Extracts or active components from Acorus gramineus Aiton for Cognitive Function Impairment: Preclinical Evidence and Possible Mechanisms

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Extracts or active components from Acorus gramineus Aiton (EAAGA) have been clinically used for cognition impairment more than hundreds of years and are still used in modern times in China and elsewhere worldwide. Previous studies reported that EAAGA improves cognition impairment in animal models. Here, we conducted a preclinical systematic review to assess the current evidence of EAAGA for cognition impairment. We searched 7 databases up until June 2019. Methodological quality for each included studies was accessed according to the CAMARADES 10-item checklist. The primary outcome measures were neurobehavioral function scores evaluated by the Morris water maze test, electrical Y-maze test, step-down test, radial eight-arm maze test, and step-through test. The secondary outcome measures were mechanisms of EAAGA for cognition function. Finally, 34 studies involving 1431 animals were identified. The quality score of studies range from 1 to 6, and the median was 3.32. Compared with controls, the results of the meta-analysis indicated EAAGA exerted a significant effect in decreasing the escape latency and error times and in increasing the length of time spent in the platform quadrant and the number of platform crossings representing learning ability and memory function (all $P < 0.01$). The possible mechanisms of EAAGA are largely through anti-inflammatory, antioxidant, antiapoptosis activities, inhibition of neurotoxicity, regulating synaptic plasticity, protecting cerebrovascular, stimulating cholinergic system, and suppressing astrocyte activation. In conclusion, EAAGA exert potential neuroprotective effects in experimental cognition impairment, and EAAGA could be a candidate for cognition impairment treatment and further clinical trials.

1. Introduction

With the average life expectancy increasing, there is concern about the proportion of cognitive impairment in the global population, which results from degeneration of the brain and very high prevalence in elderly individuals [1]. The World Health Organization estimates that the number of people over the age of 60 will be around 2 billion in 2050, while the number of cognitive impairment patients is expected to rise rapidly along with the aging population worldwide [2, 3]. However, so far, clinical trials have not identified efficacious neuroprotective therapies for cognitive impairment patients [4]. Thus, given the huge translational gap between the animal studies and clinical trials, seeking or developing innovative neuroprotectants is urgently needed.

For more than a millennium, traditional Chinese medicine (TCM), a main form of complementary and alternative medicine, has been used in Asian countries, especially in China, Japan, and Korea, to alleviate various symptoms of cognitive deficits and to facilitate learning and memory [5]. Acorus gramineus Aiton (AGA) (record 2322 (http://www...
The dry rhizomes of Acorus gramineus Solander (Shi Changpu), is listed officially in the Chinese Pharmacopoeia and used in oriental medicines for more than hundreds of years to treat neurological disorders. AGA possessed various pharmacological effects on the central nervous system, including neuroprotective effects [6, 7], central inhibitory effects [8], inhibitory effects on excitotoxic neuronal death [9], and stroke [10], and amelioration in learning and memory [5]. AGA may be effective for the improvement of amnesia [9]. AGA contains different extract fractions: volatile oil, composing mainly of β-asarone (63.2–81.2%), and α-asarone (8.8–13.7%) [11], as well as water extract, ethyl ether extract, ethyl acetate extract, N-butanol extract, and the defatted decoction fractions. AGA is often used as a component in some Chinese herbal formulas. Among 75 of the most famous Chinese herbal formulas characterized as improving intelligence both in ancient and modern time in China, more than half contain AGA, such as Kai-Xin-San [12] and Chong-Myung Tang [13].

Systematic reviews are believed to be preferred; only data that from systematic reviews will be considered as the highest level of medical evidence basis for the levels of evidence from the Centre of Evidence-Based Medicine in Oxford [14]. Preclinical systematic reviews are a powerful approach to analyze and synthesize the results of an intervention from animal data into a useful document that can help to shape further basic research, optimize the experimental studies, and enhance the success rate of future clinical trials [15]. Thus, we conducted a preclinical systematic review to assess the current evidence of extracts or active components from Acorus gramineus Aiton (EAAGA) and active component for animal models of cognitive impairment.

2. Materials and Methods

2.1. Search Strategies. Experimental studies of EAAGA for cognitive impairment were identified in the databases, including PubMed, Embase, Web of Science, Wanfang database, China National Knowledge Infrastructure (CNKI), CBM, and VIP information database. All searches were performed from inception to June 2019. Studies about assessing the effectiveness of AAGA for improving cognitive function impairment in animals were identified. The search terms were as follows: (Acorus tatarinowii Schott OR Rhizoma acori graminei OR Acorus calamus OR Acorus gramineus Soland OR acorus gramineus aiton OR Acori graminei rhizoma OR Acori tatarinowii rhizoma OR grassleaf sweetflag Rhizome) AND (cognitive function impairment OR amnesia OR dementia OR Alzheimer’s disease).

2.2. Inclusion Criteria. Experimental studies on EAAGA for cognitive impairment models were included, regardless of publication status or animal species, gender, age, and methods of model establishment. The primary outcome
Table 1: Basic characteristics of the included studies.

| Study (years) | Species (sex, n = experimental/control group) | Weight | Random method | Model (method) | Anesthetic | Method of administration | Outcome index (time) | Intergroup differences |
|---------------|-----------------------------------------------|--------|----------------|----------------|-------------|-------------------------|----------------------|------------------------|
| Yang et al. [17] | SD rats (mix, 7/7) | NR | NR | Chronic lead-induced dysmnesia model | CO2 | β-Asarone (2.5, 10, and 40 mg kg\(^{-1}\), ip); from 9 to 11 weeks old; once daily for 3 weeks | (1) MWM test (escape latency) (2) MWM test (swimming speed) (3) MWM test (time spent in target quadrant) (4) MWM test (times crossed the platform) (5) Dendritic spine density | (1) P < 0.001 (2) P > 0.05 (3) P < 0.05 (4) P > 0.05 (5) P < 0.001 |
| Wei et al., 2013 | AβPP/PS1 double-transgenic mice (13/13) | NR | NR | AβPP/PS1 double-transgenic mice | NR | β-Asarone (7 and 21 mg kg\(^{-1}\), ig); onset the experiment; once daily for 4 months | (1) MWM test (escape latency) (2) Cell viability | (1) P < 0.001 (2) P < 0.05 |
| Sundaramahalingam et al. [18] | Wister strain albion rats (male, 6/6) | 200-220 g | NR | Noise stress induced memory impairment model | NR | α-Asarone (9 mg kg\(^{-1}\), ip); onset the experiment; once daily for 30 d | (1) RAM test (number of errors) (2) Hsp 70 mRNA levels (3) Ache activity (4) SOD/CAT/GPx activity (5) VC/VE/GSH levels (6) G6PD activity | (1) P < 0.05 (2) P < 0.05 (3) P < 0.05 (4) P < 0.05 (5) P < 0.05 (6) P < 0.05 |
| | Wister strain albion rats (male, 6/6) | 200-220 g | NR | Noise stress exposed rats | NR | Ethyl acetate extract (50 mg kg\(^{-1}\), ip); onset the experiment; once daily for 30 d | (1) RAM test (number of errors) | (1) P < 0.05 (2) P < 0.05 |
| Study (years)          | Species (sex, n = experimental/control group) | Weight | Random method | Model (method) | Anesthetic | Method of administration | Experimental group | Control group | Outcome index (time) | Intergroup differences |
|-----------------------|---------------------------------------------|--------|---------------|----------------|------------|--------------------------|--------------------|---------------|---------------------|------------------------|
| Shin et al. [19]      | C57BL/6 mice (male, 12/12)                  | 25-28 g | NR            | LPS-induced cognitive handicap model | NR         | α-Asarone (7.5, 15, and 30 mg kg⁻¹, ig); 3 days before the LPS injection; once daily for 3 d | Normal saline (same volume, ig); 3 days before the LPS injection; once daily for 3 d | Normal saline; (same volume, ig) | (2) Hsp 70 mRNA levels | (3) P < 0.05 |
|                       |                                             |        |               |                |            |                          |                    |               | (3) P < 0.05                 |                        |
|                       |                                             |        |               |                |            |                          |                    |               | (4) Ache activity | (4) P < 0.05 |
|                       |                                             |        |               |                |            |                          |                    |               | (4) SOD/CAT/GPx activity |                        |
|                       |                                             |        |               |                |            |                          |                    |               | (5) VC/VE/GSH levels | (5) P < 0.05 |
|                       |                                             |        |               |                |            |                          |                    |               | (5) P < 0.05                 |                        |
|                       |                                             |        |               |                |            |                          |                    |               | (6) G6PD activity |                        |
|                       |                                             |        |               |                |            |                          |                    |               | (6) P < 0.05                 |                        |
| Ma et al. [11]        | Six-week-old NIH mice (male, 6/6)           | 20-25 g | NR            | Aβ₁₋₄₂-induced AD model | Sodium pentobarbital | Water extract (20 mg g⁻¹, ig); after the first MWM test; once daily for 3 weeks | Normal saline; (same volume, ig); after the first MWM test; once daily for 3 weeks | Normal saline; (same volume, ig); | (1) MWM test (escape latency) | (1) P < 0.05 |
|                       |                                             |        |               |                |            |                          |                    |               | (1) MWM test (escape latency) |                        |
|                       |                                             |        |               |                |            |                          |                    |               | (2) Aβ positive cells count | (2) P < 0.05 |
|                       |                                             |        |               |                |            |                          |                    |               | (3) DCX expression | (3) P < 0.05 |
|                       |                                             |        |               |                |            |                          |                    |               | (4) Nestin positive cells count | (4) P < 0.05 |
|                       |                                             |        |               |                |            |                          |                    |               | (4) P < 0.05                 |                        |
|                       |                                             |        |               |                |            |                          |                    |               | (5) P < 0.05                 |                        |
|                       |                                             |        |               |                |            |                          |                    |               | (6) BACE1/Iba1 protein expressions | (6) P < 0.05 |
|                       |                                             |        |               |                |            |                          |                    |               | (6) P < 0.05                 |                        |
| Study (years) | Species (sex, n = experimental/control group) | Weight | Random method | Model (method) | Anesthetic | Method of administration | Outcome index | Intergroup differences |
|--------------|-----------------------------------------------|--------|---------------|---------------|------------|--------------------------|---------------|------------------------|
|              | Six-week-old NIH mice (male, 6/6)             | 20-25 g | NR            | Aβ₁₋₄₂-induced AD model | Sodium pentobarbital | after the first MWM test; once daily for 3 weeks | (1) MWM test (escape latency) | (1) P < 0.05 |
|              |                                               |        |               |               |            |                          | (2) Aβ positive cells count | (2) P < 0.05 |
|              |                                               |        |               |               |            |                          | (3) DCx expression | (3) P < 0.05 |
|              |                                               |        |               |               |            |                          | (4) Nestin positive cells count | (4) P < 0.05 |
| Liu et al. [20] | APPswe/PS1dE9 double transgenic mice (male, 11/11) | NR    | NR            | APPswe/PS1dE9 double transgenic mice | Chloral hydrate | β-Asarone (21.2, 42.4, and 84.8 mg kg⁻¹, i.g); onset the experiment; once daily for 2.5 months | (1) MWM test (escape latency) | (1) P < 0.05 |
|              |                                               |        |               |               |            |                          | (2) MWM test (time spent in target quadrant) | (2) P < 0.05 |
|              |                                               |        |               |               |            |                          | (3) MWM test (times crossed the platform) | (3) P < 0.05 |
|              |                                               |        |               |               |            |                          | (4) SYP/GluR1 expression | (4) P < 0.05 |
| Limón et al. [21] | Wistar rats (male, 8/8)                       | 230–250 g | NR            | Aβ₁₋₄₂-induced AD model | Chloral hydrate | α-Asarone (10 mg kg⁻¹, i.h.); after injection of amyloid-β; once daily for 16 d | (1) RAM test (percentage of correct responses) | (1) P < 0.001 |
|              |                                               |        |               |               |            |                          | (2) Nitrite levels | (2) P < 0.05 |
| Li et al. [22] | Wistar rats (female, 7/7)                     | 150–180 g | NR            | D-gal and AlCl₃ induced AD model | Sodium pentobarbital | β-Asarone (25, 50 and 100 mg kg⁻¹, i.h.); 28 d after injection of AlCl₃ and D-gal | (1) MWM test (escape latency) | (1) P < 0.05 |
|              |                                               |        |               |               |            |                          | (2) MWM test (time spent in target quadrant) | (2) P < 0.05 |
| Study (years) | Species (sex, \( n = \) experimental/ control group) | Weight | Random method | Model (method) | Anesthetic | Method of administration | Experimental group | Control group | Outcome index (time) | Intergroup differences |
|--------------|----------------------------------------------------------|--------|---------------|----------------|------------|--------------------------|-------------------|--------------|---------------------|-----------------------|
| Aged Kunming mice (male, 10/10) | 40-50 g NR Aged mice NR | Essential oil (0.02, 0.04, and 0.08 g kg\(^{-1}\), orally); onset the experiment; once daily for 15 d | Tween 80 (same volume, orally); onset the experiment; once daily for 15 d | (1) SD test (escape latency) | (1) \( P < 0.01 \) |
| Aged Kunming mice (male, 10/10) | 40-50 g NR Scopolamine-induced dysmnesia model NR | Essential oil (0.02, 0.04, and 0.08 g kg\(^{-1}\), orally); onset the experiment; once daily for 15 d | Tween 80 (same volume, orally); onset the experiment; once daily for 15 d | (1) SD test (escape latency) | (1) \( P < 0.05 \) |
| Aged Kunming mice (male, 10/10) | 40-50 g NR Ethanol-induced dysmnesia model NR | Essential oil (0.02, 0.04, and 0.08 g kg\(^{-1}\), orally); onset the experiment; once daily for 15 d | Tween 80 (same volume, orally); onset the experiment; once daily for 15 d | (1) SD test (escape latency) | (1) \( P < 0.01 \) |
| Aged SD rats (male, 10/10) | 550-650 g NR Aged rats NR | Essential oil (0.02, 0.04, and 0.08 g kg\(^{-1}\), orally); onset the experiment; once daily for 15 d | Tween 80 (same volume, orally); onset the experiment; once daily for 15 d | (1) EY-M test (number of errors) | (1) \( P < 0.01 \) |
| Study (years)                      | Species (sex, n = experimental/control group) | Weight | Random method | Model (method)                          | Anesthetic                     | Method of administration Experimental group | Control group | Outcome index (time) | Intergroup differences |
|----------------------------------|-----------------------------------------------|--------|---------------|----------------------------------------|-------------------------------|---------------------------------------------|---------------|----------------------|------------------------|
| Aged SD rats (male, 10/10)       | Sodium nitrite-induced dysmnesia model        | NR     | NR            | AGA (100 mg kg\(^{-1}\), ip); after occlusion; once daily for 21 d | Normal saline; (same volume, ip); after occlusion; once daily for 21 d | (1) MWM test (escape latency) | (1) P < 0.05 |                       | (2) P < 0.05            |
| Lee et al. [10]                   | SD rats (male, 5/7)                            | 250-280 g | NR            | MCAO-induced cognitive impairments model | Isoflurane                    | (1) MWM test (escape latency) | (1) P < 0.05 | (2) Cell density      | (2) P < 0.05            |
| Lee et al. [23]                   | SD rats (male, 7/7)                            | 200-220 g | NR            | Chronic corticosterone-exposed model    | Sodium pentobarbital           | β-Asarone (50, 100, and 200 mg kg\(^{-1}\), ip); 30 min prior to the CORT; once daily for 21 d | Normal saline; (same volume, ip); 30 min prior to the CORT; once daily for 21 d | (1) MWM test (swimming speed) | (1) P > 0.05            |
| Kumar et al. 2012                | ICR mice (8/8)                                 | NR     | NR            | Scopolamine-induced amnesic model mode  | NR                            | α-Asarone (3, 10, and 30 mg kg\(^{-1}\), ip); 15 d before scopolamine injection; once daily for 15 d | 0.5% methylcellulose solution containing 1% Tween 80 (same volume, po); 15 d before scopolamine injection; once daily for 15 d | (1) SD test (escape latency) | (1) P < 0.01            |
| Kim et al. [25]                   | SD rats (male, 5/5)                            | 260–280 g | NR            | Ibotenic acid-induced amnesia           | Sodium pentobarbital           | AGA (100 mg kg\(^{-1}\), ip); Saline (same volume, ip); after | (1) MWM test (escape latency) | (1) P < 0.01            | (2) P < 0.001          |

