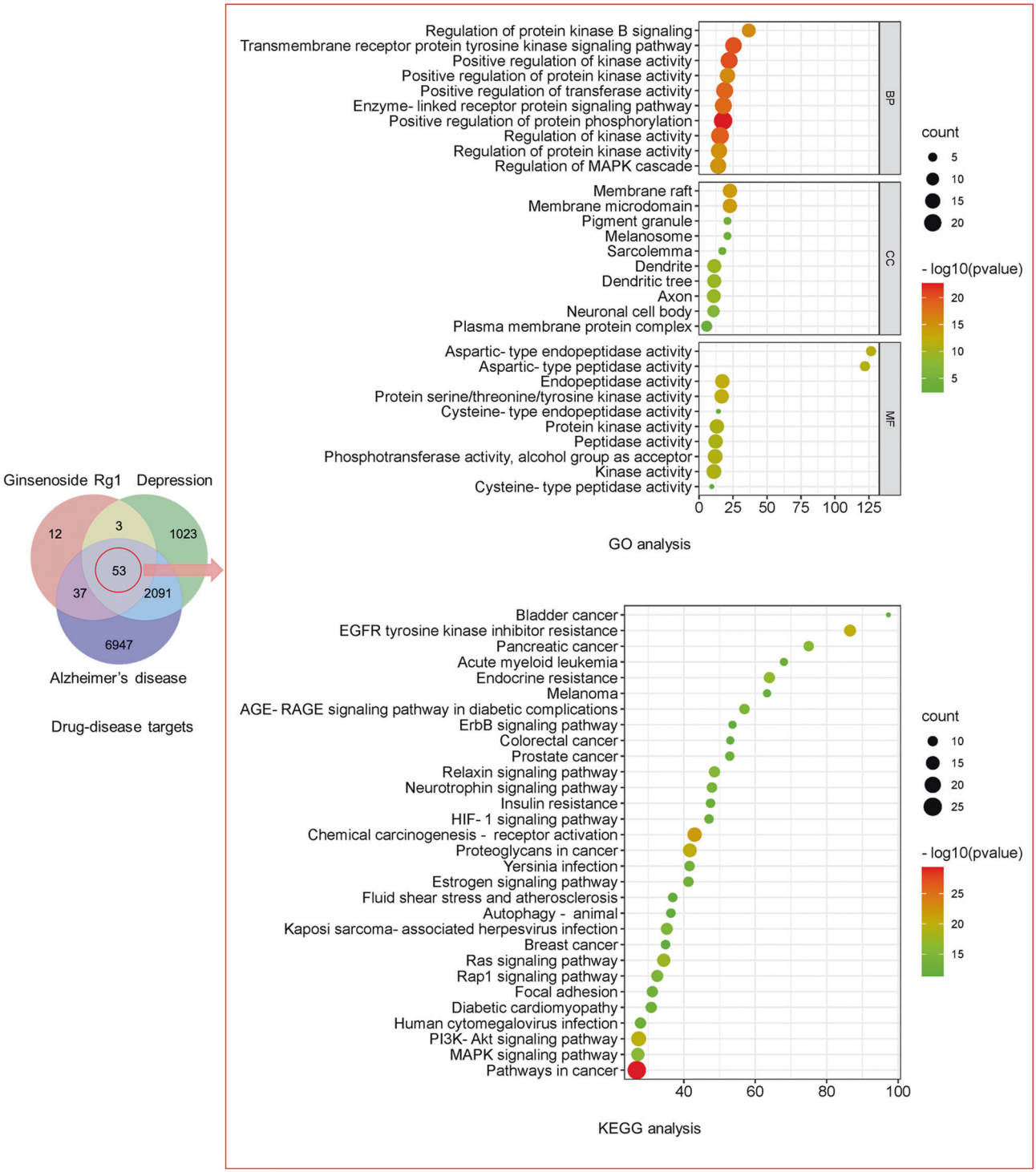

Fig. 6 "Drug-disease" targets of Rg1, depression and AD, and GO (Top 10) and KEGG (Top 30) enrichment analysis of common targets. The 53 targets include PIK3CA, SELP, STAT3, IL2, FGF2, BCL2L1, VEGFA, FGF1, ATP1A1, HSP90AA1, REN, TACR2, AKT2, RPS6KA1, AKT1, LGALS3, PSEN2, HSD11B1, OPRD1, IGF1R, EGFR, MMP1, MAPK8, MAP2K1, PTPN1, BCL2A1, MTOR, DPP4, EPHX2, ADK, XIAP, BACE1, CSF1R, ADRB2, PPARA, NTRK1, NTRK2, PLG, HDAC6, ITGB1, MMP9, F3, CASP3, PPARG, CTSD, MMP2, ADORA1, CCR5, SELL, CASP1, AGTR1, SRC, PSEN1. GO enrichment analysis includes biological processes (BP), cellular components (CC) and molecular functions (MF).

PROSPECTS FOR THE FUTURE DEVELOPMENT DIRECTION OF RG1

Based on the above discussions, we believe that Rg1 needs to carry out more researches in the following aspects in the future. First of all, the exploration of the mechanism of neuropsychiatric disorders by Rg1 should be more in-depth, not in a simple exploration of the anti-inflammatory, antioxidant and neuroprotective effects, but should be combined with the deeper mechanism of neuropsychiatric disorders to trace the target of Rg1. The protective effect of Rg1 on brain neurons has been validated by experiments, and it is also a research fact that it cannot pass through BBB effectively, so how can Rg1 exert its

protective effect on brain neurons without passing through BBB? Previous studies have confirmed that Rg1 can improve brain injury through peripheral effects, but there is few similar study [104]. Therefore, the in-depth study of the mechanism is the main direction of future research on Rg1. Secondly, Rg1 is a natural product extracted from ginseng, which has defects in chemical structure. The strong hydrophilicity of Rg1 may be an important reason why it is difficult to pass through the BBB, and the strength of Rg1's protective effect on brain neurons is related to whether it can pass through the BBB to achieve effective brain exposure [105]. At present, there are only a few drug dosage forms designed by Rg1 in improving the permeability of BBB. We believe that the modification of chemical structure is also the key to solve the problem. The acquisition of a Rg1 modification molecule that can effectively penetrate into the brain means that ordinary drug dosage forms may also complete the task of Rg1 delivery into the brain. Therefore, the modification of the chemical structure of Rg1 is crucial to the exertion of drug action. Finally, the clinical research data of Rg1 should be completed and improved as soon as possible. Several preclinical studies have been done on Rg1, the effects of the drug have been scientifically explained, and clinical research is imminent. From the development experience of Rg3, the research mode focusing on a single disease may be the right choice for the further development of Rg1.

In summary, Rg1 is a natural product that integrates antioxidant, anti-inflammatory and neuroprotective effects, and its effectiveness on neuropsychiatric disorders has been confirmed by a large number of experimental studies, indicating that Rg1 has good application prospects in the future. However, the difficulties and challenges faced by the experiment also imply that there are still limitations in the current researches. Based on the coexistence of development potential and research challenges of Rg1, we prefer to call Rg1 an urgently developed drug for neuropsychiatric disorders. The transition between Rg1 in current research and Rg1 in future applications requires more systematic exploration. Of course, we hope to call Rg1 a widely used clinical drug for neuropsychiatric disorders as soon as possible.

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ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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