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*CORRESPONDENCE Tao Sun, I suntao513@gmail.com Ying Xu, I xuying.doctor@gmail.com

[†]These authors have contributed equally to this work

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Glucagon-like peptide 1 (GLP-1) receptor agonists in experimental Alzheimer's disease models: a systematic review and meta-analysis of preclinical studies

Fanjing Kong^{1†}, Tianyu Wu^{2†}, Jingyi Dai¹, Zhenwei Zhai¹, Jie Cai¹, Zhishan Zhu¹, Ying Xu^{3*} and Tao Sun^{1.4*}

¹School of Intelligent Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, China, ²School of Acupuncture-Moxibustion and Tuina, Chengdu University of Traditional Chinese Medicine, Chengdu, China, ³Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China, ⁴State Key Laboratory of Southwestern Chinese Medicine Resources, School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, China

Alzheimer's disease (AD) is a degenerative disease of the nervous system. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), a drug used to treat type 2 diabetes, have been shown to have neuroprotective effects. This systematic review and meta-analysis evaluated the effects and potential mechanisms of GLP-1 RAs in AD animal models. 26 studies were included by searching relevant studies from seven databases according to a predefined search strategy and inclusion criteria. Methodological quality was assessed using SYRCLE's risk of bias tool, and statistical analysis was performed using ReviewManger 5.3. The results showed that, in terms of behavioral tests, GLP-1 RAs could improve the learning and memory abilities of AD rodents; in terms of pathology, GLP-1 RAs could reduce A β deposition and phosphorylated tau levels in the brains of AD rodents. The therapeutic potential of GLP-1 RAs in AD involves a range of mechanisms that work synergistically to enhance the alleviation of various pathological manifestations associated with the condition. A total of five clinical trials were retrieved from ClinicalTrials.gov. More large-scale and high-quality preclinical trials should be conducted to more accurately assess the therapeutic effects of GLP-1 RAs on AD.

KEYWORDS

glucagon-like peptide 1 receptor agonists, Alzheimer's disease, animal models, neuroprotective effects, meta-analysis, systematic review

1 Introduction

Alzheimer's disease (AD), a chronic neurodegenerative disease, usually manifests clinically as significant amnestic cognitive impairment and, to a lesser extent, as non-amnestic cognitive impairment (Knopman et al., 2021). As the global population ages, the prevalence of AD has increased dramatically and has become the fourth leading cause of human death (Prince et al., 2015). According to surveys, the prevalence of dementia worldwide is estimated to rise to 131.5 million people by 2050 (Shah et al., 2016). While

causing suffering for patients and families, it also imposes a severe economic burden on society. AD has become one of the most serious, expensive and burdensome diseases of this century (Scheltens et al., 2021).

AD is a complex multifactorial disease, and the specific pathogenesis is still unclear (Querfurth and LaFerla, 2010). The drugs currently approved for treating AD mainly target cholinergic and glutamatergic neurotransmission, such as donepezil, rivastigmine, galantamine, and memantine. Although these drugs may improve symptoms to some extent, they do not alleviate or stop disease progression (Mangialasche et al., 2010). Furthermore, almost all current attempts to design effective drugs have ultimately failed (Jeremic et al., 2021). It has become extremely urgent to find new drugs to treat AD effectively. The lack of improved treatments for the disease, as well as the difficulty and cost of developing new drugs have drawn attention to existing drugs for other indications (Ferrari et al., 2022). Type 2 diabetes mellitus (T2DM) and AD have overlapping pathophysiological mechanisms, including insulin resistance, inflammation, oxidative stress, altered glucose metabolism, etc., (Watson and Craft, 2003; Ferrari et al., 2022). As early as the 1980s, Siegfried Hoyer had already realized that brain glucose and energy metabolism were the sites of major abnormalities in AD (Hoyer et al., 1988). Cognitive impairment could be caused by insulin resistance in the AD brain, which is similar to patients with T2DM, and some scholars even believe AD may be considered type 3 diabetes (Steen et al., 2005; Stanley et al., 2016). Several studies have shown that antidiabetic drugs may exert neuroprotective effects by alleviating insulin resistance, reducing tissue inflammation, in addition to counteracting potentially harmful metabolic and vascular changes in the brain (Patrone et al., 2014). Hence, the application of drugs for T2DM in the treatment of AD seems to be a new and prospective approach.

Glucagon-like peptide 1 (GLP-1), an incretin hormone, can enhance glucose-dependent insulin secretion and lower blood glucose (Kieffer and Habener, 1999; Du et al., 2010), which is widely used to treat T2DM. According to research, GLP-1 receptors are broadly distributed in the central nervous system (CNS), particularly in the hypothalamus and hippocampus (Alvarez et al., 2005; Egefjord et al., 2012; Campbell and Drucker, 2013). When activated, the receptor can heighten neuroexcitability and improve cognitive performance (During et al., 2003; Abbas et al., 2009; Hamilto and Holscher, 2009). Unfortunately, with a rapid degradation by dipeptidyl peptidase IV (DPPIV), natural GLP-1 peptide has a half-life of only 2-3 min in plasma, affecting clinical applications (Deacon et al., 1995). To address this phenomenon, glucagon-like peptide 1 receptor agonists (GLP-1 RAs), whose function similarly to GLP-1 but have a longer half-life, have been developed. GLP-1 RAs was originally used to treat type 2 diabetes and currently approved drugs include exenatide, liraglutide, lixisenatide, dulaglutide, semaglutide, albiglutide (discontinued in July 2017), etc., (Trujillo et al., 2021). In the past few years, the GLP-1 RAs as a potential therapy has been evaluated in a several studies for ameliorating neurodegenerative disease (Bassil et al., 2014; Talbot, 2014). Notably, GLP-1 RAs have displayed neuroprotective effects in a variety of AD preclinical models, particularly in models with the deposition of β -amyloid (A β) (Querfurth and LaFerla, 2010). However, these studies are still in an initial stage, and have a long way to go to fully validate their therapeutic effects in AD.

This paper presents a meta-analysis and systematic review of studies on GLP-1 RAs treatment in AD animal models. We summarize the effects of GLP-1 RAs on behavioral tests and main pathological features (A β and phosphorylated tau), and discuss the therapeutic mechanisms. These results provide insight into the GLP-1 RAs ameliorating AD, and a reference for further research and clinical translation.

2 Methods

2.1 Review protocol

This study was based on the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) and the Cochrane Collaboration. It has been registered in PROSPERO (CRD42022367674).

2.2 Search strategy

The MeSH terms "GLP-1 receptor agonists (GLP-1RAs)" and "Alzheimer's Disease (AD)" were used as keywords to search in seven databases: PubMed, Web of Science, Embase, Cocharne library, China National Knowledge Infrastructure (CNKI), Wanfang Data Information Site, and China Science and Technology Journal Database (VIP). We searched for articles up to 20 September 2022. Two authors (Fanjing Kong and Tianyu Wu) independently judged the retrieved literature by reading the title, abstract and full text according to inclusion and exclusion criteria. Inconsistent results were discussed or decided by a third author (Tao Sun).

2.3 Inclusion and exclusion criteria

The inclusion criteria for AD animal experiments with GLP-1RAs were as follows:

- (1) Object: rodents;
- Intervention type: the study must include GLP-1 RAs group and control group;
- Outcome indicators: behavioral test must include Morris water maze (MWM);
- (4) Article type: articles without full text or original data were excluded.

2.4 Data extraction and quality assessment

The extracted information from the included studies was as follow: 1) basic information (first author, year of publication); 2) test animals (species, sex, age); 3) interventions (drug, dose, administration period); 4) experimental results (behavioral experiments, neuropathological change). When a study contained multiple outcomes, they were considered as independent data. Plot



digitizer 1.3 software was applicated to extract data from the graphs. The risk of bias was assessed by the SYRCLE Risk of Bias (RoB) tool, primarily designed for animal research.

2.5 Statistical analysis

ReviewManager 5.3 software was applied to conduct metaanalysis of the study data. Data were continuous variables, described as mean and standard deviation (SD), and analyzed by calculating standard mean differences (SMD). The heterogeneity of study results was determined by Q-test and I^2 statistic: $I^2 \le 40\%$ means low heterogeneity; $30\% < I^2 \le 60\%$ means mild heterogeneity; $I^2 \ge 50\%$ means a high degree of heterogeneity (Higgins and Green, 2011). A random effect model was chosen for analysis when the study with high heterogeneity. *p*-value <0.05 was considered statistically significant.

3 Results

3.1 Study selection

A total of 803 articles were retrieved from the seven databases, and 489 articles were identified after removing duplicates (n = 314).



After browsing through the titles and abstracts, 369 papers were removed for at least one of the following reasons: 1) non-experimental articles (n = 264) 2) no reported studies of GLP-1 RAs on AD animal models (n = 63) 3) cell model or non-rodent (n = 32) 4) full text was not available (n = 10). Finally, after reading the full text, we selected 26 articles for analysis (Figure 1).

3.1.1 Assessment of the quality of literature

The RoB tool, developed by Hooijmans and other scholars (Hooijmans et al., 2014) from the SYRCLE Centre for Laboratory Animals in the Netherlands in 2014, was based on the Cochrane Randomized Controlled Trial Risk of Bias Assessment Tool. In this study, the RoB tool was selected to assess the risk of bias in the included studies. Here, a total of 26 studies were examined

TABLE 1 Characteristics of the included studies.

Study	Animal	Experimental group	С	Outcome	Mechanisms	
(year)		administration route)	Behavioral change	Pathological change		
An, J. (2019)	5×FAD transgenic mice AD	Exenatide	MWM	$A\beta_{1-42}$ area [†] ; PSD95 and SYN [†] ;	Reduce $A\beta_{1-42}$ deposition,	
An et al. (2019)	model (male, 5 months)	100 μg/kg; twice a day for 16 weeks; s.c.		the numerical density of mitochondria; volume density of mitochondria; specific surface area of mitochondria [†] ; MDA [↓] and SOD [†] ; ATP level [†] ; respiratory chain complex I activity [†] ; Drp1 [↓] ; Mfn2 and Opa1 [↑]	alleviate synaptic degradation, improve mitochondrial morphology, relieve oxidative damage, correct the crisis of mitochondrial energy production, and normalize mitochondrial dynamics.	
Bomba, M. (2019)	3×Tg transgenic mice AD model (male and female, 6 months)	Exenatide	MWM, ORT	Aβ plaque; p-Tau; BDNF↑; pCREB↑; pTrkB↑; pERK5↑; pSvn↑: PSD95↑: pIRS-1↑;	Revert the adverse changes of BDNF signaling and the neuroinflammation status	
Bomba et al. (2019)		500 μg/kg; 5 days per week for 3 months; i.p.		proBDNF↓; p75NTR↓; NF-κB; PPARs		
Bomfim, T. R. (2012)	APP/PS1 transgenic mice AD model (male, 9 months)	Exenatide	MWM	IRS-1pSer636↓; IRS- 1pSer312↓; p-JNK↓; plaque burden↓; soluble Aβ↓	Prevent disruption of brain insulin signaling in AD	
Bomfim et al. (2012a)		25 nmol/kg; twice a day for 3 weeks; i.p.				
Cai, H. Y. (2014)	A β_{25-35} -injected rat AD model (SD rats, male, adult, 200–230 g)	Lixisenatide	MWM	LTP↑; pGSK3β(S9) ↑; pGSK3β(Y216) ↓	Prevent Aβ-related impairments in synaptic plasticity and spatial memory	
Cai et al. (2014)	200 200 g)	10 nmol; once; i.h.			(by affecting the PI3K-Akt- GSK3β pathway)	
Chen, S. Y. (2017)	3×Tg transgenic mice AD model (male, 7 months)	Liraglutide	MWM	tau↓; p-Tau (pt231, 217, ps396, 214, 199/20) ↓; phosphorylation or total NF-H	Reduce hyperphosphorylation of tau and NFs and reduce neuronal degeneration (by	
Chen et al. (2017)		300 μg/kg; once a day for 8 weeks; s.c.		and NF-M↓; p-ERK1/2↑; p-JNK/SAPKs↓	alterations in JNK and ERK signaling)	
Garabadu, D. (2019)	Aβ-injected rat AD model (Wistar rats, male, 6–8 weeks, 160–200 g)	Exenatide	MWM, Y maze	level of Aβ ₁₋₄₂ ↓; ACh level↑; ChAT level↑; AChE level↑; the level of formazan produced in	Mitigate AD-like manifestations including mitochondrial toxicity perhaps	
Garabadu and Verma (2019)		5 µg/kg; once a day for 14 days; i.p.		MTT assay [†] ; integrity in terms of the fluorescence intensity of TMRM [†] ; oxygen consumption [†] ; mitochondrial respiratory control ratio and ADP/O [†] ; mitochondrial complex enzyme-I, II, IV and V [↓] ; Akt and p-Akt [†]	(by PI3K/Akt-mediated pathway)	
Han, W. N. (2013)	A β_{25-35} -injected rat AD model (SD rats, male, adult, 230–250 g)	Liraglutide	MWM	L-LTP↑; cAMP↑	Improve spatial memory deficits and L-LTP deficits; activate the cAMP signaling	
Han et al. (2013)	200 200 g)	0.05 nmol, 0.5 nmol, 5 nmol; once; i.h.			pathway in the brain	
Hansen, H. H. (2016)	hAPP Lon/PS1 A246E transgenic mice AD model	Liraglutide	MWM	Total brain volume; total plaque volume; total relative	N/A	
Hansen et al. (2016)	(male, 5 months)	100 μg/kg, 500 μg/kg; once a day for 3 months; s.c.		piaque ioad		
Jia, X. T. (2016)	$A\beta_{1-42}$ -injected rat AD model (SD rats, male, adult,	Exenatide	MWM	Bcl2↑; Caspase 3↓; Bax↓	Modulate the expression of Bcl2, Bax and caspase-3	
Jia et al. (2016)	230–250 g)	0.02 nmol, 0.2 nmol, 2 nmol; once; i.c.v.			•	
Li, J. X. (2019)	STZ-induced rat AD model (SD rats, male and female,	(Val8) GLP-1	MWM	MDA \downarrow ; SOD \uparrow ; AKT \uparrow ; ERK \uparrow	Activate AKT/ERK signal transduction pathway (by	
Li et al. (2019b)	20-24 months, 320-400 g)	5 μl; twice; i.c.v.			strengthening the antioxidant activity of the brain tissue and reducing oxidative stress injury)	

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TABLE 1 (Continued) Characteristics of the included studies.

Study	Animal	Experimental group	C	Outcome	Mechanisms	
(year)		administration route)	Behavioral change	Pathological change		
McClean, P. L. (2011)	APPswe/PS1DE9 transgenic mice AD model (male,	Liraglutide	MWM, ORT	LTP↑; PPF (paired-pulse facilitation) ↑; Aβ plaque↓;	Prevent key neurodegenerative developments (prevented	
McClean et al. (2011)	/ months)	25 nm/kg; once a day for 8 weeks; i.p.		dense-core Congo red plaques↓; activated glia (Iba1 stain) ↓; young neurons (doublecortin-positive cells) ↑; Synaptophysin levels↑; Soluble Aβ oligomer and total APP levels↓	synapse loss and deterioration of synaptic plasticity in the hippocampus; enhance synaptic plasticity; reduce $A\beta$ plaque count and dense- core plaque numbers; reduce levels of soluble amyloid oligomers; reduce inflammation response; increase numbers of young neurons in the dentate gyrus)	
McClean, P. L. (2014)	APPswe/PS1DE9 transgenic mice AD model (male,	Liraglutide	MWM, ORT	LTP \uparrow ; A β plaque load \downarrow ; dense core plaque load \downarrow ; activated glia	Reverse some of the key pathological hallmarks of AD	
McClean and Hölscher (2014)	14 months)	25 nm/kg; once a day for 8 weeks; i.p.		(Iba1 stain) ↓; new neurons (doublecortin-positive cells); soluble amyloid oligomer levels↓; total APP levels↓; synaptophysin levels↑; IDE levels↑; GSK3β levels↑; Nrk2b levels↑	(reduce plaque load; reduce inflammation; increase neuronal progenitor cell count in the dentate gyrus; enhance LTP; increase synapse numbers; reduce total brain APP and beta-amyloid oligomer levels; increase IDE)	
McClean, P. L. (2015)	APPswe/PS1DE9 transgenic mice AD model (male, 8 weeks)	Liraglutide	MWM, ORT, open field	LTP↑; plaque load↓; dense-core Congo-red plaques↓; activated microglia (IBA-1 stain) ↓:	Reduce the main hallmarks of AD (prevent synapse and synaptic plasticity loss; reduce	
McClean et al. (2015)		25 nm/kg; once a day for 8 months; i.p.		young neurons (doublecortin- positive cells) ↑; Synaptophysin levels↑	amplie plasteri loss, reduce amyloid plaque load and dense core congophilic plaques; reduce chronic inflammation; enhance neurogenesis)	
Qi, L. (2016)	Aβ ₁₋₄₂ -injected mice AD model (C57BL/6 mice, male,	Liraglutide	MWM, Y maze	p-Tau↓; p-Akt↑; p-GSK3β↑; synaptic structure in the	Decrease the phosphorylation of tau (via the protein kinase B	
Qi et al. (2016)	8 weeks)	25 nmol/kg; once a day for 8 weeks; s.c.		CA1 regionĵ; cell structure degradation↓	and glycogen synthase kinase- $_{3\beta}$ pathways); alleviate the ultra-structural changes of pyramidal neurons and chemical synapses in the hippocampal CA1 region	
Robinson, A. (2019)	Tg2576 transgenic mice AD model (male, 4 months)	Exenatide	MWM	GSK3 β ↓; A β ₁₋₄₂ ; AKT1; IRS1; CTNNB1; INSR; AKT3; IGF1R	Reduced expression of IRSP genes, restore insulin signal transmission in brain	
Robinson et al. (2019)		0.075µg; 6 days a week for 8 months; i.n.				
Wang, X. (2016)	A β_{1-42} -injected rat AD model (SD rats, male, adult, 220–260 g)	Exenatide	MWM	LTP↑; cAMP↑; p-CREB↑	Modify impaired LTP; modifying the cAMP/PKA/ CREB signaling pathway	
Wang et al. (2016a)	220 200 8)	0.2 nmol; once; i.h.			eren orginality paulity	
Wang, X. (2016)	A β_{31-35} -injected mice AD model (C57BL/6 mice, male, 8–10 weeks, 18–22 g)	Exenatide	Circadian rhythm, MWM, locomotor	N/A	N/A	
Wang et al. (2016b)	o-10 weeks, 10-22 g)	0.05 nmol, 0.5 nmol; once; i.n.	activity			
Wang, Y. (2018)	APP/PS1 transgenic mice AD model (male, 6 months,	Exenatide	MWM	GnT-III \downarrow ; aberrant bisecting GlcNAc levels \downarrow ; β -catenin \uparrow ;	Downregulate aberrant GnT- III expression through the Akt/	
Wang et al. (2018)	JU-4J 8/	25 nmol/kg; once a day for 4 weeks; s.c.		p-Akt; p-Gokop; Ap plaques↓; p-Tau↓	pathway in neurons	
Xiong, H. (2013)	STZ-induced mice AD model (Kunming mice, male, 3 months, 38.66 ± 1.80 g)	Liraglutide	MWM	hyperphosphorylation of NFs↓; glycosylation level↑; p-Tau↓; microtubule binding tau↑;	Decrease p-Tau and neurofilament proteins by enhancing O-glycosylation of	

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TABLE 1 (Continued) Characteristics of the included studies.

Study	Animal	Experimental group	С	Outcome	Mechanisms	
(year)		administration route)	Behavioral change	Pathological change		
Xiong et al. (2013)		300 µg/kg; once a day for 30 days; s.c.		p-ERK1↑; p-JNK1↓; p-JNK2↓; degenerated neurons↓	neuronal cytoskeleton protein, improving the JNK and ERK signaling pathway, and reducing neural degeneration	
Yu, C. J. (2020)	OA-induced rat AD model	Liraglutide	MWM, Y maze	the level of neuronal	Prevent neuronal apoptosis	
Yu et al. (2020)	(C5/BL/6 rats, female)	300 μg/kg; once a day for 30 days; s.c.		apoptosisį; p-1auį; BACEIį	and inhibit the activation of tau and the expression of BACE1	
Zhang, M. J. (2022)	5×FAD transgenic mice AD model (male, 5 months)	Exenatide	MWM	$A\beta_{1-42}\downarrow$; NLRP2 \downarrow ; GFAP \downarrow ; IL- 1 $\beta\downarrow$; TNF- $\alpha\downarrow$; the number of	Mitigate AD-related cognitive impairment and	
Zhang et al. (2022)		100 μg/kg; twice a day for 16 weeks; s.c.		NeuN-positive cells	neuroinflammation by suppressing NLRP2 activation	
Lu Chong (2019)	STZ-induced rat AD model (SD rats, male, 8–9 months,	Liraglutide	MWM	$A\beta_{1-42}\downarrow; PPAR\gamma\uparrow$	Inhibit the accumulation of A β by activating PPAR γ	
Lu et al. (2019)	200–240 g)	200 μg/kg; once a day for 28 days; i.p.				
Sun Jie (2015)	APP/PS1/Tau transgenic	Liraglutide	MWM	$A\beta_{1\text{-}42} \downarrow$	Improve insulin signaling	
Sun et al. (2015)	10–14 g)	300 μg/kg; once a day for 2 months; i.p.				
Zhang Zhihua (2019)	APP/PS1 transgenic mice AD model (male, 6 months,	Geniposide	Novel object recognition, MWM	number of neurons \uparrow ; senile plagues \downarrow ; $A\beta_{1-40}\downarrow$; $A\beta_{1-42}\downarrow$	Downregulation of mTOR signal pathway and	
Zhang (2019)	25 ± 2.8 g)	50 mg/kg; once a day for 6 weeks; i.g.			ennancement of autophagy	
Zhao Li (2021)	STZ-induced rat AD model	Liraglutide	MWM	p-Tau↓	Decrease the expression of	
Zhao et al. (2021)	(wistar rats, male, 180–220 g)	300 μg/kg; once a day for 4 weeks; s.c.			p-Tau in hippocampus	
Zheng Jiaping (2021)	5×FAD transgenic mice AD model (male, 4 months)	Liraglutide	MWM	A β accumulation \downarrow ; the number of neurons \uparrow ; morphology of	Reduce oxidative stress and improve astrocyte's neuronal	
Zheng (2021)		25 μg/kg; once a day for 8 weeks; s.c.		GFAP↓; glycolytic enzymes (HIF-1α, HK1, PKM1/2, PKM2, PFKFB3) ↑; PDK2↑; p-PDH↓; ROS↓; GSH↑; ATP↑; p-PI3K↑; p-AKT↑	supportive functions	

Note: A β , β -amyloid; MWM, morris water maze; PSD95, postsynaptic density protein 95; SYN, synaptophysin; MDA, malondialdehyde; SOD, superoxide dismutase; ATP, adenosine triphosphate; Drp1, dynamin-related protein 1; Mfn2, mitofusin 2; Opa1, optic atrophy protein 1; BDNF, brain-derived neurotrophic factor; pCREB, phosphorylated cAMP response elementbinding protein; pTrkB, phosphorylated tropomyosin receptor kinase B; pERK5, phosphorylated extracellular signal-regulated kinase 5; IRS, insulin receptor substrate; NF- κ B, nuclear factor kappa B; PPARs, peroxisome proliferator-activated receptors; ORT, object recognition test; s.c., subcutaneous; i.p., intraperitoneal; i.h., hippocampal; LTP, long-term potentiation; GSK3 β , glycogen synthase kinase 3 β ; PI3K/Akt, phosphatidylinositol 3 kinase/protein kinase B; JNK, c-Jun-N-terminal kinases; cAMP, cyclic adenosine monophosphate; i.c.v., intracerebroventricular; i.g., intra-gastric; i.n., intranasal; NLRP2, nod-like receptor family pyrin domain containing 2; PPAR γ , peroxisome proliferator-activated receptor gamma; mTOR, mammalian target of rapamycin; ROS, reactive oxygen species. " \uparrow " for increase.

(Figure 2). Included articles were assessed independently by three authors (Tianyu Wu, Jie Cai and Zhishan Zhu), and where disagreements arose, they would be resolved after careful discussion with a fourth author (Ying Xu). The RoB tool consists of 10 entries, including selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases. A report is considered low risk for its accordance with the entry requirements, high risk for no accordance, or 'unclear' for the reason that the reported details are insufficient. In this analysis, two studies described the detailed method of generating the allocation sequence and were seen as low risk of bias; the other 24 studies did not clarify the specific method of random allocation and were

therefore classified as 'unclear'. For baseline characteristics, more than half of the studies had similar baseline at the start of the experiment, so they were classified as 'low risk'; seven studies did not specify and were classified as 'unclear'. Except two studies, which described in detail the method of concealing allocation, the remaining studies were not clearly stated. 15 studies which clearly indicated randomized housing was judged to have a low risk of bias, whereas 11 studies that failed to determine randomized housing were categorized as having unclear risk of bias. Two studies clearly demonstrated that the results of the allocation were hidden for the investigators; thus, they were considered to be at low risk of bias; the other 24 studies were considered to be an unclear risk of bias. Five studies explicitly demonstrated the use of blinding of testers and were therefore considered to be at low risk of bias. 13 studies reported complete experimental results and were categorized as low risk. Studies that did not explicitly report allocation concealment, randomized outcome assessment and selective reporting were considered to be at an unspecified risk of bias. The results of the quality assessment suggest that the experimental design of animal studies should be detailed in the article in order to reduce the occurrence of unspecified risks.

3.1.2 Study characteristics

In Table 1, we list the characteristics of these studies. Of the selected 26 articles, two kinds of animals were included: rats (n = 9) and mice (n = 17). And the strains of them included transgenic mice (n = 14), SD rats (n = 6), Wistar rats (n = 2), C57BL/6 mice (n = 2), Kunming mice (n = 1), C57BL/6 rats and (n = 1). There were 22 studies selecting male animals, two for both males and females, one for female animals, and one not mentioning the sex of the animals.