(1) EY-M test (number of errors) (2) NE, DA and 5-HT level (3) AChE activity (4) P < 0.01
| Study (years) | Species (sex, n = experimental/control group) | Weight | Random method | Model (method) | Anesthetic | Method of administration | Outcome index | Intergroup differences |
|--------------|---------------------------------------------|--------|---------------|----------------|------------|-------------------------|---------------|------------------------|
| Geng et al. [26] | SD rats (male, 20/20) | 220-240 g | NR | Aβ1-42-induced AD model | Sodium pentobarbital | after surgery; once daily for 3 weeks | (1) P < 0.001 | (1) MWM test (escape latency) |
| | | | | | | | (2) ChAT positive neurons count | (2) P > 0.05 |
| | | | | | | | (3) AchE neurons density | (3) P < 0.05 |
| | | | | | | | (4) Caspase-3 and Caspase-3 mRNA expression | (4) P < 0.05 |
| | | | | | | | (5) Bcl-2 and Bcl-2 mRNA levels | (5) P < 0.05 |
| | | | | | | | (6) Bcl-w and Bcl-w mRNA expression | (6) P < 0.05 |
| | | | | | | | (7) P-JNK express | (7) P < 0.05 |
| Chen et al. [27] | SAMP8 mice (13/13) | NR | NR | SAMP8 mice | NR | Tween 80 (same volume, ig); onset the experiment; once daily for 2 months | (1) MWM test (number of platform crossing) | (1) P < 0.05 |
| | | | | | | | (2) MWM test (escape latency) | (2) P < 0.05 |
| | | | | | | | (3) LC3-positive cells | (3) P < 0.05 |
| | | | | | | | (4) Beclin express | (4) P < 0.05 |
| | | | | | | | (5) 1p62 express | (5) P < 0.05 |
| | | | | | | | (6) P < 0.05 |
| Study (years) | Species (sex, n = experimental/ control group) | Weight | Random method | Model (method) | Anesthetic | Method of administration | Outcome index (time) | Intergroup differences |
|--------------|-----------------------------------------------|--------|---------------|----------------|------------|--------------------------|----------------------|----------------------|
|              | NIH mice (male, 6/6)                         | 18-20 g| NR            | $A\beta_{1-42}$-induced AD model | Sodium pentobarbital | Water extract (0.02 g g$^{-1}$, ig); after the first MWM test; once daily for 3 weeks | (1) MWM test (escape latency) | (1) $P < 0.05$ |
| Ma et al. [28]|                                              |        |               | $A\beta_{1-42}$-induced AD model | Sodium pentobarbital | Defatted decoction (0.02 g g$^{-1}$, ig); after the first MWM test; once daily for 3 weeks | (2) Beta-amyloid IOD | (2) $P < 0.05$ |
|              | NIH mice (male, 6/6)                         | 18-20 g| NR            | $A\beta_{1-42}$-induced AD model | Sodium pentobarbital | Essential oil (0.02 g g$^{-1}$, ig); after the first MWM test; once daily for 3 weeks | (1) MWM test (escape latency) | (1) $P < 0.05$ |
|              | NIH mice (male, 6/6)                         | 18-0 g | NR            | $A\beta_{1-42}$-induced AD model | Sodium pentobarbital | Defatted decoction (0.02 g g$^{-1}$, ig); after the first | (2) NOS activity | (2) $P < 0.05$ |
| Tian et al. [29]|                                              |        |               | $A\beta_{1-42}$-induced AD model | Sodium pentobarbital | Water extract (0.2 ml/10 g, ig); after surgery; once daily for 3 weeks | (1) MWM test (number of platform crossing) | (1) $P < 0.05$ |
|              | NIH mice (male, 6/6)                         | 18-0 g | NR            | $A\beta_{1-42}$-induced AD model | Sodium pentobarbital | Defatted decoction (0.02 g g$^{-1}$, ig); after the first | (1) MWM test (number of platform crossing) | (1) $P > 0.05$ |
| Study (years) | Species (sex, n = experimental/control group) | Weight | Random method | Model (method) | Anesthetic | Method of administration Experimental group | Method of administration Control group | Outcome index (time) | Intergroup differences |
|---------------|-----------------------------------------------|--------|---------------|---------------|------------|---------------------------------------------|----------------------------------------|---------------------|------------------------|
|               | NIH mice (male, 6/6)                          | 18-20 g | NR            | $\beta_{1-42}$-induced AD model | Sodium pentobarbital | MWM test; once daily for 3 weeks | Normal saline (0.2 ml/10 g, ig); after surgery; once daily for 3 weeks | (2) MWM test (time spent in target quadrant) | (2) $P > 0.05$ |
|               |                                               |        |               |               |            | Essential oil (0.02 g g$^{-1}$, ig); after the first MWM test; once daily for 3 weeks | NS (same volume, ig); onset the experiment; once daily for 21 d | (3) NOS activity | (3) $P < 0.05$ |
|               |                                               |        |               |               |            |                                               | (1) MWM test (number of platform crossing) | (1) $P < 0.05$ |                        |
| Zhou et al. [30] | SD rats (male, 10/10)                        | 250 ± 20 g | NR           | Scopolamine-induced AD model | NR | Essential oil (12 g kg$^{-1}$, ig); onset the experiment; once daily for 21 d | NS (same volume, ig); onset the experiment; once daily for 21 d | (1) MWM test (escape latency) | (1) $P < 0.01$ |
|               |                                               |        |               |               |            |                                               | (2) MWM test (number of platform crossing) | (2) $P < 0.01$ |                        |
|               |                                               |        |               |               |            |                                               | (3) GFAP - positive cells | (3) $P < 0.01$ |                        |
|               |                                               |        |               |               |            |                                               | (4) SOD content | (4) $P < 0.05$ |                        |
|               |                                               |        |               |               |            |                                               | (5) MDA content | (5) $P < 0.05$ |                        |
| Wang GM et al., 2017 | Kunming mice (mix, 12/12)       | 5-6 weeks | NR           | Chronic restraint stress-induced cognitive impairments mode | NR | Essential oil (4.5 g kg$^{-1}$, ig); onset the experiment; twice daily for 28 d | NS (same volume, ig); onset the experiment; twice daily for 28 d | (1) MWM test (escape latency) | (1) $P < 0.01$ |
|               |                                               |        |               |               |            |                                               | (2) MWM test (number of platform crossing) | (2) $P < 0.01$ |                        |
|               |                                               |        |               |               |            |                                               | (3) Body mass | (3) $P < 0.05$ |                        |
|               |                                               |        |               |               |            |                                               | (4) Plasma cortisol levels | (4) $P < 0.01$ |                        |
| Hu et al. [32] | Kunming mice (male, 11/11)                  | 18-20 g | NR            | Sodium nitrite-induced amnesic model | NR | Essential oil (0.053 g kg$^{-1}$, ig); 21 d before sodium nitrite injection; once daily for 21 d | Tween 80 (same volume, ig); 21 d before sodium nitrite injection; once daily for 21 d | (1) SD test (escape latency) | (1) $P < 0.05$ |
|               |                                               |        |               |               |            |                                               | (2) SD test (number of errors) | (2) $P < 0.05$ |                        |
|               | Kunming mice (male, 11/11)                  | 18-20 g | NR            |               |            |                                               |                       | (1) $P < 0.05$ |                        |
### Table 1: Continued.

| Study (years) | Species (sex, \( n = \) experimental/control group) | Weight | Random method | Model (method) | Anesthetic | Method of administration | Control group | Outcome index (time) | Intergroup differences |
|---------------|--------------------------------------------------|--------|---------------|----------------|------------|--------------------------|---------------|----------------------|------------------------|
|               | Kunming mice (male, 11/11)                        | 18-20 g| NR            | Sodium nitrite-induced amnesic model | NR         | Defatted decoction (5 g kg\(^{-1}\), ig); 21 d before sodium nitrite injection; once daily for 21 d | Tween 80 (same volume, ig); 21 d before sodium nitrite injection; once daily for 21 d | (1) SD test (escape latency) | (2) \( P < 0.05 \) |
|               |                                                  |        |               | Sodium nitrite-induced amnesic model | α–Asarone (0.024 g kg\(^{-1}\), ig); 21 d before sodium nitrite injection; once daily for 21 d | Tween 80 (same volume, ig); 21 d before sodium nitrite injection; once daily for 21 d | (1) SD test (escape latency) | (1) \( P < 0.05 \) |
|               | Kunming mice (male, 11/11)                        | 18-20 g| NR            | Sodium nitrite-induced amnesic model | β–Asarone (0.037 g kg\(^{-1}\), ig); 21 d before sodium nitrite injection; once daily for 21 d | Tween 80 (same volume, ig); 21 d before sodium nitrite injection; once daily for 21 d | (2) SD test (number of errors) | (1) \( P < 0.05 \) |
|               |                                                  |        |               | Essential oil (0.053 g kg\(^{-1}\), ig); 21 d before ethanol injection; once daily for 21 d | NR         | Defatted decoction (5 g kg\(^{-1}\), ig); 21 d before ethanol injection; once daily for 21 d | Tween 80 (same volume, ig); 21 d before ethanol injection; once daily for 21 d | (1) SD test (escape latency) | (1) \( P < 0.05 \) |
|               | Kunming mice (male, 11/11)                        | 18-20 g| NR            | Ethanol-induced amnesic model | NR         | α–Asarone (0.024 g kg\(^{-1}\), ig); 21 d before ethanol injection; once daily for 21 d | Tween 80 (same volume, ig); 21 d before ethanol injection; once daily for 21 d | (1) SD test (escape latency) | (1) \( P > 0.05 \) |
|               |                                                  |        |               | Ethanol-induced amnesic model | β–Asarone (0.037 g kg\(^{-1}\), ig); 21 d before ethanol injection; once daily for 21 d | Tween 80 (same volume, ig); 21 d before ethanol injection; once daily for 21 d | (2) SD test (number of errors) | (2) \( P < 0.05 \) |
|               | Kunming mice (male, 11/11)                        | 18-20 g| NR            | Ethanol-induced amnesic model | NR         | Defatted decoction (5 g kg\(^{-1}\), ig); 21 d before ethanol injection; once daily for 21 d | Tween 80 (same volume, ig); 21 d before ethanol injection; once daily for 21 d | (1) SD test (escape latency) | (1) \( P < 0.01 \) |
|               |                                                  |        |               | Ethanol-induced amnesic model | NR         | β–Asarone (0.037 g kg\(^{-1}\), ig); 21 d before ethanol injection; once daily for 21 d | Tween 80 (same volume, ig); 21 d before ethanol injection; once daily for 21 d | (1) SD test (escape latency) | (1) \( P < 0.05 \) |
|               | Kunming mice (male, 11/11)                        | 18-20 g| NR            | Ethanol-induced amnesic model | NR         | Defatted decoction (5 g kg\(^{-1}\), ig); 21 d before ethanol injection; once daily for 21 d | Tween 80 (same volume, ig); 21 d before ethanol injection; once daily for 21 d | (2) SD test (number of errors) | (2) \( P < 0.01 \) |
| Study (years) | Species (sex, n = experimental/ control group) | Weight | Random method | Model (method) | Anesthetic | Method of administration | Outcome index (time) | Intergroup differences |
|-------------|-----------------------------------------------|--------|---------------|---------------|------------|-------------------------|----------------------|------------------------|
| Kunming mice (male, 11/11) | 18-20 g | NR | Sodium pentobarbital-induced amnesic model | NR | Ethanol injection; once daily for 21 d | (2) SD test (number of errors) | (1) P < 0.05 |
| Kunming mice (male, 11/11) | 18-20 g | NR | Sodium pentobarbital-induced amnesic model | NR | Defatted decoction (5 g kg⁻¹, ig); 21 d before ethanol injection; once daily for 21 d | (1) EY-M test (number of errors) | (1) P < 0.05 |
| Kunming mice (male, 11/11) | 18-20 g | NR | Sodium pentobarbital-induced amnesic model | NR | α-Asarone (0.024 g kg⁻¹, ig); 21 d before ethanol injection; once daily for 21 d | (1) EY-M test (number of errors) | (1) P < 0.05 |
| Kunming mice (male, 11/11) | 18-20 g | NR | Sodium pentobarbital-induced amnesic model | NR | β-Asarone (0.037 g kg⁻¹, ig); 21 d before ethanol injection; once daily for 21 d | (1) EY-M test (number of errors) | (1) P < 0.05 |
| Chen et al. [33] | ICR mice (male, 10/10) | 18 ± 1 g | Random number table | D-gal-induced dementia model | NR | Water extract (70, 35, 17.5, or 8.75 mg kg⁻¹, ig); 1 week after D-galactose injection; once daily for 7 weeks | (1) MWM test (escape latency) | (1) P > 0.05 |
| Gu et al. [34] | ICR mice (male, 10/10) | 19.6 ± 1.5 g | | | NR | Water extract (70, 35, 17.5, or 8.75 mg kg⁻¹, ig); onset the | (1) SD test (escape latency) | (1) P < 0.01 |
| Study (years) | Species (sex, n = experimental/control group) | Weight | Random method | Model (method) | Anesthetic | Method of administration | Outcome index (time) | Intergroup differences |
|--------------|---------------------------------------------|--------|---------------|---------------|------------|---------------------------|----------------------|------------------------|
| ICR mice (male, 10/10) | 19.6 ± 1.5 g | Random number table | Scopolamine-induced dysmenia model | 8.75 mg kg⁻¹, ig; onset the experiment; once daily for 2 weeks | experiment; once daily for 2 weeks | (2) SD test (number of errors) | (2) P < 0.01 |
| | | | NaNO₂-induced dysmenia model | Water extract (70, 35, 17.5, or 8.75 mg kg⁻¹, ig); onset the experiment; once daily for 2 weeks | NS (same volume, ig); onset the experiment; once daily for 2 weeks | (1) SD test (escape latency) | (1) P < 0.01 |
| | | | Ethanol-induced dysmenia model | Water extract (70, 35, 17.5, or 8.75 mg kg⁻¹, ig); onset the experiment; once daily for 2 weeks | NS (same volume, ig); onset the experiment; once daily for 2 weeks | (2) SD test (number of errors) | (2) P < 0.05 |
| | | | Scopolamine-induced dysmenia model | Water extract (35, 17.5, or 8.75 mg kg⁻¹, ig); onset the experiment; once daily for 4 weeks | NS (same volume, ig); onset the experiment; once daily for 2 weeks | (1) MWM test (escape latency) | (1) P < 0.01 |
| | | | | | | (2) MWM test (number of platform crossing) | (2) P < 0.01 |
| Aged NIH mice (male, 10/10) | NR | NR | Aged mice | NR | Essential oil (0.01075 ml g⁻¹, ig); onset the experiment; twice daily for 10 d | NS (same volume, ig); onset the experiment; once daily for 10 d | (1) MWM test (escape latency) | (1) P < 0.05 |
| | | | | | | (2) AchE activity | (2) P < 0.05 |
| Wu et al., 2004 | | | | | | (3) C-jun express | (3) P < 0.05 |
| Aged NIH mice (male, 10/10) | NR | NR | Aged mice | NR | β-Asarone (0.01075 ml g⁻¹, ig); onset the experiment; twice daily for 10 d | NS (same volume, ig); onset the experiment; once daily for 10 d | (1) MWM test (escape latency) | (1) P > 0.05 |
| | | | | | | (2) MWM test (number of errors) | (2) P > 0.05 |
| | | | | | | (3) AchE activity | (3) P > 0.05 |
| Study (years) | Species (sex, \( n = \) experimental/ control group) | Weight | Random method | Model (method) | Anesthetic | Method of administration Experimental group | Method of administration Control group | Outcome index (time) | Intergroup differences |
|--------------|-------------------------------------------------|--------|--------------|---------------|------------|------------------------------------------|--------------------------------------|---------------------|-----------------------|
| Aged NIH mice (male, 10/10) | NR | NR | Aged mice | NR | Water extract (0.01075 ml g\(^{-1}\), ig); onset the experiment; twice daily for 10 d | NS (same volume, ig); onset the experiment; once daily for 10 d | \( p > 0.05 \) | \( p > 0.05 \) |
| Kunming mice (male, 10/10) | NR | NR | Ethanol-induced dysmnesia model | NR | Water extract (0.01075 ml g\(^{-1}\), ig); onset the experiment; twice daily for 10 d | NS (same volume, ig); onset the experiment; once daily for 10 d | \( p < 0.05 \) | \( p < 0.05 \) |
| Kunming mice (male, 10/10) | NR | NR | NaNO\(_2\)-induced dysmnesia model | NR | Essential oil (0.01075 ml g\(^{-1}\), ig); onset the experiment; twice daily for 10 d | NS (same volume, ig); onset the experiment; once daily for 10 d | \( p > 0.05 \) | \( p > 0.05 \) |
| Kunming mice (male, 10/10) | NR | NR | NaNO\(_2\)-induced dysmnesia model | NR | \( \beta \)-Asarone (0.01075 ml g\(^{-1}\), ig); onset the experiment; twice daily for 10 d | NS (same volume, ig); onset the experiment; once daily for 10 d | \( p < 0.05 \) | \( p > 0.05 \) |
| Kunming mice (male, 10/10) | NR | NR | NaNO\(_2\)-induced dysmnesia model | NR | Water extract (0.01075 ml g\(^{-1}\), ig); onset the experiment; twice daily for 10 d | NS (same volume, ig); onset the experiment; once daily for 10 d | \( p < 0.05 \) | \( p > 0.05 \) |
| Kunming mice (male, 10/10) | NR | NR | Scopolamine-induced dysmnesia model | NR | Essential oil (0.01075 ml g\(^{-1}\), ig); onset the experiment; twice daily for 10 d | NS (same volume, ig); onset the experiment; once daily for 10 d | \( p < 0.05 \) | \( p < 0.05 \) |
| Kunming mice (male, 10/10) | NR | NR | Scopolamine-induced dysmnesia model | NR | \( \beta \)-Asarone (0.01075 ml g\(^{-1}\), ig); onset the | NS (same volume, ig); onset the | \( p < 0.05 \) | \( p > 0.05 \) |
| Study (years) | Species (sex, n = experimental/ control group) | Weight | Random method | Model (method) | Anesthetic | Method of administration | Outcome index | Intergroup differences |
|---------------|-----------------------------------------------|--------|---------------|---------------|------------|-------------------------|---------------|-----------------------|
|               | Kunming mice (male, 10/10)                    | NR     | NR            | Scopolamine-induced dysmenia model | NR         | Water extract (0.01075 ml g\(^{-1}\), ig); onset the experiment; twice daily for 10 d | (2) SD test (number of errors) | (1) \( P < 0.05 \) |
|               | ICR mice (mix, 10/10)                        | 20 ± 2 g | NR            | Ethanol-induced dysmenia model | NR         | Water extract (3 and 12 g kg\(^{-1}\), ig); onset the experiment; twice daily for 14 d | (1) ST test (escape latency) | (1) \( P < 0.01 \) |
|               | ICR mice (mix, 10/10)                        | 20 ± 2 g | NR            | NaNO\(_2\)-induced dysmenia model | NR         | Essential oil (3 and 12 g kg\(^{-1}\), ig); onset the experiment; once daily for 14 d | (2) EY-M test (number of errors) | (1) \( P < 0.05 \) |
| Wen et al., 2009 | ICR mice (mix, 10/10)                        | 20 ± 2 g | NR            | Scopolamine-induced dysmenia model | NR         | Water extract (3 and 12 g kg\(^{-1}\), ig); onset the experiment; once daily for 14 d | (1) SD test (escape latency) | (1) \( P < 0.05 \) |
|               | ICR mice (mix, 10/10)                        | 20 ± 2 g | NR            | Scopolamine-induced dysmenia model | NR         | Essential oil (3 and 12 g kg\(^{-1}\), ig); onset the experiment; twice daily for 14 d | (2) SD test (number of errors) | (2) \( P < 0.05 \) |
|               | ICR mice (mix, 10/10)                        | 20 ± 2 g | NR            | Scopolamine-induced dysmenia model | NR         | Water extract (3 and 12 g kg\(^{-1}\), ig); onset the experiment; once daily for 14 d | (1) SD test (escape latency) | (1) \( P < 0.05 \) |
|               | ICR mice (mix, 10/10)                        | 20 ± 2 g | NR            | Scopolamine-induced dysmenia model | NR         | Water extract (3 and 12 g kg\(^{-1}\), ig); onset the experiment; twice daily for 14 d | (1) MWM test (escape latency) | (1) \( P < 0.01 \) |
| Study (years) | Species (sex, n = experimental/control group) | Weight | Random method | Model (method) | Anesthetic | Method of administration | Outcome index (time) | Intergroup differences |
|--------------|-----------------------------------------------|--------|---------------|----------------|------------|-------------------------|---------------------|----------------------|
| Yang et al. [37] | SD rats (male, 12/12) | 250 ± 30 g | NR | Aβ1-42-induced AD model | NR | β-Asarone (10, 20, and 30 mg kg⁻¹, ig); after the model finished; twice daily for 28 d | (1) MWM test (escape latency) | (1) P < 0.05 |
| Zhou et al. [38] | SD rats (male,10/10) | 200-250 g | NR | D-gal- and AlCl₃-induced AD model | NR | α-Asarone (10, 25 mg kg⁻¹, ip); after the model finished; once daily for 28 d | (1) MWM test (number of platform crossing) (2) Apβ and tau protein expression (3) ACh levels (4) AChE levels (5) ChAT levels | (1) P < 0.01 (2) P < 0.01 (3) P < 0.01 |
| Jiang et al., 2007 | Kunming mice (mix, 10/10) | 18-20 g | NR | AlCl₃-induced AD model | NR | β-Asarone (1.06, 2.12, and 4.24 mg 100 g⁻¹, ig); after the model finished; once daily for 2 months | (1) MWM test (number of errors) (2) SOD levels (3) MAD levels | (1) P < 0.01 (2) P < 0.01 (3) P < 0.01 |
| Huang et al. [40] | FMR1 gene knock mice (16/17) | 17-18 g | NR | Fragile X syndrome model | NR | α-Asarone (3, 6, 9, 12, 24 mg kg⁻¹, ip); onset the experiment; once daily for 8 d | (1) SD test (number of errors) (2) P-Akt expression (3) P < 0.05 | (1) P > 0.05 (2) P < 0.05 (3) P > 0.05 |
| Study (years)          | Species (sex, n = experimental/control group) | Weight | Random method | Model (method) | Anesthetic | Method of administration | Outcome index (time) | Intergroup differences |
|------------------------|-----------------------------------------------|--------|---------------|----------------|------------|--------------------------|----------------------|------------------------|
| Wang BL et al., 2017   | SD rats (male, 15/15)                         | 280 ± 20 g | Random number table | $\beta_1$-42-induced AD model | Phenyl sodium | $\beta$-Asarone (10, 20, and 30 mg kg$^{-1}$, ig); after the model finished; once daily for 4 weeks | (1) MWM test (escape latency) | $P < 0.01$ |
|                        |                                               |        |               |                |            | NS (same volume, ig); after the model finished; once daily for 4 weeks | (2) MWM test (number of platform crossing) | $P < 0.01$ |
|                        |                                               |        |               |                |            | (3) HIF levels | $P < 0.05$ |
| Guo et al. [42]        | Kunming mice (male, 11/11)                   | 25 ± 5 g | Random block allocation method | Scopolamine-induced AD model | NR | $\beta$-Asarone (21.2 mg kg$^{-1}$, ig); after the model finished; once daily for 14 d | (1) MWM test (escape latency) | $P < 0.01$ |
|                        |                                               |        |               |                |            | NS (same volume, ig); after the model finished; once daily for 14 d | (2) MWM test (number of platform crossing) | $P < 0.01$ |
|                        |                                               |        |               |                |            | (3) HIF levels | $P < 0.05$ |
| Jiang et al. [43]      | Wistar rats (mix, 8/8)                       | 250-300 g | NR | STZ-induced AD model | NR | Essential oil (5, 10 and 20 g kg$^{-1}$, ig); onset the experiment; once daily for 20 d | (1) MWM test (escape latency) | $P < 0.01$ |
|                        |                                               |        |               |                |            | Solvent (same volume, ig); onset the experiment; once daily for 20 d | (2) SOD levels | $P < 0.01$ |
|                        |                                               |        |               |                |            | | (3) MAD levels | $P < 0.01$ |
| Yang et al. [44]       | Wistar rats (10/10)                          | 35 ± 5 g | NR | PTZ-induced epilepsy model | NR | $\alpha$-Asarone (29 mg kg$^{-1}$, ig); after PTZ injection; twice daily for 7 d | (1) MWM test (number of platform crossing) | $P < 0.05$ |
|                        |                                               |        |               |                |            | NS (same volume, ig); after PTZ injection; twice daily for 7 d | (2) MWM test (time spent in target quadrant) | $P < 0.05$ |
|                        |                                               |        |               |                |            | | | |
| Wang et al. [45]       | ICR mice (mix, 10/10)                        | 20 ± 2 g | NR | NR | Essential oil (100, 150, and NS (same volume, ig); before the | (1) MWM test (escape latency) | $P < 0.01$ |
Table 1: Continued.