The GLP-1 RAs involved in these articles include five types: liraglutide (n = 13), exenatide (n = 10), lixisenatide (n = 1), (Val8) GLP-1 (n = 1), and geniposide (n = 1). Liraglutide is based on the natural GLP-1 sequence and has 97% homology to human GLP-1, the main difference being the replacement of lysine with arginine at position 34 (Malm-Erjefält et al., 2010). It is a long-acting GLP-1 RAs, with a half-life of up to 13 h (Bain, 2014). Liraglutide was approved by the FDA in 2010. Currently, it is primarily administered through subcutaneous injection, and data indicates that the bioavailability of liraglutide reaches 55% after subcutaneous injection. Exenatide, a synthetic 39 amino acid peptide, is the first GLP-1 RAs approved for clinical use by the FDA in 2005 (Müller et al., 2019). Exenatide shares 53% homology with human GLP-1, and it can protect against DPP-IV cleavage and is resistant to DPP-IV inactivation (Diz-Chaves et al., 2022a). Lixisenatide is an analogue of exenatide and has comparable pharmacokinetic properties (Finan et al., 2015). Like exenatide, lixisenatide is also a short-acting GLP-1 RAs with a half-life of approximately 3 h. Adlyxin, which is a drug derived from lixisenatide, was approved by the FDA in 2016. (Val8) GLP-1 is a human GLP-1 analogue formed by substituting a Val residue for Ala at the N-terminal 8-position (Lennox et al., 2013). (Val8) GLP-1 has been shown to be resistant to cleavage by DPP-IV, thereby extending the half-life (Green et al., 2006). Geniposide, an iridoid glycoside present in the fruit of Gardenia jasminoides, is the main component of the traditional Chinese medicine Gardenia jasminoides (Hou et al., 2008). Recent studies have shown that geniposide can act as a GLP-1 RAs and induce various cellular signaling pathways by activating GLP-1 receptors (Liu et al., 2006; Gao et al., 2014).

Four animal models of AD were used in the article: transgenic animals (n = 14), chemical induction including injections of A β (n = 7), streptozotocin (STZ) (n = 4), and okadaic acid (OA) (n = 1). The characteristics of the following related models are summarized so as to have a better understanding of the underlying role of these animal models in the AD pathological mechanism unveiling and in their application for therapeutic trials.

 Transgenic animal models include Tg2576 mice, APP/PS1 mice, APPswe/PS1DE9, APPSwe/PSEN1 (A246E), 5×FAD mice, and 3×Tg mice. Tg2576 mice overexpress the Swedish mutation APP^{K670N/M671L} on the APP gene. This mutation leads to elevated levels of AB, which ultimately causes plaque deposition. In addition, the mice displayed oxidative stress injury and behavioral cognitive impairment. However, Tg2576 mice have no typical tau pathological manifestations and do not show neurofibrillary tangles (NFTs) (Irizarry et al., 1997). Both APP/PS1 mice, APPswe/PS1DE9 and APPSwe/PSEN1 (A246E) mice contain transgenes with the Swedish mutations in APP and PSEN1. These mice will develop amyloid deposits in the neocortex at around six weeks and a phosphorylated tau (p-Tau) neuritis process can be observed around the plaques, but without mature tangles and no typical tau pathological changes (Radde et al., 2006). 5×FAD mice express five ADrelated mutations in the APP, such as the Swedish (APP^{K670N/M671L}), Florida (APP^{I716V}), and London (APP^{V717I}) mutations, and PSEN1 genes, like the PS1^{M146L} and PS1^{L286V} mutations. It showed that 5×FAD mice only showed cognitive impairment associated with AB levels and did not show alterations in Tau pathology (Richard et al., 2015). 3×Tg mice include three mutations related to familial AD (APP Swedish, PSEN1 M146V, and MAPT P301L). These mice exhibited behavioral deficits in learning and memory abilities. Pathologically, they show progressive age-related changes, including tau protein hyperphosphorylation and Aß pathology, with plaque and tangle formation. In addition, there is also present synaptic dysfunction and adenosine triphosphate (ATP) deficiency (Oddo et al., 2003). Transgenic mice are currently the most widely utilized animal models in preclinical studies of AD and have the advantage of exhibiting familial AD-related manifestations (Puzzo et al., 2015). A major limitation of Tg2576 mice and double transgenic mice (APP/PS1 mice, APPSwe/PSEN1 (A246E), and 5×FAD mice is the absence of typical tau pathology. Although p-Tau is observed in some models, it does not develop into NFTs. Although both amyloid plaques and NFTs were present in 3×Tg mice, the study showed that these pathologies developed late, and were not observed until the mice aged (Drummond and Wisniewski, 2017).

(2) Chemically induced models include injections of Aβ, STZ and OA. The AB infusion model induces neurotoxicity by injecting A β peptides with manifested A β deposition, inflammatory response and cognitive impairment. It is mainly used in the study of AB pathology. Since injection of AB will cause acute toxicity, this model cannot recapture the progressive onset of AD, moreover the concentration of injection sites may lead to uneven distribution of AB deposition sites and damage the brain's surrounding tissue (Jia-Yue et al., 2019). The STZ infusion model, first proposed by Professor Sigfried Hoyer, is considered to be useful in the study of sporadic AD (Hoyer et al., 1994; Salkovic-Petrisic et al., 2013). He suggested that the major biochemical perturbation in sporadic AD involves controlling cerebral glucose metabolism, which follows the failure of brain insulin receptor signaling (Hoyer et al., 1993). Intracerebroventricular (i.c.v.) injection of STZ can disrupt the control level of glucose and energy metabolism, resulting in decreased brain glucose utilization, disturbed brain metabolism and cognitive dysfunction (Nitsch and Hoyer,

Studies Only	Exp	eriment	al	0	ontrol	T	14/-1 1 /	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% Cl	IV. Random, 95% CI
An, J.2019	33	11.92	12	39.89	8.11	12	3.8%	-0.65 [-1.48, 0.17]	
Bomfim, T. R.2012	14.47	14.01	12	54.2	26.82	12	3.6%	-1.79 [-2.77, -0.82]	
Cai, H. Y.2014	15.08	2.07	10	15.74	6.22	10	3.8%	-0.14 [-1.01, 0.74]	I
Chen, S. Y.2017	16.09	21.03	10	24.8	20.46	10	3.7%	-0.40 [-1.29, 0.49]	
Garabadu, D.2019	49.23	1.88	6	52.31	3.77	6	3.2%	-0.95 [-2.18, 0.27]	
Han, W. N.2013(0.05nmol)	15.97	1.24	10	17.13	6.23	6	3.5%	-0.28 [-1.30, 0.73]	
Han, W. N.2013(0.5nmol)	14.42	1.22	10	17.13	6.23	5	3.4%	-0.71 [-1.82, 0.41]	
Han, W. N.2013(5nmol)	12.87	1.23	10	17.13	6.23	5	3.3%	-1.11 [-2.28, 0.06]	
Hansen, H. H.2016(100µg/kg)	30.77	8.65	17	41.26	17.3	9	3.8%	-0.83 [-1.67, 0.01]	
Hansen, H. H.2016(500µg/kg)	37.76	17.8	18	41.26	17.3	8	3.8%	-0.19 [-1.03, 0.64]	
Jia, X. T.2016(0.02nmol)	24.63	8.22	10	26.55	8.22	4	3.3%	-0.22 [-1.38, 0.94]	
Jia, X. T.2016(0.2nmol)	20.76	8.24	10	26.55	8.22	3	3.0%	-0.65 [-1.98, 0.67]	
Jia, X. T.2016(2nmol)	16.92	10.27	10	26.55	8.22	3	3.0%	-0.90 [-2.26, 0.45]	
Li, J. X.2019	26.1	2.8	15	41.7	5.2	15	3.2%	-3.63 [-4.85, -2.42]	
Lu Chong2019	13.57	22.23	15	62.09	25.6	15	3.7%	-1.97 [-2.86, -1.08]	
McClean, P. L.2011	27.54	10.93	12	48.5	14.91	12	3.7%	-1.55 [-2.48, -0.62]	- <u></u>
McClean, P. L.2014	20.63	7.89	12	20.63	7.89	12	3.9%	0.00 [-0.80, 0.80]	Т
McClean, P. L.2015	19.67	8.52	12	27.87	8.52	12	3.8%	-0.93 [-1.78, -0.08]	
QI, L.2016	26.67	8.27	10	34.51	11.57	10	3.7%	-0.75 [-1.66, 0.17]	1
Sun Jie2015	14.72	4.33	8	15.13	5.1	8	3.6%	-0.08 [-1.06, 0.90]	T
Wang, X.2016	33.56	3.17	10	49.39	4.75	10	2.7%	-3.75 [-5.32, -2.19]	
wang, X.2016(0.05nmol)	25.2	2.79	12	33.79	2.05	6	2.7%	-3.17 [-4.70, -1.64]	
Wang, X.2016(0.5nmol)	25.34	2.77	12	33.79	2.05	6	2.7%	-3.14 [-4.65, -1.62]	
Wang, Y.2018	20.11	3.67	6	53.68	1.23	6	0.4%	-11.32 [-16.96, -5.68]	
Xiong, H.2013	16.67	40.07	8	50	42.43	8	3.5%	-0.76 [-1.79, 0.26]	
Yu, C. J.2020	38.27	3.21	10	45.66	3.53	10	3.3%	-2.10 [-3.24, -0.96]	
Zhang Zhihua2019	46.58	58.91	15	56.17	27.85	15	4.0%	-0.20 [-0.92, 0.52]	T
Zhang, M. J.2022	32.76	3.78	12	39.97	2.4	12	3.5%	-2.20 [-3.25, -1.15]	
Zhaoli2021	12.26	5.74	6	23.01	5.74	6	2.9%	-1.73 [-3.14, -0.32]	
Zheng Jiaping2021	27.72	6.74	15	51.24	6.74	15	3.3%	-3.40 [-4.56, -2.23]	
T-1-1 (05%) OD			005			074	100 00/	4 00 1 4 00 0 001	
			0 (D	0 0000	1)· 12 =	76%			
Heterogeneity: 1au ² = 0.88; Chi Test for overall effect: Z = 6.37	* = 120.6 (P < 0.00	0, df = 2 1001)	29 (P <	0.0000				24.4 Marca D/6	-10 -5 0 5 10 Favours [experimental] Favours [control]
Heterogeneity: 1au ² = 0.88; Chi Test for overall effect: Z = 6.37 Study or Subgroup	* = 120.6 (P < 0.00 Exp Mean	0, df = 2 1001) eriment SD	al Total	C	ontrol	Total	Weight	Std. Mean Difference IV. Random, 95% Cl	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% Cl
Heterogeneity: 1au ⁺ = 0.88; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019	* = 120.6 (P < 0.00 Exp <u>Mean</u> 3.15	0001) eriment <u>SD</u> 2.49	al <u>Total</u> 12	0.0000 Mean 1.14	control SD 1.56	Total 12	Weight 3.8%	Std. Mean Difference <u>IV. Random. 95% Cl</u> 0.93 [0.08, 1.78]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% Cl
Heterogeneity: 1au ⁺ = 0.88; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomba, M.2019	F = 120.6 (P < 0.00 Exp <u>Mean</u> 3.15 3.04	eriment 2.49 1.67	al <u>Total</u> 12 7	0.0000 Mean 1.14 4.02	control SD 1.56 2.82	<u>Total</u> 12 6	Weight 3.8% 3.3%	Std. Mean Difference IV. Random. 95% Cl 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% Cl
Heterogeneity: 1au ⁴ = 0.88; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomba, M.2019 Bomfim, T. R.2012	<pre># = 120.6 (P < 0.00 Exp Mean 3.15 3.04 22.6</pre>	eriment 2.49 1.67 6.29	al <u>Total</u> 12 7 12	0.0000 Mean 1.14 4.02 16.5	control SD 1.56 2.82 4.81	Total 12 6 12	Weight 3.8% 3.3% 3.8%	Std. Mean Difference IV. Random. 95% Cl 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random, 95% Cl
Heterogeneity: 1au ² = 0.88; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomba, M.2019 Bombin, T. R.2012 Cai, H. Y.2014	<pre># = 120.6 (P < 0.00 Exp Mean 3.15 3.04 22.6 42.68</pre>	eriment 2.49 1.67 6.29 12.38	al <u>Total</u> 12 7 12 10	0.0000 Mean 1.14 4.02 16.5 26.18	control SD 1.56 2.82 4.81 15.52	Total 12 6 12 10	Weight 3.8% 3.3% 3.8% 3.6%	Std. Mean Difference <u>IV. Random, 95% Cl</u> 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.13 [0.17, 2.08]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% Cl
Heterogeneity: 1 au ² = 0.38; Chi Test for overall effect: Z = 6.37 <u>Study or Subgroup</u> An, J.2019 Bomba, M.2019 Bomfim, T. R.2012 Cai, H. Y.2014 Chen, S. Y.2017	F = 120.6 (P < 0.00) Exp Mean 3.15 3.04 22.6 42.68 30.34	eriment SD 2.49 1.67 6.29 12.38 6.54	al <u>Total</u> 12 7 12 10 10	0.0000 Mean 1.14 4.02 16.5 26.18 21.21	iontrol SD 1.56 2.82 4.81 15.52 6.54	Total 12 6 12 10 10	Weight 3.8% 3.3% 3.8% 3.6% 3.5%	Std. Mean Difference <u>IV. Random, 95% C1</u> 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.34 [0.35, 2.33]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% Cl
Heterogeneity: 1au* = 0.88; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomba, M.2019 Bomfim, T. R.2012 Cai, H. Y.2014 Chen, S. Y.2014 Garabadu, D.2019	² = 120.6 (P < 0.00 Exp <u>Mean</u> 3.15 3.04 22.6 42.68 30.34 49.04	eriment <u>SD</u> 2.49 1.67 6.29 12.38 6.54 6.76	al <u>Total</u> 12 7 12 10 10 6	0.0000 Mean 1.14 4.02 16.5 26.18 21.21 19.92	control SD 1.56 2.82 4.81 15.52 6.54 6.01	Total 12 6 12 10 10 10 6	Weight 3.8% 3.3% 3.8% 3.6% 3.5% 1.5%	Std. Mean Difference IV. Random. 95% Cl 0.93 (0.08, 1.78) -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.13 (0.17, 2.08] 1.34 [0.35, 2.33] 4.20 [1.86, 6.55]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% Cl
Heterogeneity: 1au ² = 0.38; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomba, M.2019 Bomba, M.2019 Bomfim, T. R.2012 Cai, H. Y.2014 Chen, S. Y.2014 Chen, S. Y.2017 Garabadu, D.2019 Han, W. N.2013(0.05nmol)	² = 120.e (P < 0.00 <u>Exp</u> <u>Mean</u> 3.15 3.04 22.6 42.68 30.34 49.04 31.59	eriment 2.49 1.67 6.29 12.38 6.54 6.76 3.68	al <u>Total</u> 12 7 12 10 10 6 10	0.0000 Mean 1.14 4.02 16.5 26.18 21.21 19.92 24.81	control SD 1.56 2.82 4.81 15.52 6.54 6.01 3.88	Total 12 6 12 10 10 6 6	Weight 3.8% 3.3% 3.6% 3.6% 3.5% 1.5% 3.1%	Std. Mean Difference IV. Random, 95% Cl 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.13 [0.17, 2.08] 1.34 [0.35, 2.33] 4.20 [1.86, 6.55] 1.71 [0.49, 2.93]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% Cl
Heterogeneity: 1au ² = 0.38; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomba, M.2019 Bomfim, T. R.2012 Cai, H. Y.2014 Chen, S. Y.2017 Garabadu, D.2019 Han, W. N.2013(0.55mol) Han, W. N.2013(0.55mol)	² = 120.6 (P < 0.00 <u>Exp</u> <u>Mean</u> 3.15 3.04 22.6 42.68 30.34 49.04 31.59 37.98	0, df = 2 0001) eriment 2.49 1.67 6.29 12.38 6.54 6.76 3.68 5.52	al Total 12 7 12 10 10 6 10 10	0.0000 Mean 1.14 4.02 16.5 26.18 21.21 19.92 24.81 24.81	control SD 1.56 2.82 4.81 15.52 6.54 6.01 3.88 3.88	Total 12 6 12 10 10 6 6 5	Weight 3.8% 3.3% 3.6% 3.6% 3.5% 1.5% 3.1% 2.6%	Std. Mean Difference IV. Random. 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.13 [0.17, 2.08] 1.34 [0.35, 2.33] 4.20 [1.86, 6.55] 1.71 [0.49, 2.93] 2.44 [0.96, 3.92]	-10 -5 0 5 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random, 95% Cl
Heterogeneity: 1au* = 0.38; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2019 Cai, H, Y.2014 Chen, S, Y.2014 Chen, S, Y.2014 Chan, W. N.2013(0.5nmol) Han, W. N.2013(0.5nmol) Han, W. N.2013(0.5nmol)	² = 120.e (P < 0.00 <u>Exp</u> <u>Mean</u> 3.15 3.04 22.6 42.68 30.34 49.04 31.59 37.98 43.22	0, df = 2 0001) eriment 2.49 1.67 6.29 12.38 6.54 6.76 3.68 5.52 2.45	al Total 12 7 12 10 10 6 10 10 10 10 10	0.0000 Mean 1.14 4.02 16.5 26.18 21.21 19.92 24.81 24.81 24.81	control SD 1.56 2.82 4.81 15.52 6.54 6.01 3.88 3.88 3.88	Total 12 6 12 10 10 6 6 5 5	Weight 3.8% 3.3% 3.6% 3.5% 1.5% 3.1% 2.6% 1.3%	Std. Mean Difference IV. Random, 95% Cl 0.93 (0.08, 1.78) -0.40 [-1.51, 0.70] 1.05 (0.19, 1.92] 1.13 (0.17, 2.08) 1.24 [0.35, 2.33] 4.20 [1.86, 6.55] 1.71 [0.49, 2.93] 2.44 [0.96, 3.92] 5.86 [3.18, 8.51]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% CI
Heterogeneity: 1au ² = 0.38; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomfan, X.2019 Bomfan, T. R.2012 Cai, H. Y.2014 Chen, S. Y.2014 Chen, S. Y.2014 Chen, S. Y.2014 Han, W. N.2013(0.5nmol) Han, W. N.2013(0.5nmol) Hansen, H. A2016(100µg/kg)	² = 120.e (P < 0.00 <u>Exp</u> <u>Mean</u> 3.15 3.04 22.6 42.68 30.34 49.04 31.59 37.98 43.22 32.77	0, df = 2 0001) eriment 2.49 1.67 6.29 12.38 6.54 6.76 3.68 5.52 2.45 17.55	al Total 12 7 12 10 10 6 10 10 10 10 10 10 10 10 10 10	0.0000 Mean 1.14 4.02 16.5 26.18 21.21 19.92 24.81 24.81 24.81 24.81 28.09	control SD 1.56 2.82 4.81 15.52 6.54 6.01 3.88 3.88 3.88 14.04	Total 12 6 12 10 10 6 6 5 5 9	Weight 3.8% 3.3% 3.6% 3.5% 1.5% 3.1% 2.6% 1.3% 3.9%	Std. Mean Difference IV. Random, 95% C1 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.13 [0.17, 2.08] 1.34 [0.35, 2.33] 4.20 [1.86, 6.55] 1.77 [0.49, 2.93] 2.44 [0.96, 3.92] 5.85 [3.18, 8.51] 0.28 [-0.54, 1.09]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% CI
Heterogeneity: 1au* = 0.88; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomba, M.2019 Bomfim, T. R.2012 Cai, H. Y.2014 Chen, S. Y.2017 Garabadu, D.2019 Han, W. N.2013(0.5mmol) Han, W. N.2013(0.5mmol) Han, W. N.2013(5.5mmol) Hansen, H. H.2016(f000µg/kg) Hansen, H. H.2016(f00µg/kg)	² = 120.e (P < 0.00 <u>Exp</u> <u>Mean</u> 3.15 3.04 22.6 42.68 30.34 49.04 31.59 37.98 43.22 32.77 26.38	0, df = 2 0001) eriment 2.49 1.67 6.29 12.38 6.54 6.76 3.68 5.52 2.45 17.55 12.64	al Total 12 7 12 10 10 6 10 10 10 10 10 10 10 10 10 10	Mean 1.14 4.02 16.5 26.18 21.21 19.92 24.81 24.81 24.81 28.09	control SD 1.56 2.82 4.81 15.52 6.54 6.01 3.88 3.88 3.88 3.88 14.04 14.04	Total 12 6 12 10 10 6 6 5 5 9 8	Weight 3.8% 3.3% 3.6% 3.5% 1.5% 3.1% 2.6% 1.3% 3.9% 3.8%	Std. Mean Difference IV. Random. 95% CI 0.93 (0.08, 1.78) 1.05 (0.19, 1.92) 1.13 (0.17, 2.08) 1.44 (0.35, 2.33) 4.20 (1.86, 6.55) 1.71 (0.49, 2.93) 2.44 (0.96, 3.92) 5.85 (3.18, 8.51) 0.28 (-0.54, 1.09) -0.13 (-0.96, 0.71)	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% CI
Heterogeneity: 1au ² = 0.38; Chi Test for overall effect: Z = 6.37 <u>Study or Subgroup</u> An, J.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2019 Cai, H, Y.2014 Chen, S, Y.2014 Chen, S, Y.2014 Garabadu, D.2013 (Janabadu, D.2013 (Janabadu, D.2013 Han, W. N.2013(0.5mmol) Han, W. N.2013(0.5mmol) Hansen, H. H.2016(100µg/kg) Hansen, H. H.2016(100µg/kg) Hansen, H. H.2016(0.02mmol)	² = 120.e (P < 0.00 <u>Exp</u> <u>Mean</u> 3.15 3.04 22.6 42.68 30.34 49.04 31.59 37.98 43.22 32.77 26.38 26.45	0, df = : 0001) 2.49 1.67 6.29 12.38 6.54 6.76 3.68 5.52 2.45 17.55 12.64 9.18	al Total 12 7 12 10 10 10 10 10 10 10 17 18 10	1.14 4.02 16.5 26.18 21.21 19.92 24.81 24.81 24.81 24.81 24.81 28.09 28.09 28.09 26.13	control SD 1.56 2.82 4.81 15.52 6.54 6.01 3.88 3.88 3.88 3.88 14.04 14.04 8.16	Total 12 6 12 10 10 6 6 5 5 9 8 4	Weight 3.8% 3.3% 3.6% 3.6% 1.5% 3.1% 2.6% 1.3% 3.9% 3.8% 3.2%	Std. Mean Difference IV. Random, 95% Cl 0.93 (0.08, 1.78) -0.40 [-1.51, 0.70] 1.05 (0.19, 1.92] 1.13 (0.17, 2.08) 4.20 [1.86, 6.55] 1.71 [0.49, 2.93] 2.44 [0.96, 3.92] 5.86 [3.18, 8.51] 0.28 [-0.54, 1.09] -0.13 (-0.96, 0.71] 0.03 [-1.13, 1.19]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% Cl
Heterogeneity: 1au ² = 0.38; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomba, M.2019 Bombi, M.2019 Bommi, T. R.2012 Cai, H. Y.2014 Chen, S. Y.2017 Garabadu, D.2019 Han, W. N.2013(0.5nmol) Han, W. N.2013(0.5nmol) Hansen, H. H.2016(100g/kg) Hansen, H. H.2016(100g/kg) Jia, X. T.2016(0.2nmol) Jia, X. T.2016(0.2nmol)	² = 120.e (P < 0.00 <u>Exp</u> <u>Mean</u> 3.15 3.04 22.6 42.68 30.34 49.04 31.59 37.98 43.22 32.77 26.38 26.45 35.48	0, df = : 0001) 2.49 1.67 6.29 12.38 6.54 6.76 3.68 5.52 2.45 17.55 12.64 9.18 9.18	al Total 12 7 12 10 6 10 10 10 10 10 17 18 10 10 10 10 10 10 10 10 10 10	Mean 1.14 4.02 16.5 26.18 21.21 19.92 24.81 24.81 24.81 28.09 26.13 26.13	control SD 1.56 2.82 4.81 15.52 6.54 6.01 3.88 3.88 3.88 3.88 14.04 14.04 8.16 8.16	Total 12 6 12 10 10 6 5 5 5 9 8 4 3	Weight 3.8% 3.3% 3.6% 3.6% 1.5% 3.1% 2.6% 1.3% 3.9% 3.8% 3.2% 2.8%	Std. Mean Difference IV. Random. 95% C1 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.34 [0.35, 2.33] 4.20 [1.86, 6.55] 1.71 [0.49, 2.93] 2.44 [0.96, 3.92] 5.85 [3.18, 8.51] 0.28 [-0.54, 1.09] -0.13 [-0.96, 0.71] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33]	-10 -5 0 5 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random, 95% Cl
Heterogeneity: 1au* = 0.38; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomfim, T. R.2012 Cai, H. Y.2014 Chen, S. Y.2017 Garabadu, D.2019 Han, W. N.2013(0.56nmol) Han, W. N.2013(0.56nmol) Han, W. N.2013(0.56nmol) Hansen, H. H.2016(500g/kg) Hansen, H. H.2016(500g/kg) Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Jia, X. T.2016(2cmmol)	² = 120.e (P < 0.00 <u>Exp</u> <u>Mean</u> 3.15 3.04 42.68 30.34 49.04 31.59 37.98 43.22 32.77 26.38 26.45 35.48 42.26	0, df = : 0001) 2.49 1.67 6.29 12.38 6.54 6.76 3.68 5.52 2.45 17.55 12.64 9.18 9.18 9.18 10.2	al Total 12 7 12 10 10 10 10 10 10 10 10 10 10	Mean 1.14 4.02 16.5 26.18 21.21 19.92 24.81 24.81 28.09 28.09 26.13 26.13 26.13	control SD 1.56 2.82 4.81 15.52 6.54 6.01 3.88 3.88 3.88 14.04 14.04 8.16 8.16 8.16	Total 12 6 12 10 10 6 6 5 5 9 8 8 4 3 3	Weight 3.8% 3.3% 3.6% 3.5% 1.5% 3.1% 2.6% 3.9% 3.8% 3.2% 2.8% 2.6%	Std. Mean Difference IV. Random. 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.13 [0.17, 2.08] 1.34 [0.35, 2.33] 4.20 [1.86, 6.55] 1.71 [0.49, 2.93] 2.44 [0.96, 3.92] 5.85 [3.18, 8.51] 0.28 [-0.54, 1.09] -0.13 [-0.96, 0.71] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% Cl
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Heterogeneity: 1au* = 0.88; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomba, M.2019 Bomfim, T. R.2012 Cai, H. Y.2014 Chen, S. Y.2017 Garabadu, D.2019 Han, W. N.2013(0.5mmol) Han, W. N.2013(0.5mmol) Han, W. N.2013(0.5mmol) Hansen, H. H.2016(f00µg/kg) Jia, X. T.2016(0.2nmol) Jia, X. T.2016(0.2nmol) Jia, X. T.2016(2.2nmol) Jia, X. T.2016(2.2nmol) Jia, X. T.2019	² = 120.e (P < 0.00 <u>Exp</u> <u>Mean</u> 3.15 3.04 22.6 42.68 30.34 49.04 31.59 37.98 43.22 32.77 26.38 26.45 35.48 42.26 35.48 42.26 34.37 2.88	0, df = : 0001) eriment 2.49 1.67 6.29 12.38 6.54 6.76 3.68 5.52 2.45 17.55 12.64 9.18 9.18 10.22 4.62 2.48	al Total 12 7 12 10 10 10 10 10 10 10 10 10 10	Mean 1.14 4.02 16.5 26.18 21.21 19.92 24.81 24.81 24.81 24.81 28.09 26.13 26.13 26.13 26.13 26.13 27.52 0.6	control 1.56 2.82 4.81 15.52 6.54 6.01 3.88 3.88 14.04 14.04 8.16 8.16 8.16 8.16 8.16 8.107	Total 12 6 12 10 10 10 6 6 5 5 5 9 8 8 4 4 3 3 3 15 15	Weight 3.8% 3.3% 3.6% 3.5% 1.5% 3.1% 2.6% 1.3% 3.9% 3.8% 2.8% 2.8% 2.6% 3.9%	Std. Mean Difference IV. Random. 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.13 [0.17, 2.08] 1.34 [0.35, 2.33] 4.20 [1.86, 6.55] 1.71 [0.49, 2.93] 2.44 [0.96, 3.92] 5.85 [3.18, 8.51] 0.28 [-0.54, 1.09] -0.13 [-0.96, 0.71] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99] 1.41 [0.60, 0, 2.22] 1.66 [0.38, 1.94]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random, 95% Cl
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Heterogeneity: 1au* = 0.38; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomba, M.2019 Bomfim, T, R.2012 Cai, H, Y.2014 Chen, S, Y.2017 Garabadu, D.2019 Han, W. N.2013(0.5nmol) Han, W. N.2013(0.5nmol) Han, W. N.2013(0.5nmol) Hansen, H. H.2016(500g/kg) Jia, X. T.2016(0.02mmol) Jia, X. T.2016(0.02mmol) Jia, X. T.2016(0.2mmol) Jia, X. T.2016(2.0mmol) Jia, X.	* = 120.6 (P < 0.00 Mean 3.15 3.04 22.6 42.68 30.34 49.04 31.59 37.98 43.22 32.77 26.38 26.45 35.48 42.26 35.48 42.26 35.48 42.26 34.37 2.88 36.11 38.28 38.3	0, df = ; erimenti SD 12.38 6.54 6.76 3.68 5.52 2.45 12.64 9.18 9.18 9.18 10.2 4.62 2.48 10.2 4.62 2.48 10.2 4.62 2.48 10.2 4.62 2.48 10.2 4.62 2.49 11.55 12.64 9.18 10.2 4.62 10.55 10.	al 12 7 12 10 10 10 10 10 10 10 10 10 10	C Mean 1.14 4.02 16.5 26.18 21.21 19.92 24.81 24.81 24.81 24.81 24.81 24.81 24.81 24.81 24.81 24.81 26.13 26.13 26.13 27.52 0.6 28.99 28.92 23.94	Control 1.56 SD 2.82 4.81 15.52 6.54 6.01 3.88 3.88 3.88 3.88 3.88 3.88 3.88 3.8	Total 12 6 12 10 10 6 6 5 5 9 8 8 4 4 3 3 15 15 15 12 12 12 12	Weight 3.8% 3.3% 3.6% 3.5% 3.1% 2.6% 3.9% 3.9% 3.2% 2.8% 2.6% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.8%	Std. Mean Difference IV. Random. 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.13 [0.17, 2.08] 1.34 [0.35, 2.33] 4.20 [1.86, 6.55] 1.71 [0.49, 2.93] 2.44 [0.96, 3.92] 5.85 [3.18, 8.51] 0.28 [-0.54, 1.09] -0.13 [-0.96, 0.71] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99] 1.41 [0.60, 2.22] 1.16 [0.38, 1.94] 0.45 [-0.37, 1.26] 1.16 [0.28, 2.04] 0.72 [-0.11, 1.55]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% Cl.
Heterogeneity: 1au ² = 0.38; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2019 Cai, H, Y.2014 Chen, S, Y.2017 Garabadu, D.2019 Han, W. N.2013(0.5nmol) Han, W. N.2013(0.5nmol) Han, W. N.2013(5nmol) Hansen, H. H.2016(500µg/kg) Jia, X. T.2016(0.22nmol) Jia, X. T.2016(0.22nmol) Jia, X. T.2016(0.22nmol) Li, J. X.2019 Lu Chong2019 Lu Chong2019 McClean, P. L.2011 McClean, P. L.2014 McClean, P. L.2015 Qi, L.2015	* = 120.6 (P < 0.000) Exp Mean 3.15 3.04 22.66 42.68 30.34 49.04 43.259 37.98 43.2277 26.38 26.45 35.448 42.266 34.437 2.888 36.11 38.38 36.11 38.28 38.33 21.28	0, df = ; eriment <u>SD</u> 2.49 1.67 6.29 12.38 6.54 6.54 6.54 6.54 6.54 6.52 2.45 17.55 12.64 9.18 9.18 10.24 9.18 10.24 9.18 10.24 9.18 10.24	al 12 12 12 10 10 10 10 10 10 10 10 10 10	C Mean 1.14 4.02 16.5 26.18 21.21 19.92 24.81 24.81 24.81 24.81 24.81 24.81 24.81 24.81 26.13 26.13 26.13 26.13 26.13 26.13 26.13 26.13 26.13 26.13 26.13 26.13 26.13 26.13 26.13 26.13 26.13 26.13 26.13 26.14 26.14 27.52 0.65 27.52 0.65 27.52 0.65 27.52 27.52 0.65 27.52	control <u>SD</u> 1.56 2.82 4.81 15.52 6.54 6.54 6.54 6.54 6.54 8.388 3.81 4.04 14.04 4.10 13.87 4.10 13.88 3.88 3.88 3.87 4.10 14.04 13.88 3.82 3.87 3.87 3.87 3.87 3.87 3.88 3.88 3.88 3.88 3.87 3.77 3.	Total 12 6 12 10 10 6 6 5 5 5 9 8 8 4 4 3 3 3 15 15 12 12 12 12 12 12 12 12 12 12 12 15 15 15 15 15 15 12 12 12 12 12 12 12 12 12 12 12 12 12	weight 3.8% 3.3% 3.8% 3.5% 1.5% 3.1% 2.6% 1.3% 3.9% 3.2% 2.8% 3.9% 3.9% 3.9% 3.9% 3.7% 3.5%	Std. Mean Difference IV. Random. 95% Cl 0.33 (0.08, 1.78) -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.13 (0.17, 2.08] 4.20 [1.86, 6.55] 1.71 [0.49, 2.93] 2.44 [0.96, 3.92] 5.58 [3.18, 8.51] 0.28 [-0.54, 1.09] -0.13 [-0.96, 0.71] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99] 1.41 [0.60, 2.22] 1.16 [0.38, 1.94] 0.45 [-0.37, 1.26] 1.16 [0.28, 2.04] 0.72 [-0.11, 1.55] 1.49 [0.47, 2.55]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% CI
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Heterogeneity: 1au ² = 0.38; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2019 Cai, H. Y.2014 Chen, S. Y.2017 Garabadu, D.2019 Han, W. N.2013(0.5nmol) Han, W. N.2013(0.5nmol) Han, W. N.2013(5nmol) Hansen, H. H.2016(500µg/kg) Jia, X. T.2016(0.02nmol) Jia, X. T.2016(0.02nmol) Jia, X. T.2016(0.02nmol) Li, J. X.2019 Lu Chong2019 Lu Chong2019 Lu Chong2019 Lu Chong2019 Lu Chong2019 Sun Jie2015 Sun Jie2015 Sun Jie2015 Wang, X.2016(0.5nmol) Wang, X.2016(0.5nmol) Wang, X.2016 Wang, X.2018 Xiong, H.2013 Yu, C. J.2020 Zhang Zhihua2019 Zhang, M. J.2022 Zhang Zhihua2019 Zhang, M. J.2022	≠ = 120.6 (P) < 0.00 Exp Mean 3.15 3.04 42.68 30.34 42.68 30.34 42.68 30.34 44.28 31.59 37.98 44.22 26.45 55.48 44.32 22.67 28.85 38.38 39.71 40.23 40.23 40.23 40.23 40.23 40.23 40.23 40.23 40.23 40.24 1.23 40.24 2.69 1.23	0, off = 2 0001) 2,49 1,67 6,29 1,67 6,29 1,67 6,29 2,45 1,67 6,368 6,54 2,45 2,45 2,45 2,45 2,45 2,45 2,45 2	al Total 12 12 12 12 12 12 12 12 12 12	(Mean 1.14 4.02 16.5 24.81 24.81 24.81 24.81 24.81 24.81 26.13 26.13 26.13 26.13 26.13 27.52 23.94 4.22 23.94 4.22 27.95	control sontrol 1.56 2.82 4.81 15.52 6.54 6.01 15.52 3.88 3.812 13.83 8.101 13.83 8.102 2.711 0.41 0.212 1.76 6.14 0.21	Total 12 6 12 6 12 12 10 6 5 5 9 8 4 3 3 3 15 12 12 12 10 6 6 6 6 6 10 15 12 12 10 15 12 12 10 15 12 15	Weine 3.8% 3.3% 3.3% 3.5% 1.5% 3.1% 2.6% 2.6% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.5% 3.5% 3.5%	Std. Mean Difference IV. Random. 95% C1 0.93 $[0.06, 1.76]$ 0.040 $[-1.51, 0.70]$ 1.05 $[0.19, 1.92]$ 1.13 $[0.17, 2.08]$ 1.34 $[0.35, 2.33]$ 4.20 $[1.86, 6.55]$ 1.71 $[0.49, 2.93]$ 2.44 $[0.96, 3.92]$ 5.85 $[3.18, 8.51]$ 0.28 $[-0.64, 1.09]$ 0.37 $[-1.31, 1.19]$ 0.97 $[-0.40, 2.33]$ 1.52 $[0.05, 2.99]$ 1.41 $[0.06, 2.22]$ 1.16 $[0.38, 1.94]$ 0.45 $[-0.37, 1.26]$ 1.16 $[0.38, 1.94]$ 0.45 $[-0.37, 1.26]$ 1.16 $[0.38, 1.94]$ 0.45 $[-0.37, 1.26]$ 1.16 $[0.38, 2.94]$ 0.42 $[-0.47, 2.50]$ 0.22 $[-1.20, 0.77]$ 2.41 $[1.20, 3.62]$ 3.06 $[1.56, 4.56]$ 3.23 $[1.69, 4.77]$ 1.46 $[0.13, 2.80]$ 0.54 $[-0.46, 1.55]$ 3.19 $[1.78, 4.60]$ 0.26 $[-0.45, 0.98]$ 0.72 $[-0.11, 1.55]$ 1.45 $[0.43, 2.9]$ 0.72 $[-0.11, 1.55]$ 3.19 $[1.78, 4.60]$ 0.26 $[-0.45, 0.98]$ 0.72 $[-0.11, 1.55]$ 1.45 $[0.40, 3.28]$	-10 -5 0 5 10 Favours [control] Std. Mean Difference IV. Random, 95% Cl
Heterogeneity: 1au ² = 0.38; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2019 Cai, H. Y.2014 Chen, S. Y.2017 Garabadu, D.2019 Han, W. N.2013(0.5nmol) Han, W. N.2013(0.5nmol) Hansen, H. H.2016(f000µg/kg) Hansen, H. H.2016(f00µg/kg) Hansen, H. H.2016(f00µg/kg) Jia, X. T.2016(0.2nmol) Jia, X. T.2016(0.5nmol) WacIean, P. L.2015 Wang, X.2016(0.5nmol) Wang, X.2016(0.5nmol) Wang, X.2016(0.5nmol) Wang, X.2016(0.5nmol) Wang, X.2018 Xiong, H.2013 Yu, C. J.2020 Zhang Zhihua2019 Zhang, M. J.2022 Zhaoli2021 Total (95% CI)	* = 120.6 (P) < 0.07 Mean. San. <	0, off = 2 eriment SD 2.49 1.67 6.29 1.67 6.29 1.63 6.54 6.76 8.552 2.45 17.55 12.64 8.12 2.45 17.55 12.64 8.12 2.45 17.55 5.22 2.45 17.55 5.24 9.18 10.2 2.45 17.55 12.64 8.12 2.45 1.2,55 12.64 8.12 2.45 1.2,55 12.64 8.12 2.45 1.2,55 1.2,64 1.2,55 1.2,64 1.2,55 1.2,64 1.2,67 1.2,69 1.2,88 1.2,67 1.2,68 1.2,68 1.2,68 1.2,64 1.2,69 1.2,68 1.2,68 1.2,69 1.2,69 1.2,68 1.2,65 1.2,64 1.2,55 1.2,64 1.2,55 1.2,64 1.2,55 1.2,64 1.2,55 1.2,64 1.2,24 9.18 1.2,24 9.18 1.2,24 9.18 1.2,24 9.18 1.2,24 9.18 1.2,24 9.18 1.2,24 9.18 1.2,24 9.18 1.2,24 1.2,55 1.2,64 1.2,24 1.2,24 1.2,24 1.2,24 1.2,25 1.2,64 1.2,24 1.2,25 1.2,24 1.2,25 1.2,24 1.2,25 1.2,24 1.2,25 1.2,24 1.2,25 1.2,24 1.2,25 1.2,24 1.2,25 1.2,24 1.2,25 1.2,24 1.2,25 1.2,24 1.2,25 1.2,24 1.2,25 1.2,24 1.2,25 1.2,24 1.2,27 1.2,37 1.2,21 1.2,37 1.	al Total 12 10 10 10 10 10 10 10 10 10 10	(Mean 1.14 4.02 16.5 26.18 21.21 24.81 24.81 24.81 24.81 24.81 24.81 24.81 24.81 24.81 26.13 26.13 26.13 26.13 27.52 0.6 28.99 28.52 27.95 27.95 27.95 27.95 0.41 0.83 1.22 1.23 3.6.16 0.43 0.43 1.33 3.6.16 0.49 0.41 0.43 0.41 0.43 1.44 0.45 0.41 0.43 0.45	control 15.52 SD 1.56 2.82 4.81 15.52 6.54 4.81 15.52 6.54 6.54 8.388 3.88 3.88 3.88 3.88 8.16 1.3.7 1.3.7 1.3.7 1.3.6 0.41 0	Total 12 6 12 10 6 5 5 9 8 4 3 3 15 12 12 12 12 12 10 6 6 6 6 10 6 10 6 10 6 11 12 10 15 122 10 15 122 15 122 15 122 15 125 277	Weight 3.8% 3.5% 3.5% 3.9% 3.5% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.5% 2.7% 4.1% 2.7% 4.1% 2.7% 2.7% 2.7% 2.7% 3.8% 2.7% 4.1% 3.5% 100.0%	Std. Mean Difference IV. Random. 95% CI 0.33 (0.08, 1.78) -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.13 [0.17, 2.08] 1.34 [0.35, 2.33] 4.20 [1.86, 6.55] 1.71 [0.49, 2.93] 2.44 [0.96, 3.92] 5.46 [3.18, 8.51] 0.28 [-0.54, 1.09] -0.13 [-0.96, 0.71] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99] 1.41 [0.60, 2.22] 1.66 [0.38, 1.94] 0.45 [-0.37, 1.26] 1.46 [0.38, 1.94] 0.72 [-0.11, 1.55] 1.49 [0.47, 2.50] -0.22 [-1.20, 0.77] 2.41 [1.20, 3.62] 3.60 [1.56, 4.56] 3.03 [1.78, 4.60] 0.54 [-0.46, 1.55] 3.19 [1.78, 4.60] 0.26 [-0.45, 0.98] 0.72 [-0.11, 1.55] 1.45 [0.40, 3.29] 2.47 [1.49, 3.45] 1.26 [0.91, 1.611]	-10 -5 0 5 10 Favours [control] Std. Mean Difference IV. Random, 95% Cl
Heterogeneity: 1au ² = 0.38; Chi Test for overall effect: Z = 6.37 Study or Subgroup An, J.2019 Bombin, T. R.2012 Cai, H. Y.2014 Chen, S. Y.2017 Garabadu, D.2019 Han, W. N.2013(0.5nmol) Han, W. N.2013(0.5nmol) Han, W. N.2013(5nmol) Hansen, H. H.2016(f00µg/kg) Jia, X. T.2016(0.2nmol) Jia, X. T.2016(0.2nmol) MacClean, P. L.2011 McClean, P. L.2011 McClean, P. L.2015 Sun Jie2015 Wang, X.2016(0.5nmol) Wang, X.2016(0.5nmol) Wang, X.2018 Xiu, C. J.2020 Zhang Zhihua2019 Zhang, M. J.2022 Zhaol/2021 Total (95% CI) Heterogeneity: Tau ² = 0.64: Chi	≥ = 120.02 (P < 0.07) Exp Mean 3.15 3.04 42.68 30.34 42.68 30.34 42.68 30.34 442.68 31.59 37.98 37.98 43.22 26.45 35.48 40.23 26.77 28.83 36.11 38.2 28.45 38.3 39.71 40.28 40.28 9.16 6.269 0.16 6.269 0.16 6.269 0.16 6.269 0.16 6.269 0.16 6.269 0.16 6.269 0.16 6.269 0.16 6.289 48.22 1.23	0, off = 2 0001) eriment SD 2,49 1,62 6,29 6,29 6,29 6,29 6,29 12,38 6,54 6,29 6,29 12,38 6,54 2,45 12,64 9,18 9,18 9,18 8,12 4,62 9,57 12,38 6,54 4,62 9,62 6,57 6,29 6,29 6,29 12,38 6,54 12,49 12,38 6,54 12,49 12,38 6,54 12,64 9,18 9,18 12,64 12,57 12,64 12,57 12,64 12,57 12,64 12,57 12,58	al Total 122 10 10 10 10 10 10 10 10 10 10	Construction of the second sec	iontrol 0 iontrol 15.52 6.54 6.54 6.54 6.64 6.64 6.64 8.16 13.83 8.12 13.83 8.12 13.83 13.83 14.04 14.14 1.06 6.14 0.21 17.16 6.14 0.21 11: 12 = 1000000000000000000000000000000000	Total 12 6 12 10 10 6 5 5 9 8 4 3 3 3 15 15 15 12 12 12 10 6 6 6 8 10 6 6 12 6 12 6 15 15 70% 70%	Weight 3.8% 3.3% 3.8% 3.5% 3.1% 2.6% 3.9% 3.5% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.9% 3.5% 2.8% 2.7% 4.1% 2.7% 4.1% 2.7% 4.1% 3.5% 100.0%	 Std. Mean Difference IV. Random. 95% CI 0.93 (0.08, 1.78) 0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.13 (0.17, 2.08] 1.34 [0.35, 2.33] 4.20 [1.86, 6.55] 1.71 [0.49, 2.93] 2.44 [0.96, 3.92] 2.45 [3.18, 8.51] 0.28 [-0.54, 1.09] 0.31 [-0.96, 0.71] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99] 1.41 [0.60, 2.22] 1.16 [0.28, 2.04] 0.72 [-0.11, 1.55] 1.49 [0.47, 2.50] 0.22 [-1.20, 0.77] 2.41 [1.20, 3.62] 3.06 [1.56, 4.56] 3.23 [1.69, 4.77] 1.46 [0.13, 2.80] 0.54 [-0.46, 1.55] 3.19 [1.78, 4.60] 0.62 [-0.45, 0.98] 0.72 [-0.11, 1.55] 1.85 [0.40, 3.29] 2.47 [1.49, 3.45] 1.26 [0.91, 1.61] 	-10 -5 0 5 10 Favours [control] Std. Mean Difference IV. Random. 95% Cl

Forest plot: effect of GLP-1 RAs on learning and memory abilities. (A) represents the result of the learning test, which was determined by measuring the escape latency; (B) represents the result of the memory test, which was determined by measuring the target quadrant dwell time and the percentage of time in the target quadrant dwell.

1991; Duelli et al., 1994; Grieb et al., 2004; Stranahan et al., 2008). In addition to impaired brain metabolism, the STZ model exhibited tau hyperphosphorylation, amyloid deposition, oxidative stress, and neuroinflammation (Salkovic-Petrisic et al., 2009; Tiwari et al., 2009; Saxena et al., 2011; Chen et al., 2013; Correia et al., 2013). The high mortality rate of animals after STZ injection is a limitation of this model (Lester-Coll et al., 2006). OA is a selective inhibitor of protein phosphatases that causes neuronal cell death (Kamat et al., 2014). Animals injected with OA will develop AD-like pathology, including tau protein hyperphosphorylation, amyloid deposition, memory impairment, synapse loss, etc., (Arias et al., 1998; Yoon et al., 2006; Kamat et al., 2013).

In summary, these animal models have their own advantages and limitations. Compared to the various models, their phenotypic similarities are more noteworthy (Esquerda-Canals et al., 2017). Therefore, the selection of appropriate animal strains and modeling methods deserve attention when conducting further experiments.