| Study (years) | Species (sex, n = experimental/control group) | Weight | Random method | Model (method) | Anesthetic Method of administration | Outcome index (time) | Intergroup differences |
|---------------|-----------------------------------------------|--------|---------------|----------------|--------------------------------------|----------------------|------------------------|
| Ma et al. [46] | SD rats (male, 6/6)                           | 260-280 g | NR            | Aβ1-42-induced AD model | β-Asarone (12.5, 25, 50 mg kg⁻¹, i.g); after the model finished; once daily for 4 weeks | NS (same volume, i.g); after the model finished; once daily for 4 weeks | (1) MWM test (escape latency) (2) GA P-43 mRNA levels (3) SYP mRNA levels (4) PSD-95 mRNA levels | (1) P < 0.05 (2) P < 0.05 (3) P < 0.05 |

Scopolamine-induced dysnnesia model

300 mg kg⁻¹, i.g); before the experiment; once daily for 7 d

experiment; once daily for 7 d

(2) MWM test (number of platform crossing) (3) MWM test (time spent in target quadrant) (2) P < 0.01

Ach: acetylcholine; AchE: acetylcholinesterase; SD rats: Sprague-Dawley rats; NIH mice: National Institutes of Health mice; SAMP8 mice: senescence-accelerated mouse prone 8 mice; AD: Alzheimer’s disease; AlCl₃: aluminum trichloride; ChAT: acetylcholine transferase; D-gal: D-galactose; i.g.: intragastrical injection; i.p.: intraperitoneal injection; i.h.: hypodermic injection; MWM test: Morris water maze test; MCAO: middle cerebral artery occlusion; MDA: malondialdehyde; GSH-PX: glutathione peroxidase; NR: not report; SD test: step down test; STZ: streptozotocin; SOD: superoxide dismutase; HIF: hypoxia-inducible factor; GSH-PX: glutathione peroxidase; NE: norepinephrine; 5-HT: 5-hydroxytryptamine; DA: dopamine; SYN/SYN: synaptophysin; NOS: nitric oxide synthase; Bcl-2: B-cell lymphoma/leukemia-2; MAP2: microtubule-associated protein 2; RAM: radial eight-arm maze; EY-M: electric Y-maze; Aβ1-42: amyloid beta 1-42; PTZ: pentylentetrazol; NS: normal saline.
measurements were Morris water maze test (MWM test), electric Y-maze test (EY-M test), radial eight-arm maze test (RAM test), Step down test (SD test), and/or Step through test (ST test). The secondary outcome measures were mechanisms of EAAGA for learning and/or memory function.