•	Exp	perimen	tal		Control			Std. Mean Difference	Std. Mean Difference
Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% CI	IV. Random, 95% CI
3.1.1 Liraglutide									
Chen. S. Y.2017	16.09	21.03	10	24.8	20.46	10	4.2%	-0.40 [-1.29, 0.49]	-+
Han, W. N.2013(0.05nmol)	15.97	1.24	10	17.13	6.23	6	4.0%	-0.28 [-1.30, 0.73]	-+
Han, W. N.2013(0.5nmol)	14.42	1.22	10	17.13	6.23	5	3.8%	-0.71 [-1.82, 0.41]	-+
Han, W. N.2013(5nmol)	12.87	1 23	10	17 13	6 23	5	3.7%	-1.11 [-2.28 0.06]	
Hansen, H. H. 2016/100uo/kg	30 77	8 65	17	41 26	17.3	9	4 3%	-0.83 [-1 67 0 01]	
Hansen, H. H 2016(500ug/kg	37.76	17.8	18	41.26	17.3	8	4 4%	-0.19[-1.03, 0.64]	+
Lu Chong2019	13.57	22 23	15	62 00	25.6	15	4 2%	-1.97 [-2.86 -1.08]	
McClean P I 2011	27 54	10 02	12	48 5	14 91	12	4 20%	-1 55 [-2.48 .0.62]	
McClean P L 2014	20.63	7 80	12	20.63	7 80	12	4.2.70	0.00 [-2.40, -0.02]	-
McClean P I 2015	19.67	8.52	12	27.87	8.52	12	4.4%	-0.93 [-1.78 -0.08]	~
Oi L 2016	26.67	8 27	10	24.51	11 57	10	4.3%	-0.35 [-1.76, -0.06]	-
Sup lie2015	14 72	4 33	8	15 13	5.1	8	4.2 /0	-0.08 [-1.06, 0.17]	+
Xiona H 2013	16.67	40.07	8	50	12 13	8	4.170	-0.76 [-1.70, 0.26]	
Xiu C 12020	38.27	3 21	10	45 66	3 53	10	3 7%	-2 10 [-3 24 -0.96]	
7baoli2021	12 26	5.21	6	43.00	5.00	6	3.7%	-2.10 [-3.24, -0.90]	
Zhaolizuzi	12.20	5.74	16	23.01	5.74	16	3.2%	-1.73 [-3.14, -0.32]	
Subtotal (95% CI)	21.12	0.74	193	51.24	0.74	151	5.1%	-3.40 [-4.30, -2.23]	•
Subtotal (35 % Cl)	01:2 - 40.0	0 -16 - 4	F (D -	0.00041	12 - 00	131	04.3 /0	-1.00 [-1.42, -0.00]	
Heterogeneity: Tau- = 0.47;	Chi* = 43.8	3, df = 1	5 (P =	0.0001)	; 1- = 66	70			
Test for overall effect: $Z = 4.0$	59 (P < 0.0	0001)							
2 1 2 Examplida									
An 12010	~~	11.00	40	20.00	0 44	40	4 401	0.001 4 40 0 47	4
An, J.2019	33	11.92	12	39.89	8.11	12	4.4%	-0.65 [-1.48, 0.17]	
Bomfim, T. R.2012	14.47	14.01	12	54.2	26.82	12	4.1%	-1.79 [-2.77, -0.82]	
Garabadu, D.2019	49.23	1.88	6	52.31	3.77	6	3.6%	-0.95 [-2.18, 0.27]	
Jia, X. 1.2016(0.02nmol)	24.63	8.22	10	26.55	8.22	4	3.1%	-0.22 [-1.38, 0.94]	_ <u>_</u>
Jia, X. T.2016(0.2nmol)	20.76	8.24	10	26.55	8.22	3	3.4%	-0.65 [-1.98, 0.67]	
Jia, X. 1.2016(2nmol)	16.92	10.27	10	26.55	8.22	3	3.3%	-0.90 [-2.26, 0.45]	
Wang, X.2016	33.56	3.17	10	49.39	4.75	10	2.9%	-3.75 [-5.32, -2.19]	
vvang, X.2016(0.05nmol)	25.2	2.79	12	33.79	2.05	6	3.0%	-3.17 [-4.70, -1.64]	
wang, X.2016(0.5nmol)	25.34	2.77	12	33.79	2.05	6	3.0%	-3.14 [-4.65, -1.62]	
111 110010			-			0	0 50/		
Wang, Y.2018	20.11	3.67	6	53.68	1.23	6	0.5%	-11.32 [-16.96, -5.68]	
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; (Test for overall effect: Z = 4.4	20.11 32.76 Chi ² = 42.4 48 (P < 0.0	3.67 3.78 5, df = 1 0001)	6 12 112 0 (P <	53.68 39.97 0.00001	1.23 2.4 I); I² = 7	6 12 80 6%	0.5% 3.9% 35.7%	-11.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.85 [-2.66, -1.04]	•
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; (Test for overall effect: Z = 4.4 Total (95% CI)	20.11 32.76 Chi² = 42.4 48 (P < 0.0	3.67 3.78 5, df = 1 0001)	6 12 112 0 (P < 295	53.68 39.97 0.00001	1.23 2.4 1); I ² = 7	6% 12 80 6% 231	0.5% 3.9% 35.7%	-11.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89]	•
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% Cl) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% Cl) Heterogeneity: Tau ² = 0.75;	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5	3.67 3.78 5, df = 1 0001) 5, df = 2	6 12 112 0 (P < 295 6 (P <	53.68 39.97 0.00001	1.23 2.4 1); I ² = 7	6% 12 80 6% 231 2%	0.5% 3.9% 35.7% 100.0%	-11.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89]	+ + -10 -5 0 5 10
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% Cl) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% Cl) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6.	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0	3.67 3.78 5, df = 1 0001) 5, df = 2 0001)	6 12 112 0 (P < 295 6 (P <	53.68 39.97 0.00001	1.23 2.4 1); l ² = 7 1); l ² = 7	6% 80 6% 231 2%	0.5% 3.9% 35.7% 100.0%	-11.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89]	-10 -5 0 5 10 Favours (experimental) Favours (control)
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference:	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3.	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df =	6 12 112 0 (P < 295 6 (P < 1 (P =	53.68 39.97 0.00001 0.00001	1.23 2.4 1); l ² = 7 1); l ² = 7	6 12 80 6% 231 2%	0.5% 3.9% 35.7%	-11.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89]	-10 -5 0 5 10 Favours [experimental] Favours [control]
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% Cl) Heterogeneity: Tau ² = 1.32; Tost for overall effect: Z = 4. Total (95% Cl) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference:	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3.	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df =	6 12 112 0 (P < 295 6 (P < 1 (P =	53.68 39.97 0.00001 0.00001 0.00001	1.23 2.4 1); l ² = 7 1); l ² = 7 : = 70.19	6 12 80 6% 231 2%	0.5% 3.9% 35.7%	-11.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89]	-10 -5 0 5 10 Favours [experimental] Favours [control]
$\label{eq:constraints} \begin{array}{l} \mbox{Wang, Y.2018} \\ \mbox{Zhang, M. J.2022} \\ \mbox{Subtotal (95% CI)} \\ \mbox{Heterogeneity: Tau^2 = 1.32;} \\ \mbox{Total (95% CI)} \\ \mbox{Total (95% CI)} \\ \mbox{Heterogeneity: Tau^2 = 0.75;} \\ \mbox{Test for overall effect: Z = 6.} \\ \mbox{Test for subgroup difference: } \\ \mbox{Better Subgroup difference: } \\ Better Subgroup diff$	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3.	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df =	6 12 112 0 (P < 295 6 (P < 1 (P =	53.68 39.97 0.00001 0.00001 0.0001	1.23 2.4 1); l ² = 7 1); l ² = 7 2 = 70.19	6 12 80 6% 231 2%	0.5% 3.9% 35.7%	-11.32 [-16.86, -5.68] -22 [0]:225 -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89]	-10 -5 0 5 10 Favours [experimental] Favours [control]
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference: Subdy or Subgroup	20.11 32.76 Chi ² = 42.4 48 ($P < 0.0$ Chi ² = 93.5 36 ($P < 0.0$ s: Chi ² = 3. Experi Mean	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = mental SD_T	6 12 112 0 (P < 295 6 (P < 1 (P =	53.68 39.97 0.00001 0.00001 0.07), 1 ² Cor	1.23 2.4 1); $l^2 = 7$ 1); $l^2 = 7$ r = 70.19 htrol SD T	6 12 80 6% 231 2% %	0.5% 3.9% 35.7% 100.0% S	-11.32 [-16.86, -5.68] -22 [-25.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] UK Fixed 95% CI	-10 -5 0 5 10 Favours (experimental) Favours (control)
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% Cl) Heterogeneity: Tau ² = 1.32; Tost for overall effect: Z = 4. Total (95% Cl) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference: Study or Subgroup 3.5.1 transgenic.	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3. Experi Mean	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = mental <u>SD To</u>	6 12 112 0 (P < 295 6 (P < 1 (P = 1 (P =	53.68 39.97 0.00001 0.00001 0.07), 1 ² Cor ean	1.23 2.4 1); $l^2 = 7l^2$ 1); $l^2 = 7l^2$ $l^2 = 70.19$ htrol SD T	6 12 80 6% 231 2% %	0.5% 3.9% 35.7% 100.0% S [*] /eight	-11.32 [-16.86, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] td. Mean Difference IV. Fixed, 95% Cl	-10 -5 0 5 10 Favours (experimental) Favours (control) Std. Mean Difference IV. Fixed, 95% Cl
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference: Study or Subgroup 3.5.1 transgenic A = 0.2019	20.11 32.76 Chi ² = 42.4 48 ($P < 0.0$ Chi ² = 93.5 36 ($P < 0.0$ s: Chi ² = 3. Experi Mean	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = mental <u>SD Ta</u>	6 12 112 0 (P < 295 6 (P < 1 (P = 1 (P =	53.68 39.97 0.00001 0.00001 0.07), 1 ² Cor ean	1.23 2.4 1); $l^2 = 7^2$ 1); $l^2 = 7$ 2 = 70.19 htrol SD T 8 11	6 12 80 6% 231 2% % 0tal V	0.5% 3.9% 35.7% 100.0% S ¹ /eight	-11.32 [-16.86, -5.68] -22 [-23.57, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89]	-10 -5 0 5 10 Favours [experimental] Favours [control]
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% Cl) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% Cl) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference: Study or Subgroup 3.5.1 transgenic An, J.2019 Reading, T, B. 2012	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3. Experi Mean	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = mental <u>SD Tc</u> 1.92	6 12 112 0 (P < 295 6 (P < 1 (P = 1 (P = 12 32	53.68 39.97 0.00001 0.00001 0.07), 1 ² Col ean	1.23 2.4 1); $ ^2 = 7$ 1); $ ^2 = 7$ = 70.19 htrol SD T 8.11 6 82	6 12 80 6% 231 2% % 0 tal V 12	0.5% 3.9% 35.7% 100.0% S <u>/eight</u> 20.2%	-11.32 [-16.86, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.65 [-1.48, 0.71] -0.65 [-1.48, 0.71] -7.05 [-1.48, 0.71]	-10 -5 0 5 10 Favours (experimental) Favours (control) Std. Mean Difference IV. Fixed, 95% Cl
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Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for overall effect: Z = 6. Study or Subgroup 3.5.1 transgenic An, J.2019 Bomfim, T. R.2012 Wang, Y.2018	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3. Hean 33 1 ¹ 14.47 14 20.11 3 20.76	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = mental SD To 1.92 4.01 3.67 5.79	6 12 112 0 (P < 295 6 (P < 1 (P = 1 (P = 12 12 3 12 12 3 12 12 3 12 5 5	53.68 39.97 0.00001 0.00001 0.07), 1 ² Cor ean 0.89 54.2 2 3.68	1.23 2.4 1); $l^2 = 7$ 1); $l^2 = 7$ $l^2 = 70.19$ htrol SD T 8.11 6.82 1.23 2.4	6 12 80 6% 231 2% % 0tal V 12 12 6 12	0.5% 3.9% 35.7% 100.0% \$ <u>keight</u> 20.2% 14.5% 0.4%	-11.32 [-16.86, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.55 [-1.48, -0.7] -1.79 [-2.77, -0.82] -1.79 [-2.77, -0.82]	-10 -5 0 5 10 Favours (experimental) Favours (control)
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% Cl) Heterogeneity: Tau ² = 1.32; Tost for overall effect: Z = 4. Total (95% Cl) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference: Study or Subgroup 3.5.1 transgenic An, J.2019 Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Substat (95% Cl)	20.11 32.76 Chi ² = 42.4 48 ($P < 0.0$ Chi ² = 93.5 36 ($P < 0.0$ s: Chi ² = 3. Experi Mean 33 1 ⁻ 14.47 11 20.11 3 32.76 3	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = mental <u>SD To</u> 1.92 4.01 3.67 3.78	6 12 112 0 (P < 295 6 (P < 1 (P = 1 (P = 12 12 3 12 12 12 12 12 12 12 12 12	53.68 39.97 0.00001 0.00001 0.07), l ² Col ean 0.89 54.2 2 3.68 9.97	1.23 2.4 1); $l^2 = 7$ 1); $l^2 = 7$ r = 70.19 htrol SD T 8.11 6.82 1.23 2.4	6 12 80 6% 231 2% % 0tal V 12 12 6 12	0.5% 3.9% 35.7% 100.0% <u>S'</u> /eight 20.2% 14.5% 0.4% 12.5% 0.4%	-11.32 [-16.86, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.65 [-1.48, 0.17] -0.65 [-1.48, 0.17] -1.79 [-2.77, -0.82] -1.32 [-1.636, -5.68] -2.20 [-3.25, -1.15]	std. Mean Difference IV. Fixed, 95% Cl
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6.3; Test for overall effect: Z = 6.3; Test for overall effect: Z = 6.3; Study or Subgroup difference: Study or Subgroup 3.5.1 transgenic An, J.2019 Bomfim, T. R. 2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI)	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3. Experi Mean 33 1 ¹ 14.47 1 ⁴ 20.11 2 20.11 2 20.11 2 20.11 2	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = SD To 1.92 4.01 3.67 3.78	6 12 112 0 (P < 295 6 (P < 1 (P = 1 (P = 12 12 12 12 12 12 12 12 12 12 12 12 12	53.68 39.97 0.00001 0.00001 0.07), 1 ² Col ean 54.2 2 3.68 9.97	1.23 2.4 1); $ ^2 = 7$ 1); $ ^2 = 7$ = 70.19 SD T 8.11 6.82 1.23 2.4	6 12 80 6% 231 2% % 0tal V 12 12 6 12 42	0.5% 3.9% 35.7% 100.0% <u>Sifest</u> 20.2% 14.5% 0.4% 12.5% 47.7%	-11.32 [-16.86, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.78 [-2.77, -0.82] -1.79 [-2.77, -0.82] -1.132 [-16.96, -5.68] -1.50 [-2.04, -0.96]	Std. Mean Difference
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% Cl) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% Cl) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference: Subudy of Subgroup 3.5.1 transgenic An, J.2019 Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% Cl) Heterogeneity: Chi ² = 17.74	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3. Experi Mean 33 1 ¹ 14.47 1 ⁴ 20.11 3 32.76 3 , df = 3 (P	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = SD To 1.92 3.01 3.67 3.78 = 0.000	6 12 112 0 (P < 295 6 (P < 1 (P = 1 (P = 12 3 4 2 5); l ² =	53.68 39.97 0.00001 0.00001 0.07), 1 ² Col ean 0.89 54.2 2 3.68 0.97 83%	1.23 2.4 1); $ ^2 = 7$ 1); $ ^2 = 7$ = 70.19 ntrol SD T 8.11 6.82 1.23 2.4	6 12 80 6% 231 2% % otal V 12 6 12 42	0.5% 3.9% 35.7% 100.0% 5 /eight 20.2% 14.5% 0.4% 12.5% 47.7%	-11.32 [-16.86, -5.88] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.79 [-2.77, -0.82] -1.79 [-2.77, -0.82] -1.79 [-2.77, -0.82] -1.32 [-1.69, -5.68] -2.20 [-3.25, -1.15] -1.50 [-2.04, -0.96]	+ -10 -5 0 5 10 Favours (experimental) Favours (control) Std. Mean Difference IV. Fixed. 95% Cl
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% Cl) Heterogeneity: Tau ² = 1.32; t Total (95% Cl) Heterogeneity: Tau ² = 0.75; t Test for overall effect: Z = 6. Test for subgroup difference: Study or Subgroup 3.5.1 transgenic An, J.2019 Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% Cl) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3. Experi Mean 33 1 ² 14.47 14 20.11 3 32.76 3 , df = 3 (P < 0.	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = 9 0001) 35, df = 1.92 4.01 3.67 3.78 = 0.000 00001)	6 12 12 12 12 295 6 (P < 1 (P = 1 (P = 12 12 12 12 12 12 12 12 12 12	53.68 39.97 0.00001 0.0001 0.07), I ² Cor ean 0.89 9.89 9.89 9.89 9.89 83%	1.23 2.4 1); $ ^2 = 7$ 1); $ ^2 = 7$ = 70.19 ntrol SD T 8.11 6.82 1.23 2.4	6 12 80 6% 231 2% % 0 0 12 12 6 12 42	0.5% 3.9% 35.7% 100.0% 100.0% 20.2% 14.5% 0.4% 12.5% 47.7%	-11.32 [-16.86, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.65 [-1.48, 0.17] -1.79 [-2.77, -0.82] -1.132 [-1.68, -5.68] -1.132 [-1.65, -5.68] -1.50 [-2.04, -0.96]	Std. Mean Difference IV. Fixed, 95% CI
Wang, Y.2018 Thang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for overall effect: Z = 6. Study or Subgroup 3.5.1 transgenic An, J.2019 Bomfirn, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3. <u>Mean</u> 33 1 ⁻ 14.47 14 20.11 3 32.76 3 , df = 3 (P < 0.	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = mental SD To 1.92 4.01 3.67 3.78 = 0.000 00001)	6 6 12 2112 112 112 112 112 112 112 112	53.68 39.97 0.00001 0.00001 0.07), l ² 0.0001 0.07), l ² 8an 9.89 4.2 2 3.68 9.97 83%	1.23 2.4 1); $ ^2 = 7$ 1); $ ^2 = 7$ = 70.19 htrol SD T 8.11 6.82 1.23 2.4	6 12 80 6% 231 2% % 0 0 12 12 12 42	0.5% 3.9% 35.7% 100.0% 100.0% \$ feight 20.2% 14.5% 0.4% 12.5% 47.7%	-11.32 [-16.96, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.55 [-1.48, 0.17] -1.79 [-2.77, -0.82] -1.79 [-2.77, -0.82] -1.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.50 [-2.04, -0.96]	Std. Mean Difference IV. Fixed. 95% Cl
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference: Subuck of Subgroup Study or Subgroup Study or Subgroup Study or Subgroup Study or Subgroup Study or Subgroup Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5 3.5.2 chemical-induced	20.11 32.76 Chi ² = 42.4 48 ($P < 0.0$ Chi ² = 93.5 36 ($P < 0.0$ s: Chi ² = 3. Experi Mean 33 1 ⁻ 14.47 14 20.11 3 32.76 3 , df = 3 ($P < 0.0$	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = 2 0001) 35, df = 1 8.67 3.78 = 0.000 00001)	6 12 12 12 12 12 12 12 12 16 (P < 1 (P = 1 1 (P = 12 3 12 12 12 12 12 12 12 12 12 12	53.68 39.97 0.00001 0.00001 0.07), I ² Con esan 0.89 44.2 2 8.68 9.97 83%	1.23 2.4 1); ² = 7 = 70.19 	6 12 80 6% 231 2% % % • • • • • • • •	0.5% 3.9% 35.7% 100.0% \$ /dight 20.2% 14.5% 0.4% 12.5% 47.7%	-11.32 [-16.86, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.65 [-1.48, 0.17] -0.65 [-1.48, 0.17] -0.65 [-1.48, 0.17] -1.79 [-2.77, -0.82] -1.32 [-1.69, -5.68] -2.20 [-3.25, -1.15] -1.50 [-2.04, -0.96]	+ -10 -5 0 5 10 Favours (experimental) Favours (control) Std, Mean Difference IV. Fixed, 95% Cl
$\label{eq:constraints} \begin{array}{l} \mbox{Wang, Y,2018} \\ \mbox{Wang, Y,2016} \\ \mbox{Subtotal (95% CI)} \\ \mbox{Heterogeneity: Tau^2 = 1.32; Test for overall effect: Z = 4.7 \\ \mbox{Total (95% CI)} \\ \mbox{Heterogeneity: Tau^2 = 0.75; Test for overall effect: Z = 6.3 \\ \mbox{Test for overall effect: Z = 6.3 \\ \mbox{Subtorup difference:} \\ $	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3. Experi Mean 33 1 ¹ 14.47 1 20.11 3 32.76 3 32.76 4 (F < 0.0 48 (P < 0.0	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = 2 0001) 35, df = 1 8.5 7 8.67 3.78 = 0.000 00001)	6 6 7 12 112 295 6 (P < 1 1 (P = 1 12 12 12 12 12 12 12 12 12 1	53.68 39.97 0.00001 0.00001 0.07), I ² Con ean 0.89 9.89 9.89 83% 83%	1.23 2.4 1); $ ^2 = 7$ 2.4 1); $ ^2 = 7$ 2.7 1); $ ^2 = 7$ 2.7 1); $ ^2 = 7$ 2.7 2.7 2.7 2.7 2.4 3.77	6 12 80 6% 231 2% % 0 0 12 12 6 12 42 6	0.5% 3.9% 35.7% 100.0% 100.0% 5 7 7 7 8 7 8 7 8 9.2%	-11.32 [-16.86, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.65 [-1.48, 0.17] -1.79 [-2.77, -0.62] -1.132 [-16.96, -5.68] -2.20 [-3.25, -5.15] -1.50 [-2.04, -0.96] -0.95 [-2.18, 0.27]	Std. Mean Difference IV. Fixed, 95% CI
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference: Study or Subgroup 3.5.1 transgenic An, J.2019 Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5 3.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.02nm0)	$\begin{array}{c} 20.11\\ 32.76\\ \\ 20.11\\ 32.76\\ \\ 20.76\\ \\ 32.76\\ \\ 36\\ \\ 93.5\\ \\ 36\\ \\ 93.5\\ \\ 36\\ \\ 93.5\\ \\ 36\\ \\ 93.5\\ \\ 32.76\\ $	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = 2 0001) 35, df = 1 1,92 4.01 3.67 3.78 = 0.000 00001)	$\begin{array}{c} 6 \\ 6 \\ 12 \\ 112 \\ 0 \\ (P < \\ 295 \\ 6 \\ (P < \\ 295 \\ 6 \\ (P < \\ 1 \\ 12 \\ 31 \\ 12 \\ 12 \\ 12 \\ 12 \\ 12 $	53.68 39.97 0.00001 0.00001 0.07), l ² Cor ean 9.89 9.89 9.89 83% 83%	1.23 2.4 1); ² = 7 1); ² = 7 1); ² = 7 1 = 70.19 1; ² = 7 2, ² = 7 1 = 70.19 1; ² = 7 2, ² = 7 1; ² = 7 2, ²	6 12 80 6% 231 2% % 0 0 12 12 6 12 42 6 4	0.5% 3.9% 3.5.7% 100.0% 100.0% S Veight 20.2% 14.5% 0.4% 12.5% 47.7% 9.2% 10.2%	-11.32 [-16.86, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.79 [-2.77, -0.82] -1.79 [-2.77, -0.82] -1.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.50 [-2.18, 0.27] -0.22 [-1.38, 0.94]	Std. Mean Difference IV. Fixed. 95% CI
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6.3; Test for subgroup difference: Study or Subgroup 3.5.1 transgenic An, J.2019 Bomfirn, T. R.2012 Subtotal (95% CI) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5 3.5.2 chemical-induced Garabadu, D.2019 Jang, M. J.2022 Subtotal (95% CI) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5 3.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol)	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 56 (P < 0.0 s: Chi ² = 3. Experi Mean 33 1 ⁻ 14.47 1 20.11 : 32.76 : 48 (P < 0. 48 (P < 0. 49.23 : 24.63 4 20.76	3.67 3.78 5. df = 1 0001) 5. df = 2 0001) 35. df = 2 9.001) 35. df = 2 9.001) 35. df = 2 9.001) 35. df = 2 9.001 1.92 8.67 3.78 = 0.0000 00001) 1.88 3.22 2.24	6 6 72 112 112 112 112 112 112 10 (P < 295 6 (P < 1 (P = 11 (P = 11 (P =) 11 (P =) 12 33 12 33 12 35 12 33 42 6 55; 2 = 6 55; 2 = 6 55; 2 = 10 (P < 10 (P <	53.68 39.97 0.00001 0.00001 0.07), I ² ean 9.89 9.89 9.89 9.97 83% 2.31 5.55 3.55	1.23 2.4 1); ² = 7 1); ² = 7 1); ² = 7 1; ² = 70.19 1; ² = 7 1; ² = 7 2, ² = 7 1; ² = 7 2,	6 12 80 6% 231 2% % 0 12 12 6 12 42 6 42 6 43	0.5% 3.9% 3.5.7% 100.0% 100.0% 20.2% 14.5% 0.4% 12.5% 47.7% 9.2% 10.2% 7.9%	-11.32 [-16.36, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.65 [-1.48, 0.17] -1.79 [-2.77, -0.82] -11.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.50 [-2.04, -0.96] -0.95 [-2.18, 0.27] -0.25 [-2.18, 0.67]	Std. Mean Difference IV. Fixed, 95% CI
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for overall effect: Z = 6. Study or Subgroup 3.5.1 transgenic An, J.2019 Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2029 Subtotal (95% CI) Heterogeneity: Ch ² = 17.74 Test for overall effect: Z = 5 3.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.2nmol) Jia, X. T.2016(0.2nmol)	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3. Experi- Mean 33 1 ¹ 14.47 11 20.11 2 32.76 2 df = 3 (P 48 (P < 0. 49.23 2 24.63 4 20.76 4 16.92 11 20.76 4 16.92 11 16.92 11 17.94 12 17.94 12	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = 2 0001) 35, df = 1 1, 92 1, 01 3.67 3.78 = 0.000 00001) 1.88 3.22 3.24 3.24 3.27	$\begin{array}{c} 6\\ 6\\ 12\\ 112\\ 295\\ 6\\ 6\\ (P < 1\\ 1\\ (P = 1\\ 1\\ 1\\ 1\\ 1\\ 2\\ 3\\ 1\\ 1\\ 1\\ 2\\ 3\\ 1\\ 1\\ 2\\ 3\\ 1\\ 1\\ 2\\ 3\\ 1\\ 1\\ 2\\ 3\\ 1\\ 1\\ 2\\ 3\\ 1\\ 1\\ 2\\ 1\\ 1\\ 1\\ 2\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\$	53.68 39.97 0.00001 0.00001 0.07), I ² 0.07), I ³ 0.07), I ³ 0.	1.23 2.4 1); $ ^2 = 7$ 1); $ ^2 = 7$ 1, 2] 1,	6 12 80 6% 231 2% % 0 12 12 6 12 42 6 4 3 3	0.5% 3.9% 35.7% 100.0% 100.0% 100.0% 14.5% 0.4% 14.5% 0.4% 12.5% 47.7%	-11.32 [-16.96, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.55 [-1.48, 0.17] -1.79 [-2.77, -0.82] -11.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.50 [-2.04, -0.96] -0.95 [-2.18, 0.27] -0.22 [-1.38, 0.94] -0.65 [-1.98, 0.67]	Std. Mean Difference IV. Fixed, 95% Cl
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference: Subuct of Subgroup Study or Subgroup Study or Subgroup Study or Subgroup Study or Subgroup Mang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5 3.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.02mmol) Jia, X. T.2016(0.02mmol) Jia, X. T.2016(2mmol) Mang, X.2016	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3. Experi Mean 33 1 14.47 1 20.11 : 32.76 : 48 (P < 0. 49.23 : 49.23 : 24.63 48 (P < 0. 49.23 : 20.76 4 16.92 11 33.56 : 33.56 : 20.76 4 20.76 4 2	3.67 3.78 5, df = 1 0001) 5, df = 2 0001) 35, df = 2 0001) 35, df = 1 1.92 1.92 1.92 1.92 1.92 1.92 1.92 1.9	$\begin{array}{c} 6 \\ 6 \\ 12 \\ 12 \\ 212 \\ 295 \\ 6 \\ (P < 1 \\ 295 \\ 6 \\ (P < 1 \\ 1 \\ 1 \\ 1 \\ 2 \\ 1 \\ 1 \\ 2 \\ 1 \\ 2 \\ 1 \\ 1$	53.68 39.97 0.00001 0.00001 0.07), l ² Con ean 0.89 9.89 44.2 2 8.68 9.97 83% 2.31 5.55 5.55 5.55 5.55	1.23 2.4 1); ² = 7 = 70.19 	6% 231 2% % 0tal V 12 6 12 42 6 4 3 3 10	0.5% 3.9% 35.7% 100.0% \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	-11.32 [-16.86, -5.68] -220 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.65 [-1.48, 0.17] -0.65 [-1.48, 0.17] -1.50 [-2.04, -0.96] -0.22 [-1.38, 0.94] -0.65 [-1.38, 0.94] -0.65 [-1.38, 0.94] -0.65 [-2.6, 0.45]	favours (experimental) Std. Mean Difference IV. Fixed. 95% Cl
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% C1) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% C1) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for overall effect: Z = 6. Subtotal (95% C1) Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% C1) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5 3.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Wang, X.2016(0.5mmot)	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Ch ² = 3.5 56 (P < 0.0 s: Ch ² = 3.5 (Ch ² = 3.5	3.67 3.78 5. df = 1 0001) 5. df = 2 0001) 35. df = 2 0001) 35. df = 2 1.92 1.92 1.92 1.92 1.92 1.92 1.92 1.9	6 6 7 12 12 12 12 12 12 12 12 12 12 12 12 12	53.68 39.97 0.00001 0.00001 0.07), I ² Col ean 0.89 9.89 9.89 9.89 9.89 9.89 9.89 2.31 5.55 5.55 5.55 5.55 5.55	1.23 2.4 1); $ ^2 = 7$ 1); $ ^2 = 7$ 1); $ ^2 = 7$ 1; $ $	6 12 80 6% 231 2% % 0 12 12 6 12 42 6 4 3 3 10 6	0.5% 3.9% 35.7% 100.0% 100.0% 100.0% 100.0% 12.5% 47.7% 9.2% 10.2% 7.5% 5.6%	-11.32 [-16.86, -5.88] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.65 [-1.48, 0.17] -1.79 [-2.77, -0.82] -11.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.50 [-2.04, -0.96] -0.95 [-2.18, 0.87] -0.95 [-2.18, 0.87] -0.95 [-5.32, -2.19] -3.75 [-5.32, -2.19]	Std. Mean Difference IV. Fixed, 95% Cl
Wang, X2018 Zhang, M. J.2022 Subtotal (95% Cl) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% Cl) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference: 3 Study or Subgroup Subtotal (95% Cl) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5 3.5.2 themical-induced Garabadu, D.2019 Jia, X. T.2016(0.2nmol) Jia, X. T.2016(0.2nmol) Jia, X. T.2016(0.2nmol) Jia, X. 7.2016(0.5nmol) Wang, X.2016(0.5nmol)	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3. Experi Mean 33 1: 14.47 1: 20.11 : 32.76 : 49.23 : 49.23 : 49.23 : 24.63 4 20.69 2 10 33.56 : 25.2 : 25.34 : 2	3.67 3.78 5, df = 1 00001) 5, df = 2 00001) 35, df = 9 00001) 35, df = 9 0001) 35, df = 9 0001) 35, df = 9 0001) 1.88 8.67 8.78 9 0.000 00001) 1.88 8.22 8.24 0.27 7.79 2.77	$\begin{array}{c} 6\\ 6\\ 12\\ 112\\ 295\\ 6\\ 6\\ (P < \\ 295\\ 6\\ 6\\ (P < \\ 1\\ 1\\ 295\\ 6\\ 6\\ (P < \\ 1\\ 1\\ 1\\ 2\\ 3\\ 42\\ 10\\ 2\\ 10\\ 2\\ 10\\ 2\\ 10\\ 2\\ 10\\ 2\\ 10\\ 2\\ 10\\ 2\\ 10\\ 2\\ 10\\ 2\\ 10\\ 2\\ 12\\ 3\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 2\\ 3\\ 12\\ 2\\ 3\\ 12\\ 2\\ 3\\ 12\\ 2\\ 3\\ 12\\ 2\\ 3\\ 12\\ 2\\ 3\\ 12\\ 2\\ 3\\ 12\\ 2\\ 3\\ 12\\ 2\\ 3\\ 1\\ 1\\ 12\\ 3\\ 1\\ 12\\ 1\\ 12\\ 3\\ 1\\ 12\\ 1\\ 12\\ 3\\ 1\\ 12\\ 1\\ 12\\ 3\\ 1\\ 12\\ 1\\ 12\\ 3\\ 1\\ 12\\ 1\\ 12\\ 1\\ 12\\ 1\\ 12\\ 1\\ 12\\ 1\\ 12\\ 1\\ 12\\ 1\\ 12\\ 3\\ 1\\ 12\\ 1\\ 12\\ 3\\ 1\\ 12\\ 1\\ 12\\ 3\\ 1\\ 1\\ 12\\ 3\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\$	53.68 39.97 0.00001 0.00001 0.07), I ² Con esan 9.89 9.54.2 2 8.68 8.3% 8.3% 2.31 8.55 8.55 8.55 8.55 8.55 8.55	1.23 2.4 1); ² = 7 = 70.19 http://www.actionary. 8.11 6.82 1.23 2.4 3.77 8.22 8.22 8.22 4.75 2.05 2.05	6% 231 2% % 0tal V 12 6 12 42 6 42 6 42 6 42 6 6 6	0.5% 3.9% 35.7% 100.0% (eight 20.2% 14.5% 0.4% 9.2% 10.2% 7.9% 5.6% 5.6% 5.6%	-11.32 [-16.86, -5.83] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.79 [-2.77, -0.82] -1.79 [-2.77, -0.82] -0.25 [-1.88, -0.87] -0.22 [-1.38, -0.84] -0.59 [-2.86, -0.45] -3.75 [-5.22, -2.19] -3.17 [-4.70, -1.64]	Std. Mean Difference IV. Fixed. 95% CI
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6.3; Test for overall effect: Z = 6.3; Test for overall effect: Z = 6.3; Study or Subgroup 3.5.1 transgenic An, J.2019 Bomfirn, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5 3.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Jia, X. Z.2016(0.2mmol) Wang, X.2016(0.5mmol) Wang, X.2016(0.5mmol) Wang, X.2016(0.5mmol)	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Ch ² = 93.5 36 (P < 0.0 s: Ch ² = 3.5 (P < 0.0 s: Ch ² = 3.5 (P < 0.0 s: Ch ² = 3.7 (P < 0.0 (P < 0.0	3.67 3.78 5, df = 1 00001) 5, df = 2 00001) 35, df = 2 00001) 35, df = 2 1.02 1.02 1.02 1.02 1.02 1.02 1.02 1.0	6 6 12 112 112 112 112 112 112 112 112 1	53.68 39.97 0.00001 0.00001 0.07), I ² con ean 0.89 2.31 3.55 3.55 3.55 3.55 3.39 3.79	1.23 2.4 1); ² = 7 1); ² = 7 3.0 1; ² = 7 0.19 8.11 6.82 1.23 2.4 3.77 8.22 8.22 8.22 8.22 8.22 8.22 8.22 2.05	b 12 80 6% 231 2% % 4 12 6 12 42 6 4 3 3 10 6 6 38	0.5% 3.9% 3.5.7% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 12.5% 47.7% 9.2% 10.2% 7.5% 5.6% 5.6% 5.9% 6.0%	-11.32 [-16.36, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.65 [-1.48, 0.17] -1.79 [-2.77, -0.82] -11.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -2.20 [-2.26, -4.5] -0.55 [-1.98, 0.67] -0.55 [-1.98, 0.67] -0.55 [-5.32, -2.19] -3.75 [-5.32, -2.19] -3.75 [-5.32, -2.19] -3.75 [-5.32, -2.19] -3.75 [-5.32, -2.19] -3.75 [-5.32, -2.19]	Std. Mean Difference IV. Fixed, 95% CI
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference: Subtotal (95% CI) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5 3.5.2 transgenic An, J.2019 Bomfim, T. R. 2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5 3.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.02nmol) Jia, X. T.2016(0.05nmol) Wang, X.2016(0.05nmol) Wang, X.2016(0.5nmol) Subtotal (95% CI)	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 56 (P < 0.0 s: Chi ² = 3. Experi Mean 33 1 ¹ 14.47 14 20.11 2 32.76 2 49.23 4 24.63 4 20.62 1 24.63 4 20.62 2 25.34 2 25.34 2 chi ² = 6 (P, C)	3.67 3.78 5, df = 1 00001) 5, df = 2 00001) 35, df = 2 00001) 35, df = 2 00001) 35, df = 2 00001) 35, df = 2 00001) 1.88 8.67 8.78 = 0.000 00001) 1.88 8.22 2.27 3.77 = 0.0000	6 12 122 122 295 6 6 (P < 12) 295 6 (P < 12) 1 12 31 12 31 12 31 12 31 12 31 12 31 12 31 12 31 12 31 12 31 12 31 12 31 12 31 12 31 12 31 12 31 12 55 55 12 55 12 12 32 422 55 10 22 10 24 12 33 32 33 32	53.68 39.97 0.00001 0.00001 0.07), I ² con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con concon con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con con co	1.23 2.4 1); ² = 7 = 70.19 http://www.end/files/fil	6 12 80 6% 231 2% % 0 0 12 12 42 6 4 3 3 10 6 6 38	0.5% 3.9% 35.7% 100.0% \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	-11.32 [-16.36, -5.63] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.55 [-1.48, 0.17] -1.79 [-2.77, -0.82] -11.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.50 [-2.04, -0.96] -0.95 [-2.18, 0.27] -0.92 [-1.38, 0.94] -0.65 [-1.98, 0.64] -3.75 [-5.32, 2.19] -3.17 [-4.70, -1.64] -3.14 [-4.56, -1.62] -1.56 [-2.07, -1.05]	Std. Mean Difference IV. Fixed. 95% Cl
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference: 3 Study or Subgroup Mang, Y.2018 Zhang, M. J.2029 Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5 3 .5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.02mrol) Jia, X. T.2016(0.02mrol) Jia, X. T.2016(0.02mrol) Jia, X. T.2016(0.02mrol) Wang, X.2016(0.5mrol) Wang, X.2016(0.5mrol) Wang, X.2016(0.5mrol) Subtotal (95% CI) Heterogeneity: Chi ² = 24.69 Test for overall effect: Z = 24.69	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3. Experi Mean 33 1: 14.47 1/2 20.11 : 32.76 : 48 (P < 0. 49.23 : 49.23 : 24.63 4 20.76 4 16.92 10 33.56 : 25.2 : 25.34 : 25.34 : 45.2 : 25.34 : 27.34	3.67 3.78 5. df = 1 00001) 5. df = 2 00001) 5. df = 2 00001) 5. df = 2 00001) 5. df = 2 00001 1.88 3.22 3.24 3.77 1.88 3.22 3.27 7.79 0.0000 1.277 2.777 0.00001	$\begin{array}{c} 6\\ 12\\ 112\\ 295\\ 6\\ (P < 1 \\ 295\\ 6\\ (P < 1 \\ 1 \\ (P = 1 \\ 1 \\ 295\\ 6\\ 1 \\ 1 \\ 295\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 12\\ 3\\ 12\\ 12\\ 3\\ 12\\ 12\\ 3\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12$	53.68 39.97 0.00001 0.00001 0.07), I ² con ean 9.89 9.87 83% 2.31 5.55 5.55 5.55 5.55 5.55 3.79 3.79 76%	1.23 2.4 1); l ² = 7 1); l ² = 7 1; l ² = 7 0.19 1; l ² = 7 0.19 8.11 6.82 1.23 2.4 3.77 8.22 8.22 4.75 2.05	6 0 12 80 66% 231 22% 42 12 6 12 42 6 4 3 3 10 6 6 38	0.5% 3.9% 3.9% 3.5.7% 100.0% 100.0% 5.0% 10.2% 7.5% 5.9% 5.9% 5.2.3%	-11.32 [-16.36, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.65 [-1.48, 0.17] -1.79 [-2.77, -0.82] -11.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.50 [-2.04, -0.96] -0.95 [-2.18, 0.27] -0.22 [-1.38, 0.94] -0.65 [-1.98, 0.67] -0.95 [-2.28, 0.45] -3.75 [-5.20, -2.19] -3.17 [-4.70, -1.64] -3.14 [-4.65, -1.62] -1.56 [-2.07, -1.05]	Std. Mean Difference IV. Fixed. 95% Cl
$\label{eq:constraints} \begin{array}{l} \mbox{Wang, Y,2018} \\ \mbox{Wang, Y,2018} \\ \mbox{Heterogeneity: Tau^2 = 1.32; Test for overall effect: Z = 4. \\ \mbox{Total (95% CI)} \\ Heterogeneity: Tau^2 = 0.75; Test for overall effect: Z = 6. \\ \mbox{Test for overall effect: Z = 5. \\ \mbox{Test for overall effect: Z = 5 \\ \mbox{T$	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Ch ² = 3.5 Chi ² = 93.5 36 (P < 0.0 s: Ch ² = 3.5 40 (P < 0.0 33.11 14.47 14.47 14.47 14.47 14.20.11 32.76 35.77 32.76 32.777 32.7777 32.777777777777777777777777777777777777	3.67 3.78 5. df = 1 0001) 5. df = 2 0001) 35. df = 2 0001) 1.82 3.78 8.22 3.24 8.22 3.24 8.22 3.24 8.22 3.27 5.27 7 7 9 0.000 00001)	$\begin{array}{c} 6\\ 6\\ 12\\ 112\\ 0\\ (P < 12)\\ 295\\ 6\\ (P < 12)\\ 295\\ 6\\ (P < 12)\\ 1\\ 1\\ (P = 12)\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 3\\ 12\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 3\\ 12\\ 12\\ 3\\ 1$	53.68 39.97 0.00001 0.00001 0.007), I ² con ean 3.89 54.2 2 3.68 3.997 83% 2.31 3.55 5.55 3.55 3.55 3.79 3.79 76%	1.23 2.4 1); l ² = 7 1); l ² = 7 1; l ² = 70.19 1; l ² = 7 3.77 8.11 6.82 2.4 3.77 8.22 8.22 8.22 8.22 8.22 8.22 8.22 8	ь б 12 80 6% 2311 2% % 0tal V 12 6 12 42 6 42 6 42 6 33 10 6 38	0.5% 3.9% 35.7% 100.0% 20.2% 14.5% 0.4% 47.7% 9.2% 10.2% 47.7% 9.2% 6.0% 5.6% 6.0% 52.3%	-11.32 [-16.36, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.65 [-1.48, 0.17] -1.79 [-2.77, -0.62] -1.132 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.50 [-2.04, -0.96] -0.55 [-1.98, 0.67] -0.25 [-1.98, 0.67] -0.37 [-5.32, -2.19] -3.17 [-4.70, -1.64] -3.14 [-4.65, -1.62] -1.56 [-2.07, -1.05]	Std. Mean Difference IV. Fixed, 95% CI
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for subgroup difference: Subtotal (95% CI) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5 3.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.02nmol) Jia, X. T.2016(0.02nmol) Jia, X. T.2016(0.05nmol) Wang, X.2016(0.05nmol) Wang, X.2016(0.05nmol) Subtotal (95% CI) Heterogeneity: Chi ² = 24.69 Test for overall effect: Z = 5 Total (95% CI)	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Chi ² = 3. Experi Mean 33 1: 14.47 11 20.11 : 32.76 : 49.23 : 49.23 : 49.23 : 24.63 4 20.62 4 33.56 : 25.24 : 25.34 : 25.34 : 4f = 6 (P < 0.0)	3.67 3.78 5. df = 1 0001) 5. df = 2 0001) 35. df = 2 0001) 1.88 3.22 3.78 1.88 3.22 3.77 1.88 3.22 3.77 1.88 3.22 3.77 1.88 3.24 3.27 3.78 3.78 3.78 3.78 3.78 3.78 3.78 3.7	$\begin{array}{c} 6 \\ 12 \\ 112 \\ 112 \\ 295 \\ 66 \\ (P < 1 \\ 1 \\ (P = 1 \\ 12 \\ 31 \\ 6 \\ 51 \\ 12 \\ 31 \\ 6 \\ 51 \\ 12 \\ 31 \\ 6 \\ 51 \\ 12 \\ 31 \\ 12 \\ 31 \\ 5); ^2 = 6 \\ 6 \\ 52 \\ 10 \\ 21 \\ 10 \\ 21 \\ 10 \\ 43 \\ 12 \\ 33 \\ 70 \\ 4); ^2 = 1 \\ 112 \end{array}$	53.68 39.97 0.00001 0.00001 0.07), I ² 0.0000 200 200 200 200 200 200 200 200	1.23 2.4 1); l ² = 7 1); l ² = 7 1; l ² = 7 1; l ² = 7 0.19 8.11 6.82 1.23 2.4 3.77 8.22 8.22 8.22 8.22 8.22 8.22 8.22 8	b b 12 80 231 2% %	0.5% 3.9% 35.7% 100.0% \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	-11.32 [-16.36, -5.63] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.65 [-1.48, 0.17] -1.79 [-2.77, -0.82] -11.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.50 [-2.04, -0.96] -0.95 [-2.18, 0.27] -0.95 [-2.18, 0.94] -0.65 [-1.98, 0.64] -3.75 [-5.32, -2.19] -3.17 [-4.70, -1.64] -3.14 [-4.55, -1.62] -1.56 [-2.07, -1.05]	Std. Mean Difference IV. Fixed. 95% Cl
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; T Test for overall effect: Z = 4.4 Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6.3 Test for subgroup difference: 3 <u>Study or Subgroup</u> <u>3.5.1 transgenic</u> An, J.2019 Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5 <u>3.5.2 chemical-induced</u> Garabadu, D.2019 Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Wang, X.2016(0.5mmol) Wang, X.2016(0.5mmol) Subtotal (95% CI) Heterogeneity: Chi ² = 24.69 Test for overall effect: Z = 5 Total (95% CI)	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 56 (P < 0.0 s: Chi ² = 3. Experi Mean 33 1: 14.47 1/ 20.11 : 32.76 : 48 (P < 0. 49.23 : 24.63 48 (P < 0. 49.23 : 24.63 48 (P < 0. 49.23 : 25.2 : 25.2 : 25.2 : 25.2 : 25.3 4 : 45 (P < 0. 45 (P < 0.) 45 (P < 0.) 45 (P < 0.) 45 (P < 0.) 46 (P < 0.) 47 (P < 0.) 48 (P < 0.) 48 (P < 0.) 49 (P < 0.) 40 (P < 0.)	3.67 3.78 3.78 3.78 3.78 5. df = 1 00001) 5. df = 2 0001) 35. df = 2 0001) 35. df = 2 1.0	6 6 12 112 112 112 112 112 112 112 112 1	53.68 39.97 0.00001 0.00001 0.007), I ² Con ean 9.89 54.2 2 8.68 9.97 83% 2.31 5.55 5.55 5.55 5.55 3.79 3.79 76% = 76%	1.23 2.4 1); ² = 7 1); ² = 7 1; ² = 7 2; ² = 7 1; ² = 7 2; ²	6 12 80 6% 2311 2% % 12 12 6 12 42 42 6 4 3 3 10 6 6 38 80 1	0.5% 3.9% 35.7% 100.0% \$ 20.2% 14.5% 0.4% 47.7% 9.2% 47.7% 9.2% 5.9% 6.0% 5.9% 6.0% 5.2,3%	-11.32 [-16.36, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.65 [-1.48, 0.17] -1.79 [-2.77, -0.82] -11.32 [-16.96, -5.68] -2.20 [-3.25, -1.15] -1.50 [-2.04, -0.96] -0.95 [-2.18, 0.27] -0.22 [-1.38, 0.41] -0.55 [-1.98, 0.67] -0.95 [-2.28, 0.45] -3.75 [-2.20, -4.5] -3.75 [-2.20, -4.5] -3.17 [-4.70, -1.64] -3.14 [-4.65, -1.62] -1.55 [-1.90, -1.16]	Std. Mean Difference IV. Fixed, 95% CI
Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Tau ² = 1.32; Test for overall effect: Z = 4. Total (95% CI) Heterogeneity: Tau ² = 0.75; Test for overall effect: Z = 6. Test for overall effect: Z = 6. Subtotal (95% CI) Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2029 Subtotal (95% CI) Heterogeneity: Chi ² = 17.74 Test for overall effect: Z = 5 3.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.5mmol) Wang, X.2016 Wang, X.2016(0.5mmol) Subtotal (95% CI) Heterogeneity: Chi ² = 24.69 Test for overall effect: Z = 5 Total (95% CI)	20.11 32.76 Chi ² = 42.4 48 (P < 0.0 Chi ² = 93.5 36 (P < 0.0 s: Ch ² = 3.5 Ch ² = 3.5 33 1 ² 14.47 14 20.11 : 32.76 : 49.23 : 49.23 : 24.63 4 20.76 2 133.56 : 25.2 : 25.34 : 25.34 : 49.25 (P < 0.0 49.23 : 25.2 : 25.34 : 25.2 :	3.67 3.78 3.78 3.78 3.78 5. df = 1 0001) 5. df = 2 0001) 5. df = 2 0001) 5. df = 2 0001 1.92 1	$\begin{array}{c} 6\\ 6\\ 12\\ 112\\ 295\\ 6\\ 6\\ (P < 12\\ 295\\ 10\\ 295\\ 10\\ 295\\ 10\\ 295\\ 10\\ 21\\ 12\\ 31\\ 42\\ 12\\ 31\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 1$	53.68 39.97 0.00001 0.00001 0.07), I ² Col ean 0.89 9.89 9.83% 2.31 8.3% 2.31 8.55 5.55 5.55 3.93 3.79 76%	1.23 2.4 2.1 1); ² = 7 1); ² = 7 1; ² = 70.19 5D T 8.21 8.21 8.21 8.22 8.22 8.22 8.22 8.22	b b 12 80 231 2% % 4 0tal Y 12 6 12 42 6 4 3 10 6 6 38 88	0.5% 3.9% 35.7% 100.0% \$ (eight 20.2% 14.5% 0.4% 9.2% 10.2% 41.5% 0.4% 5.6% 5.6% 6.0% 5.9% 6.0%	-11.32 [-16.36, -5.68] -22 [-3.25, -1.15] -1.85 [-2.66, -1.04] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -1.28 [-1.68, -0.89] -0.65 [-1.48, 0.77] -1.79 [-2.77, -0.82] -1.79 [-2.77, -0.82] -1.59 [-2.18, 0.87] -0.59 [-2.18, 0.87] -0.59 [-2.18, 0.67] -0.59 [-2.18, 0.67] -0.59 [-2.28, -2.19] -3.17 [-4.70, -1.64] -3.14 [-4.65, -1.62] -1.58 [-1.90, -1.16]	Std. Mean Difference IV. Fixed. 95% Cl