2.3. Exclusion Criteria. Exclusion criteria were prespecified as follows: (1) the article was a review, case report, comment, clinical trial, abstract, or editorial; (2) the article was a clinical or in vitro study; (3) the article was not a research about cognitive impairment model; (4) EAAGA was used as combination; (5) there was no control group; and (6) the article was a duplicate publication.

2.4. Data Extraction. The information of each included study was extracted: (1) author and publication year, animal model species, method of anesthesia, and random method; (2) characteristics of animals, including species, sex, animal number, and weight; (3) treatment information from treatment and control groups, including drug, dose, method of treatment, timing for initial treatment, frequency, and duration of treatment; and (4) outcome measures, sample size, and corresponding data including mean value, standard deviation, and intergroup differences. If outcomes were presented at different time points, we extracted data from the last time point. If studies utilized dose gradient of the drug, we extracted data from the highest dose of EAAGA and active

| Study (years) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Total |
|--------------|---|---|---|---|---|---|---|---|---|----|-------|
| Yang et al. [17] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 6 |
| Wei et al., 2013 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 3 |
| Sundaramahalingam et al. [18] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 3 |
| Shin et al. [19] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 4 |
| Ma et al. [11] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 5 |
| Liu et al. [20] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 6 |
| Limón et al. [21] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 5 |
| Li et al. [22] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 5 |
| Zhang et al. [5] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 3 |
| Lee et al. [10] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 4 |
| Lee et al. [23] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 5 |
| Kumar et al., 2012 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 3 |
| Kim et al. [25] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 3 |
| Geng et al. [26] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 4 |
| Chen et al. [27] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 3 |
| Ma et al. [28] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 5 |
| Tian et al. [29] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 2 |
| Zhou et al. [30] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 3 |
| Wang GM et al., 2017 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 2 |
| Hu et al. [32] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 2 |
| Chen et al. [33] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 2 |
| Gu et al. [34] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 2 |
| Wu et al., 2004 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 2 |
| Wen et al., 2009 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 2 |
| Yang et al. [37] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 6 |
| Zhou et al. [38] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 2 |
| Jiang et al., 2007 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 2 |
| Huang et al. [40] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 1 |
| Wang BL et al., 2017 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 5 |
| Guo et al. [42] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 2 |
| Jiang et al. [43] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 3 |
| Yang et al. [44] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 2 |
| Wang et al. [45] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 3 |
| Ma et al. [46] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 | 4 |

1: peer-reviewed publication; 2: statements describing control of temperature; 3: randomization to treatment group; 4: allocation concealment; 5: blinded assessment of outcome; 6: avoidance of anesthetics with known notable intrinsic neuroprotective properties; 7: use of animals with relevant comorbidities; 8: sample size calculation; 9: compliance with animal welfare regulations; 10: declared any potential conflict of interest.
| Study or subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. mean difference | IV, random, 95% CI |
|------------------|------------------|----|-------|--------------|----|-------|--------|---------------------|------------------|
| Chen 2013        | 35.8             | 22.4| 10    | 51.8         | 16.1| 10    | 4.3%   | -0.79               | [-1.70, 0.13]    |
| Geng 2010        | 13.87            | 3.6 | 18    | 19.38        | 2.13| 18    | 4.9%   | -1.82               | [-2.61, -1.03]   |
| Gu 2012          | 11.2             | 12.97| 9      | 46.4         | 21.19| 10    | 3.6%   | -1.92               | [-3.02, -0.82]   |
| Guo 2012         | 18.63            | 9.18| 11    | 38.73        | 35.45| 11    | 4.5%   | -0.75               | [-1.62, 0.12]    |
| Jiang 2018       | 19.02            | 11.32| 8      | 68            | 15.42| 8     | 2.1%   | -3.42               | [-5.10, -1.74]   |
| Lee 2003         | 27.59            | 13.89| 5      | 102           | 63.87| 7     | 2.9%   | -1.37               | [-2.69, -0.04]   |
| Li 2012          | 7.48             | 4.6 | 7     | 20.29        | 13.52| 7     | 3.3%   | -1.19               | [-2.36, -0.02]   |
| Liu 2016         | 32.89            | 14.62| 12     | 51.45        | 18.26| 12    | 4.5%   | -1.08               | [-1.95, -0.22]   |
| Ma 2011          | 23.13            | 10.84| 6      | 26.89        | 15.18| 6     | 3.4%   | -0.26               | [-1.40, 0.88]    |
| Ma 2011          | 24.27            | 9.88 | 6      | 26.89        | 15.18| 6     | 3.5%   | -0.19               | [-1.32, 0.95]    |
| Ma 2011          | 21.07            | 6.51 | 6      | 26.89        | 15.18| 6     | 3.4%   | -0.46               | [-1.61, 0.69]    |
| Ma 2015          | 21.14            | 4.46 | 6      | 27.05        | 11.15| 6     | 3.3%   | -0.64               | [-1.82, 0.33]    |
| Ma 2015          | 14.22            | 5.9  | 6      | 27.05        | 10.63| 6     | 2.9%   | -1.38               | [2.69, -0.06]    |
| Ma 2015          | 24.34            | 8.84 | 6      | 27.05        | 10.63| 6     | 3.4%   | -0.26               | [-1.39, 0.88]    |
| Ma 2017          | 26.94            | 4.64 | 6      | 46.72        | 8.66 | 6     | 1.7%   | -3.12               | [-5.01, -1.22]   |
| Shin 2014        | 13.68            | 6.3  | 12     | 18.47        | 6.3 | 12    | 4.7%   | -0.73               | [-1.57, 0.10]    |
| Wang 2019        | 48.1             | 23.6 | 10     | 98.2         | 30.4 | 10    | 3.7%   | -1.76               | [-2.83, -0.70]   |
| Wang BL 2017     | 10.21            | 1.84 | 12     | 17.38        | 3.05 | 12    | 3.3%   | -2.75               | [-3.92, -1.58]   |
| Wang GM 2017     | 27.1             | 7.24 | 8      | 50.9         | 10.7 | 8     | 2.7%   | -2.46               | [-3.85, -1.08]   |
| Wen 2009         | 40.88            | 19.63| 10     | 56.67        | 16.3 | 10    | 4.3%   | -0.84               | [-1.76, 0.09]    |
| Wen 2009         | 42.6             | 16.9 | 10     | 56.67        | 16.3 | 10    | 4.3%   | -0.81               | [-1.73, 0.11]    |
| Wu 2004          | 30.75            | 18.68| 10     | 43.5         | 20   | 10    | 4.4%   | -0.63               | [-1.53, 0.27]    |
| Wu 2004          | 26               | 11.11| 10     | 43.5         | 20   | 10    | 4.2%   | -1.04               | [-1.98, -0.09]   |
| Wu 2004          | 33.89            | 13.86| 10     | 43.5         | 20   | 10    | 4.4%   | -0.53               | [-1.43, 0.36]    |
| Yang 2016        | 12.45            | 6.11 | 7      | 16.6         | 8.55 | 7     | 3.7%   | -0.52               | [-1.60, 0.35]    |
| Yang 2017        | 37.4             | 11.82| 12     | 60.1         | 11.1 | 12    | 4.8%   | -0.28               | [-1.08, 0.33]    |
| Zhou 2015        | 43.5             | 7.5  | 10     | 58           | 9.6  | 10    | 3.8%   | -1.61               | [-2.65, -0.57]   |
| Total (95% CI)   |                  |     |        | 244          |     |       | 100.0%| -1.09               | [-1.37, -0.82]   |

Heterogeneity: $\tau^2 = 0.25$; $\chi^2 = 49.48$, df = 26 ($P = 0.004$); $I^2 = 47$

Test for overall effect: $Z = 7.69$ ($P < 0.00001$)

(b)

Figure 2: Continued.
component since the dose-response relationship. If the data were incomplete or presented in graphs, we tried to contact the authors for data needed or calculated using relevant software. Information of the mechanism studies of EAAGA and active component for cognitive impairment models among the included articles was extracted.

2.5. Quality Assessment. The methodological quality of included studies was evaluated by two independent reviewers using Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) 10-item checklist [16]. For calculating an aggregate quality score, each item of this scale was attributed one point.

2.6. Statistical Analysis. Meta-analysis was conducted via RevMan version 5.3. To estimate the effect of EAAGA on cognitive impairment, the random effects model and standard mean difference (SMD) with 95% confidence intervals (CIs) were calculated. Heterogeneity was assessed via $I^2$ statistics test. If probability value was less than 0.05, the difference was considered statistically significant. In addition, to explore potential sources of high heterogeneity, subgroup analyses were performed according to animal species and models. Difference between groups was determined by partitioning heterogeneity and utilizing the $\chi^2$ distribution with degrees of freedom (df).