Forest plot depicting subgroup analyses to determine the effects of different factors on learning ability. (A) Drugs; (B) Animal models treated with exenatide.

3.2 Behavioral test analysis

MWM is one of the most widely used tasks for researching the spatial learning and memory abilities of AD animal models (Pantoni and Anagnostaras, 2019). In this study, escape latency was chosen as an indicator to evaluate learning ability, while the target quadrant dwell time and the percentage of time in the target quadrant dwell were used as indicators to assess memory ability. A total of 24 studies (30 groups) with 606 animals (experimental group n = 335, control group n = 271) were used to assess learning ability (Figure 3A). In addition, there were 25 studies (31 groups) with 619 animals (experimental group n = 277) used to

assess memory ability (Figure 3B). Compared to the control group, learning ability (SMD = -1.28, 95% CI = -1.68 to -0.89, p < 0.01, $I^2 = 76$ %) and memory ability (SMD = 1.26, 95% CI = 0.91 to 1.61, p < 0.01, $I^2 = 70$ %) were significantly improved in AD animals after GLP-1 RAs treatment. Separate subgroup comparisons of learning and memory abilities were performed according to drugs and modeling methods, which were used to reduce heterogeneity and further analyze the effect of GLP-1 RAs. Due to the fact that only one study is available for each of lixisenatide, (Val8) GLP-1, and geniposide, subgroup analysis cannot be performed on them. Therefore, this study only conducts subgroup analysis on the studies involving liraglutide and exenatide.

	E	xperim	ental		Contro	Ы		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mea	in S	D Tota	I Mean	n SI	D Tot	al Weigh	IV. Random, 95% CI	IV. Random. 95% Cl
6.1.1 Liraglutide									
Chen, S. Y.2017	30.3	6.5	64 10	21.2	1 6.5	4	10 3.9%	1.34 [0.35, 2.33]	
Han, W. N.2013(0.05nmol)	31.5	59 3.6	8 10	24.8	1 3.8	8	6 3.5%	1.71 [0.49, 2.93]	
Han, W. N.2013(0.5nmol)	37.9	98 5.5	2 10	24.8	1 3.8	8	5 3.0%	2.44 [0.96, 3.92]	
Han, W. N.2013(5nmol)	43.2	22 2.4	5 10	24.8	1 3.8	8	5 1.5%	5.85 [3.18, 8.51]	
Hansen, H. H.2016(100ug/kg	32.7	7 17.5	5 1	28.0	9 14.0	4	9 4.3%	0.28 [-0.54, 1.09]	+
Hansen H H 2016(500ug/kg	26.	88 126	4 11	3 28 0	9 14 0	4	8 4 3%	-0 13 [-0 96 0 71]	
Lu Chong2019	3) 20.0	28 24	9 10	20.0	6 10	7	15 4.49	1 16 (0 38 1 04)	
La Chong2019	2.0	14 46 6		20.0	0 120	2	10 4.4%	0 45 (0 27 4 26)	<u> </u>
McClean, P. L.2011	36.	11 16.8	4 1.	28.9	9 13.8	3	12 4.3%	0.45 [-0.37, 1.26]	
McClean, P. L.2014	38.2	28 8.1	2 12	28.5	2 8.1	2	12 4.2%	1.16 [0.28, 2.04]	
McClean, P. L.2015	38	.3 20.2	27 13	2 23.94	4 18.4	3	12 4.3%	0.72 [-0.11, 1.55]	
Qi, L.2016	21.2	28 6.1	2 10) 12.	8 4.7	1	10 3.9%	1.49 [0.47, 2.50]	
Sun Jie2015	4.0	0.9	7 1	3 4.2	2 0.6	6	8 4.0%	-0.22 [-1.20, 0.77]	
Xiong, H.2013	1.8	37 2.1	6 1	3 0.8	3 1.3	6	8 3.9%	0.54 [-0.46, 1.55]	
Yu. C. J.2020	2.6	59 0.4	7 10	1.2	2 0.4	1	10 3.1%	3.19 [1.78, 4.60]	
Zhaoli2021	48 3	2 59	2	36.1	6 6 1	4	6 3.0%	1.85 [0.40, 3.29]	
Zhang lipping2021	1 1	22 0.2	6 1	5 0.4	0.1	2	15 4.0%	2 47 [1 49 2 45]	
Subtetel (05% CI)	1.4	23 0.3	401	0.4	9 0.	2 44	4.0%	2.47 [1.49, 3.45]	
Subtotal (95% CI)			10.	,		15	59.47	1.27 [0.76, 1.77]	•
Heterogeneity: Tau ² = 0.74; C Test for overall effect: Z = 4.9	94 (P < 0	.48, df = .00001)	: 15 (P <	0.0000)1); I* =	74%			
6.1.2 Exenatide									
An, J.2019	3.1	15 2.4	9 1:	2 1.14	4 1.5	6	12 4.2%	0.93 [0.08, 1.78]	
Bomba, M.2019	3.0	04 1.6	7	4.0	2 2.8	2	6 3.7%	-0.40 [-1.51. 0.70]	
Bomfim, T. R.2012	22	6 6 2	9 1	16	5 4.8	1	12 4.2%	1.05 [0.19.1.92]	
Garabadu D 2010	40 /	14 67	6 4	10.0	2 60	1	6 1 00	4 20 [1 96 6 65]	
Jie V T 2016(0 00	49.0	- 0./	0	19.9	0.0		4 0.00	4.20 [1.00, 0.05]	
Jia, A. 1.2016(0.02nm0l)	20.4	9.1	0 10	20.1	0.1	0	4 3.6%	0.03 [-1.13, 1.19]	
Jia, X. 1.2016(0.2nmol)	35.4	18 9.1	8 10	26.1	3 8.1	6	3 3.2%	0.97 [-0.40, 2.33]	
Jia, X. T.2016(2nmol)	42.2	26 10	.2 10	26.1	3 8.1	6	3 3.0%	1.52 [0.05, 2.99]	
Wang, X.2016	39.7	71 5.1	8 10	28.3	5 3.7	4	10 3.5%	2.41 [1.20, 3.62]	
Wang, X.2016(0.05nmol)	40.2	23 4.2	3 12	2 27.9	5 2.7	1	6 3.0%	3.06 [1.56, 4.56]	
Wang, X.2016(0.5nmol)	40.8	38 4.2	2 12	2 27.9	5 2.7	1	6 2.9%	3.23 [1.69, 4.77]	
Wang, Y.2018	4.6	32 3.7	3 (5 0.4	1 0.4	1	6 3.2%	1.46 [0.13, 2.80]	
Zhang M .1 2022	28	39 23	7 1	1 3	3 17	6	12 4.3%	0.72 [-0.11 1.55]	
Subtotal (95% CI)						•		0.1	•
Heterogeneity: Tau ² = 0.84; C Fest for overall effect: Z = 4.3 Fotal (95% CI)	Chi² = 36 36 (P < 0	.86, df = .0001)	119 11 (P = 302	0.0001	l); l² = 7	2:	36 40.6% 37 100.0%	1.41 [0.78, 2.05]	•
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% Cl) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² =	.86, df = .0001) .83, df = .00001) 0.13, df	119 = 11 (P = 302 = 27 (P < = 1 (P =	0.0001 0.0000 0.0000	1); I ² = 7 01); I ² = I ² = 0%	2: 72%	36 40.6% 37 100.0%	5 1.41 [0.78, 2.05] 1.32 [0.93, 1.71]	Favours [experimental] Favours [control]
Heterogeneily: Tau ² = 0.84; (Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneity: Tau ² = 0.73; (Test for overall effect: Z = 6.6 Test for subgroup differences	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² =	.86, df = .0001) .83, df = .00001) 0.13, df	119 = 11 (P = 302 = 27 (P < = 1 (P =	0.0001 2 0.0000 0.72),	1); l² = 7)1); l² = l² = 0%	70% 2: 72%	36 40.6% 37 100.0%	5 1.41 [0.78, 2.05] 5 1.32 [0.93, 1.71]	-4 -2 0 2 4 Favours [experimental] Favours [control]
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 6 Test for subgroup differences	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = 1	.86, df = .0001) .83, df = .00001) 0.13, df	115 = 11 (P = 302 = 27 (P < = 1 (P =	0.0001 0.0000 0.72),	1); l ² = 7 (1); l ² = l ² = 0%	70% 2: 72%	36 40.69 37 100.09	 1.41 [0.78, 2.05] 1.32 [0.93, 1.71] d. Mean Difference 	Favours [experimental] Favours [control]
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = Expe	.86, df = .0001) .83, df = .00001) 0.13, df	115 = 11 (P = 302 = 27 (P < = 1 (P =	0.0001 2 0.0000 0.72), Co	1); l ² = 7)1); l ² = l ² = 0%	2: 72%	36 40.6% 37 100.0% S Weicht	 1.41 [0.78, 2.05] 1.32 [0.93, 1.71] <li< td=""><td>Favours [experimental] Favours [control]</td></li<>	Favours [experimental] Favours [control]
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = Expe Mean	.86, df = .0001) .83, df = .00001) 0.13, df rimenta SD	115 = 11 (P = 302 = 27 (P < = 1 (P = al Total M	0.0001 2 0.0000 0.72), Co Mean	1); l ² = 7)1); l ² = l ² = 0% ntrol <u>SD T</u>	2: 72%	36 40.6% 37 100.0% S Weight	 1.41 [0.78, 2.05] 1.32 [0.93, 1.71] 	Favours [experimental] Favours [control]
Heterogeneily: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneily: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = Expe <u>Mean</u>	.86, df = .0001) .83, df = .00001) 0.13, df rimenta	115 = 11 (P = 302 = 27 (P < = 1 (P = al Total M	0.0001 2 0.0000 0.72), Co <u>Mean</u>	1); l ² = 7)1); l ² = l ² = 0% ntrol <u>SD T</u>	2: 72%	36 40.69 37 100.09 S Weight	 1.41 [0.78, 2.05] 1.32 [0.93, 1.71] d. Mean Difference IV. Fixed, 95% CI 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% C1) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = Expe <u>Mean</u> 3.15	.86, df = .0001) .83, df = .00001) 0.13, df riment: <u>SD</u> 2.49	115 = 11 (P = 302 = 27 (P < = 1 (P = al Total M 12	0.0001 2 0.0000 0.72), Co Mean	1); l ² = 7 (1); l ² = l ² = 0% ntrol <u>SD T</u> 1.56	70% 2: 72%	36 40.69 37 100.09 S Weight 15.3%	 1.41 [0.78, 2.05] 1.32 [0.93, 1.71] 	Favours [experimental] Favours [control]
Heterogeneily: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneily: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = Expe <u>Mean</u> 3.15 3.04	.86, df = .0001) .83, df = .00001) 0.13, df riment: <u>SD</u> 2.49 1.67	115 = 11 (P = 302 = 27 (P < = 1 (P = al Total M 12 7	0.0001 0.0000 0.72), Co Mean 1.14 4.02	 i); i² = 7 i); i² = 1 i); i² = 0% ii); i² = 0% ii); i² = 0% iii); i³ = 0% ii³ = 0%<td>2: 72%</td><td>86 40.69 87 100.09 8 Weight 15.3% 9.1%</td><td> 1.41 [0.78, 2.05] 1.32 [0.93, 1.71] d. Mean Difference IV. Fixed, 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] </td><td>Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl</td>	2: 72%	86 40.69 87 100.09 8 Weight 15.3% 9.1%	 1.41 [0.78, 2.05] 1.32 [0.93, 1.71] d. Mean Difference IV. Fixed, 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% Cl) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomfan, T. R.2012	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = Expe <u>Mean</u> 3.15 3.04 22.6	.86, df = .0001) .83, df = .00001) 0.13, df rimenta <u>SD</u> 2.49 1.67 6.29	115 = 11 (P = 302 = 27 (P < = 1 (P = al Total M 12 7 12	0.0001 0.0000 0.72), Co Mean 1.14 4.02	 i); l² = 7 i); l² = 0 l² = 0% ntrol SD T 1.56 2.82 4.81 	2: 72% <u>fotal</u> 12 6 12	 40.6% 37 100.0% S Weight 15.3% 9.1% 14.9% 	 d. Mean Difference IV, Fixed, 95% CI 0.93 (0.08, 1.78) -0.40 (-1.51, 0.70) 1.05 (0.01, 1.92) 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneily: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneily: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bomba, M.2019 Bombin, T. R.2012 Wana, Y.2018	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = Expe Mean 3.15 3.04 22.6 4.62	.86, df = .0001) .83, df = .00001) 0.13, df riment: <u>SD</u> 2.49 1.67 6.29 3.73	115 = 11 (P = 302 = 27 (P < = 1 (P = al Total M 12 7 12 6	0.0001 0.0000 0.72), Co Mean 1.14 4.02 16.5 0.41	(); $l^2 = 7$ ()1); $l^2 = 0$ ($l^2 = 0$ % ()1); l^2 = 0% ()1); l^2 = 0% ()1); l^2 = 0% ()1); l^2 = 0% (70% 2: 72% Cotal 12 6 12 6	 40.6% 40.6% 100.0% S Weight 15.3% 9.1% 14.9% 6.2% 	 d. 41 [0.78, 2.05] 1.32 [0.93, 1.71] d. Mean Difference IV. Fixed, 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.46 [0.13, 2.80] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bomfar, T. R.2012 Wang, Y.2018 Zhang, M. J.2022	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = Expe Mean 3.15 3.04 22.6 4.62 2.89	.86, df = .0001) .83, df = .00001) 0.13, df rimenta SD 2.49 1.67 6.29 3.73 2.37	115 11 (P = 302 27 (P < = 1 (P = al <u>Total M</u> 12 7 12 6 12	0.0001 0.0000 0.72), Co Mean 1.14 4.02 16.5 0.41 1.33	 1); l² = 7 1); l² = 7 1); l² = 0% 1² = 0% 1² = 0% 1256 2.82 4.81 0.41 1.76 	2: 72% 72%	 40.6% 40.6% 7 100.0% S Weight 15.3% 9.1% 14.9% 6.2% 16.1% 	 i.41 [0.78, 2.05] i.32 [0.93, 1.71] i.32 [0.93, 1.71] i.4. Mean Difference IV. Fixed, 95% CI 0.93 [0.08, 1.78] 0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneily: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% Cl) Heterogeneily: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% Cl)	Chi ² = 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = Expe Mean 3.15 3.04 22.6 4.62 2.89	.86, df = .0001) .83, df = .00001) 0.13, df riment: <u>SD</u> 2.49 1.67 6.29 3.73 2.37	115 11 (P = 302 27 (P < = 1 (P = al Total M 12 7 12 6 12 49	0.0001 0.0000 0.72), Co Mean 1.14 4.02 16.5 0.41 1.33	1); $ ^2 = 7$ ()1); $ ^2 = 7$ ()1); $ ^2 = 0\%$ ()2 = 0\% ()2 = 0\% ()2 = 0\% ()2 = 0\% ()2 = 7 ()2 = 7 (2: 72% Total 12 6 12 6 12 6 12 48	 40.6% 37 100.0% 37 38 40.6% 9.1% 14.9% 6.2% 16.1% 61.5% 	 d. Mean Difference IV. Fixed. 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed. 95% Cl
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% Cl) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.6.1 transgenic An, J.2019 Bomba, M.2019 Bombim, T. R.2012 Wang, Y.2018 Subtotal (95% Cl)	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = Expe Mean 3.15 3.04 22.6 4.62 2.89	.86, df = .0001) .83, df = .00001) 0.13, df riment: SD 2.49 1.67 6.29 3.73 2.37	$\begin{array}{c} 119\\ 302\\ 27 (P < \\ = 1 (P = \\ 1$	0.0001 0.0000 0.72), Co Mean 1.14 4.02 16.5 0.41 1.33	1); $ ^2 = 7$ ()1); $ ^2 = 0\%$ ()2 = 0% ()3 = 0% ()4 = 0% ()5 = 0% ()5 = 0% ()6 = 0% ()7 = 0% ()	2: 72% 72% 12 6 12 6 12 48	 40.6% 37 100.0% S Weight 15.3% 9.1% 14.9% 16.1% 6.15% 	 d. 441 [0.78, 2.05] 1.32 [0.93, 1.71] d. Mean Difference IV. Fixed, 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneily: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneily: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneily: Chi ² = 5.91, Test for overall effect: Z = 3	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = Expe Mean 3.15 3.04 22.6 4.62 2.89 df = 4 (P 5.52 (P =	.86, df = .0001) .83, df = .00001) 0.13, df riment. <u>SD</u> 2.49 1.67 6.29 3.73 2.37 2.37 2.37	$\begin{array}{c} 119\\ 119\\ 302\\ 27 (P < \\ = 1 (P = \\ 1 (P = \\ 12 \\ 7 \\ 12 \\ 6 \\ 12 \\ 49 \\); ^2 = 32 \\)\end{array}$	0.0001 2 0.0000 0.72), 0.72), 1.14 1.02 16.5 16.5 10.41 1.33	 1); l² = 7 1); l² = 7 1); l² = 2 1); l² = 0% 1); l² = 0%<td>2: 72% 12 6 12 6 12 48</td><td> 40.6% 40.6% 100.0% S Weight 15.3% 9.1% 14.9% 6.2% 16.1% 61.5% </td><td> d. 4.41 [0.78, 2.05] 1.32 [0.93, 1.71] d. Mean Difference IV. Fixed, 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] </td><td>Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl</td>	2: 72% 12 6 12 6 12 48	 40.6% 40.6% 100.0% S Weight 15.3% 9.1% 14.9% 6.2% 16.1% 61.5% 	 d. 4.41 [0.78, 2.05] 1.32 [0.93, 1.71] d. Mean Difference IV. Fixed, 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bomba, M.2019 Bombim, T. R.2012 Wang, Y.2018 Subtotal (95% CI) Heterogeneity: Chi ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = Expe Mean 3.15 3.04 22.6 4.62 2.89 df = 4 (P 5.52 (P =	.86, df = .0001) .83, df = .00001) 0.13, df riment. <u>SD</u> 2.49 1.67 6.29 3.73 2.37 2.37 2 = 0.21 0.0004	115 116 27 (P < = 1 (P = 1(P	2 0.0001 2 0.0000 0.72), 1.14 4.02 1.13 1.13 22%	 i); l² = 7 i); l² = 7 i); l² = 0% i); l² =	2: 72% 72% 12 6 12 6 12 48	 40.6% 40.6% 100.0% S Weight 15.3% 9.1% 14.9% 16.1% 61.5% 	 d. 4.41 [0.78, 2.05] 1.32 [0.93, 1.71] d. Mean Difference IV. Fixed, 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% Cl) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 6 6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% Cl) Heterogeneity: Ch ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced Garabadu D 2019	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = $\frac{1}{2}$ Expe Mean 3.15 3.04 22.6 4.62 2.89 df = 4 (F 8.52 (P = $\frac{1}{2}$.86, df = .0001) .83, df = .00001) 0.13, df riment: <u>SD</u> 2.49 1.67 6.29 3.73 2.37 2.37 2.37 2.0004 6.76	115 117 119 300 207 (P < 27 (P < 27 (P < 21 (P = 11 (P = 12 7 12 6 12 7 12 6 12 49 9); 2 = 3;)	2 0.0001 2 0.0000 0.72), Co 1.14 16.5 0.41 1.33 2%	 i); l² = 7 i); l² = 7 i); l² = 7 i); l² = 0% i); l² =	2: 72% 72% 12 6 12 6 12 48	 40.69 40.69 100.09 37 100.09 S Weight 15.3% 41.9% 6.2% 16.1% 61.5% 2.0% 	 d. Mean Difference IV. Fixed. 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bombim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Chl ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced Garabadu, D.2019 Bombie (0.000mcl)	Chi ² = 36 36 (P < 0 Chi ² = 94 69 (P < 0 s: Chi ² = Expe Mean 3.15 3.04 22.6 4.62 2.89 df = 4 (F 9.52 (P =	.86, df = .0001) .83, df = .00001) 0.13, df rimentu SD 2.49 1.67 6.29 2.37 2.37 2.37 2 = 0.21 0.0004 6.76	115 117 118 117 117 117 127 12 12 12 12 12 12 12 12 12 12	0 0.0001 2 0.0000 0.72), Co 10.72), 1.14 16.5 0.41 1.33 2%	 i); l² = 7 i); l² = 7 i); l² = 0% il² = 0%	2: 72% 72% 6 12 6 12 12 48	 40.6% 57 100.0% S Weight 15.3% 9.1% 6.2% 16.1% 61.5% 2.0% 8 2% 	 d. 4.41 [0.78, 2.05] 1.32 [0.93, 1.71] 4.84 Mean Difference IV. Fixed, 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 4.20 [1.86, 6.55] 0.03 [1.12, 1.12] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% Cl) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% Cl) Heterogeneity: Chi ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.02mm))	Chi ² = 36 36 (P < 0 69 (P < 0 s: Chi ² = 94 69 (P < 0 s: Chi ² = Expe Mean 3.15 3.04 22.6 4.62 2.89 df = 4 (F 8.52 (P = 49.04 26.45 20.64	.86, df = .0001) .83, df = .00001) 0.13, df riment: <u>SD</u> 2.49 1.67 6.29 3.73 2.37 2 = 0.21 0.0004 6.76 9.18	115 117 118 119 207 (P < 27 (P < 27 (P < 27 (P < 12 12 12 12 12 12 12 12 12 12	0 0.0001 2 0.0000 0.72), 0.72), 1.14 4.02 16.5 0.41 1.33 2%	 i); l² = 7 i); l	2: 72% 72% 12 6 12 6 12 48 6 48	 40.6% 40.6% 100.0% S Weight 15.3% 9.1% 14.9% 6.2% 2.0% 8.2% 2.0% 	 d. Mean Difference IV. Fixed. 95% CI 0.93 (0.08, 1.78) -0.40 [-1.51, 0.70] 1.05 (0.19, 1.92) 1.46 (0.13, 2.80) 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 4.20 [1.86, 6.55] 0.03 [-1.13, 1.19] 0.72 (-0.02) 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneily: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneily: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneily: Chi ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.02nmol) Jia, X. T.2016(0.02nmol)	Chi ² = 36 (P < 0 Chi ² = 94 99 (P < 0 Mean 3.15 3.04 4.62 2.89 df = 4 (F 5.52 (P = 49.04 26.45 35.48	.86, df = .0001) .83, df = .00001) 0.13, df riment: SD 2.49 1.67 2.37 2.37 2 = 0.211 0.0004 6.76 9.18 9.18	$\begin{array}{c} 119\\ 119\\ 119\\ 119\\ 119\\ 119\\ 119\\ 119$	0.0001 2 0.0000 0.72), Co Mean 1.14 4.02 16.5 0.41 1.33 2% 9.92 9.92 66.13	 i); l² = 7 i); l² = 7 i); l² = 0% i); l² = 0%<!--</td--><td>2: 72% 72% 0 0 12 6 12 6 12 48 6 4 3</td><td> 40.6% 40.6% 100.0% 8 9.1% 14.9% 6.2% 6.1% 61.5% 2.0% 8.2% 6.0% </td><td> 1.41 [0.78, 2.05] 1.32 [0.93, 1.71] 1.32 [0.93, 1.71] 4.41 [0.78, 2.05] 1.32 [0.93, 1.71] 4.41 [0.78] 4.42 [0.95% CI 4.20 [1.86, 6.55] 0.74 [0.40, 2.33] </td><td>Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed. 95% Cl</td>	2: 72% 72% 0 0 12 6 12 6 12 48 6 4 3	 40.6% 40.6% 100.0% 8 9.1% 14.9% 6.2% 6.1% 61.5% 2.0% 8.2% 6.0% 	 1.41 [0.78, 2.05] 1.32 [0.93, 1.71] 1.32 [0.93, 1.71] 4.41 [0.78, 2.05] 1.32 [0.93, 1.71] 4.41 [0.78] 4.42 [0.95% CI 4.20 [1.86, 6.55] 0.74 [0.40, 2.33] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed. 95% Cl
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 0.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomfan, T. R.2012 Wang, Y.2018 Bomfan, T. R.2012 Subtotal (95% CI) Heterogeneity: Chi ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol)	Chi ² = 36 36 (P < 0 Chi ² = 94 59 (P < 0 Expe Mean 3.15 3.04 4.62 2.89 df = 4 (F 5.52 (P = 49.04 26.45 35.48	.86, df = .0001) .83, df = .00001) 0.13, df riment. <u>SD</u> 2.49 1.67 6.29 3.73 2.37 2 = 0.21 0.0004 6.76 9.18 9.18 10.2	$\begin{array}{c} 116\\ 111(P = 30);\\ 227(P < 27(P < 27($	0 0.0001 2 0.0000 0.72), 1.14 1 4.02 1 1.33 22% 9.92 0 9.92 0 9.93 1 8.13 1 8.13 1 8.13 1 8.13 1	 i); i² = 7 i); i³ = 7 i); i	2: 72% 72% 12 6 12 6 12 48 6 43 3 3	 40.6% 40.6% 100.0% S Weight 15.3% 44.9% 6.2% 16.1% 2.0% 8.2% 6.0% 5.1% 	 1.41 [0.78, 2.05] 1.32 [0.93, 1.71] 1.32 [0.93, 1.71] d. Mean Difference IV. Fixed. 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 4.20 [1.86, 6.55] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneily: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% C1) Heterogeneily: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% C1) Heterogeneity: Chi ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.2nmol) Jia, X. T.2016(0.2nmol) Jia, X. T.2016(0.2nmol)	Chi ² = 36 (P < 0 36 (P < 0 69 (P < 0 7 80 (P < 0 7 80 (P < 0 7 80 (P < 0 80 (P < 0)))))))))))))))))))))))))))))))))))	.86, df = .0001) .13, df = .00001) .13, df .0001) .13, df .0001) .13, df .001 .001 .001 .001 .001 .001 .001 .00	115 = 11 (P = 300 = 27 (P < = 1 (P = al Total N 12 6 12 49); P = 3;) 6 10 2 10 2 10 2 10 2	0 0.0001 2 0.0000 0.72), 1.14 2 1.14 4.02 2 1.14 1 1.33 2 2% 9.92 1 6.13 4 6.13 4 8.35 2	 i); i² = 7 i); i² = 7 i)1); i² = 7 i² = 0% ii² = 0% i² = 0% i³ = 0%<td>2: 72% 72% 12 6 12 6 12 48 6 4 3 3 10</td><td> 40.69 37 100.09 37 100.09 37 100.09 38 39.1% 41.9% 6.2% 6.0% 5.1% 7.6% </td><td> d.41 [0.78, 2.05] 1.32 [0.93, 1.71] 1.32 [0.93, 1.71] 4.32 [0.93, 1.71] 4.41 [0.78, 2.05% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.45 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 4.20 [1.86, 6.55] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99] 2.41 [1.20, 3.62] </td><td>Favours [experimental] Favours [control]</td>	2: 72% 72% 12 6 12 6 12 48 6 4 3 3 10	 40.69 37 100.09 37 100.09 37 100.09 38 39.1% 41.9% 6.2% 6.0% 5.1% 7.6% 	 d.41 [0.78, 2.05] 1.32 [0.93, 1.71] 1.32 [0.93, 1.71] 4.32 [0.93, 1.71] 4.41 [0.78, 2.05% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.45 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 4.20 [1.86, 6.55] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99] 2.41 [1.20, 3.62] 	Favours [experimental] Favours [control]
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% Cl) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 0.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomfam, T. R.2012 Wang, Y.2018 Subtotal (95% Cl) Heterogeneity: Chi ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol)	Chi ² = 36 36 (P < 0 Chi ² = 94 0 S9 (P < 0 Chi ² = 94 Chi ² =	.86, df = .0001) .83, df = .00001) 0.13, df riment. <u>SD</u> 2.49 1.67 6.29 3.73 2.37 2.37 2.37 2.37 2.37 2.37 2.37	115 = 11 (P = 30;; = 27 (P < = 1 (P = al Total N 12 7 12 6 12 49); l ² = 3; 0 2 10 10 10 10 10 10 10 10 10 10	0 0.0001 2 0.0000 0.72), 1.14 1 1.55 - 1.14 1 1.33 1 2% 9.92 1 66.13 4 86.13 4 86.13 4 86.13 3	 i); i² = 7 i); i³ = 7<	2: 72% Cotal 12 6 12 48 6 4 3 3 10 6	 40.69 37 100.09 37 100.09 37 38 9.1% 14.9% 6.2% 16.1% 61.5% 2.0% 8.2% 6.1% 7.6% 4.9% 	 4.41 [0.78, 2.05] 1.32 [0.93, 1.71] 4.32 [0.93, 1.71] 4.4.0 [0.78] 4.50 [0.91, 1.78] 4.20 [1.86, 6.55] 0.76 [0.34, 1.19] 4.20 [1.86, 6.55] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99] 2.41 [1.20, 3.62] 3.06 [1.64, 4.56] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneily: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneily: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomfan, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Chi ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.02nmol) Jia, X. T.2016(0.02nmol) Jia, X. T.2016(0.05nmol) Wang, X.2016(0.55nmol) Wang, X.2016(0.55nmol)	Chi ² = 36 (P < 0 Signature) Chi ² = 94 Signature) Chi ² = 94 Signature) Chi ² = 94 Signature) Chi ² = 94 Signature) Chi ² = 1 Signature) Chi ² = 1	.86, df = .00001) .83, df = .00001) 0.13, df riment: <u>SD</u> 2.49 1.67 6.29 2.37 2.37 2 = 0.21 0.0004 6.76 9.18 9.18 9.18 9.18 9.18 9.18 9.18 2.42	1115 = 11 (P = 300 = 27 (P < = 1 (P = al 10 1 10 2 10 2 1	9 0.0001 2 0.0000 0.72), Co Mean 1.14 1.42 1.55 0.41 1.33 2% 9.92 (0.613 1.6.13 1.6.13 1.8.35 1.7.95 .7.95 	 i); i² = 7 	2: 72% 50tal 12 6 12 6 12 48 6 4 3 3 10 6 6	 40.69 37 100.09 37 100.09 37 100.09 38 39.1% 9.1% 9.1% 14.9% 6.2% 6.1% 6	 d. Mean Difference IV. Fixed. 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.45 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 4.20 [1.86, 6.55] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99] 2.41 [1.20, 3.62] 3.08 [1.56, 4.56] 3.28 [1.66, 4.77] 	Favours [experimental] Favours [control]
Heterogeneily: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneily: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bomba, M.2019 Bomfim, T. R.2012 Wang, Y.2018 Subtotal (95% CI) Heterogeneily: Chi ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Jia, X. Z.2016(0.2mmol) Wang, X.2016(0.56mmol) Wang, X.2016(0.56mmol)	Chi ² = 36 36 (P < 0 Chi ² = 94 (P < 0 A Chi ² = 4 (F 2.89 df = 4 (F 5.2 (P = 4 2.55,48 42.26 55,48 42.26 39.71 40.23 40.28	.86, df = .0001) .83, df = .00001) .13, df riment: SD 2.49 1.67 6.29 3.73 2.37 9 = 0.21 0.0004 6.76 9.18 10.2 5.18 4.23 4.22	$\begin{array}{c} 111 \\ 1111 \\ 111 \\ 111 \\ 111 \\ 111 \\ 111 \\ 111 \\ 111 \\ 111 \\ 111 \\ 111 $	9 9 0.0001 2 0.0000 0.72), Co 1.14 4.02 1.14 4.02 2% 9.92 (6.13 4.13 1.33 (6.13 4.13 (7.95 (7.95)	 i); i² = 7 i); i² = 7 i² = 0% it² = 0%<td>2: 72% Cotal 12 6 12 6 12 6 12 48 6 4 3 3 10 6 6 38</td><td> 40.69 40.69 100.09 8 9.1% 15.3% 9.1% 16.1% 6.2% 6.15% 2.0% 5.1% 7.6% 4.6% 4.6% 38.8% </td><td> 4.41 [0.78, 2.05] 1.32 [0.93, 1.71] 4.32 [0.93, 1.71] 4.41 [0.78, 2.05] 4.42 [0.93, 1.78] 4.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 4.20 [1.86, 6.55] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99] 2.41 [1.20, 3.62] 3.06 [1.56, 4.56] 3.23 [1.59, 4.77] 1.84 [19, 2.37] </td><td>Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl</td>	2: 72% Cotal 12 6 12 6 12 6 12 48 6 4 3 3 10 6 6 38	 40.69 40.69 100.09 8 9.1% 15.3% 9.1% 16.1% 6.2% 6.15% 2.0% 5.1% 7.6% 4.6% 4.6% 38.8% 	 4.41 [0.78, 2.05] 1.32 [0.93, 1.71] 4.32 [0.93, 1.71] 4.41 [0.78, 2.05] 4.42 [0.93, 1.78] 4.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 4.20 [1.86, 6.55] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99] 2.41 [1.20, 3.62] 3.06 [1.56, 4.56] 3.23 [1.59, 4.77] 1.84 [19, 2.37] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneily: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneily: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Heterogeneil effect: Z = 6.6 Study or Subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneily: Ch ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.2nmol) Jia, X. T.2016(0.2nmol) Jia, X. T.2016(0.2nmol) Wang, X.2016(0.5nmol) Wang, X.2016(0.5nmol) Subtotal (95% CI) Heterogeneily: Ch ² = 21.50 Test for overall effect: Z = 1	Chi ² = 36 (P < 0 36 (P < 0 Chi ² = 94 (P < 0 Chi ² = 94 (P < 0 (P < 0 String of (P < 0	.86, df = .0001) .83, df = .00001) .0.13, df 	$\begin{array}{c} 1115\\ 111 (P = 300)\\ 227 (P < 300)\\ 300 = 11 (P = 100)\\ 110 = 100$	9 0.0001 9 0.0001 0.72). 1.14 4.02 1.14 4.02 1.13 1.33 9.92 9.92 9.92 9.92 9.92 1.13 1.35 1.33 1.35 1.33 1.35 1.33 1.35 1.	i); i ² = 7 i); i ² = 7 i); i ² = 0% introl <u>SD T</u> 1.56 2.82 4.81 0.41 1.76 6.01 8.16 8.16 8.16 3.74 2.71 2.71	2: 72% interfection interfectio	 40.69 37 100.09 37 100.09 38 38 39.1% 39.1% 39.1% 39.1% 49.9% 4.6% 38.5% 	 d. Mean Difference IV. Fixed. 95% CI 0.93 [0.08, 1.78] 0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.45 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 4.20 [1.86, 6.55] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99] 2.41 [1.20, 3.62] 3.26 [1.56, 4.56] 3.23 [1.94, 4.77] 1.84 [1.30, 2.37] 	Favours [experimental] Favours [control]
Heterogeneily: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneily: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bomba, M.2019 Bombi, T. R.2012 Wang, Y.2018 Chang, M. J.2022 Subtotal (95% CI) Heterogeneily: Chi ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Wang, X.2016(0.5mmol) Wang, X.2016(0.5mmol) Wang, X.2016(0.5mmol) Subtotal (95% CI) Heterogeneily: Chi ² = 21.50 Test for overall effect: Z = 6	Chi ² = 36 6(P < 0 Chi ² = 94 4 59 (P < 0 Chi ² = 94 4 59 (P < 0 S: Chi ² = Expe Mean 3.15 3.04 4.62 2.89 df = 4 (F 5.52 (P = 49.04 42.64 35.48 42.26 39.71 40.23 40.28 40.23 40.28 40.28 40.23 40.28 40.23 40.28 40.23 40.28 40.23 40.28 40.23 40.28 40.23 40.28 40.23 40.28 40.23 40.28 40.28 40.23 40.28	.86, df = .0001) .83, df = .00001) .13, df .249 .237 .237 .237 .237 .237 .237 .237 .237	$\begin{array}{c} 111 \\ 111 \\ (P = 300) \\ 227 \\ (P < 300) \\ 227 \\ (P < 300) \\ 300 \\$	9 0.00001 2 0.0000 0.72), Co 6an 1.14 4.02 1.33 4.02 2% 9.92 0.41 1.33 2% 9.92 0.41 1.33 2% 9.92 0.613 1.613 1.835 1.725 1.725 1.725 1.725 1.72%	 i); i² = 7 ii); i² = 7 iii); i² = 2 iii = 1² = 0% iii = 1.56 2.82 4.81 0.41 1.76 6.01 8.16 8.16 8.16 8.16 3.74 2.71 2.71 	Total 12 6 12 6 12 6 12 6 3 10 6 38	 36 40.69 37 100.09 37 100.09 38 38 39.1% 14.9% 61.7% 14.9% 61.5% 14.9% 61.5% 2.0% 8.2% 6.1% 7.6% 38.5% 	 4.41 [0.78, 2.05] 1.32 [0.93, 1.71] 4.32 [0.93, 1.71] 4.41 [0.78, 2.05] 4.42 [0.93, 1.71] 4.45 [0.19, 1.92] 4.46 [0.19, 1.92] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 4.20 [1.86, 6.55] 0.03 [-1.13, 1.19] 4.20 [1.86, 6.55] 0.37 [-0.40, 2.33] 1.52 [0.05, 2.99] 2.41 [1.20, 3.62] 3.06 [1.56, 4.56] 3.23 [1.59, 4.77] 1.84 [1.30, 2.37] 	Favours [experimental] Favours [control]
Heterogeneily: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneily: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bomfim, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneily: Ch ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.5mmol) Wang, X.2016(0.5mmol) Subtotal (95% CI) Heterogeneily: Ch ² = 21.50 Test for overall effect: Z = 6 Total (95% CI)	$Chi^2 = 36 (P < 0)$ $Chi^2 = 36 (P < 0)$ $Chi^2 = 94 (P < 0)$ $Expe$ $Mean$ 3.15 3.04 4.62 2.89 $df = 4 (F (P < 0)$ 49.04 26.45 35.48 40.23 35.44 40.23 40.88 40.88 40.86 40.86	8.86, df = .0001) .83, df = .00001) .013, df .013, df .014, df .014, df .014, df .015,	111 (P = 300) 27 (P < = 1 (P = 30) 300 (P < 1 = 1 (P = 1 = 1 (P = 1 = 1 (P = 1(P	9 0.0001 0.0001 0.72). Co Mean 1.14 1.33 1.14 1.33 2% 9.92 0.613 1.613 1.835 2% 9.92 7.95 7.2%	 i); i² = 7 i); i² = 7 i); i² = 0% i); i); i² = 0% i); i); i); i); i); i); i); i); i); i);	2: 72% iotal 12 6 12 6 12 48 6 4 3 3 10 6 6 38 86	 36 40.69 37 100.09 37 100.09 37 100.09 38 Weight 15.3% 9.1% 14.9% 15.3% 2.0% 8.2% 6.1% 5.1% 2.0% 8.2% 6.0% 5.1% 2.0% 8.2% 6.0% 5.1% 38.5% 100.0% 	 d. Mean Difference IV. Fixed. 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 4.20 [1.86, 6.55] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.56, 2.99] 2.41 [1.20, 3.62] 3.06 [1.56, 4.56] 3.23 [1.59, 4.77] 1.84 [1.30, 2.37] 	Favours [experimental] Favours [control]
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for overall effect: Z = 6.6 Test for subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2019 Bomba, M.2022 Subtotal (95% CI) Heterogeneity: Chi ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Jia, X. T.2016(0.2mmol) Wang, X.2016(0.5mmol) Wang, X.2016(0.5mmol) Wang, X.2016(0.5mmol) Subtotal (95% CI) Heterogeneity: Chi ² = 21.50 Test for overall effect: Z = 6 Total (95% CI)	Chi ² = 36 6 (P < 0 Chi ² = 94 4 S9 (P < 0 Chi ² = 94 4 S9 (P < 0 S: Chi ² = Expe Mean 3.15 3.04 4.62 2.89 df = 4 (F 5.52 (P = 49.04 426.45 2.69 df = 4 (0.23 40.28 40.23 40.28 0, df = 6 .71 (P <	.86, df = .0001) .83, df = .00001) 0.13, df riment. <u>SD</u> 2.49 1.67 6.29 1.67 6.29 9.18 9.18 10.2 9.18 9.18 10.2 9.18 9.18 9.18 10.2000 9.18 9.18 9.18 9.18 10.2000 9.18 9.18 9.18 9.18 9.18 9.18 9.18 9.18	111 (P = 300, 277 (P < 277 (P < all Total N 12 6 12 49 10 2 49 10 2 10 2 7 10 2 7 10 2 7 10 2 7 10 2 7 10 2 7 10 2 7 10 2 7 10 2 7 10 2 7 10 2 7 10 10 10 10 10 10 10 10 10 10	9 0.0001 2 0.0000 0.72), Co 1.14 1.5 1.5 1.5 1.5 1.5 1.5 1.5 1.5	 i); i² = 7 ii); i² = 7 iii); i³ = 7 <li<sup></li<sup>	2: 72% cotal 12 6 12 6 12 6 12 48 6 4 3 3 10 6 38 86	 40.69 40.69 100.09 8 9.1% 14.9% 6.2% 16.1% 61.5% 2.0% 8.2% 6.0% 5.1% 7.6% 38.5% 100.0% 	 1.41 [0.78, 2.05] 1.32 [0.93, 1.71] 1.32 [0.93, 1.71] 4.41 [0.78, 2.05] 1.32 [0.93, 1.71] 4.41 [0.78, 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 4.20 [1.86, 6.55] 0.03 [-1.13, 1.19] 4.20 [1.86, 6.55] 0.03 [-1.13, 1.19] 4.20 [1.86, 6.55] 0.33 [-1.13, 1.19] 4.20 [1.86, 4.55] 0.36 [1.56, 4.56] 3.23 [1.69, 4.77] 1.84 [1.30, 2.37] 1.18 [0.84, 1.51] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneity: Tau ² = 0.84; C Test for overall effect: Z = 4.3 Total (95% CI) Heterogeneity: Tau ² = 0.73; C Test for overall effect: Z = 6.6 Test for subgroup differences Study or Subgroup 6.5.1 transgenic An, J.2019 Bomba, M.2019 Bomfan, T. R.2012 Wang, Y.2018 Zhang, M. J.2022 Subtotal (95% CI) Heterogeneity: Chi ² = 5.91, Test for overall effect: Z = 3 6.5.2 chemical-induced Garabadu, D.2019 Jia, X. T.2016(0.02nmol) Jia, X. T.2016(0.02nmol) Jia, X. T.2016(0.05nmol) Wang, X.2016(0.05nmol) Subtotal (95% CI) Heterogeneity: Chi ² = 21.50 Test for overall effect: Z = 6 Total (95% CI)	Chi ² = 36 $(P < 0)$ Signature (P < 0) Chi ² = 94 $(P < 0)$ (P < 0) Chi ² = 94 $(P < 0)$ Expre Mean 3.15 3.04 4.62 2.89 df = 4 (f 1.52 (P = 1) 49.04 26.45 35.48 40.22 49.04 40.28 30.71 40.28 0, df = 61 () .7.1 (P < 1) .7.1 (P <	.86, df = .0001) .83, df = .00001) .013, df riment: .5D .2.49 1.67 6.29 3.73 2.37 2 = 0.212 0.0004 6.76 9.18 10.2 5.18 4.22 P = 0.0 0.0000 (P = 0.0	1115 11 (P = 302 27 (P < 27 (P < all 10 P = 12 7 12 7 10 2 10 2 1	0.0001 0.0001 0.72), 0.72), 0.72), 0.72), 1.14 1.05 1.14 1.13	 i); i² = 7 i); i³ = 7<	Total 12 6 12 6 12 6 12 6 3 10 6 33 10 6 38 86	 36 40.69 37 100.09 37 100.09 37 100.09 38 Weight 15.3% 9.1% 14.9% 16.1% 6.1% 6.1% 6.1% 6.1% 7.6% 4.9% 38.5% 100.0% 	 d. Mean Difference IV. Fixed. 95% CI 0.93 [0.08, 1.78] -0.40 [-1.51, 0.70] 1.05 [0.19, 1.92] 1.46 [0.13, 2.80] 0.72 [-0.11, 1.55] 0.76 [0.34, 1.19] 4.20 [1.86, 6.55] 0.03 [-1.13, 1.19] 0.97 [-0.40, 2.33] 1.52 [0.05, 2.99] 2.41 [1.20, 3.62] 3.06 [1.56, 4.56] 3.23 [1.56, 4.76] 3.23 [1.58, 4.77] 1.84 [1.30, 2.37] 	Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% Cl