3. Results

3.1. Study Selection. We identified 2368 potentially relevant papers after systematical search from six databases. After removing duplicates, 1887 studies remained. By reading titles and abstracts, 1602 articles were excluded that were reviews, case reports, comments, abstracts, clinical trials, letters, or editorials. After reading the remaining 285 full-text articles, 228 studies were excluded for at least one of following reasons: (1) not an animal study; (2) the article was not a research about cognitive impairment; (3) the study did not access the effects of AGA or active component on the animal model of cognitive impairment; (4) EAAGA was not used as a monotherapy; and (5) lack of control group. Ultimately, 34 eligible articles [5, 6, 10, 11, 17–46] were selected (Figure 1).
| Study or subgroup | Experimental | Control | Weight | Std. mean difference | Std. mean difference |
|------------------|--------------|---------|--------|----------------------|----------------------|
|                  | Mean | SD | Total | Mean | SD | Total | IV, random | 95% CI | IV, random | 95% CI |
| Gu 2012          | 241.7 | 90.12 | 5     | 107  | 110.68 | 8        | 3.8% | 1.21 | -0.04, 2.46 |
| Gu 2012          | 201.4 | 108.15 | 6     | 59.9 | 88.23 | 9        | 4.1% | 1.38 | 0.20, 2.56 |
| Hu 1999          | 67.4  | 52.5 | 11     | 32.4 | 37.2 | 11       | 6.0% | 0.74 | -0.13, 1.61 |
| Hu 1999          | 104.2 | 35.4 | 11     | 69.4 | 25.2 | 11       | 5.7% | 1.09 | 0.18, 2.00 |
| Hu 1999          | 97.5  | 32.7 | 11     | 69.4 | 25.2 | 11       | 5.9% | 0.93 | 0.04, 1.81 |
| Hu 1999          | 102   | 34.2 | 11     | 69.4 | 25.2 | 11       | 5.8% | 1.04 | 0.14, 1.95 |
| Hu 1999          | 71.4  | 38.6 | 11     | 32.4 | 37.2 | 11       | 5.8% | 0.99 | 0.09, 1.89 |
| Hu 1999          | 70.2  | 39.5 | 11     | 32.4 | 37.2 | 11       | 5.9% | 0.95 | 0.06, 1.84 |
| Hu 1999          | 109.9 | 14   | 11     | 69.4 | 25.2 | 11       | 4.8% | 1.91 | 0.87, 2.95 |
| Hu 1999          | 80.9  | 43.7 | 11     | 32.4 | 37.2 | 11       | 5.7% | 1.15 | 0.23, 2.07 |
| Huang 2016       | 190.58 | 108.4 | 16     | 191.76 | 114.86 | 16 | 7.6% | -0.01 | -0.70, 0.68 |
| Wu 2009          | 114.88 | 43.6 | 10     | 51.67 | 22.39 | 10 | 4.7% | 1.75 | 0.68, 2.81 |
| Wu 2009          | 138.6 | 22.9 | 10     | 51.67 | 22.39 | 10 | 2.7% | 3.68 | 2.13, 5.22 |
| Wu 2004          | 86.2  | 81.74 | 10     | 13.7 | 20.27 | 10 | 5.3% | 1.17 | 0.20, 2.13 |
| Wu 2004          | 107.56 | 72.73 | 10     | 27.3 | 56.75 | 10 | 5.3% | 1.18 | 0.21, 2.15 |
| Wu 2004          | 71    | 89.8 | 10     | 27.3 | 56.75 | 10 | 5.8% | 0.56 | -0.34, 1.45 |
| Wu 2004          | 119.33 | 77.06 | 10     | 13.7 | 20.27 | 10 | 4.6% | 1.80 | 0.72, 2.87 |
| Wu 2004          | 125.6 | 78.72 | 10     | 27.3 | 56.75 | 10 | 5.1% | 1.37 | 0.38, 2.37 |
| Wu 2004          | 98.22 | 88.98 | 10     | 13.7 | 20.27 | 10 | 5.2% | 1.25 | 0.28, 2.23 |
| Total (95% CI)   | 195   |        | 201    | 100.0% | 1.15 | [0.87, 1.43] |

Test for overall effect: $Z = 8.00$ ($P < 0.00001$)

Favours experimental Favours control

(a)

(b)

Figure 3: The forest plot in Step-down test. Effects of EAAGA for increasing right reaction latency in the retention test (a) and decreasing the error times in the retention test (b) compared with control group.

chloral hydrate was used in 2 studies [20, 21], 1 study [41] used phenytoin sodium, 1 study [17] used CO₂, and 1 study [10] used isoflurane, while the remaining 21 studies did not report the type of anesthetics. Cognitive impairment models were induced by lead [17], noise stress [18], LPS [19], amyloid beta 1-42 [11, 21, 26, 28, 29, 37, 41, 46], D-gal plus AlCl₃ [22], scopolamine [5, 24, 30, 34-36, 42, 45], ethanol [5, 32, 34-36], sodium nitrite [5, 32], corticosterone [23], ibotenic acid [25], chronic restraint stress [31], pentobarbital sodium [32], D-galactose [33, 38], AlCl₃ [40], streptozotocin (STZ) [43], pent ylenetetrazol (PTZ) [44], and NaNO₂ [34-36]. As an intervention, fourteen studies [6, 17, 20, 22, 23, 26, 27, 32, 35, 37, 39, 41, 42, 46] used β-asarone, eight studies [18, 19, 21, 24, 33, 38, 40, 44] used α-asarone, three studies [10, 25, 44] utilized AGA, twelve studies [5, 11, 22, 28-32, 35, 36, 43, 45] used essential oil, seven studies [11, 28, 29, 33-36] researched water extract, four studies [11, 28,
used defatted decoction, and one study [18] researched ethyl acetate extract. Normal distilled water control was used in 2 studies [17, 33]; Tween 80 control was used in 6 studies [5, 6, 18, 20, 27, 32]; normal saline control was used in 24 studies; 0.5% methylcellulose solution containing 1% Tween 80 control was used in 1 study [24], and 2% propylene glycol containing 2% polyethylene glycol stearate control was used in 1 study [43]. Neurobehavioral function indices as primary outcome measures were carried out by the Morris water maze test (MWM test) \( (n = 28) \), step-down test (SD test) \( (n = 6) \), electrical Y-maze test (EY-M test) \( (n = 3) \), step-through test (ST test) \( (n = 4) \), and radial eight-arm maze test (RAM test) \( (n = 3) \). The characteristics of the 34 studies are shown in Table 1.

### 3.3. Study Quality

The quality scores of the 34 included studies varied from 1/10 to 6/10 with the average of 3.32. One study [40] got 1 point; 11 studies [29, 31–36, 38, 39, 42, 44] got 2 points; 9 studies [5, 6, 18, 24, 25, 27, 30, 43, 45] got 3 points; 4 studies got 4 points; 7 studies got 5 points; and 2 studies [20, 37] got 6 points. Thirty-four studies were published. Sixteen studies described control of temperature [6, 10, 17–26, 30, 37, 41, 45]. Random allocation was declared in 28 studies [5, 6, 11, 17, 19–23, 26–28, 30–39, 41–46]; 1 study [42] used random block allocation method, and 2
studies used the method of random digit table [34, 41]. Two studies [23, 37] described the use of blinded assessment of outcome. Thirteen studies did not use anesthetics with significant intrinsic neuroprotective activity, and the remaining 21 studies did not report the type of anesthetics [5, 6, 18, 19, 24, 27, 30–40, 42–45]. Sixteen studies reported compliance with animal welfare regulations [5, 10, 11, 17–22, 24, 27, 28, 37, 41, 43, 45]. Four studies mentioned statement of potential conflict of interests [11, 20, 28, 37]. None of the included studies reported allocation concealment, sample size calculation, and the utilization of animal or model with relevant comorbidities. The quality scores for the included studies are shown in Table 2.

3.4. Effectiveness. The Morris water maze test, including the probe test and the spatial test, was conducted in 28 studies [6, 10, 11, 17, 19, 20, 22, 23, 25–31, 33–39, 41–46]. Twenty-seven studies reported the spatial test using the escape latency as an outcome measure. Meta-analysis of 20 studies with 27 comparisons showed EAAGA significantly decreased the escape latency compared with the control (n = 490, SMD = −1.09, 95% CI [−1.37 to −0.82], P < 0.00001; heterogeneity: χ² = 49.48, df = 26 (P = 0.004); I² = 47%; Figure 2(a)). In the probe test, meta-analysis of 16 studies [17, 19, 20, 22, 26, 27, 29–31, 33, 34, 37, 38, 41, 44, 45] with 19 comparisons showed EAAGA were significant for increasing number of platform crossings (n = 398, SMD = 1.60, 95% CI [1.25 to 1.94], P < 0.00001; heterogeneity: χ² = 34.29, df = 18 (P = 0.01); I² = 47%; Figure 2(b)) compared with controls. Meta-analysis of 6 studies [17, 20, 22, 29, 34, 44] with 7 comparisons showed a significant effect of EAAGA in increasing the length of time spent in platform quadrant compared with control (n = 144, SMD = 1.78, 95% CI [0.90 to 2.67], P < 0.0001; heterogeneity: χ² = 22.41, df = 6 (P = 0.001); I² = 73 %). As the values of I² were greater than 50%, we sequentially omitting each study; two studies [20, 22] were removed and markedly reduced the heterogeneity (n = 86, SMD = 2.34, 95% CI [1.55 to 3.12], P < 0.00001; heterogeneity: χ² = 6.57, df = 4 (P = 0.16); I² = 39%; Figure 2(c)). Two studies [20, 22] used relatively large doses of β-arsoare that might have potential toxic effects [47]. Meta-analysis of 3 studies [20, 23, 25] for increasing percentage of time in the platform quadrant (n = 44, SMD = 4.01, 95% CI [2.86 to 5.15], P < 0.00001; heterogeneity: χ² = 0.03, df = 2 (P = 0.98); I² = 0%; Figure 2(d)). Three studies [17, 22, 23] showed there were not a significant difference in improving the swimming velocity compared with controls.

The step-down test, including the training test which represents learning ability and retention test which represents memory ability, was conducted in 6 studies [5, 32, 34–36, 40]. Meta-analysis of 5 studies with 19 comparisons showed EAAGA were significant for increasing right reaction latency in the retention test (n = 396, SMD = 1.15, 95% CI [0.87 to 1.43], P < 0.00001; heterogeneity: χ² = 28.98, df = 18 (P = 0.05); I² = 38%; Figure 3(a)) and 1 study [5] for increasing right reaction latency (P < 0.05) in the training test. Meta-analysis of 3 studies [32, 35, 36] with 16 comparisons showed EAAGA were significant for decreasing the error times (n = 336, SMD = −1.06, 95% CI [−1.30 to −0.83], P < 0.00001; heterogeneity: χ² = 15.01, df = 15 (P = 0.45); I² = 0%; Figure 3(b)) in the retention test and 1 study [5] for decreasing the error times (P < 0.05) in the training test.

The electrical Y-maze test was conducted in 3 studies [5, 32, 36]. Meta-analysis of 3 studies showed EAAGA were significant for decreasing error reaction times (n = 168, SMD = −1.22, 95% CI [−1.56 to −0.88], P < 0.00001; heterogeneity: χ² = 3.95, df = 7 (P = 0.79); I² = 0%; Figure 4).

| Study or subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. mean difference IV, random, 95% CI | Std. mean difference IV, random, 95% CI |
|------------------|------------------|----|-------|--------------|----|-------|--------|---------------------------------------|---------------------------------------|
| Lee 2003         | 4.28             | 1.84 | 4     | 3.56         | 0.42 | 5     | 46.1%  | 0.51 [−0.84, 1.87]                     |                                        |
| Limón 2009       | 53.06            | 37.53 | 8     | 4.08         | 10.1 | 8     | 53.9%  | 1.69 [0.50, 2.87]                      |                                        |
| Total (95% CI)   | 12               |    | 13    |              |      |       | 100.0% | 1.15 [0.00, 2.29]                      |                                        |

Heterogeneity: τ² = 0.26; χ² = 1.63, df = 1 (P = 0.20); I² = 38% Test for overall effect: Z = 1.96 (P = 0.05)
### Table 3: Characteristics of mechanism studies of EAAGA on cognition impairment.

| Study (years)            | Model                                      | Method of administration (experimental group versus control group) | Observations                                                                 | Possible mechanisms                                      |
|-------------------------|--------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------|
| Yang et al. [17]         | Chronic lead-induced dysmnesia model       | β-Asarone versus distilled water                                  | Attenuated memory deficits                                                   | Arc/Arg3.1 and Wnt pathway Increased dendritic spine density |
|                         |                                            |                                                                    | Increased dendritic spine density                                             |                                                         |
|                         |                                            |                                                                    | Up-regulated NR2B, Arc/Arg3.1, and Wnt7a protein expression                  |                                                         |
| Wei et al., 2013         | AβPP/PS1 double-transgenic mice            | β-Asarone versus Tween 80                                         | Improved cognitive function                                                  | CaMKII/CREB/Bcl-2 signaling pathway Inhibition of apoptosis |
|                         |                                            |                                                                    | Prevents PC12 cell and cortical neuron damage                               |                                                         |
|                         |                                            |                                                                    | Inhibited the apoptosis of PC12 cells and cortical neurons                  |                                                         |
| Sundaramahalingam et al. [18] | Noise stress induced memory impairment model | α-Asarone versus Tween 80                                         | Prevent memory impairment                                                     | Reduction of oxidative reactions                         |
|                         |                                            |                                                                    | Decreased hsp 70 mRNA levels                                                 |                                                         |
|                         |                                            |                                                                    | Decreased SOD and AChE activity.                                             |                                                         |
|                         |                                            |                                                                    | Increased CAT and G6PD activity                                              |                                                         |
|                         |                                            |                                                                    | Increased VC, VE, and GSH levels                                             |                                                         |
| Shin et al. [19]         | LPS-induced cognitive handicap mode        | α-Asarone versus NS                                                | Ameliorated memory deficits                                                  | Repression of inflammatory reactions Inhibition of apoptosis |
|                         |                                            |                                                                    | Reduced Iba1 protein expression                                              |                                                         |
|                         |                                            |                                                                    | Reduced TNF-α and IL-1β mRNA                                                |                                                         |
|                         |                                            |                                                                    | Reduced BACE1 expression                                                     |                                                         |
|                         |                                            |                                                                    | Increased CA1 neurons                                                       |                                                         |
|                         |                                            |                                                                    | Reduced TUNEL-labeled cells                                                  |                                                         |
| Ma et al. [11]           | Aβ1,42-induced AD model                   | Water extract versus NS                                           | Ameliorated memory deficits                                                  | Inhibition of neurotoxicity                              |
|                         |                                            | Essential oil versus NS                                           | Reduced Aβ positive cells                                                    |                                                         |
|                         |                                            | Defatted decoction versus NS                                     | Decreased DCx and nestin expression                                          |                                                         |
|                         |                                            |                                                                    | Decreased nestin positive cells                                             |                                                         |
| Liu et al. [20]          | APPswe/PS1dE9 double transgenic mice       | β-Asarone versus Tween 80                                         | Improved the learning and memory ability                                     | Regulation of synaptic plasticity                        |
|                         |                                            |                                                                    | Increased SYP and GluR1 expression                                           |                                                         |
| Limón et al. [21]        | Aβ-induced AD model                        | α-Asarone versus NS                                                | Ameliorated memory deficits                                                  | Reduction of oxidative reactions                         |
|                         |                                            |                                                                    | Decreased NO levels                                                         |                                                         |
| Study (years) | Model | Method of administration (experimental group versus control group) | Observations | Possible mechanisms |
|--------------|-------|---------------------------------------------------------------|--------------|-------------------|
| Li et al. [22] | D-gal- and AlCl3-induced AD model | β-Asarone versus NS | Improved the learning and memory ability | Protection of cerebrovascular |
| | | | Increased rCBF and the activity of Na–K-ATP | |
| | | | Decreased pyruvic acid contents | |
| | | | Decreased ET-1, eNOS, and APP mRNA expression | |
| Zhang et al. [5] | Aged mice | Essential oil versus Tween 80 | Improved cognitive function | |
| | | | Increased 5-HT, NE, DA, and NE levels | Improvement of cognitive function |
| | | | Decreased AChE activity | |
| | | | | |
| | | | | |
| | Ethanol-induced dysnesia model | Essential oil versus Tween 80 | | |
| | Aged rats | Essential oil versus Tween 80 | Improved cognitive function | |
| | | | Increased 5-HT, NE, DA, and NE levels | |
| | | | Decreased AChE activity | |
| | | Sodium nitrite-induced dysnesia model | Essential oil versus Tween 80 | |
| Lee et al. [10] | MCAO/2 h-induced cognitive impairments model | AGA versus NS | Attenuated learning and memory deficits | Inhibition of apoptosis |
| | | | Increased cell density | |
| Lee et al. [23] | Chronic corticosterone exposed | β-Asarone versus NS | Improved cognitive function | |
| | | | Increased BDNF and CREB expression | |
| | | | | Inhibition of apoptosis |
| | Kumar et al., 2012 | Scopolamine-induced amnesic model | α-Asarone versus vehicle | Improved cognitive function | |
| | | | Increased of AchE activity | Reduction of oxidative reactions |
| | | | Inhibition MDA expression and SOD levels | |
| | | | Reduced SOD activity | |
| Kim et al. [25] | Ibotenic acid-induced amnesia | AGA versus NS | Ameliorated learning and memory deficits | Stimulation of cholinergic system |
| | | | Increased ChAT positive neurons | |
| | | | Increased AchE neurons | |
| Geng et al. [26] | Aβ1-42-induced AD rat model | β-Asarone versus NS | Ameliorated learning and memory deficits | |
| | | | Increased Bcl-2, Bcl-w expression | |
| | | | Increased Bcl-2 and Bcl-w mRNA levels | Inhibition of apoptosis |
| | | | Decreased cleavage of caspase-3 | |
| | | | Reduced caspase-3 mRNA levels | |
| | | | Decreased p-JNK expression | |
| Chen et al. [27] | SAMP8 mice | β-Asarone versus NS | Improved cognitive function | Reduction of autophagy |
| | | | Reduced ROCK, beclin1, and LC3 expression | |
| | | | Increased p62 expression | |
| Study (years) | Model | Method of administration (experimental group versus control group) | Observations | Possible mechanisms |
|--------------|-------|---------------------------------------------------------------|--------------|-------------------|
| Ma et al. [28] | Aβ-induced AD model | Water extract versus NS Water extract without oil versus NS Essential oil versus NS | Ameliorated learning and memory deficits Decreased Aβ plaques depositions | Improvement of cognitive function |
| Tian et al. [29] | Aβ-induced AD model | Water extract versus NS Defatted decoction versus NS Essential oil versus NS | Ameliorated learning and memory deficits Decreased NOS activity | Inhibition of neurotoxicity |
| Zhou et al. [30] | Scopola-induced AD model | Essential oil versus NS | Ameliorated learning and memory deficits Decreased GFAP expression Decreased MDA levels Increased SOD levels | Reduction of oxidative reactions |
| Wang GM et al., 2017 | Chronic restraint stress-induced cognitive impairments mode | Essential oil versus NS | Ameliorated learning and memory deficits Increased body mass Decreased plasma cortisol levels | Inhibition of chronic stress |
| Hu et al. [32] | Sodium nitrite-induced amnesic model | Essential oil versus Tween 80 Defatted decoction versus Tween 80 α-Asarone versus Tween 80 β-Asarone versus Tween 80 Essential oil versus Tween 80 | Increased learning and memory deficits | Improvement of cognitive function |
| Gu et al. [34] | D-galactose-induced dementia model | Water extract versus distilled water | Ameliorated memory deficits Decreased MDA levels Increased SOD activity | Reduction of oxidative reactions |
| Chen et al. [33] | Scopolamine-induced dysnesia mice | Water extract versus NS | Ameliorated memory deficits | |
| Gu et al. [34] | NaNO₂-induced dysnesia model | Water extract versus NS | Ameliorated memory deficits | |
| Gu et al. [34] | 45% ethanol-induced dysnesia mice | Water extract versus NS | Ameliorated memory deficits The AChE activity of mice brain was not influenced | |
| Wu et al., 2004 | Aged mice | Essential oil versus NS β-Asarone versus NS Water extract versus NS Water extract versus NS | Ameliorated memory deficits Decreased AChE activity Increased c-jun mRNA levels | Inhibition of apoptosis |
| Study (years) | Model | Method of administration (experimental group versus control group) | Observations | Possible mechanisms |
|--------------|-------|---------------------------------------------------------------|--------------|---------------------|
| Ethanol-induced dysnesia model | NaNO₂-induced dysnesia model | Essential oil versus NS | Ameliorated memory deficits | |
| Wen et al., 2009 | NaNO₂-induced dysnesia model | β-Asarone versus NS | Inhibition of apoptosis | |
| | Scopolamine-induced dysnesia model | Essential oil versus NS | Ameliorated memory deficits | |
| | Scopolamine-induced dysnesia model | Water extract versus NS | | |
| | Scopolamine-induced dysnesia model | Essential oil versus NS | | |
| | Scopolamine-induced dysnesia model | Water extract versus NS | | |
| | Scopolamine-induced dysnesia model | Essential oil versus NS | | |
| Yang et al. [37] | Aβ₁₋₄₂-induced AD model | β-Asarone versus NS | Improved cognitive function | Suppression of astrocyte activation |
| Zhou et al. [38] | D-gal- and AlCl₃-induced AD model | α-Asarone versus NS | Improved cognitive function | |
| Jiang et al. 2007 | AlCl₃-induced AD model | β-Asarone versus NS | Improved cognitive function | |
| Huang et al. [40] | Fragile X syndrome model | α-Asarone versus NS | Improved cognitive function | |
| Wang BL et al., 2017 | Aβ₁₋₄₂-induced AD model | β-Asarone versus NS | Improved cognitive function | |
| Guo et al. [42] | Scopolamine-induced AD model | β-Asarone versus NS | Improved cognitive function | |
| Jiang et al. [43] | STZ-induced AD model | Essential oil versus solvent | Improved cognitive function | |
| | | | Inhibition of apoptosis | |
Table 3: Continued.

| Study (years) | Model | Method of administration (experimental group versus control group) | Observations | Possible mechanisms |
|--------------|-------|---------------------------------------------------------------|--------------|---------------------|
| Yang et al. [44] | PTZ-induced epilepsy model | AGA versus NS | Improved cognitive function | Improved cognitive function | Inhibition of apoptosis |
| Wang et al. [45] | Aβ1-42-induced AD model | Essential oil versus NS | Improved cognitive function | Improved cognitive function | Improvement of cognitive function |
| Ma et al. [46] | D-gal- and AlCl3-induced AD model | β-Asarone versus NS | Improved cognitive function | Decreased GA P-43 mRNA levels | Increased SYP mRNA levels |

Ach: acetylcholine; AchE: acetylcholinesterase; AD: Alzheimer’s disease; AlCl3: aluminum trichloride; ChAT: acetylcholine transferase; D-gal: D-galactose; MCAO: middle cerebral artery occlusion; MDA: malondialdehyde; STZ: streptozotocin; SOD: superoxide dismutase; HIF: hypoxia-inducible factor; SYN/SYN: synaptophysin; MAP2: microtubule-associated protein 2; Aβ1-42: amyloid beta 1–42; NS: normal saline; PTZ: pentylenetetrazol; GSH-Px: glutathione peroxidase; NE: norepinephrine; 5-TH: 5-hydroxytryptamine; DA: dopamine; NOS: nitric oxide synthase; Bcl-2: B-cell lymphoma/leukemia-2.