Forest plot depicting subgroup analyses to determine the effects of different factors on memory ability. (A) Drugs; (B) Animal models treated with exenatide.

3.2.1 Learning ability

Among the 24 studies (30 groups) in which learning ability was tested, 16 groups chose liraglutide, while 11 groups chose exenatide (Figure 4A). As for the ability of GLP-1 RAs to correct learning deficits, the exenatide group (SMD = -1.85, 95% CI = -2.66 to -1.04, p < 0.01, $I^2 = 76\%$) and the liraglutide group (SMD = -1.00, 95% CI = -1.42 to -0.58, p < 0.01, $I^2 = 66\%$) were respectively compared with the control group, suggesting that exenatide group displayed more significant improvements.

In the exenatide group, four groups selected the transgenic animal model (SMD = -1.50, 95% CI = -2.04 to -0.96, p < 0.01,

 I^2 = 83%), and seven groups selected the chemical-induced animal model (SMD = -1.56, 95% CI = -2.07 to -1.05, p < 0.01, I^2 = 76%) (Figure 4B). The result showed that chemical-induced animal model group displayed more significant amelioration in learning ability compared to the control group.

3.2.2 Memory ability

Among the 25 studies (31 groups) in which memory ability was tested, 16 groups chose liraglutide, while 12 groups chose exenatide (Figure 5A). As for the ability of GLP-1 RAs to correct memory deficits, the exenatide group (SMD = 1.41, 95% CI = 0.78 to 2.05, p <



0.01, $I^2 = 70\%$) and the liraglutide group (SMD = 1.27, 95% CI = 0.76 to 1.77, p < 0.01, $I^2 = 74\%$) were respectively compared with the control group, suggesting that exenatide group displayed more significant improvements.

In the exenatide group, five groups selected the transgenic animal model (SMD = 0.76, 95% CI = 0.34 to 1.19, p < 0.01, $I^2 = 32\%$) and seven groups selected the chemical-induced animal model (SMD = 1.84, 95% CI = 1.30 to 2.37, p < 0.01, $I^2 = 72\%$) (Figure 5B). The result showed that chemical-induced animal model group displayed more significant amelioration in memory ability compared to the control group.

This indicates that, in comparison to liraglutide, exenatide shows a greater improvement in learning and memory abilities in AD animals. Furthermore, concerning the modeling methods, exenatide demonstrates a better ability to correct cognitive deficits in the chemically induced animal model.

3.3 Neuropathological features

Plaques and NFTs are two important pathological features in the diagnosis of AD (Scheltens et al., 2021). A β plaques are obtained through the cleavage of amyloid precursor proteins (APP) by β -secretase and γ -secretase (Calsolaro and Edison, 2016). Hyperphosphorylation of tau protein is an early sign of NFT pathogenesis (Kannanayakal et al., 2006). Tau proteins are microtubule neuronal proteins involved in the polymerization and stabilization of microtubule assembly to maintain the integrity of the cytoskeleton (Khan et al., 2020). Both A β and tau can aggregate and cause synaptic damage as well as neuronal cell death. In this study, A β deposition and p-Tau were selected as secondary indicators to investigate the therapeutic effects of GLP-1 RAs in AD animals.

3.3.1 A β deposition

For a more comprehensive assessment of Aβ pathology in the brains of AD animals, we selected the indicators of Aβ plaque burden (Figure 6A) and A β_{1-42} deposition (Figure 6B) to analyze the effect of GLP-1 RAs. Aβ plaque burden (SMD = -1.43, 95% CI = -2.44 to -0.41, p < 0.01, $I^2 = 79\%$) was tested by immunohistochemistry in six studies (seven groups), involving 122 animals (experimental group n = 69, control group n = 53). A β_{1-42} deposition (SMD = -1.88, 95 %CI = -2.99 to -0.78, p < 0.01, $I^2 = 80\%$) was detected by ELISA in nine studies involving 139 animals (experimental group n = 71, control group n = 68). The results indicated that GLP-1 RAs treatment could effectively reduce A β plaque burden and A β_{1-42} in the brains of AD animals to some extent.

3.3.2 Phosphorylated tau

p-Tau levels were measured in six studies involving 74 animals (experimental group n = 36, control group n = 38) (Figure 7). The results suggested that GLP-1 RAs were effective in reducing p-Tau levels (SMD = -1.41, 95% CI = -2.14 to -0.68, p < 0.01, $I^2 = 35\%$) in animal models of AD.

3.4 Administration method

Based on the above research findings, this study investigates the therapeutic effects of different doses and administration methods of exenatide on improving learning (Figure 8A) and memory impairments (Figure 8B) in AD. The doses were firstly standardized to μ g/kg and the doses given by rats were converted to mice doses by means of the formula (Janhavi et al., 2022), followed by a comparison. The administration methods of exenatide involve a total of five approaches, including intranasal



(i.n.) administration, subcutaneous (s.c.) administration, intraperitoneal (i.p.) administration, hippocampal (i.h.) and i.c.v. In this study, i.p. and administration, i.c.v. administrations are categorized collectively as intracerebral (i.c.) injections. The analysis will be conducted on these four administration methods.

According to our findings, among the four administration routes compared with the control group, i.n. administration (SMD = -3.15, 95% CI = -4.23 to -2.08, p < 0.01, $I^2 = 0\%$) demonstrated a significant improvement in learning ability. Specifically, the other statistical results are as follows: s.c. administration (SMD = -2.75, 95% CI = -5.20 to -0.29, p < 0.05, $I^2 = 88\%$), i.p. administration (SMD = -1.46, 95% CI = -2.26 to -0.65, p < 0.01, $I^2 = 9\%$) and i.e. administration (SMD = -1.32, 95% CI = -2.76 to 0.12, p = 0.07, $I^2 =$ 78%). Additionally, among the four administration routes, i.n. administration (SMD = 3.14, 95% CI = 2.07 to 4.22, p < 0.01, $I^2 = 0\%$) demonstrated a significant improvement in memory ability compared to the control group. Specifically, the other statistical results are as follows: i.p. administration (SMD = 1.32, 95% CI = -0.57 to 3.21, p = 0.17, $I^2 = 85\%$), i.e. administration (SMD = 1.22, 95% CI = 0.16 to 2.28, p < 0.05, $I^2 = 63\%$) and s.c. administration (SMD = 0.93, 95% CI = 0.39 to 1.47, p < 0.01, I^2 = 0%). Therefore, we conclude that single i.n. administration of exenatide demonstrates advantages in improving learning and memory abilities in AD animals, with dosages ranging from 10.47 µg/kg to 104.68 µg/kg.

4 Discussion

GLP-1 RAs can exert neuroprotective effects by binding to GLP-1 receptors and activating downstream signaling, thus having therapeutic potential for AD (Cantini et al., 2016; Hölscher, 2020). In GLP-1 RAs treatment, several mechanisms have been indicated to have beneficial effects on the brain, including reduction of neuroinflammation, enhancement of synaptic transmission, and reduction of learning deficits (During et al., 2003; Salcedo et al., 2012). In addition, GLP-1 RAs can promote the proliferation of neural stem cells in rodents (Bertilsson et al., 2008; Hamilton et al., 2011). The current studies on the therapeutic use of GLP-1 RAs for AD are mainly in the preclinical stage. The reliability of the conclusions can be improved by analyzing and integrating existing experiments. In this study, rodent models were selected to explore the ameliorating effects and mechanisms of action of GLP-1 RAs on AD.

In this study, MWM was selected as the main indicator to evaluate the effects of GLP-1 RAs for ameliorating the cognitive function of AD animals by escape latency, and the target quadrant dwell time or the percentage of time in the target quadrant dwell, respectively. The results of the meta-analysis indicated that GLP-1 RAs could effectively increase the cognitive function of AD animals. According to subgroup analysis, in different modeling methods, GLP-1 RAs could ameliorate cognitive performance more markedly in chemically induced model animals; in terms of animal strains, GLP-1 RAs showed more significant improvement in rats for cognitive impairment. For pathological features, $A\beta$ deposition and p-Tau protein were selected. The results showed that GLP-1 RAs reduced $A\beta$ deposition and tau protein hyperphosphorylation in the brains of AD animals.

The incidence and clinical manifestations of AD show gender differences. Investigation reveals that women suffer from AD at a much higher rate than men, and female AD patients have more prominent pathologic manifestations, such as greater brain atrophy and cognitive impairment (Guo et al., 2023). This disparity seems to be influenced by various factors, with some studies suggesting that the association between APOE4 and AD is more prominent in females (Corder et al., 2004; Ungar et al., 2014). A network analysis showed that Lipoprotein receptor-related protein 10 (LRP10), with high sex differential expression, is a critical regulatory factor in female AD. And the finding was successfully validated by the EFAD mouse model (Guo et al., 2023). LRP10 is considered to influence cognitive function and AD pathology in a manner that is specific to gender and APOE genotype. LRP10 is thought to reduce Aβ production by influencing the maturation of APP(Brodeur et al., 2012). In studies involving AD patients, it was observed that the levels of LRP10 protein in the brains of AD patients were significantly lower compared to the control group, with a more pronounced reduction observed in females (Brodeur et al., 2012). In female AD, reduced LRP10 protein expression leads to impaired APP transport and increased A β . Furthermore, the reduction of LRP10 also results in a decrease in microglia clearance of Aß (Brodeur et al., 2012; Guo et al., 2023). Moreover, a recent study unveiled that the propagation of NFTs occurs at a higher pace in the brains of females compared to males. This accelerated spread could potentially be attributed to the unique network structures of brain regions influenced by tau (Shokouhi et al., 2020). Meanwhile, it has been suggested by studies that intact mitochondrial function could more effectively shield females from the toxic effects of AB. This might be attributed to estrogen-mediated ROS inhibition, which, when estrogen levels decline after menopause, could result in greater

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Ideterogeneity: Tau ² = 0.03; (Fest for overall effect: Z = 3.9 4.5.3 i.n. Wang, X.2016(0.05nmol) Wang, X.2016(0.5nmol) Subtotal (95% CI) Heterogeneity: Tau ² = 0.00; (Fest for overall effect: Z = 5.7 4.5.4 i.c. 16.5.4 i.c. 16.5.4 i.c.	Chi ² = 1 55 (P = 25.2 25.34 Chi ² = 0 74 (P <	.10, df = 0.0004) 2.79 2.77 0.00, df = 0.00001	1 (P 12 12 24 1 (P	= 0.29); 33.79 33.79	2.05 2.05				
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Wang, X.2016(0.5nmol) Subtotal (95% CI) Heterogeneity: Tau ² = 0.00; fest for overall effect: Z = 5.1 1.5.4 i.c. lia, X. T.2016(0.02nmol) lia, X. T.2016(0.2nmol)	25.34 Chi ² = 0 74 (P <	2.77 0.00, df = 0.00001	12 24 1 (P	33.79	2.05	0	8.8%	-3.17 [-4.70, -1.64]	
subtotal (95% CI) Heterogeneity: Tau ² = 0.00; (Fest for overall effect: Z = 5.1 1.5.4 i.c. lia, X. T.2016(0.02nmol) lia, X. T.2016(0.2nmol)	Chi² = 0 74 (P <	0.00, df = 0.00001	24 1 (P		2.00	6	8.9%	-3.14 [-4.65, -1.62]	
reterogeneity: Tau ² = 0.00; (Fest for overall effect: Z = 5.1 I.5.4 i.c. Iia, X. T.2016(0.02nmol) Iia, X. T.2016(0.2nmol)	⊂ni* = 0 74 (P <	0.00001	1 (P :	- 0 00'	12 - 001	12	17.7%	-3.15 [-4.23, -2.08]	▼
I.5.4 i.c. lia, X. T.2016(0.02nmol) lia, X. T.2016(0.2nmol)			/	= 0.98);	12 = 0%	•			
lia, X. T.2016(0.02nmol) lia, X. T.2016(0.2nmol)	04.00								
lia, X. T.2016(0.2nmol)	24.63	8.22	10	26.55	8.22	4	10.2%	-0.22 [-1.38, 0.94]	+
	20.76	8.24	10	26.55	8.22	3	9.6%	-0.65 [-1.98, 0.67]	
lia, X. T.2016(2nmol)	16.92	10.27	10	26.55	8.22	3	9.5%	-0.90 [-2.26, 0.45]	
Wang, X.2016 Subtotal (95% CI)	33.56	3.17	10	49.39	4.75	10	8.7%	-3.75 [-5.32, -2.19]	
Heterogeneity: Tau ² = 1.67; (Frest for overall effect: Z = 1.8	Chi² = 1 80 (P =	3.74, df 0.07)	= 3 (F	P = 0.00	3); I² = 7	78%	37.378	-1.32 [-2.70, 0.12]	
Cotal (95% CI)			112			80	100.0%	-1 85 [-2 66 -1 04]	•
Heterogeneity: Tau ² = 1.32; (Fest for overall effect: Z = 4.4 Fest for subgroup differences	Chi² = 4 48 (P < s: Chi² =	2.45, df 0.00001 = 7.35, di	= 10 () f = 3 ((P < 0.0	0001); l 6), l² = 5	² = 76% 59.2%	%	-1.05 [-2.00, -1.04]	-10 -5 0 5 10 Favours [experimental] Favours [control]
	Expe	rimenta	1	Co	ontrol		S	td. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD T	otal	Mean	SD -	Total	Weight	IV. Random. 95% CI	IV. Random, 95% Cl
1.0.1 S.C.	2 16	2 40	12	1 14	1 66	12	10 2%	0.02 (0.09 1.79)	
Nang Y 2018	4 62	3.73	6	0.41	0.41	6	8 1%	1 46 [0 13 2 80]	
Zhang, M. J.2022	2.89	2.37	12	1.33	1.76	12	10.3%	0.72 [-0.11, 1.55]	
Subtotal (95% CI)			30			30	28.6%	0.93 [0.39, 1.47]	◆
Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 3.	Chi ² = (.36 (P =	0.85, df = 0.0008)	= 2 (P	= 0.65)); I ² = 0%	%			
I.6.2 i.p.									
Bomba, M.2019	3.04	1.67	7	4.02	2.82	6	9.1%	-0.40 [-1.51, 0.70]	-+
Bomfim, T. R.2012	22.6	6.29	12	16.5	4.81	12	10.2%	1.05 [0.19, 1.92]	
Garabadu, D.2019	49.04	6.76	6	19.92	6.01	6	4.6%	4.20 [1.86, 6.55]	
Subtotal (95% CI)	01-12		25			24	23.9%	1.32 [-0.57, 3.21]	
reterogeneity: Tau ² = 2.24; Fest for overall effect: Z = 1.3	Chi ² = 1 .37 (P =	0.17)	= 2 (1	r = 0.00	J2); I ² =	85%			
l.6.3 i.n.									
Vang, X.2016(0.05nmol)	40.23	4.23	12	27.95	2.71	6	7.4%	3.06 [1.56, 4.56]	
wang, X.2016(0.5nmol) Subtotal (95% CI)	40.88	4.22	12 24	27.95	2.71	6 12	7.2%	3.23 [1.69, 4.77]	
Heterogeneity: $Tau^2 = 0.00$	$Chi^2 = 0$	0 02 df -	= 1 /P	= 0.881	· 12 = 00	12	14.0%	5.14 [2.07, 4.22]	-
Test for overall effect: Z = 5.	.73 (P <	0.00001)	- 0.00)	,, - 07				
I.6.4 i.c.									
lia, X. T.2016(0.02nmol)	26.45	9.18	10	26.13	8.16	4	8.8%	0.03 [-1.13, 1.19]	
lia, X. T.2016(0.2nmol)	35.48	9.18	10	26.13	8.16	3	7.9%	0.97 [-0.40, 2.33]	
lia, X. T.2016(2nmol)	42.26	10.2	10	26.13	8.16	3	7.5%	1.52 [0.05, 2.99]	
wang, X.2016 Subtotal (95% CI)	39.71	5.18	10 40	28.35	3.74	10	8.6%	2.41 [1.20, 3.62]	
Heterogeneity: Tau ² = 0.73; Fest for overall effect: Z = 2.	Chi ² = 8 .26 (P =	3.02, df =	= 3 (P	= 0.05)); l² = 63	3%	52.370	1.22 [0.10, 2.20]	•
Cotal (95% CI)			110			96	100.0%	1 41 [0 79 2 06]	
Heterogeneity: Tau ² = 0.94.	Chi ² = 4	N 38 36	= 11	(P = 0.0	0011-12	2 = 700	6		
Test for overall effect: Z = 4.	.36 (P <	0.0001) = 13.04	- 11	(F = 0.0	005) 12	2 = 77 (° 1%		-4 -2 0 2 4 Favours [experimental] Favours [control]

Forest plot: the effects of different administration method of exenatide on the improvement of cognitive function. (A) Learning ability (B) Memory ability.

susceptibility of females to mitochondrial dysfunction (Viña and Lloret, 2010).

Furthermore, research on T2DM has revealed that estrogen also exerts an influence on insulin resistance and glucose metabolism (Mauvais-Jarvis et al., 2013; Root-Bernstein et al., 2014). Moreover, influenced by estrogen, central stimulation of GLP-1 RAs has been found to be more sensitive in females (Richard et al., 2016). Therefore, whether there is a differential therapeutic effect of GLP-1 RAs on AD warrants further attention and in-depth investigation.

Despite abundant evidence supporting the gender-specificity of AD, only a few experiments have focused on gender differences,

leading to an underestimation of the importance of gender (Guo et al., 2022). One of the studies included in our research did not differentiate animal sex. Furthermore, the selection of animal gender in previous studies has been uneven. Our research found that most of the current research has predominantly chosen male animals as subjects, which may be an attempt to control for variables and prevent sex differences from having an effect on AD pathology. However, as the deepening of AD gender research, the use of female animals as AD models is gradually gaining attention. In our research, there has one study selected female mice as subjects, and more AD experiments specifically targeting female animals should be carried out in the future.