Figure 7: A schematic representation of possible mechanisms of EAAGA for improving learning and memory function. The possible mechanisms of different active ingredients are as follows: (1) AGA: the dry rhizomes of Acorus gramineus Solander can inhibit apoptosis and stimulate cholinergic system. (2) Essential oil: AGA contains up to 4.86% essential oil, which displayed antioxidation effects by decreasing the levels of MDA and increasing the levels of SOD, exhibited anticytotoxicity effects via decreasing NOS activity, exerted antineurotoxicity effects by decreasing Aβ plaques depositions, and improved cognitive function by decreasing the activity of CHβE. (3) β-Asarone: a major component of essential oil (63.2–81.2%) displayed antioxidation effects by decreasing the levels of MDA and HIF, increasing the levels of SOD, CAT, and GSH-Px; exerted antiapoptotic activity through regulating CaMKII/CREB/Bcl-2 signaling pathway and decreasing the levels of Bax mRNAs, caspase-3 mRNA, and JNK; inhibited synaptic loss through reducing ROCK expression; mediated synaptogenesis via Arc/Arg3.1 and Wnt pathway; improved circulation by decreasing the activity of CHβE and exerted antineurotoxicity by decreasing Aβ plaques depositions. (4) α-Asarone: another major component of essential oil (8.8–13.7%) exerted antioxidation effects by increasing the levels of SOD, CAT, and GSH-Px; displayed anti-inflammatory activity through reducing the expression of proinflammatory mediators; improved circulation via decreasing the activity of CHβE; and exerted antineurotoxicity by decreasing Aβ plaques depositions. (5) Water extract: displayed antioxidation effects by decreasing the levels of MDA and increasing the levels of SOD, exerted antineurotoxicity by decreasing Aβ plaques depositions and improved cognitive function by decreasing the activity of CHβE. (6) Defatted decoction: exerted antineurotoxicity by decreasing Aβ plaques depositions and displayed anticytotoxicity effects via decreasing the activity of NOS.
The step-through test was conducted in 4 studies [24, 34–36]. Meta-analysis of 4 studies with 7 comparisons showed EAAGA were significant for decreasing latency in the retention test \( n = 134, \text{SMD} = 1.26, 95\% \text{ CI} [0.81 to 1.71], P < 0.00001 \); heterogeneity: \( \chi^2 = 8.09, df = 6 (P = 0.23); \; I^2 = 26\% \); Figure 5(a) and 2 studies [35, 36] with 5 comparisons showed EAAGA significantly decreased the number of errors in the retention test \( n = 100, \text{SMD} = -1.02, 95\% \text{ CI} [-1.145 to -0.60], P < 0.000001 \); heterogeneity: \( \chi^2 = 1.05, df = 4 (P = 0.90); \; I^2 = 0\% \); Figure 5(b) compared with controls.

The eight-arm maze test was conducted in 3 studies [10, 18, 21]. Meta-analysis of 2 studies [10, 21] showed EAAGA were significant for increasing number of correct choices \( n = 25, \text{SMD} = 1.15, 95\% \text{ CI} [0.00 to 2.29], P = 0.05 \); heterogeneity: \( \chi^2 = 1.63, df = 1 (P = 0.20); \; I^2 = 38\% \); Figure 6(a) and 2 studies [10, 18] with 3 comparisons showed EAAGA significantly decreased the number of errors in the training test \( n = 33, \text{SMD} = -2.36, 95\% \text{ CI} [-3.36 to -1.37], P < 0.00001 \); heterogeneity: \( \chi^2 = 1.00, df = 2 (P = 0.61); \; I^2 = 0\% \); Figure 6(b) compared with controls.

3.5. Neuroprotective Mechanisms. The mechanisms of neuroprotection of EAAGA on cognitive impairment were studied in 34 included articles [5, 6, 10, 11, 17–46] as follows: (1) reduction of oxidative reactions by increasing the activity of SOD and AChE [18, 24], decreasing the levels of MDA [24, 30, 33] and nitric oxide [21], decreasing the mRNA levels of hsp 70, increasing the levels of VC, VE, and GSH, and increasing the activity of CAT and G6PD [18]; (2) inhibition of apoptosis by increasing the mRNA levels of Bcl-2, BDNF, CREB [6, 23, 42], Bcl-w and Bcl-2 [26], and c-jun [35], decreasing the mRNA levels of Bax [23], increasing the expression of BDNF, CREB [23], Bcl-w, and Bcl-2 [26], decreasing the expression of caspase-3, p-JNK [26], and BACE1 [19], and preventing cell loss [10], Aβ, and Tau protein [38]; (3) repression of inflammatory reactions by decreasing the expression of TNF-α and IL-1β mRNA levels [19]; (4) repression of autophagy by decreasing LC3, ROCK, and beclin1 expression and increasing p62, GAP43, MAP2, and SYN expression [27]; (5) protection of cerebrovascular by increasing rCBF and the Na-K-ATP activity, decreasing pyruvic acid contents, and decreasing the mRNA levels of ET-1, eNOS, and APP [22]; (6) promotion of cognitive function by increasing the levels of 5-HT, NE, DA, and NE [5] and suppression of astrocyte activation [37]; (7) stimulation of cholinergic system by increasing AChE and ChAT neurons [25]; (8) improvement of memory impairments through regulation of synaptogenesis, which is mediated via Arc/Arg3.1 and Wnt pathway [17]; (9) neuroprotection through damage of Akt pathway [40]; (10) inhibition of neurotoxicity by decreasing the expression of DCx and nestin, decreasing nestin positive cells [11], decreasing Aβ plaques depositions, and decreasing NOS activity [29]; (11) regulation of synaptic plasticity by increasing the expression of SYP and GluR1 [20, 46] and decreasing the expression of GAP-43 and PSD-95 [46]; and (12) inhibition of chronic stress by decreasing plasma cortisol levels [41]. Characteristics of mechanism studies of EAAGA on experimental ischemic stroke are shown in Table 3 and Figure 7.

4. Discussion

As far as we know, it is the first preclinical systematic review that determined the efficacy of EAAGA for learning and memory function. In the present study, 34 studies with 1431 animals showed that EAAGA significantly improve learning and memory function, suggesting the potential neuroprotective functions of EAAGA in cognitive function impairment. However, given methodological weaknesses, the overall available evidence from the present study should be interpreted cautiously.

Some limitations should be considered while interpreting this study. First, we only searched databases in Chinese and English. The absence of studies published in other languages may cause certain degree selective bias [48]. Second, the methodological quality of included studies showed some inherent drawback. Most of the research had methodological flaws in aspects of blinding, randomization, allocation concealment, sample size calculation, and lacking statement of potential conflict of interests [49, 50]. The studies without adequate sample sizes, allocation concealment, or randomization may result in inflated estimates of treatment efficacy [51, 52]. Lower quality trials could attribute to statistically significant 30–50% exaggeration of treatment efficacy [53]. Third, no study adopted animals with comorbidities, which would have created more relevant models for human pathology [49]. Thereby, the results should be interpreted cautiously.

The poor design of animal research hindered the translation of animal research into effective preclinical drug treatments for human disease [54, 55]. Thus, it is necessary to take a rigorous experimental design to overcome methodology quality issues for further research. The Animal Research: Reporting of In Vivo Experiments (ARRIVE) [56, 57] is a reporting guideline consisting of a 20-item checklist that provides recommendations on Introduction, Methods, Results, and Discussion which were recommended to be utilized as guidelines when designing and reporting animal research on EAAGA for improving the cognitive function impediment. Meanwhile, many drugs that exerted significant effects in animal researches failed to translate into effective clinical drug treatments [58, 59]. One of the possible reasons is the application of drug doses and the timing of drug administration in animal models that are inapplicable for human disease [55]. In the present study, doses of EAAGA and timing for initial administration in animal models were inconsistent among the 34 included studies. Thus, we suggest further studies to determine the optimal gradient doses and timing of administration in animal models of cognition impairment.

The present study showed that EAAGA had cognitive enhancing effects through different mechanisms as follows: (1) reduction of oxidative reactions by increasing the activity of SOD [30, 35, 39, 41, 43] activity, while decreasing the activity of SOD and AChE [18, 24], decreasing the levels of MDA [24, 30, 33] and nitric oxide [21], decreasing the mRNA levels of hsp 70, increasing the levels of VC, VE and
GSH, and increasing the activity of CAT and G6PD [18]; (2) inhibition of apoptosis by increasing the mRNA levels of Bcl-2, BDNF, CREB [6, 23, 42], Bcl-w and Bcl-2 [26], and c-jun [35], decreasing the mRNA levels of Bax [23], increasing the expression of BDNF, CREB [23], Bcl-w, and Bcl-2 [26], decreasing the expression of caspase-3, p-JNK [26], and BACE1 [19], and preventing cell loss [10], Aβ, and Tau protein [38]; (3) repression of inflammatory reactions by decreasing the expression of TNF-α and IL-1β mRNA levels [19]; (4) repression of autophagy by decreasing LC3, ROCK, and beclin1 expression and increasing p62, GAP43, MAP2, and SYN expression [27]; (5) protection of cerebrovascular by increasing rCBF and the Na-K-ATP activity, decreasing pyruvic acid contents, and decreasing the mRNA levels of ET-1, eNOS, and APP [22]; (6) promotion of cognitive function by increasing the levels of 5-HT, NE, DA, and NE [5] and suppression of astrocyte activation [37]; (7) stimulation of cholinergic system by increasing AchE and ChAT neurons [25]; (8) improvement of memory impairments through regulation of synaptogenesis, which is mediated via Arc/Arg3.1 and Wnt pathway [17]; (9) neuroprotection through damage of Akt pathway [40]; (10) inhibition of neurotoxicity by decreasing the expression of DCx and nestin, decreasing nestin positive cells [11], and decreasing Aβ plaques depositions, decreased NOS activity [29]; (11) regulation of synaptic plasticity by increasing the expression of SYP and GluR1 [20, 46] and decreasing the expression of GAP-43 and PSD-95 [46]; and (12) inhibition of chronic stress by decreasing plasma cortisol levels [41]. However, cellular and molecular alteration mechanisms of EAAGA and active components for cognition impairment have not been clearly explored yet, which presented an exciting investigative direction of further studies. All 5 measuring methods for learning and memory ability were used in the 34 included studies, which showed that the measuring methods for cognition impairment were inconsistent. The diverse measuring methods for learning and memory ability need further study.

5. Conclusions

Although some factors such as study quality may undermine the validity, EAAGA exert potential neuroprotective effects in cognition impairment. In addition, AGA and active components may be a promising candidate for clinical trials.

Conflicts of Interest

The authors declare no conflicts of interest.

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