A comprehensive analysis of the improvement of learning and memory abilities by drugs. Based on our conclusions, exenatide administered intranasally at doses ranging from 10.47 to 104.68 µg/kg exhibited a more significant enhancement of cognitive function in mice. After converting the mouse doses to human doses, we recommend a human dose range of exenatide between 59.42 and 594.13 µg/70 kg. The i.n. administration facilitates direct drug delivery to the brain, enabling faster access to the CNS. Moreover, it effectively circumvents the first-pass effect through the gastrointestinal tract and liver, thereby enhancing the drug's bioavailability (Shehata et al., 2023). While our study highlights the pronounced advantages of intranasal administration, it is noteworthy that current clinical practice primarily employs subcutaneous injection for exenatide, which boasts benefits such as simplicity, safety, and rapid absorption. Therefore, the doses and cycles given in this study are only preliminary recommendations, and future optimization and exploration of the results based on bioavailability are necessary to find the appropriate cycles and doses for clinical application.

4.1 Potential mechanisms

Drawing from the compilation of 26 studies, it becomes evident that GLP-1 RAs play a therapeutic role in AD by collaboratively ameliorating diverse pathological manifestations associated with AD.

The connection between T2DM and AD may potentially stem from abnormalities in insulin signaling and insulin resistance mechanisms (Grieco et al., 2019). A large number of studies have shown that insulin signaling is impaired in the brains of AD patients and AD animals (Bomfim et al., 2012b; Talbot et al., 2012). The insulin signaling process consists of insulin binding to the insulin receptor (IR), enabling IR activation and autophosphorylation (Hubbard, 1997; Hubbard, 2013). Activation of tyrosine kinases on IR can aggregate and phosphorylate insulin receptor substrate (IRS), which binds and activates downstream pathways after phosphorylation (Nguyen et al., 2020). Phosphatidylinositol 3 kinase/protein kinase B (PI3K/AKT) and Mitogen-activated protein kinase (MAPK) are the two main signaling pathways (Griffith et al., 2018). PI3K/AKT signaling promotes energy metabolism, protein and lipid synthesis, and glucose transport (Kleinridders et al., 2014). It has also been found to ameliorate cognitive function by improving memory consolidation and modulating synaptic plasticity (Chiang et al., 2010). Glycogen synthase kinase 3β (GSK3 β) is a protein kinase that is considered to accelerate tau protein phosphorylation and the formation of NFTs (Zheng and Wang, 2021). Tau contains more than 80 potential phosphorylation sites located at serine, tyrosine and threonine (Noble et al., 2013), and phosphorylation of these sites is regulated by protein kinases and protein phosphatases. When GSK3 β is activated, it can increase the phosphorylation of Tau proteins (Yu et al., 2020). When tau is hyperphosphorylated, it decreases the affinity for microtubules, and leads to the formation of NFTs (Lee et al., 2001; Reddy and Reddy, 2011). Moreover, the activation of GSK3 β has been observed to elevate A β levels and promote oxidative stress, which ultimately contributes to cognitive deterioration. When PI3K/AKT is activated, GSK3 β activity can be inhibited to alleviate AD symptoms.

MAPK is another major insulin signaling pathway, consisting mainly of ERK, c-Jun-N-terminal kinases (JNKs) and p38 (Sędzikowska and Szablewski, 2021). In clinical practice, it has been found that patients with AD exhibit excessive expression of P38 in the brain (Gourmaud et al., 2015). The overexpression of P38 increases the risk of tau protein phosphorylation and promotes abnormal processing of APP (Ali et al., 2017). In AD mouse models, it was found that JNK is excessively activated and disrupts synaptic plasticity before cognitive decline occurs (Sclip et al., 2014). At the same time, when JNK is activated, it inhibits tyrosine phosphorylation of IRS-1, thereby disrupting insulin signaling. A β oligomers in the brain promote activation of the JNK signaling pathway, resulting in reduced IRS, inhibition of PI3K/ AKT, and increased GSK3β activity, ultimately leading to an increase in Aβ, p-Tau and a decline in cognitive function. GLP-1 RAs can activate G proteins by binding to GLP-1 R. This activation will lead to an increase in PI3K levels, which restores insulin signaling and inhibits GSK3ß activity (Hölscher and Li, 2010). As a result, AB and p-Tau levels are reduced and cognitive function is improved. Studies in AD rodent models have found that AKT activation and GSK3ß inhibition were observed in the brain following the administration of GLP-1 RAs (Cai et al., 2014; Qi et al., 2016; Wang et al., 2018; Li J. X. et al., 2019; Garabadu and Verma, 2019; Robinson et al., 2019; Zheng, 2021). In addition, GLP-1 RAs were found to reduce the phosphorylation levels of JNK and IRS-1 serine in animals, thereby restoring insulin signaling (Bomfim et al., 2012a; Xiong et al., 2013; Chen et al., 2017; Li J. X. et al., 2019). In addition to reducing Aβ levels by restoring insulin signaling channels GLP-1 RAs can also directly reduce AB production by reducing abnormal cleavage of APP. AB is a toxic fragment produced when APP is abnormally cleaved by β -secretase and γ secretase, and these fragments accumulate and precipitate to form plaques (Götz and Ittner, 2008; Woodruff et al., 2013). Aß aggregation could lead to neuronal loss and increase the risk of oxidative stress, mitochondrial dysfunction and inflammation (Bateman et al., 2022). GLP-1 RAs have been found to reduce the generation of A β by inhibiting the level of BACE1 and increasing the level of $\alpha\mbox{-secretase},$ thus exerting a therapeutic effect on AD (McClean et al., 2015; Wang et al., 2016a; Wang et al., 2016b).

Impaired insulin signaling and A β accumulation are factors that promote the occurrence of insulin resistance (Pelle et al., 2023). Insulin resistance refers to decreased sensitivity of tissues to insulin, and neuronal insulin resistance is considered a key feature of AD (Jantrapirom et al., 2020). Insulin plays a crucial role in various brain functions, including cognitive function and synaptic plasticity.

Substantial evidence indicates a correlation between reduced insulin sensitivity and the development of AD (Dou et al., 2005; Rivera et al., 2005; Chiu et al., 2008; Hölscher and Li, 2010). The impact of insulin resistance on AD pathology involves multiple aspects. Insulin resistance can lower the activity of insulin-degrading enzyme (IDE) in the brain (Jantrapirom et al., 2020). IDE is responsible for clearing insulin and Aβ. When IDE activity is reduced, Αβ insufficient clearance leads to its accumulation. Simultaneously, insulin resistance can enhance BACE-1 activity, thereby increasing A production. A paccumulation further elevates serine phosphorylation of IRS-1, disrupting insulin signaling, releasing inflammatory factors, and exacerbating insulin resistance (Kurochkin et al., 2018). Furthermore, insulin resistance has been found to heighten oxidative stress, manifested by increased reactive oxygen species (ROS) levels, consequently promoting the secretion of inflammatory factors and mitochondrial dysfunction (Boccardi et al., 2019). Meanwhile, states of insulin resistance influence PI3K-mediated vasodilation. This could contribute to a reduction in nutrient supply to the brain (Lynn et al., 2022).

It has been observed that patients with AD have reduced brain glucose metabolism rates, specifically within areas linked to memory consolidation and cognitive acquisition (Reiman et al., 2004; Mosconi et al., 2008; Mistur et al., 2009). Glucose primarily generates ATP to supply energy for various neuronal activities in the brain. Decreased glucose metabolism leads to insufficient ATP production, affecting a cascade of physiological functions. This manifests as impaired Ca2+ signaling and depolarization (Alzheimer's Association Calcium Hypothesis Workgroup, 2017), resulting in endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and increased ROS generation (Hachinski et al., 2019). Concurrently, compromised brain glucose metabolism compels the brain to seek alternative sources of energy. For instance, the brain activates lipid-digesting enzymes to produce ATP (Klosinski et al., 2015). However, this process triggers the generation of hemolytic phospholipids, inducing inflammation and oxidative stress (Schönfeld and Reiser, 2013; Sato et al., 2016). GLP-1 RAs have been found to enhance brain glucose metabolism by regulating glucose transporter proteins GLUT1 and GLUT3 through cyclic adenosine monophosphate (cAMP) activation (Yassine et al., 2022). Research indicates that concentrations of GLUT1 and GLUT3 are reduced in the neocortex and hippocampus of AD patients, suggesting this may be one of the primary reasons for decreased glucose uptake (Simpson et al., 1994; Harr et al., 1995). Therefore, GLP-1 RAs hold promise in improving glucose metabolism by restoring GLUT1 and GLUT3 concentrations, potentially offering a treatment avenue for AD. Autopsy reports of AD patients have shown increased brain glucose levels, even in the absence of coexisting T2DM(An et al., 2018). Hyperglycemia affects the accumulation of advanced glycation end products (AGEs). The binding of AGEs to the receptor for advanced glycation end products (RAGE) triggers a series of pathological reactions, including disruption of insulin receptor binding to IRS-1, promoting pro-inflammatory cytokine production, increasing ROS generation, and leading to synaptic dysfunction (Lynn et al., 2022). AGEs can also induce glycation of A β and tau proteins, resulting in the aggregation of $A\beta$ into plaques and the entanglement of neurofibrillary tangles (Iannuzzi et al., 2014; Vlassara and Uribarri, 2014). Simultaneously, RAGE is believed to be involved in Aβ-induced ER stress. ER stress plays a complex role in neuroprotection, amyloid-beta deposition, and synaptic function regulation in AD. The endoplasmic reticulum is a fundamental organelle responsible for synthesizing essential biomolecules such as proteins, lipids, and carbohydrates within cells. When cells are exposed to stress stimuli, improper and incomplete folding of proteins and disrupted calcium ion balance can lead to ER stress. ER stress has been shown to be involved in various metabolic disorders and neurodegenerative diseases. Upon activation of ER stress, JNK is activated, leading to serine phosphorylation of IRS1, thus compromising insulin signaling (Urano et al., 2000; Nakatani et al., 2005; Kawasaki et al., 2012). Insulin resistance may also exacerbate ER stress in AD. GLP-1 RAs have been demonstrated to intervene in ER stress and protect against neurodegenerative diseases, suggesting that they hold promise as potential therapeutic agents for AD by modulating ER stress (Cheng et al., 2022).

Oxidative stress is caused by a disruption in the body's homeostasis between oxidative and antioxidant action, mainly manifested as excessive production or insufficient clearance of ROS and reactive nitrogen species (Reddy et al., 2009). Oxidative stress is one of the pathogenic mechanisms of AD, and an increase in ROS can be observed in AD patients (Ahmad et al., 2017). Aβ deposits exist in the AD brain, and these $A\beta$ can penetrate the mitochondrial membrane and bind to mitochondria, thereby disrupting mitochondrial oxidative phosphorylation, increasing ROS levels, and ultimately leading to mitochondrial dysfunction and synaptic degeneration (An et al., 2019). Excessive ROS generation can produce various AGEs and advanced lipid end products (ALE) (Sayre et al., 2006). AGEs and ALEs can interact with the RAGE, inducing a pro-inflammatory cytokine response. Meanwhile, RAGE can also interact with Aβ, exacerbating neuroinflammation and causing a decline in learning ability (Harris et al., 2000). Oxidative stress can also increase the levels of p-Tau and AB by activating p38MAPK. In addition, increased oxidative stress may accelerate apoptosis, produce inflammatory mediators and damage neurons. Superoxide dismutase (SOD) and malondialdehyde (MDA) as important markers of oxidative stress are often used to assess the level of oxidative stress (Chen et al., 2020). Studies have shown that treatment with GLP-1 RAs could significantly increase the level of SOD and reduce the level of MDA in the AD rodents' brains (An et al., 2019; Li J. X. et al., 2019). Meanwhile, GLP-1 RAs can also reduce oxidative stress by increasing the level of reduced glutathione (GSH), an important intracellular antioxidant in the body that counteracts the damage caused by antioxidants to cells, and reducing ROS levels (Zheng, 2021; Zhang et al., 2022). Oxidative stress and inflammation interact, which contributes to the pathology of AD (Tadokoro et al., 2020). The brain generates an inflammatory response primarily through the activation of microglia and astrocytes (Chakrabarti et al., 2015). Studies have found that the levels of pro-inflammatory cytokines are significantly increased in serum and brain tissue of AD patients, and activated microglia and astrocytes could be observed in the brain (Fillit et al., 1991; Strauss et al., 1992; Sastre et al., 2006). Not only can oxidative stress promote the production of pro-inflammatory factors that exacerbate inflammation, but microglia stimulated by AB can also release

ROS, causing oxidative stress (Akiyama et al., 2000). Microglia and astrocytes are essential for maintaining brain homeostasis and supporting neuronal function (Jha et al., 2019). During the progression of AD, microglia will lose their homeostatic phenotype and be activated for a long time, manifested as glial proliferation and the secretion of pro-inflammatory factors, and these mediators will promote astrogliosis and intensify the inflammatory response (Diz-Chaves et al., 2022b). Activated microglia and astrocytes, in addition to producing direct neurotoxicity, also lead to increased AB deposition (Guo et al., 2002). At the same time, the accumulation of A β also promotes the secretion and release of pro-inflammatory cytokines, exacerbating the inflammatory response (Akiyama et al., 2000). GLP-1 RAs are considered to improve the inflammatory response in AD by increasing the level of brain-derived neurotrophic factor (BDNF) (Bomba et al., 2019). Meanwhile, GLP-1 RAs have also been found to inhibit the activation of microglia (McClean et al., 2011; 2015; McClean and Hölscher, 2014) and astrocytes (Matsuoka et al., 2019; Zheng, 2021; Zhang et al., 2022) as well as reduce the expression of pro-inflammatory factors such as tumor necrosis factor-a (TNF-a), interleukin 1 β (IL-1 β) and interleukin 18 (IL-18) (Zhang et al., 2022).

Mitochondrial dysfunction is also one of the pathological manifestations of AD. Mitochondria serve as the main energy production system within cells, and impairment of mitochondria can lead to neuronal dysfunction, resulting in cognitive impairment. Peroxisome proliferator-activated receptor c coactivator 1a (PGC-1a), an important factor in mitochondrial biogenesis, plays a crucial role in synaptic and CNS function. Research has shown that GLP-1 RAs can directly reduce p-Tau levels and restore mitochondrial function through modulation of the PGC-1a pathway (An et al., 2015). Meanwhile, GLP-1 RAs may also improve mitochondrial function by activating the extracellular signal-regulated kinase-Yesassociated protein signaling pathway and the CREB/adiponectin axis (Li J. et al., 2019; Xiong et al., 2020). Mitochondrial dysfunction leads to abnormalities in multiple biological processes, such as excessive production of ROS. These abnormalities subsequently result in synaptic degeneration of neurons, characterized by structural and functional alterations at the synapses (Tillement et al., 2011). Synaptic dysfunction is considered one of the main neuropathological changes that occur before clinical symptoms of AD appear (Fu and Ip, 2022). It found that synaptic loss can be observed in the mild cognitive impairment of AD early stage (Scheff et al., 2006). The basis of normal synaptic function is recognized as synaptic plasticity, and when synaptic plasticity is impaired, information transmission in the CNS is disrupted, leading to impaired cognitive function (Yu et al., 2022). It has been found that A β deposition can affect the levels of presynaptic markers and postsynaptic markers which disrupt synaptic plasticity (Bakota and 2016; Forner et al., 2017). In Brandt, addition. hyperphosphorylation of tau is another factor that leads to synaptic dysfunction (Wu et al., 2021). When p-Tau increases, it destroys microtubule structures, consequently disrupting microtubule-based cellular transport, and synaptic loss occurs when mitochondria are not efficiently transported to the synapse (Forner et al., 2017). Damage to synaptic structure and function can lead to symptom aggravation, such as impaired memory and difficulty moving, so AD symptoms could be ameliorated by restoring synaptic structure and function (John and Reddy, 2021). It was found that GLP-1 RAs intervention can alleviate synaptic structure and functional damage in AD rodent models, specifically manifested as an increase in levels of postsynaptic markers (postsynaptic density protein 95, PSD95) and presynaptic markers (synaptophysin, SYN), and significant enhancement of hippocampal long term potentiation (LTP) (McClean et al., 2011; McClean et al., 2015; Han et al., 2013; Cai et al., 2014; McClean and Hölscher, 2014; Wang et al., 2016a; Qi et al., 2016; Zheng, 2021). Meanwhile, clearer synaptic structures can be observed after GLP-1 RAs treatment (Qi et al., 2016; An et al., 2019; Zheng, 2021). The therapeutic effects of GLP-1 RAs on synapses may involve several aspects. GLP-1 RAs can activate G proteins, which in turn activate the adenylate cyclase system, leading to an increase in cAMP and protein kinase A (PKA). The increase in PKA can lead to an increase in synaptic neurotransmitters and LTP enhancement. Adenosine diphosphate, which is produced by the adenylate cyclase system during cAMP production, acts on ATPsensitive K⁺ channels. This can promote the opening of Ca²⁺ channels and an increase in Ca2+ in the cytosol, which can also promote the release of neurotransmitters (Hölscher and Li, 2010). At the same time, Ca²⁺ acts as a second messenger. When the second messenger signaling pathway is activated, it can promote energy utilization and cell growth, while also reducing cell apoptosis, ultimately restoring synaptic function and improving metabolic capacity (Li et al., 2010; Sharma et al., 2014).

In addition to the mechanisms mentioned above, it is worth noting that several studies have suggested additional potential therapeutic mechanisms of GLP-1 RAs for AD. For example, research indicates that these agents may also address AD by enhancing vascular function (blood flow and blood-brain barrier integrity) and offering protection to nerve cells (Grieco et al., 2019). It is believed that the blood-brain barrier and cerebral blood flow are reduced in AD patients before the appearance of AB and p-Tau. Animal studies have demonstrated that liraglutide could restore brain dysfunction and thus treat AD (Kelly et al., 2015; Hachinski et al., 2019; Nation et al., 2019). Furthermore, GLP-1 RAs can promote the proliferation of neural precursor cells and facilitate their differentiation into mature neurons, thereby protecting and increasing the number of neurons in the brain (Grieco et al., 2019). GLP-1 RAs are also believed to increase the levels of Mash1 protein through the activation of the PI3K-Akt pathway, which regulates neurogenesis, leading to improved cognitive function in AD patients.

4.2 Clinical research advances

The purpose of animal studies is to contribute to drug development with a view to better application in the clinical setting. Based on research, there are sufficient results to demonstrate that GLP-1 RAs are effective in treating AD animal models. However, it is inconclusive whether the results of animal studies can be validated in the human clinic. We identified five clinical studies of GLP-1 RAs for treating AD on ClinicalTrials.gov (Table 2), a global database of privately and publicly funded clinical studies provided by the US National Library of Medicine. A Phase II clinical study of exenatide on AD patients (NCT01255163)

TABLE 2 GLP-1 RAs clinical trials on ClinicalTrials.gov.

Study	Drug (dose; duration)	Sample (age, sex)	Outcomes	Status
A Pilot Clinical Trial of Exendin-4 in Alzheimer's Disease (NCT01255163)	Exenatide (5 mcg or 10 mcg twice daily, s.c.)	n = 57 (60 years and older; male and female)	MMSE; ADAS-cog70; CDR Global Score; CDR Sum of Boxes; CSF p181-tau; CSF Aβ42; BMI	Terminated; Has Results
Identifying Potential Effects of Liraglutide on Degenerative Changes (NCT01469351)	Liraglutide (1.8 mg once daily, s.c.)	n = 34 (50 years-80 years; male and female)	intra-cerebral amyloid deposit; neuro- psychological tests; the change in glucose uptake in the CNS	Completed
Evaluating Liraglutide in Alzheimer's Disease (ELAD) (NCT01843075)	Liraglutide (1.8 mg once daily, s.c.)	<i>n</i> = 204 (50 years and older; male and female)	Cerebral glucose metabolic rate; z-scores for the ADAS Exec, MRI changes, microglial activation, and CSF markers; the incidence and severity of treatment emergent adverse events; the change in microglial activation, tau deposition, and cortical amyloid	Unknown
A Research Study Investigating Semaglutide in People with Early Alzheimer's Disease (EVOKE Plus) (NCT04777409)	semaglutide (dose gradually increased to 14 mg once daily; oral)	n = 1840 (55 years-85 years; male and female)	CDR-SB score; ADCS-ADLMCI score; time to progression to dementia; ADAS-Cog-13 score; MoCA score; ADCOMS; MMSE; the 10-item NPI score; time to progression in disease stage; Number of TEAEs; high sensitivity C-reactive protein level; time to first occurrence of MACE; time to first occurrence of stroke; EQ- 5D-5L proxy score; CDR-SB score; ADCS- ADL-MCI score	Recruiting
A Research Study Investigating Semaglutide in People with Early Alzheimer's Disease (EVOKE) (NCT04777396)	semaglutide (dose gradually increased to 14 mg once daily; oral)	n = 1840 (55 years-85 years; male and female)	CDR-SB score; ADCS-ADLMCI score; time to progression to dementia; ADAS-Cog-13 score; MoCA score; ADCOMS; MMSE; the 10-item NPI score; time to progression in disease stage; Number of TEAEs; high sensitivity C-reactive protein level; time to first occurrence of MACE; time to first occurrence of stroke; EQ- 5D-5L proxy score; CDR-SB score; ADCS- ADL-MCI score	Recruiting

Note: MMSE, mini mental state examination; ADAS-cog70, 70-item Alzheimer's Disease Assessment Scale-cognitive Subscale; CDR, clinical dementia rating; CSF, cerebrospinal fluid; CSF p181-tau, Cerebrospinal Fluid phospho181-tau; CSF Abeta42, Cerebrospinal Fluid Amyloid-beta 42; BMI, body mass index; CDR-SB, Clinical Dementia Rating–Sum of Boxes; ADCS-ADLMCI, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for MCI; ADAS-Cog-13, 13-item Alzheimer's Disease Assessment Scale Cognitive Subscale; MoCA, montreal cognitive assessment; ADCOMS, Alzheimer's Disease Composite Score; NPI, neuropsychiatric inventory; TEAEs, treatment emergent adverse events; MACE, major adverse cardiovascular event.

showed that exenatide was safe and well-tolerated in humans. Neuropsychological measures, which assess attention and shortterm memory, showed significant improvements in the exenatide group at 6 months compared to the placebo group. Furthermore, although the results showed that exenatide reduced the deposition of $A\beta_{42}$ in plasma neuronal extracellular vesicles, no significant changes were shown for other biomarkers (p-Tau, total tau, etc.). Unfortunately, the project was prematurely discontinued due to the cessation of commercial support by the sponsor, and some patients did not complete the trial. Based on the existing current research results (Mullins et al., 2019), the cerebrospinal fluid level of patients after exenatide administration has improved, but whether it is sufficient to produce a therapeutic effect needs to be verified in larger scale trials. There were two clinical studies on liraglutide for the treatment of AD. A 6-month double-blind clinical trial (NCT01469351) investigated the therapeutic effect of liraglutide on AD. The research (Gejl et al., 2016) showed that although liraglutide treatment prevented the negative changes in brain glucose metabolism and cognition function over time, there were no significant differences in amyloid deposition and cognitive function compared to placebo group. Another study (NCT01843075) randomized 204 patients to receive liraglutide or a placebo. The trial used changes in patients' brain glucose metabolism rate, cognitive assessment scores, microglial activation levels, and tau and amyloid levels as outcomes of treatment efficacy. The results of this trial have not yet been published. In addition, there are two Phase III clinical trials (NCT04777409 and NCT04777396) on semaglutide for AD are in the recruitment stage. The two studies will test the efficacy of semaglutide in patients with mild cognitive impairment (MCI) or mild AD (with and without significant cerebellar vascular disease). According to published studies, GLP-1 RAs have a good safety profile. In addition, we also noted the limitations of existing experiments with small sample sizes and short experimental periods, which may impact the results. Animal models are essentially reductions of specific pathological manifestations of the disease but it cannot cover the pathophysiology of AD patients, so there is still a certain gap between the results of animal experiments and practical clinical applications (Ferrari et al., 2022). More intensive studies should be conducted in the future to develop clinical translation.

It was also observed that the patients recruited for the clinical trials of GLP-1 RAs in the treatment of AD are those with mild AD and MCI. This is consistent with the conclusions of our research,

indicating that GLP-1 RAs may have therapeutic effects on earlystage AD. Furthermore, we found that the currently registered clinical trials for exenatide therapy in AD are utilizing doses of 10 μ g or 20 μ g, which lower than the dosage range calculated in our study. This variance could stem from disparities in animal and human metabolism, pharmacokinetics. Additionally, our study utilized intranasal administration, while clinical application primarily involves subcutaneous injections. These differing administration routes may also contribute to result disparities. Currently, only one clinical study investigating the use of exenatide for AD has been retrieved from ClinicalTrials.gov. Based on the above, the research of exenatide for AD is still in its preliminary stage. Therefore, the findings of this study can provide new insights and references for future research.

Meanwhile, the results of the present study showed that the intranasal administration of exenatide was more effective than subcutaneous administration in the treatment of AD, which provides a new insight for further research. Due to the limited clinical trials, more researches should be carried out, and the introduction of the intranasal administration route should be considered, and the bioavailability and efficacy differences between it and the traditional subcutaneous administration route should be comprehensively compared and explored.

4.3 Advantages and limitations

To the best of our knowledge, this is the first meta-analysis of GLP-1 RAs-treated AD animals. This study comprehensively assessed the therapeutic effects of GLP-1 RAs in AD animal models based on two main aspects: behavioral tests and pathological features. We included 26 articles, and overall, the study results provide convincing evidence that GLP-1 RAs are neuroprotective in AD.

However, this study has certain limits, including the fact that the analysis was performed on published literature and may not involve grey literature, thereby leading to biased information. Secondly, the different quality of the included articles, for example, in allocation concealment and blinding, needed to be clearly stated, which to some extent, affected the reliability of the results. There is some heterogeneity among the studies, which may be caused by the type of GLP-1 RAs, the way of administration, the dose of administration, the cycle of administration, the gender of animals, etc. Due to the limited number of included articles, only subgroup analysis was performed based on different modeling methods and animal strains, which may have some influence on the results. We evaluated the funnel plot by the Trim and Fill method, and while the study had some publication bias, the findings were robust and reliable.

5 Conclusion

This study comprehensively evaluated the efficacy of GLP-1 RAs in AD animal models. Twenty-six studies were selected from seven

databases based on inclusion and exclusion criteria. The metaanalysis found that GLP-1 RAs can significantly improve AD animals' learning and memory abilities, reducing the deposition of A β and hyperphosphorylation of tau protein in the brain. The results indicate that GLP-1 RAs are promising candidate agents for AD treatment, which may improve cognitive performance and alleviate pathological features through multiple mechanisms. Although the study has some limitations, the results of the study are still worthy of attention, and can provide reference for further experimental design and clinical research.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

FJK: Conceptualization, Writing—Original Draft, Writing—Review and Editing, Visualization, Article screening, Data extraction. TYW: Writing—Original Draft, Writing—Review and Editing, Visualization, Article screening, Quality assessment. JYD: Writing—Review and Editing, Visualization, Article screening, Data extraction. ZWZ: Writing—Review and Editing, Visualization, Data extraction, Software. JC and ZSZ: Quality assessment. YX and TS: Conceptualization, Methodology, Supervision, Project administration, Funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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